Adrenal Steroid Hormones

Adrenal Cortex

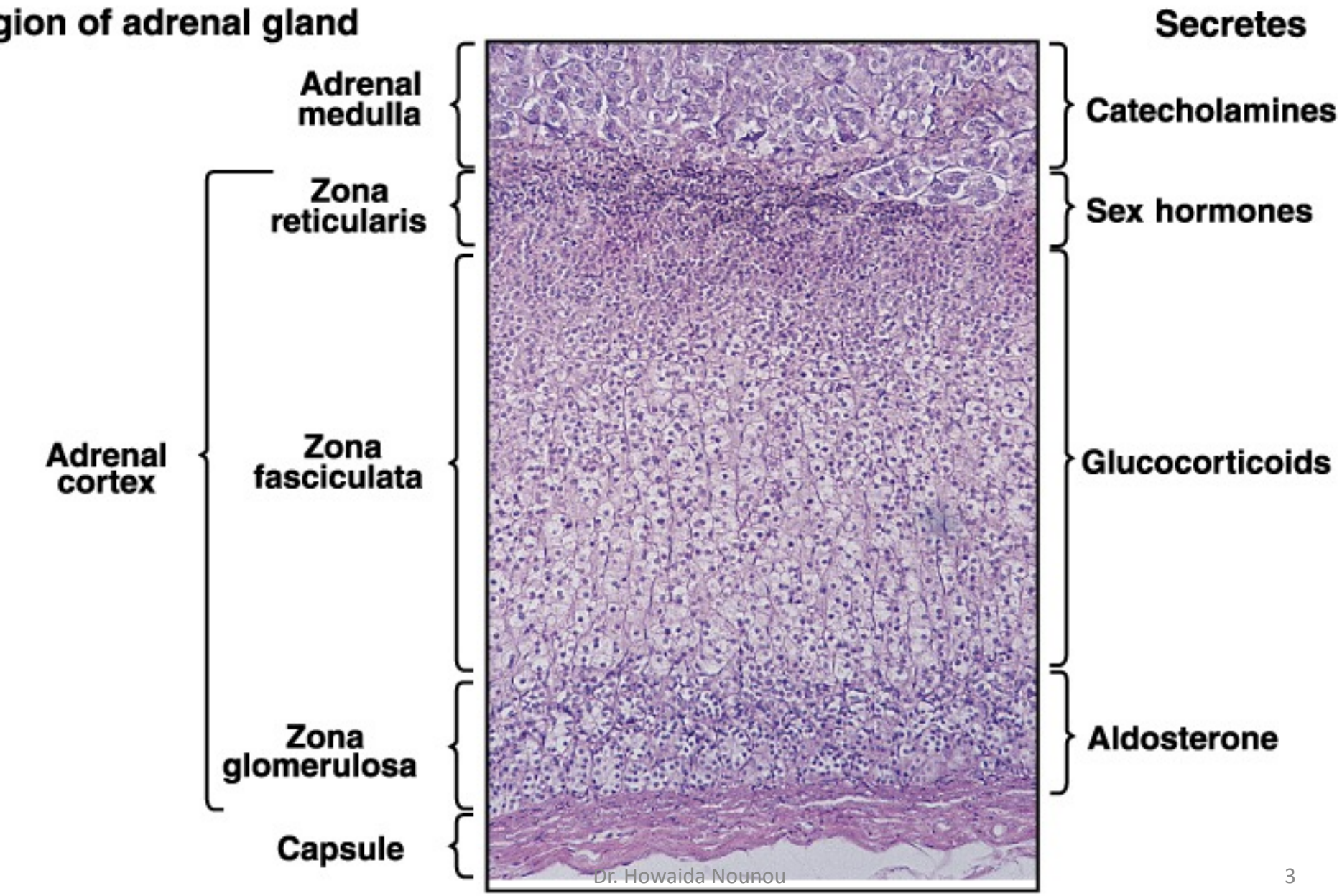
- Hormones produced by the adrenal cortex are referred to as corticosteroids.

- These comprise:

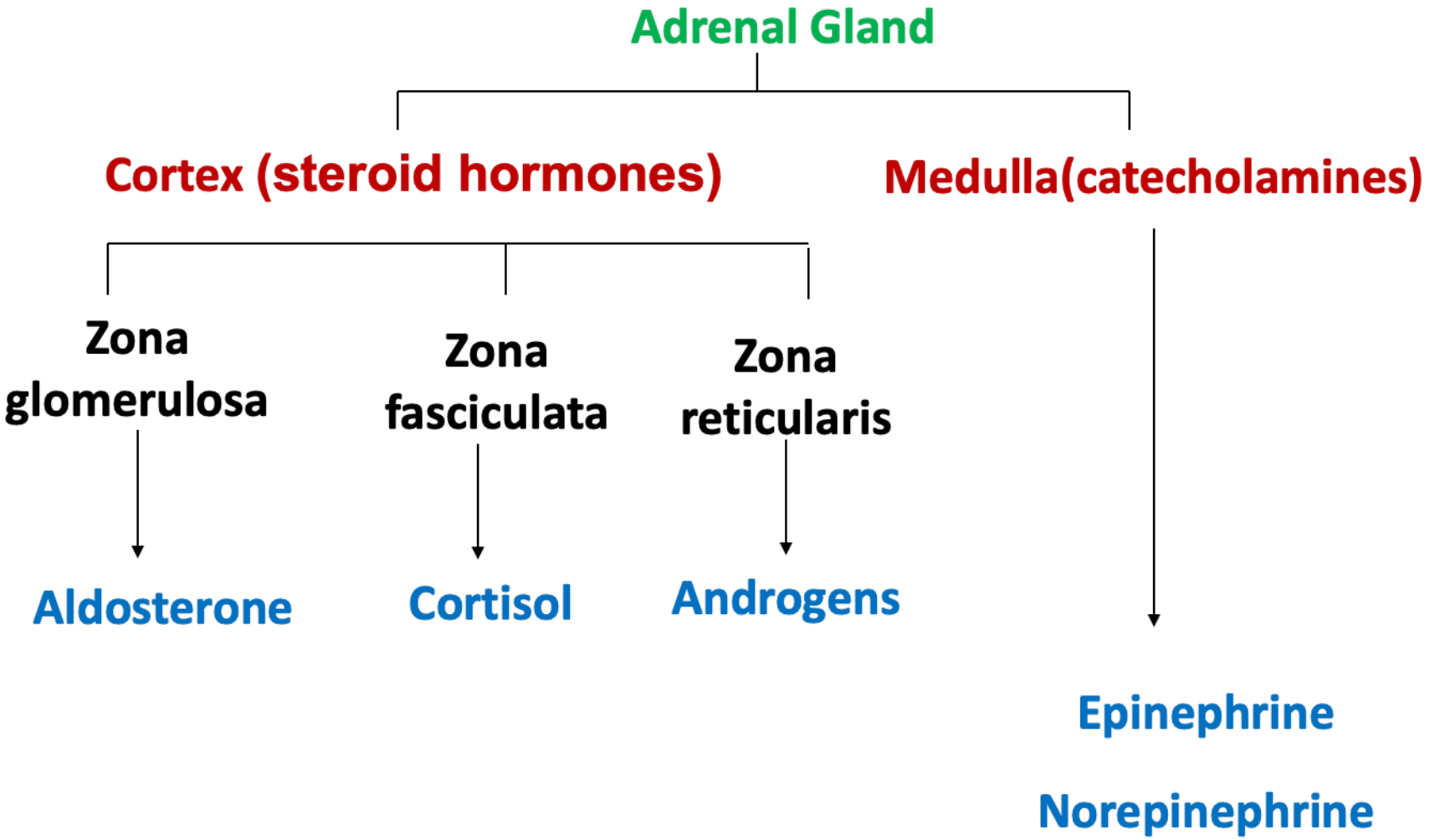
1. Mineralocorticoids
2. Glucocorticoids
3. Androgens.

Steroids are made in the 3 zones of the adrenal cortex:

- mineralocorticoids (aldosterone): zona glomerulosa
- glucocorticoids (cortisol): zona fasciculata
- androgens (sex hormones): zona reticularis


gion of adrenal gland
Secretes
Adrenal medulla
Catecholamines
Zona reticularis
Sex hormones
Adrenal cortex
Zona fasciculata
Glucocorticoids
Zona glomerulosa
Aldosterone
Capsule

Hormone production of the adrenal gland



Zona Glomerulosa

- Outermost zone – just below the adrenal capsule
- Secretes mineralocorticoids.
- Mineralocorticoids are termed as they are involved in regulation of electrolytes in ECF.
- The naturally synthesized mineralocorticoid of most importance is aldosterone.

Zona Fasciculata

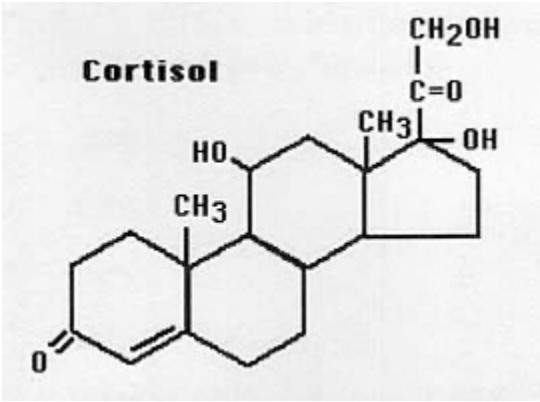
- Middle zone – between the glomerulosa and reticularis
- Primary secretion is glucocorticoids.
- Glucocorticoids, are involved the increasing of blood glucose levels. However they have additional effects in protein and fat metabolism.
- The naturally synthesized glucocorticoid of most importance is cortisol.

Zona Reticularis

- Innermost zone – between the fasciculata and medulla
- Primary secretion is androgens.
- Androgenic hormones exhibit approximately the same effects as the male sex hormone – testosterone.

