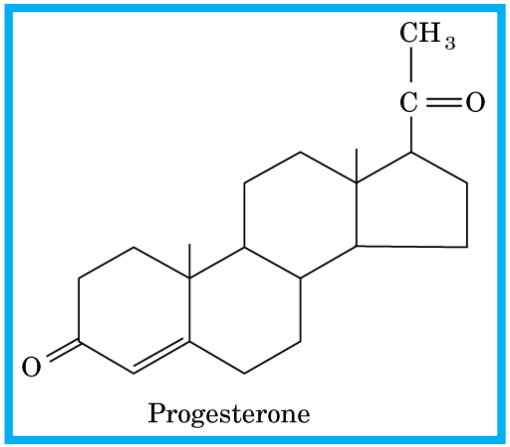
HORMONES



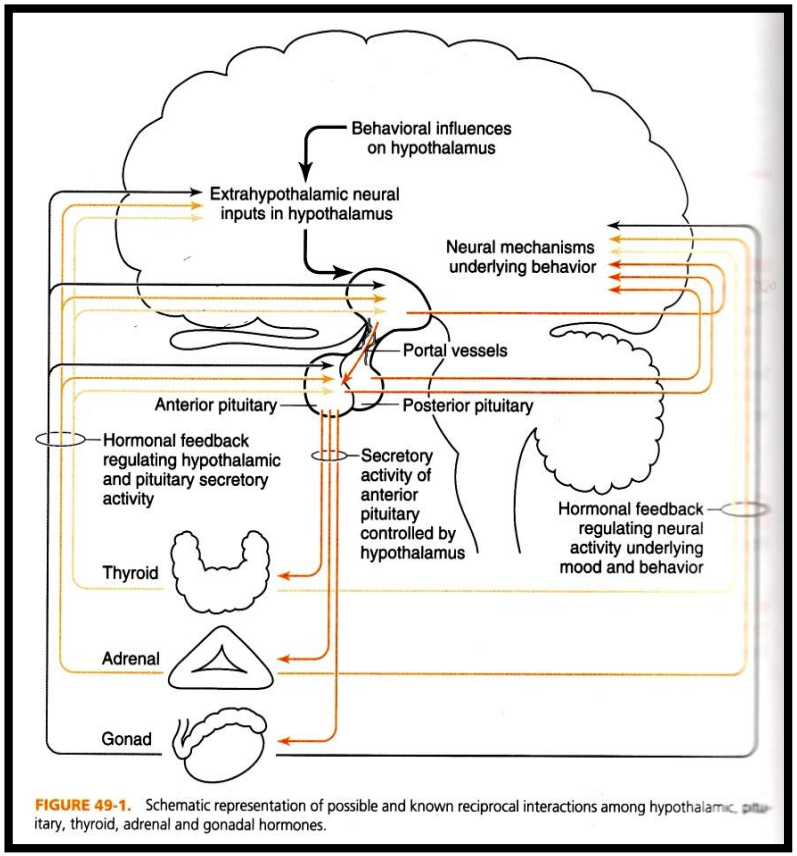
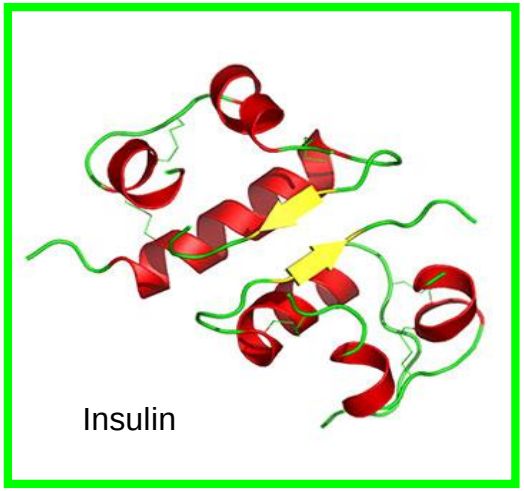


FIGURE 49-1. Schematic representation of possible and known reciprocal interactions among hypothalamic, pituitary, thyroid, adrenal and gonadal hormones.



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ABILITY OF CELLS TO RECOGNIZE AND RESPOND TO VARIOUS SIGNALS FROM ENVIRONMENT IS FUNDAMENTAL TO LIFE.

SIGNAL TRANSDUCTION

SIGNAL → SPECIFIC RECEPTORS → CELLULAR RESPONSE
(by conversion of signal involving a chemical process)

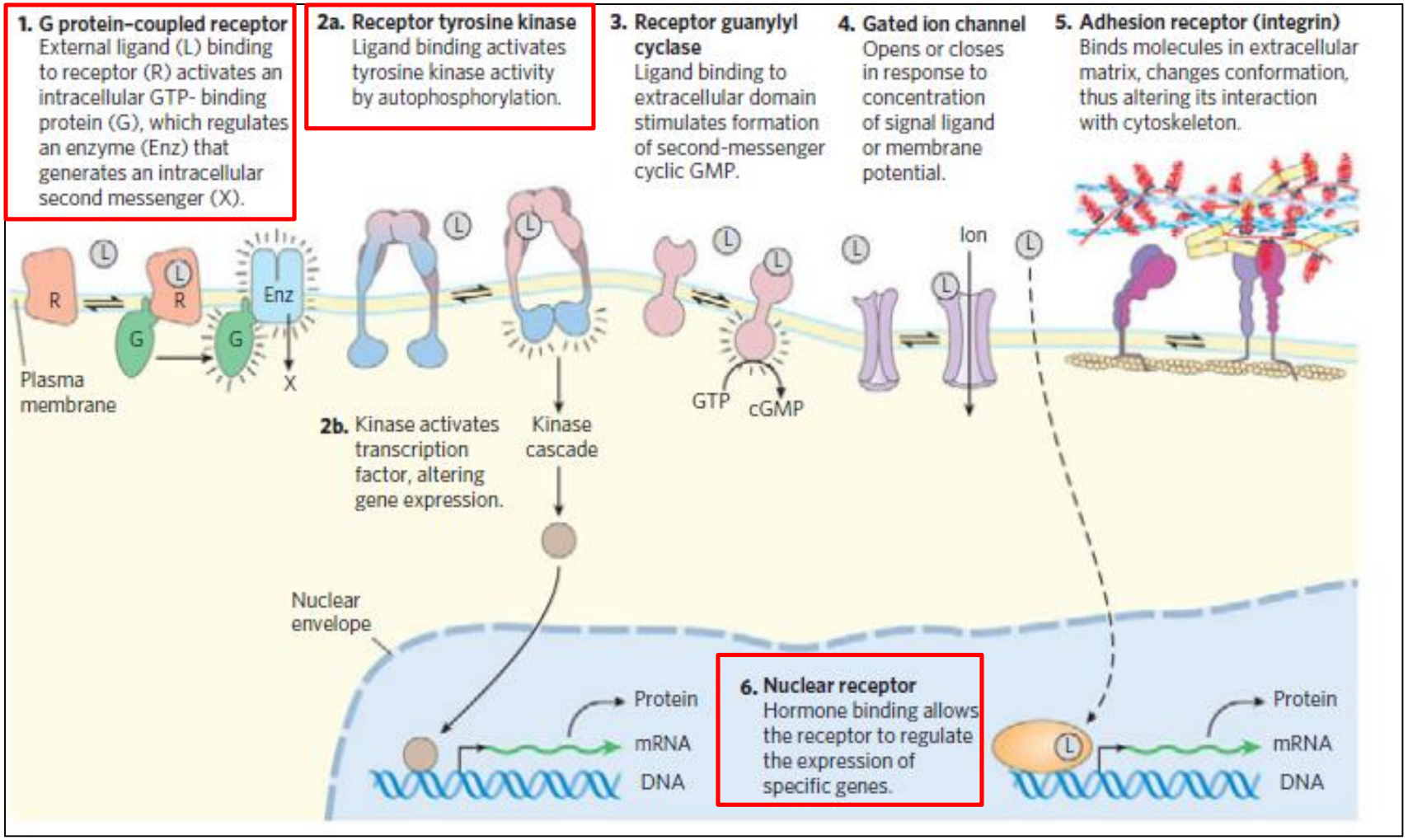
Some Signals to Which Cells Respond

Antigens	Light
Cell surface glycoproteins/ oligosaccharides	Mechanical touch
Developmental signals	Microbial, insect pathogens
Extracellular matrix components	Neurotransmitters
Growth factors	Nutrients
Hormones	Odorants
Hypoxia	Pheromones
	Tastants

BASIC SIGNALING MECHANISMS

Signaling mechanisms used by majority of hormones are:

- G protein-coupled receptor used by glucagon and adrenaline
- Receptor tyrosine kinase used by insulin
- Nuclear receptor used by steroid hormones and thyroid hormones



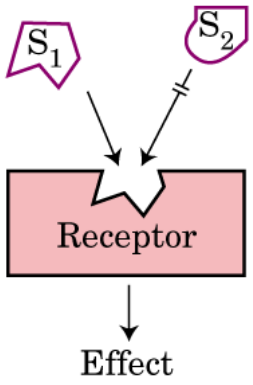
MOLECULAR MECHANISMS OF SIGNAL TRANSDUCTION

MAIN FEATURES OF SIGNAL-TRANSDUCING SYSTEMS

a) SPECIFICITY; b) AMPLIFICATION; c) DESENSITIZATION/ADAPTATION
d) INTEGRATION

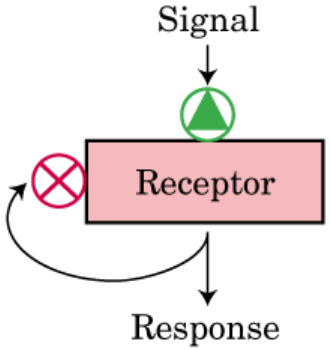
(a) Specificity

Signal molecule fits binding site on its complementary receptor; other signals do not fit.



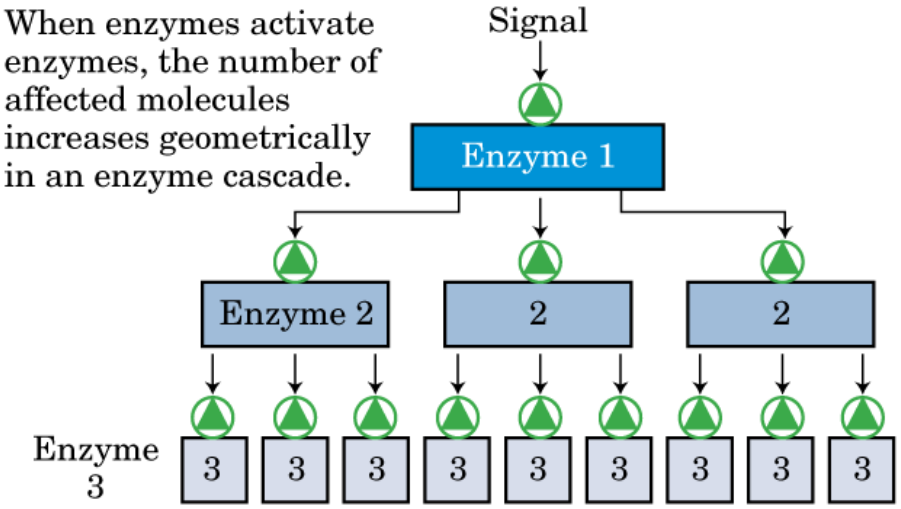
(c) Desensitization/Adaptation

Receptor activation triggers a feedback circuit that shuts off the receptor or removes it from the cell surface.



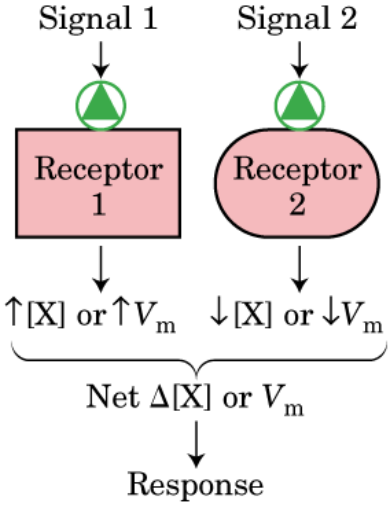
(b) Amplification

When enzymes activate enzymes, the number of affected molecules increases geometrically in an enzyme cascade.



(d) Integration

When two signals have opposite effects on a metabolic characteristic such as the concentration of a second messenger X, or the membrane potential V_m, the regulatory outcome results from the integrated input from both receptors.



CLASSIFICATION OF HORMONES

I. CHEMICAL COMPOSITION

II. SITE OF SYNTHESIS AND DISTANCE TO TARGET TISSUE/CELLS

III. MECHANISM OF ACTION

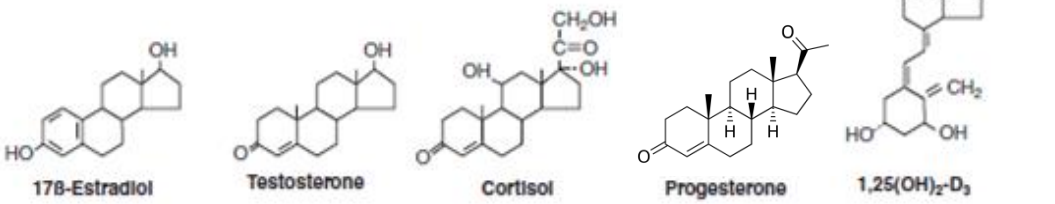
CLASSIFICATION OF HORMONES

I. CHEMICAL COMPOSITION

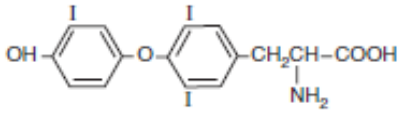
1. PEPTIDE HORMONES
2. CATECHOLAMINES
3. EICOSANOIDS
4. STEROID HORMONES
5. VITAMINE D
6. RETINOIDS
7. THYROID HORMONES
8. NITRIC OXIDE (NO)

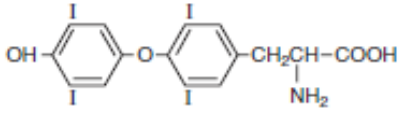
There is huge diversity and numerous hormones acting in human organism. The most abundant ones are different peptide and lipid structures displaying hormone actions.

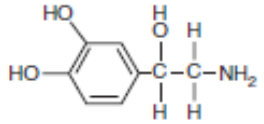
A. CHOLESTEROL DERIVATIVES

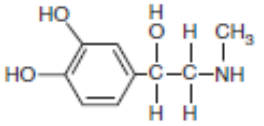


B. TYROSINE DERIVATIVES



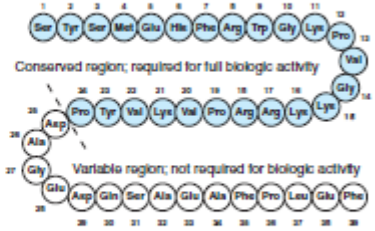






C. PEPTIDES OF VARIOUS SIZES

TRH



Structure of human ACTH.

