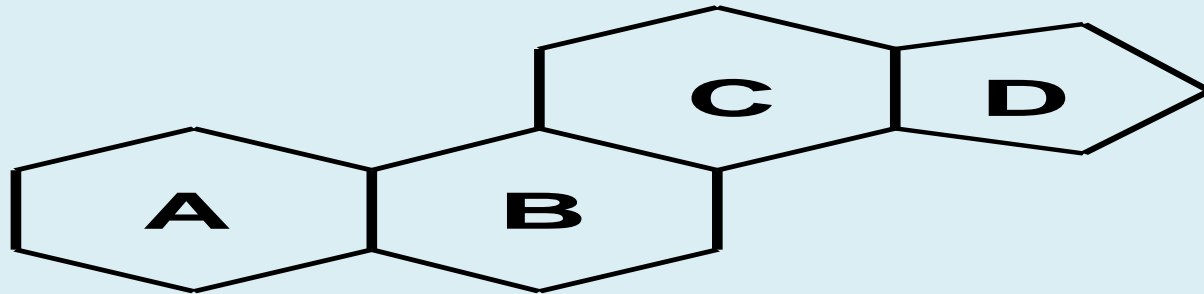


Steroidogenesis 2



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- **Congenital adrenal hyperplasia (CAH):**
- is a group of diseases caused by a genetically determined deficiency in a variety of enzymes required for cortisol synthesis.
- The deficiency causes a decreased ability to synthesize cortisol, and leads to hyperplasia of the adrenal and (usually) to elevated levels of other adrenal steroid products.
- One additional (rare) cause of CAH, usually termed Congenital Adrenal Lipoid Hyperplasia, is due to a defect in the mitochondrial cholesterol transport pathway.

- **Deficiency in :**

- **3 β -HSD (type II)**
- **11 β -hydroxylase**
- **or 21-hydroxylase activity**

21-hydroxylase activity deficiency

The most common deficiency is that of 21- hydroxylase (P450-21), the activity of which is necessary to convert progesterone to 11-deoxycorticosterone and 17- α hydroxyl progesterone to 11-deoxycortisol.

Thus, this deficiency reduces both aldosterone and cortisol production, without affecting androgen production.

If the enzyme deficiency is severe, the precursors for aldosterone and cortisol production are shunted to androgen synthesis, which leads the body produces more androgen, a type of male sex hormone.

This causes male characteristics to appear early (or inappropriately).

11- β hydroxylase deficiency

Another enzyme deficiency in this group of diseases is that of 11- β hydroxylase, which results in the accumulation of 11-deoxycorticosterone.

- In this form of CAH, 11-deoxycortisol also accumulates, but its biological activity is minimal, and no specific clinical signs and symptoms result.
- The androgen pathway is unaffected, and the increased ACTH levels may increase the levels of adrenal androgens in the blood.

Testicular Steroidogenesis

Production of steroids in the testis

- The main steroid produced in the male is **testosterone**, from the testis.

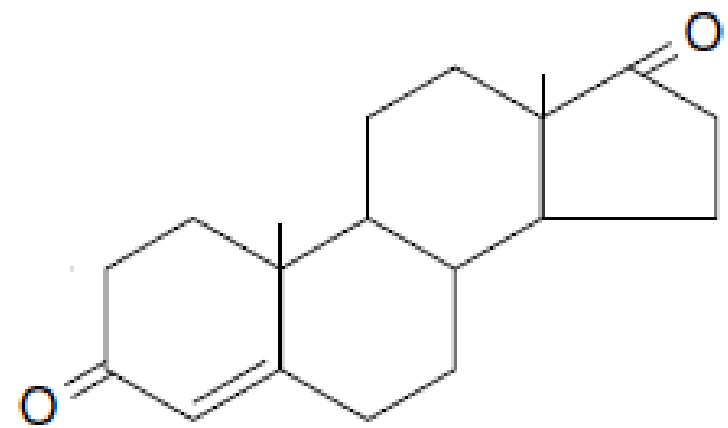
In addition, the testis makes some *androstenedione*, *dihydrotestosterone*, and *estradiol*.

- In the male, there is peripheral conversion of testosterone to:
 - *Dihydrotestosterone* (in androgen target tissues, like muscle)
 - *Estradiol* (mostly in adipose tissue).

Testosterone

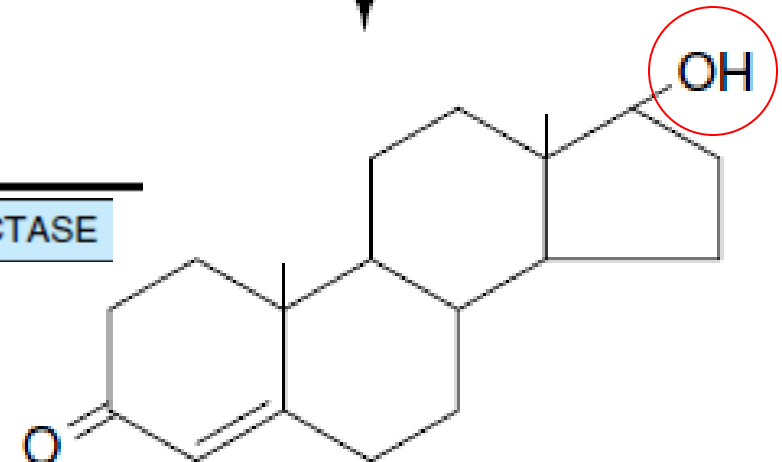
Testosterone is formed by the reduction of the 17-keto group of androstenedione by 17 β -Hydroxysteroid Dehydrogenase enzyme

Testosterone can be converted into a much more potent dihydrotestosterone by 5 α -reductase enzyme

