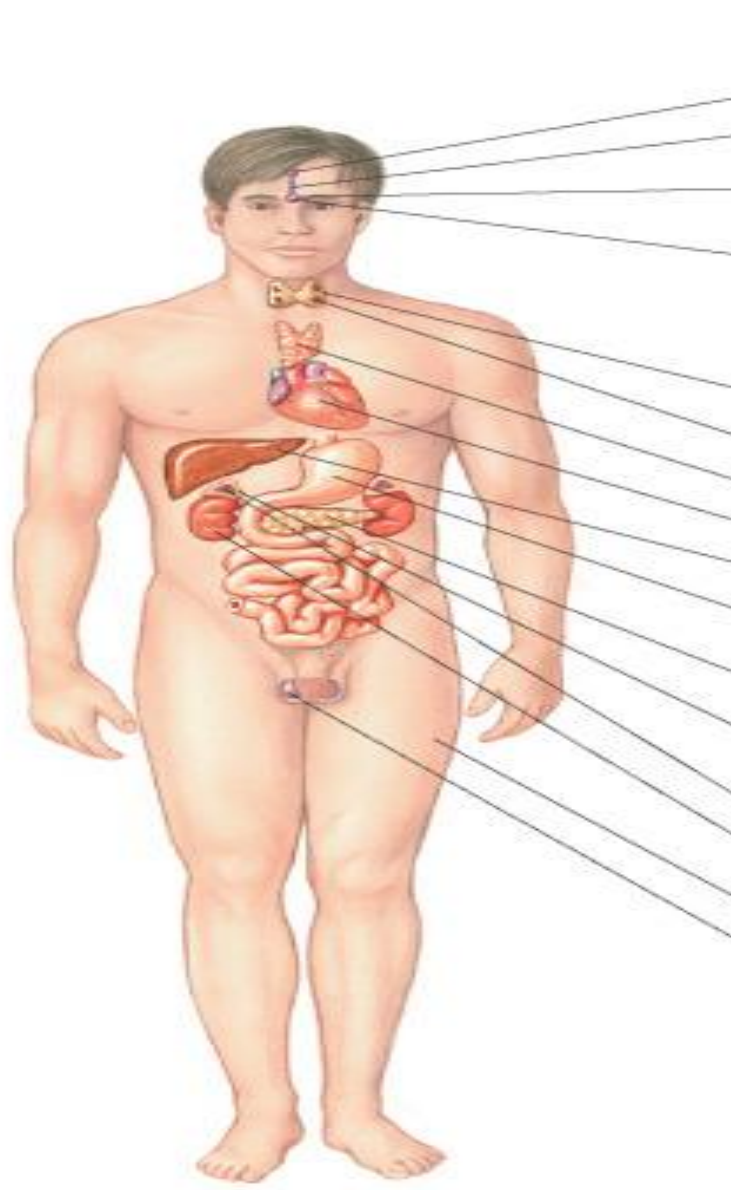


ENDOCRINE SYSTEM

Dr Safa Abdul Ghani

Summary of the Endocrine System



Location	Gland or cell?	Chemical class
Pineal gland	Gland	Amine
Hypothalamus	Clusters of neurons	Peptides
Posterior pituitary	Extensions of hypothalamic neurons	Peptides
Anterior pituitary	Gland	Peptides
Thyroid	Gland	Iodinated amines
Parathyroid	Gland	Peptide
Thymus	Gland	Peptide
Heart	Cells	Peptides
Liver	Cells	Peptides
Stomach and small intestine	Cells	Peptides
Pancreas	Gland	Peptide
Adrenal cortex	Gland	Steroids
Adrenal medulla	Gland	Amines
Kidney	Cells	Peptide
Skin	Cells	Steroid
Testes (male)	Glands	Steroids
Ovaries (female)	Glands	Peptide
Adipose tissue	Cells	Steroids
Placenta (pregnant females only)	Gland	Peptide

Figure 7-2-1: ANATOMY SUMMARY: Hormones

<i>Hormone</i>	<i>Target</i>	<i>Main Effect</i>
Melatonin	Unclear in humans	Circadian rhythms. Other effects uncertain
Trophic hormones (see Fig. 7-13) See posterior pituitary	Anterior pituitary	Release or inhibit pituitary hormones
Oxytocin (OT)	Breast and uterus	Milk ejection; labor and delivery; behavior
Vasopressin (ADH)	Kidney	Water reabsorption
Prolactin (PRL)	Breast	Milk production
Growth hormone (GH, somatotropin)	Many tissues	Growth and metabolism
Corticotropin (ACTH)	Adrenal cortex	Cortisol release
Thyrotropin (TSH)	Thyroid gland	Thyroid hormone synthesis and release
Follicle stimulating hormone (FSH)	Gonads	Egg or sperm production; sex hormone production
Luteinizing hormone (LH)	Gonads	Sex hormone production; egg or sperm production
Triiodothyronine and thyroxine (T_3 , T_4)	Many tissues	Metabolism, growth and development
Calcitonin (CT)	Bone	Plasma calcium levels (minimal effect in humans)
Parathyroid hormone (PTH)	Bone, kidney	Regulate plasma calcium and phosphate levels
Thymosin, thymopoietin	Lymphocytes	Lymphocyte development
Atrial natriuretic peptide (ANP)	Kidneys	Increase sodium excretion
Angiotensinogen	Adrenal cortex, blood vessels, brain	Aldosterone secretion, increase blood pressure
Insulin-like growth factors (IGF)	Many tissues	Growth

Figure 7-2-2: ANATOMY SUMMARY: Hormones

<i>Hormone</i>	<i>Target</i>	<i>Main Effect</i>
Gastrin, cholecystokinin (CCK), secretin, and others	GI tract and pancreas	Assist digestion and absorption of nutrients
Insulin, glucagon, somatostatin (SS), pancreatic polypeptide	Many tissues	Metabolism of glucose and other nutrients
Aldosterone	Kidney	Na ⁺ and K ⁺ homeostasis
Cortisol	Many tissues	Stress response
Androgens	Many tissues	Sex drive in females
Epinephrine, norepinephrine	Many tissues	Fight-or-flight response
Erythropoietin (EPO)	Bone marrow	Red blood cell production
1,25 Dihydroxy-vitamin D ₃ (calciferol)	Intestine	Increase calcium absorption
Vitamin D ₃	Intermediate form of hormone	Precursor of 1,25 dihydroxy -vitamin D ₃
Androgen	Many tissues	Sperm production, secondary sex characteristics
Inhibin	Anterior pituitary	Inhibit FSH secretion
Estrogens and progesterone	Many tissues	Egg production, secondary sex characteristics
Ovarian inhibin	Anterior pituitary	Inhibit FSH secretion
Relaxin (pregnancy)	Uterine muscle	Relaxes muscle
Leptin	Hypothalamus, other tissues	Food intake, metabolism, reproduction
Estrogens and progesterone (P)	Many tissues	Fetal and maternal development
Chorionic somatomammotropin (CS)	Many tissues	Metabolism
Chorionic gonadotropin (CG)	Corpus luteum of ovary	Hormone secretion

Figure 1-2-3: ANATOMY SUMMARY: Hormones

Overview of Cell to Cell Communication:

- Two basic types of physiological signals:
 - I. **Electrical** : changes in a cell s membrane potential
 - II. **Chemical** : molecules secreted by cells into the extracellular Fluid.

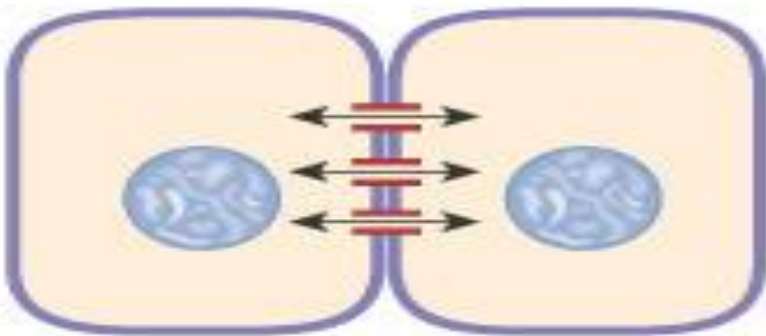
Chemical signals are responsible for most communication within the body.

The cells that receive electrical or chemical signals are called target cells

- Electrical
 - Nervous System: Fast, Specific, Distant Target
 - Gap Junction: Local
- Chemical
 - Endocrine system: Distant, Diffuse Target
 - Autocrine & Paracrine: Local Signaling

□ Direct and local cell-to-cell communication

(a) Gap junctions form direct cytoplasmic connections between adjacent cells.



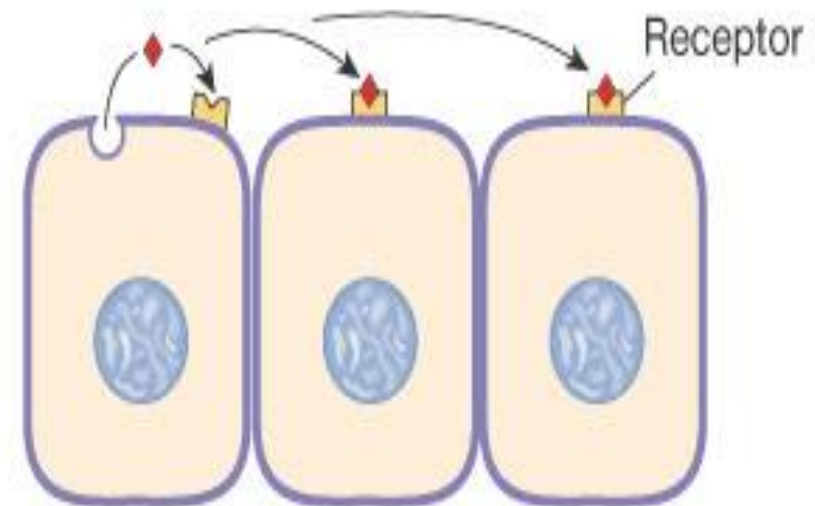
Protein channels

Direct flow to neighbors

- Electrical-ions (charge)

b) Autocrines and Paracrines: Local communication

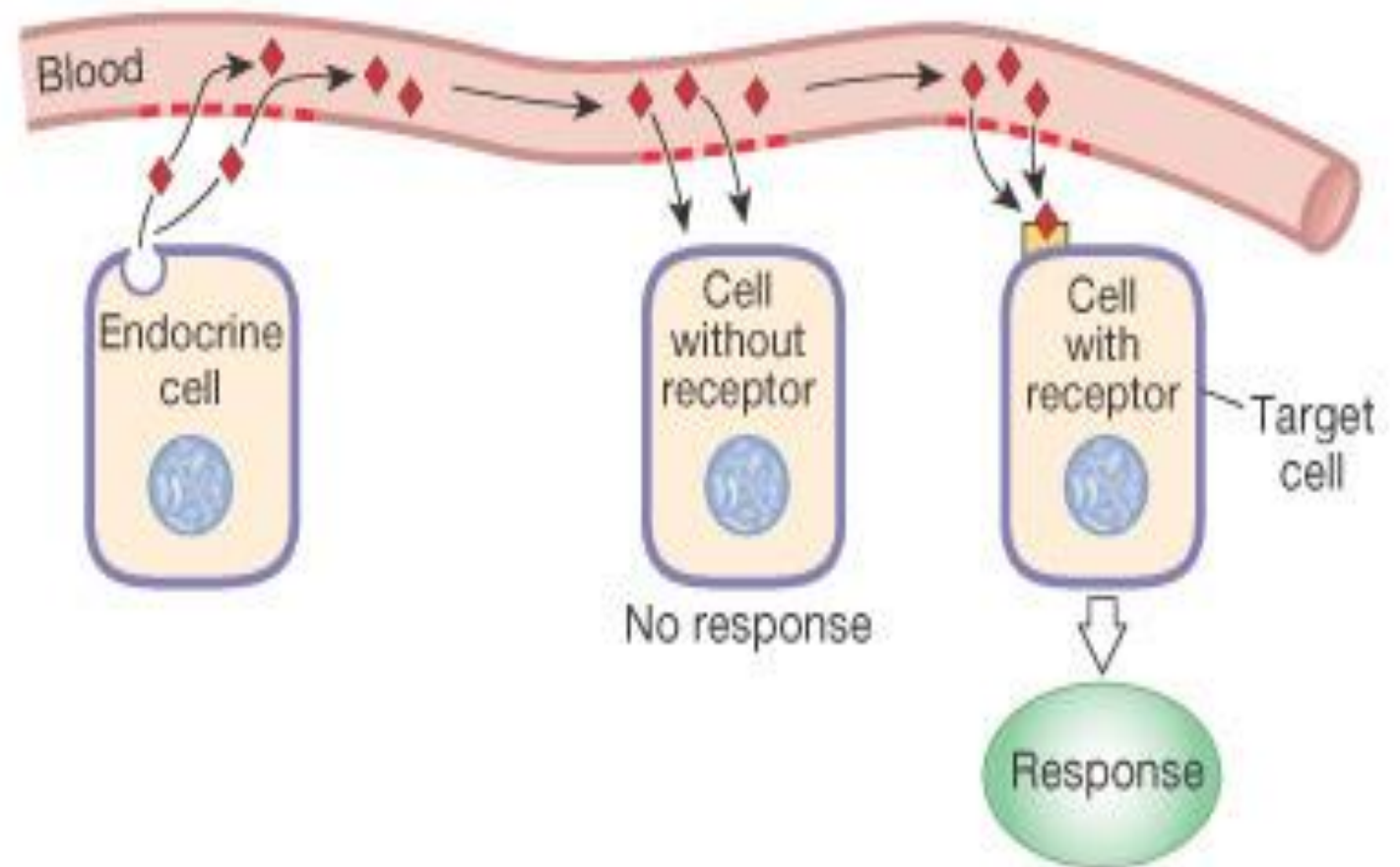
- Autocrines – chemicals that exert effects on the same cells that secrete them
- Paracrines – locally acting chemicals that affect cells other than those that secrete them
- These are not considered hormones since hormones are long-distance chemical signals



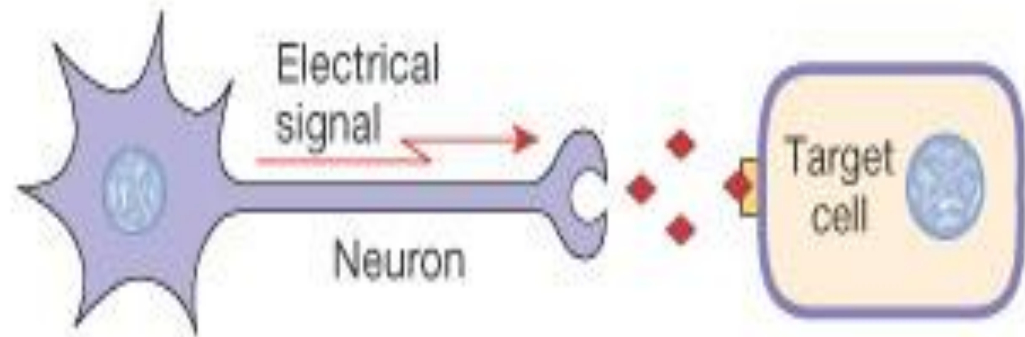
C) HORMONES (Endocrine)

- Signal Chemicals
- Made in **Endocrine** Cells
- Transported via Blood
- Receptors on Target Cells

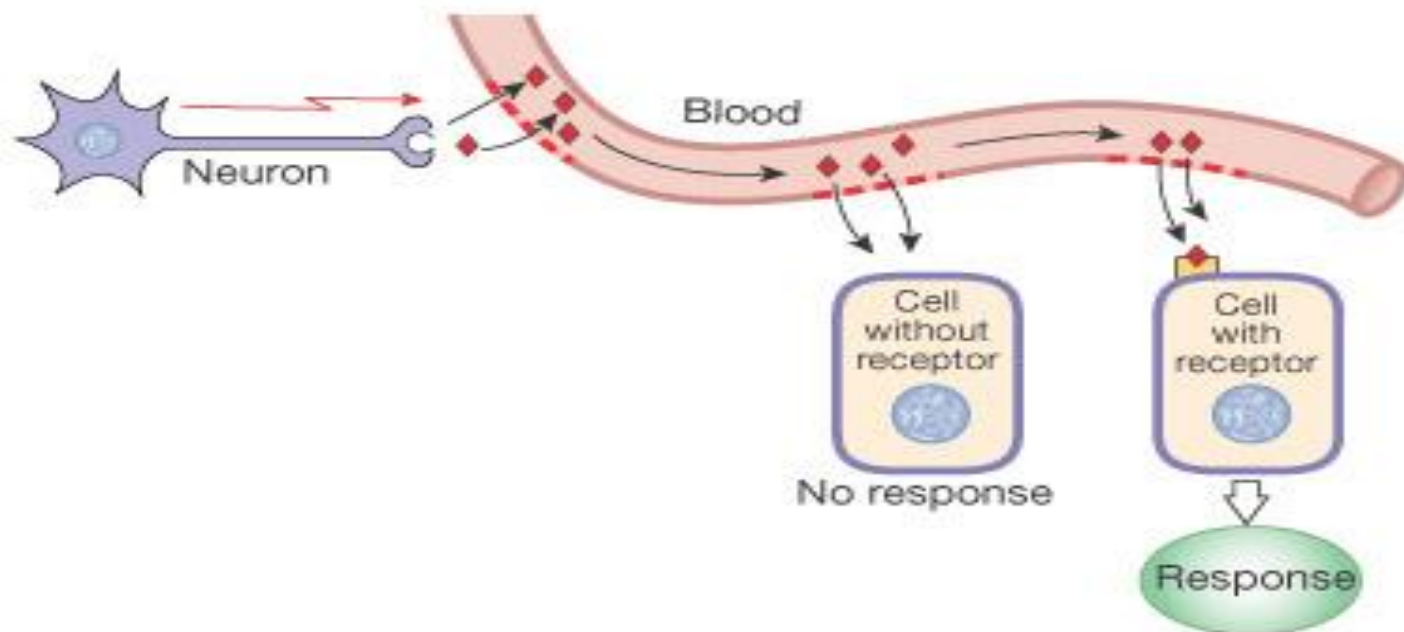
(a) **Hormones** are secreted by endocrine glands or cells into the blood. Only target cells with receptors for the hormone will respond to the signal.

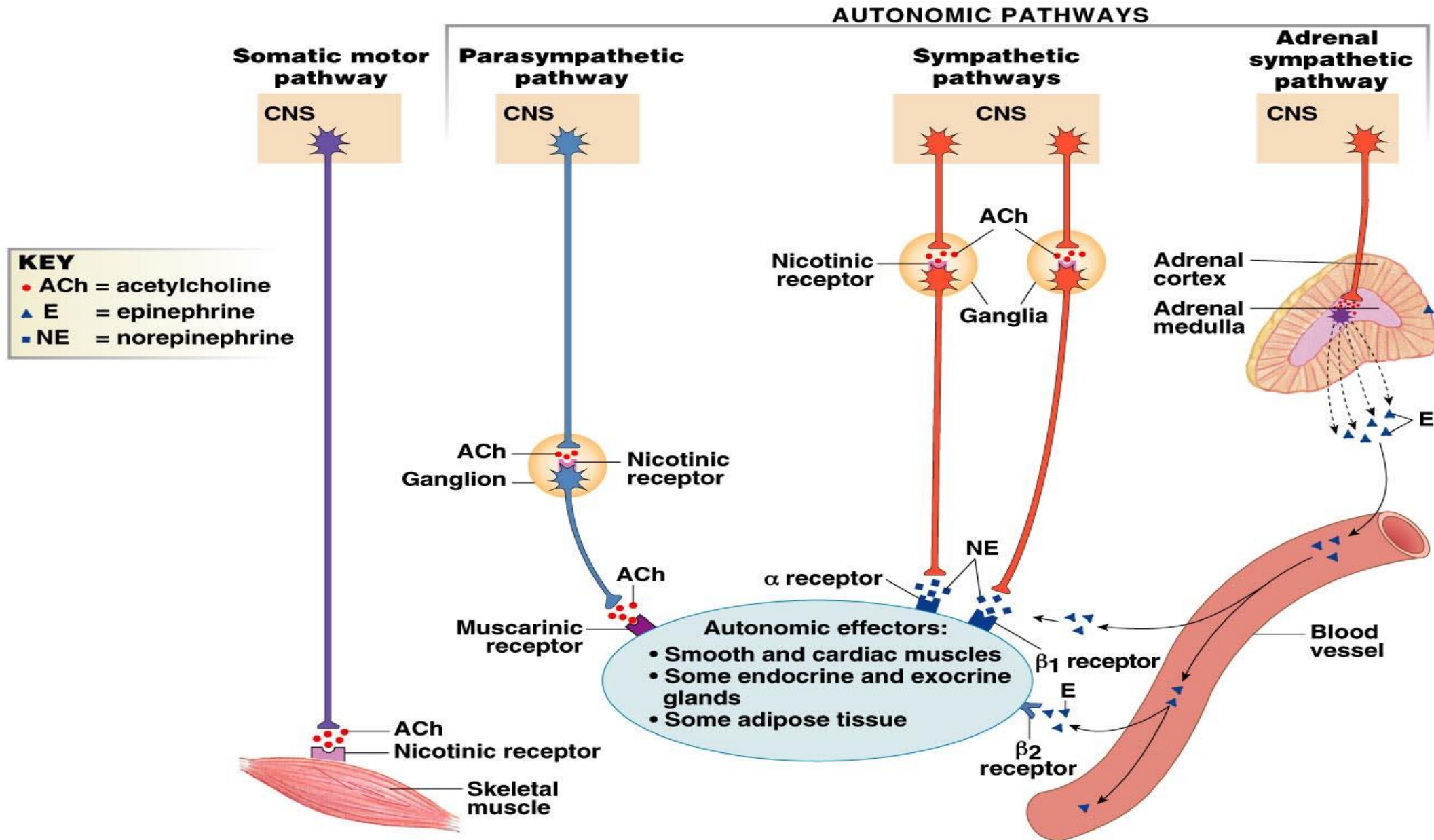


Neurotransmitters are chemicals secreted by neurons that diffuse across a small gap to the target cell. Neurons use electrical signals as well.

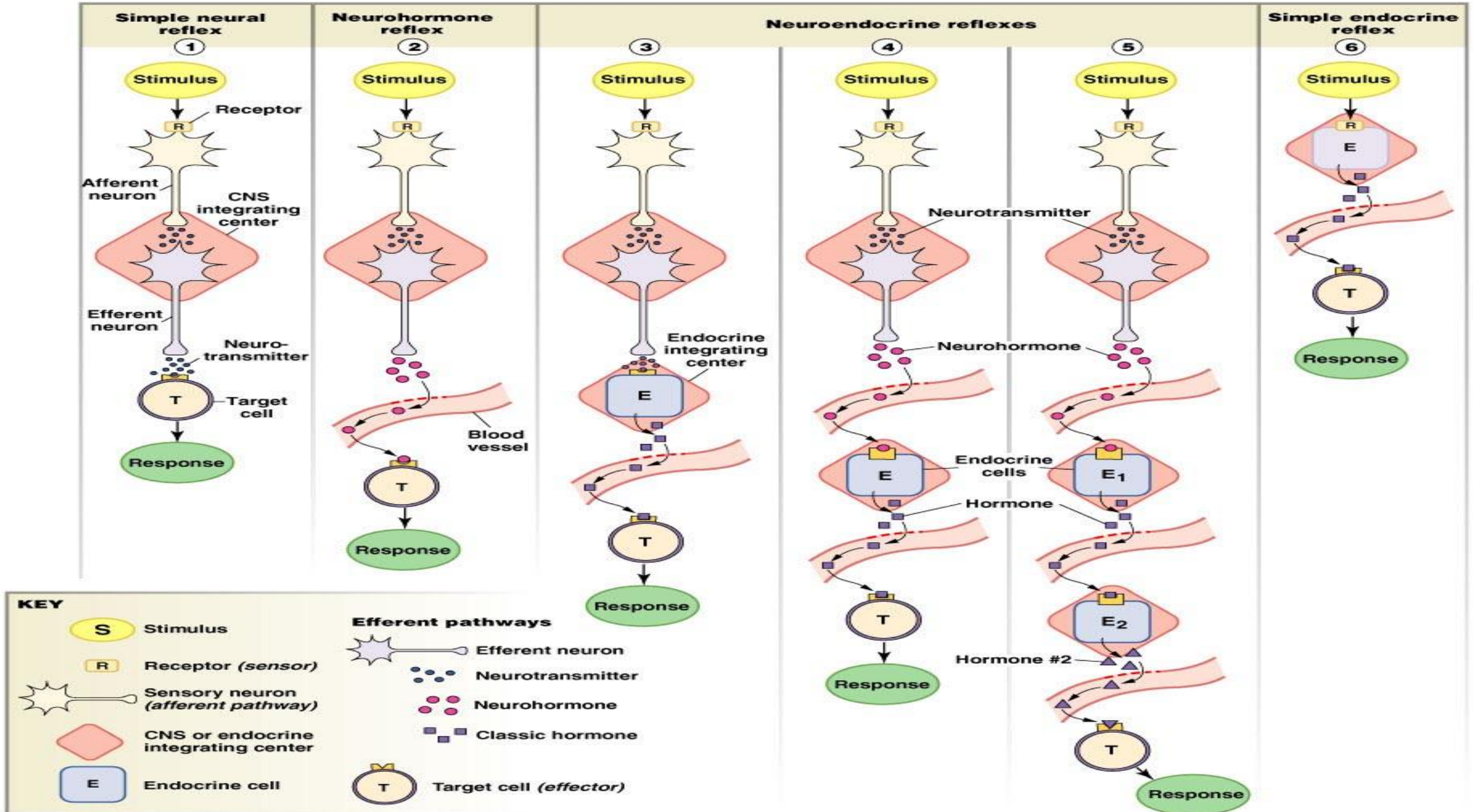


Neurohormones are chemicals released by neurons into the blood for action at distant targets.