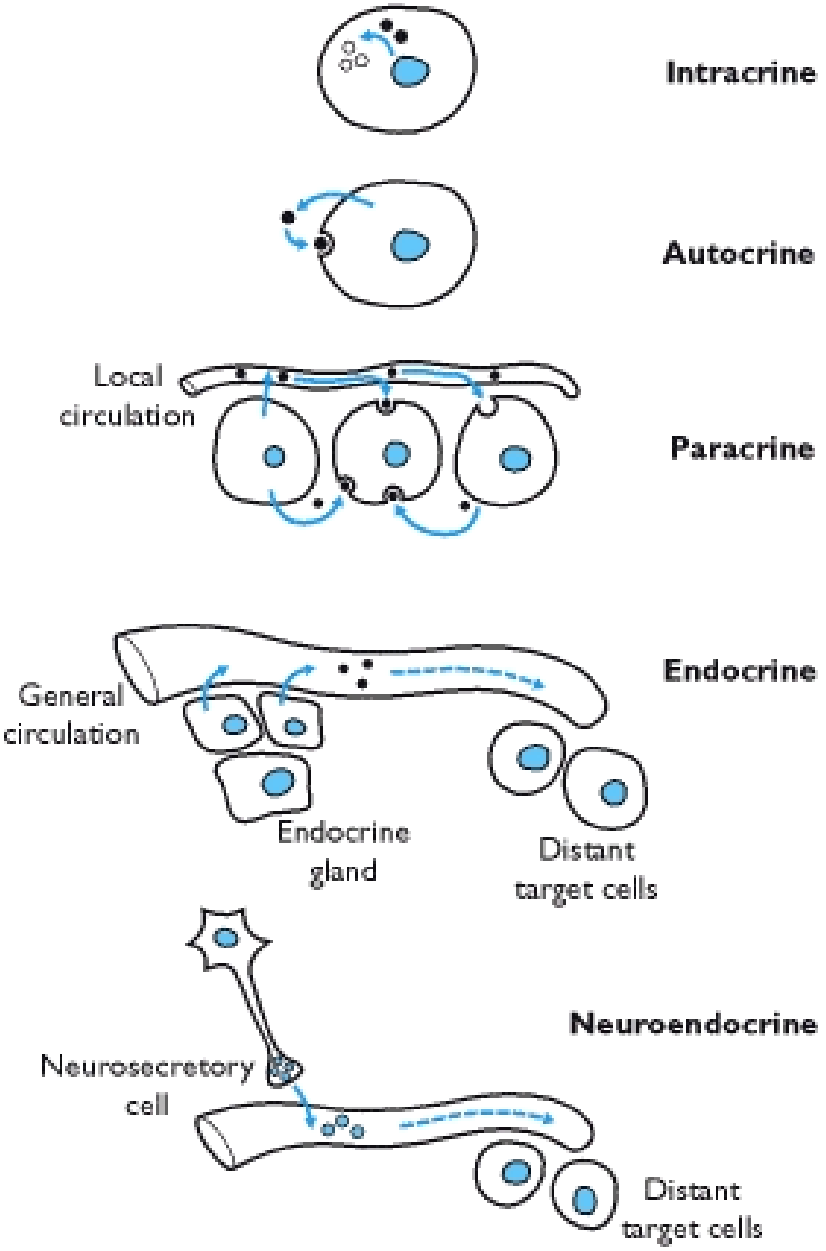
D. GLYCOPROTEINS (TSH, FSH, LH)

ACTH

CLASSIFICATION OF HORMONES

II. SITE OF SYNTHESIS AND DISTANCE TO TARGET CELLS/TISSUE

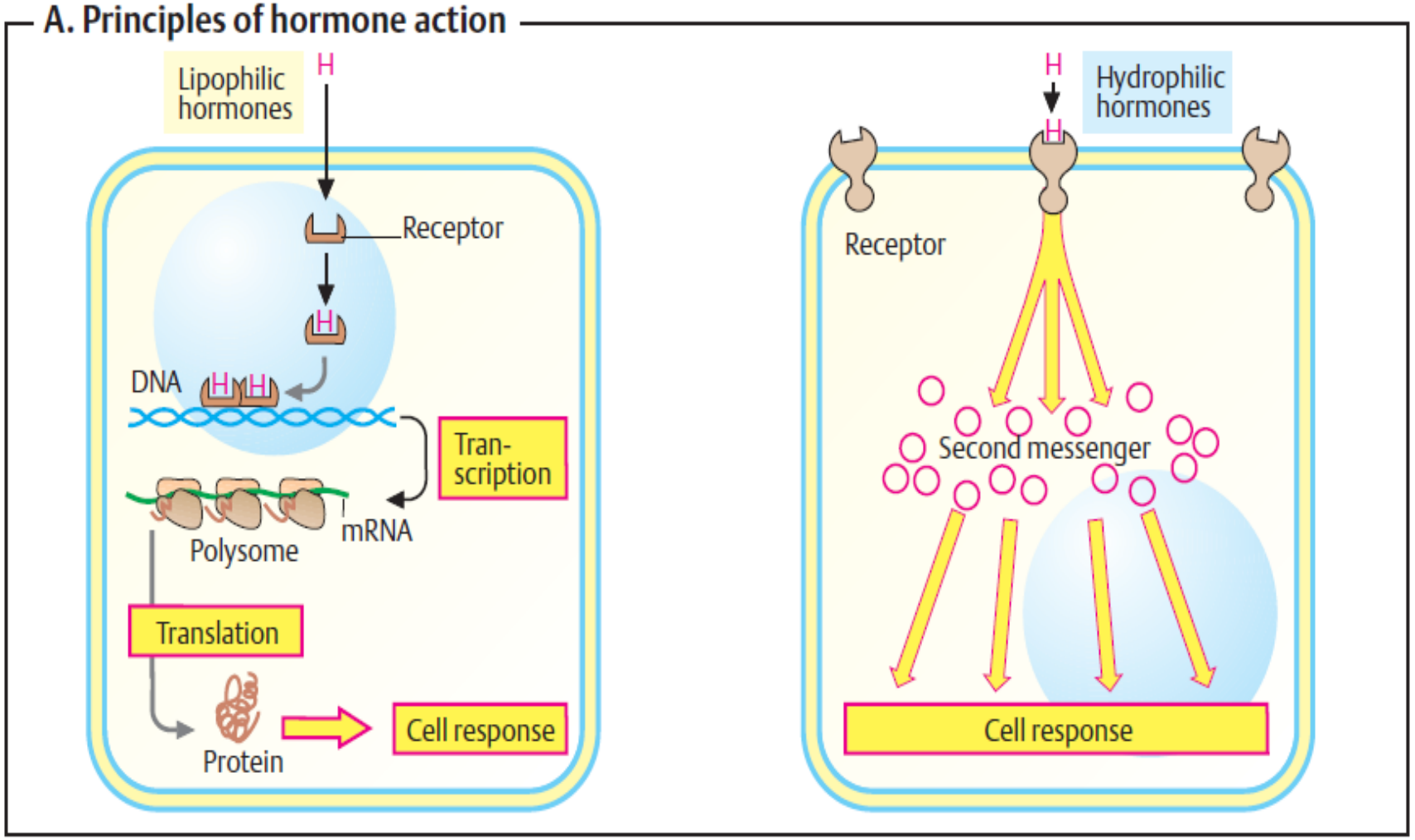
1. ENDOCRINE HORMONES (*insulin*)
2. PARACRINE HORMONES (*eicosanoids*)
3. AUTOCRINE HORMONES (*growth factors*)



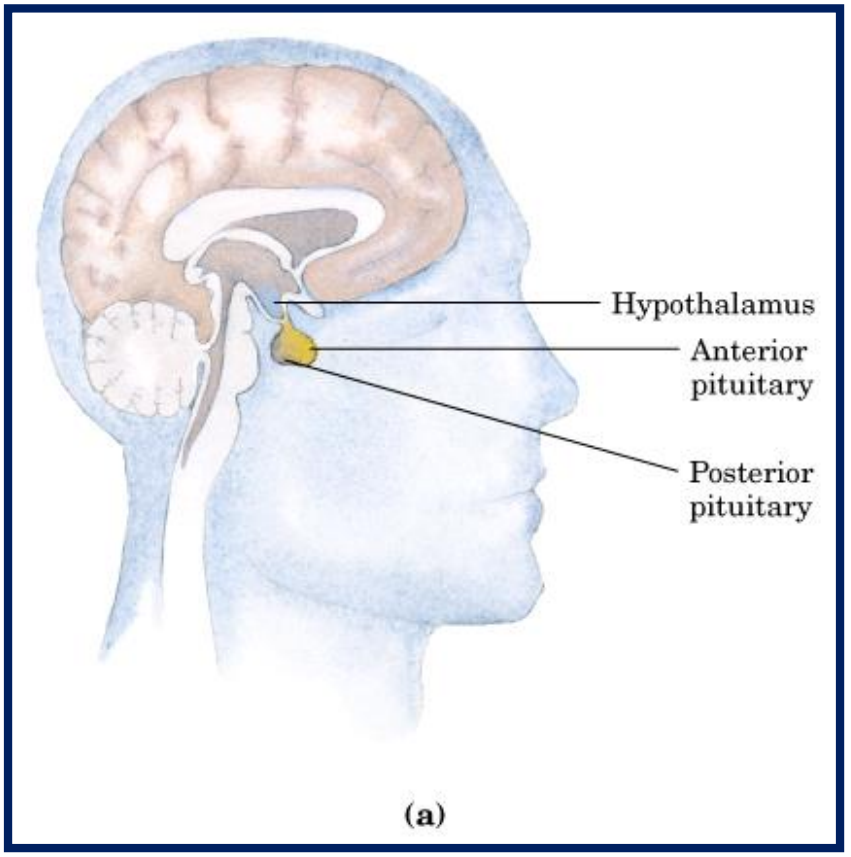
CLASSIFICATION OF HORMONES

III. MECHANISM OF ACTION

Depends on the chemical structure/properties of the hormone.