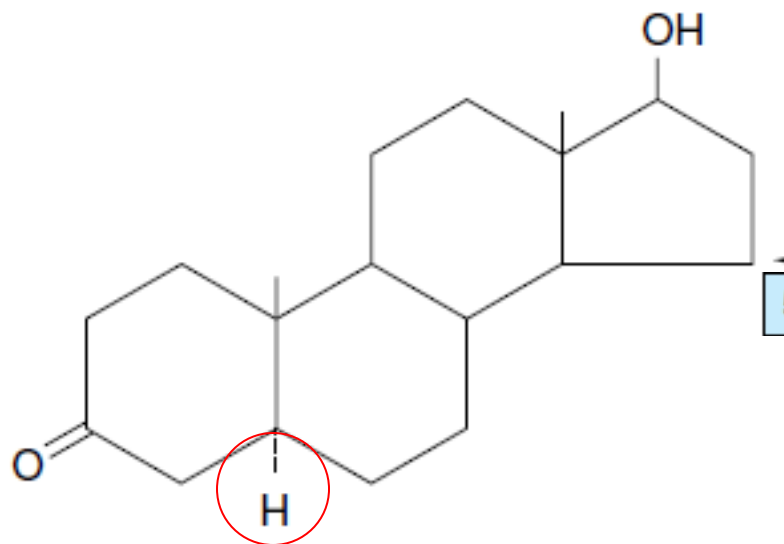


Androstenedione

17 β -HYDROXYSTEROID
DEHYDROGENASE



TESTOSTERONE



DIHYDROTESTOSTERONE (DHT)

5 α -REDUCTASE

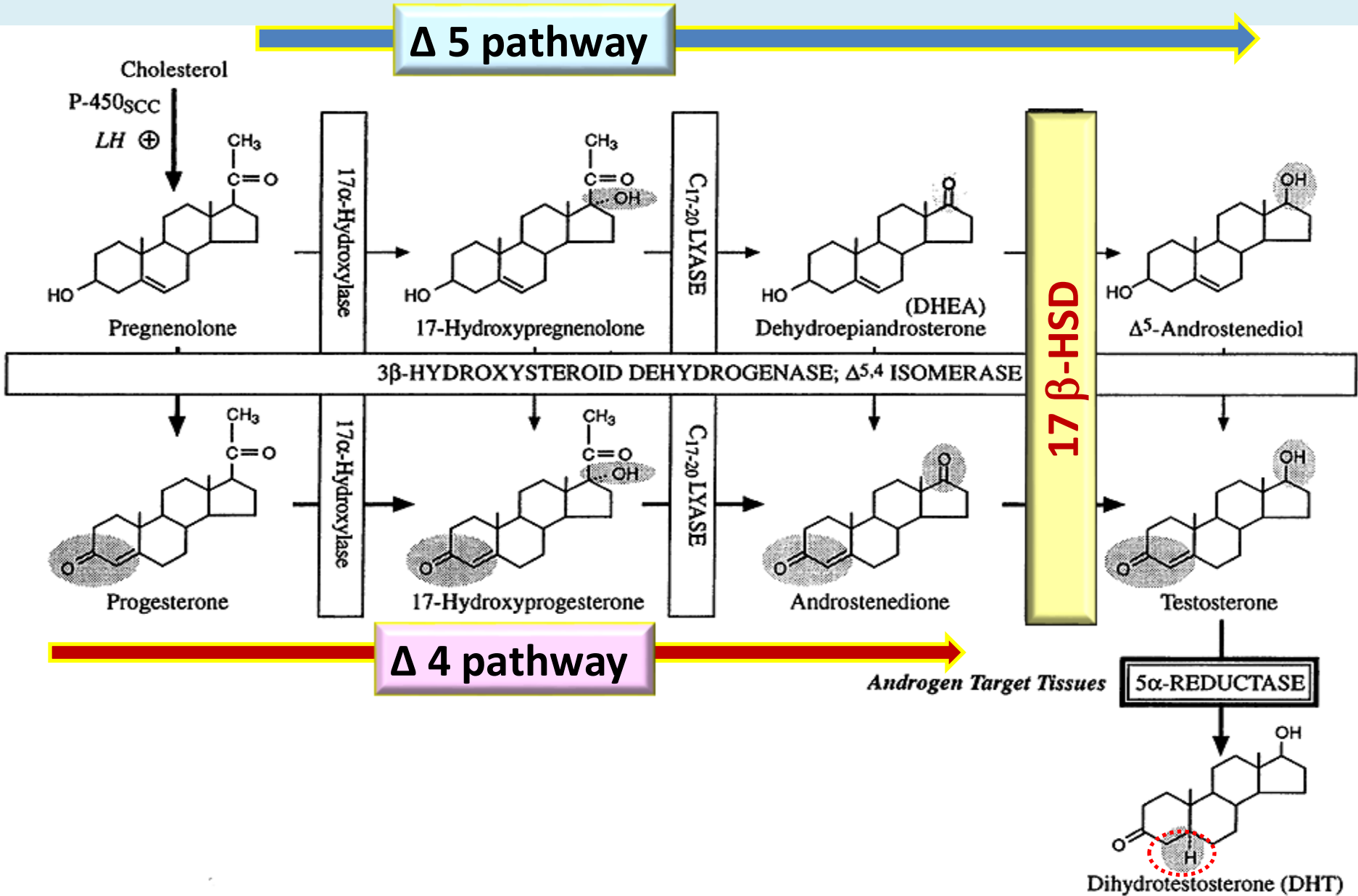
Testosterone & DHT biosynthesis

- **Dihydrotestosterone (DHT)**, is the most potent androgen, it is formed from testosterone, by the reduction of the A ring through the action of the enzyme **5 α -Reductase (NADPH-dependent)**.
- Testosterone thus can be considered as pro-hormone since it is converted into a much more potent compound (DHT) and since most of this conversion occurs outside the testis.
- The testis also produce **17 β -estradiol**, in small amounts, but most of the estrogens produced by the male are derived from **peripheral aromatization of testosterone**.

Testicular Androgens:

- A. Pregnenolone is formed from cholesterol in mitochondria.
- B. The conversion of pregnenolone to testosterone requires enzymes which are found in the ER of the testis cells.
- C. The conversion of pregnenolone to testosterone may occur through the Δ^4 "Progesterone Pathway" or by DHEA or Δ^5 pathway which appears to be most important in humans.
- D. it requires the following 5 enzymes:
 - 3β -Hydroxysteroid dehydrogenase (3beta-HSD) and Δ^5 -4 Isomerase.
 - 17alpha-Hydroxylase and C17,20 Lyase.
 - 17beta-Hydroxysteroid Dehydrogenase (17beta-HSD).

Testosterone biosynthesis



Ovarian steroidogenesis

- The ovary produces estrogens (primarily **estradiol**), **progesterone**, and **androgens**.
- It relies largely on **LDL** as a source of cholesterol for steroid synthesis.
- Ovarian steroids are secreted primarily from ovarian follicles and corpora lutea.