Hormones of the Adrenal Cortex

- all adrenal cortex hormones are steroid



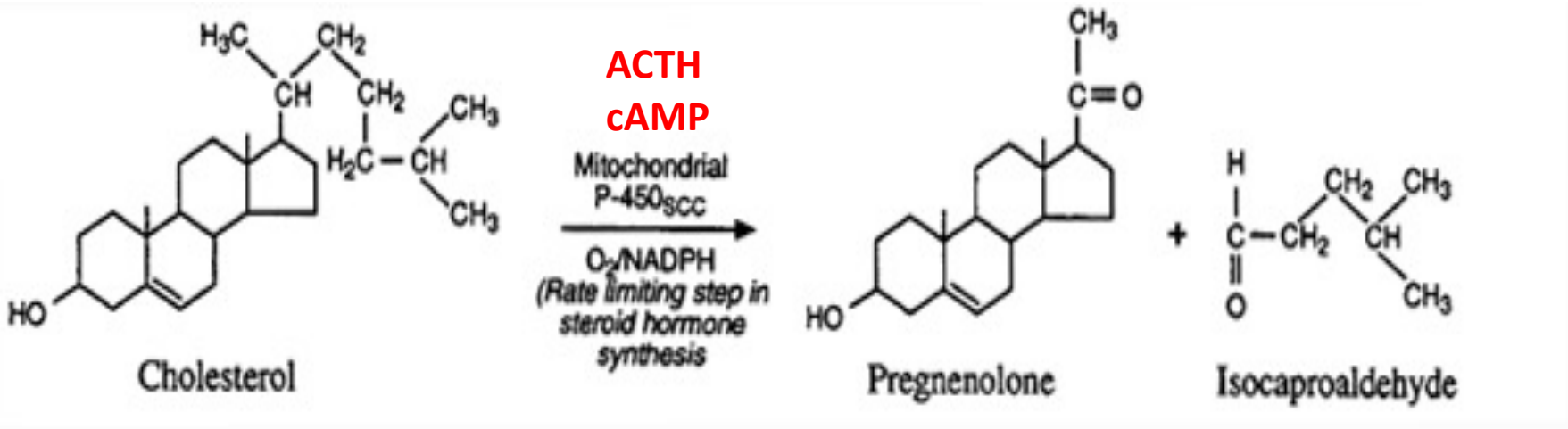
cortisol

- not stored, synthesized as needed

Adrenal Steroidogenesis

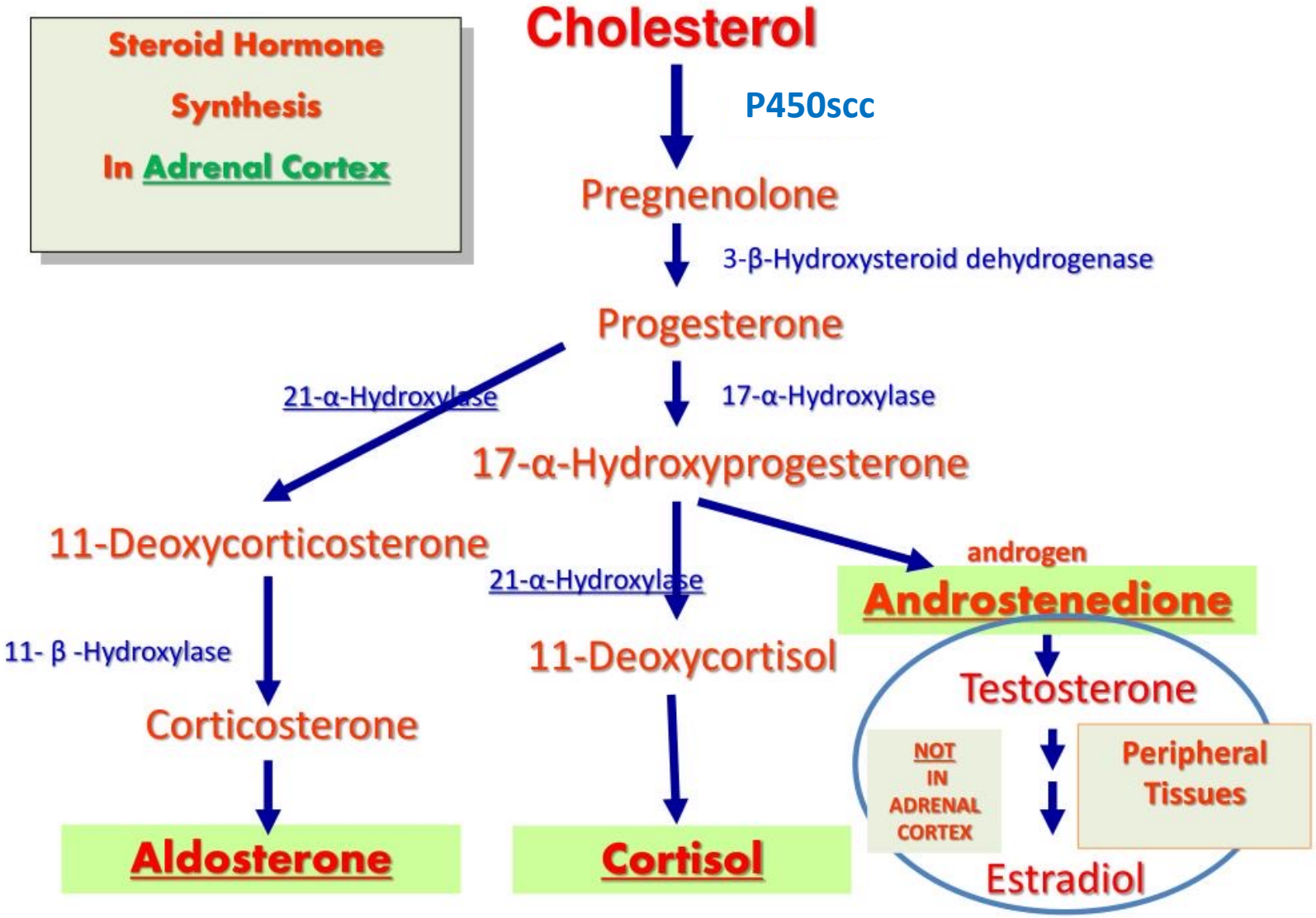
- The first step is the conversion of cholesterol to pregnenolone, which occurs in the mitochondria.