Some basic patterns of nervous, endocrine, and neuroendocrine control pathways



Hormones

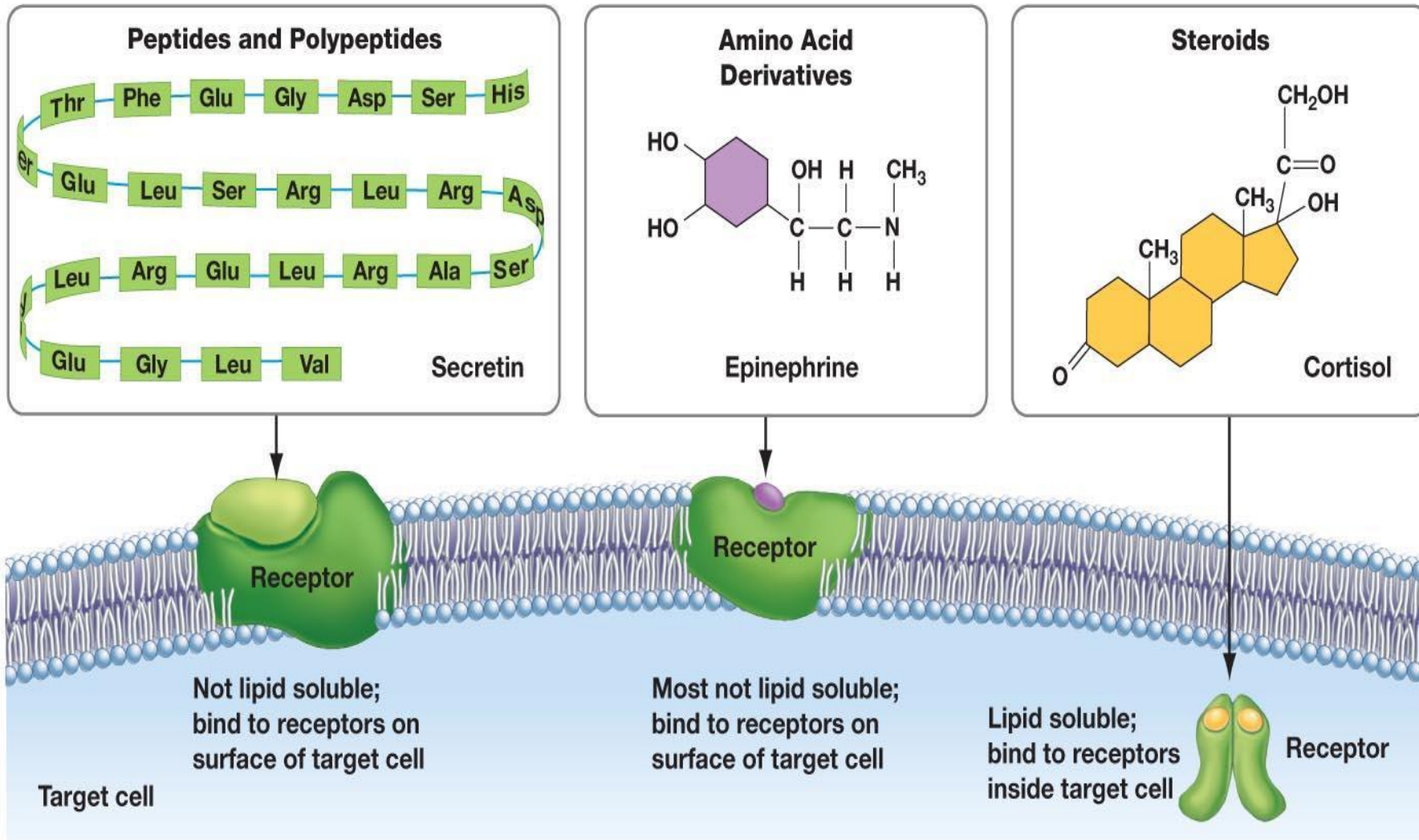
- Hormones – chemical substances secreted by cells into the extracellular fluids
 - Regulate the metabolic function of other cells
 - Have lag times ranging from seconds to hours
 - Tend to have prolonged effects

Types of Hormones:

□ **Proteins/Polypeptides**

□ **Amino acid derivatives** – from *Tyrosine*
(ex. Thyroxine, catecholamine)

□ **Steroids** – gonadal and adrenocortical hormones



Amine Hormone Structures and Functions

- Made of 1-2 amino acids
- Receptors
 - Surface
 - Intracellular
- Small size, OH group
- Benzene ring
- Examples
 - Thyroxin
 - Epinephrine

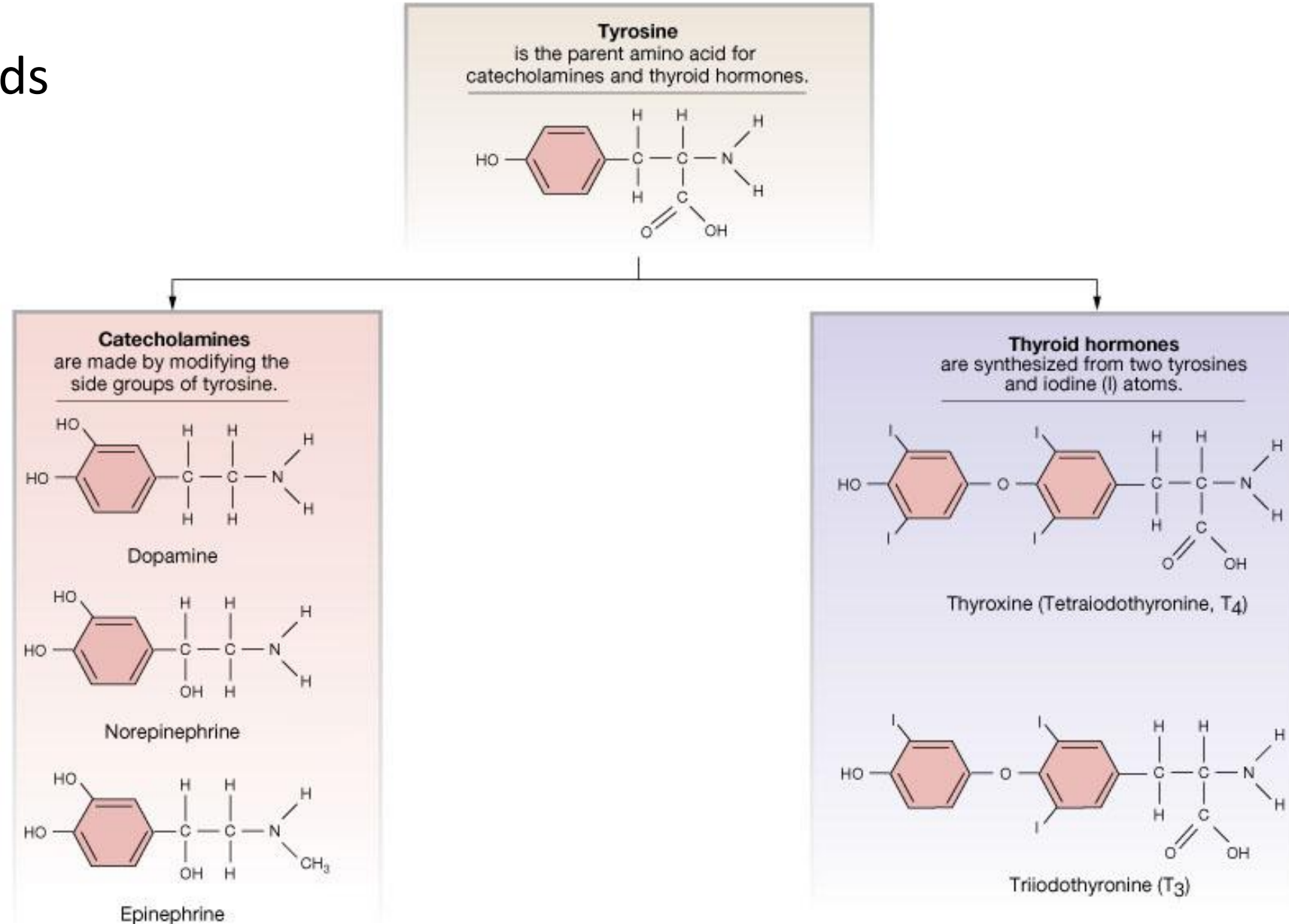


Figure 7-8: Tyrosine-derived amine hormones

Steroid Hormones: Structure and Action

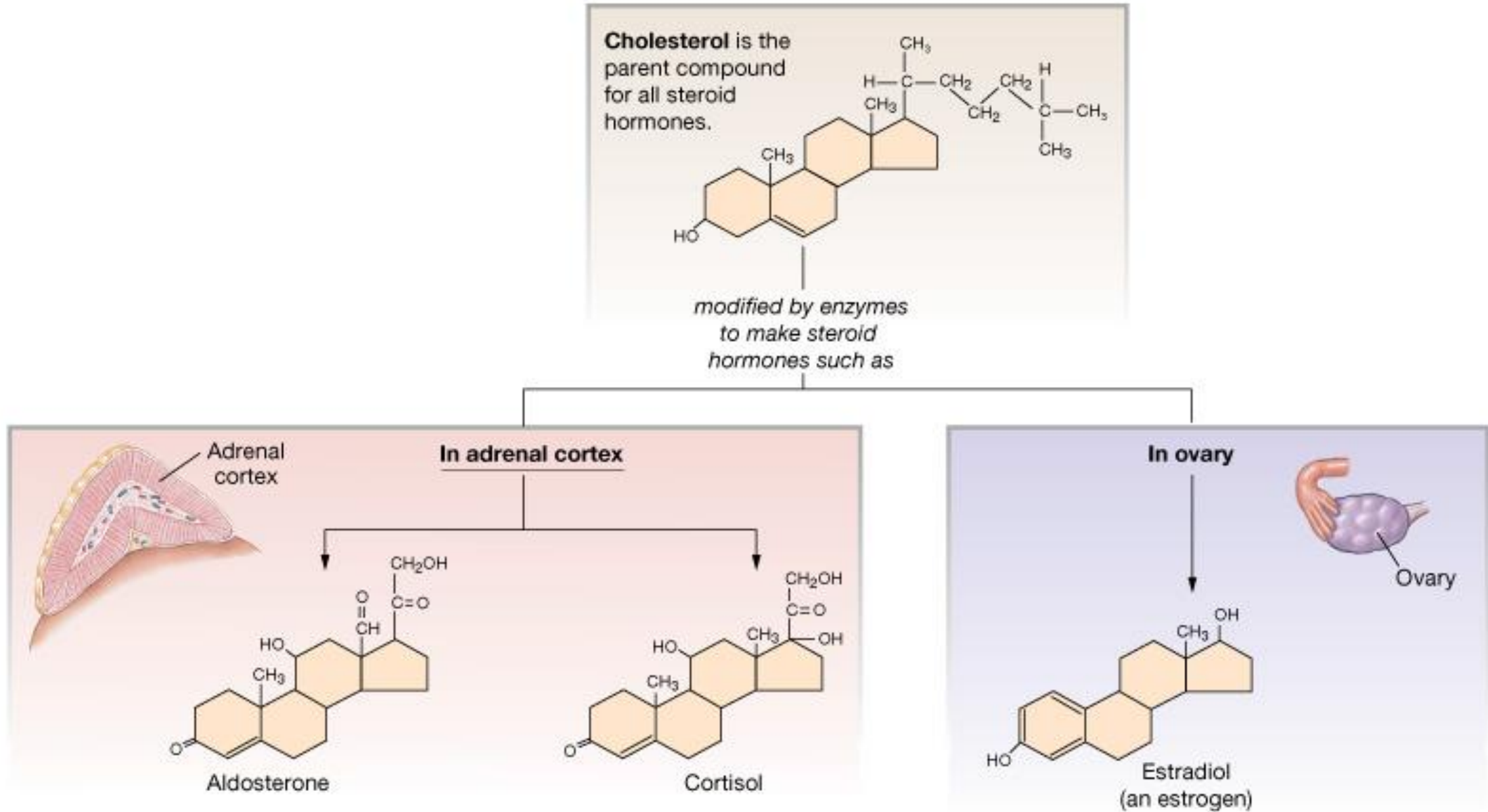
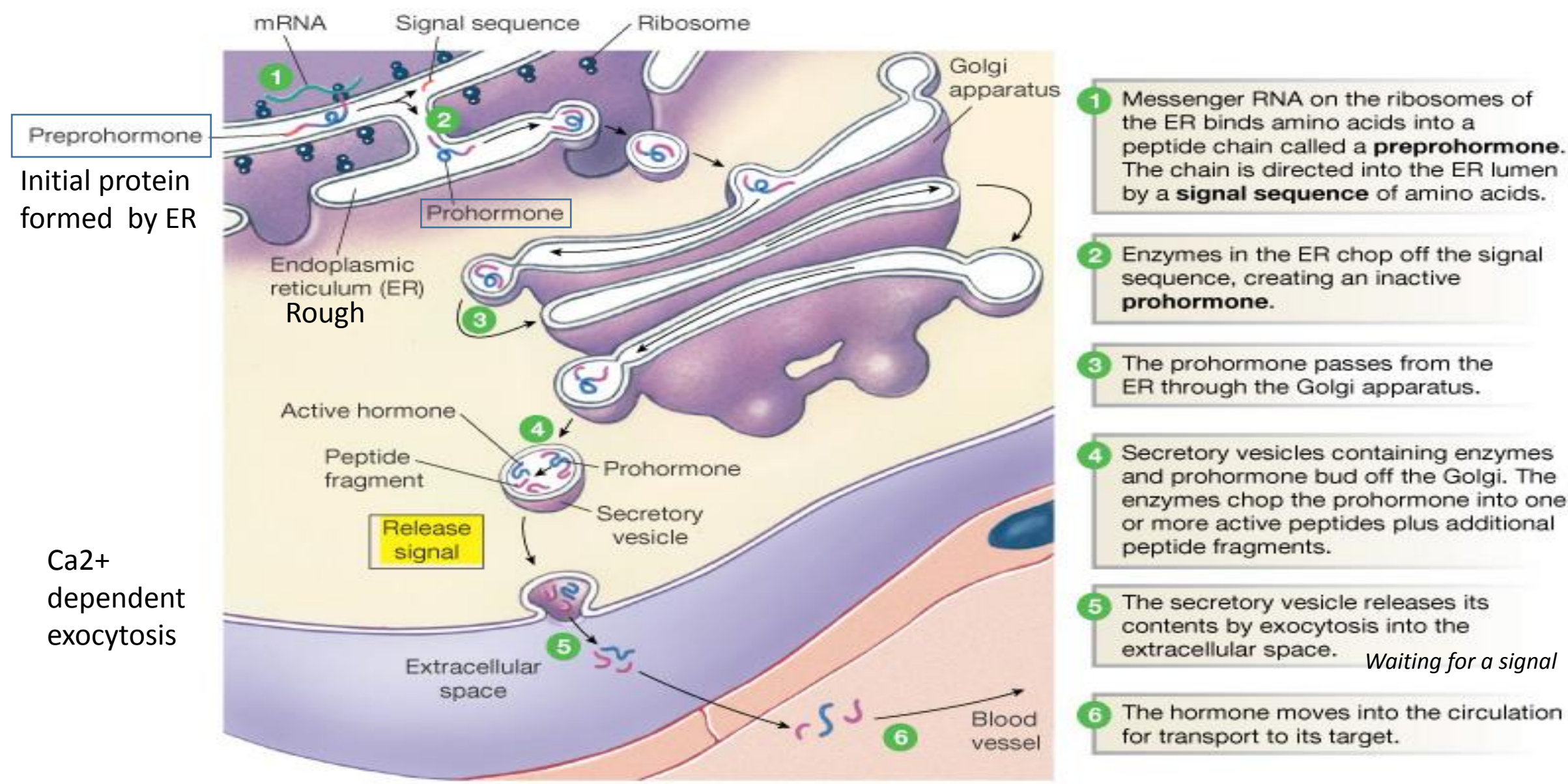


Figure 7-6: **Steroid hormones are derived from cholesterol**

TABLE 7-1**Comparison of Peptide, Steroid, and Amine Hormones**

	PEPTIDE HORMONES	STEROID HORMONES	AMINES	
			CATECHOLAMINES	THYROID HORMONES
Synthesis and storage	Made in advance; stored in secretory vesicles	Synthesized on demand from precursors	Made in advance; stored in secretory vesicles	Made in advance; precursor stored in secretory vesicles
Release from parent cell	Exocytosis	Simple diffusion	Exocytosis	Simple diffusion
Transport in blood	Dissolved in plasma	Bound to carrier proteins	Dissolved in plasma	Bound to carrier proteins
Half-life	Short	Long	Short	Long
Location of receptor	Cell membrane	Cytoplasm or nucleus; some have membrane receptors also	Cell membrane	Nucleus
Response to receptor-ligand binding	Activation of second messenger systems; may activate genes	Activation of genes for transcription and translation; may have nongenomic actions	Activation of second messenger systems	Activation of genes for transcription and translation
General target response	Modification of existing proteins and induction of new protein synthesis	Induction of new protein synthesis	Modification of existing proteins	Induction of new protein synthesis
Examples	Insulin, parathyroid hormone	Estrogen, androgens, cortisol	Epinephrine, norepinephrine	Thyroxine (T ₄)

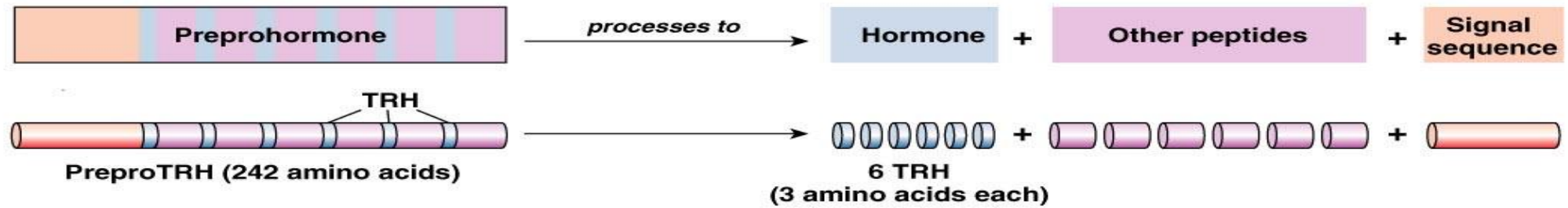
Protein and Polypeptide Hormones: Synthesis and Release



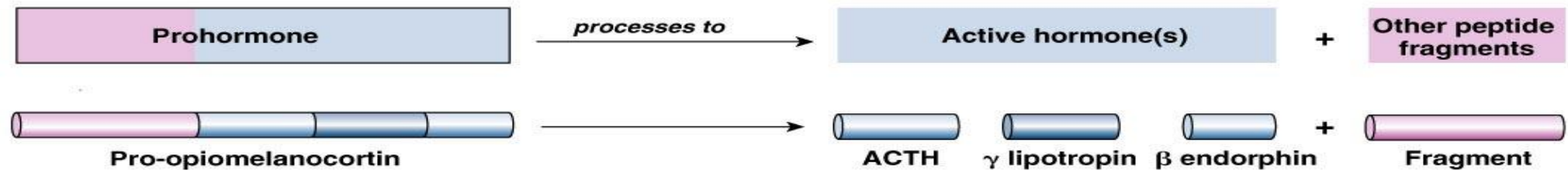
Glandular cells

Figure 7-3: Peptide hormone synthesis, packaging, and release

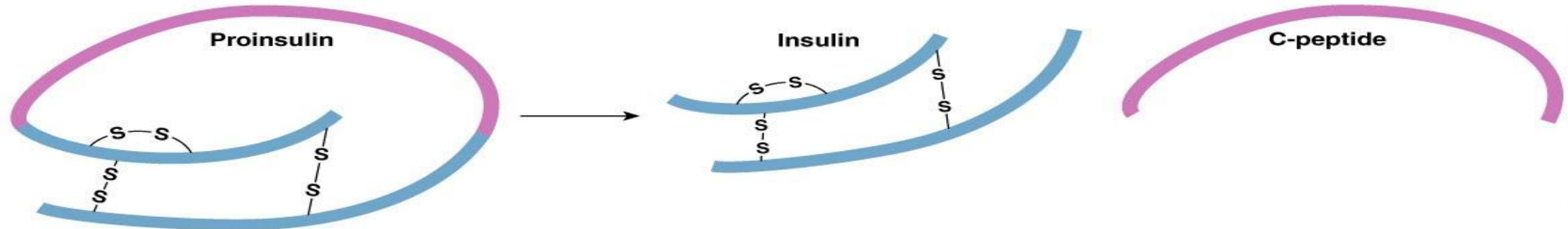
(a) PreproTRH (thyrotropin-releasing hormone) has six copies of the 3-amino acid hormone TRH.



(b) Prohormones (such as pro-opiomelanocortin, the prohormone for ACTH) may contain several peptide sequences with biological activity.



(c) The peptide chain of insulin's prohormone folds back on itself with the help of disulfide (S-S) bonds. The prohormone cleaves to insulin and C-peptide.



Onset of hormone secretion and duration

- Some hormones such as (norepinephrine and epinephrine) are secreted within second after the gland is stimulated--- Full action within few second to minute
- Other hormones(thyroxine or growth hormones) may require months for full effect
- Concentrations: from 1 picogram to few microgram per ml of blood

Target Cell Specificity

- Hormones circulate to all tissues but only activate cells referred to as **target cells**
- Target cells must have specific receptors to which the hormone binds
- These receptors may be intracellular or located on the plasma membrane
- Examples of hormone activity
 - ACTH (adrenocorticotrophic hormone) receptors are only found on certain cells of the adrenal cortex
 - Thyroxin receptors are found on nearly all cells of the body

Receptor locations

Cytosolic or Nuclear

- Lipophilic ligand enters cell
- Often activates gene
- Slower response

Cell Membrane

- Lipophobic Ligand can't enter cell
- Outer Surface Receptor
- Fast Response

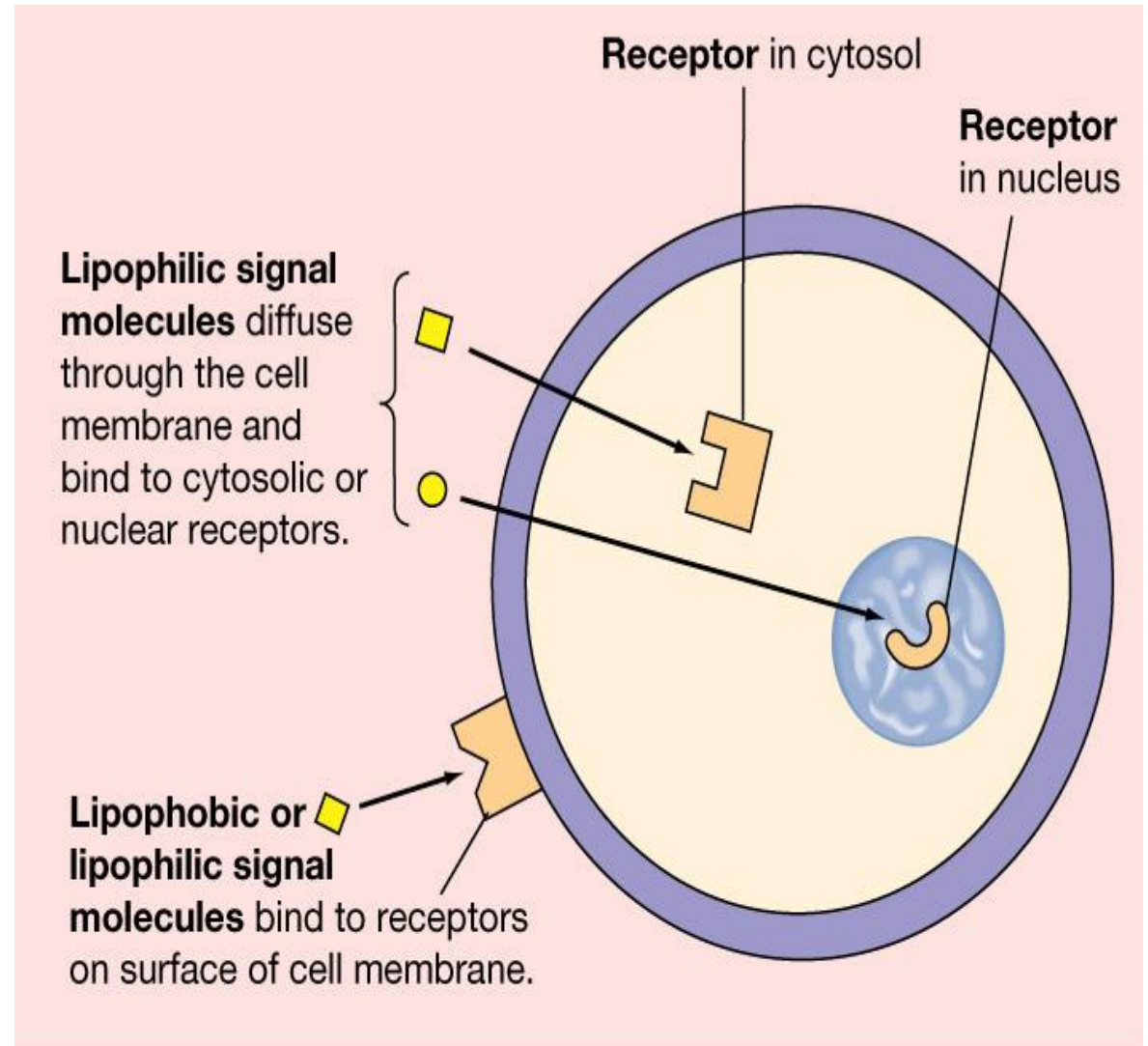
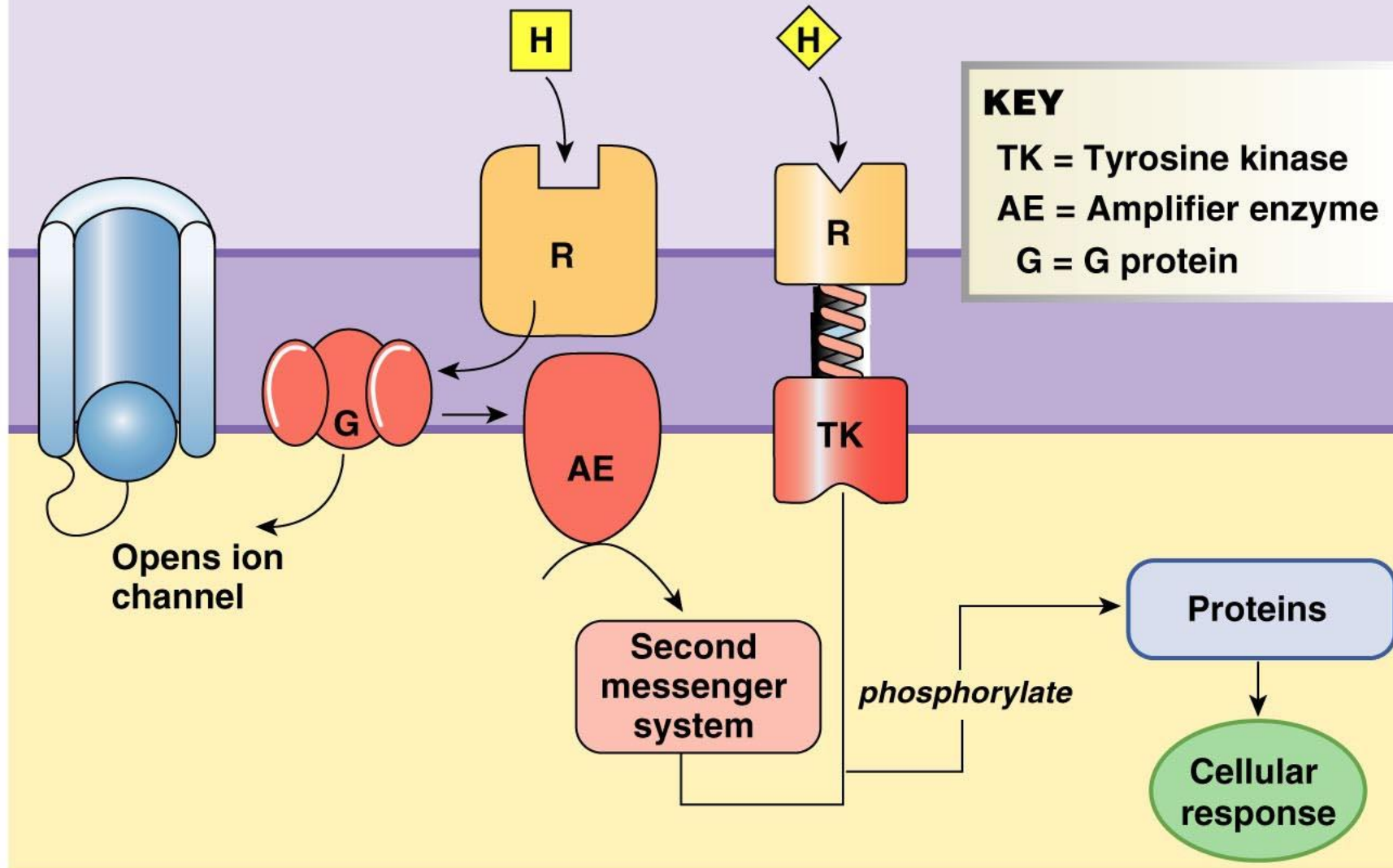


Figure 6-4: **Target cell receptors**

Peptide hormones (H) cannot enter their target cells and must combine with membrane receptors (R) that initiate signal transduction processes.



Hormone Action

- Hormones alter target cell activity by one of two mechanisms
 - **Second messengers:**
 - Regulatory G proteins
 - Amino acid–based hormones
 - **Direct gene activation**
 - Steroid hormones
- The precise response depends on the type of the target cell

Mechanism of Hormone Action

- **Hormones produce one or more of the following cellular physiological changes in target cell**
 - Alter plasma membrane permeability
 - Stimulate protein synthesis
 - Activate or deactivate enzyme systems
 - Induce secretory activity
 - Stimulate mitosis

Protein and Polypeptide Hormone Receptors

- Surface Receptor
- Hormone Binds
- Transduction
- Enzyme Activation
- Open Channels
- Second Messenger Systems
- Synthesis

