In the name of Allah, Most Gracious, Most Merciful.

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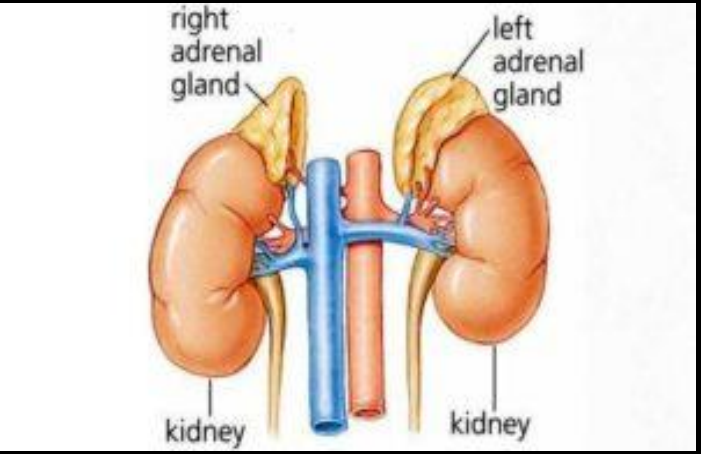
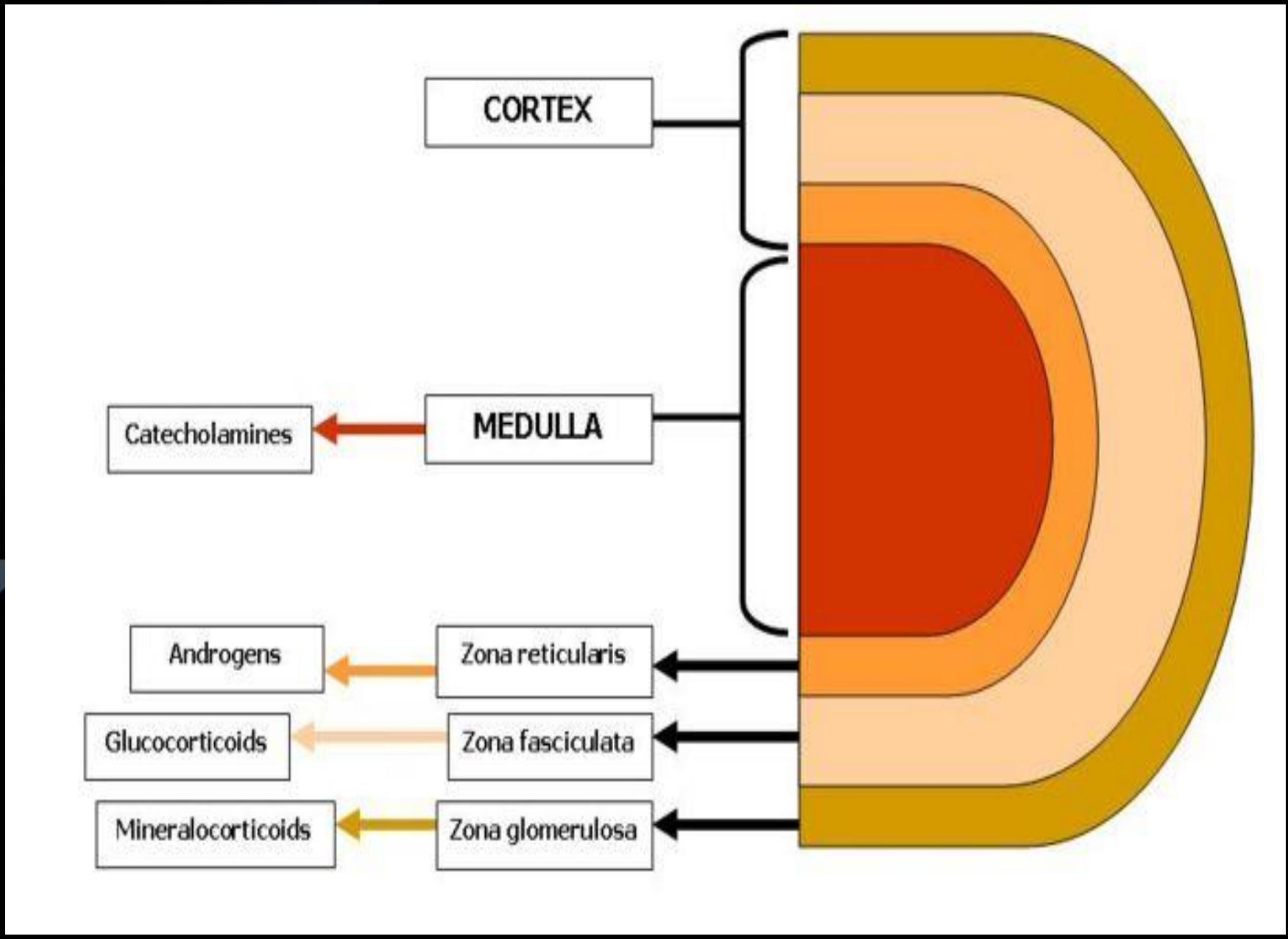
Adrenal Gland



Learning objectives

- Adrenal cortex hormones
- Classification
- Synthesis of steroid hormones
- Functions of mineralocorticoids and glucocorticoids
- Regulation
- Diseases


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

CLASSIFICATION

According to structure

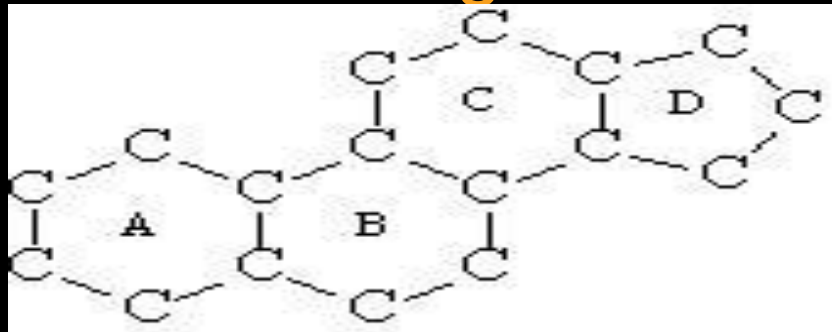
- C-21 steroids
- C-19 steroids

According to function

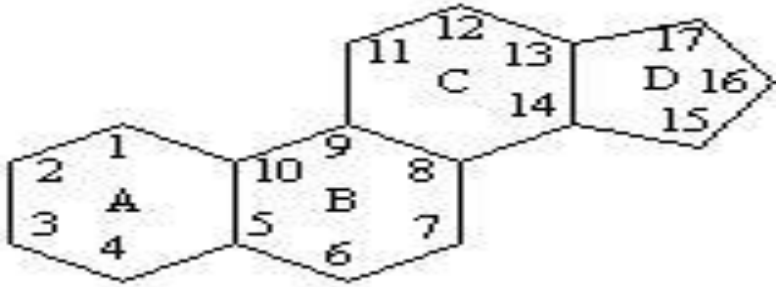
- Glucocorticoids
- Mineralocorticoids
- Androgens

Chemistry

- All adrenal cortex hormones are steroids(contain steroid nucleus i-e ***cyclo-pentano perhydro phenanthrene***),
- About 50 different steroids are made in adrenal gland