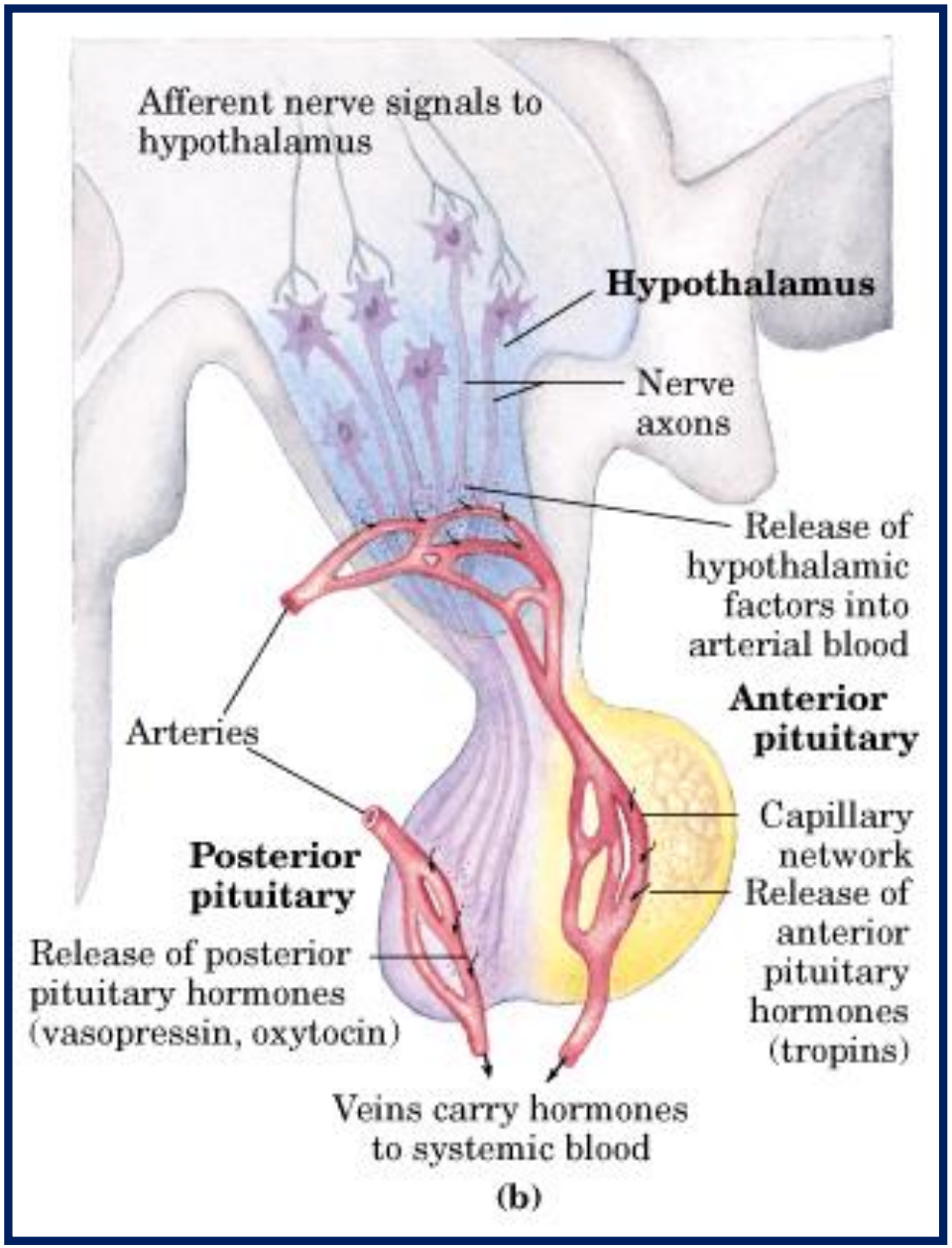
NEUROENDOCRINE SYSTEM REGULATES AND COORDINATES METABOLISM

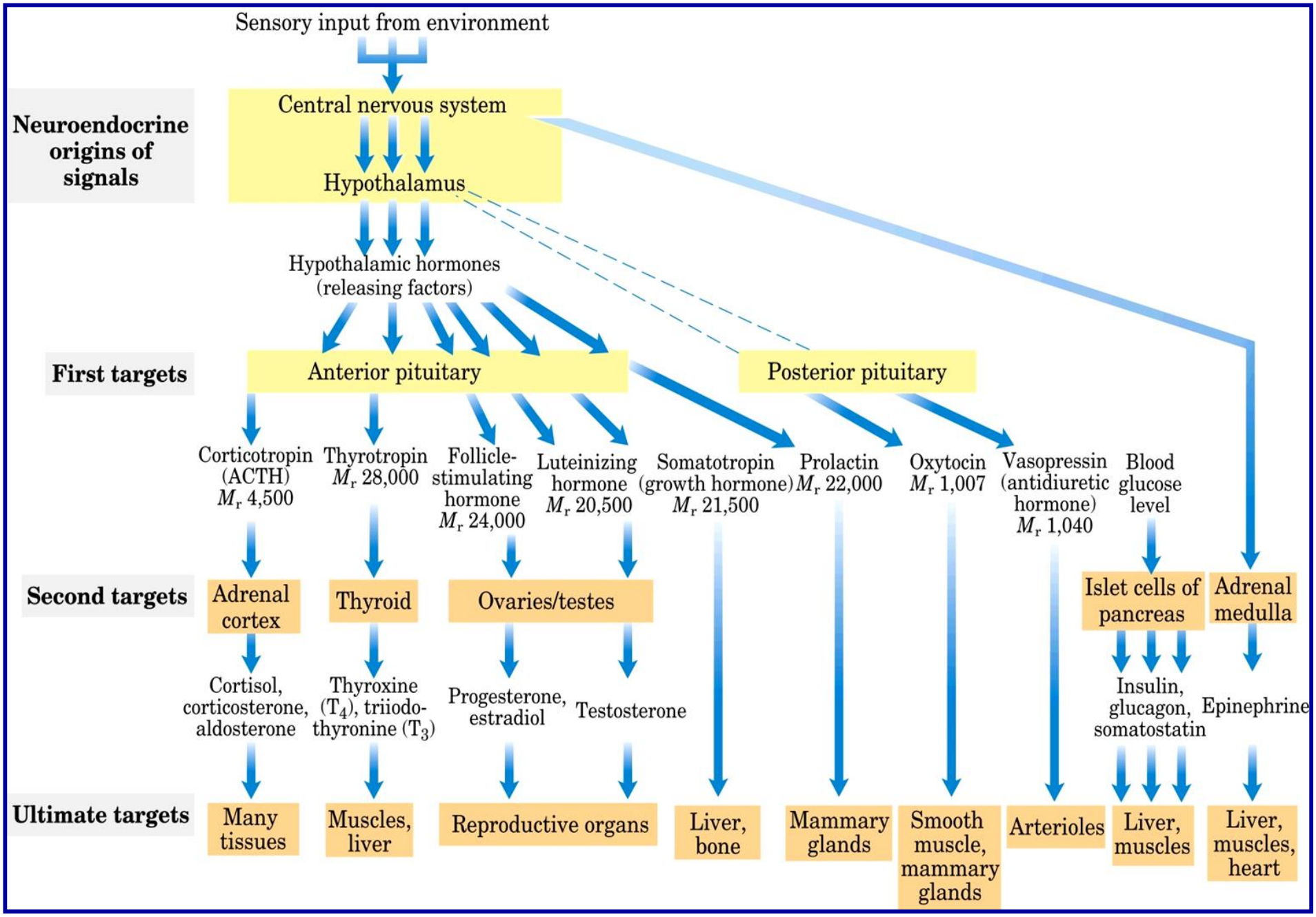


Neuroendocrine system

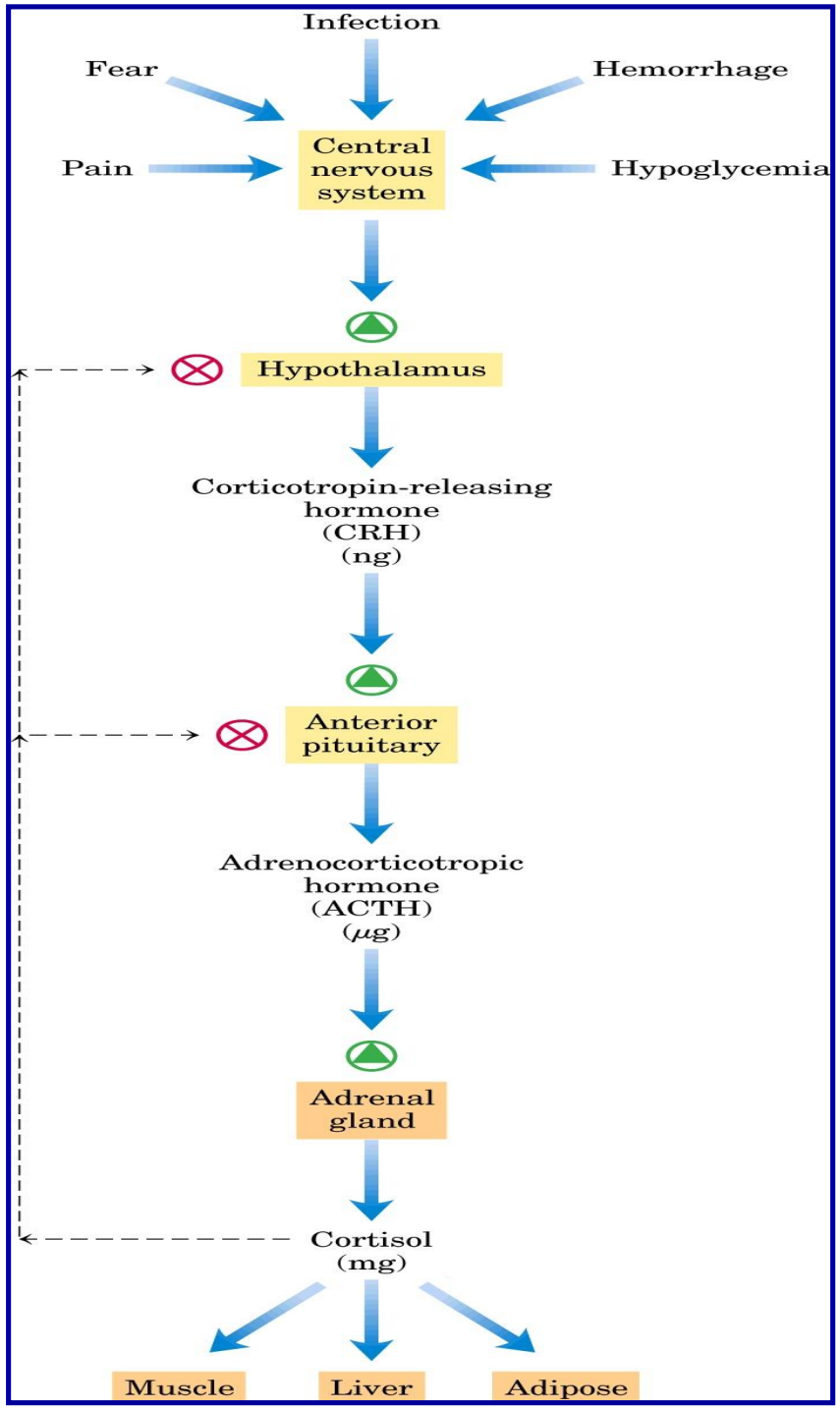
a. Hypothalamus and pituitary

b. Hypothalamic-pituitary system





Endocrine system and target tissues



Cascade of hormone secretion and regulation of cascade by feed-back control:

For example, increased concentration of cortisol in circulation inhibits hypothalamic secretion of CRH and pituitary secretion of ACTH in order to regulate blood cortisol level (regulation may occur in the opposite direction, depending on the blood cortisol as the stimulus for neuroendocrine system response).

Depending on chemical composition, hormones are differently stored in cells.

Hormone	*Intracellular store*
Steroids	no stores
Catecholamines and parathormone	hours
Insulin	days
Thyroid hormones	weeks

Depending on chemical composition and solubility, there are different ways of transporting hormones by circulation.

- ***Steroid hormones*** **have carrier proteins in circulation (CBG – "corticosteroid binding globulin"; SHBG – "sex hormone binding globulin")**
- ***Peptide hormones*** **do not require transport carriers**

HORMONES PRESENTED IN THIS LECTURE

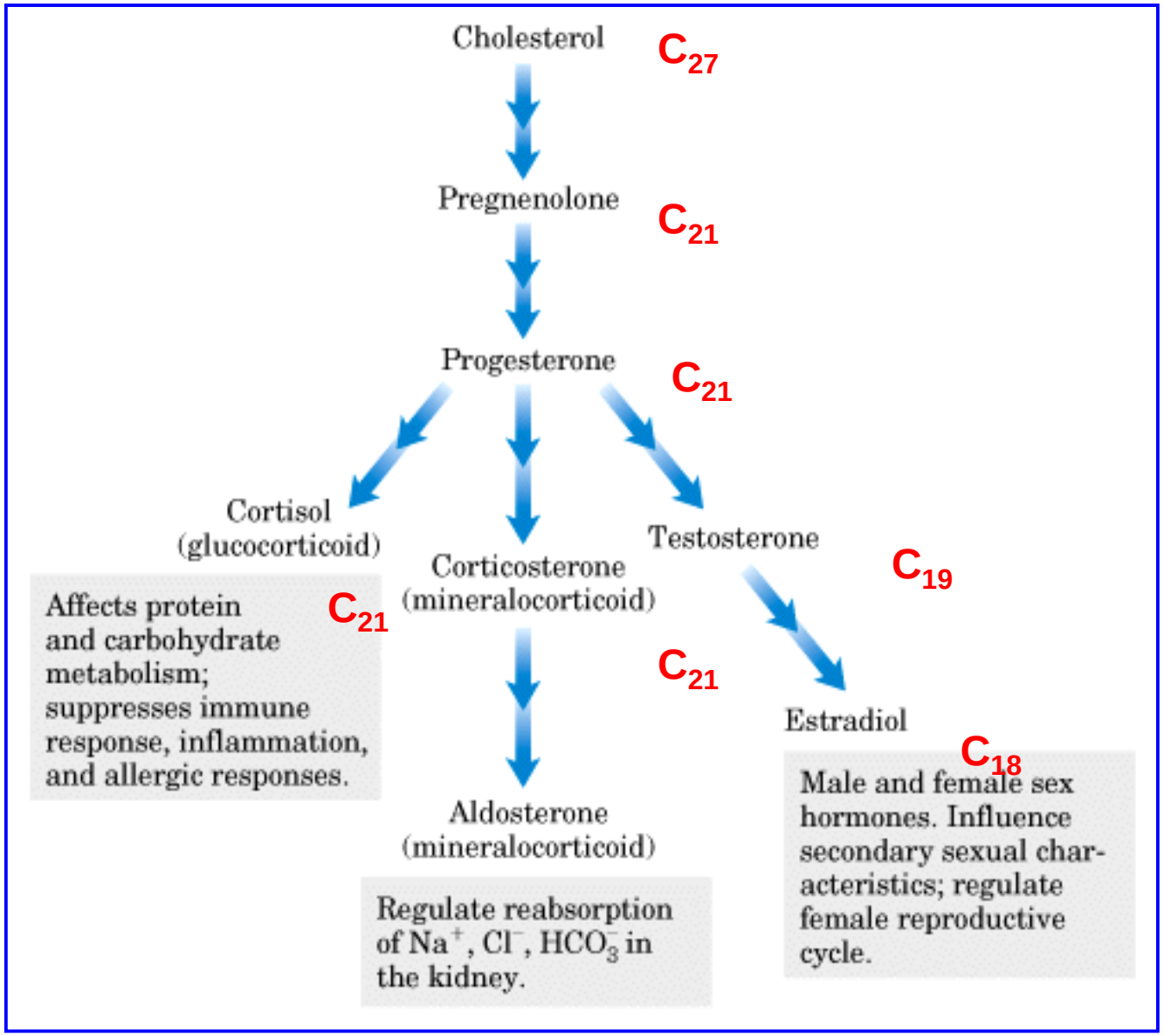
I. Steroid hormones
1. corticosteroids of adrenal cortex
2. sex hormones
3. calcitriol

II. Catecholamines

III. Peptide/protein hormones
1. insulin
2. thyroid hormones

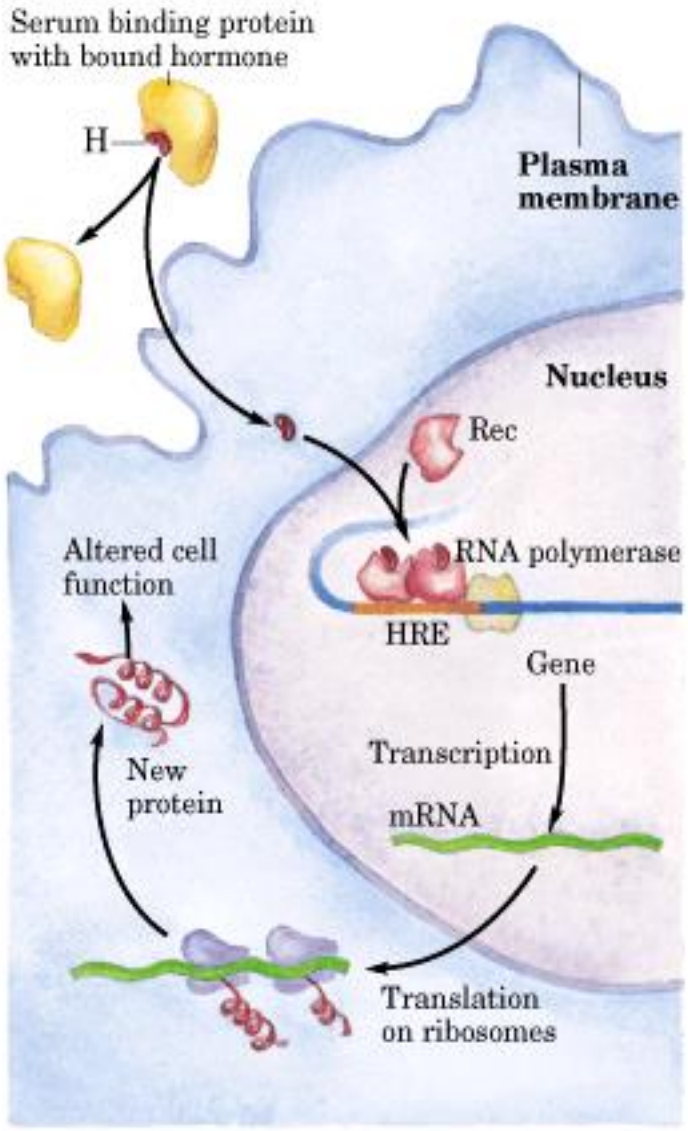
IV. Hormones involved in regulation of energy metabolism
insulin, glucagon, glucocorticoids, thyroid hormones, growth hormone

I. STEROID HORMONES



Cholesterol is precursor for synthesis of steroid hormones.

STEROID HORMONES – MECHANISM OF ACTION IS REGULATION OF TRANSCRIPTION (GENOMIC EFFECTS)

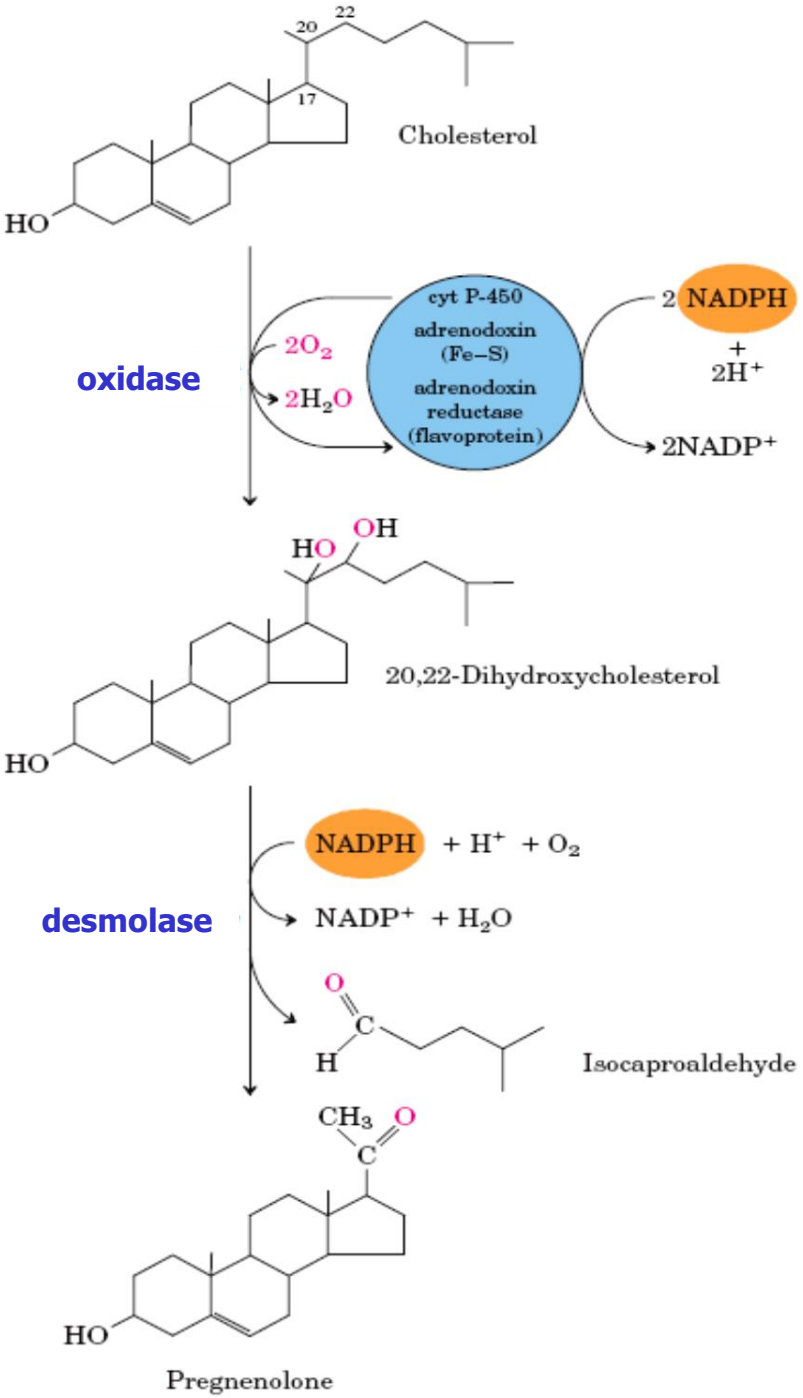


① Hormone (H), carried to the target tissue on serum binding proteins, diffuses across the plasma membrane and binds to its specific receptor protein (Rec) in the nucleus.

② Hormone binding changes the conformation of Rec; it forms homo- or heterodimers with other hormone-receptor complexes and binds to specific regulatory regions called hormone response elements (HREs) in the DNA adjacent to specific genes.

③ Binding regulates transcription of the adjacent gene(s), increasing or decreasing the rate of mRNA formation.