- This reaction is carried out by the enzyme, **cytochrome P450 side chain cleavage** (**P450scc**) that need NADPH and oxygen and activated by ACTH through cAMP..



Next, pregnenolone can be converted in smooth ER and **mitochondria** into three different pathways, depending upon whether you want to make mineralcorticoids, glucocorticoids, or androgens:

Adrenal steroid hormones

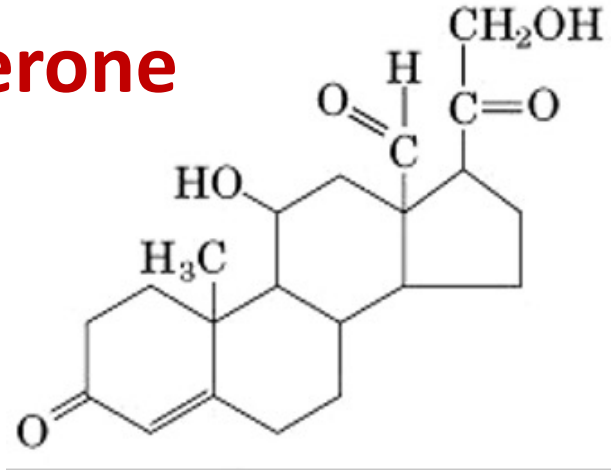


Aldosterone

C11: hydroxyl group

C18: aldehyde group

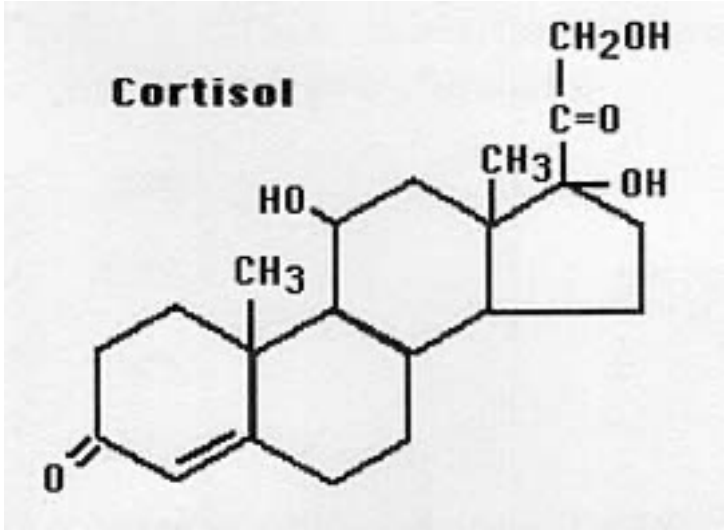
C21: hydroxyl group



C11: hydroxyl group

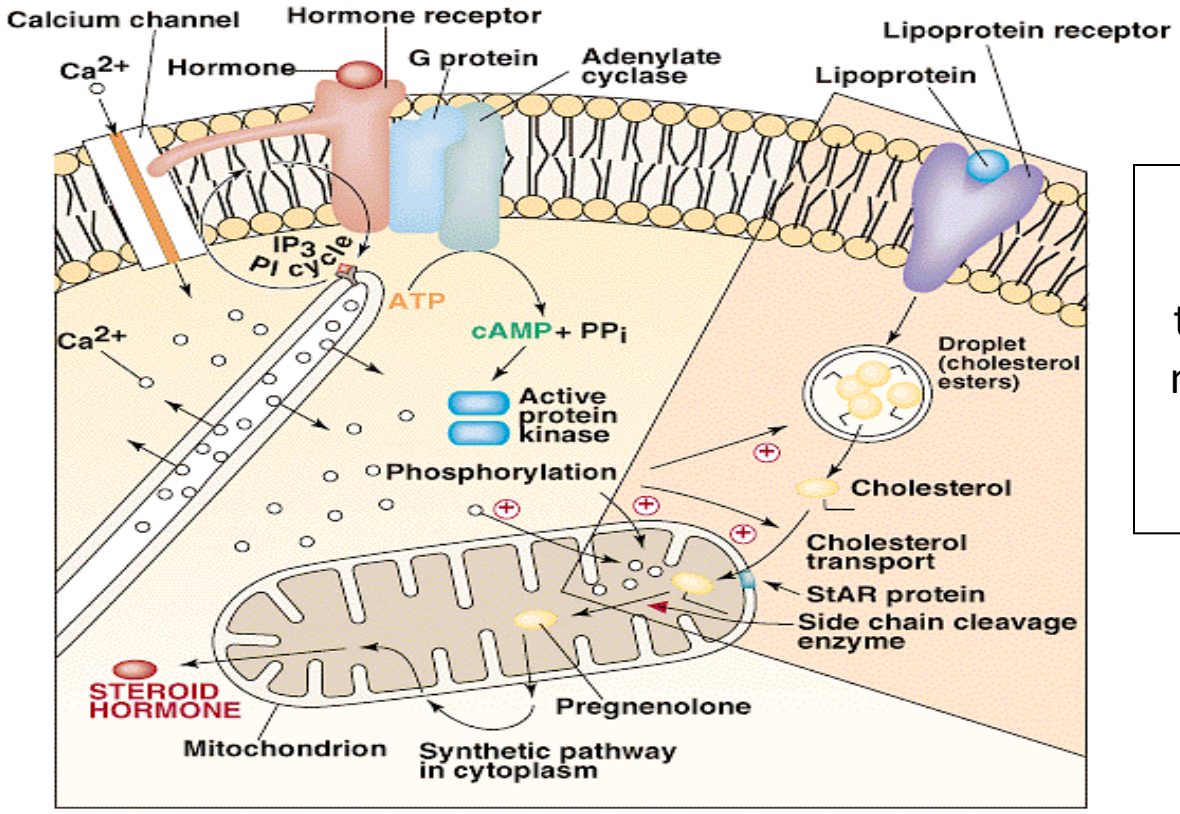
C17: hydroxyl group

C21: hydroxyl group



Cortisol

Hormonal stimulation of biosynthesis of steroid hormones



steroidogenic acute regulatory protein (STAR) mediated transport of cholesterol to inner mitochondrial membrane where **side chain cleavage enzyme is found in the mitochondria**

Figure was assumed from book T. M. Devlin et al.: Textbook of Biochemistry With Clinical Correlations, 4th ed., Wiley-Liss, Inc., New York, 1997.