Carbon skeleton of the steroid nucleus



Steroid nucleus

IMPORTANT STEROIDS (ADRENAL GLAND)

- 11-dehydrocorticosterone
- Corticosterone
- Cortisol
- Aldosterone
- Dehydroepiandrosterone (DHEA)

(cortisone,prednisone,9α-flourocortisol,dexamethasone;synthetic)

Sites of steroid synthesis

- Adrenal cortex , gonads and placenta
- Synthesized from cholesterol in mitochondria and smooth endoplasmic reticulum of cell

SYNTHESIS OF CORTICOSTEROIDS

» Precursor ⟶ cholesterol

» source of cholesterol;

> newly sythesised,

> taken from lipoproteins or

> released from cholesteryl esters stored in steroidogenic tissues

SYNTHESIS

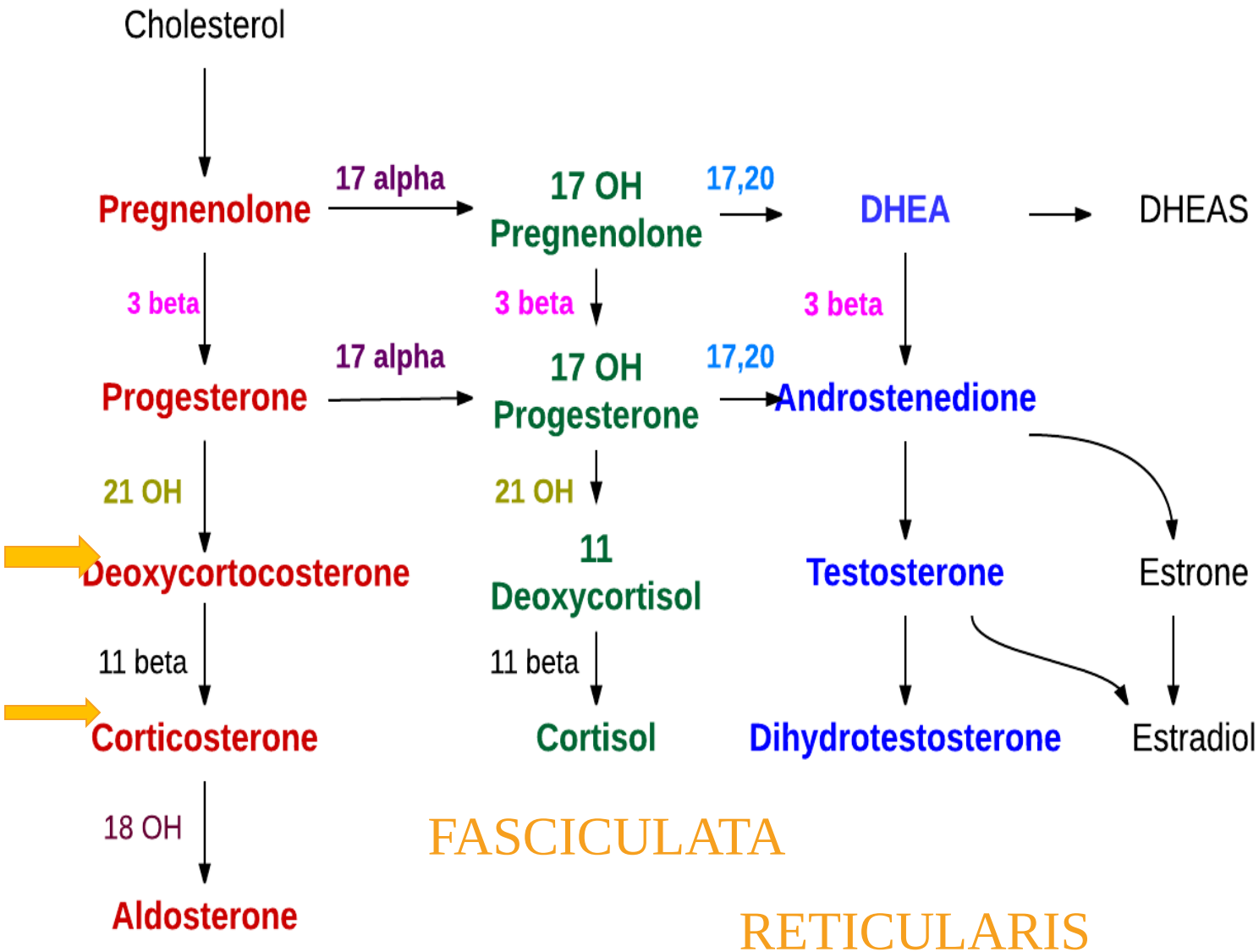
- 1st step is rate limiting

cholesterol —desmolase→ pregnenolone

- this step requires O2 and NADPH
- COMMON PATHWAY FOR ALL CORTICOSTEROIDS
- Occurs in mitochondria,all the three zones of gland

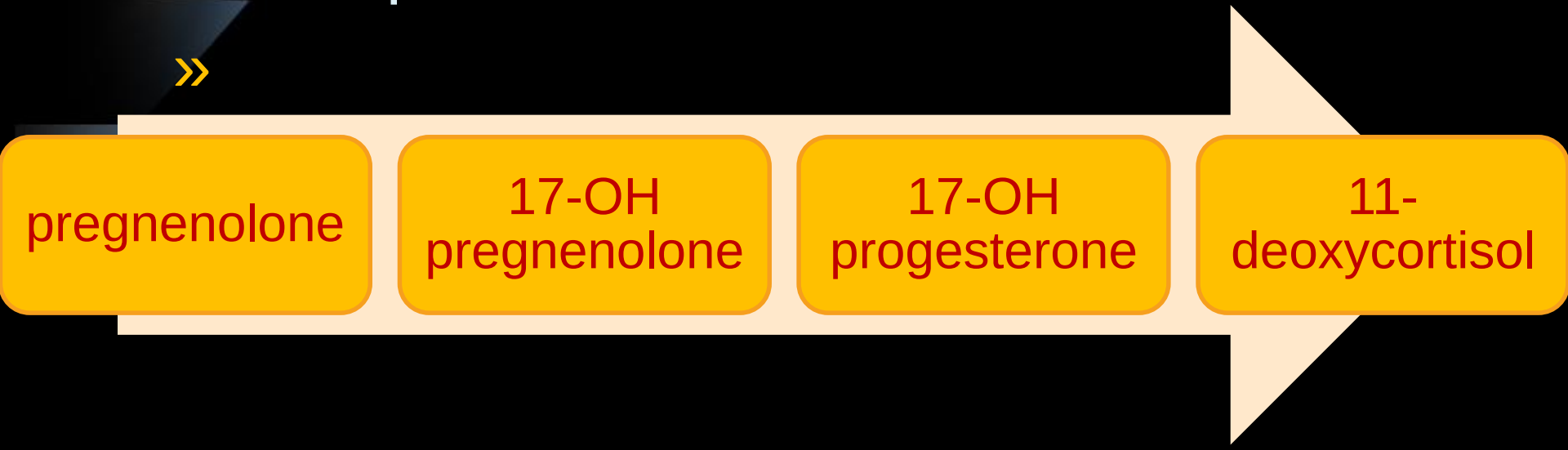
ACTION OF ACTH

- Increases availability of free cholesterol
- Increases the conversion of cholesterol to pregnenolone(rate limiting step)
- Acts in all three zones of adrenal cortex