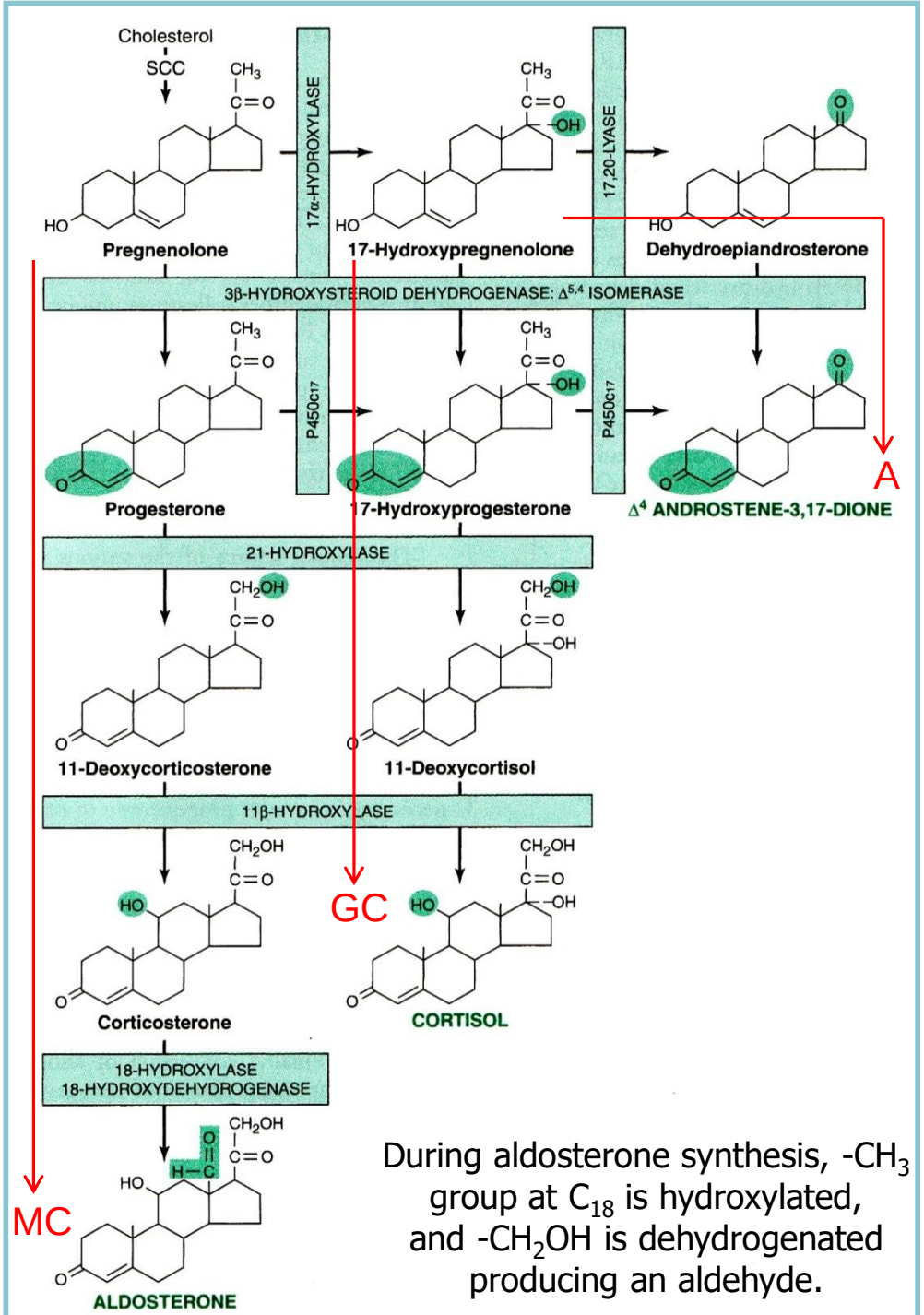
④ Altered levels of the hormone-regulated gene product produce the cellular response to the hormone.



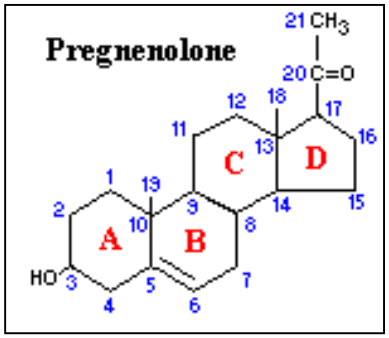
Common precursor of steroid hormones synthesis is **pregnenolone**.

Reaction of pregnenolone formation is catalyzed by **desmolase** (**P450 scc**, P450 side chain cleavage enzyme).

ACTH, LH or angiotensin II stimulate production of cAMP and activation of lipase and desmolase (P450scc).

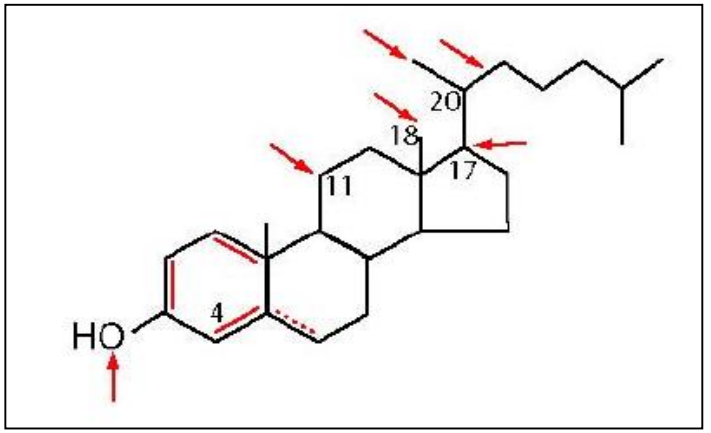


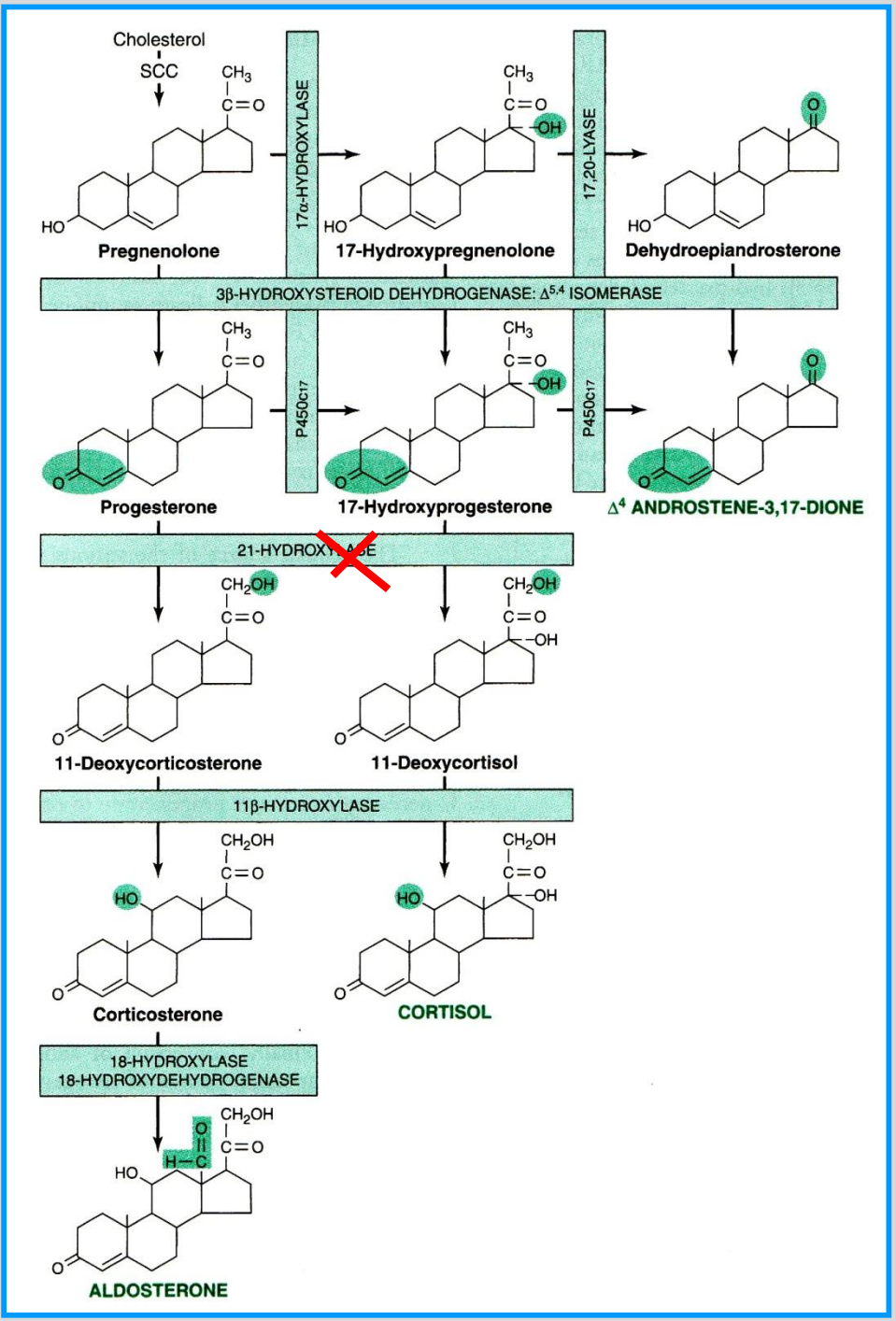
During aldosterone synthesis, -CH_3 group at C_{18} is hydroxylated, and -CH_2OH is dehydrogenated producing an aldehyde.



Steroid hormones are synthesized in adrenal cortex. Enzymes ***hydroxylases*** catalyze the reactions of synthetic patway in a precise sequential order:

- C_{17}, C_{21} and C_{11} (synthesis of cortisol/glucocorticoids, GC);
- C_{21}, C_{11} and C_{18} (mineralocorticoid synthesis, MC);
- C_{17}, oxidation and removal of side chain (androgene synthesis, A).





Disorders of cortisol synthesis

1. ***Congenital adrenal hyperplasia, 21-hydroxylase deficiency***

- Decreased cortisol concentrations lead to **increased ACTH secretion** and **increased secretion of androgens**

Symptoms:

- Masculinization of female newborn children
- Early puberty in male children

Testosterone biosynthesis

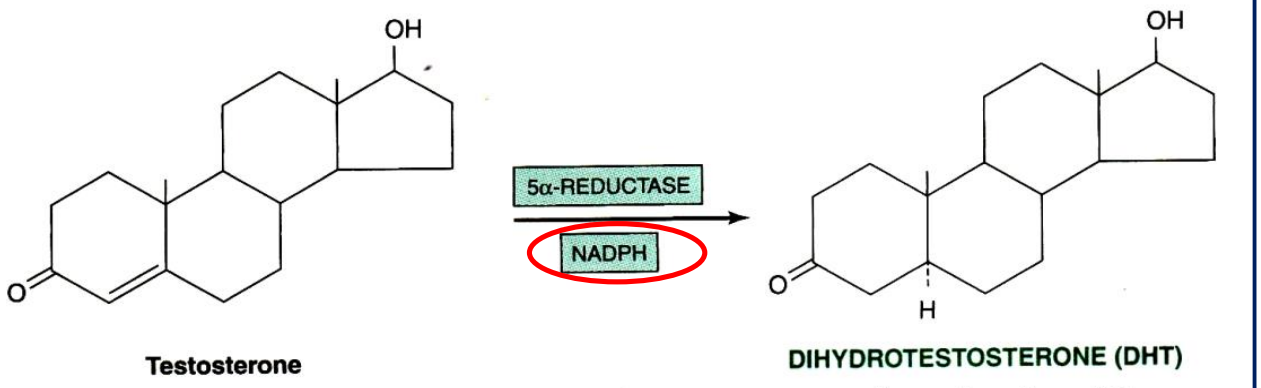


Figure 41–6. Dihydrotestosterone is formed from testosterone through action of the enzyme 5α-reductase.

Testosterone synthesis in male gonads is stimulated by secretion of LH.

Both testosterone and DHT are bound to androgene receptors (higher affinity for DHT!).

Deficiency of 5*α*-reductase may cause disorders in sexual development (male pseudohermafroditism).

Anabolic actions of testosterone in skeletal muscles – stimulated protein synthesis!

Estrogen biosynthesis in female gonads

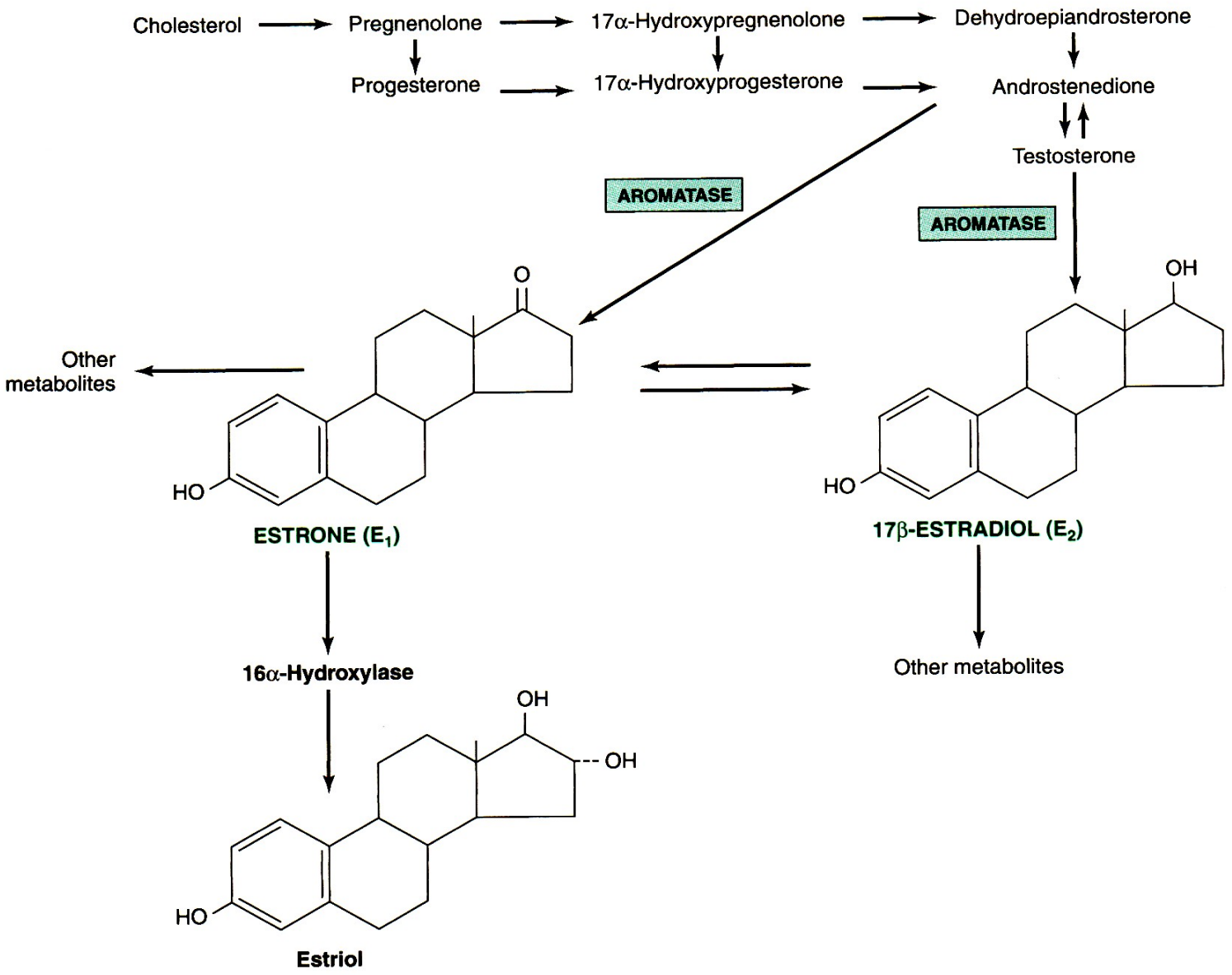
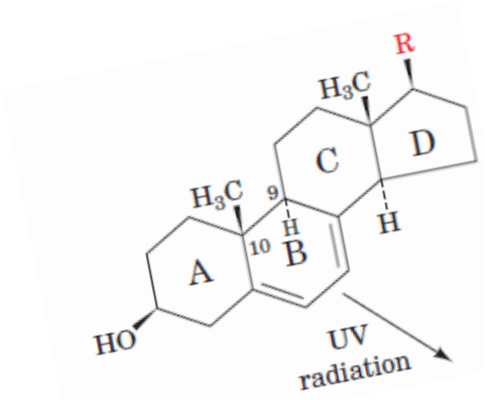
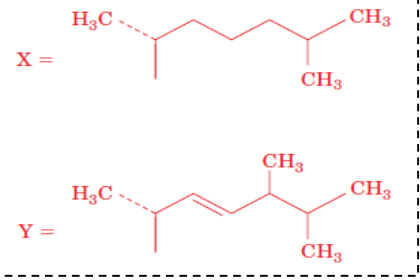


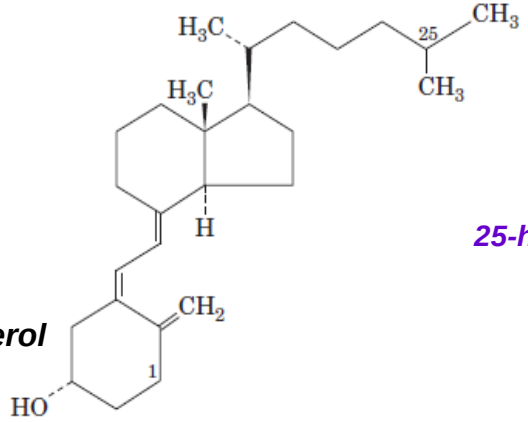
Figure 41–7. **Biosynthesis of estrogens.** (Slightly modified and reproduced, with permission, from Ganong WF: *Review of Medical Physiology*, 20th ed. McGraw-Hill, 2001.)