Biochemical subdivisions of the adrenal cortex

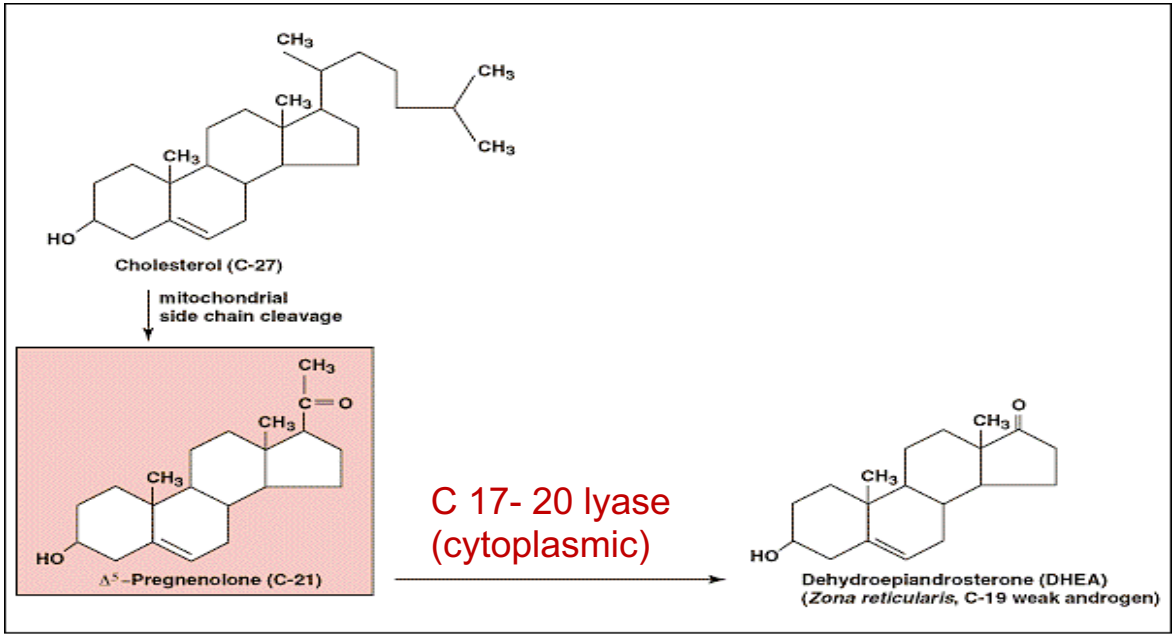
The **zona glomerulosa** produces aldosterone, and **lacks the enzyme 17a-hydroxylase** and thus cannot produce cortisol or androgens.

The two inner zones (**zona fasciculata and zona reticularis**) appear to function as a unit: they both produce cortisol and androgens . Those zones lack the enzyme **Aldosterone synthase (18-hydroxylase + 18-hydroxy steroid dehydrogenase)** thus cannot produce aldosterone.

Male sex hormones produced in adrenal cortex

- in zona reticularis: cholesterol → pregnenolone → **DHEA**

(dehydroepiandrosterone) → androstenedione



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Androgen synthesis in the zona fasciculata and the zona reticularis

The adrenal androgens (dehydroepiandrosterone) **DHEA, DHEA-sulfate, and androstenedione** have **minimal** androgenic activity.