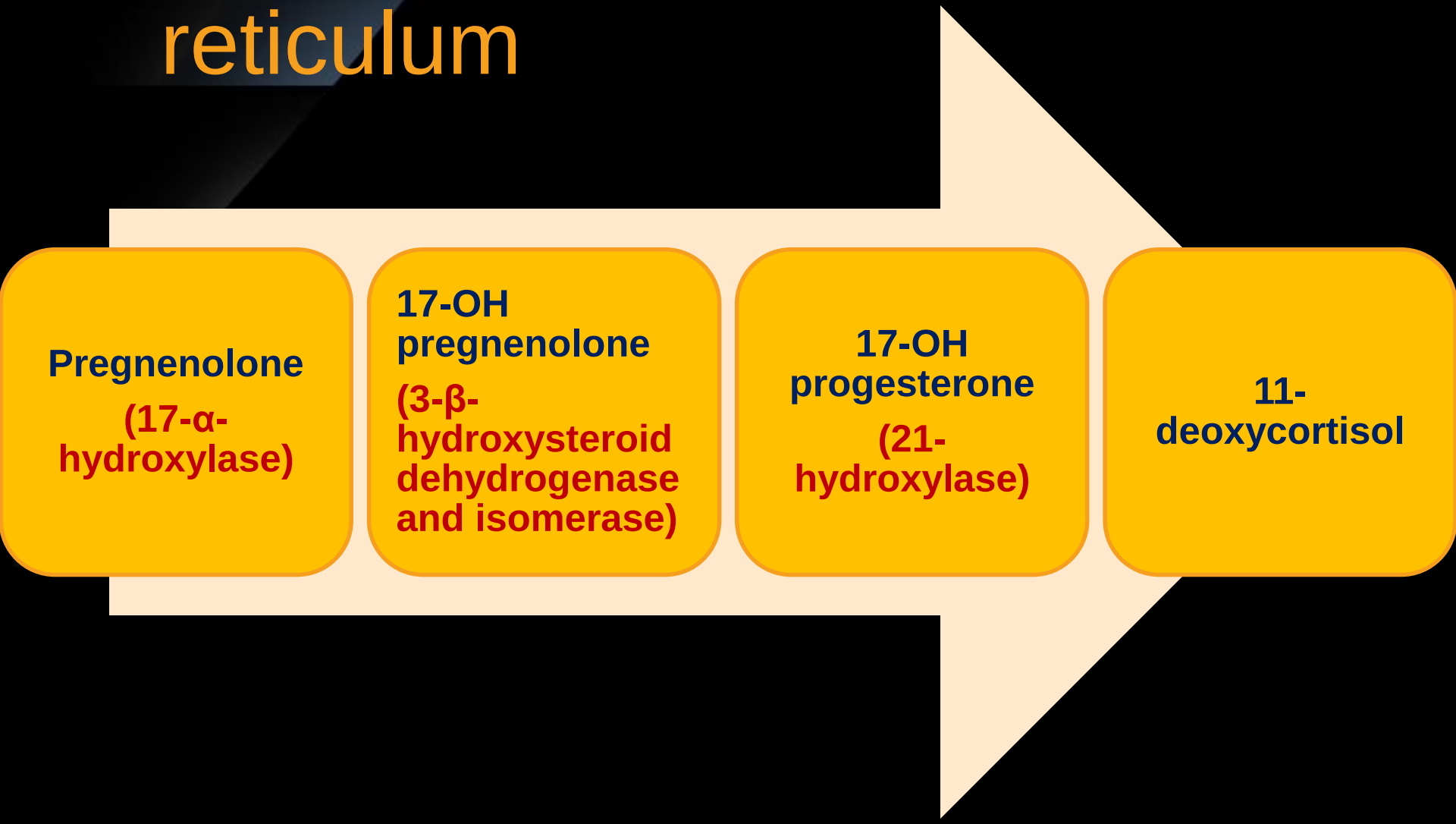

Cholesterol
Pregnenolone
17 alpha
17 OH Pregnenolone
17,20
DHEA
DHEAS
3 beta
3 beta
3 beta
Progesterone
17 alpha
17 OH Progesterone
17,20
Androstenedione
21 OH
21 OH
Deoxycortocosterone
11 Deoxycortisol
Testosterone
Estrone
11 beta
11 beta
Corticosterone
Cortisol
Dihydrotestosterone
Estradiol
18 OH
FASCICULATA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

1.Glucocorticoid synthesis

- In zona fasciculata
- Pregnenolone transferred to smooth endoplasmic reticulum
-