Calcitriol synthesis



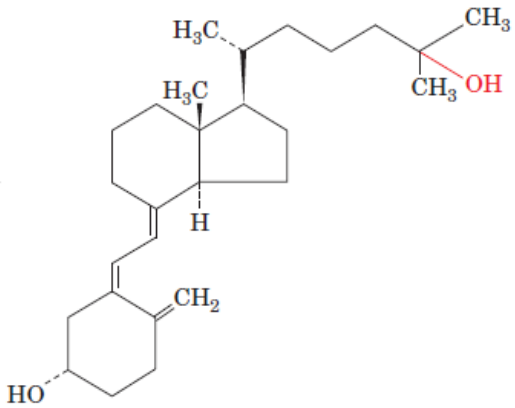
R = X 7-Dehydro-cholesterol
R = Y Ergosterol → *Plant sterol*





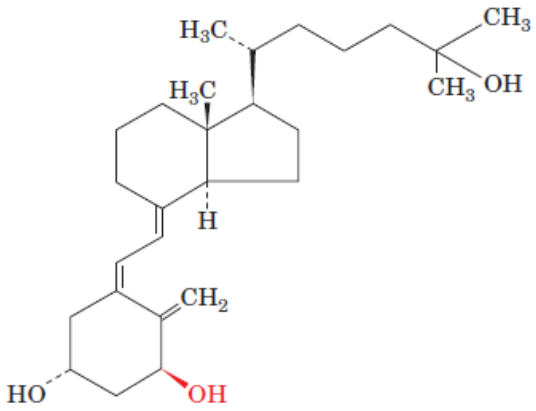
Cholecalciferol
(Vitamin D_3)
(inactive)

CYP27A1
CYP2R1
(liver)
O_2
25-hydroxylase



25-Hydroxycholecalciferol

O_2
PTH (+)
CYP27B1 (kidney)
1α-hydroxylase



1α,25-Dihydroxycholecalciferol
[1,25$(OH)_2$D]
(active)

→**calcitriol**

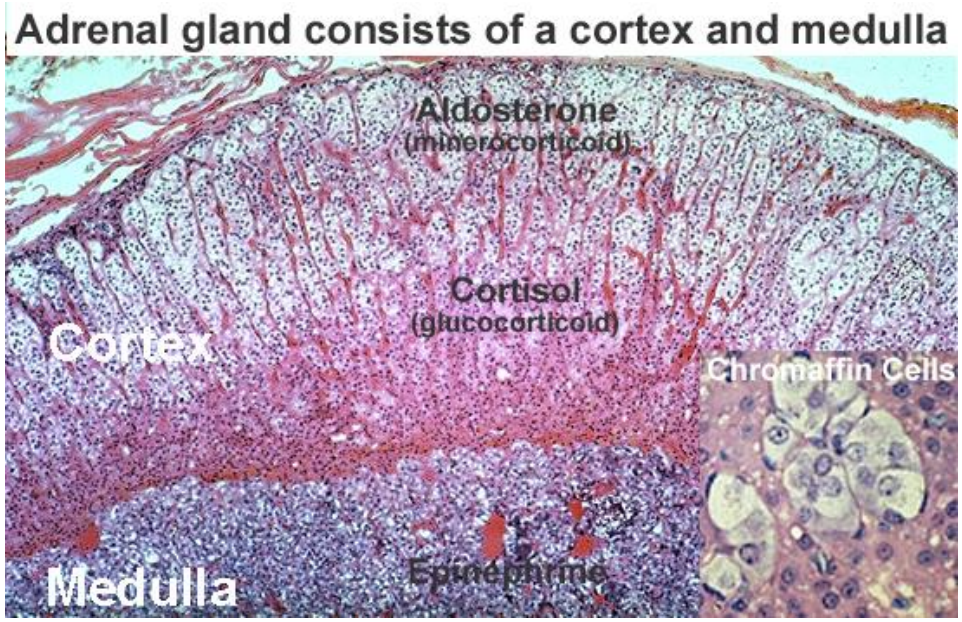
Calcitriol is active form of vitamine D (**steroid**); **calcitriol synthesis begins in skin, modifications occur in liver and kidney;** calcitriol binds to intracellular receptors in cells of digestive system, kidney and bones; Calcitriol actions include: **increased intestinal absorption of calcium** (by induced expression of protein calbindin); **increased reanal reabsorption of phosphate and calcium;** stimulated **bone mineralisation**.

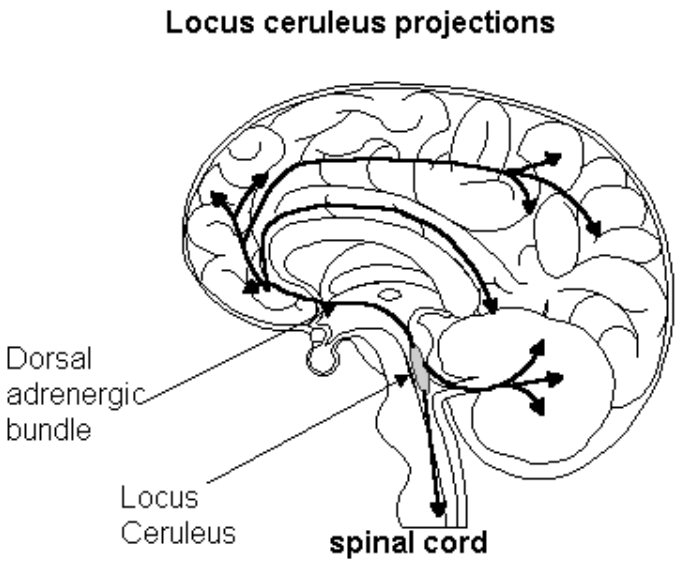
Inactivation and elimination of steroid hormones

-inactivation in liver, to lesser extent in kidneys, and in target tissue after hormonal action

-reductions, hydroxylations

-conjugation with glucuronic acid or in sulphated form and elimination in urine in the glucuronide form.



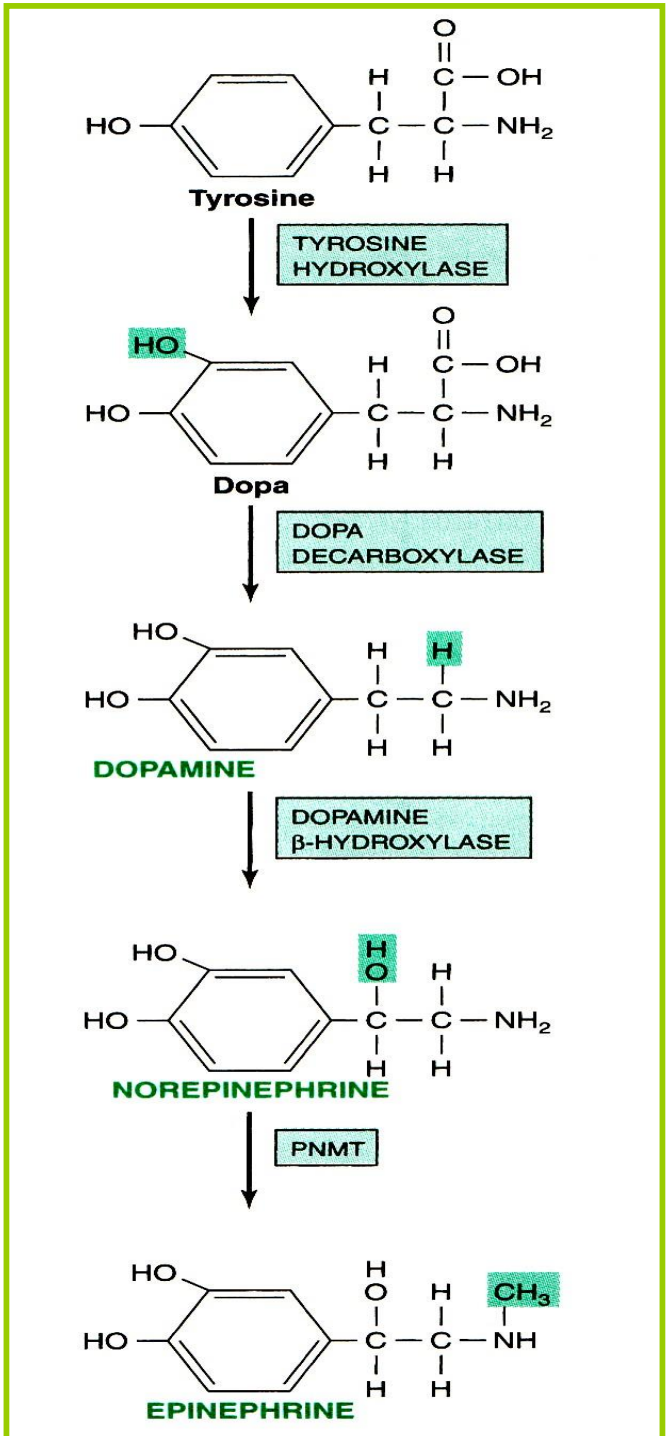


II. HORMONES OF THE ADRENAL MEDULLA - CATECHOLAMINES

Adrenaline synthesis

Catecholamines are synthesized as active compounds and are stored in granules of cromaffine cells in adrenal medulla; catecholamines are released by exocytosis as a response to stimuli.

Catecholamines cannot pass through blood-brain barrier and are synthesized *in situ* as neurotransmitters.

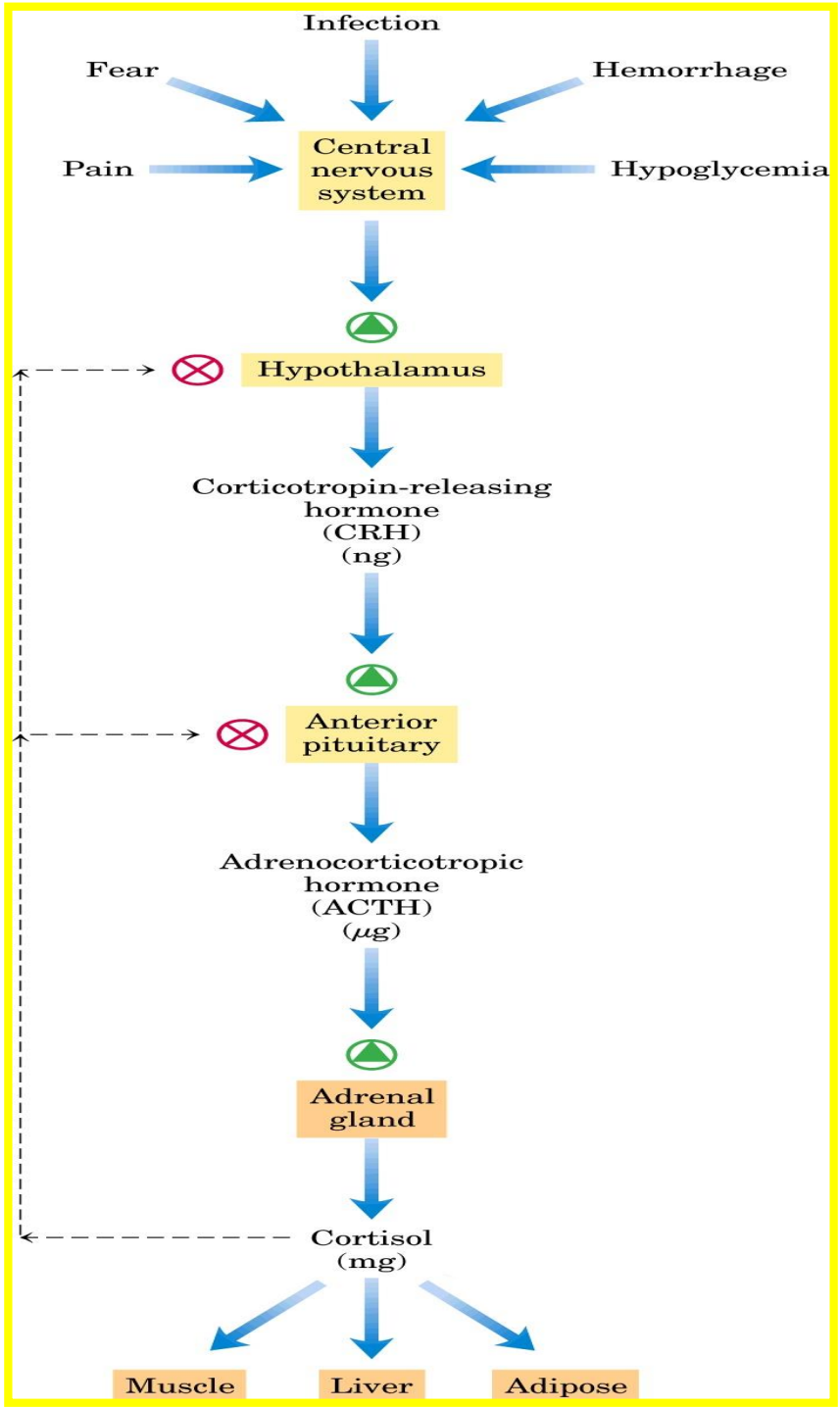


Amino acid tyrosine is precursor for synthesis of catecholamines.

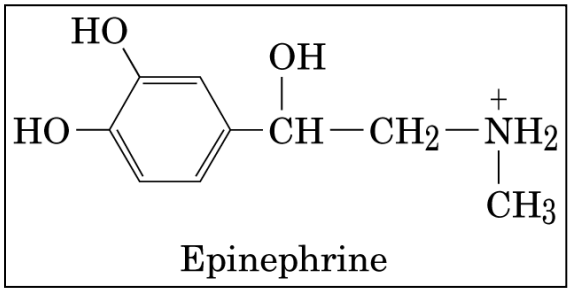
Final conversion of norepinephrine-epinephrine occurs in cytoplasm of adrenal medullar cells and is catalyzed by the enzyme PNMT (phenylethanolamine-*N*-methyltransferase).

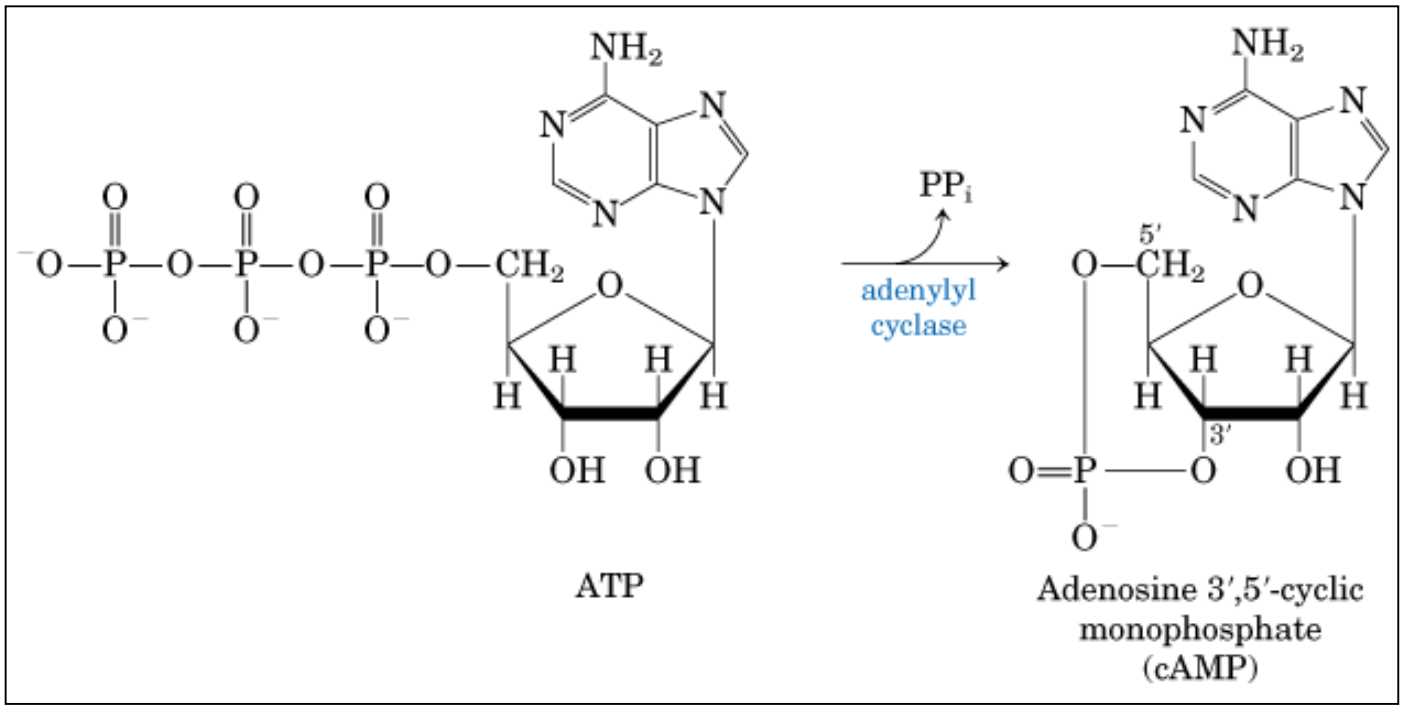
Glucocorticoid hormones induce PNMT synthesis.