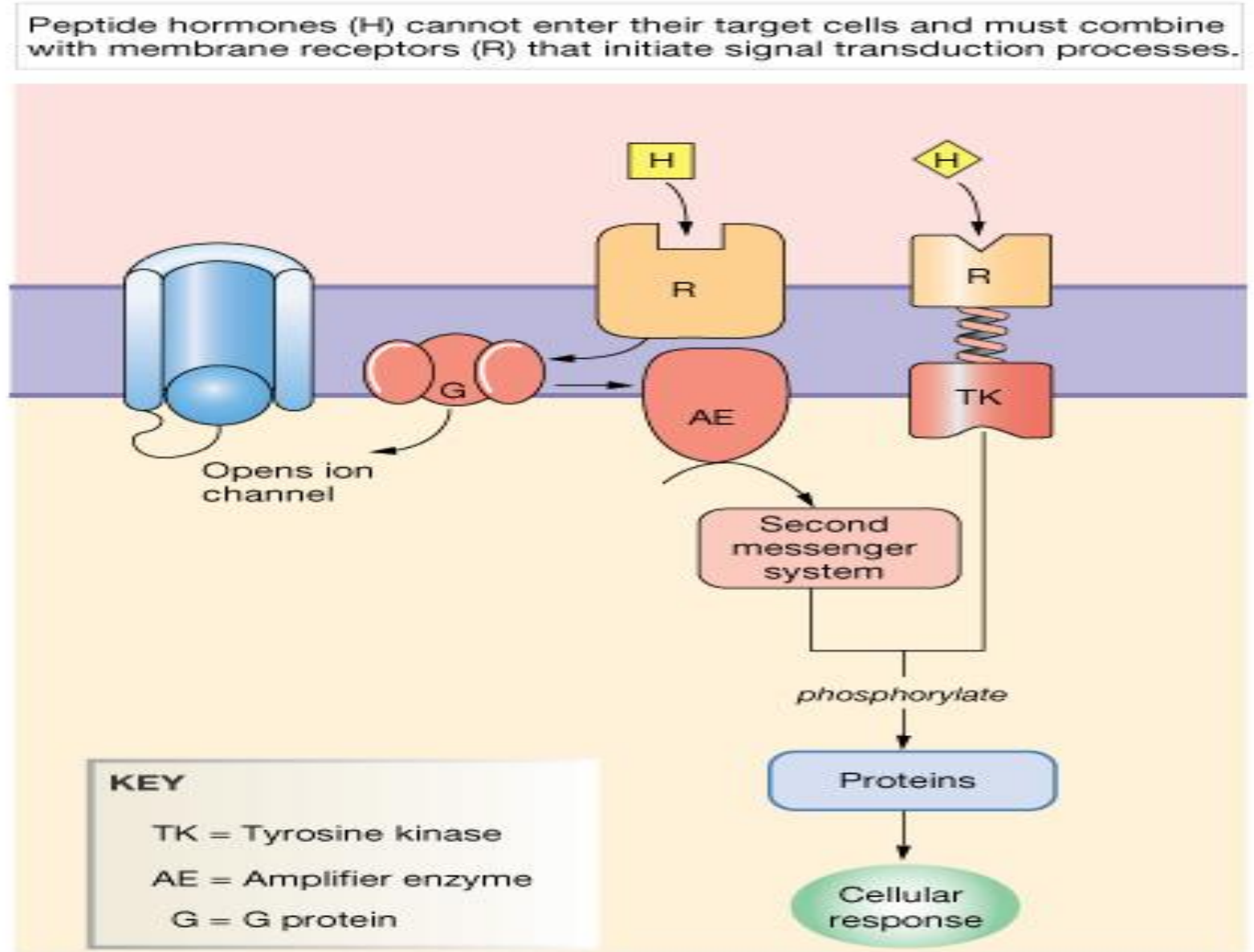


Figure 7-5: Membrane receptors for peptide hormones

Signal Transduction

Transforms Signal
Energy

Protein Kinase

Second Messenger

Activate Proteins

- Phosphorylation
- Bind Calcium

Cell Response

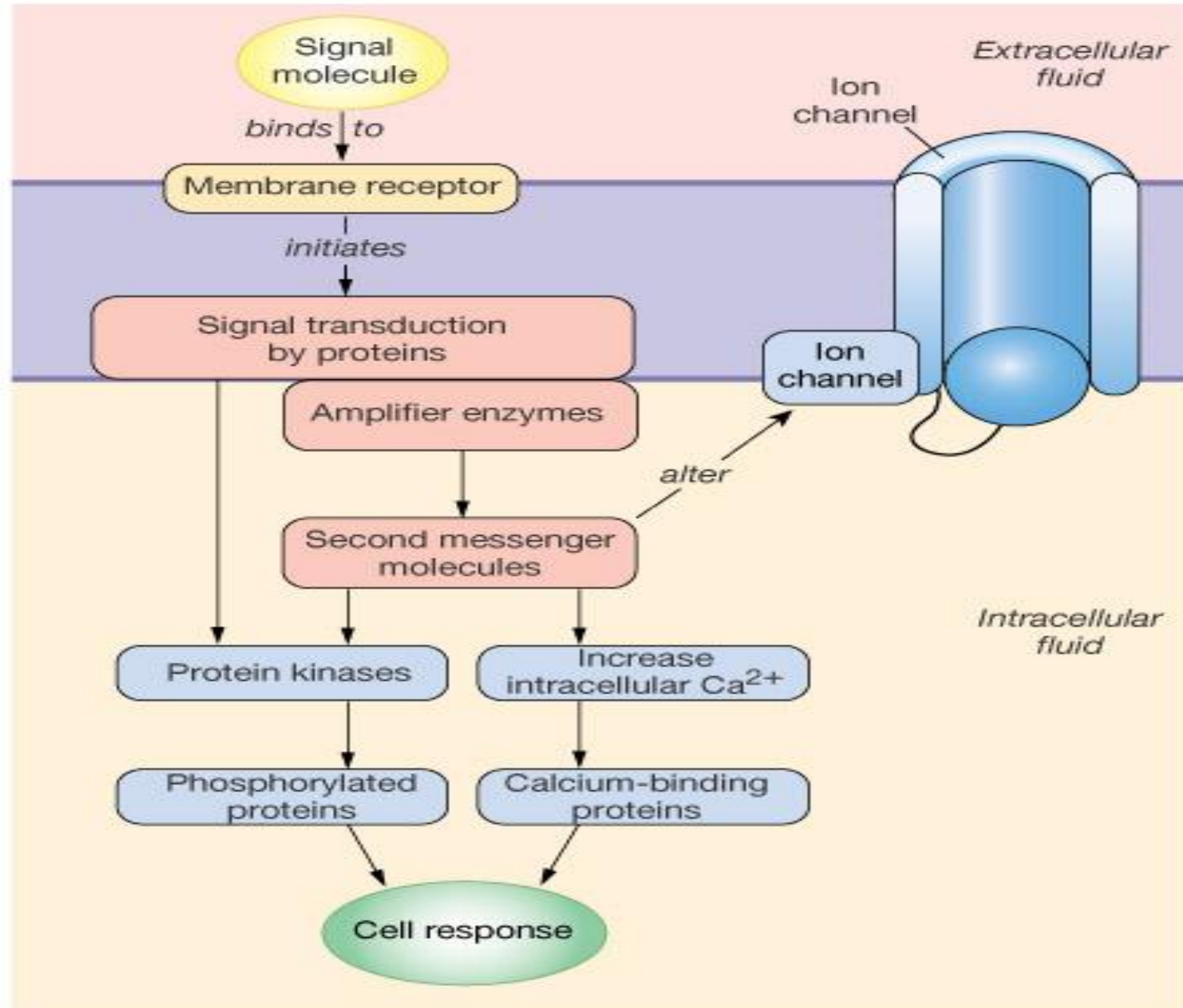
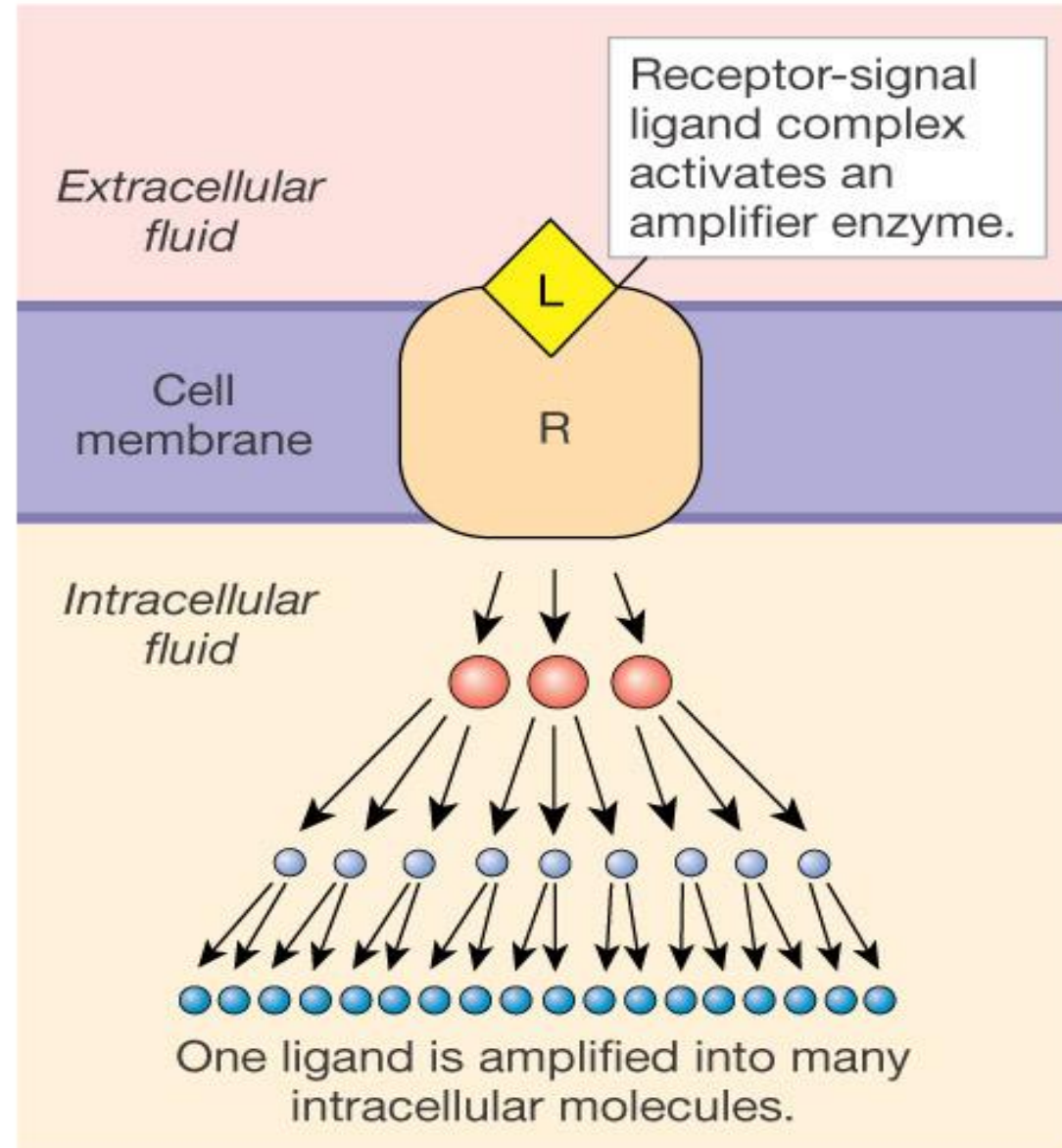


Figure 6-8: Biological signal transduction

Signal Amplification

- Small Signal Produces Large Cell Response
- Amplification Enzyme
- Cascade

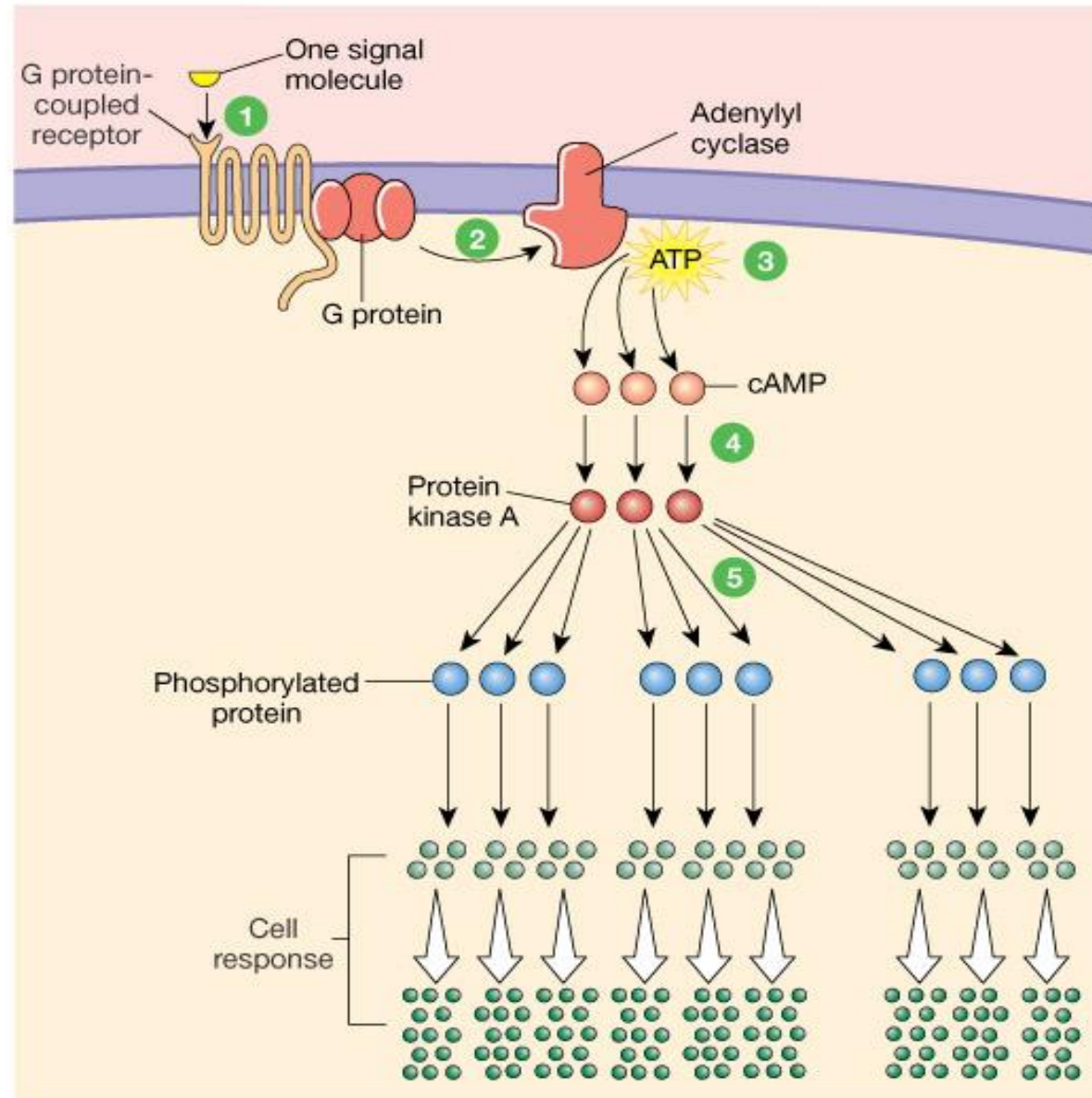


G-Protein-coupled Receptors

Hundreds of Types

Main Signal Transducers

- Activate Enzymes
- Open Ion Channels
- Amplify:
Adenyl Cyclase-cAMP
- Activates Synthesis



- 1 Signal molecule binds to G protein-linked receptor, which activates the G protein.
- 2 G protein turns on adenylyl cyclase, an amplifier enzyme.
- 3 Adenylyl cyclase converts ATP to cyclic AMP.
- 4 cAMP activates protein kinase A.
- 5 Protein kinase A phosphorylates other proteins, leading ultimately to a cellular response.

The G protein-coupled adenylyl cyclase-cAMP system

Receptor Enzymes

Transduction

Activation Cytoplasmic
- Side Enzyme

Example:
Tyrosine Kinase

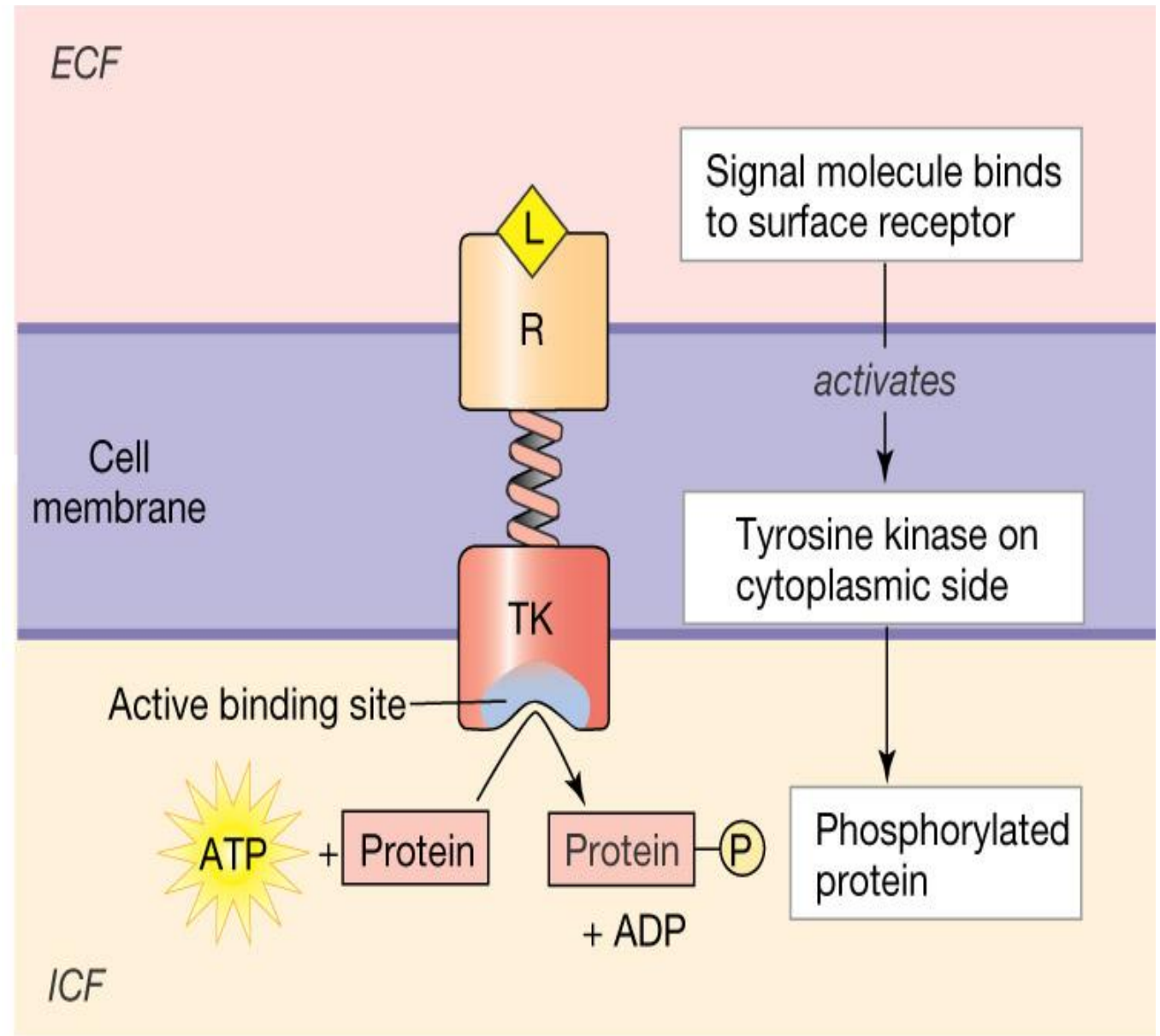


Figure 6-10: **Tyrosine kinase**, an example of a receptor-enzyme

The diagram illustrates the process of signal transduction across a cell membrane. It is divided into three main regions: Extracellular fluid (top), Cell membrane (middle), and Intracellular fluid (bottom).

Extracellular fluid: A yellow oval labeled "Signal molecule" is shown.

Cell membrane: A blue horizontal band representing the membrane. It contains a "Gated ion channel" (yellow) and a "Membrane receptor" (yellow diamond).

Intracellular fluid: The bottom section, containing various cellular components and responses.

Signal Transduction Pathways:

- Ion Channel Pathway:** A signal molecule binds to a gated ion channel, causing it to open. Ions move into or out of the cell, leading to a change in ion concentration, which creates an electrical signal.
- Membrane Receptor Pathway:** A signal molecule binds to a membrane receptor, which activates a G protein. This G protein then activates or inhibits an amplifier enzyme, activates tyrosine kinase, or alters the cytoskeleton.
- Second Messenger Pathway:** The amplifier enzyme produces second messenger molecules, which activate protein kinases. These kinases phosphorylate altered proteins, leading to cellular responses.
- Direct Pathways:** The membrane receptor also directly activates tyrosine kinase and alters the cytoskeleton.

Cellular Responses: The final stage, where the signal leads to a change in various cellular components:

- Motor proteins
- Enzyme activity
- Membrane receptors and transporters
- Gene activity and protein synthesis

Amino Acid-Based Hormone Action: cAMP Second Messenger

- Hormone (first messenger) binds to its receptor, which then binds to a G protein
- The G protein is then activated as it binds GTP, displacing GDP
- Activated G protein activates the effector enzyme adenylate cyclase
- Adenylate cyclase generates cAMP (second messenger) from ATP
- cAMP activates protein kinases, which then cause cellular effects

Amino Acid-Based Hormone Action: cAMP Second Messenger

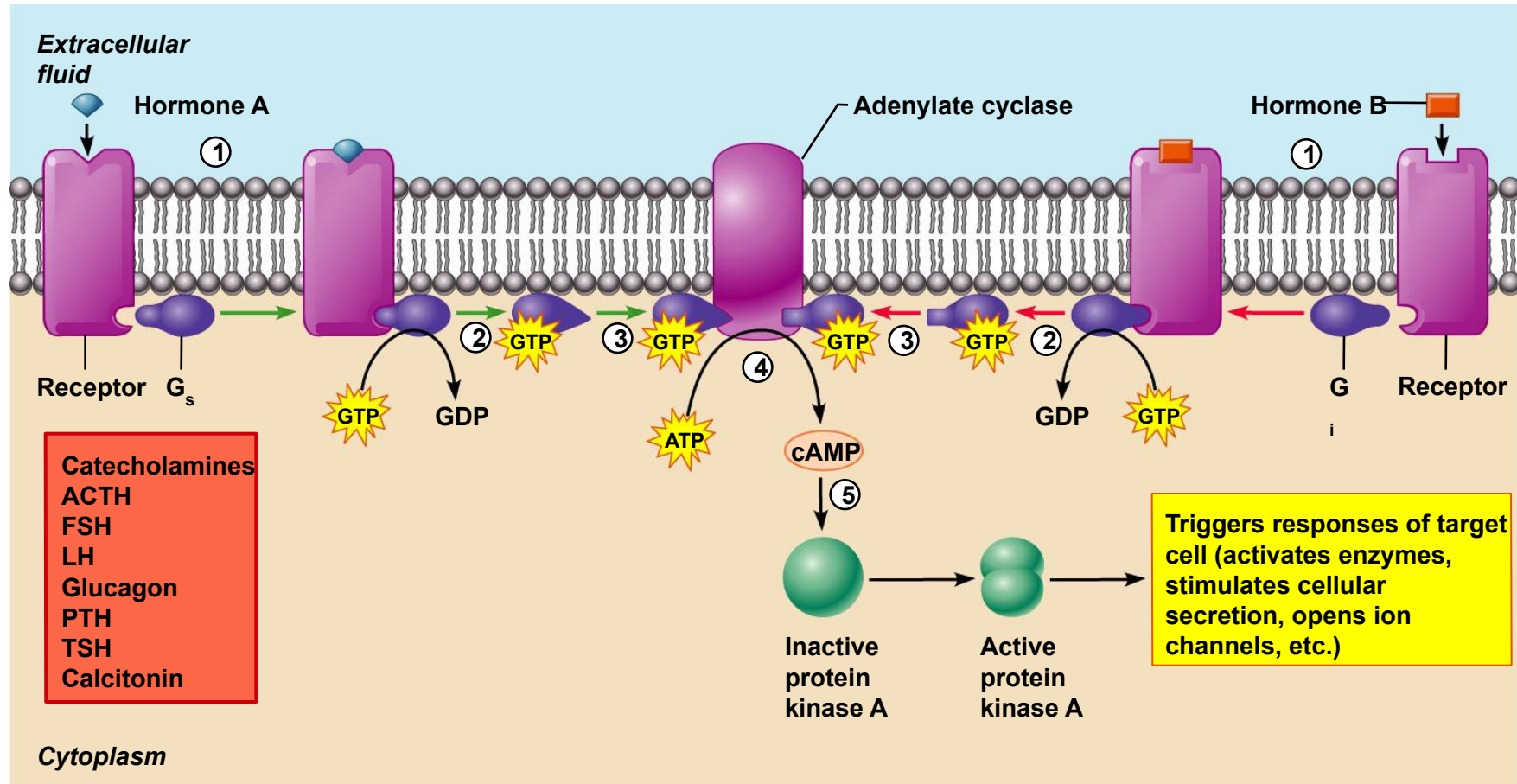


Figure 16.2

Amino Acid-Based Hormone Action: cAMP Second Messenger

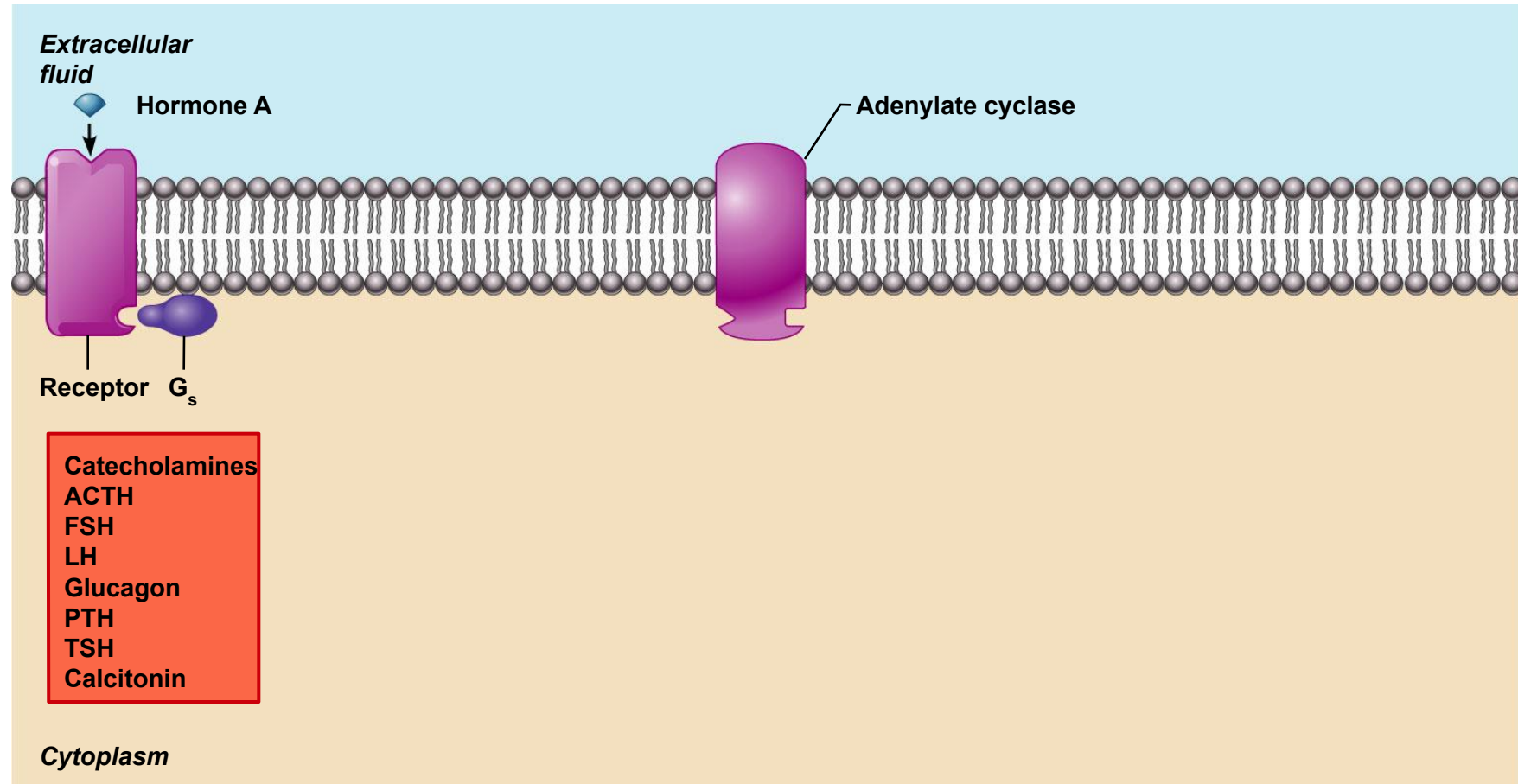


Figure 16.2

Amino Acid-Based Hormone Action: cAMP Second Messenger

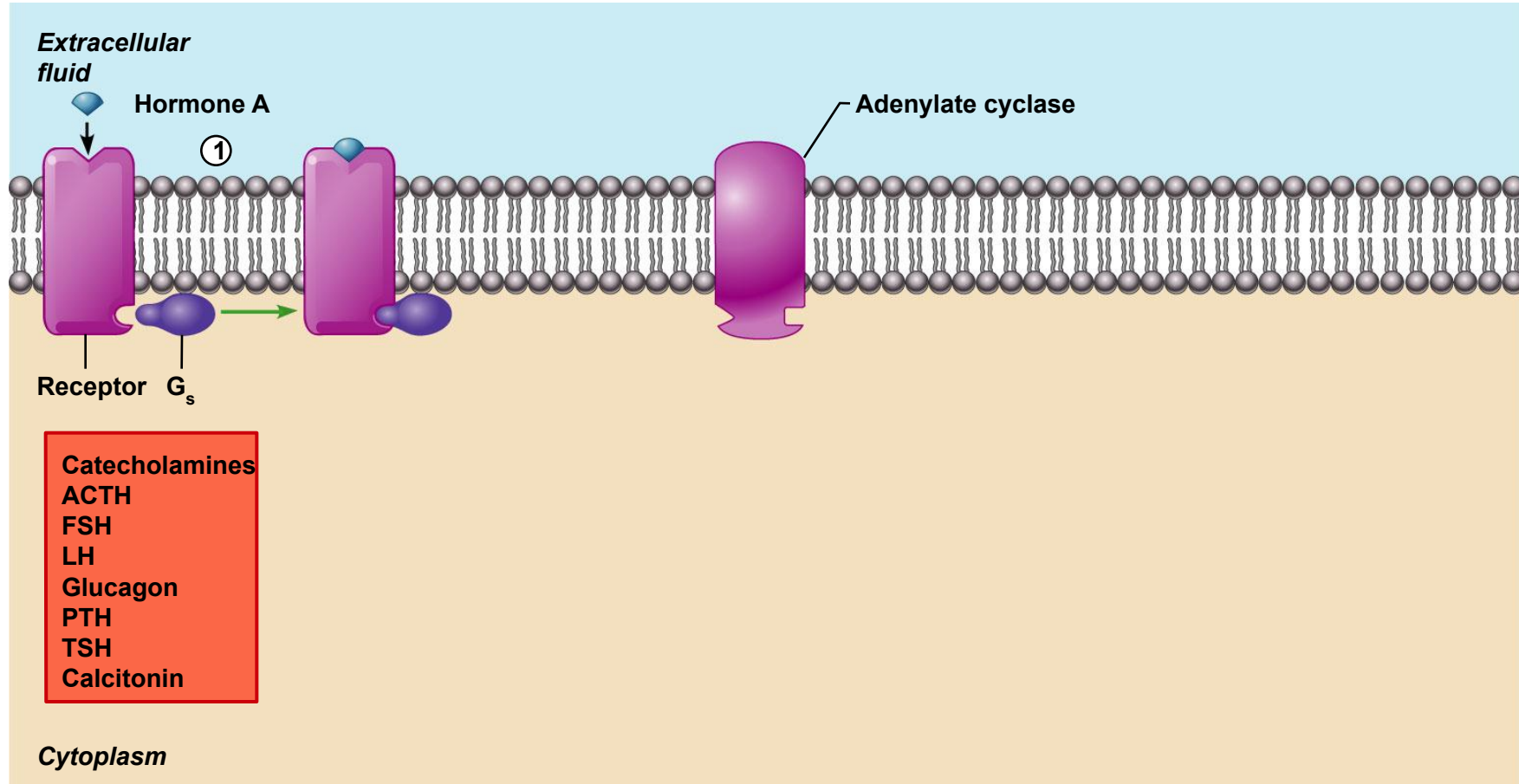


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Amino Acid-Based Hormone Action: cAMP Second Messenger