Chemical Structure:

- Each estrogen contains a **phenolic A ring**.
- The phenolic A ring is the principal structural feature responsible for selective, high-affinity binding to receptors.

Estrogen sources

- The most active naturally occurring hormones of these classes are **17 β -estradiol (E2)** and **progesterone**.
- **Estrogen is produced:**
 - **primarily** by **ovaries**, the **corpus luteum**, and **placenta**.
 - **in smaller amounts** by other tissues such as the **liver**, **adrenal glands**, and the **breasts**.
- **In premenopausal women:** The ovaries are the principal source of circulating estrogen, with estradiol being the main secretory product.
- **In postmenopausal women,** the principal circulating estrogen estrone, which is synthesized from dehydroepiandrosterone and secreted by the adrenals.
- **In pregnancy,** relatively more estriol is produced.

Estrogen synthesis

- In the ovary (granulosa cell):

- Estradiol is formed from the conversion of testosterone into estradiol by the enzyme *cytochrome P450 aromatase*. It requires O₂ & NADPH.
- However, granulosa cells do not have the enzyme *17alpha-hydroxylase/lyase*, and thus cannot convert progesterone into androgens.

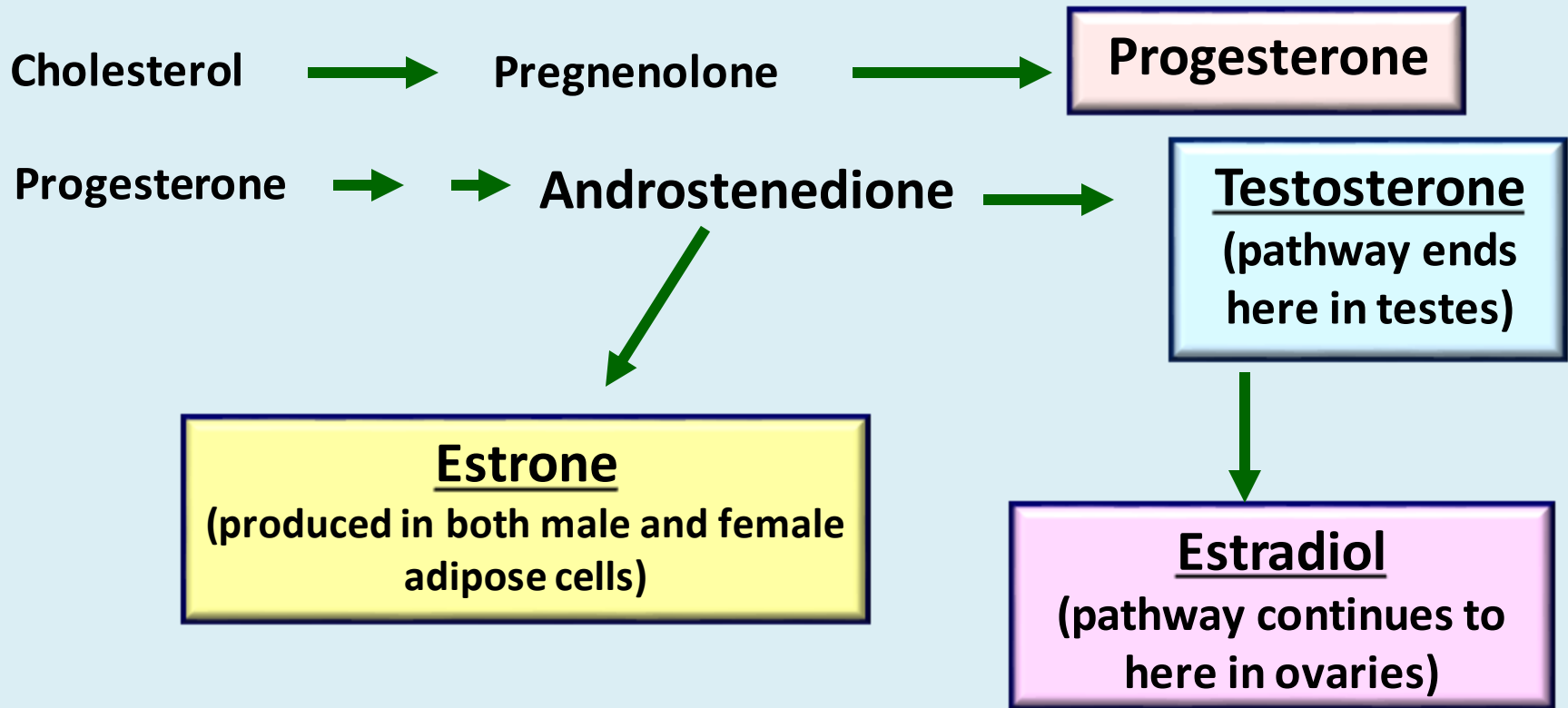
- In the ovary (theca cell):

- the androgens required for estrogen production in granulosa cells come from the neighboring theca cells.

Progesterone synthesis

1. After ovulation, the corpus luteum produces progesterone and estradiol, to support the uterine endometrium during pregnancy.
2. Progesterone is also produced from theca cells and granulosa cells. It is secreted as end product hormone because granulosa cells do not contain the enzymes necessary to convert progesterone to other steroids.

Pathways for the synthesis of testosterone (testis) and estrogens; estradiol (ovaries) and estrone (adipose cells)