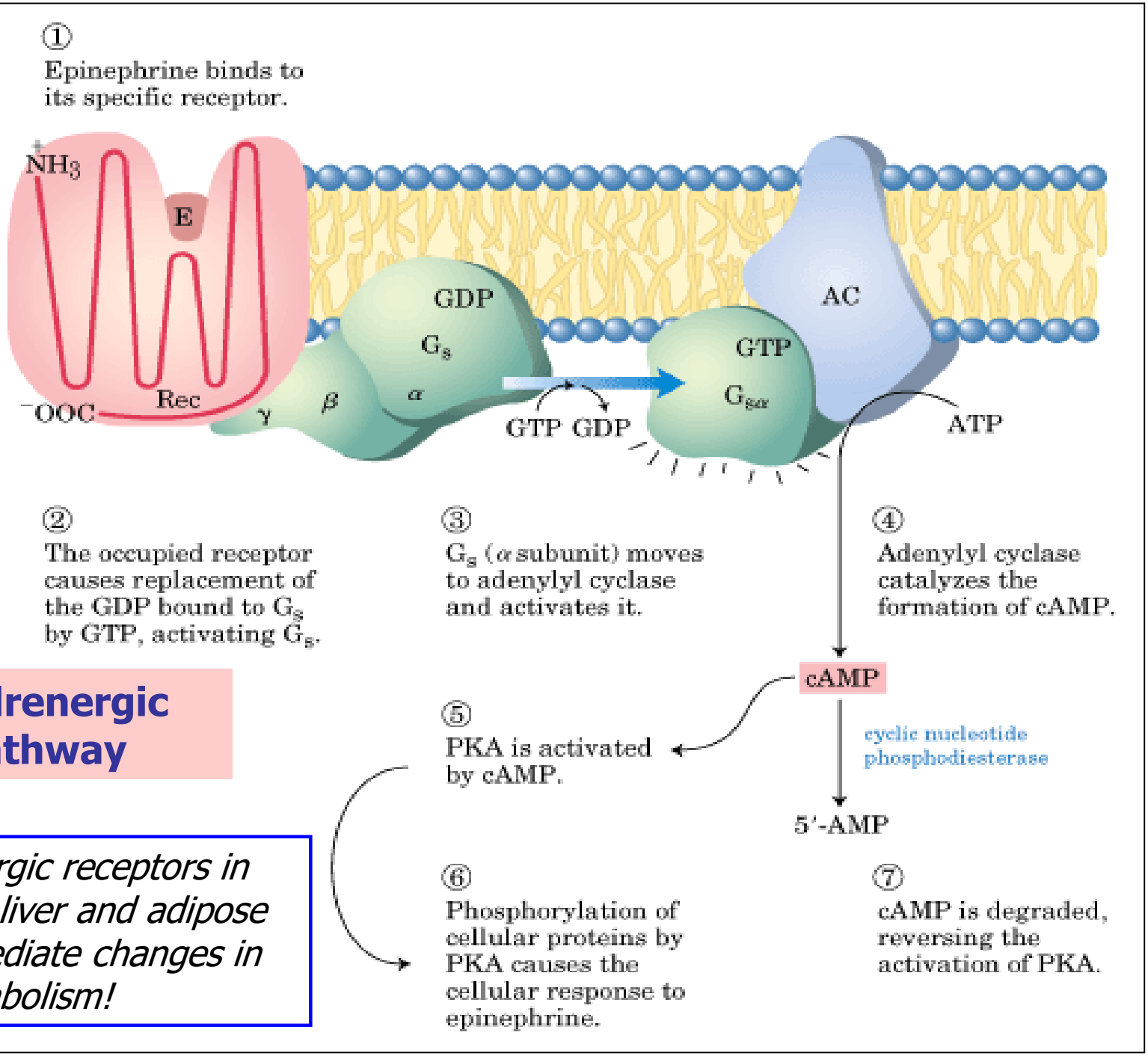
The effects of glucocorticoids (and adrenalin) are involved in response to different stressors.



β-adrenergic receptor system utilizes cAMP as second messenger





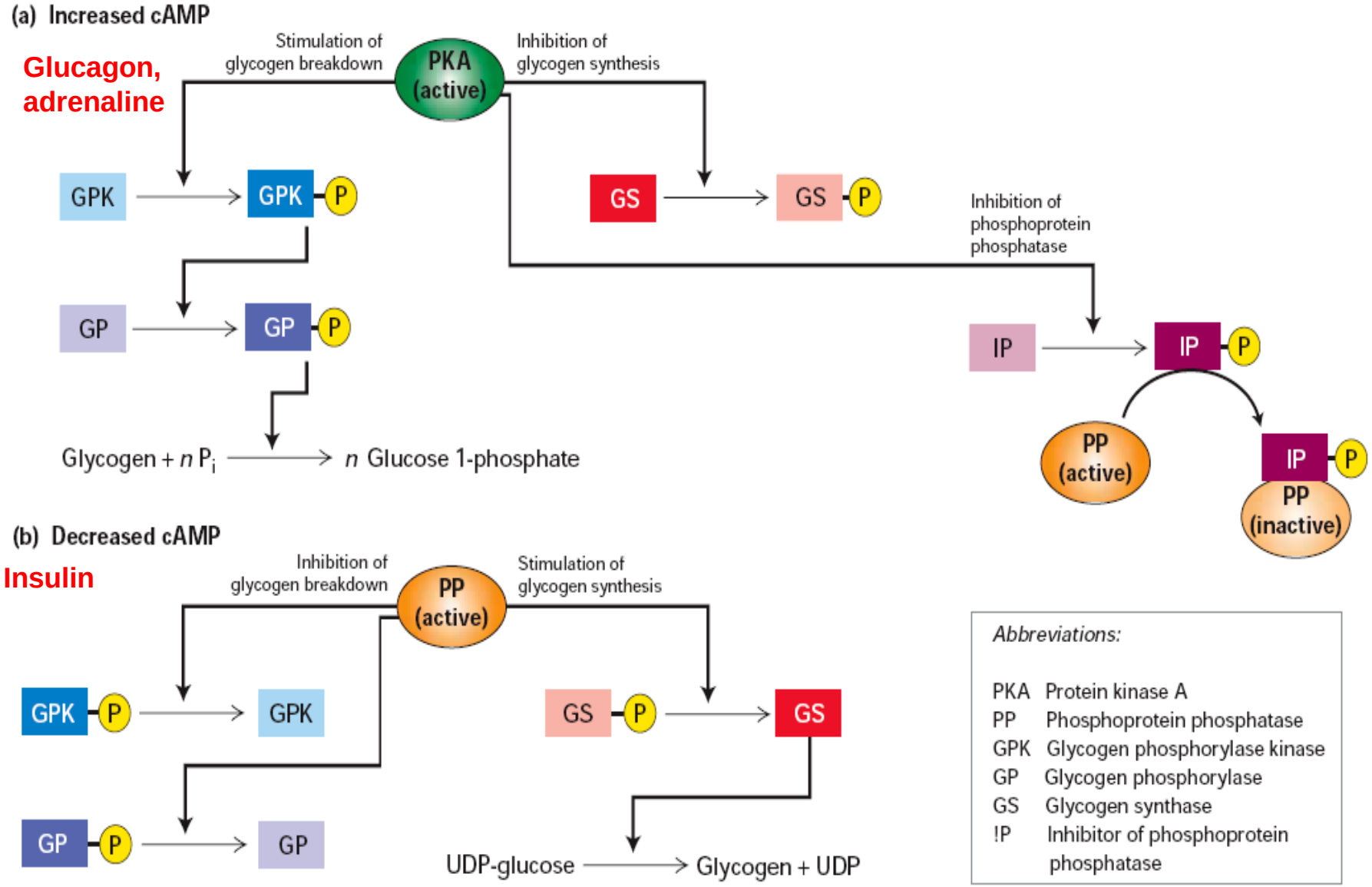


β-adrenergic pathway

β-adrenergic receptors in muscles, liver and adipose tissue mediate changes in fuel metabolism!

Example from metabolism: GLYCOGEN METABOLISM IS REGULATED BY HORMONE-INDUCED ACTIVATION OF PROTEIN KINASE A (PKA).

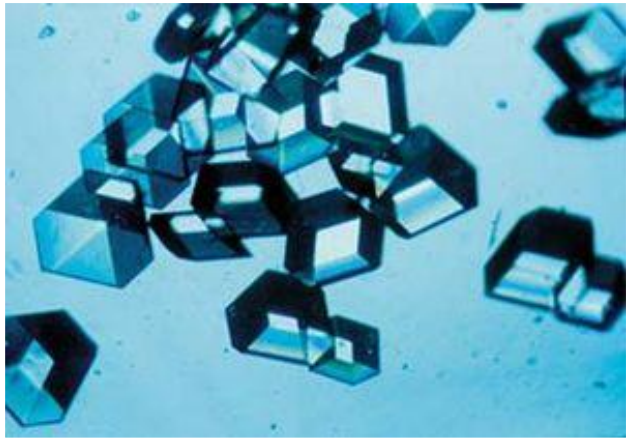
REGULATION OF GLYCOGEN METABOLISM BY cAMP IN LIVER AND MUSCLE



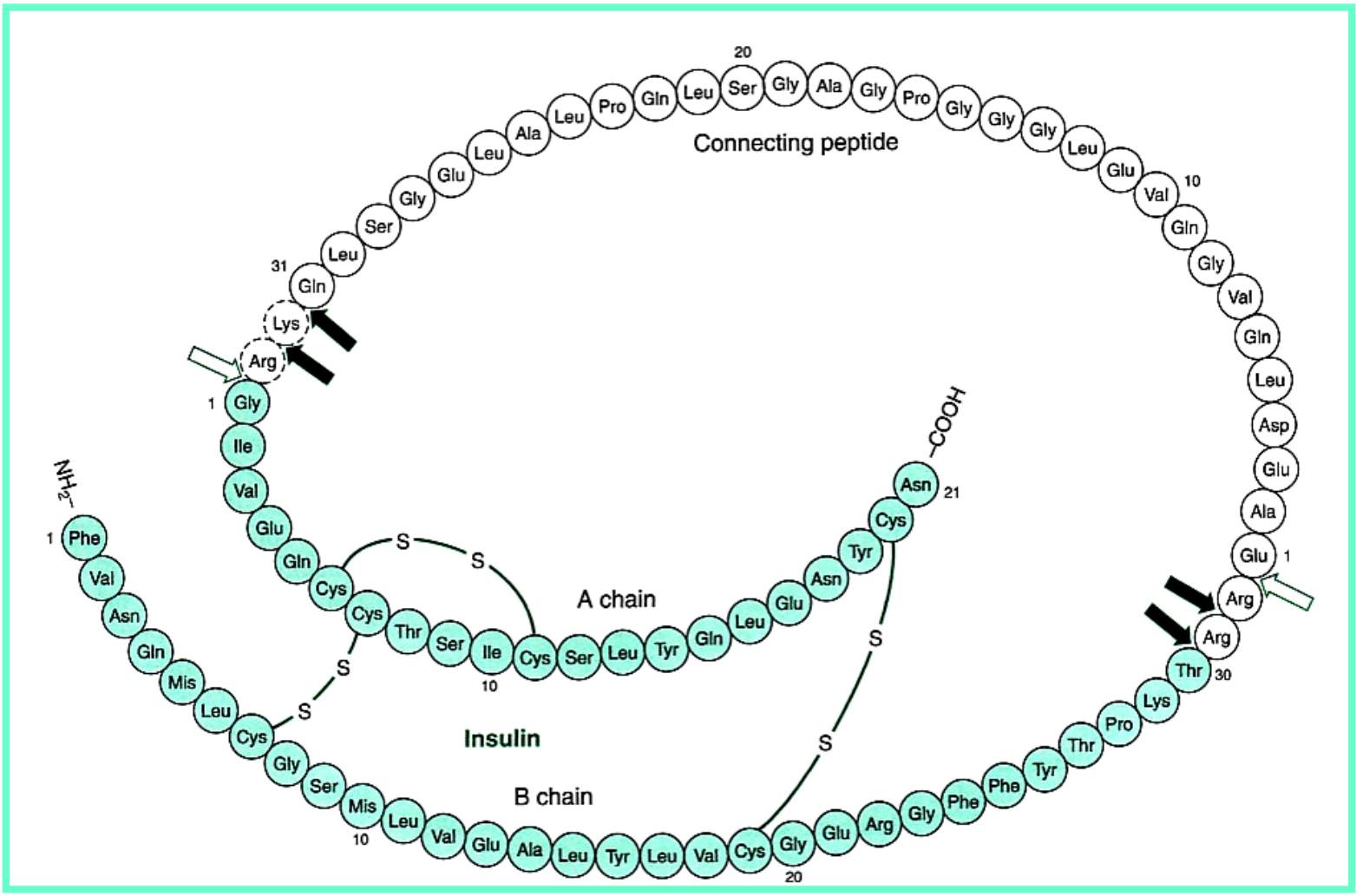
III. PEPTIDE HORMONES

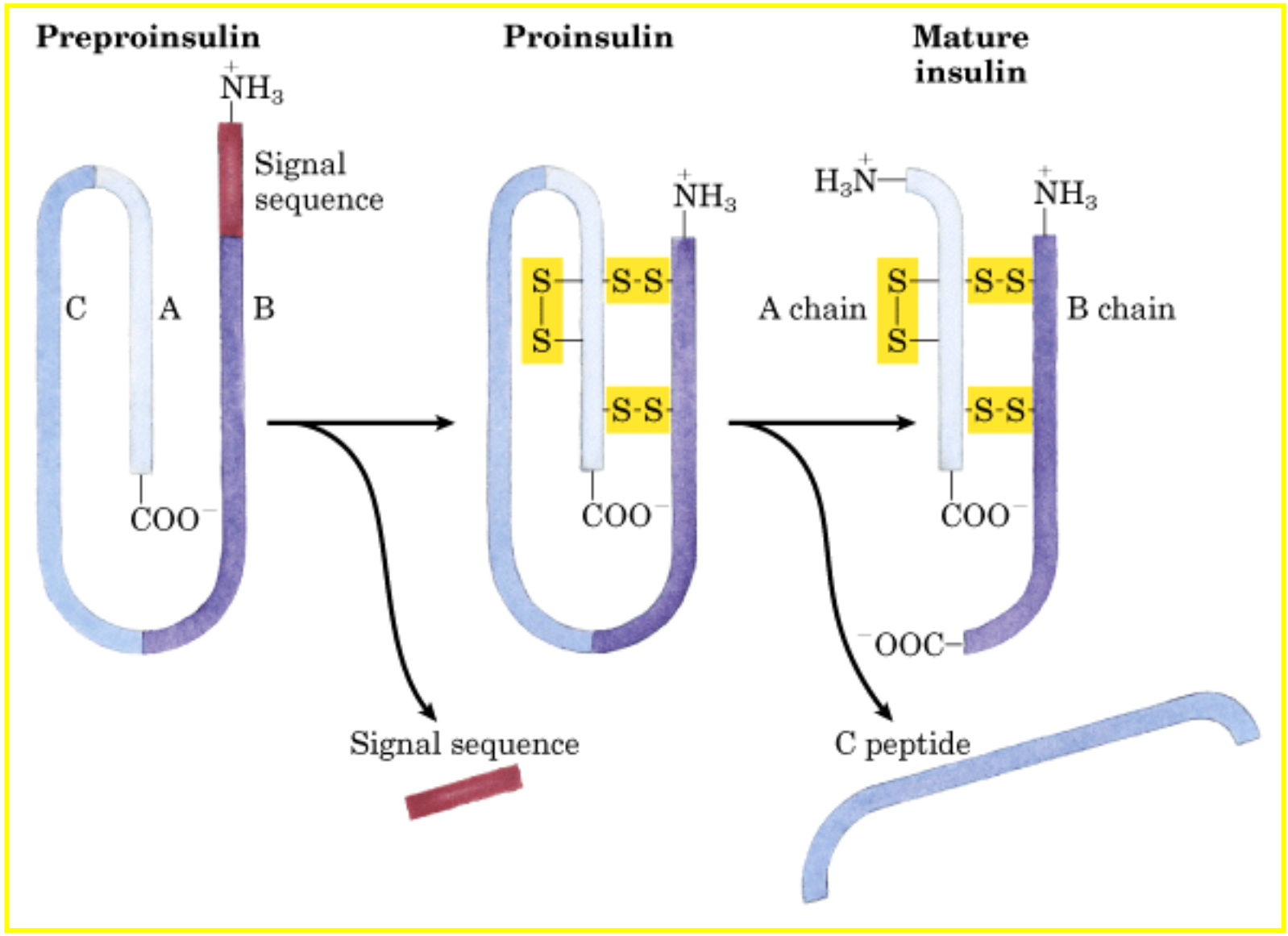
- 3 to 200 or more amino acids
- Synthesized on ribosomes as precursors of active hormones (prohormones)
- Prohormones are stored in vesicles
- Active hormones are liberated by proteolysis in response to certain stimulus (for instance, increased concentration of blood glucose)

Peptide hormone examples: insulin, glucagon, somatostatin, parathormone, all hypothalamic and pituitary hormones.