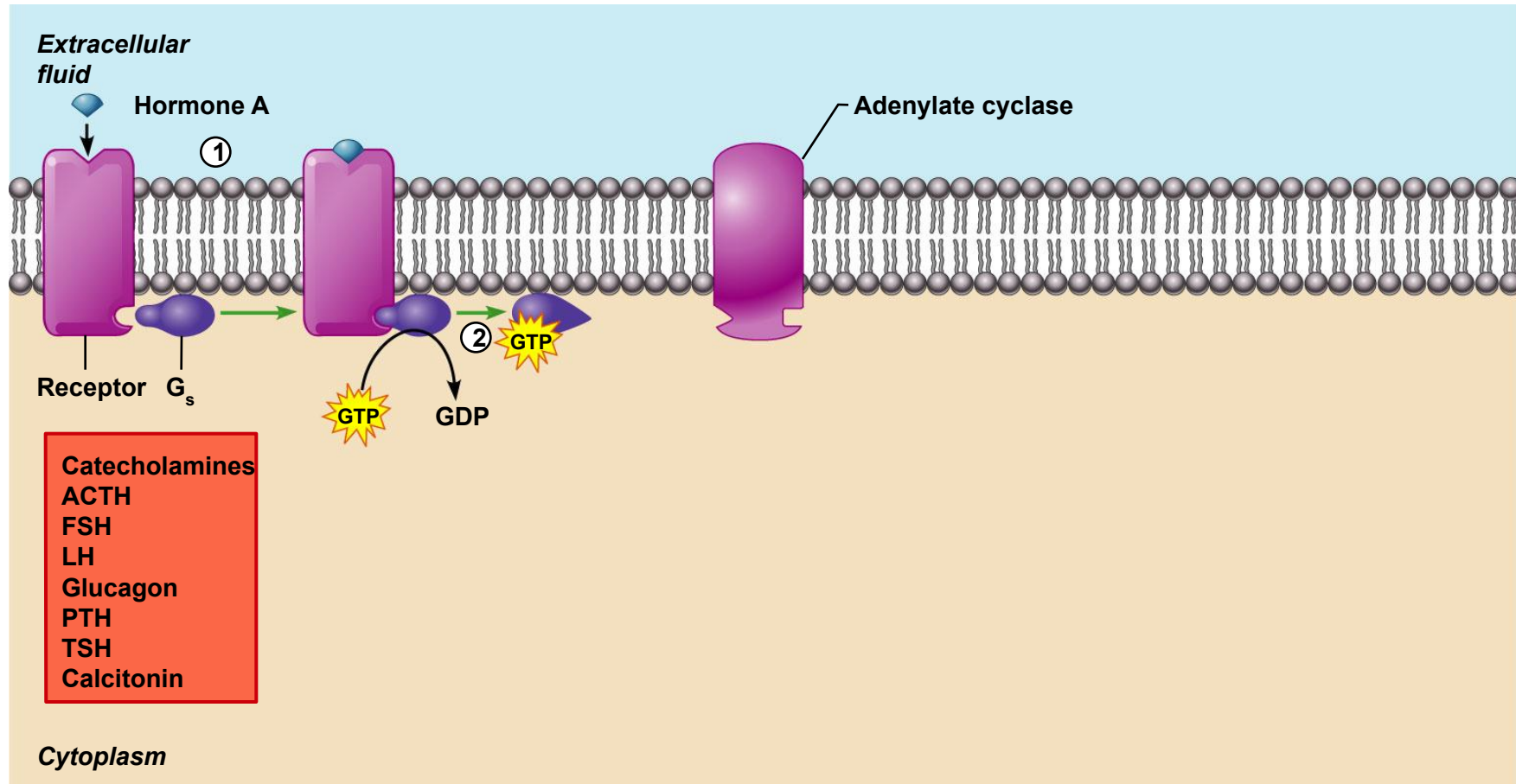


Figure 16.2

Amino Acid-Based Hormone Action: cAMP Second Messenger

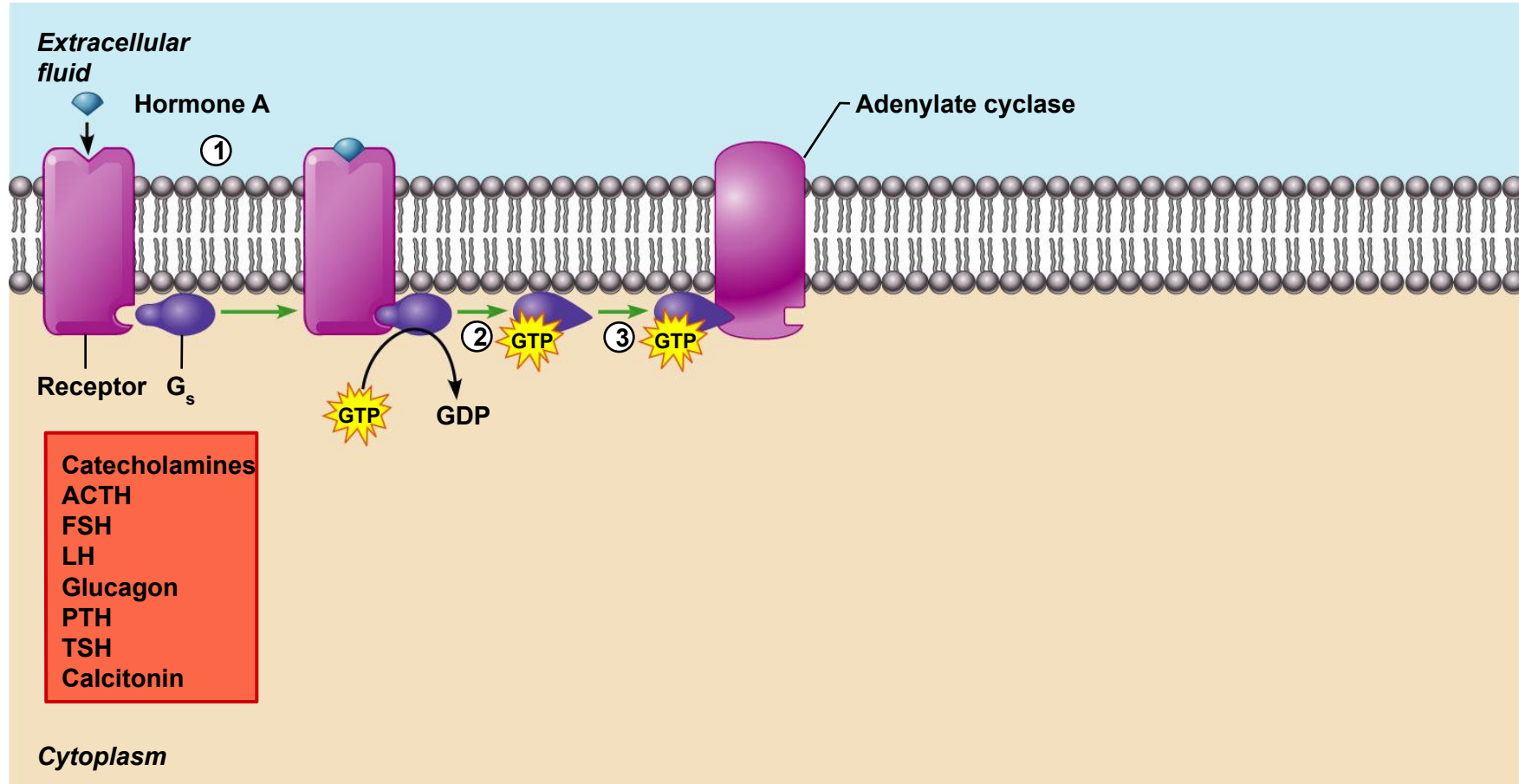


Figure 16.2

Amino Acid-Based Hormone Action: cAMP Second Messenger

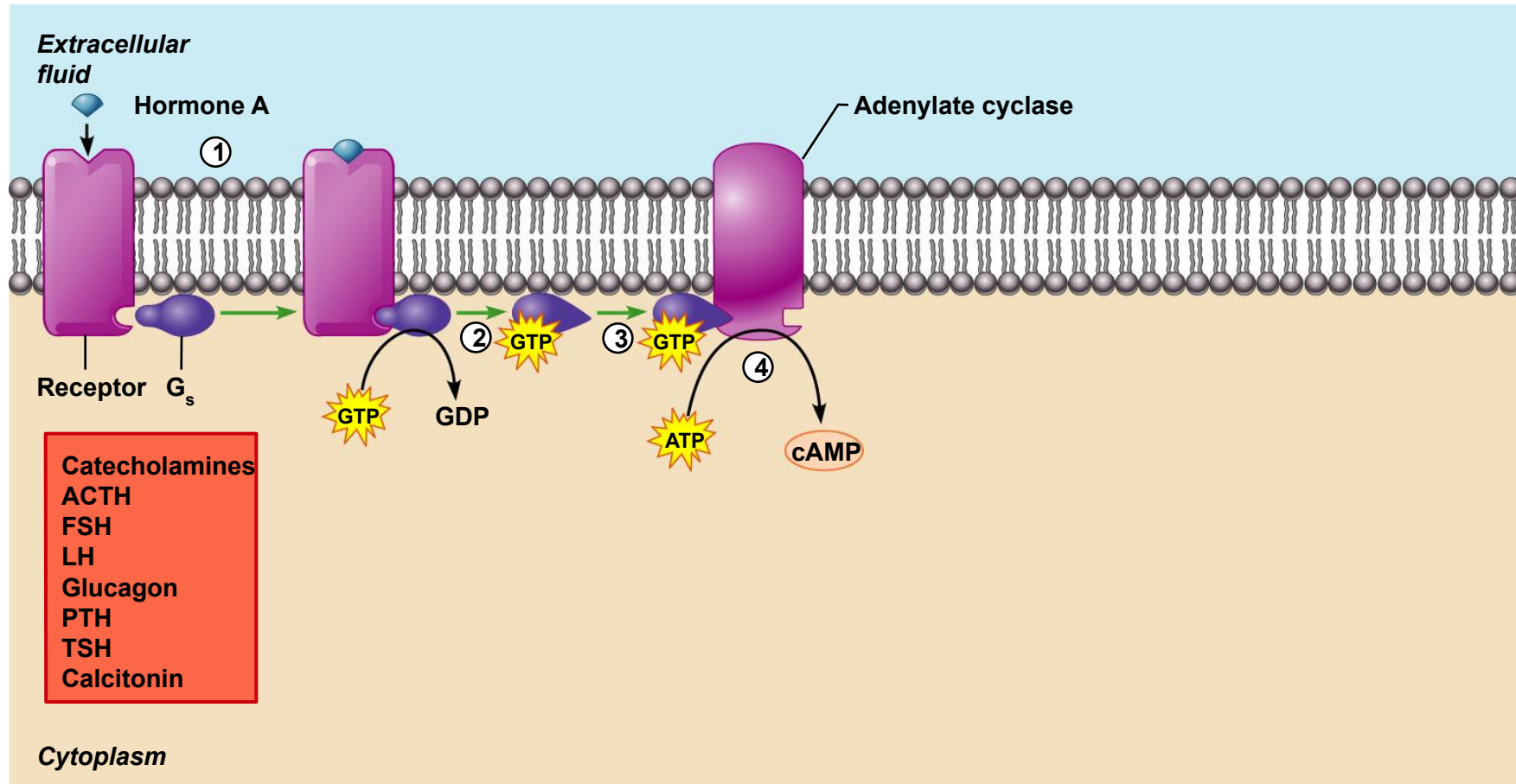


Figure 16.2

Amino Acid-Based Hormone Action: cAMP Second Messenger

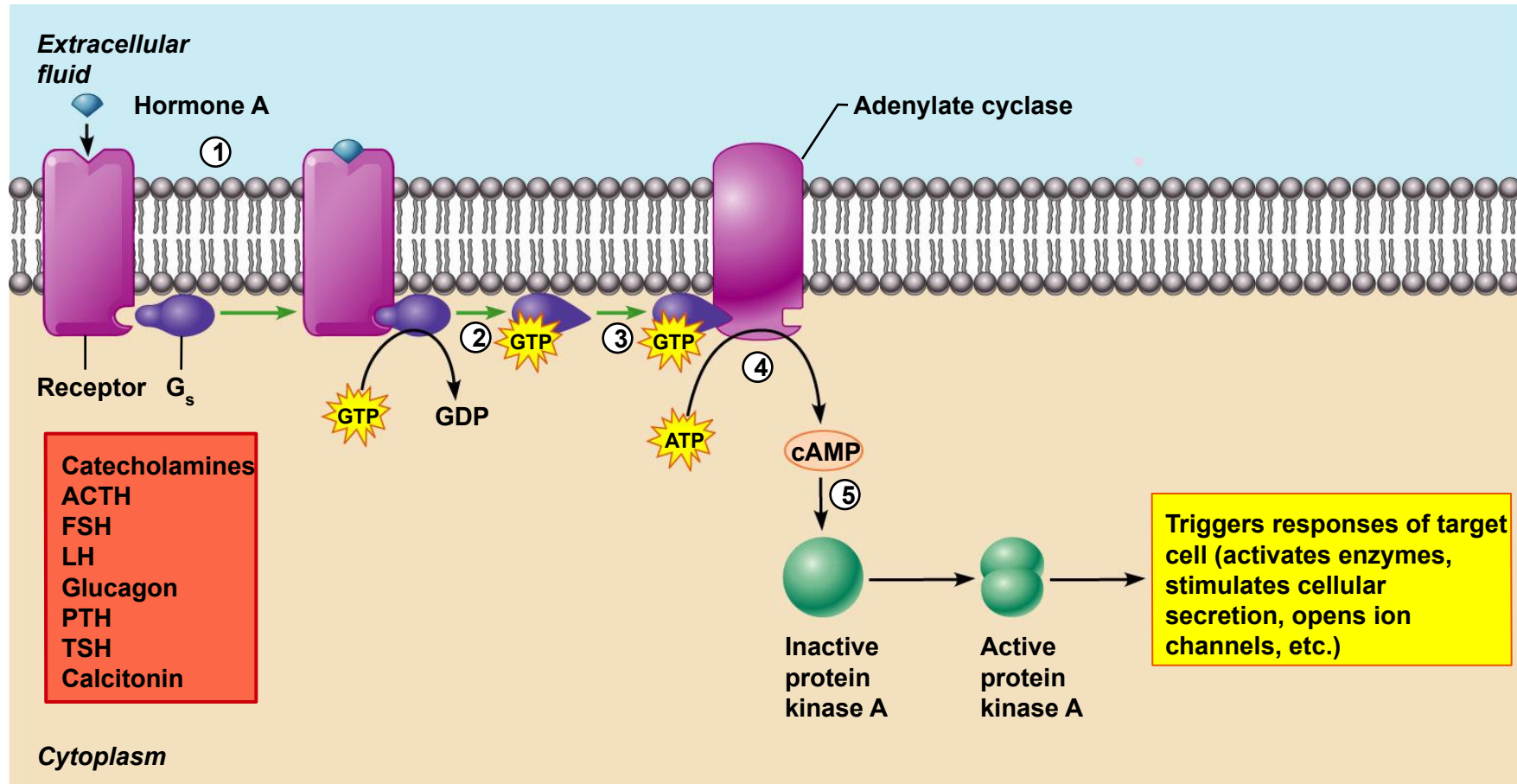
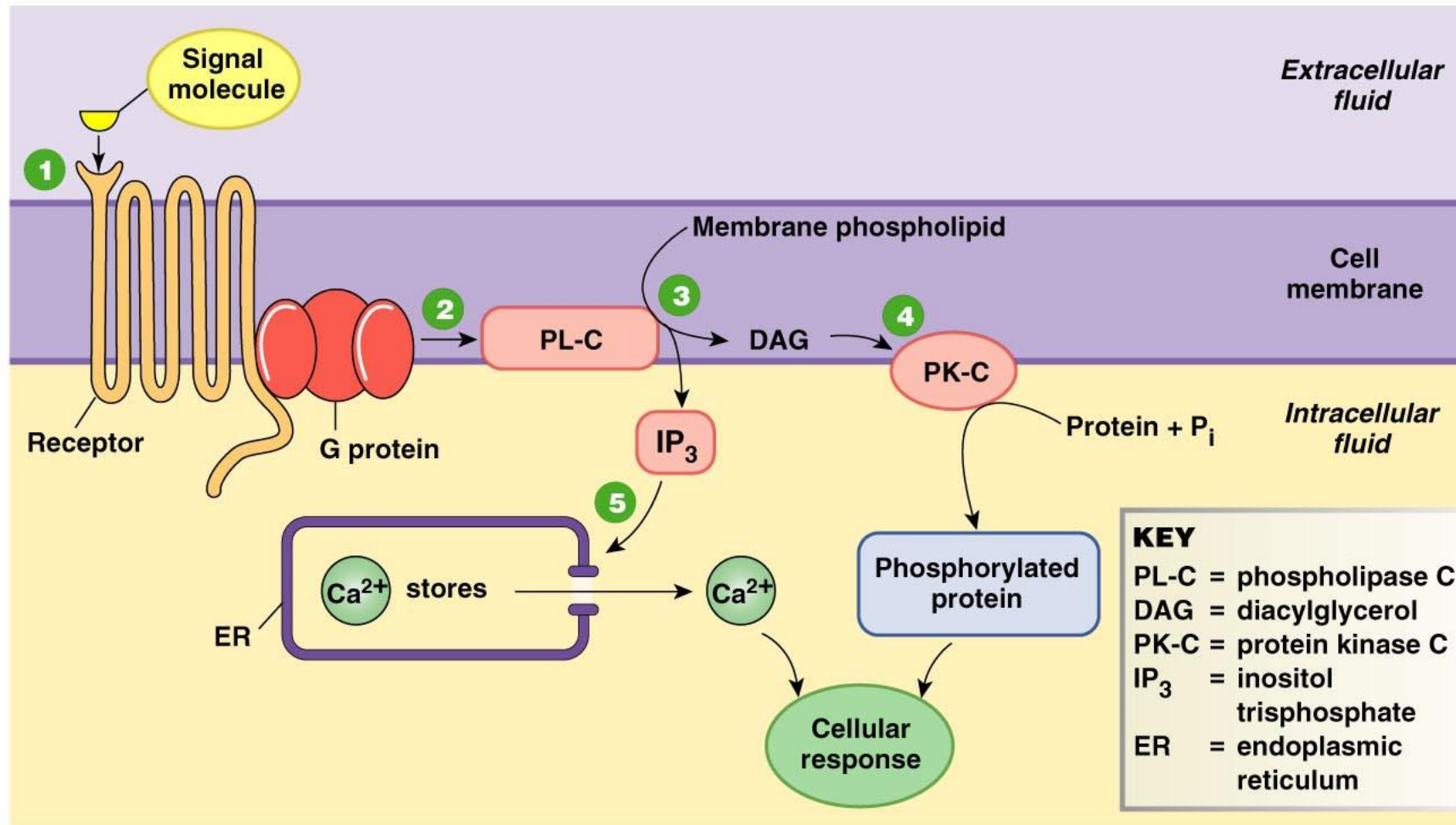


Figure 16.2

Amino Acid-Based Hormone Action: PIP-Calcium

- Hormone binds to the receptor and activates G protein
- G protein binds and activates phospholipase
- Phospholipase splits the phospholipid PIP_2 into diacylglycerol (DAG) and IP_3 (both act as second messengers)
- DAG activates protein kinases; IP_3 triggers release of Ca^{2+} stores
- Ca^{2+} (third messenger) alters cellular responses



- 1 Signal molecule activates receptor and associated G protein.
- 2 G protein activates phospholipase C (PL-C), an amplifier enzyme.
- 3 PL-C converts membrane phospholipids into diacylglycerol (DAG), which remains in the membrane, and IP₃, which diffuses into the cytoplasm.
- 4 DAG activates protein kinase C (PK-C), which phosphorylates proteins.
- 5 IP₃ causes release of Ca²⁺ from organelles, creating a Ca²⁺ signal.