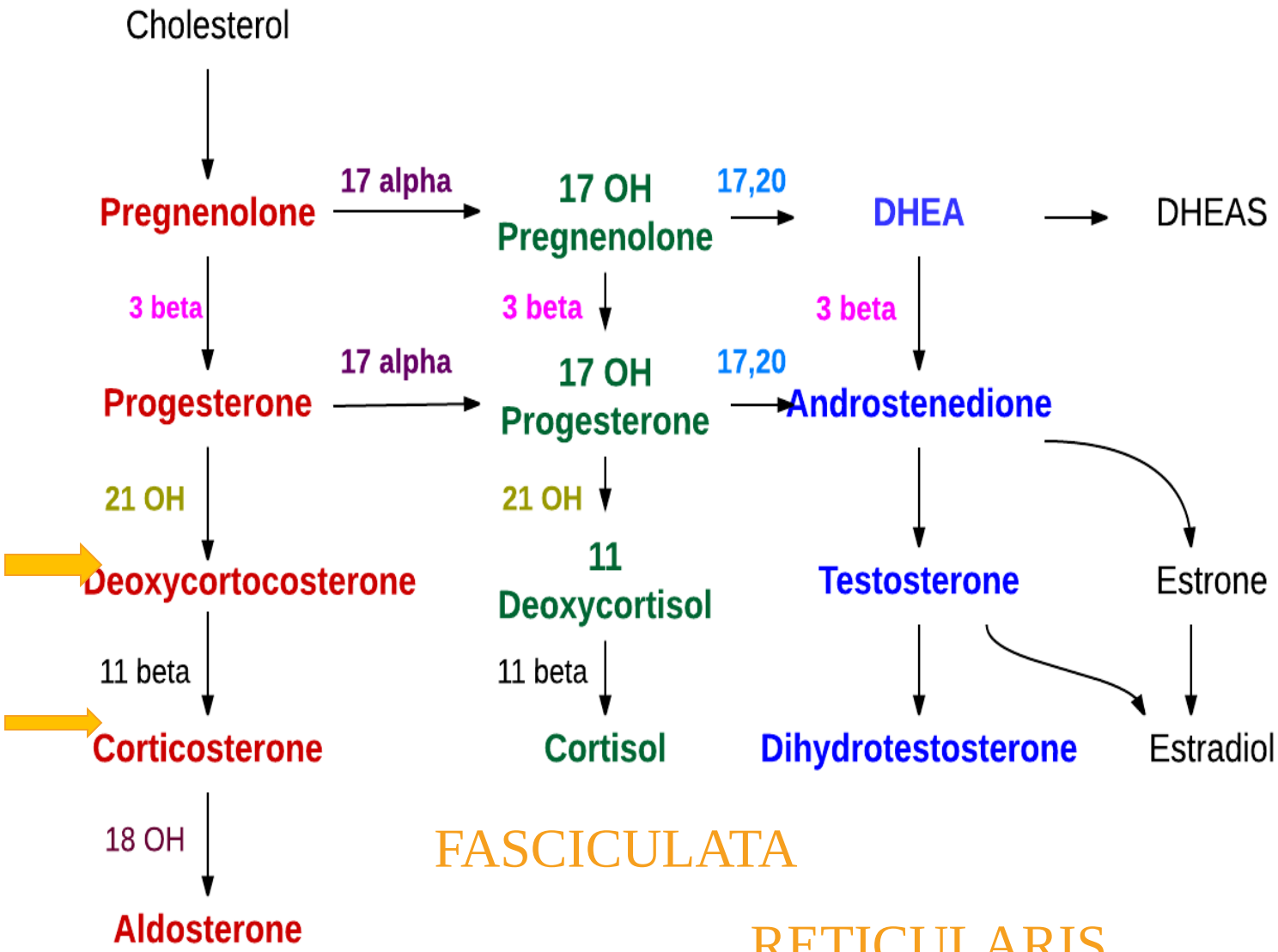
In smooth endoplasmic reticulum



- 11-deoxycortisol is transferred to mitochondria
- Converted to CORTISOL
- Enzyme:11-β-hydroxylase

2.Mineralocorticoid synthesis

- Zona glomerulosa
- 17-α-hydroxylase is absent in this zone
- so progesterone is directly hydroxylated by 21-hydroxylase to form 11-deoxycorticosterone
- 11-deoxycorticosterone to corticosterone(11-β-hydroxylase)
- Corticosterone to aldosterone(aldosterone synthase)


Cholesterol
Pregnenolone
17 alpha
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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
GLOMERULOSA
FASCICULATA
RETICULARIS

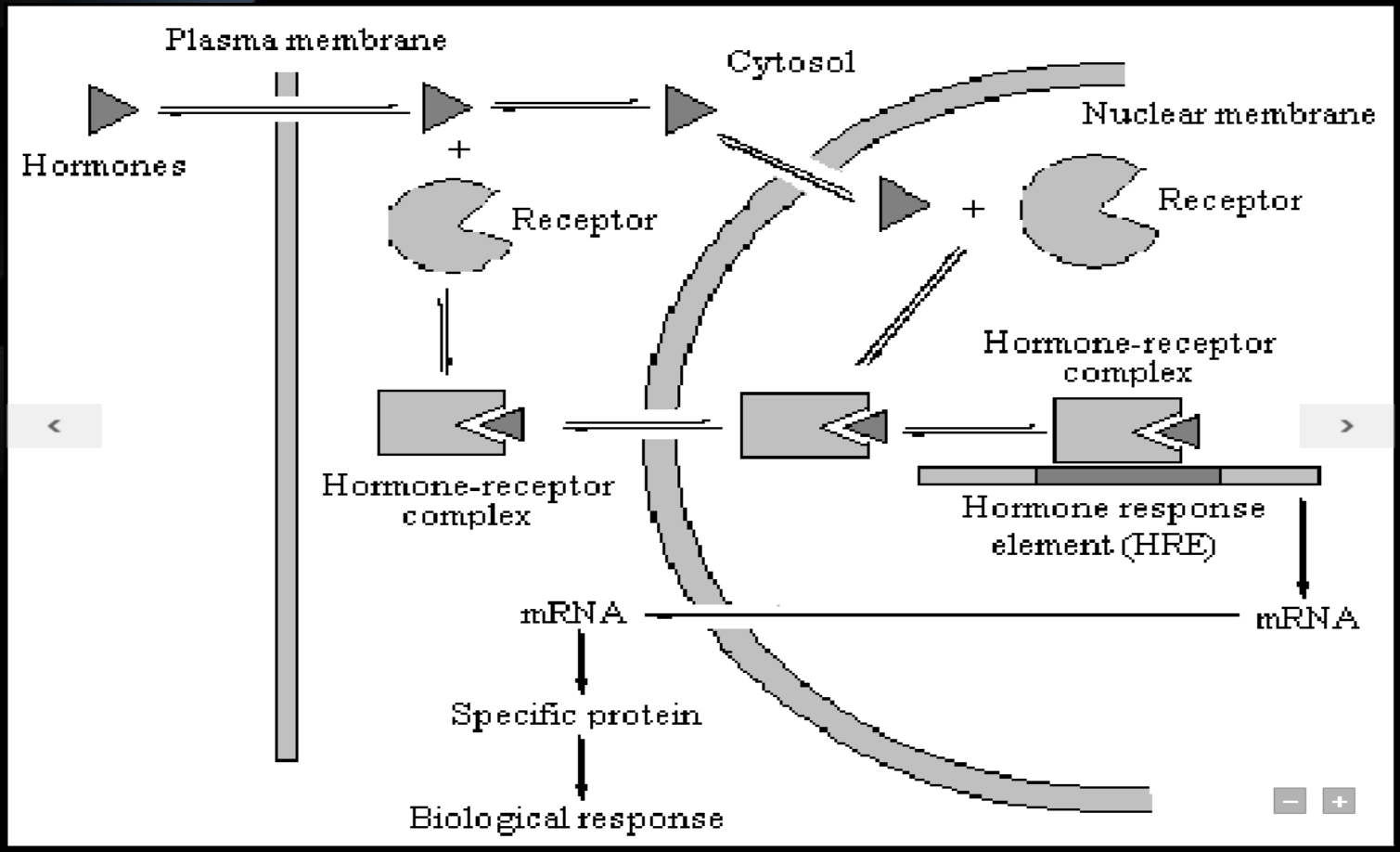
3.Androgen synthesis

- Zona reticularis
- 17-hydroxyprogesterone to DHEA(17-20 lyase)
- DHEA to androstenedione
- Androstenedione to testosterone

PERIPHERAL TISSUE:

- testosterone to estradiol(aromatase)
- testosterone to dihydrotestosterone(5α-reductase)