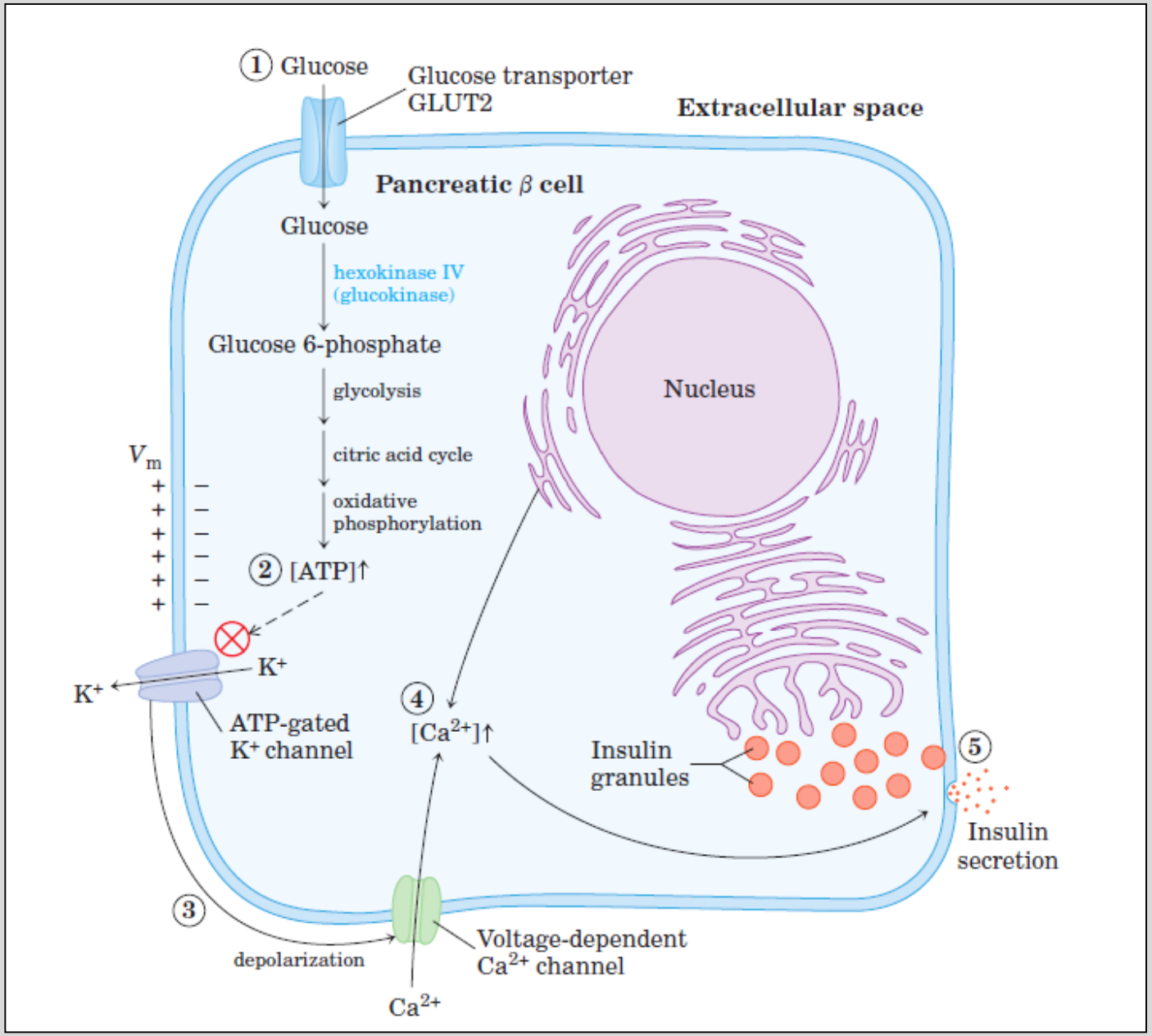
Insulin – aminoacid sequence in mature peptide

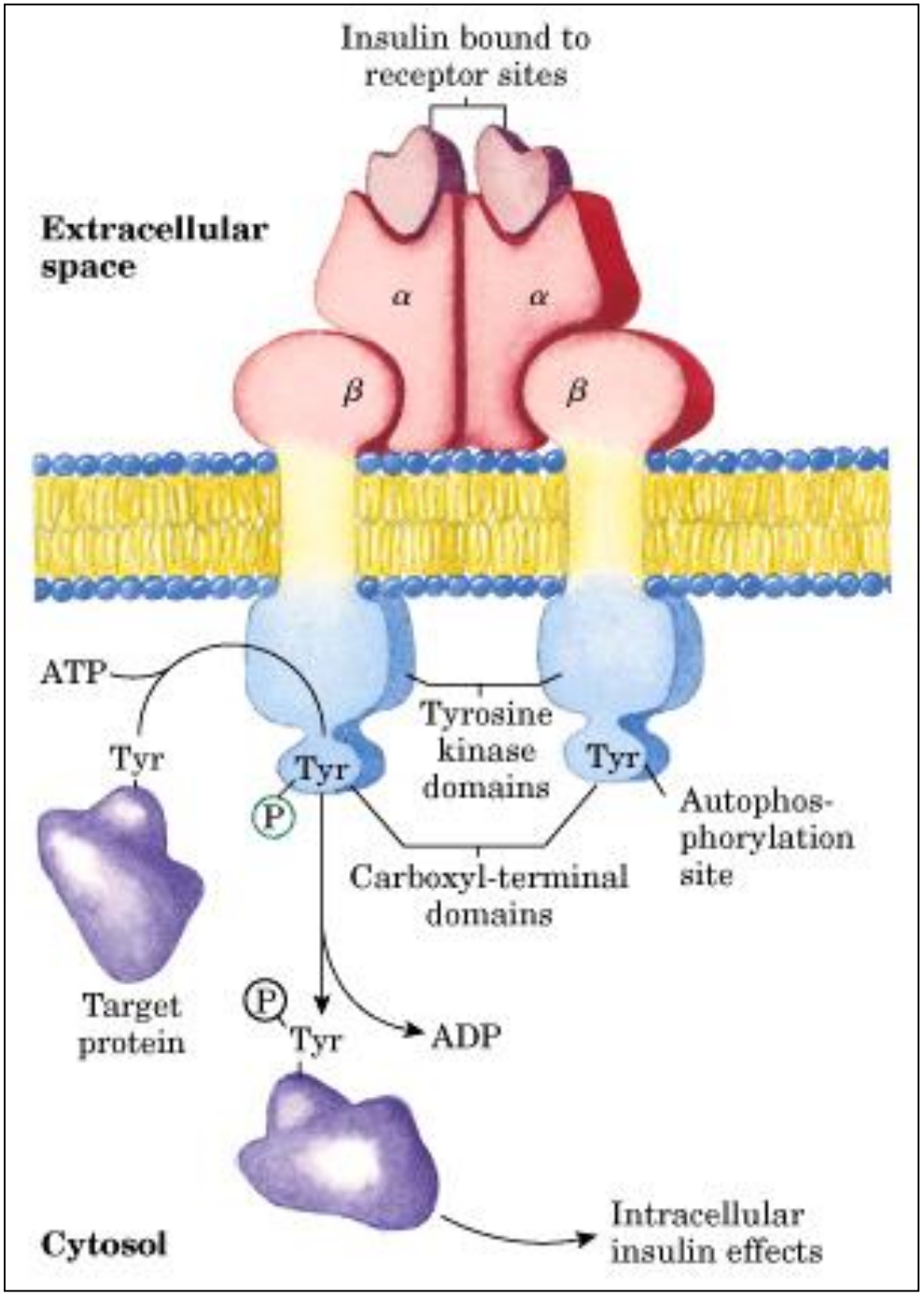




Proteolytic cleavage and formation of active insulin form

Secretion of insulin from β pancreatic cells in response to rise in blood glucose



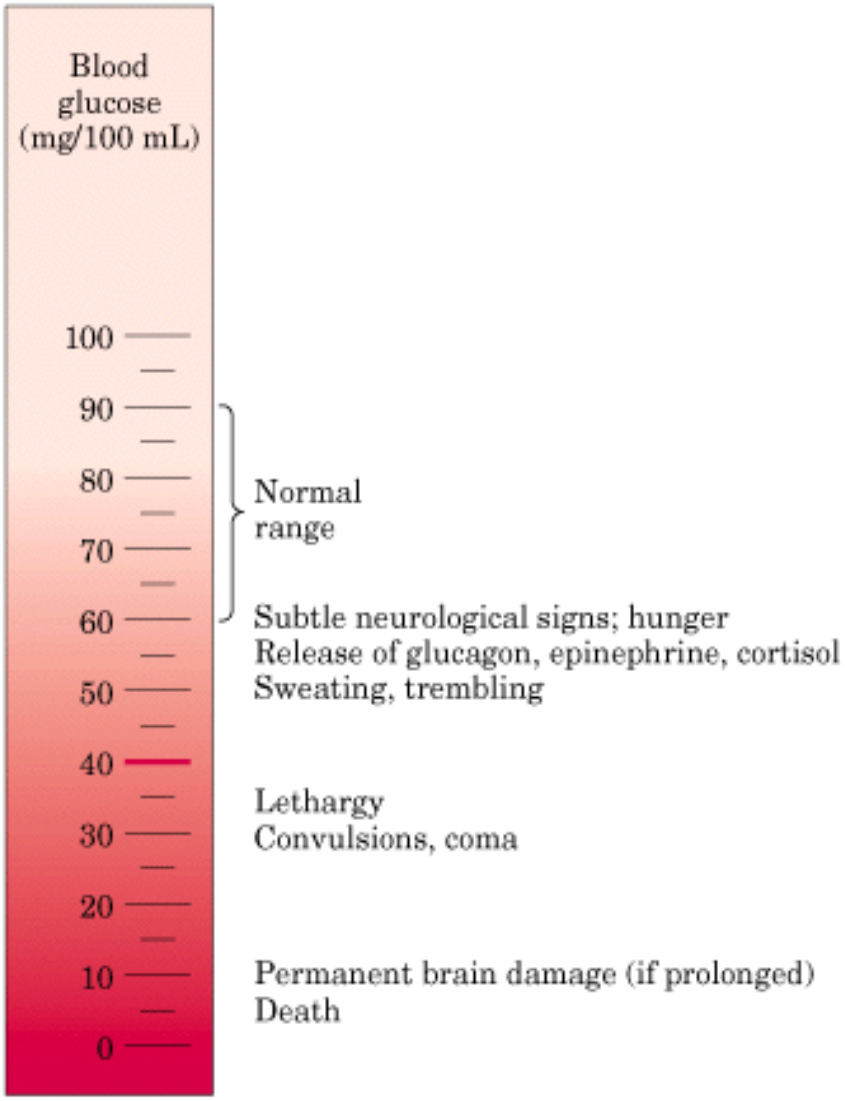


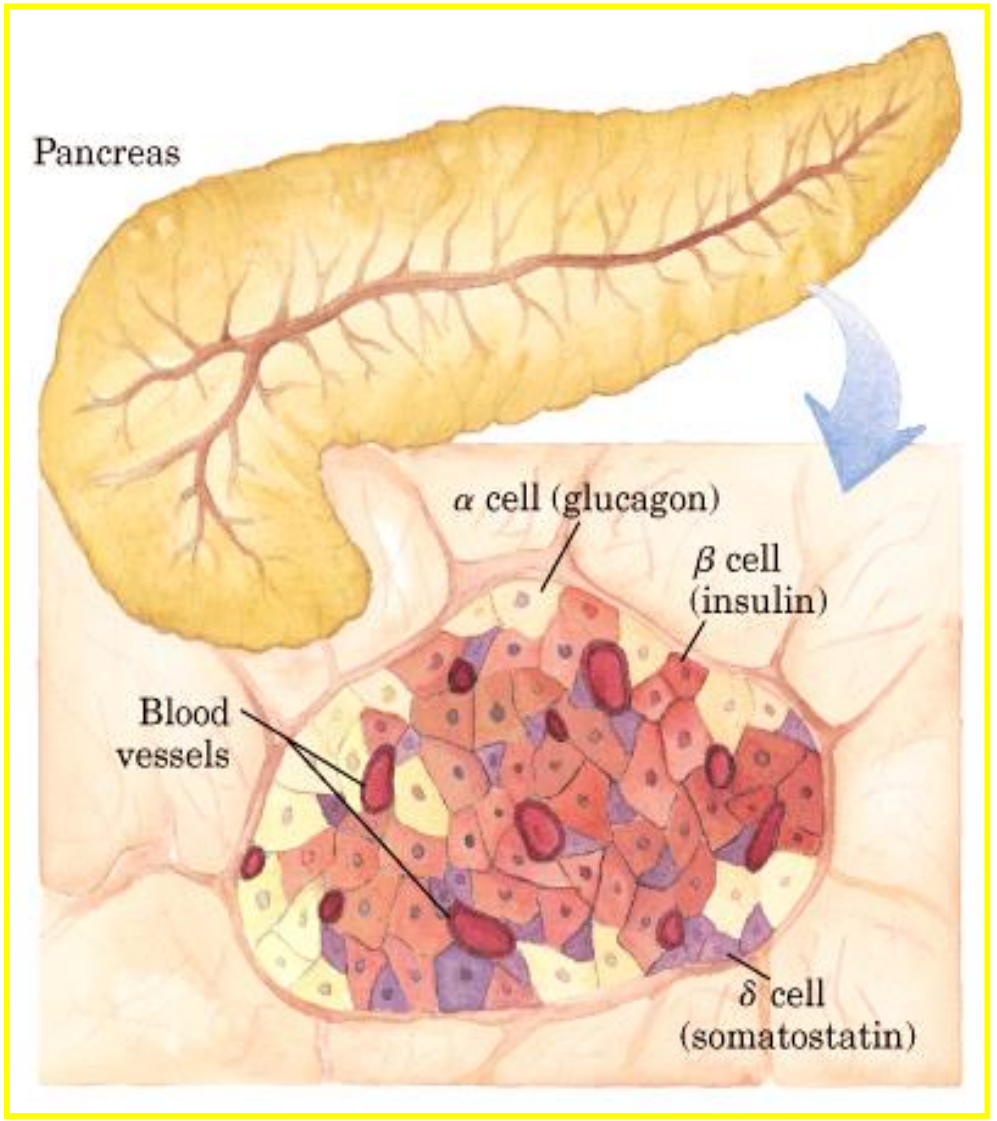
Insulin receptor

-Specific tyrosin kinase activity (receptor enzyme)

Insulin is involved in regulation of both gene expression and metabolism.