Amino Acid-Based Hormone Action: PIP Mechanism

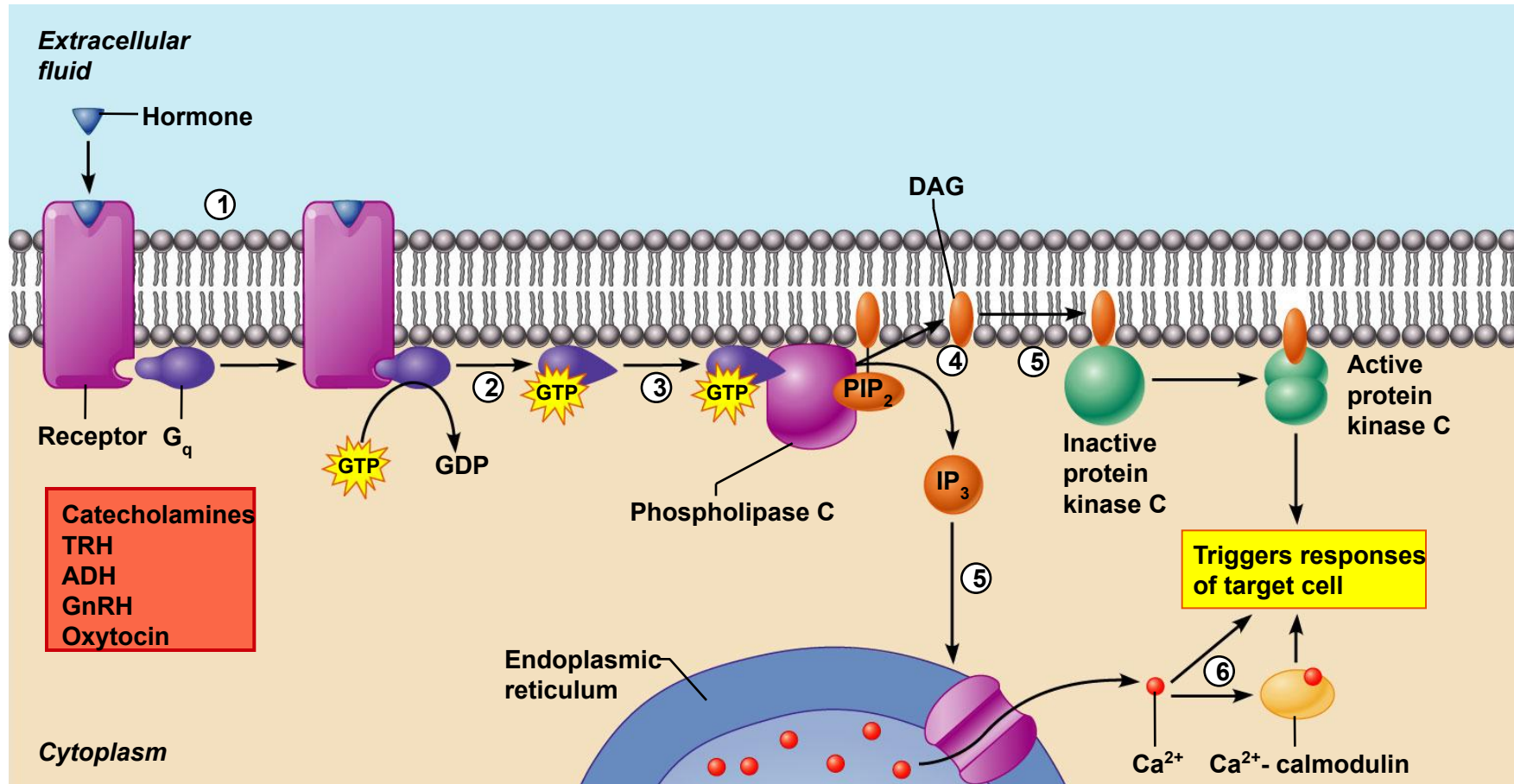


Figure 16.3

Amino Acid-Based Hormone Action: PIP Mechanism

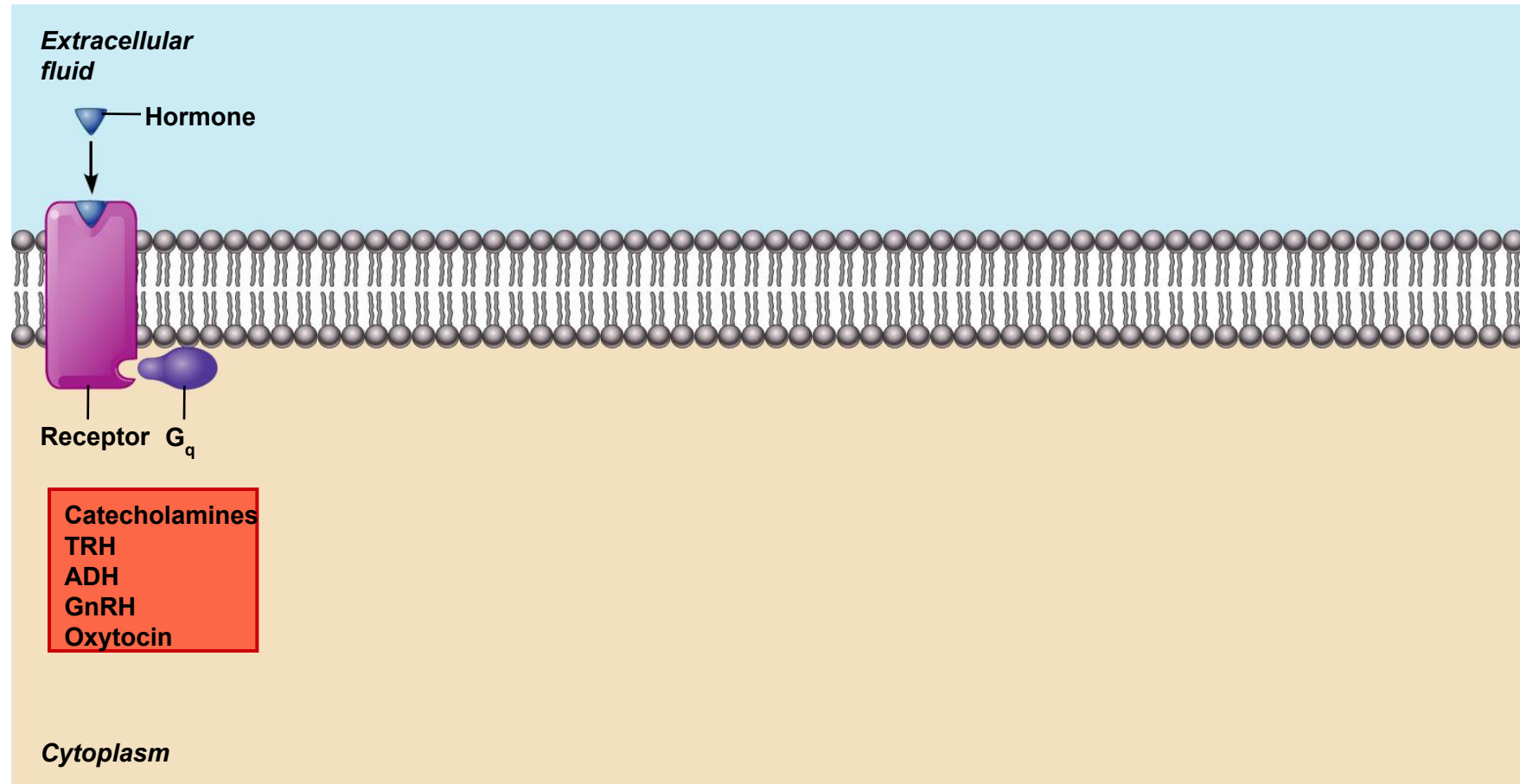


Figure 16.3

Amino Acid-Based Hormone Action: PIP Mechanism

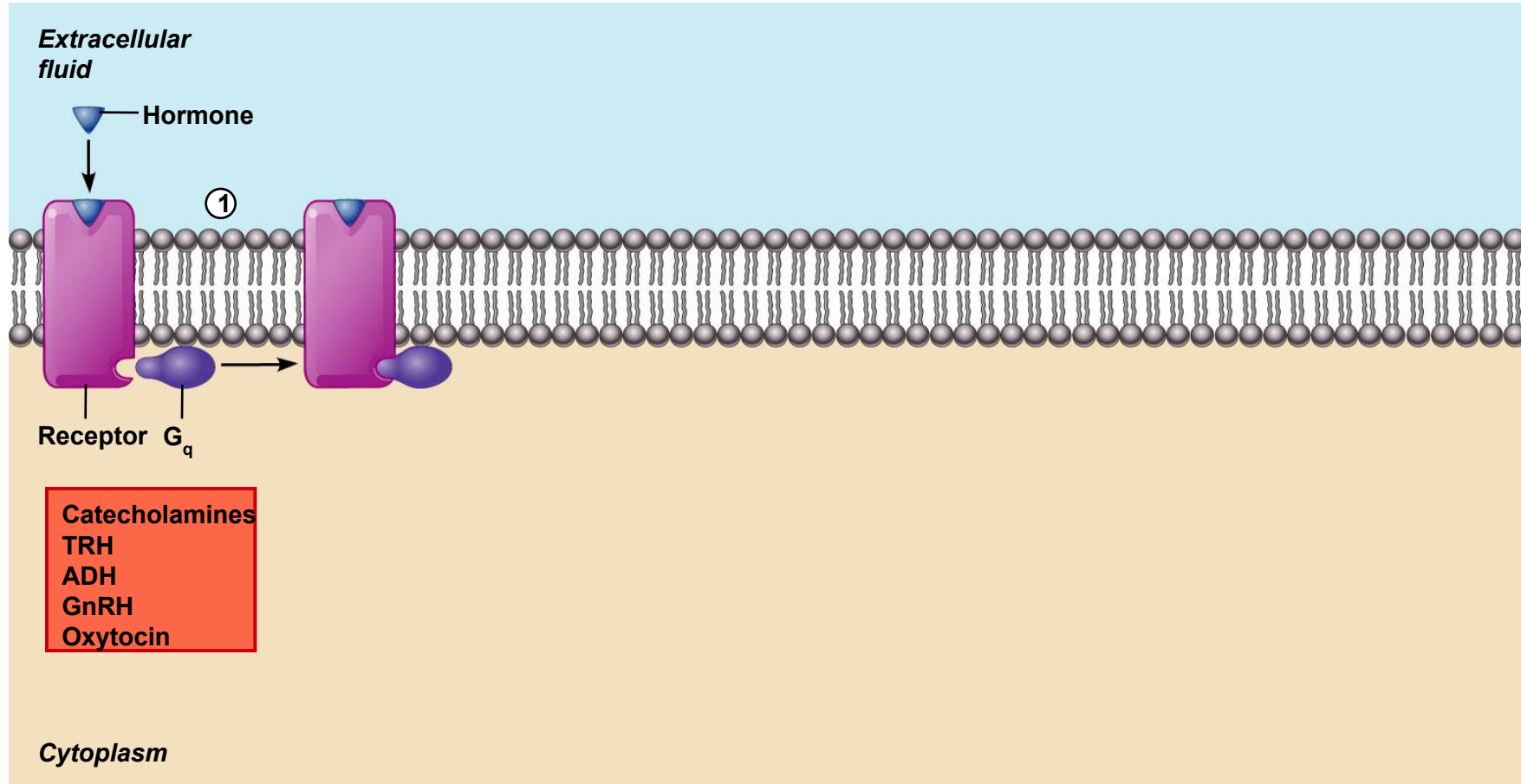


Figure 16.3

Amino Acid-Based Hormone Action: PIP Mechanism

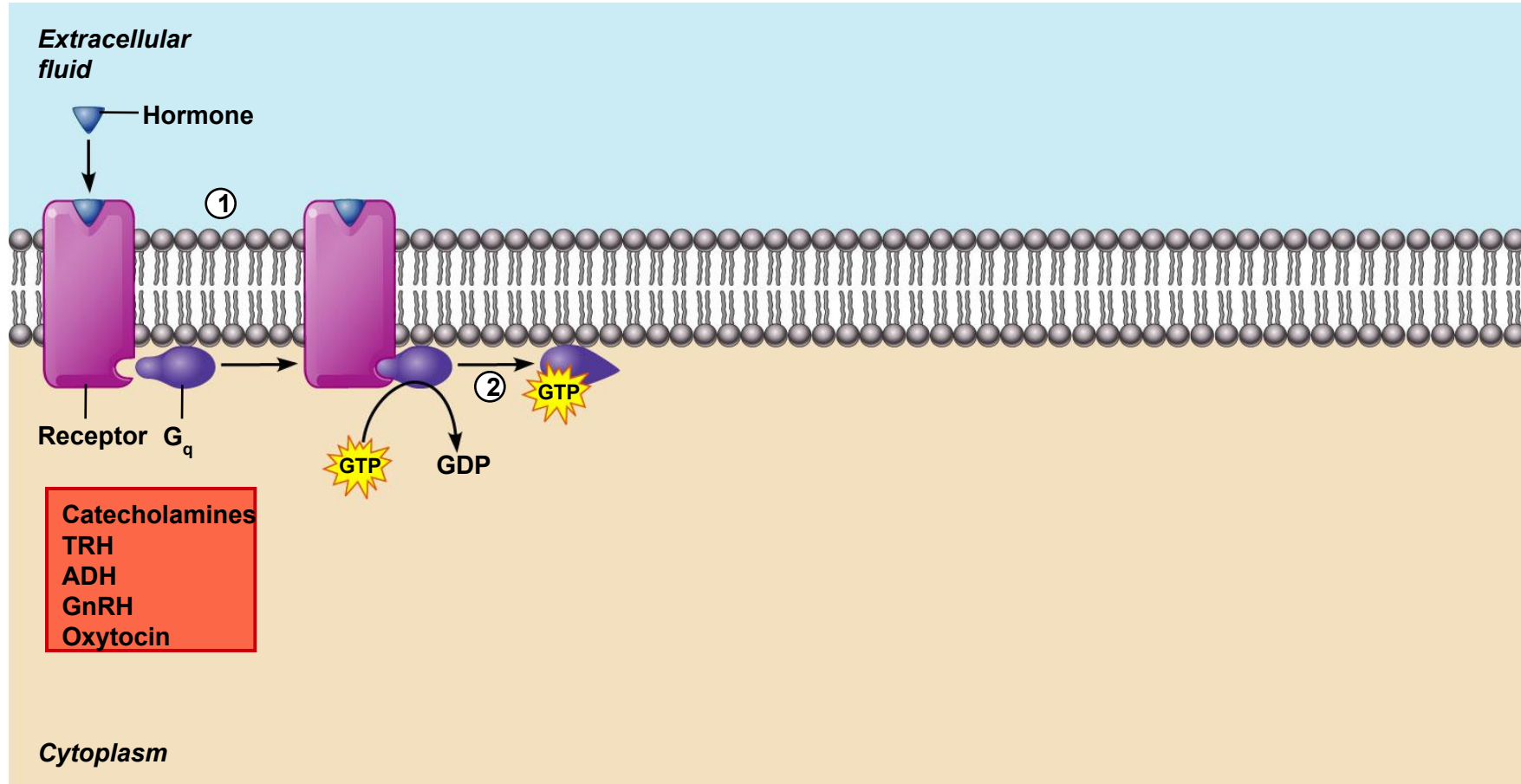


Figure 16.3

Amino Acid-Based Hormone Action: PIP Mechanism

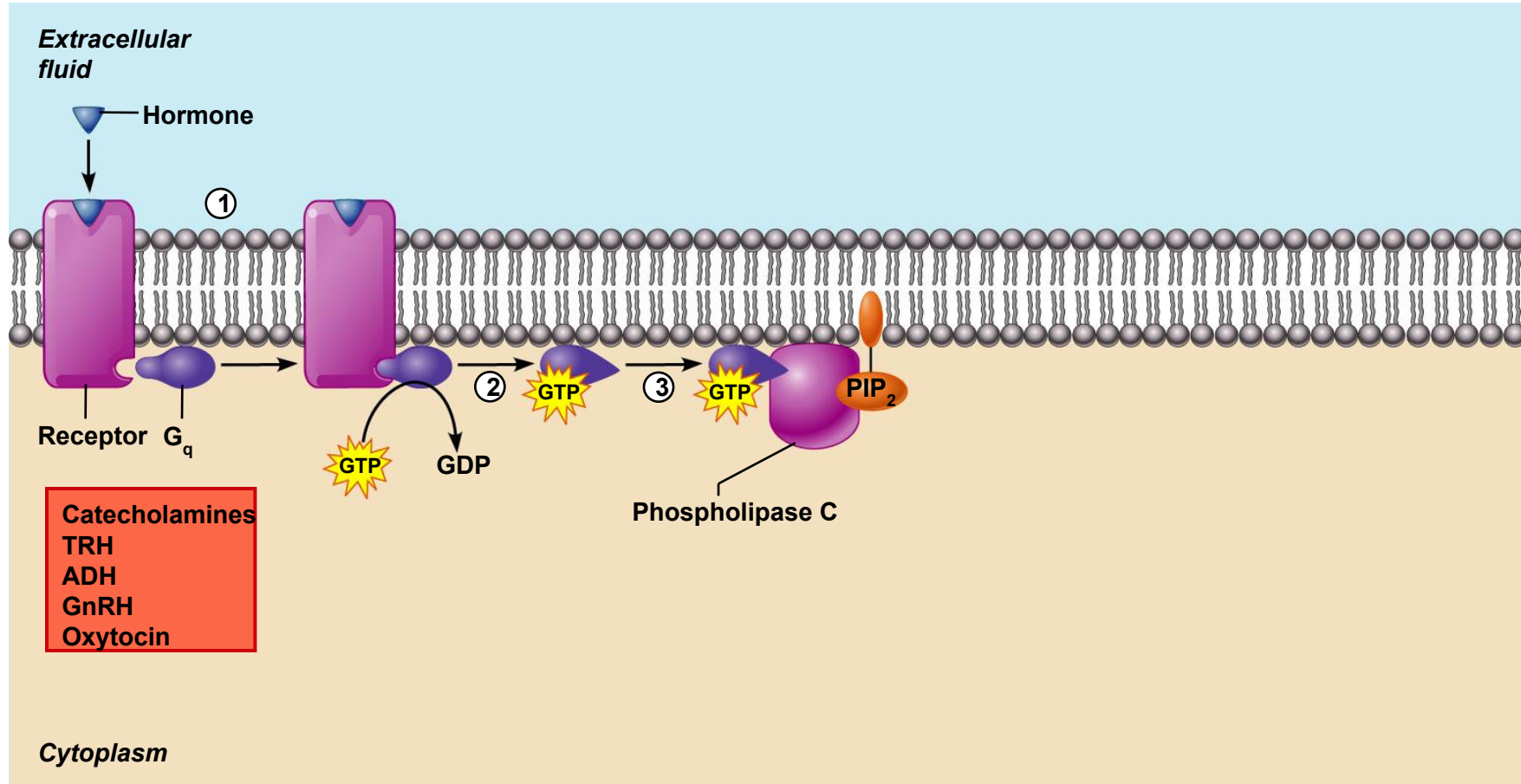


Figure 16.3

Amino Acid-Based Hormone Action: PIP Mechanism

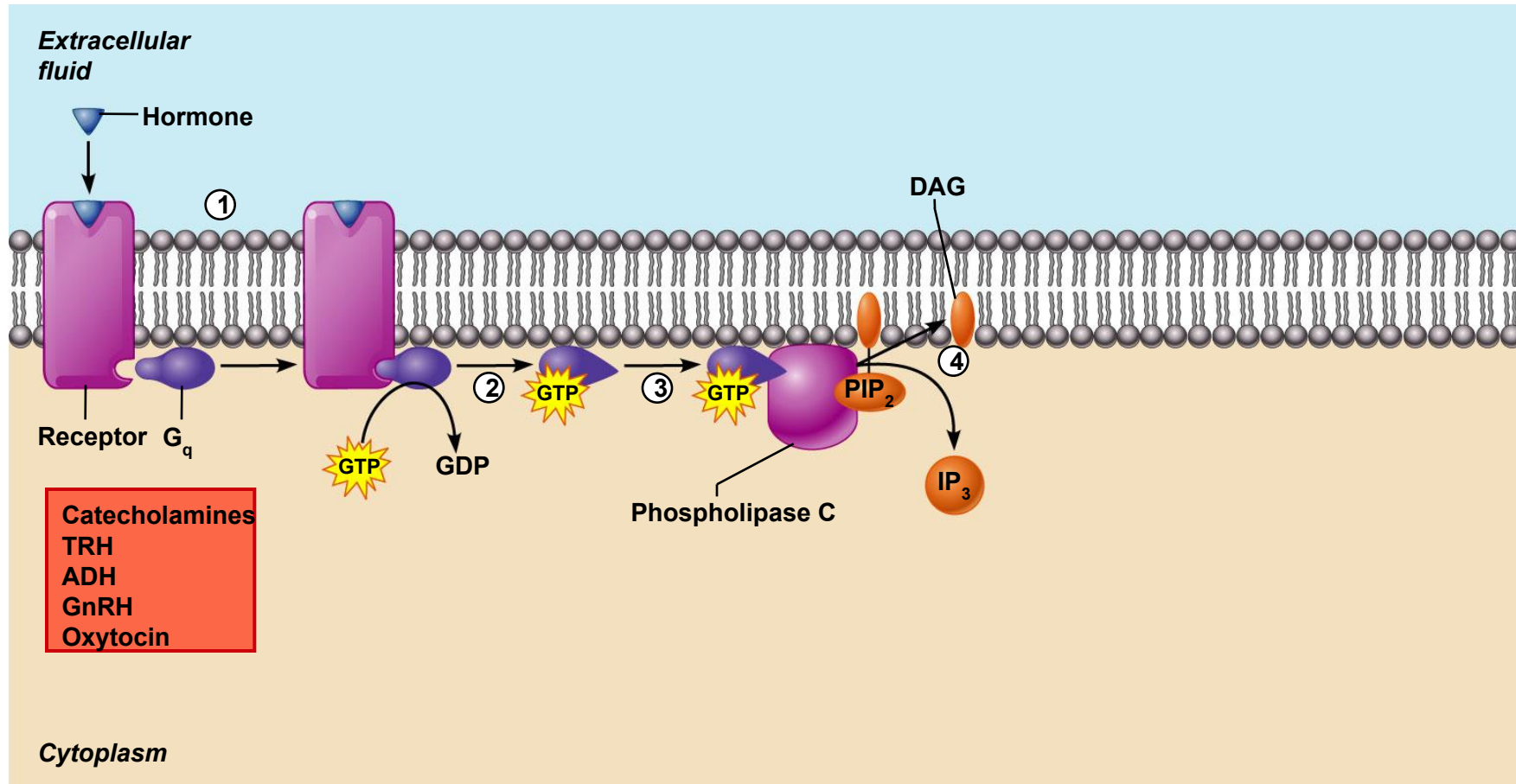


Figure 16.3

Amino Acid-Based Hormone Action: PIP Mechanism

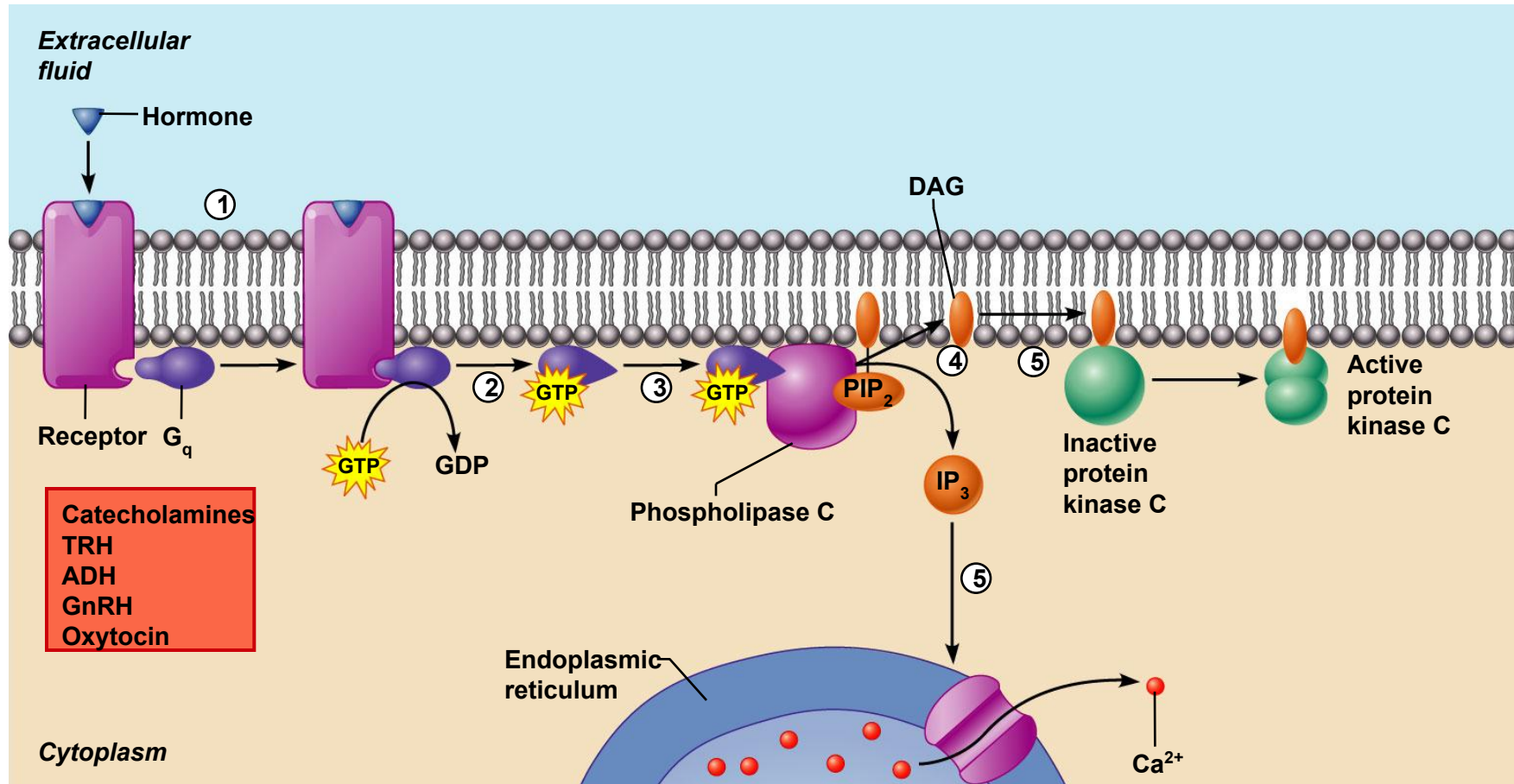


Figure 16.3

Amino Acid-Based Hormone Action: PIP Mechanism

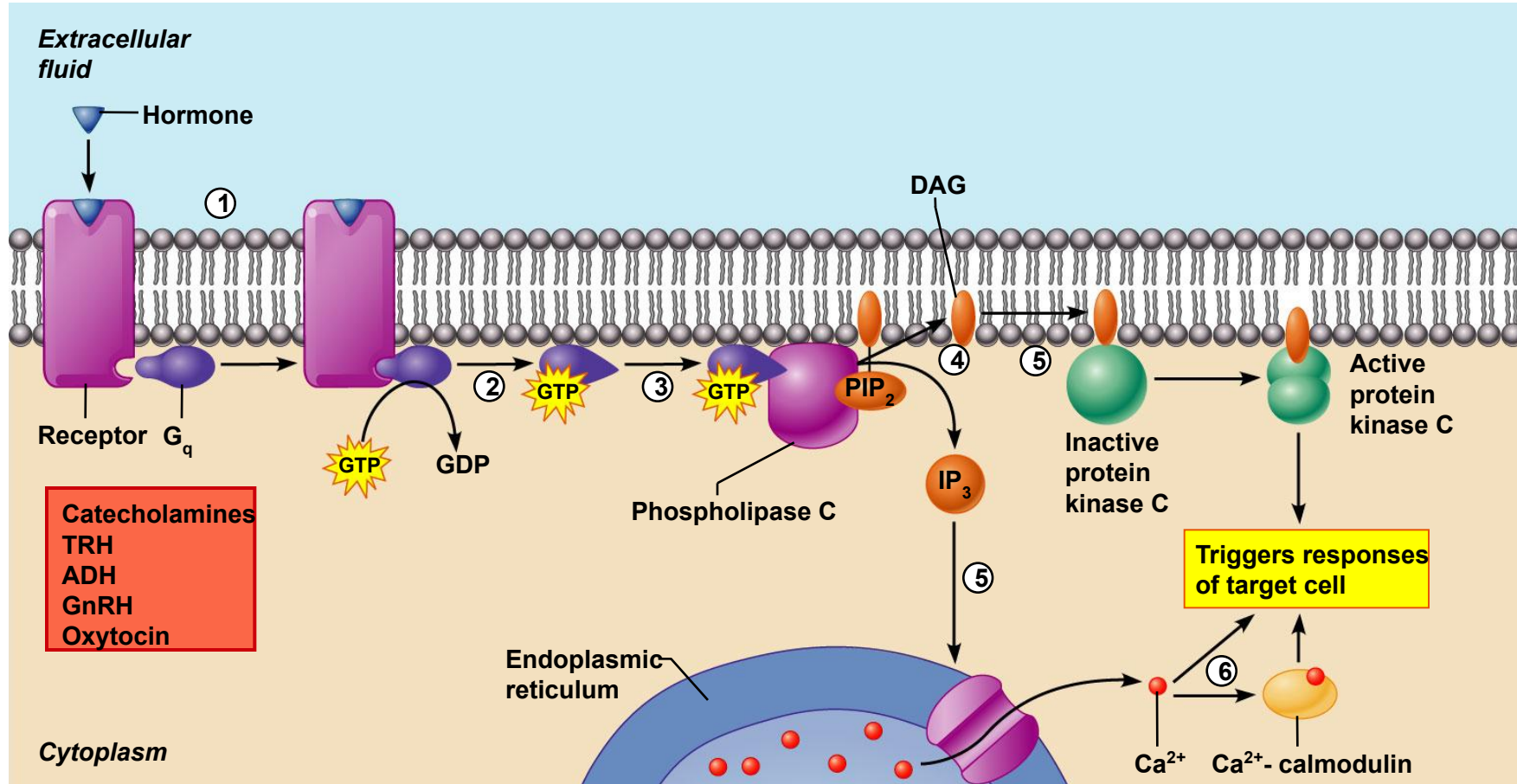
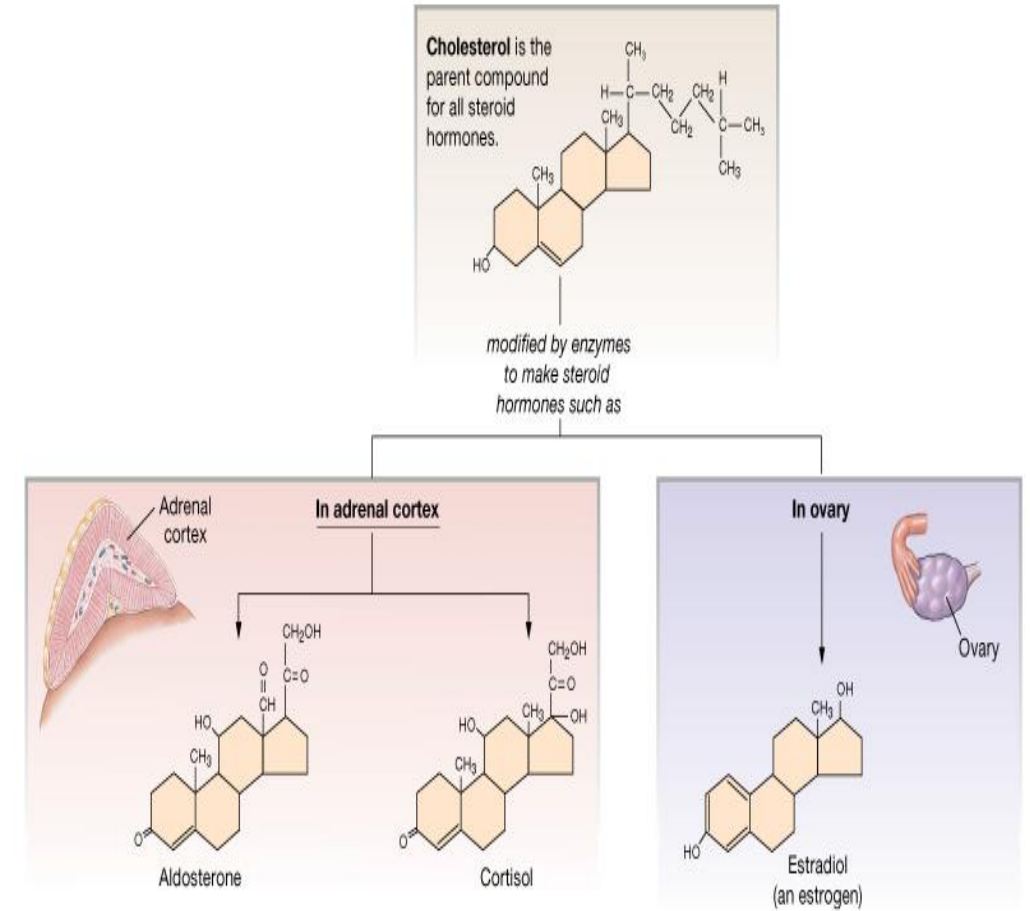


Figure 16.3

Steroid Hormones: Structure and Action

- From Cholesterol, Lipophilic, Enter Target Cell
- Cytoplasmic or Nuclear Receptors (mostly)
- Activate DNA for Protein Synthesis
- Slower Acting, Longer Half-Life
- Examples: Cortisol, Estrogen & Testosterone

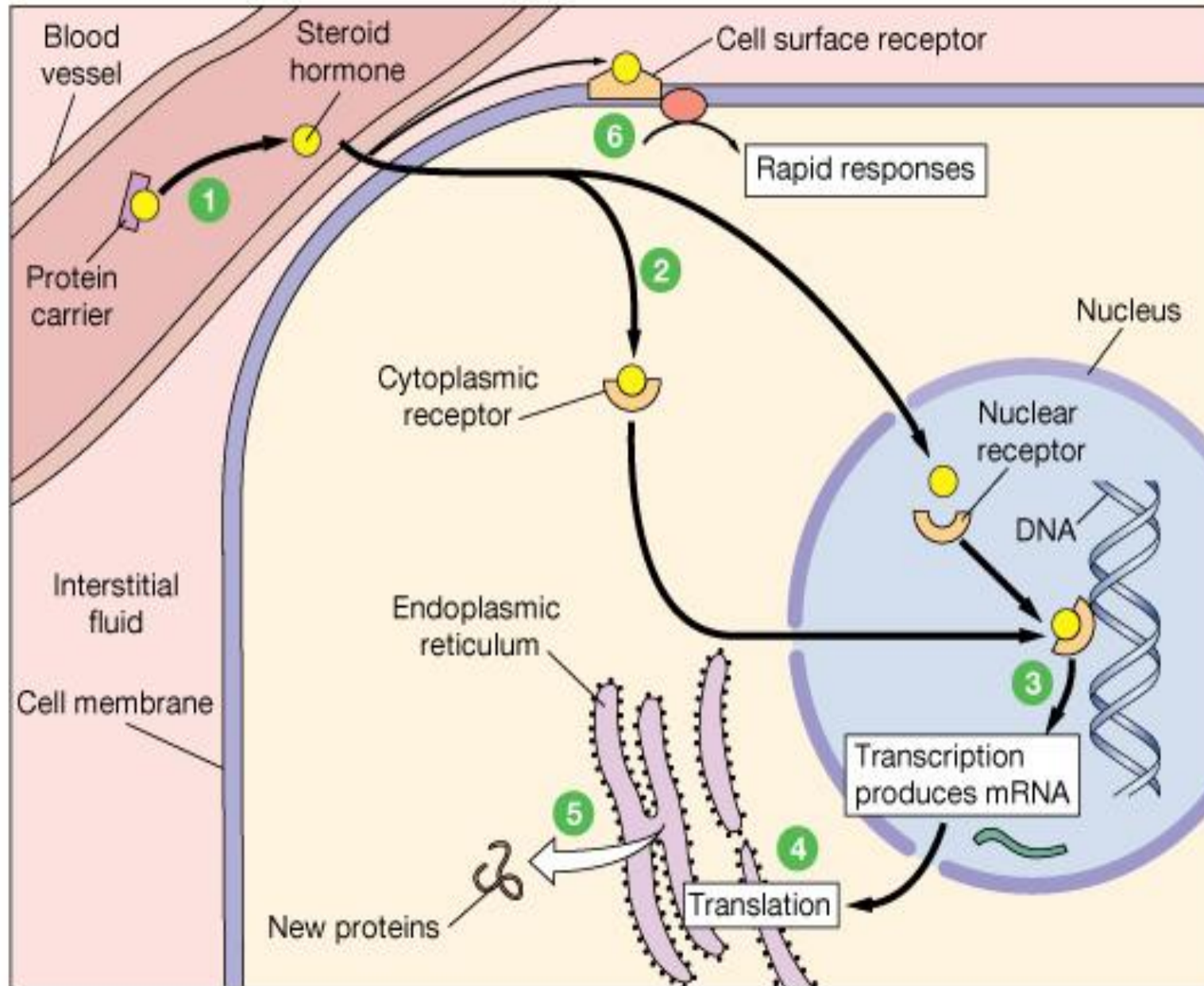


Steroid Hormones

- Direct gene activation:
 - a) Diffusion through target cell membrane
 - b) Binding to specific receptor in cytoplasm or nucleus
 - c) This interaction prompts DNA transcription to produce mRNA
 - d) The mRNA is translated into specific proteins
 - e) formation of specific channels
 - which bring about a cellular effect

Example: In the renal tubules, protein enzymes are formed in response to aldosterone (steroid hormone) stimulation to cause sodium absorption and potassium secretion

Steroid Hormones: Structure and Action



- 1 Most hydrophobic steroids are bound to plasma protein carriers. Only unbound hormones can diffuse into the target cell.
- 2 Steroid hormone receptors are in the cytoplasm or nucleus.
- 3 The receptor-hormone complex binds to DNA and activates or represses one or more genes.
- 4 Activated genes create new mRNA that moves back to the cytoplasm.
- 5 Translation produces new proteins for cell processes.
- 6 Some steroid hormones also bind to membrane receptors that use second messenger systems to create rapid cellular responses.