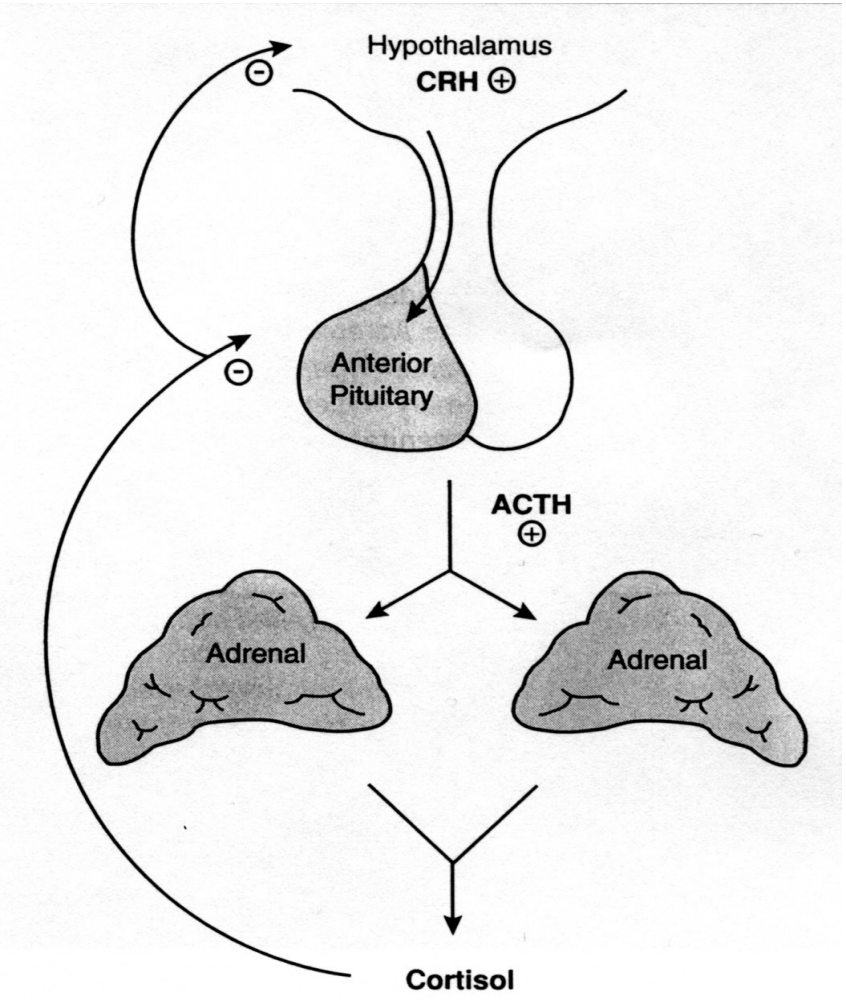
They are however converted in **peripheral tissues** (gonads) to the **more potent testosterone and dihydroxytestosterone.**

Adrenal cortex

Glucocorticoids

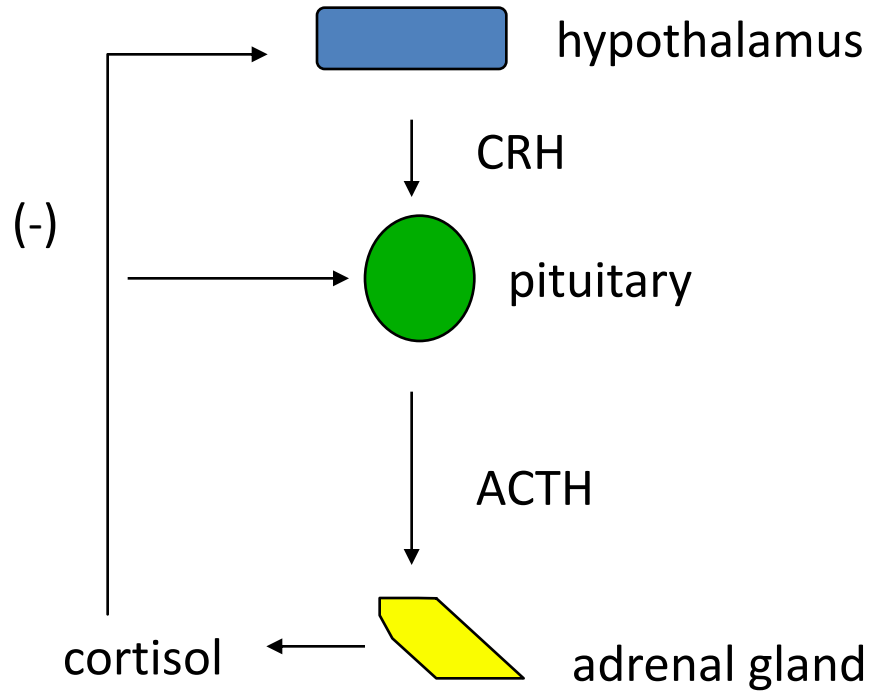
Regulation of Cortisol Release

- cortisol release is regulated by ACTH
- release follows a daily pattern - circadian
- negative feedback by cortisol inhibits the secretion of ACTH and CRH(corticotropin-releasing hormone)



Regulation of Cortisol Release

- Cortisol release is primarily under neuroendocrine control.