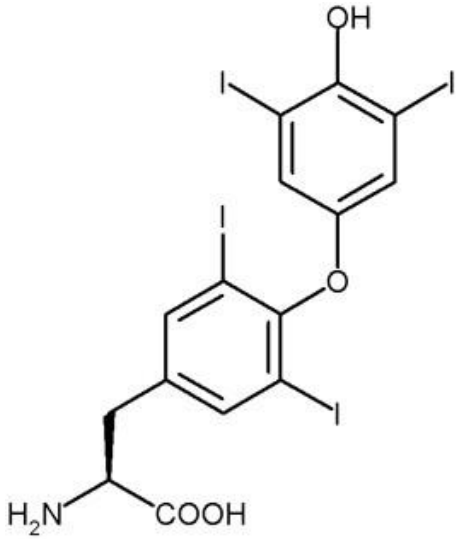
HORMONAL REGULATION OF BLOOD GLUCOSE HOMEOSTASIS





Thyroid hormones

- amino acid tyrosine is required for thyroid hormones synthesis
- tyrosyl residues are iodinated in storage form of hormone, a large size protein named thyroglobulin
- thyroglobulin is cleaved to active forms of hormones, thyroxine and triiodothyronine
- although thyroid hormones are proteins, due to their more hydrophobic properties than other protein/peptide hormones, their mechanism of action is similar to steroid hormones
- thyroid hormones show genomic effects, upon binding to specific nuclear receptors.



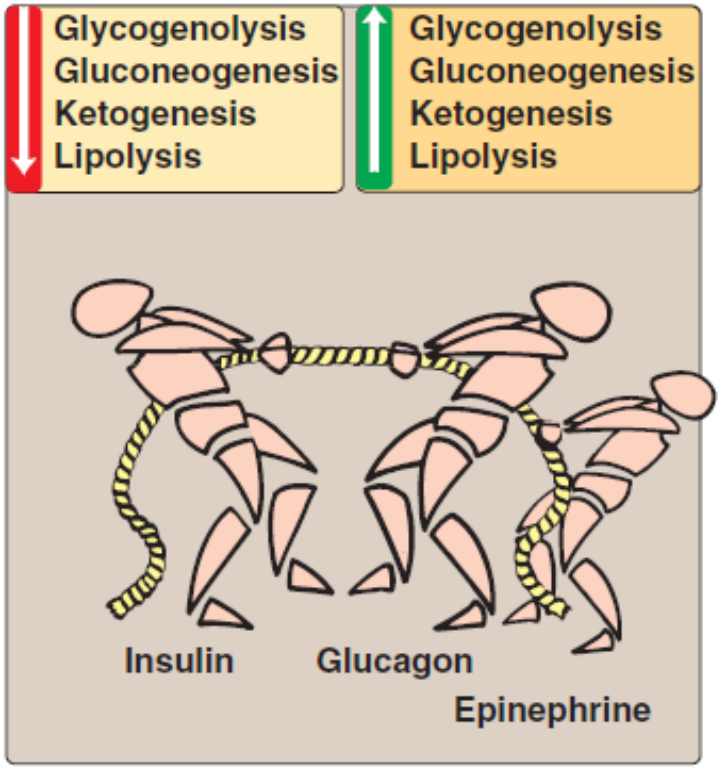
Thyroglobulin–Tyr

↓

Thyroglobulin–Tyr–I
(iodinated Tyr residues)

↓ proteolysis

Thyroxine (T_4)
and
triiodothyronine (T_3)



Several hormones are involved in regulation of energy metabolism:

METABOLIC HORMONES

- **insulin, glucagon, adrenalin**
- **steroids/glucocorticoids, growth hormone, thyroid hormones**

Insulin metabolic effects

- **Glucose enters the cells and is stored in the form of glycogen or is used for triacylglycerol synthesis**
- **Stimulation of protein synthesis (inhibition of protein degradation)**

TABLE 23-3 Effects of Insulin on Blood Glucose: Uptake of Glucose by Cells and Storage as Triacylglycerols and Glycogen

Metabolic effect	*Target enzyme*
↑ Glucose uptake (muscle, adipose)	↑ Glucose transporter (GLUT4)
↑ Glucose uptake (liver)	↑ Glucokinase (increased expression)
↑ Glycogen synthesis (liver, muscle)	↑ Glycogen synthase
↓ Glycogen breakdown (liver, muscle)	↓ Glycogen phosphorylase
↑ Glycolysis, acetyl-CoA production (liver, muscle)	↑ PFK-1 (by ↑ PFK-2)
	↑ Pyruvate dehydrogenase complex
↑ Fatty acid synthesis (liver)	↑ Acetyl-CoA carboxylase
↑ Triacylglycerol synthesis (adipose tissue)	↑ Lipoprotein lipase

Glucagon metabolic effects

Main target tissue for glucagon – liver and adipose tissue!

TABLE 23–4 Effects of Glucagon on Blood Glucose: Production and Release of Glucose by the Liver

Metabolic effect	*Effect on glucose metabolism*	*Target enzyme*
↑ Glycogen breakdown (liver)	Glycogen ⟶ glucose	↑ Glycogen phosphorylase
↓ Glycogen synthesis (liver)	Less glucose stored as glycogen	↓ Glycogen synthase
↓ Glycolysis (liver)	Less glucose used as fuel in liver	↓ PFK-1
↑ Gluconeogenesis (liver)	Amino acids, Glycerol, Oxaloacetate ⟶ glucose	↑ FBPase-2
		↓ Pyruvate kinase
		↑ PEP carboxykinase
↑ Fatty acid mobilization (adipose tissue)	Less glucose used as fuel by liver, muscle	↑ Triacylglycerol lipase
		Perilipin phosphorylation

Metabolic effects of adrenaline

Similar to glucagon effects, but there are additional actions in muscular and other tissues expressing adrenaline receptors!

table 23–2

Physiological and Metabolic Effects of Epinephrine: Preparation for Action

Physiological	
↑ Heart rate	Increased delivery of O_2 to tissues (muscle)
↑ Blood pressure	
↑ Dilation of respiratory passages	
Metabolic	
↑ Glycogen breakdown (muscle, liver)	Increased production of glucose for fuel
↓ Glycogen synthesis (muscle, liver)	
↑ Gluconeogenesis (liver)	
↑ Glycolysis (muscle)	Increased ATP production in muscle
↑ Fatty acid mobilization (adipose tissue)	Increased availability of fatty acids as fuel
↑ Glucagon secretion	Reinforce metabolic effects of epinephrine
↓ Insulin secretion	

Glucocorticoids have important role in regulation of carbohydrate metabolism

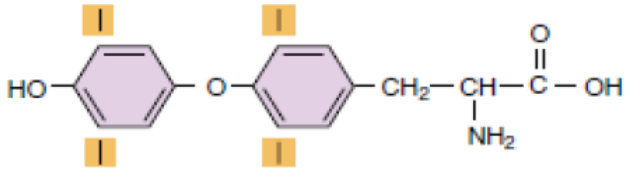
-Stimulation of gluconeogenesis (induced synthesis of phosphoenolpyruvate carboxykinase)

Other effects

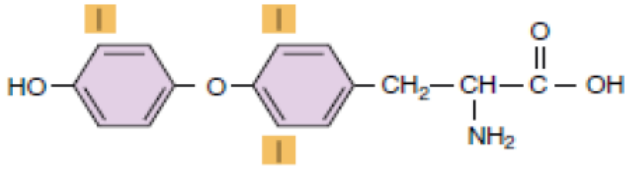
-Catabolic action in protein metabolism

-Mobilisation of amino acids and fatty acids for gluconeogenesis

-Stimulation of urea cycle



3,5,3'-tetraiodothyronine, thyroxine, T_4



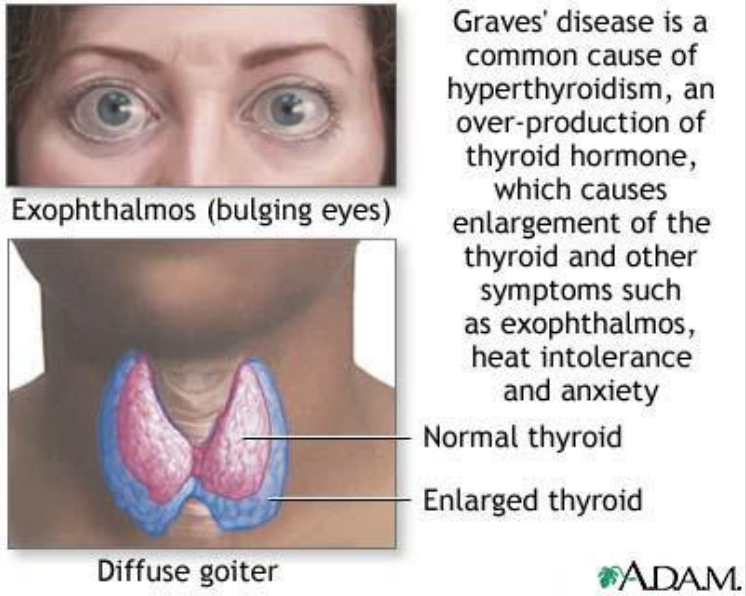
3,5,3'-triiodothyronine , T_3 (more active hormone form)

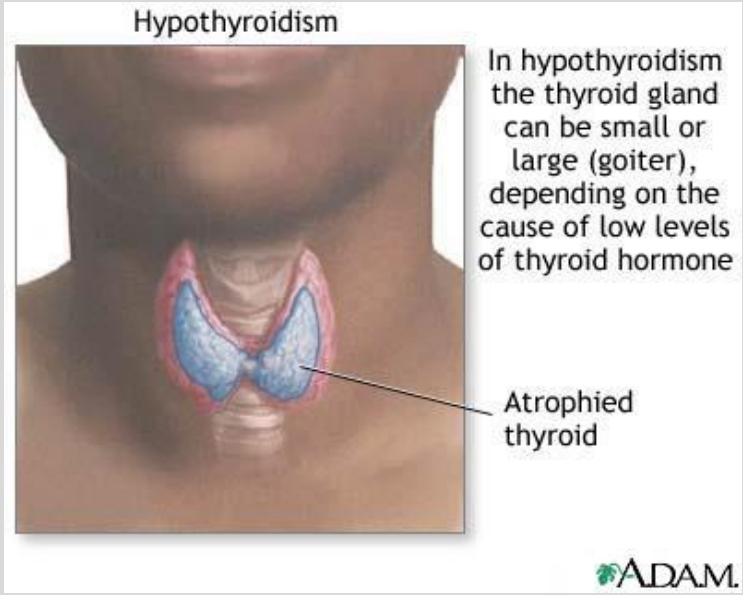
Actions of thyroid hormones

-RNA and protein synthesis (development!)

-oxygen consumption and heat production

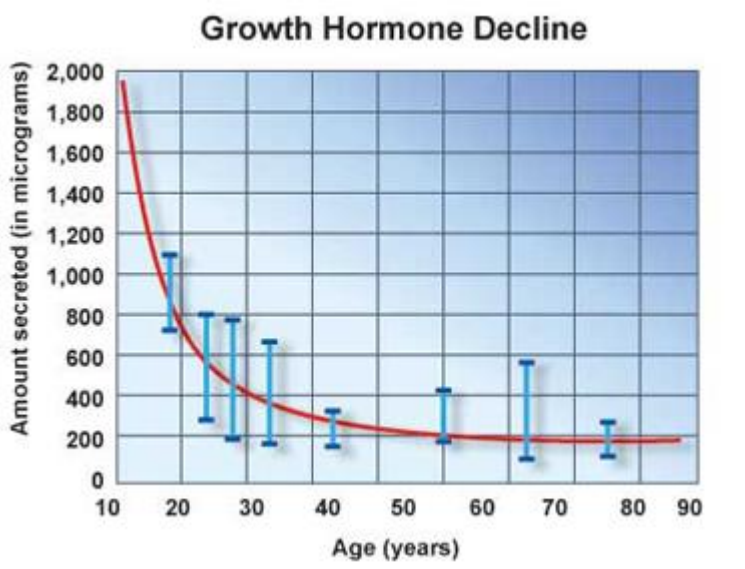
Thyroxine acts *via* nuclear receptors!

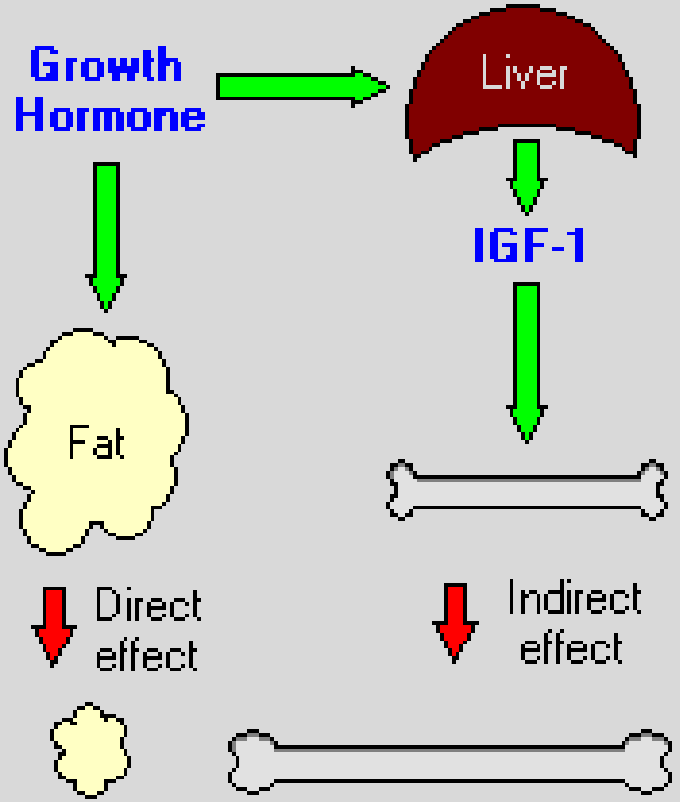




Growth hormone actions

-stimulates protein synthesis
-stimulates lipolysis
- "spares" amino acids and carbohydrates





REMEMBER:

- **PRINCIPLE OF SYNTHESIS – for selected groups of hormones**

  - **steroid hormones** are derived from cholesterol in adrenal gland, and sex gonads
  - **peptide hormones** insulin and glucagon are synthesized in pancreas; synthesis of final peptide products depends on the expression of specific genes, transcription, translation, and posttranslational modifications
  - **catecholamines** are synthesized in the adrenal medulla and nervous system, from amino acid precursor tyrosine
  - **thyroid hormones** are classified as protein hormones, require tyrosine as the amino acid precursor and adequate iodination of tyrosyl residues in the storage hormone form thyroglobuline

- **MECHANISMS OF HORMONE ACTION DEPENDING ON THE CHEMICAL STRUCTURE OF THE HORMONE**

  - **lypophilic structures** (steroid hormones) pass through membrane lipid bilayers of target cells, act upon binding to intracellular and nuclear receptors, and display genomic effects
  - **hydrophilic structures** (insulin, glucagon, catecholamines) bind to receptors at the surface of target cells, activate intracellular signaling pathway using different second messengers, and regulate the activity of target enzymes; glucagon utilizes cAMP, catecholamines use cAMP, calcium ions, and phospholipid-derived compounds, as second messengers; insulin binds to specific receptor-enzymes and activates tyrosine kinase
  - note that *thyroid hormones* are *exception* of that rule, as they are peptide structures but acting intracellularly on nuclear receptors and exerting genomic effects

- **HORMONES AS REGULATORS OF METABOLISM**

  Remember specific actions of glucagon, catecholamines and insulin in regulation of major energy metabolism pathways: glycolysis, gluconeogenesis, glycogenesis, glycogenolysis, fatty acid and cholesterol metabolism!

REVIEW QUESTIONS

1. Explain briefly the main difference in mechanism of action of peptide vs steroid hormones?
2. Represent by structural formulas and name the compounds which act as the precursors for first biosynthesis reaction of:
    a. Adrenaline
    b. Cortisol
3. Explain briefly the main difference in mechanism of action of peptide vs steroid hormones?
4. Name the target enzymes, target tissues and final metabolic effects of glucagon in fatty acid and cholesterol metabolism.