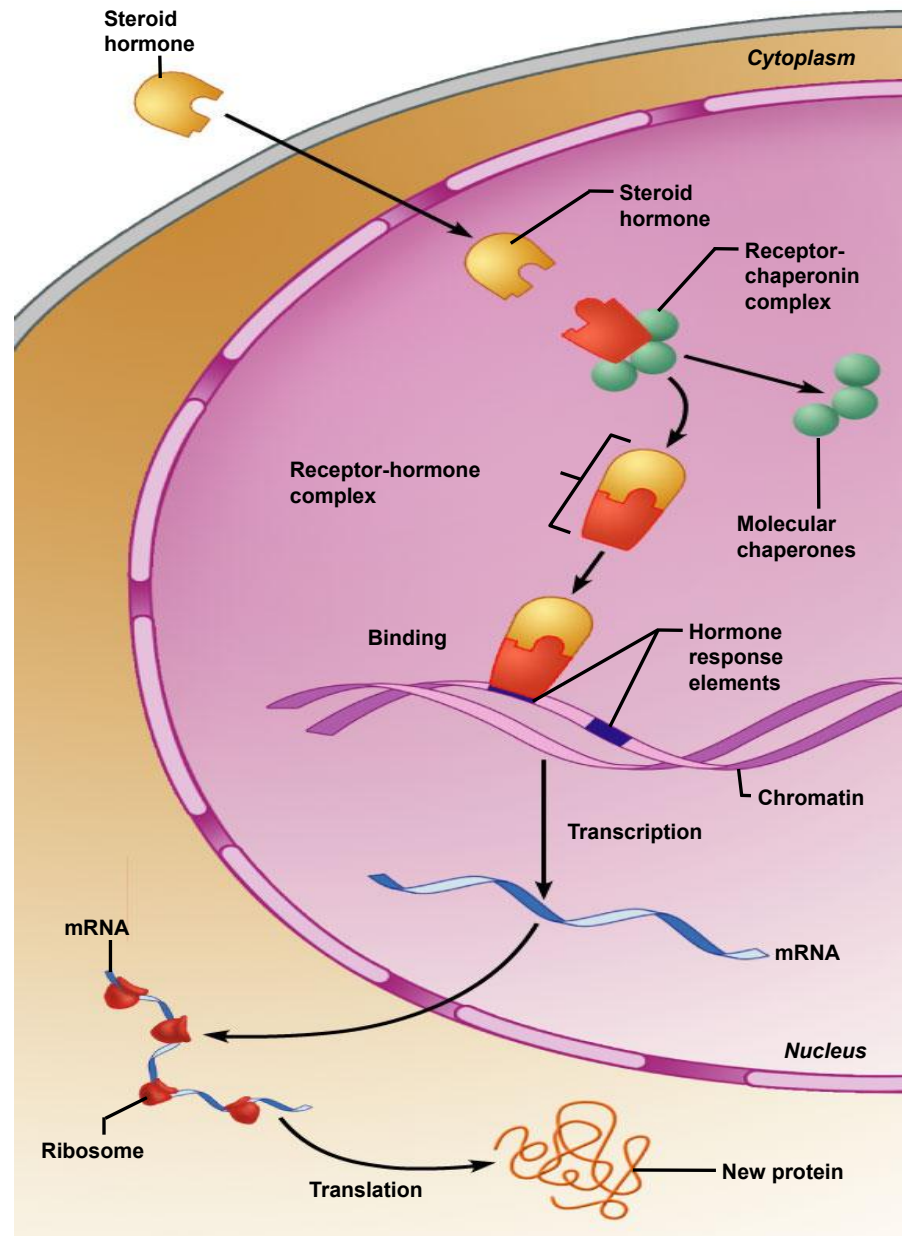


Figure 16.4

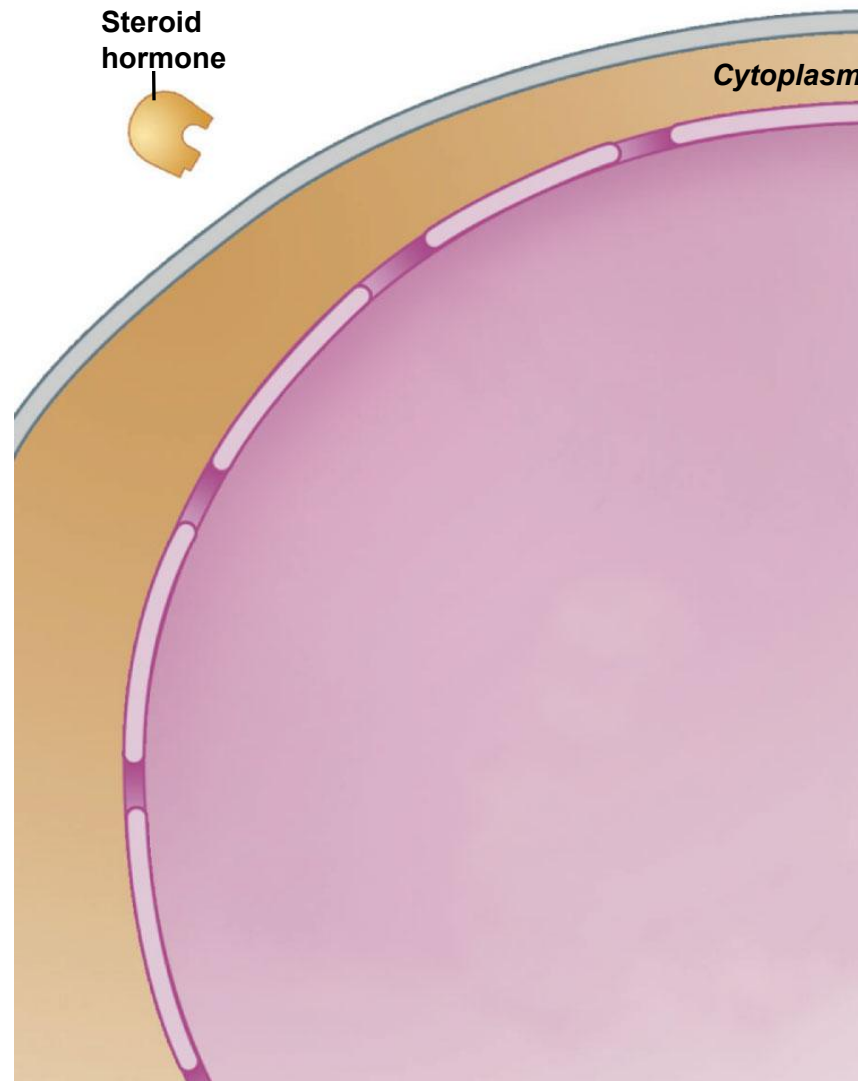


Figure 16.4

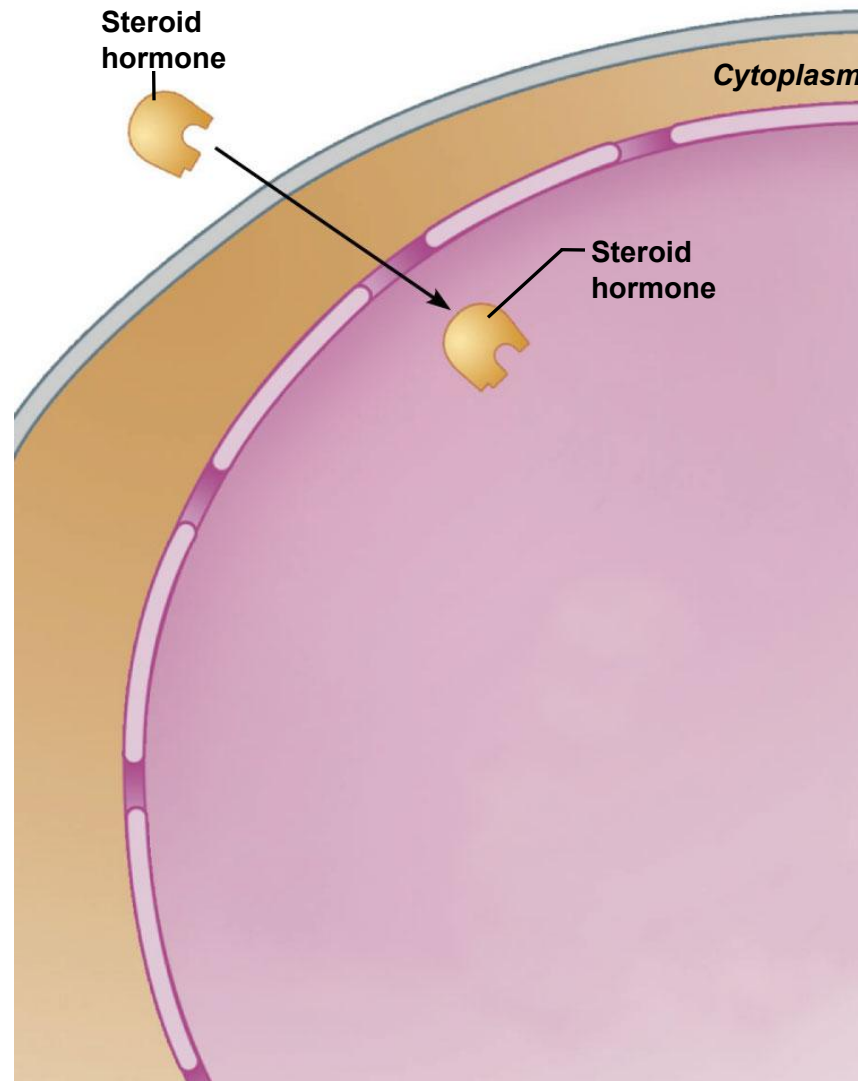


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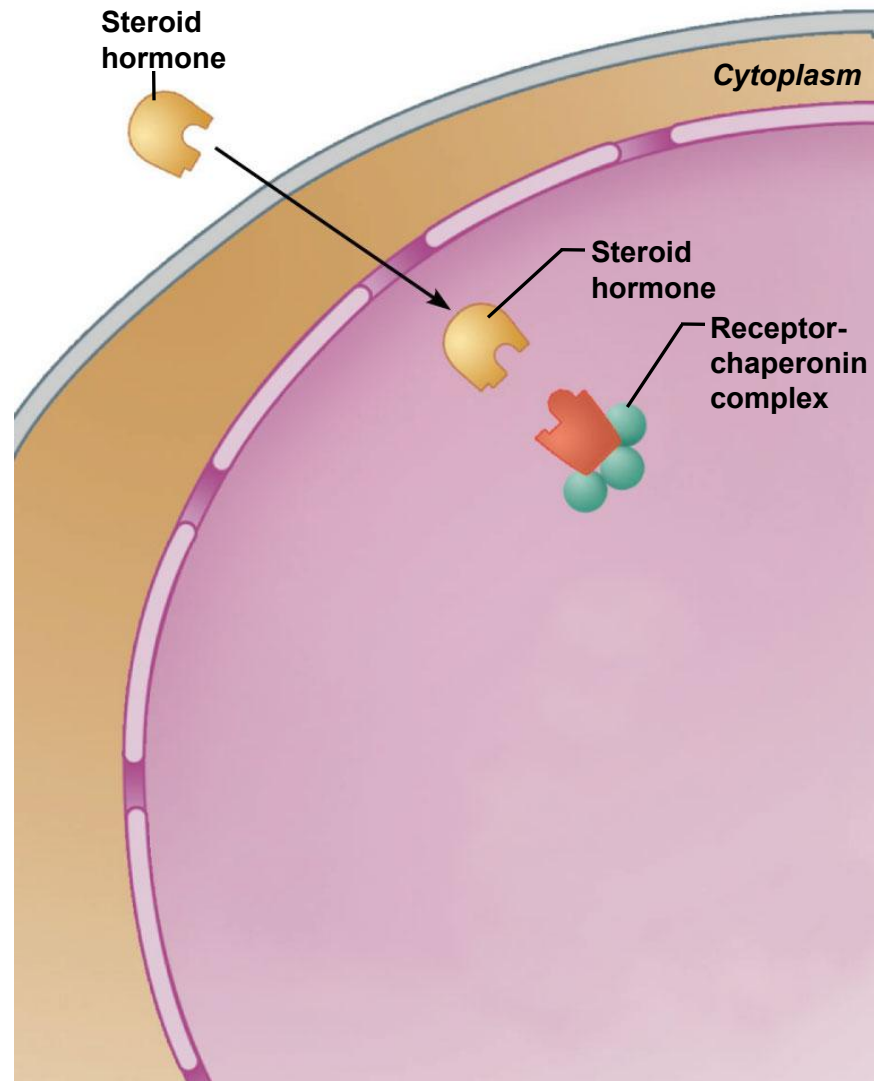


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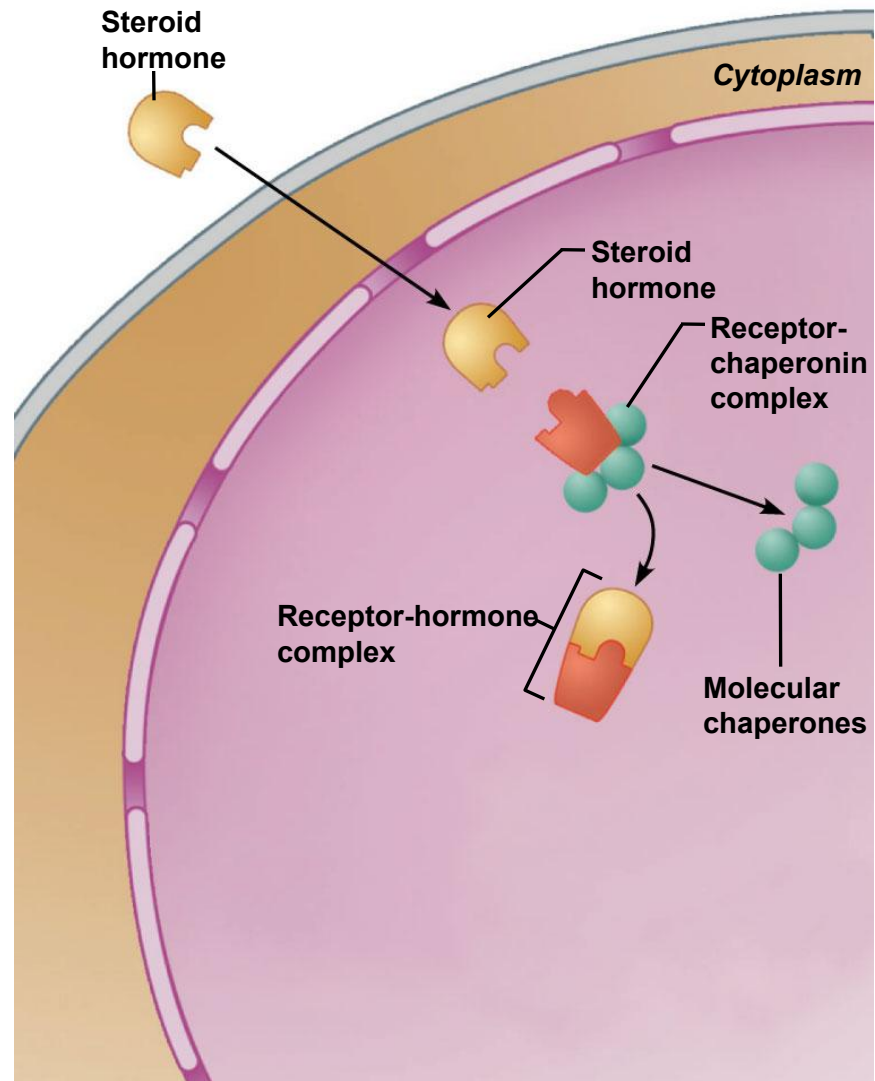


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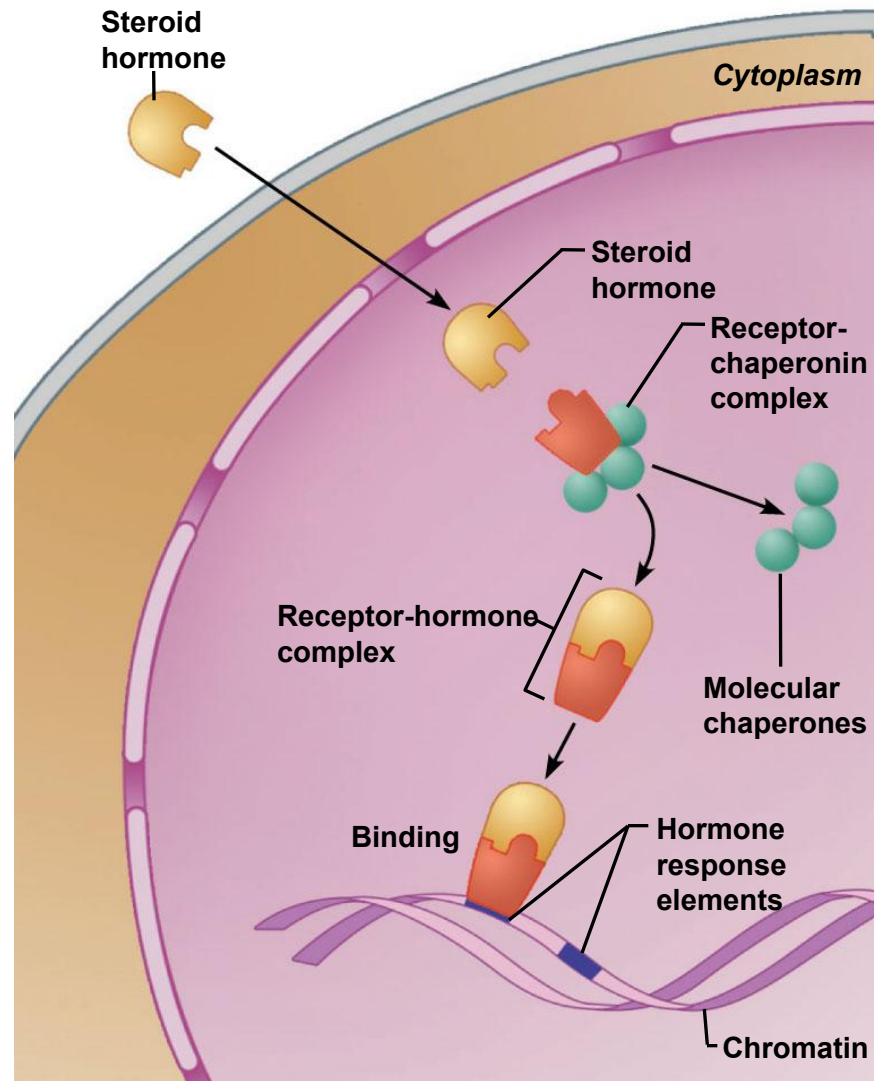


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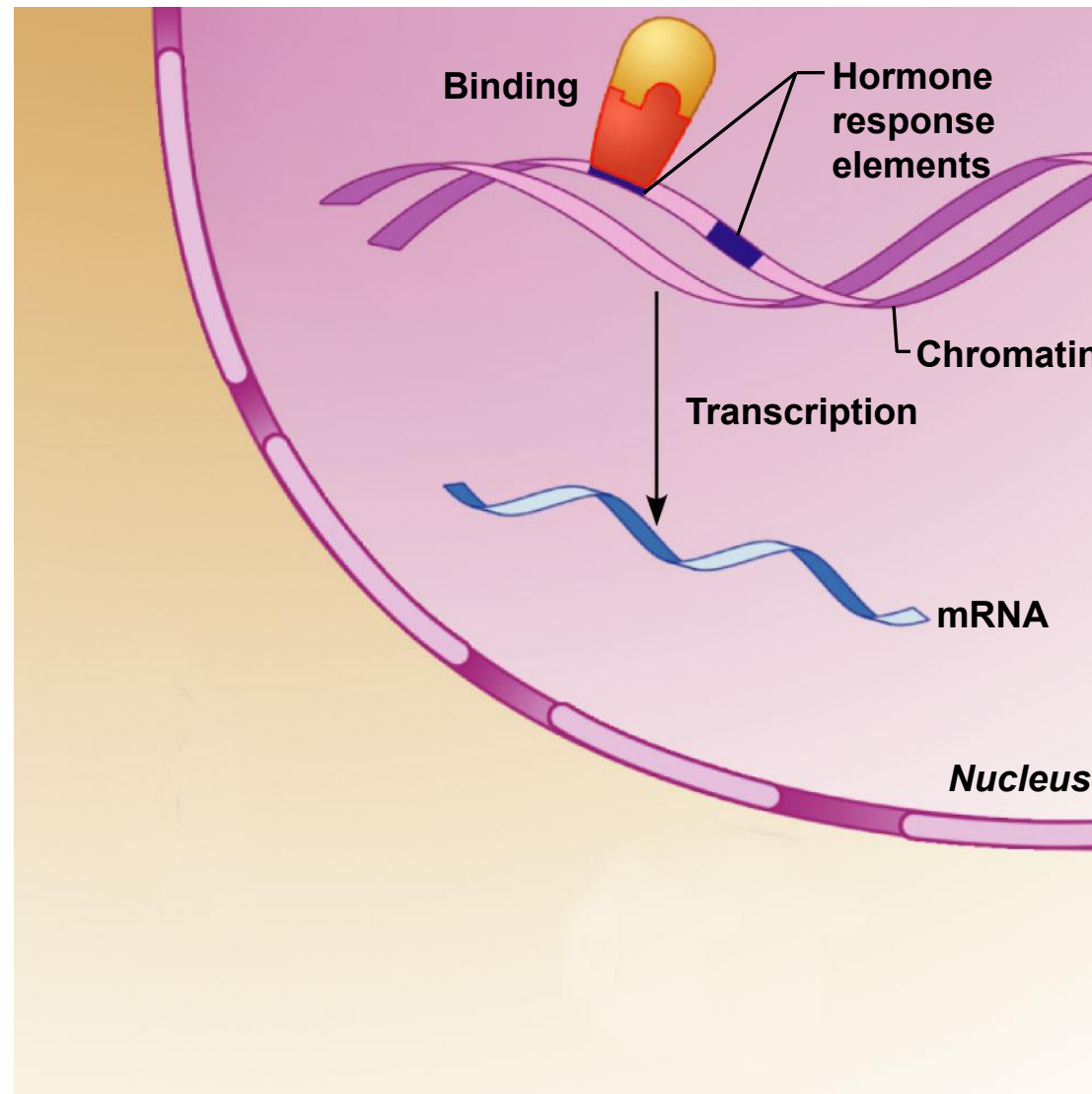


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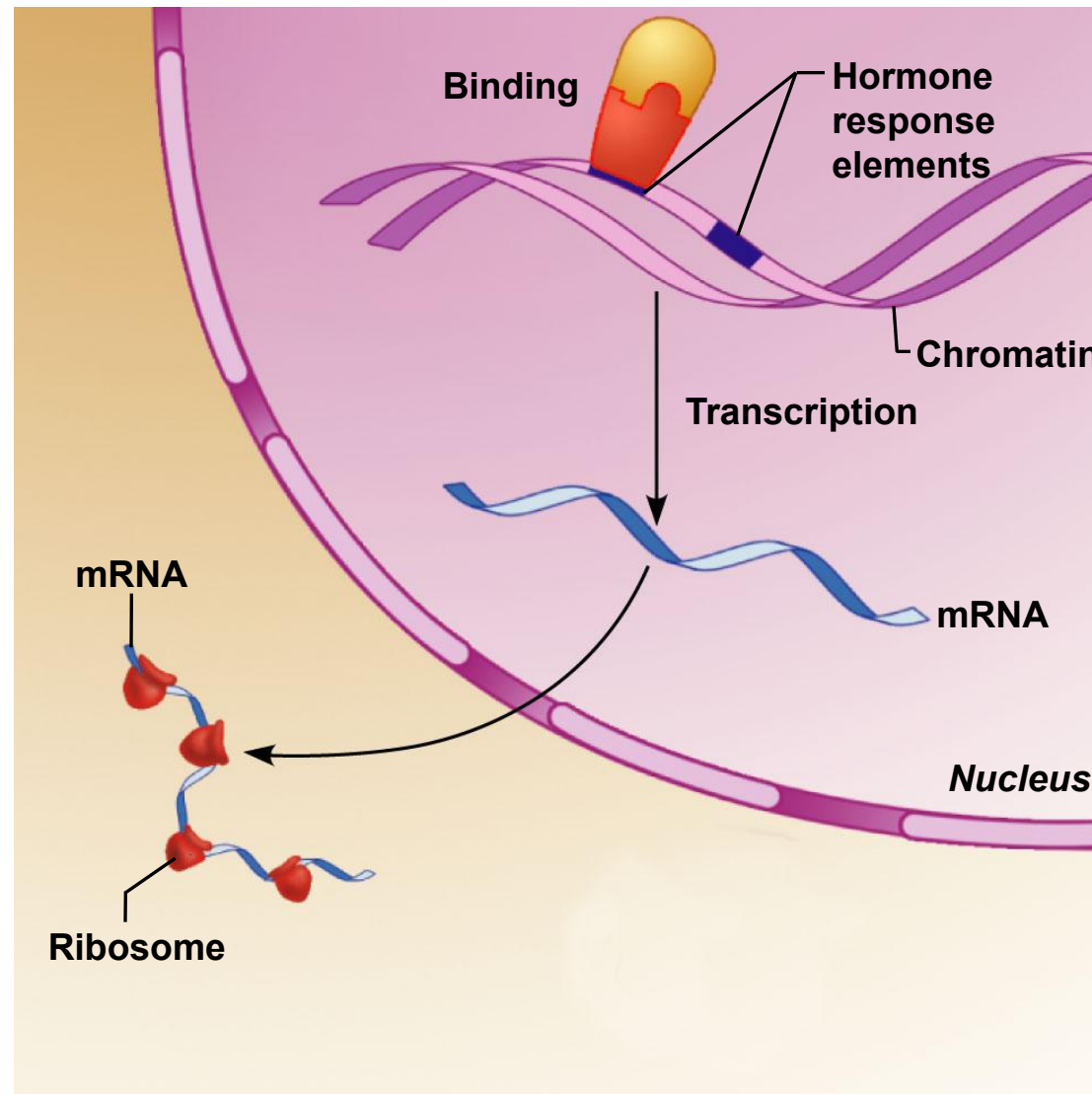


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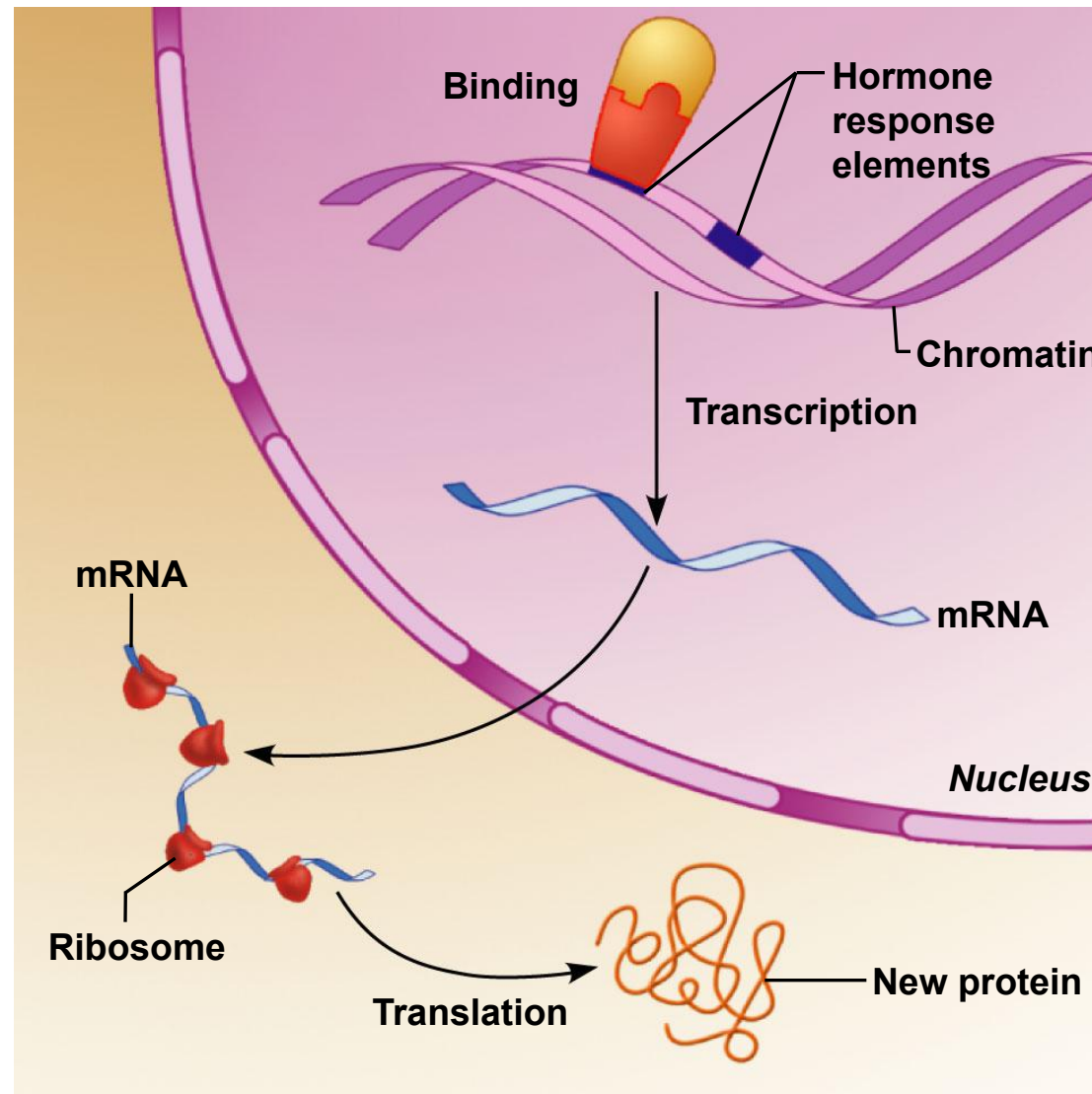


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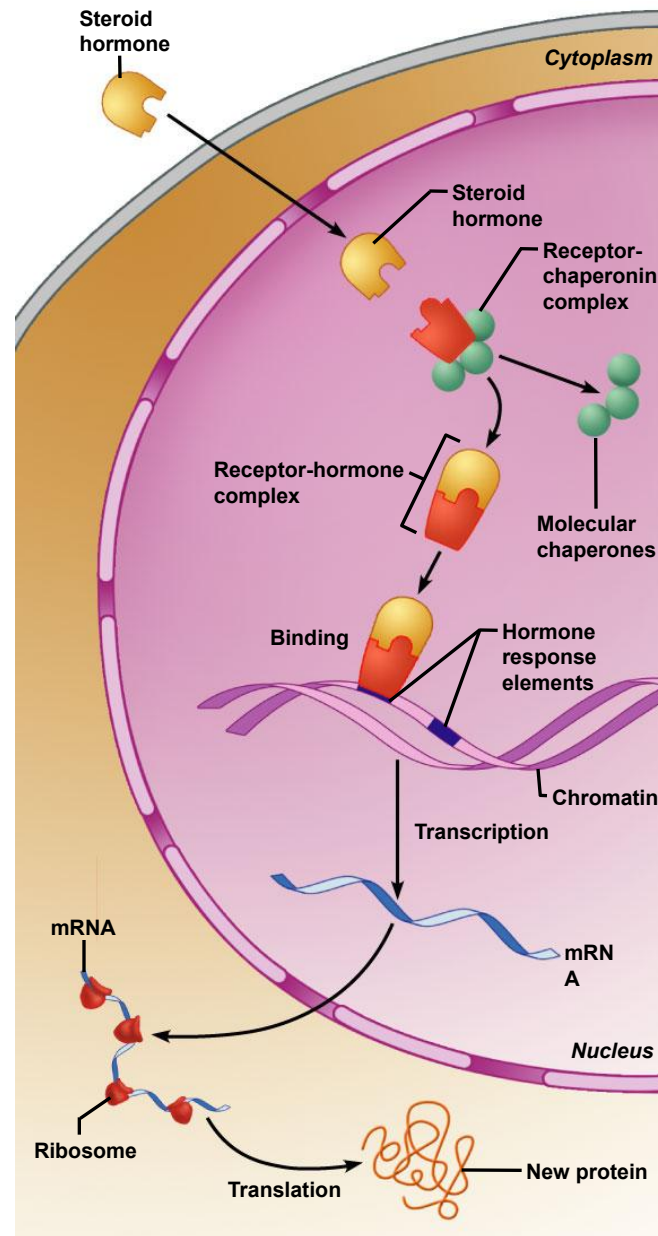


Figure 16.4

Target Cell Activation

- **Target cell activation depends on three factors**
 - Blood levels of the hormone
 - Relative number of receptors on the target cell
 - The affinity of those receptors for the hormone
- Up-regulation – target cells form more receptors in response to the hormone
- Down-regulation – target cells lose receptors in response to the hormone

Hormone Concentrations in the Blood

- Hormones circulate in the blood in two forms –
free or bound
 - Steroids and thyroid hormone are attached to plasma proteins
 - All others are free