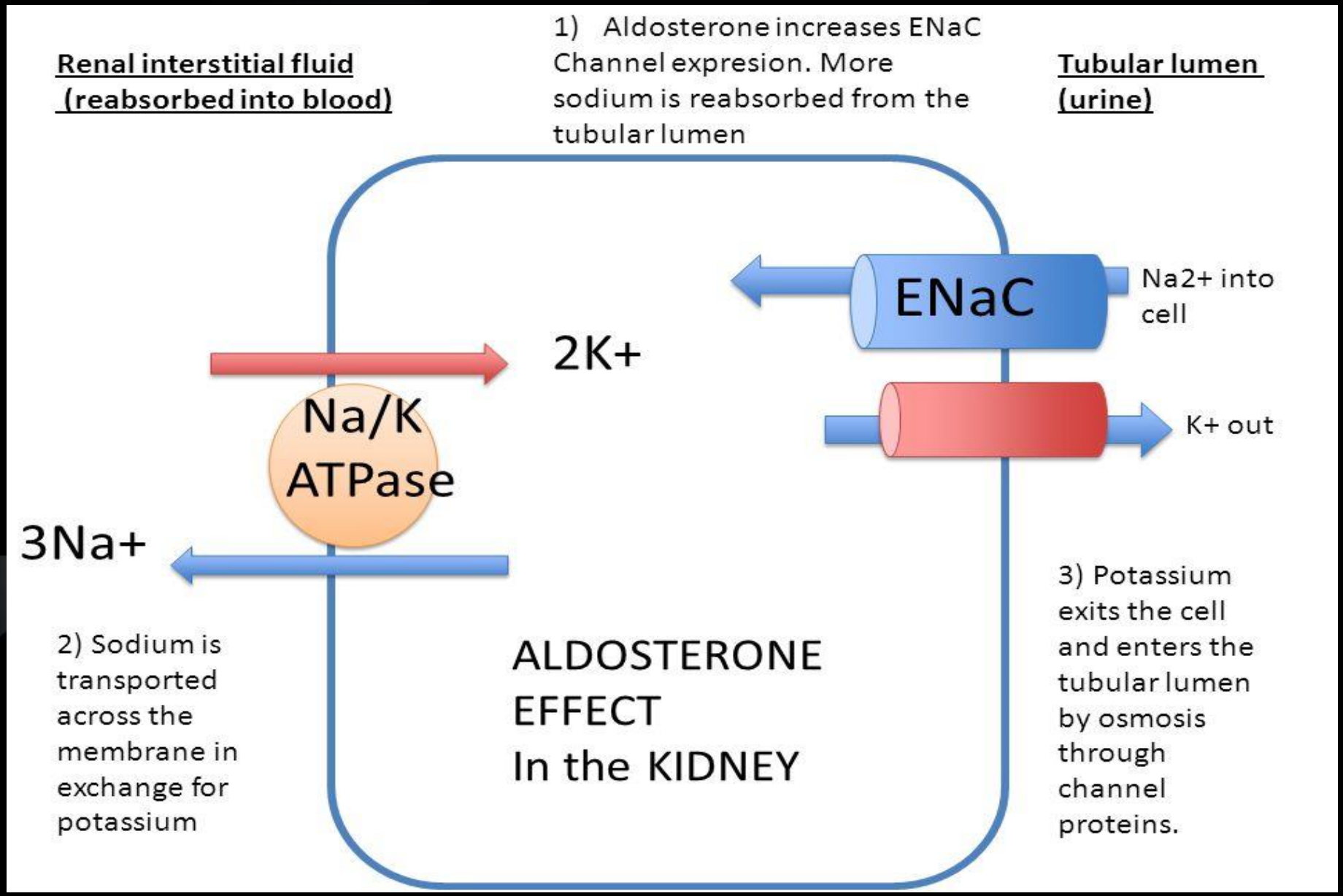
Mechanism of action



FUNCTIONS

FUNCTIONS OF ALDOSTERONE

a) Renal effects
b) Effect on fluid volume
c) Effect on sweat glands ,salivary glands and gastric mucosa


Renal interstitial fluid (reabsorbed into blood)
1) Aldosterone increases ENaC Channel expresion. More sodium is reabsorbed from the tubular lumen
Tubular lumen (urine)
ENaC
Na2+ into cell
2K+
Na/K ATPase
K+ out
3Na+
2) Sodium is transported across the membrane in exchange for potassium
ALDOSTERONE EFFECT In the KIDNEY
3) Potassium exits the cell and enters the tubular lumen by osmosis through channel proteins.

a)Renal effects

- Increase Na+ reabsorption by stimulating Na+/K+ pump and increasing sodium channels(ENaC) in principal cells
- Increase K+ secretion
- Increase H+ secretion by stimulating H+ ATPase(α-intercalated cells) hence promotes alkalosis

- In principal cells aldosterone increases
- activity of basolateral membrane sodium potassium ATPase and apical epithelial sodium channels .
- These actions increase sodium reabsorption and potassium secretion .
- Since more sodium is reabsorbed than potassium secreted , it also makes the

- Lumen more electrically negative causing chloride to follow sodium .
- Water than follows sodium and chloride by osmosis .

b) Effect on fluid volume

- Increases ECF fluid volume(when Na+ is absorbed,water follows) by:
- ✓Increased osmolarity of ECF
- ✓ADH secretion
- ✓Thirst stimulation due to high electrolyte conc.
- Increase plasma volume(blood volume)

c) Other effects

- Same effect on sweat glands,salivary glands and gastric mucosa as kidney
- i-e PREVENTS LOSS OF SODIUM AND CHLORIDE

Regulation of mineralocorticoid secretion

» Four factors:

1. Potassium ion(stimulates secretion)
2. Renin- angiotensin system
3. Sodium ion(suppresses secretion)
4. ACTH necessary for secretion but little effect on controlling rate of secretion

FUNCTIONS OF GLUCOCORTICOIDS

GLUCOCORTICOIDS ARE ANABOLIC TO LIVER AND CATABOLIC PERIPHERALLY AND DIABETOGENIC

Effect on carbohydrate metabolism

1. Decrease glucose uptake by adipocytes(anti-insulin)
2. Increase gluconeogenesis by increasing enzymes and by providing more substrate(increased protein catabolism)
3. Decrease glycolysis

- Decrease glucose uptake and utilization in muscles , adipocytes and lymphoid cells by inhibiting the membrane transport of glucose into these cells .
- Increases gluconeogenesis in liver
- Increases the synthesis of key gluconeogenic enzymes
- By making more substrate required for

- Gluconeogenesis
- Increasing protein catabolism in extra heptic tissues
- Increases synthesis of enzymes required forprotein catabolism .
- Decreases glycolysis in peripheral tissues .

Effect on lipid metabolism

- Increased lipolysis in adipocytes
- Net effect is increased FFA and glycerol
- Glycerol is used in gluconeogenesis

Effect on protein metabolism

- Catabolic peripherally and anabolic in liver
- Net effect is negative nitrogen balance
- Increase synthesis of urea in liver

OTHER EFFECTS

» Anti-inflammatory(in therapeutic doses)

1. stabilises lysosomal cell membrane
2. Prevent formation of bradykinin
3. Decrease capillary permeability
4. Decrease formation of prostaglandins and leukotrienes
5. Decrease no.of circulating lymphocytes ,monocyte and eosinophils

» Steroids have been used as an anti inflammatory drugs in treatment of rheumatoid arthritis , rheumatic fever and acute glomerulonephritis .

- Immunosuppressive in high doses(decreased proliferation of lymphocytes)
- Chronic use of glucocorticoids cause increase in HCl and pepsinogen secretion in stomach
- Reduces osteiod matrix of bones favouring OSTEOPOROSIS
- BLOOD: **lymphopenia** and increase RBC

- Glucorticoids have been used in organ transplantation as it prevents graft rejection .
- As an antiallergic action been used to treat bronchial asthma and status asthmaticus patients .