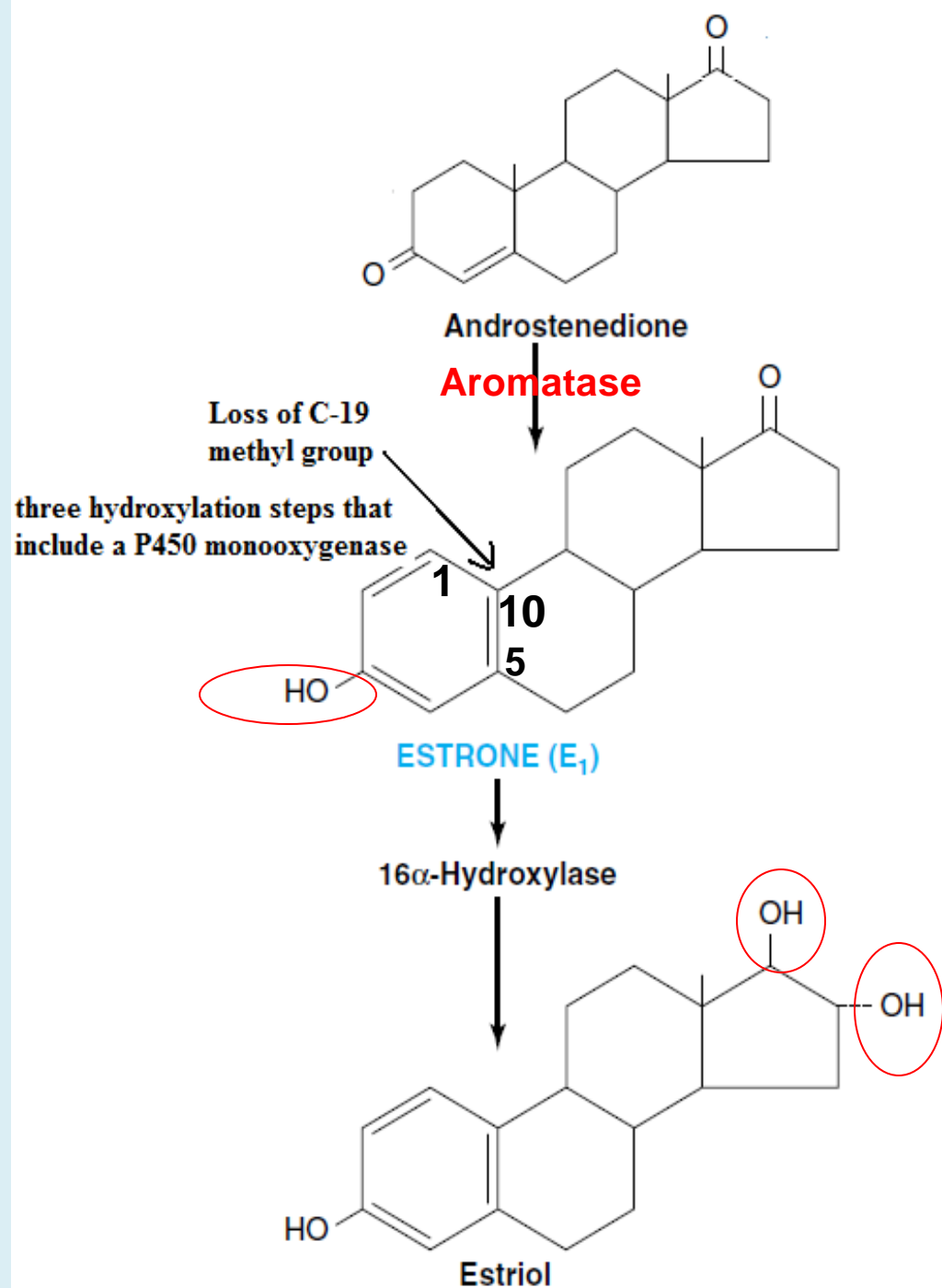
- **Estrogens**

- 1- **Loss of the C-19 angular methyl group**

- 2- **Aromatization of androgens in a complex process that involves three hydroxylation steps, each of which requires O₂ and NADPH.**

- The aromatase enzyme complex is thought to include a P450 monooxygenase.

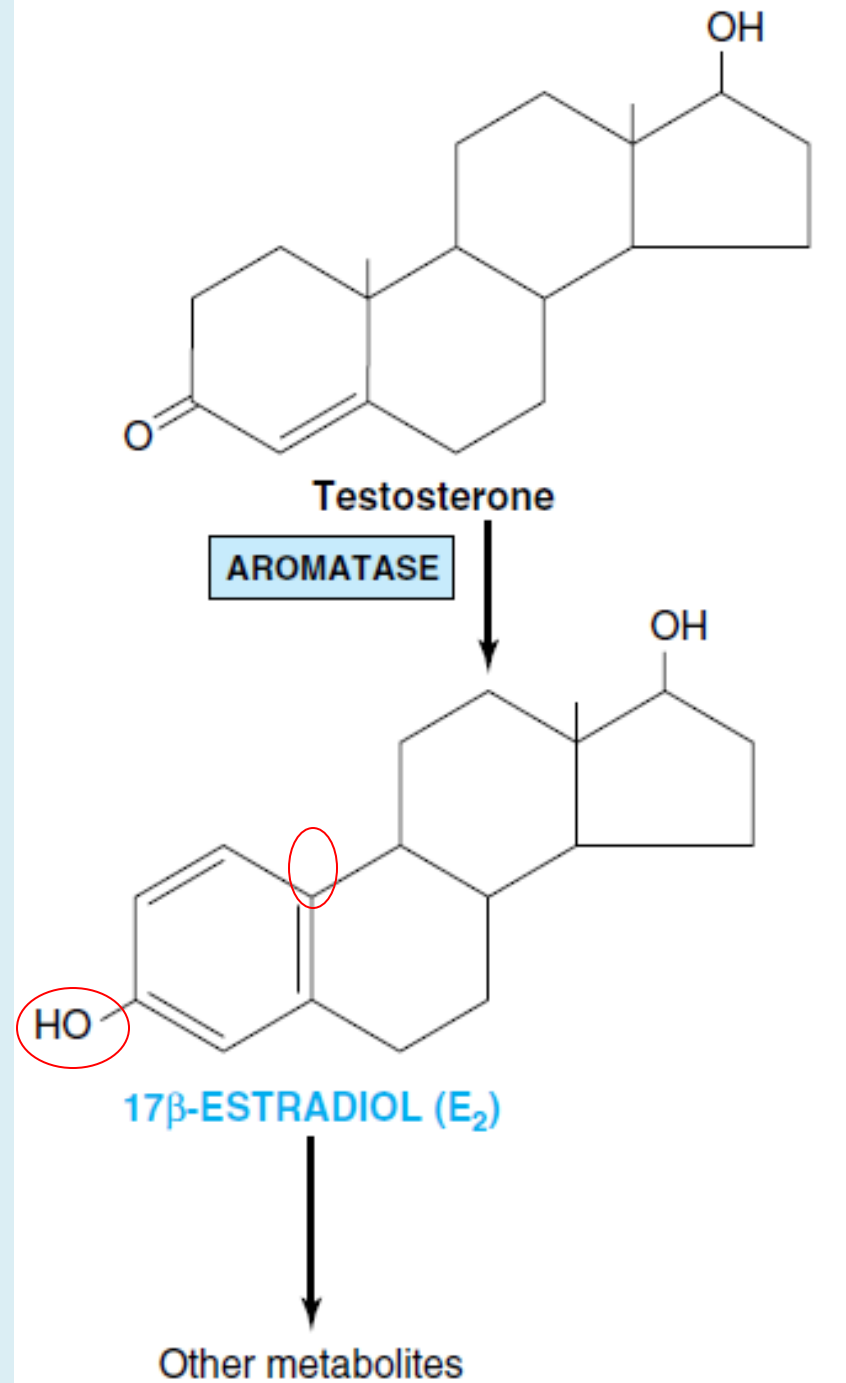
- Estrone results from the aromatization of androstenedione.