Regulation of Cortisol Release…

Enhanced release can be caused by:

- physical trauma
- infection
- Inflammation
- extreme heat and cold
- exercise to the point of exhaustion
- extreme mental anxiety
- stress

Action of ACTH on Cortisol Production

- **ACTH** binds to the ACTH receptor (Gs-coupled), resulting in **increased cyclic AMP** and **activation of PKA pathway**.
- **This results in:**

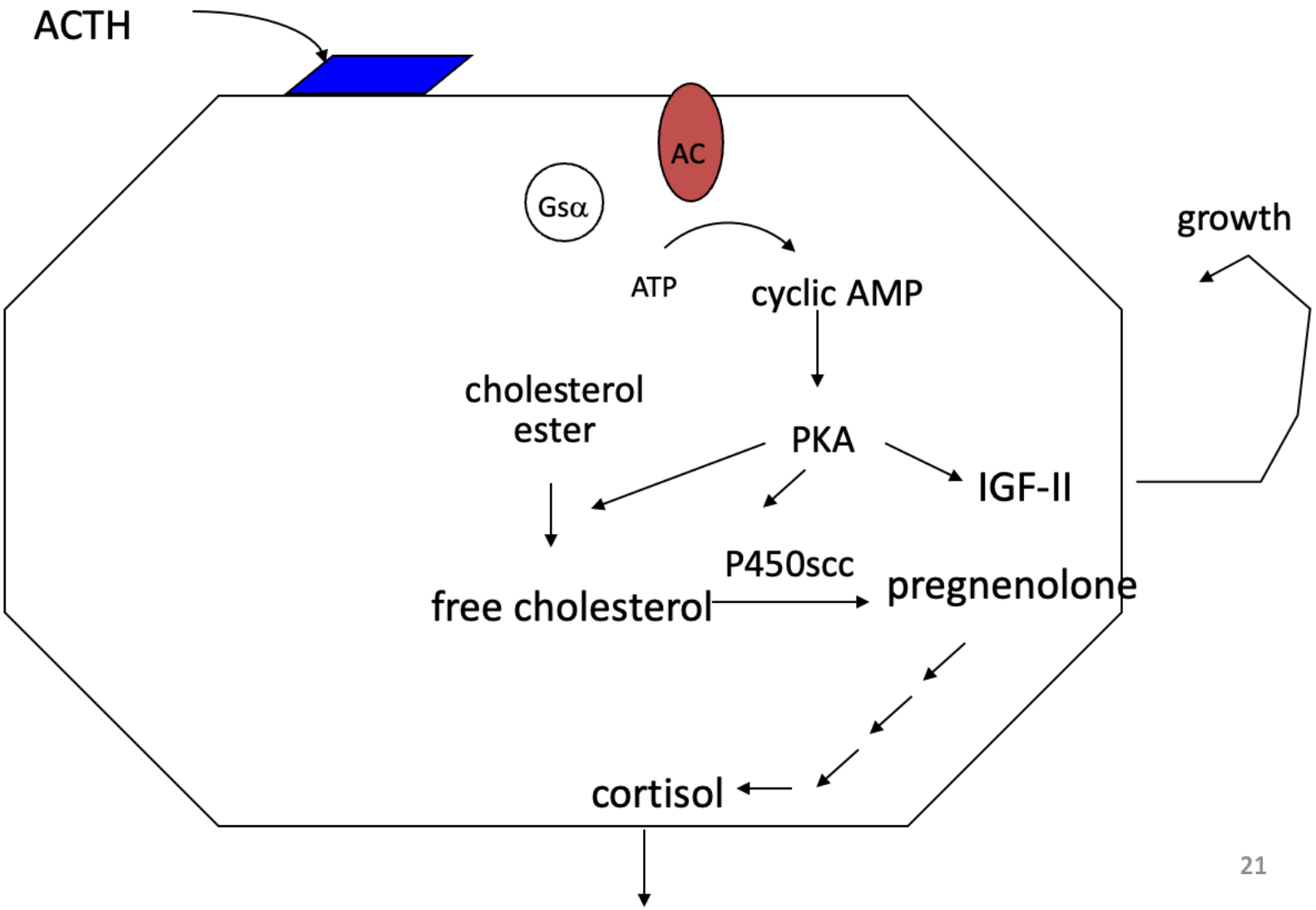
  1- increased conversion of cholesterol esters to free cholesterol

  2- increased expression of steroidogenic acute regulatory protein (STAR) (transfer cholesterol to the P450scc in the mitochondria)

  3- increased expression of P450 side chain cleavage enzyme

  4- increased production of IGF-II (stimulation of cell growth)

Action of ACTH on Cortisol Production



Daily Pattern of Cortisol Release

- Changes in cortisol levels occur about 30 minutes after corresponding changes in ACTH.
- Cortisol usually increases a few hours after sleep, then declines Also an increase shortly after wakening in the morning, and sporadically throughout the day.
- However, Cortisol levels are highest in the morning shortly after awakening, lowest in late afternoon& early evening.

Transport of Cortisol

- The majority of cortisol(90%) is bound to cortisol binding globulin(CBG) (also called transcortin). 4% bound to albumin.
- Only 6% of circulating cortisol is in free form, the biologically active fraction.
- CBG is produced by the liver.
- Production of CBG is increased by estradiol.

Metabolism of Cortisol

- Cortisol has a half-life of about 90 minutes.
- Cortisol is metabolized in the liver, where it is conjugated to a glucuronic acid.