Hormone Concentrations in the Blood

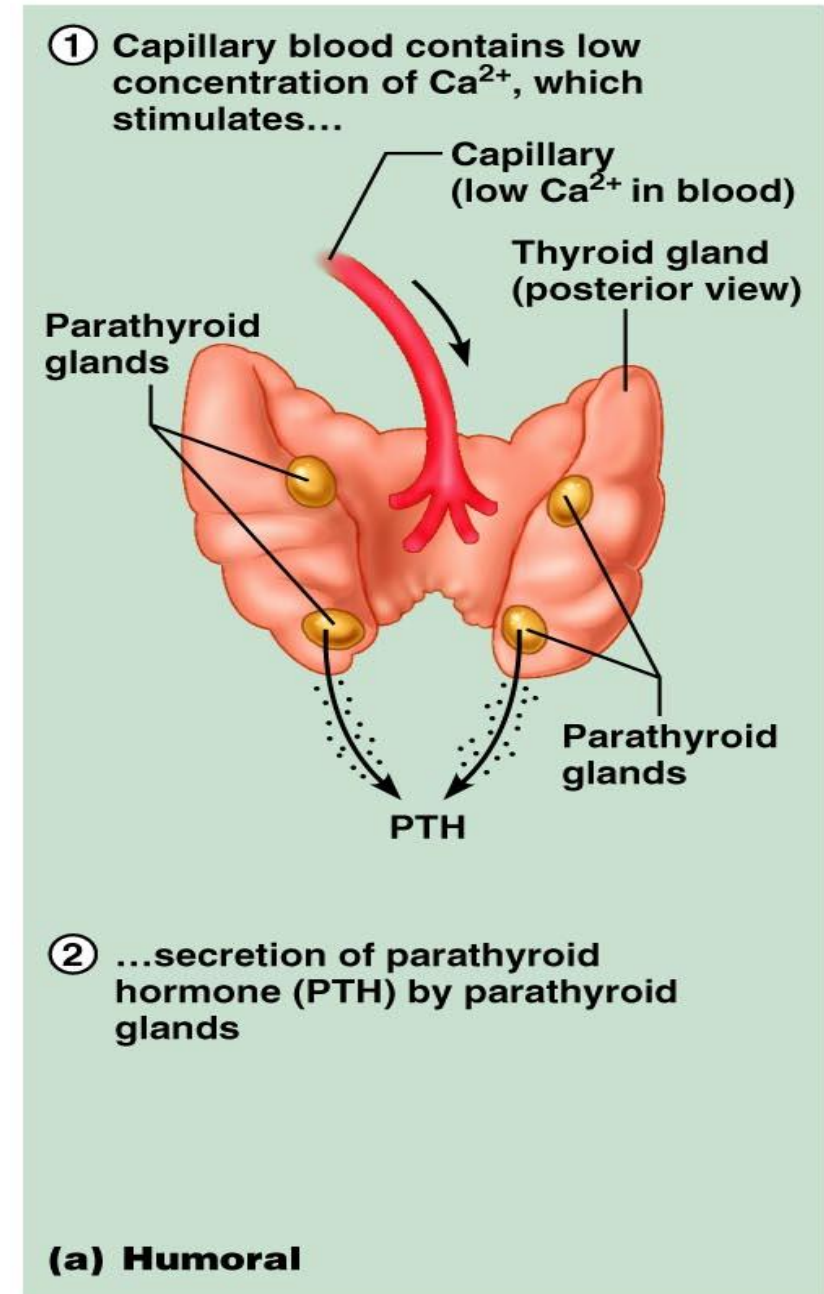
- Concentrations of circulating hormone reflect:
 - Rate of release
 - Speed of inactivation and removal from the body
- Hormones are removed from the blood by:
 - Degrading enzymes
 - The kidneys
 - Liver enzyme systems
- Blood levels of hormones:
 - Are controlled by negative feedback systems
 - Vary only within a narrow desirable range

Control of Hormone Release

- Hormones are synthesized and released in response to:
 - Humoral stimuli
 - Neural stimuli
 - Hormonal stimuli
 - Negative feedback mechanism

Humoral Stimuli

- Humoral stimuli – secretion of hormones in direct response to changing blood levels of ions and nutrients (ex. Oxygen, Sodium, water, glucose and Calcium)
- Example: concentration of calcium ions in the blood
 - Declining blood Ca^{2+} concentration stimulates the parathyroid glands to secrete PTH (parathyroid hormone)
 - PTH causes Ca^{2+} concentrations to rise and the stimulus is removed



Neural Stimuli

- Neural stimuli – nerve fibers stimulate hormone release

Ex: Stimulation of sympathetic

Inhibition of sympathetic

Stimulation of parasympathetic

Inhibition of parasympathetic

- Preganglionic sympathetic nervous system (SNS) fibers stimulate the adrenal medulla to secrete catecholamines

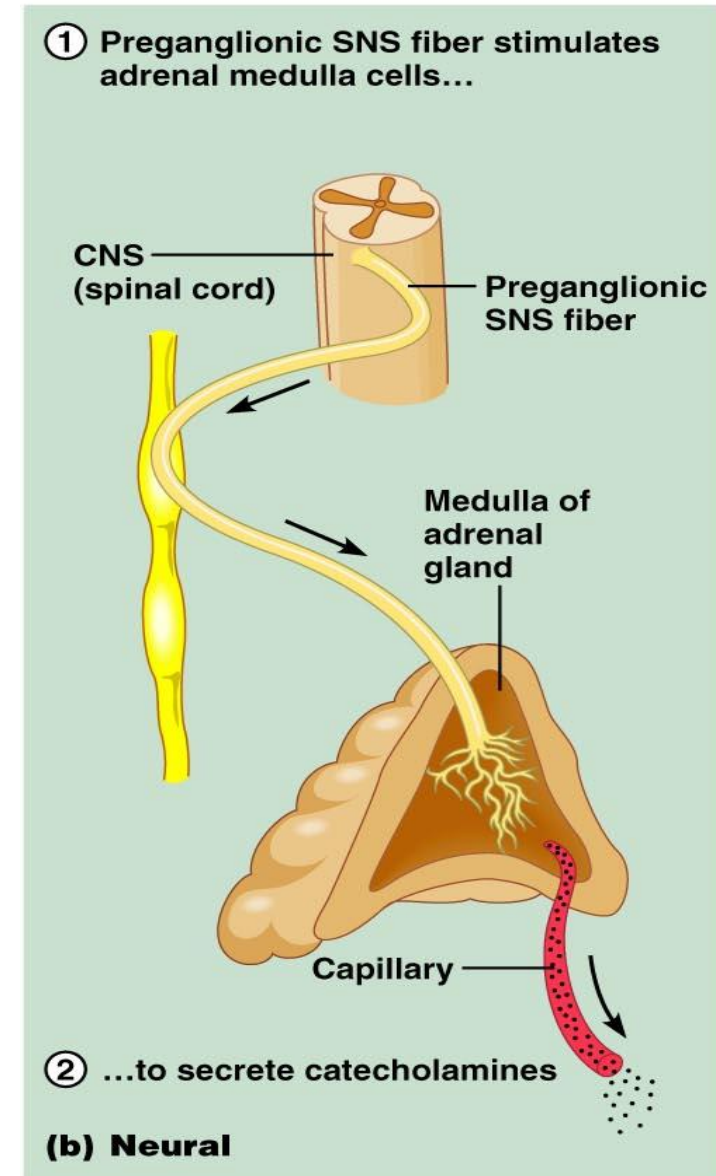
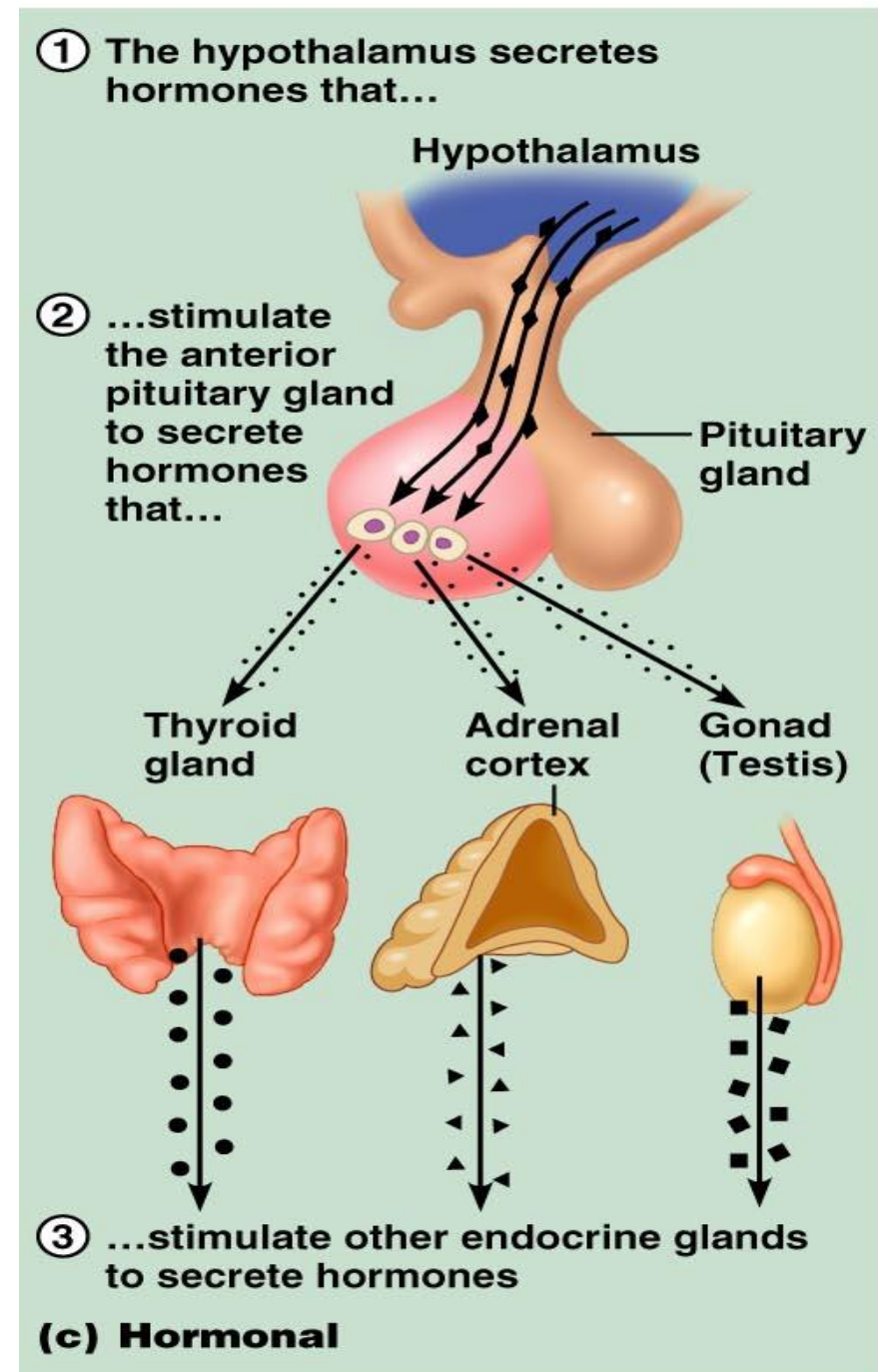


Figure 16.50

Hormonal Stimuli

- Hormonal stimuli – release of hormones in response to hormones produced by other endocrine organs
 - The hypothalamic hormones stimulate the anterior pituitary
 - In turn, pituitary hormones stimulate targets to secrete still more hormones

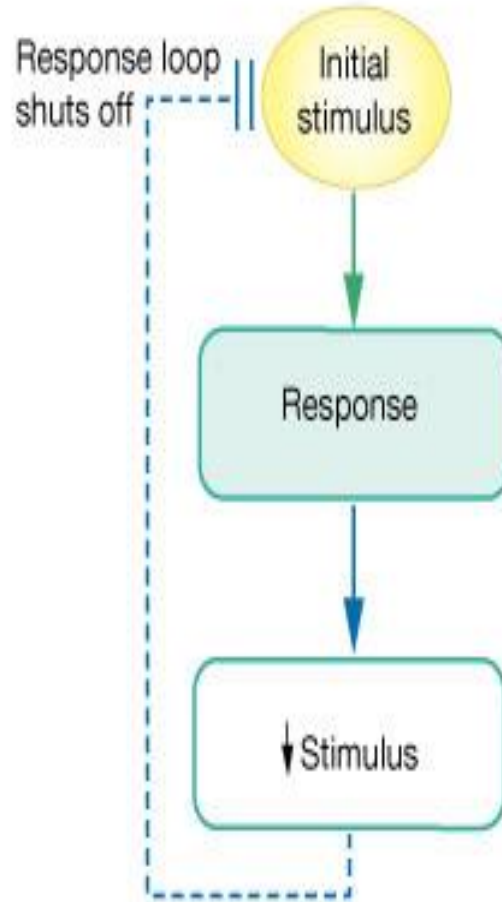


Feedback Loops

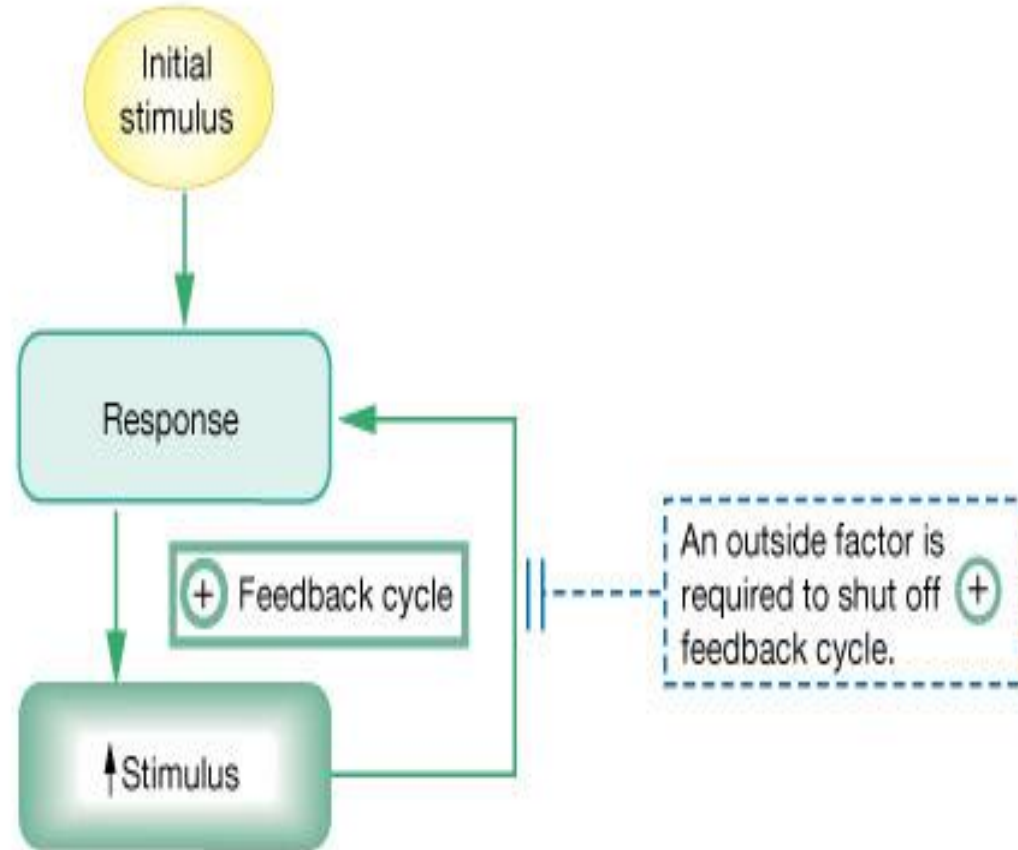
- **Negative Feedback:** Are Homeostatic
Response Slows Stimulation
Return to Optimal Range
- **Positive Feedback:**
Stimulation Drives more Stimulation

Feedback Loops

(a) Negative feedback: the response counteracts the stimulus shutting off the response loop.

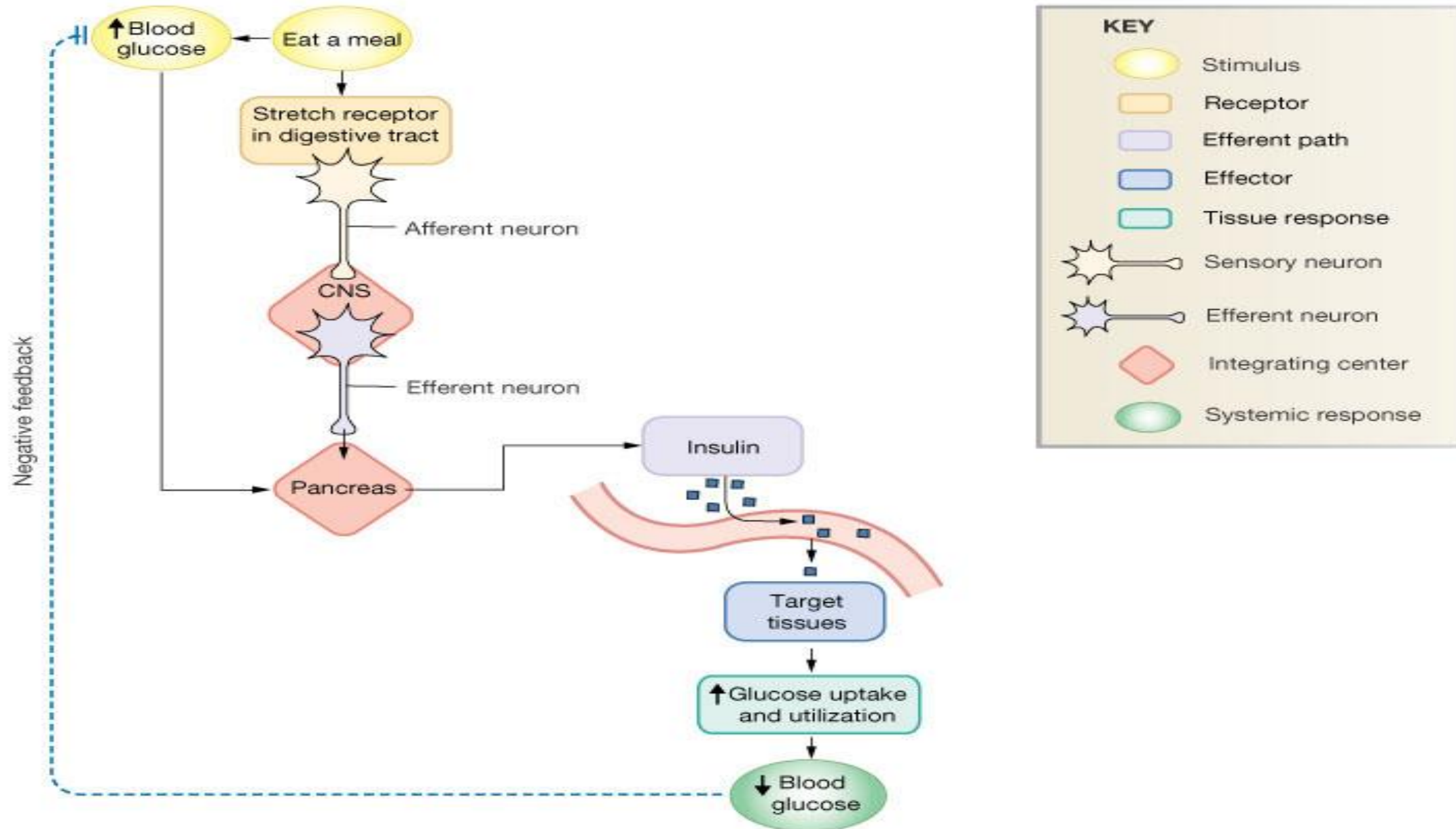


(b) Positive feedback: the response reinforces the stimulus sending the parameter farther from the setpoint.

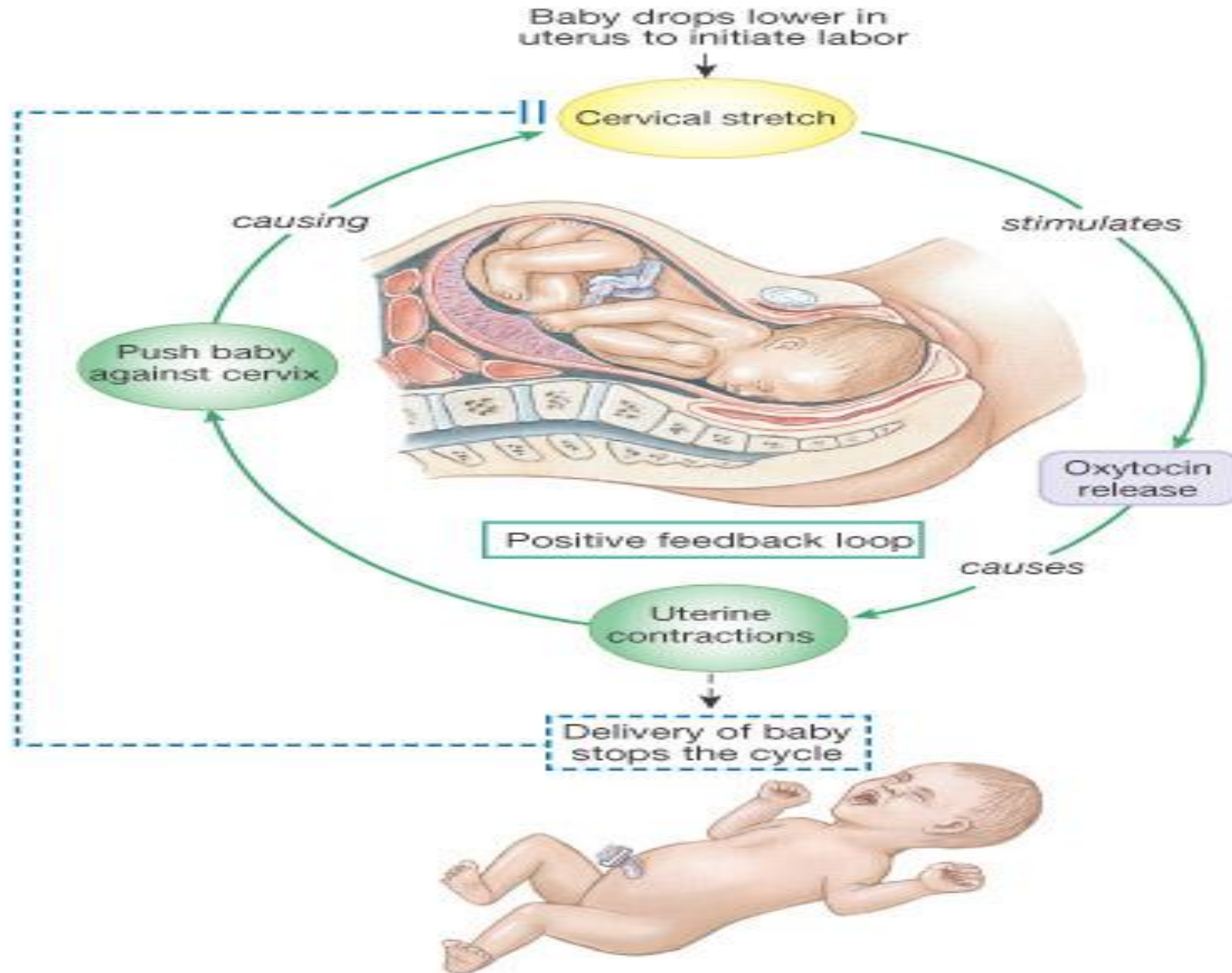


: **Negative and positive feedback**

Endocrine Reflex Pathways: Overview



Feedback Loops



Endocrine Reflex Pathways: Overview

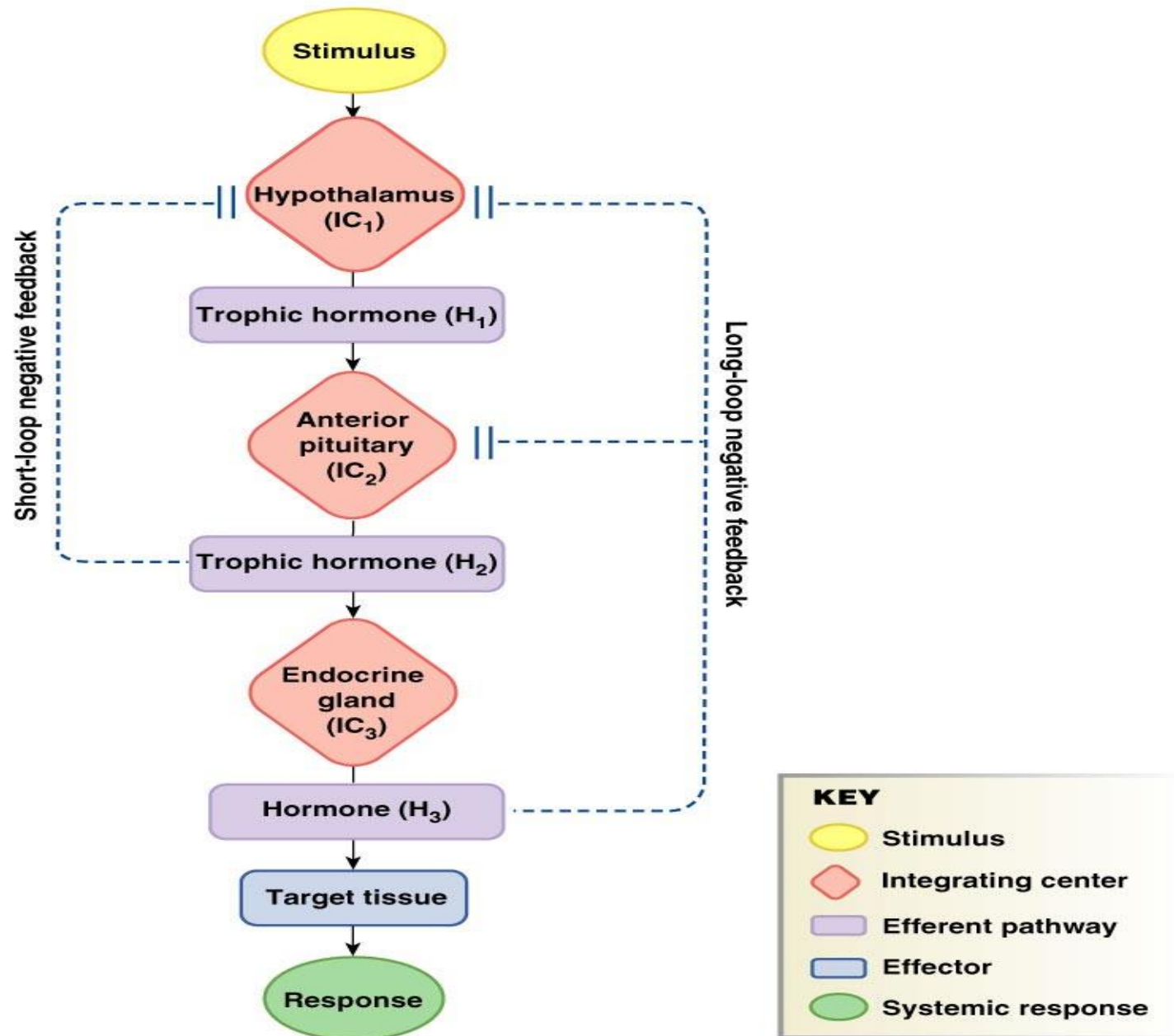
- Stimulus
- Afferent Signal
- Integration
- Efferent Signal (the hormone)
- Physiological Action
- Negative Feedback

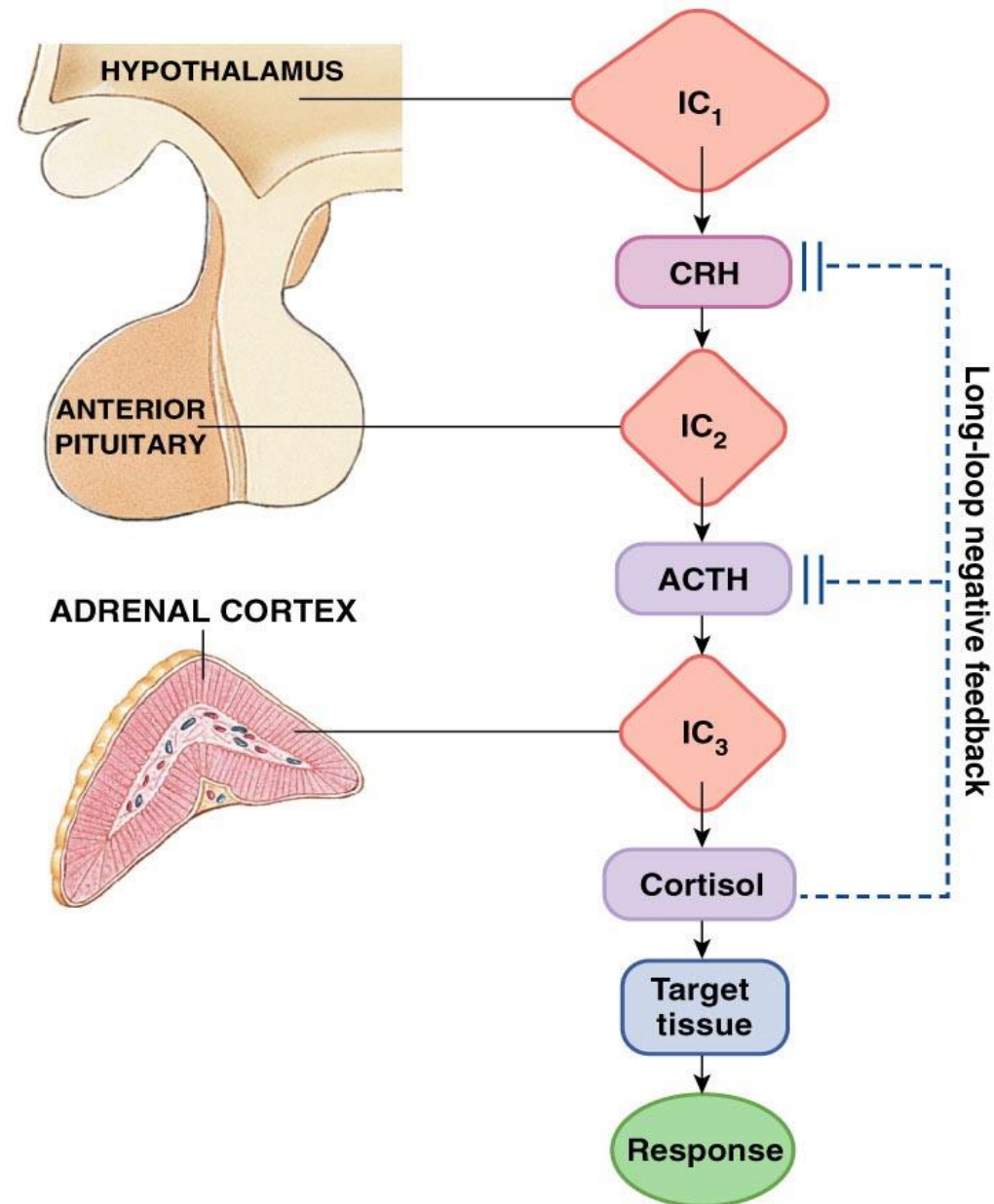
Endocrine Control: Three Levels of Integration

- Hypothalamic Stimulation—from CNS
- Pituitary Stimulation—from Hypothalamic Trophic Hormones
- Endocrine Gland Stimulation—from Pituitary Trophic Hormones

Neurohormones: Secreted into the Blood by Neurons

- Adrenal Medulla–Catecholamines
- Hypothalamus to:
 - Anterior Pituitary
 - Trophic Hs
 - Growth H.
 - Prolactin
 - Posterior Pituitary
 - Vasopressin
 - Oxytocin