Estradiol

1- Loss of the C-19 angular methyl group

2- Aromatization of androgens in a complex process that involves three hydroxylation steps, each of which requires O₂ and NADPH.



Regulation of Metabolism

- **Metabolic homeostasis**

- The balance between need and availability is referred to as metabolic homeostasis.
- Insulin and glucagon
- Epinephrine and other stress hormones also increase the availability of fuels.
- The special role of glucose (**normal blood glucose levels in the range of 80 to 100 mg/dL**) in metabolic homeostasis is dictated by the fact that many tissues (e.g., the brain, red blood cells, the lens of the eye, the kidney medulla, exercising skeletal muscle) are dependent on glucose
- In the adult, a minimum of 190 gm of glucose is required per day; approximately 150 gm for the brain and 40 gm for other tissues.
- Significant decreases of blood glucose below 60 mg/dL limit glucose metabolism in the brain that leads to hypoglycemic symptoms.

Blood glucose level

- The **minute-by-minute adjustments** that keep the blood glucose level involve the integrated actions of:
 - Several hormones:
 - **Insulin** - signals that blood glucose concentration is higher than necessary.
 - **Glucagon** - signals that blood glucose is too low.
 - **Epinephrine** - released into the blood to prepare the muscles, lungs, and heart for a burst of activity.
 - Many tissues, primarily *liver, muscle, and adipose tissue*.

Major hormones of metabolic homeostasis

1- Insulin

- produced by β cells of the pancreas
- Stimulation: high blood glucose level
- The highest levels of insulin occur approximately 30 to 45 minutes after a high-carbohydrate meal.
- Insulin returns to its normal levels once the blood glucose concentration falls, approximately 120 minutes after the meal.

Insulin promotes

- 1- the storage of glucose as glycogen in liver and muscle
- 2- conversion of glucose to triacylglycerols in liver and their storage in adipose tissue,
- 3- amino acid uptake and protein synthesis in skeletal muscle.
- 4- increases the synthesis of albumin and other blood proteins by the liver.
- 5- promotes transport of glucose into muscle and adipose tissue.
- 6- Inhibit fuel mobilization.

In muscle cells, insulin favours glycogen formation and storage by:

- (1) increasing glucose transport into the cell,**
- (2) stimulating the key enzyme (glycogen synthase) that catalyses the rate-limiting step in glycogen synthesis**
- (3) inhibiting the key enzyme (glycogen phosphorylase) that catalyses glycogen catabolism.**

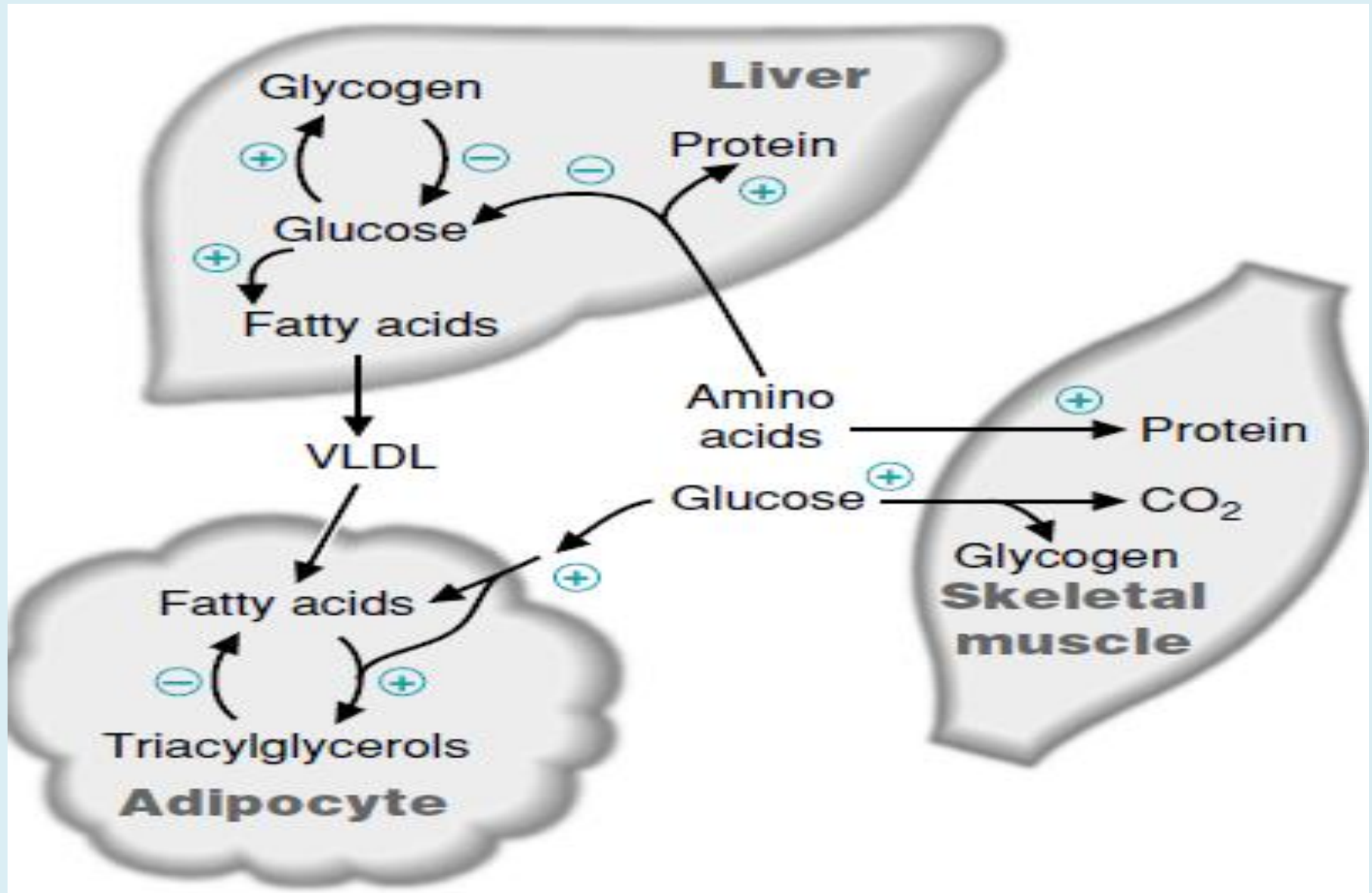
In muscle cells, insulin stimulate protein synthesis by