  - conjugation increases solubility in water

  - conjugated hormone is excreted via the kidneys

Functions of Cortisol

- Cortisol is the primary glucocorticoid in humans.
- The net effects of cortisol are **catabolic**
- **Roles of cortisol**:

    1- Carbohydrate metabolism

    2- Effects on body functions and development (epinephrine release, lipid metabolism)

    3- Mineralocorticoid activity at the kidney (minor)

    4- Anti-inflammatory compound

1. Effect of glucocorticoids: on carbohydrate metabolism

- stimulation of **gluconeogenesis** by the liver (rate increases 6 to 10 fold) prevents against hypoglycemia.
- decreases uptake of circulating glucose by muscle and adipose tissue
- increase in glycogen storage in liver cells
- Decreased glucose utilization by the cells

- **Overall, increases plasma glucose levels.**
- **Cortisol release is inhibited by high blood glucose.**

2. Effect of glucocorticoids : on protein metabolism

- mobilization of amino acids (increase proteolysis of muscle protein for energy)
- decreased protein synthesis
- decreased amino acids transport into muscles

3. Effect of glucocorticoids : on fat metabolism

- mobilization of fatty acids from adipose tissue . for energy (increase lipolysis).
- moderately enhance the oxidation of fatty acids (lower glucose utilization stimulates the cells to utilize energy from fatty acids)

Other Actions of Cortisol

Cortisol is required for:

- synthesis of epinephrine (adrenal medulla)

- **normal vasoconstriction** (absence leads to decreased blood pressure)

Effects of Elevated Cortisol on Bone

High glucocorticoid levels cause decreased bone mass.

This is due to:

- antagonizing the effects of vitamin D on calcium uptake
- inhibiting collagen synthesis
- Synergizing(combine effect) with PTH to break down bone

Mineralocorticoid Activity of Cortisol

- Under normal conditions of blood pressure and sodium levels, cortisol has some mineralocorticoid activity (increasing sodium and water reabsorption at the kidney).
- Cortisol has low affinity for the mineralocorticoid receptor.
- However, much more cortisol than aldosterone is secreted.

Cortisol as an Anti-Inflammatory Agent

- The body responds to bacteria or tissue damage with an inflammatory response:

  1- increased production of chemicals such as **interleukins**

  2- these cause increased **vasodilation** and blood flow to the area

  3- increased blood flow brings in **phagocytes, mast cells, and lymphocytes**

  4- these cells stimulate **lysosomal reactions**, **histamine release**, and **collagenase** production

- Result: destruction of bacteria; healing of tissue.

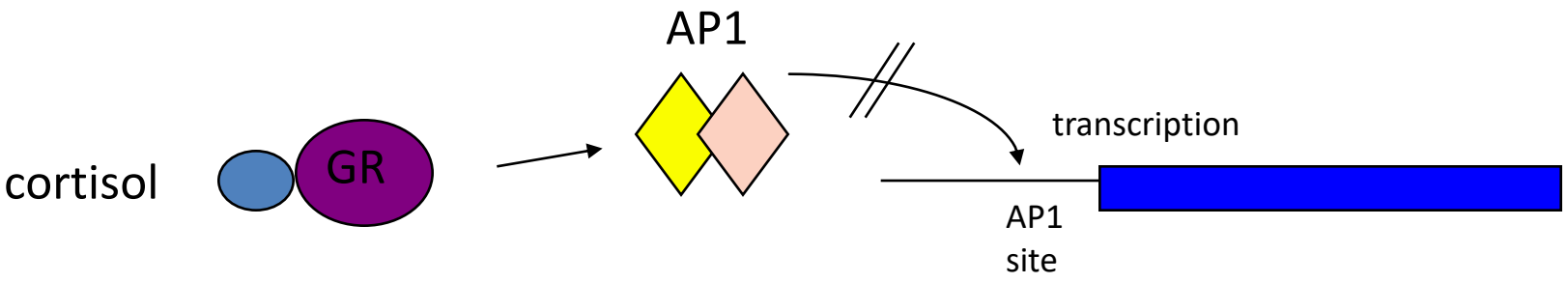
Cortisol and Chronic Stress

Prolonged exposure to high cortisol levels can lead to:

- break down of muscle,
- excessive epinephrine release,
- hyperglycemia,
- weakening of bone,
- destruction of the immune system,
- inhibition of reproductive function, and other complications.

Mechanisms of Cortisol Action

- The actions of cortisol are mediated through the glucocorticoid receptor (intracellular receptor).
- **Stimulates** transcription of target genes by interaction of hormone receptor complex with GRE (glucocorticoid response element).
- **Inhibits** transcription of ***some*** **genes** by interaction of receptor with AP1 (activated protein 1).



Cushing's Syndrome

"moon face"

- Hypercortisolism
- Can be caused by:
- Primary
  - Adrenal tumors (adenoma, carcinoma)
- Secondary

  1-Pharmacological use of steroids.

  2- ACTH secreting pituitary adenoma.

Excess of hormones of adrenal cortex

Symptoms include:

- redistribution of body fat – central obesity but thin limbs “buffalo hump”, “moon” rounded face
- hypertension
- steroid (adrenal) diabetes – increased glucose concentration
- decreased protein synthesis in immune system
- osteoporosis
- fragile skin.
- Excess protein catabolism cause muscle weakness.
- poor wound healing.

Treatment

- Removal of adrenal tumor if this is the cause
- Microsurgical removal of hypertrophied pituitary elements to reduce ACTH secretion
- Partial or total adrenalectomy followed by administration of adrenal steroids to compensate insufficiencies that develop