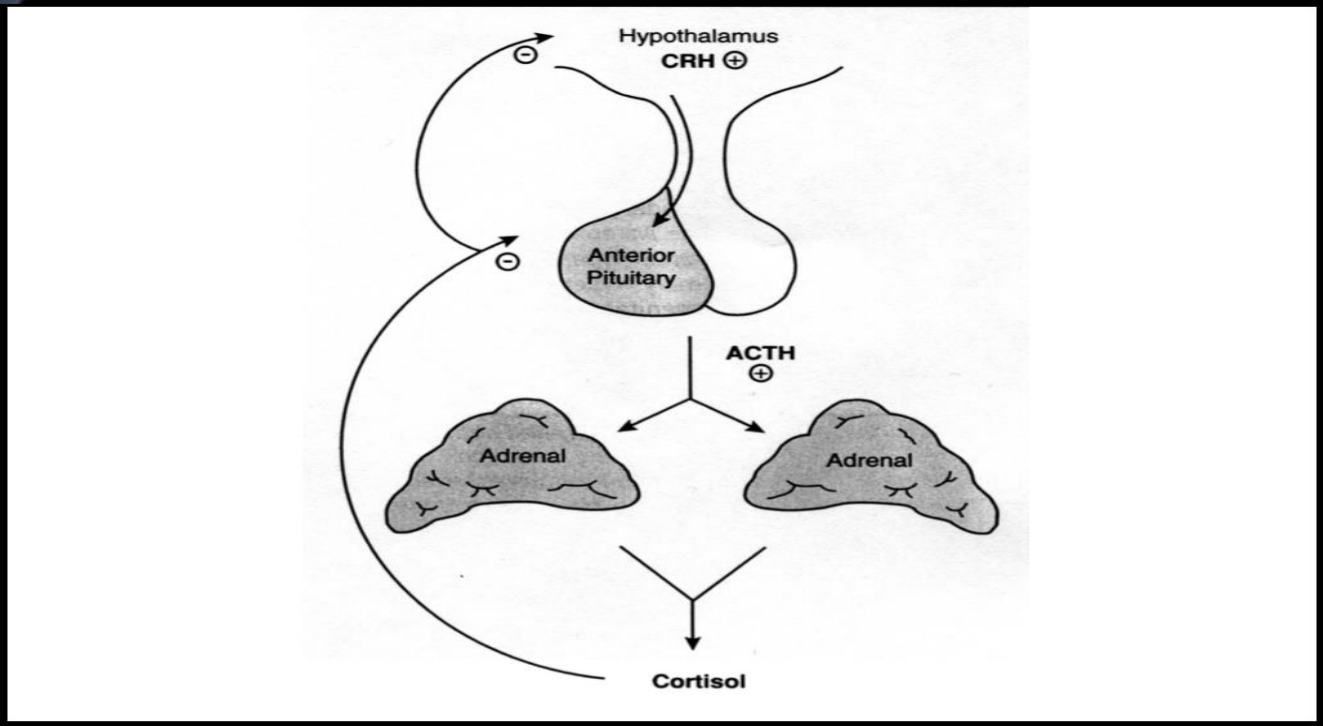
Glucocorticoids;

Table 38.1. Effects of glucocorticoids

System	*Effect*
Carbohydrates	Activity of transaminases and gluconeogenic enzymes (PC, PEPCK, FDP and GP) are stimulated, increasing gluconeogenesis. Glycolytic enzymes (GK, PFK and PK) are suppressed. Decreased glucose uptake by peripheral tissues. All of them lead to hyperglycemia (Diabetogenic).
Lipids	Increase lipid mobilisation; facilitate lipolytic hormones leading to hyperlipidemia.
Proteins and nucleic acids	Catabolism of proteins and nucleic acids increased. Increase urea production.
Fluid and electrolytes	Promote water excretion by increase in GFR and inhibition of ADH secretion.
Bone and calcium	Decrease serum calcium by inhibiting osteoblast function, leading to osteoporosis.
Secretory action	Stimulate secretion of gastric acid and enzyme. Induce acid peptic disease.
Connective tissue	Impaired collagen formation. Poor wound healing.
Immune system	Immunosuppressant. Lysis of lymphocytes. Antiinflammatory and antiallergic.

Regulation of glucocorticoid secretion

» Follows circadian rhythm(highest levels in the morning and lowest in the evening)



Pathology

- Adrenocortical insufficiency

a. primary (Addisons disease)

b. Secondary (ACTH deficiency)

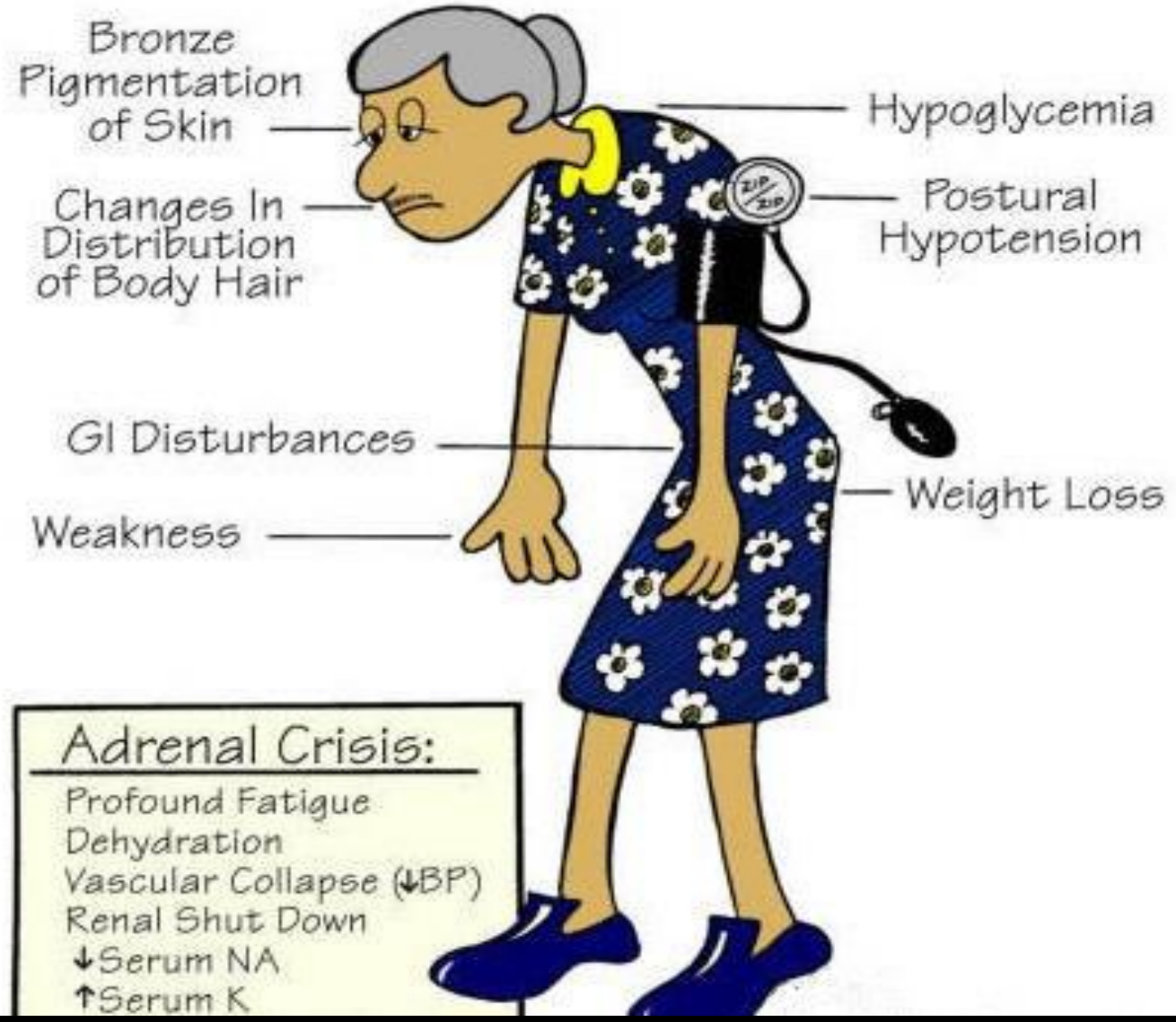
- Adrenocortical excess(Cushing syndrome)
- Hyperaldosteronism(Conn syndrome)
- Congenital adrenal hyperplasia