- (1) increases amino acid transportation to the cells,**
- (2) stimulates the ribosomal enzymes that mediate the synthesis of protein from these amino acids**
- (3) inhibits the enzymes that mediate protein catabolism.**

Major sites of insulin action on fuel metabolism

+ stimulated by insulin

- inhibited by insulin

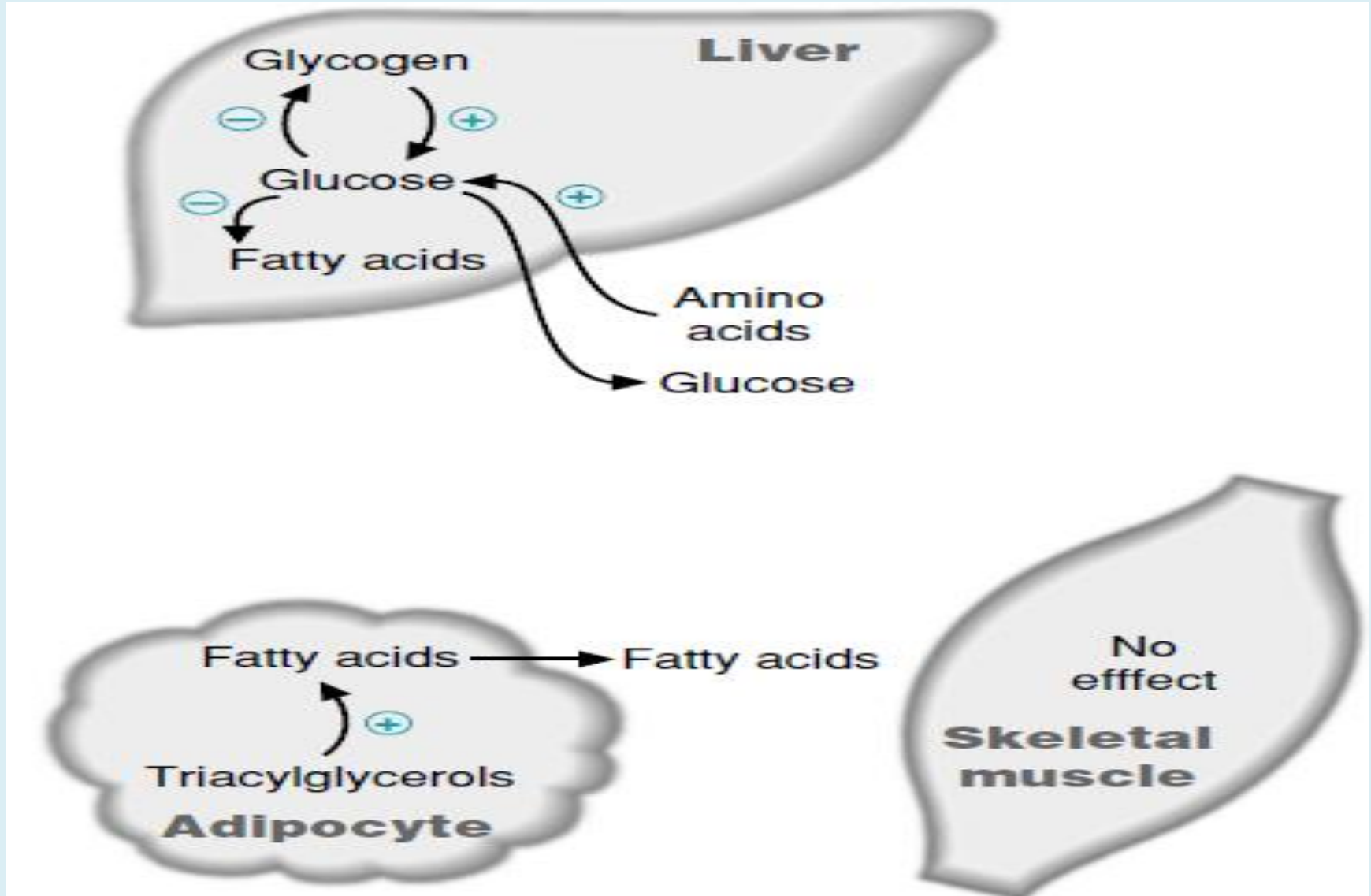


2-Glucagon

- produced by α cells of the pancreas
- Stimulation: low level of insulin and blood glucose (all of the effects of glucagon are opposed by insulin)
- Glucagon maintain fuel availability by
 - 1- Stimulating the release of glucose from liver glycogen,
 - 2- Stimulating gluconeogenesis from lactate, glycerol, and amino acids
 - 3- Mobilizing fatty acids from adipose triacylglycerols to provide an alternate source of fuel.
- Its sites of action are principally the liver and adipose tissue; it has no influence on skeletal muscle metabolism because muscle cells lack glucagon receptors.

Major sites of glucagon action in fuel metabolism

+ pathways stimulated by glucagon - pathways inhibited by glucagon.



3-Insulin counter regulatory hormones

- Include: epinephrine, norepinephrine, cortisol
- Stimulation (for all) neuronal signals (stress signals)
- These hormones oppose the actions of insulin by mobilizing fuels.
- Rising levels of the insulin counter regulatory hormones in the blood reflect, for the most part, a current increase in the demand for fuel.

Cortisol :

- Secreted by the *adrenal cortex*.
 - It **stimulates** protein catabolism, and gluconeogenesis from amino acids
 - In extra hepatic tissues, it **decreases** glucose utilization.
- protein catabolism → amino acids (as an important substrates for *hepatic* gluconeogenesis).

Epinephrine

- Secreted by the **adrenal medulla** in response to stressful stimuli (fear, excitement, hemorrhage, hypoxia, hypoglycemia, etc).
- Both liver and muscle cells have receptors to epinephrine.
- **Stimulates glucagon secretion .**
- **inhibits insulin secretion.**

1. Carbohydrate metabolism:

- **Increases glycogen breakdown in the *liver* and *muscle*.**
- **decreases glycogenesis.**
- **decreases uptake of glucose by the tissues.**
- **increases gluconeogenesis.**

2. lipid metabolism:

- **increases fat mobilization in *adipose tissue***
- **increases F.A. release and oxidation.**

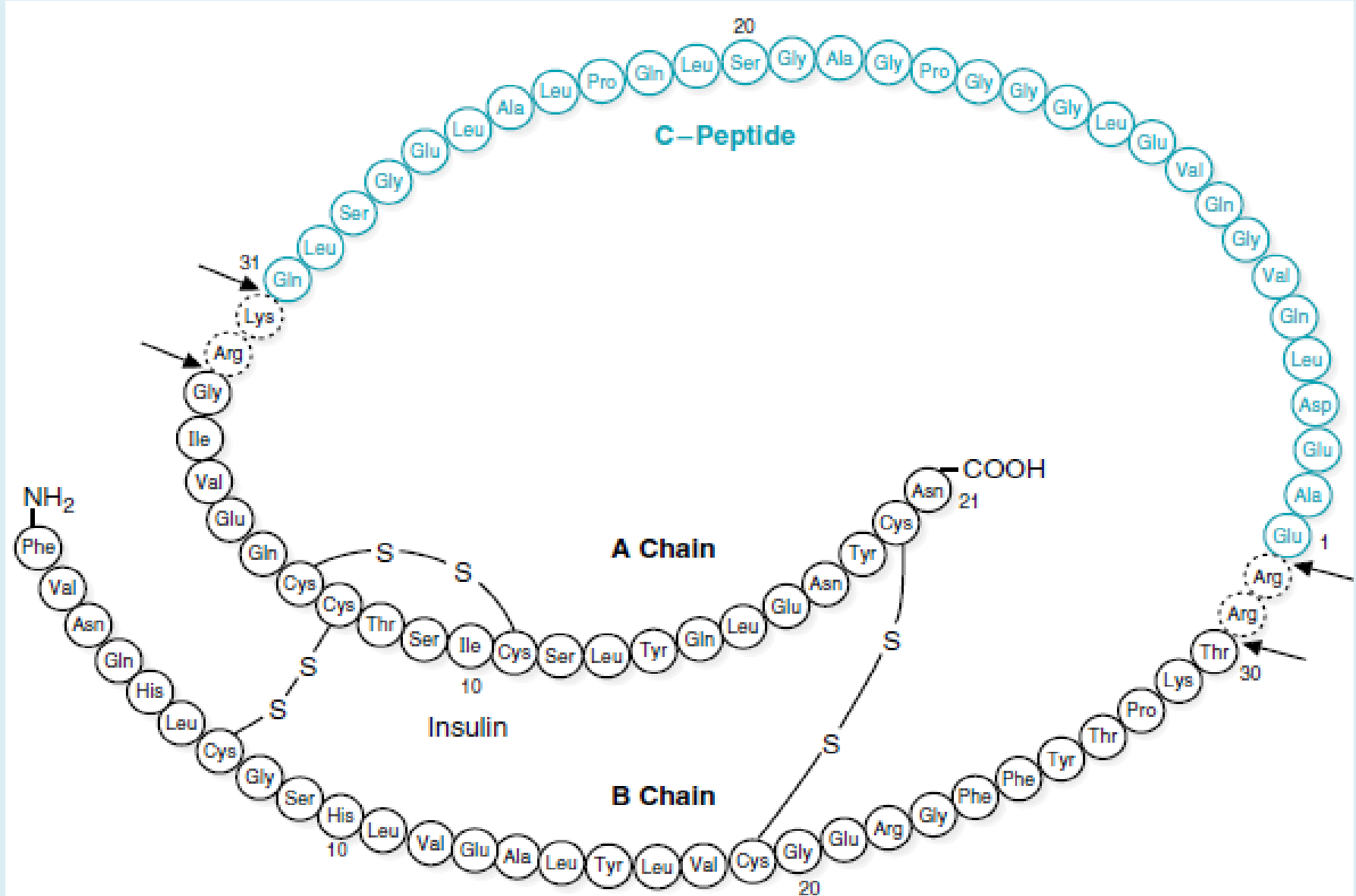
Physiologic Actions of Insulin and Insulin Counterregulatory Hormones

Hormone	Function	Major Metabolic Pathways Affected
Insulin	<ul style="list-style-type: none">• Promotes fuel storage after a meal• Promotes growth	<ul style="list-style-type: none">• Stimulates glucose storage as glycogen (muscle and liver)• Stimulates fatty acid synthesis and storage after a high-carbohydrate meal• Stimulates amino acid uptake and protein synthesis
Glucagon	<ul style="list-style-type: none">• Mobilizes fuels• Maintains blood glucose levels during fasting	<ul style="list-style-type: none">• Activates gluconeogenesis and glycogenolysis (liver) during fasting• Activates fatty acid release from adipose tissue
Epinephrine	<ul style="list-style-type: none">• Mobilizes fuels during acute stress	<ul style="list-style-type: none">• Stimulates glucose production from glycogen (muscle and liver)• Stimulates fatty acid release from adipose tissue
Cortisol	<ul style="list-style-type: none">• Provides for changing requirements over the long-term	<ul style="list-style-type: none">• Stimulates amino acid mobilization from muscle protein• Stimulates gluconeogenesis• Stimulates fatty acid release from adipose tissue

• Synthesis and Secretion of Insulin

- The active form of insulin is composed of two polypeptide chains (the A-chain and the B-chain) linked by two interchain disulfide bonds. The A-chain has an additional intrachain disulfide bond.
- Insulin is synthesized as a preprohormone that is converted in the rough endoplasmic reticulum to proinsulin.
- The “pre” sequence, a short hydrophobic signal sequence at the N-terminal end, is cleaved as it enters the lumen of the endoplasmic reticulum.
- Proinsulin folds into the proper conformation and disulfide bonds are formed between the cysteine residues.
- It is then transported to the Golgi complex.
- It leaves the Golgi complex in storage vesicles, where a protease removes the C-peptide (a fragment with no hormonal activity) and a few small pieces, resulting in the formation of biologically active insulin.