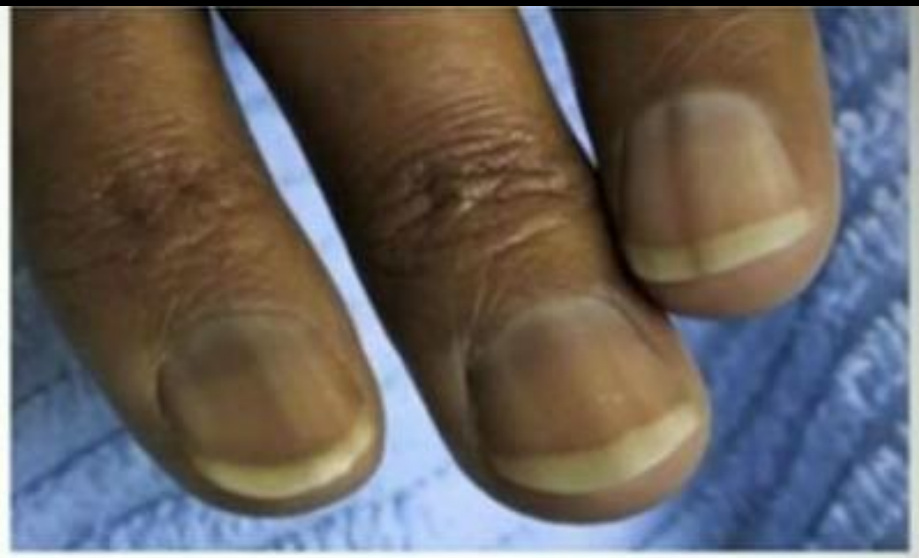
Addison disease

- Causes:autoimmunity,cancer,TB,drugs
- Mineralocorticod, glucocorticoid and androgen deficiency
- ⬇ cortisol ⬆ ACTH
- **Signs and symptoms**:

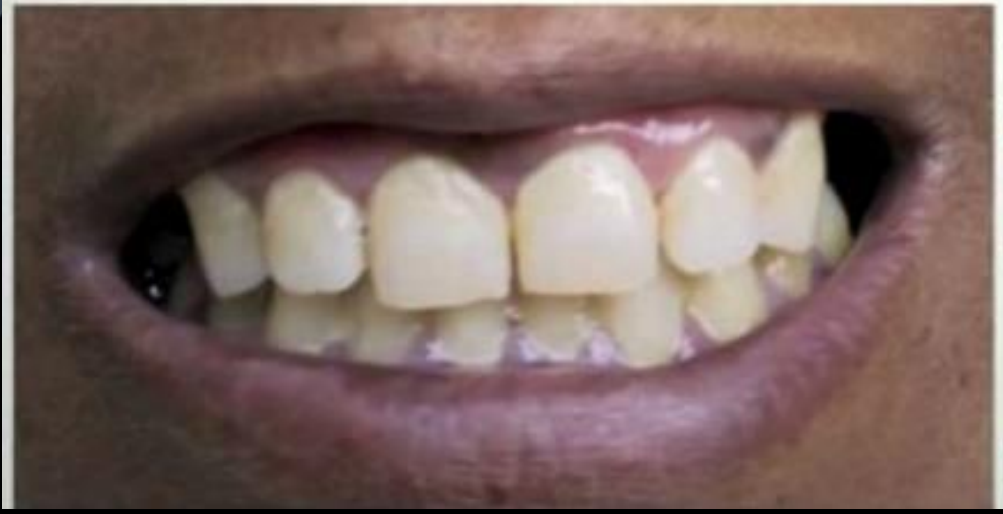
  hypotension,skin and mucosal pigmentation,metabolic acidosis,acute may present with shock

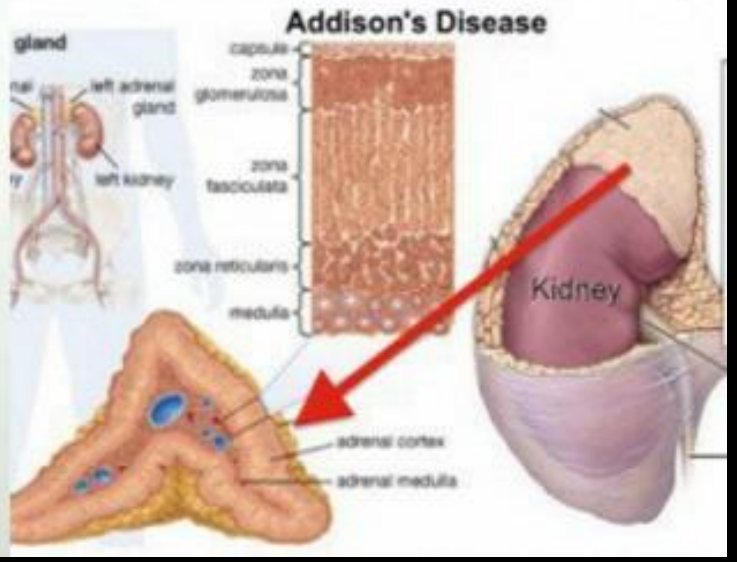
ADDISON'S DISEASE





Addison's disease:





Secondary adrenocortical deficiency

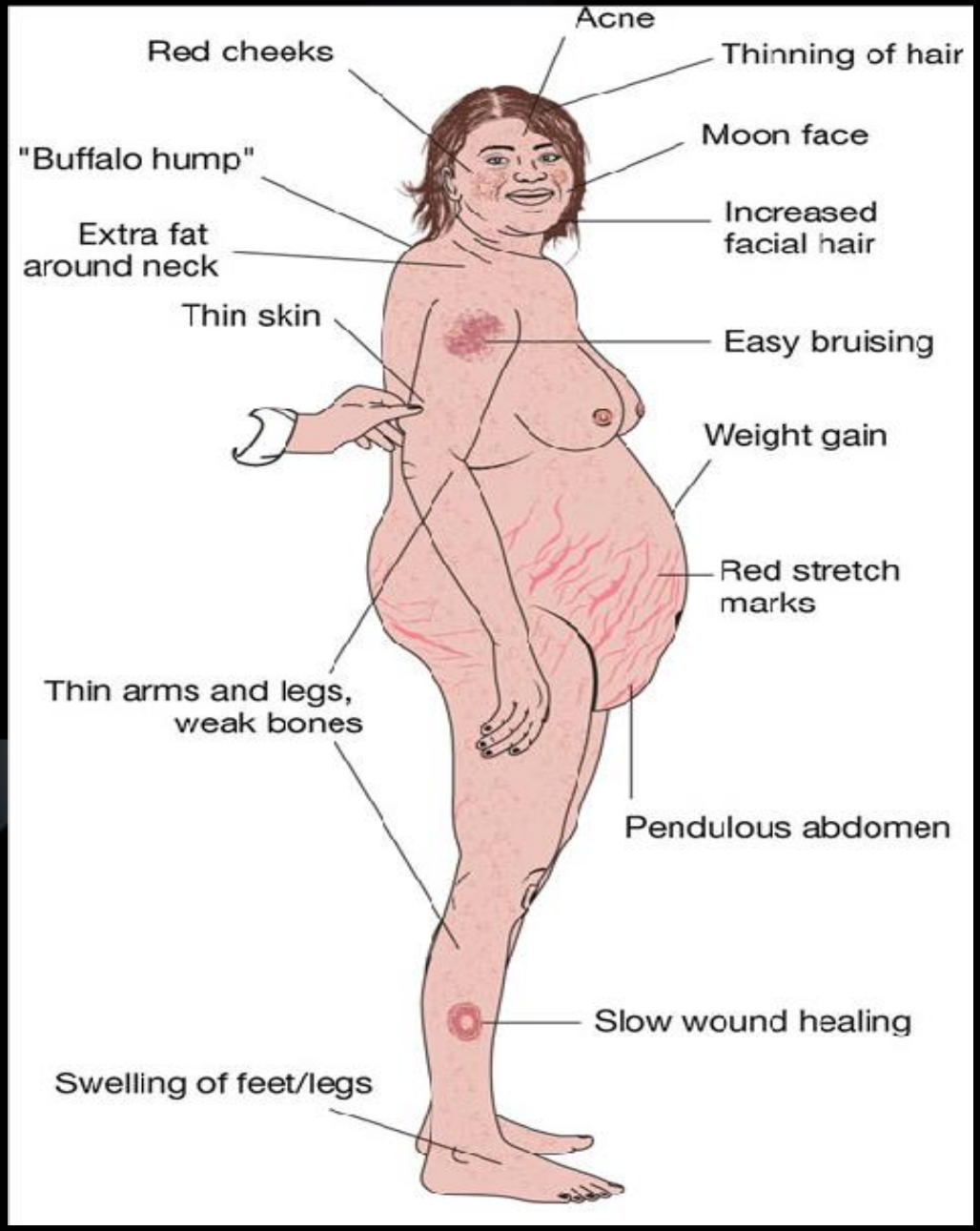
- No hyperpigmentation (ACTH low)
- No hypotension (normal aldosterone)
- Other signs same as addisons

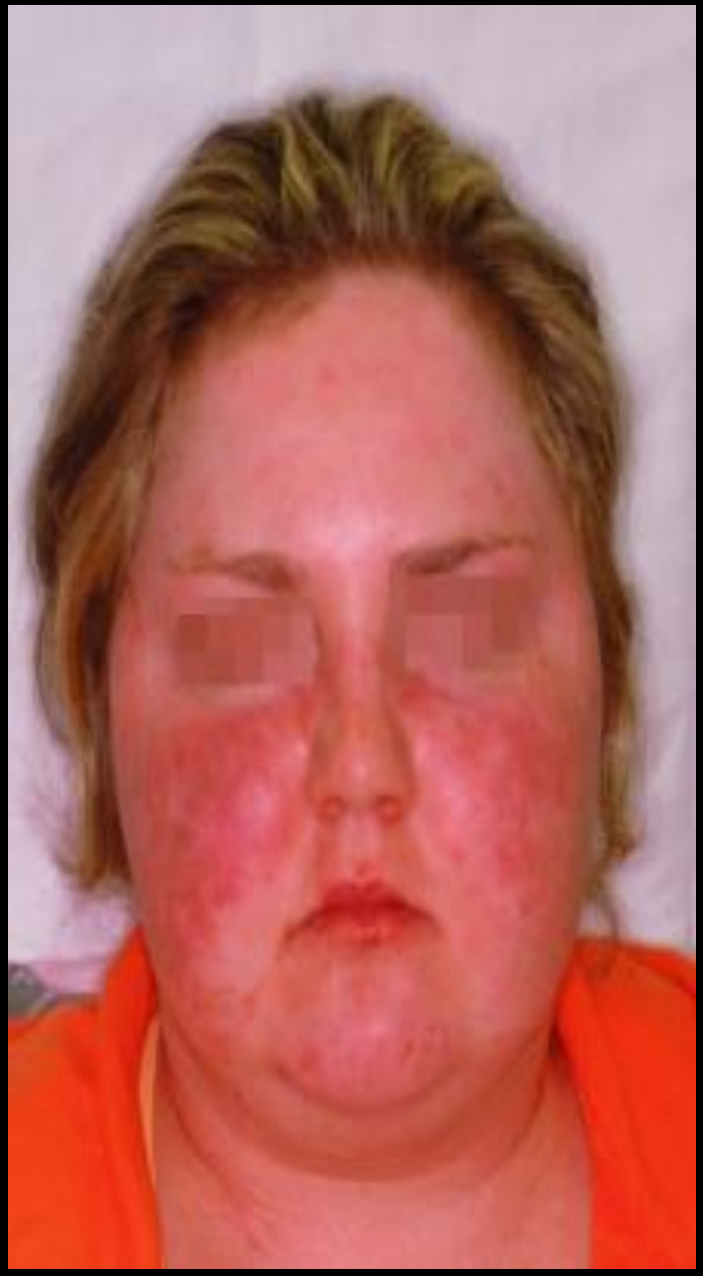
Cushing syndrome

- High cortisol
- Exogenous corticosteroids is most common cause
- Endogenous causes:pituitary,adrenal or ectopic ACTH
- Adrenal diabetes,moon face,truncal obesity,hypertension,skin changes,osteoporosis,ammenorhea,immunosuppresion

Cushing syndrome vs disease

- **Cushing syndrome** refers to the signs and symptoms associated with excess cortisol in the body, regardless of the cause.
- **Cushing disease** is caused by a pituitary gland tumor (usually benign) that over-secretes the hormone ACTH, thus overstimulating the adrenal glands' cortisol production


Acne
Red cheeks
Thinning of hair
Moon face
"Buffalo hump"
Increased facial hair
Extra fat around neck
Thin skin
Easy bruising
Weight gain
Red stretch marks
Thin arms and legs, weak bones
Pendulous abdomen
Slow wound healing
Swelling of feet/legs



Conn syndrome

- Primary hyperaldosteronism
- High blood pressure,low serum K+,high aldosterone and low renin levels
- Common causes are adrenal adenoma,adrenal hyperplasia,adrenal carcinoma

Congenital adrenal hyperplasia

- Congenital deficiency of steroid hydroxylases
- Decreased cortisol;loss of negative feedback;ACTH elevated causing hyperplasia

21β- Hydroxylase deficiency

- Most common
- Androgens increased
- Ambiguous genitalia
- Virilization of women
- Cortisol and aldosterone are low

17α-Hydroxylase deficiency

- High mineralocorticoid levels
- Low cortisol and androgens due to enzyme block
- So lack of pubic hair in women,hypertension,alkalosis, hypokalemia,hypoglycemia
- High ACTH (due to loss of negative feedback of cortisol)