Cleavage of proinsulin to insulin. Proinsulin is converted to insulin by proteolytic cleavage, which removes the C-peptide and a few additional amino acid residues. Cleavage occurs at the arrows.

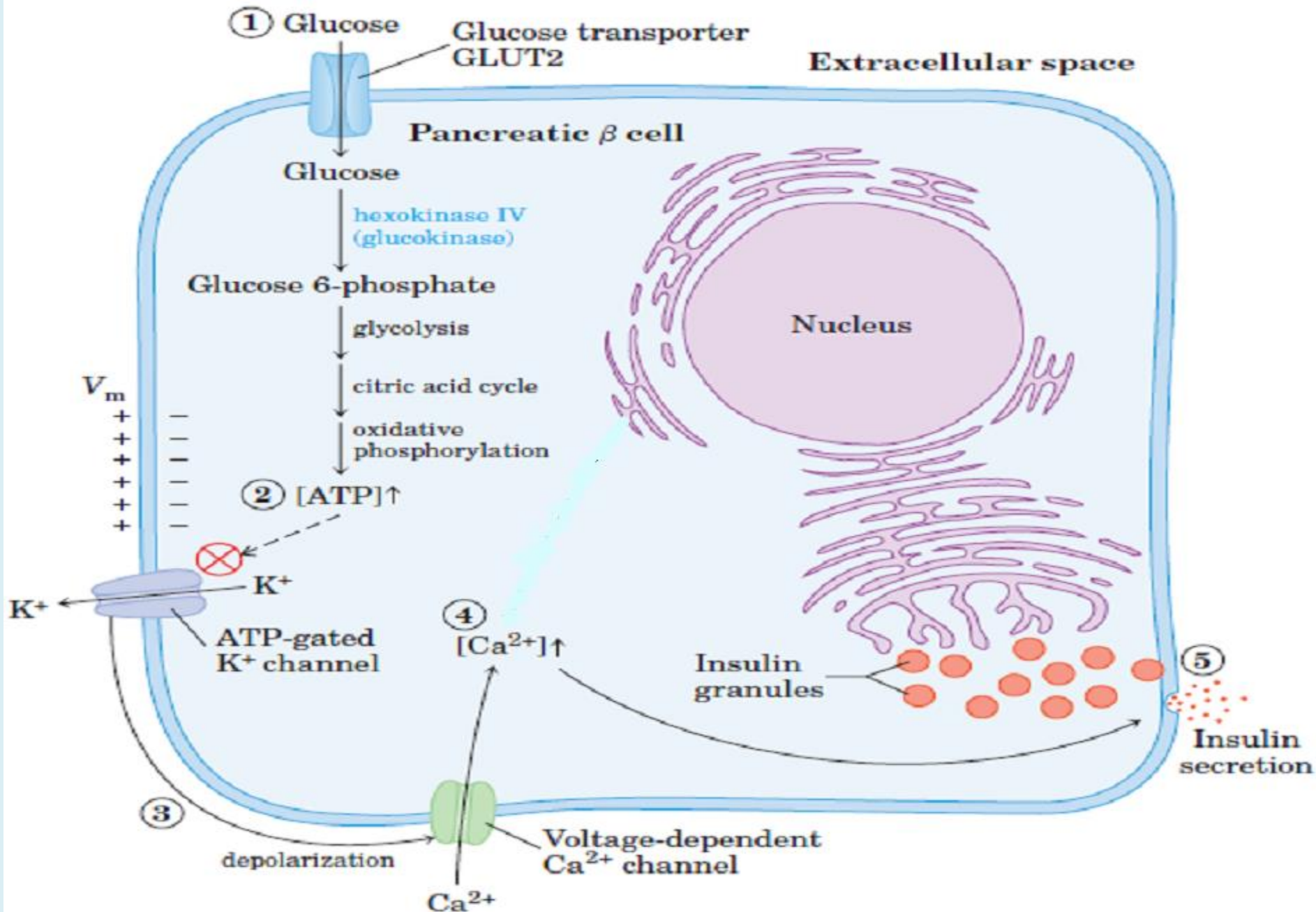


Insulin release

- Exocytosis of the insulin storage vesicles from the cytosol of the β cell into the blood is stimulated by rising levels of glucose in the blood bathing the β cells.
- Glucose enters the β cell via glucose transporter protein, GLUT2.
- Glucose is phosphorylated through the action of glucokinase to form glucose 6-phosphate, which is metabolized through glycolysis, the TCA cycle, and oxidative phosphorylation.
- These reactions result in an increase in ATP levels within the β cell.
- As the β cell $[ATP]/[ADP]$ ratio increases, the activity of a membrane-bound, ATP-dependent K^+ channel (K^+ ATP) is inhibited (i.e., the channel is closed).
- The closing of this channel leads to a membrane depolarization, which activates a voltage-gated Ca^{2+} channel that allows Ca^{2+} to enter the β cell such that intracellular Ca^{2+} levels increase significantly.
- The increase in intracellular Ca^{2+} stimulates the fusion of insulin containing exocytotic vesicles with the plasma membrane, resulting in insulin secretion.

Thus, an increase in glucose levels within the β cells initiates insulin release.

Release of insulin by β cells



- **Stimulation and Inhibition of Insulin Release**

- 1- **Blood glucose concentration. The threshold for insulin release is approximately 80 mg glucose/dL. Above 80 mg/dL, the rate of insulin release is proportional to the glucose concentration.**
- **Insulin is rapidly removed from the circulation and degraded by the liver (and, to a lesser extent, by kidney and skeletal muscle), so that blood insulin levels decrease rapidly once the rate of secretion slows.**
- 2- **Certain amino acids also can stimulate insulin secretion, although the amount of insulin released during a high-protein meal is very much lower than that released by a high-carbohydrate meal.**
- 3- **Gastric inhibitory polypeptide (GIP, a gut hormone released after the ingestion of food) also aids in insulin release.**
- 4- **Epinephrine, norepinephrine and cortisol decreases the release of insulin.**