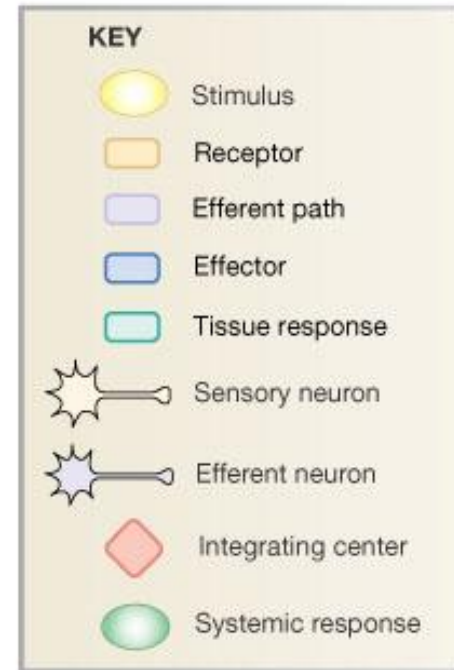
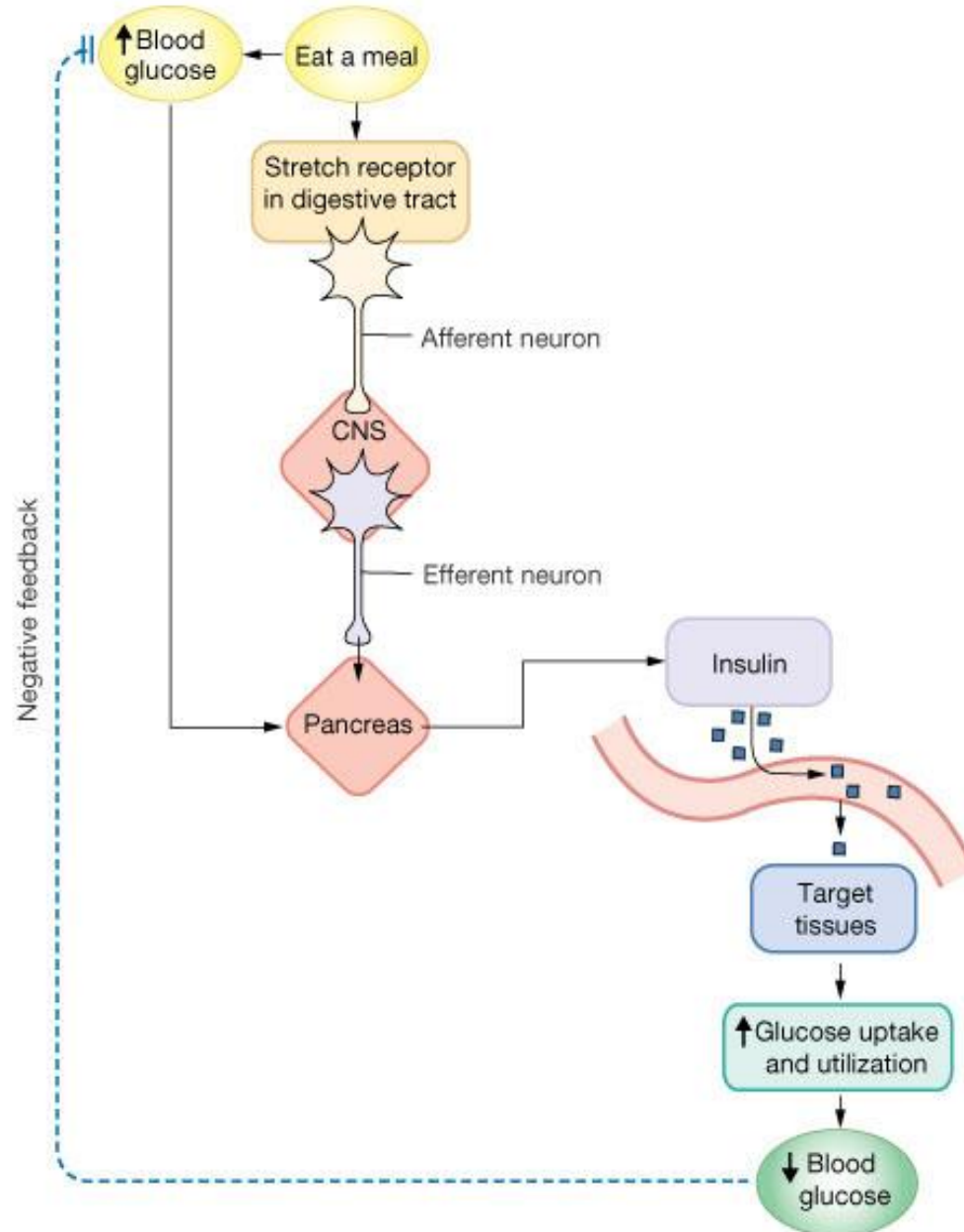
Multiple Stimuli for Hormone Release: Nervous & Endocrine

Stimuli:

- Stretch
- Glucose
- Insulin Levels

Reflex:

- Lower Blood Glucose
- Reduces Stimulus
- Reduces Insulin Release



Multiple Hormones Can Target a Cell/Tissue

- Growth H
- Thyroxin
- All have Receptors on Many Tissues
- Stimulate Pathways for Growth

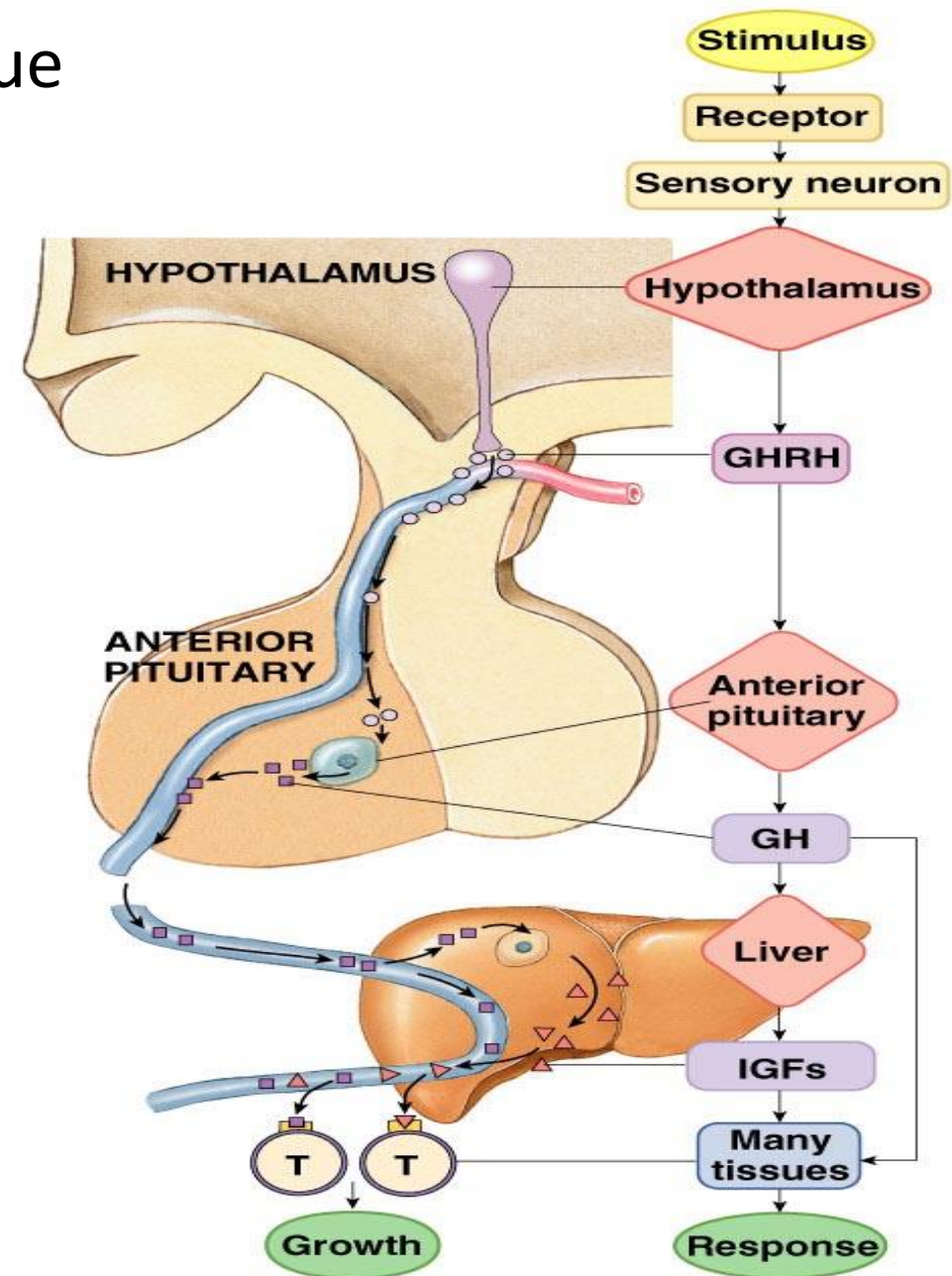
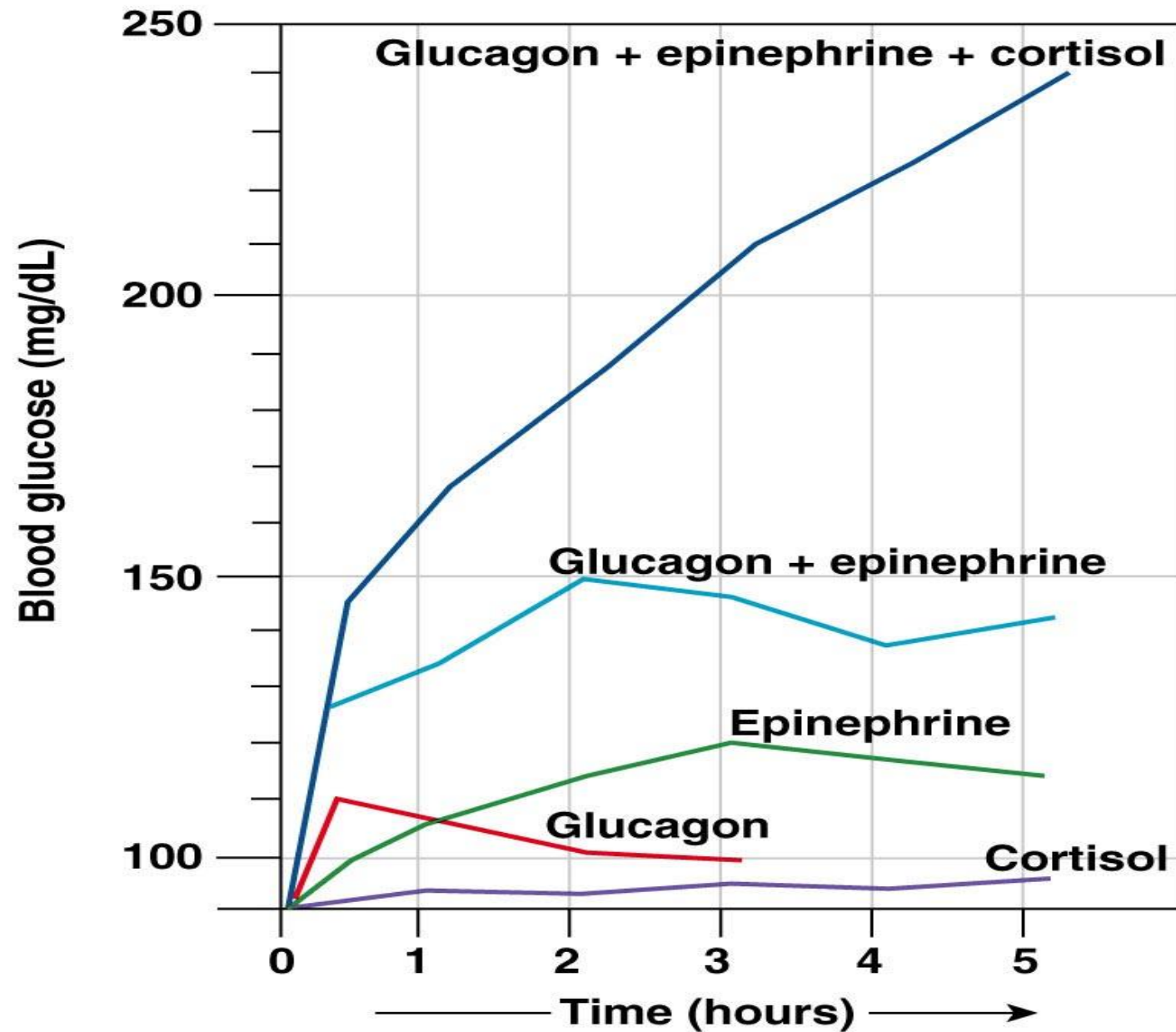


Figure 7-17: A complex endocrine pathway

Interaction of Hormones at Target Cells

- Two types of hormone interaction
 - Synergism – more than one hormone produces the same effects on a target cell
 - Antagonism – one or more hormones opposes the action of another hormone
- Synergism: Multiple Stimuli more than Additive
 - Cortisol +5
 - Glucagon +10
 - Epinephrine +20 (added = +35)
 - Synergistic Effect + 140
- Antagonism: Glucagons Opposes Insulin



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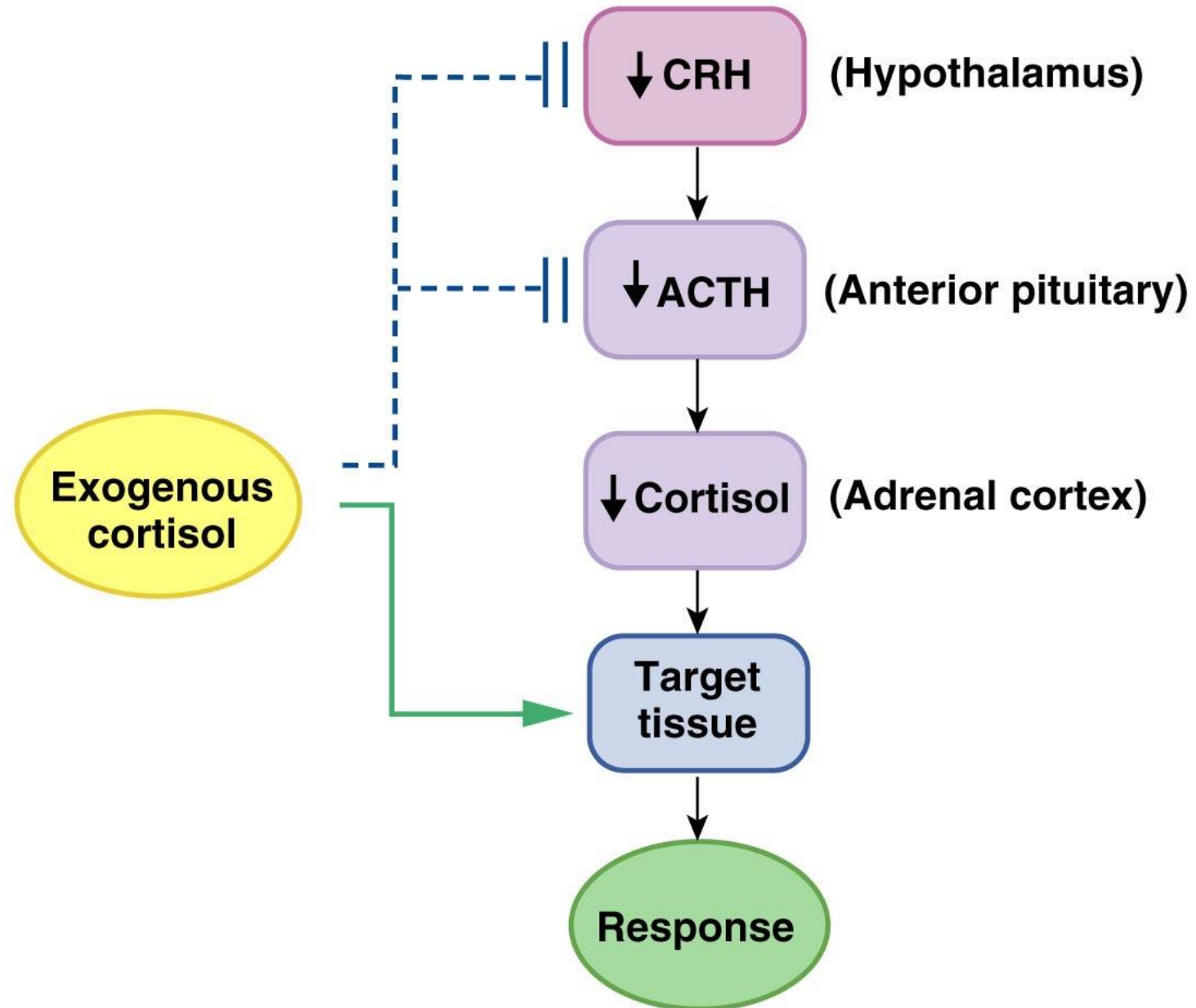
Figure 7-18

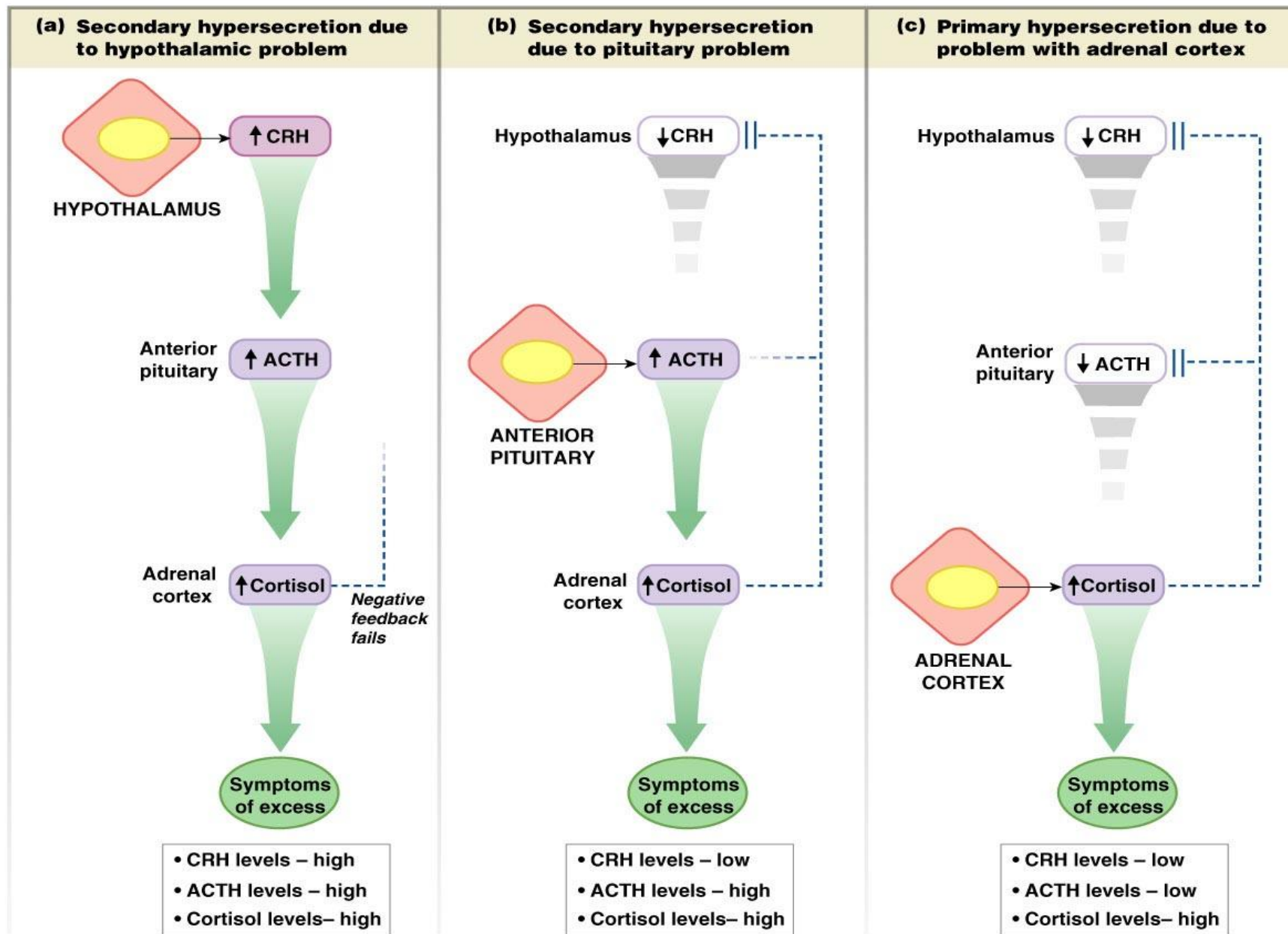
Nervous System Modulation

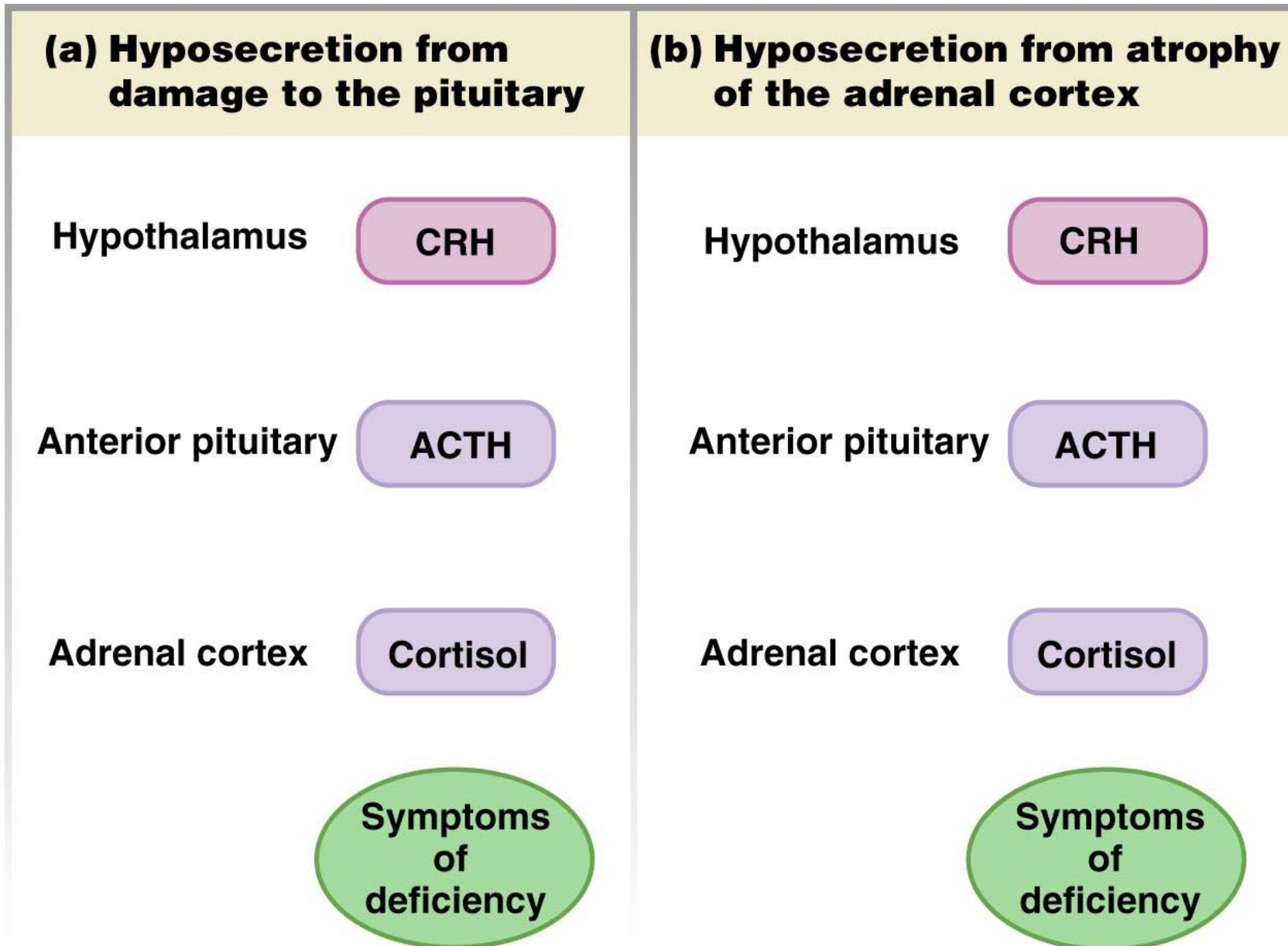
- The nervous system modifies the stimulation of endocrine glands and their negative feedback mechanisms
- The nervous system can override normal endocrine controls
 - For example, control of blood glucose levels
 - Normally the endocrine system maintains blood glucose
 - Under stress, the body needs more glucose
 - The hypothalamus and the sympathetic nervous system are activated to supply ample glucose

Pathologies: Over or Under Production

- “No Bad Hormones – Just Too Much or Too Little”
- Exogenous medication
 - Replaces & Exceeds Normal
 - Cause Atrophy of Gland
- Hypersecretion: Too Much
 - Tumors or Cancer
 - Grave's Disease- Thyroxin
- Hyposecretion: Too Little
 - Goiter – Thyroxin
 - Diabetes – Insulin







Hypothalamus releasing factors and the pituitary gland

Dr Safa Abdul Ghani

Major Endocrine Organs

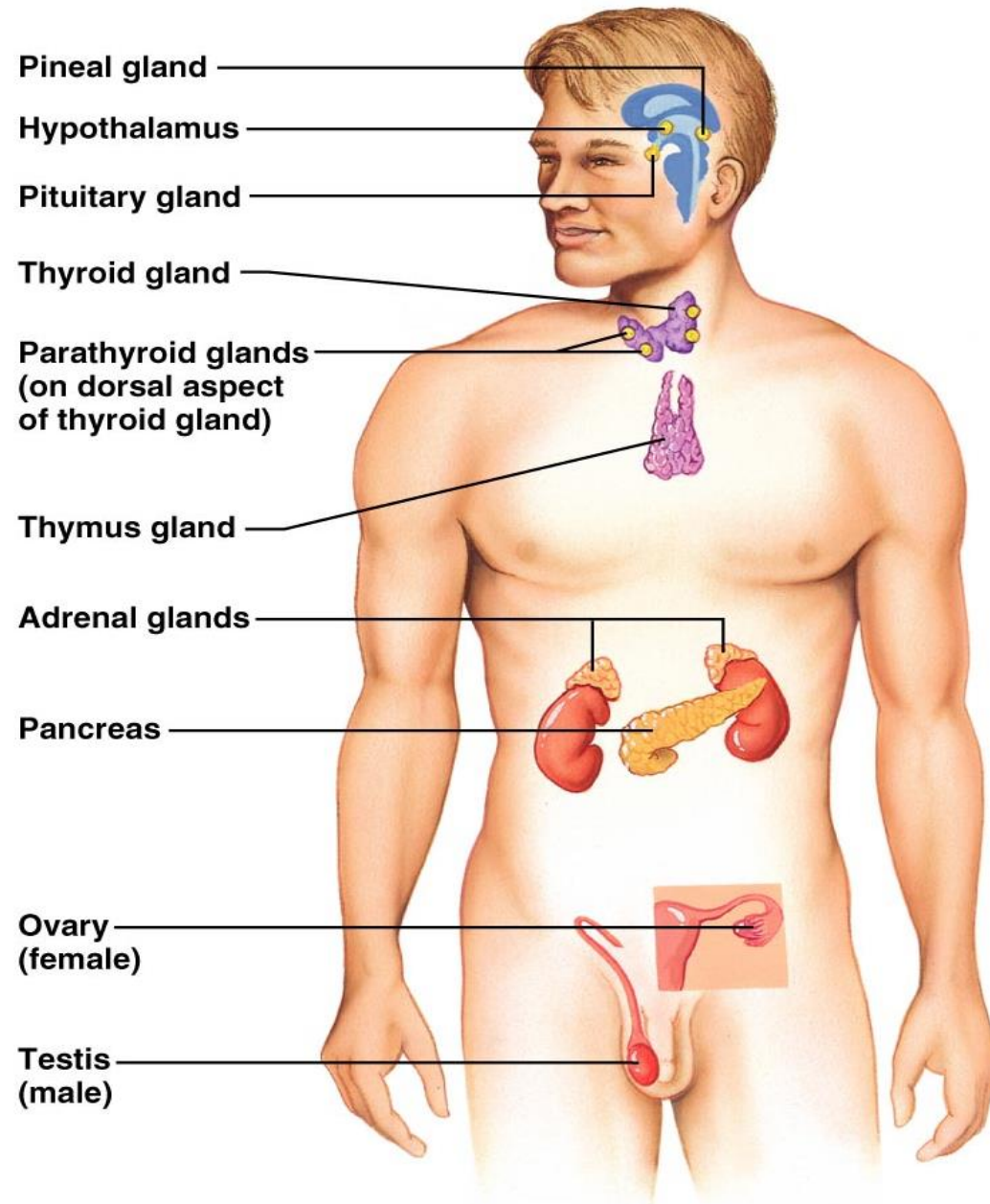


Figure 16.1

Regulatory functions of Hormones

Growth Balance

- Growth Hormones
- Thyroxin Hormones: released from thyroid glands essential for metabolic reactions, production of energy and control of growth and maturation
- Corticosteroidal Hormones: released from the cortex of adrenal medulla (regulate fat, carbo, protein metabolism)

Control of Energy Balance

- **Insulin**: Secreted from Langerhans cells at the pancreas. Decrease blood glucose and increase glucose uptake
- **Glucagon**: Increase blood glucose and decrease glucose uptake
- **Adrenaline**: secreted from the medulla of adrenal gland
 1. Increase energy production
 2. Stimulates lipids activity by converting lipids to fatty acids
 3. Stimulate degradation of glycogen
 4. Increase heart rate and blood pressure
 5. Bronchodilation
 6. Decrease secretions and intestinal motility

Control of Electrolyte Balance

- **Ca²⁺ Balance:**

- A. **Parathyroid Hormones (PTH)** → increase Ca²⁺ intestinal absorption, adsorption from bones and reabsorption from tubule of nephron
- B. **Calcitonin** (secreted from thyroid) → decrease Ca²⁺ intestinal absorption and reabsorption from tubule of nephron, increase absorption to the bones

- **Na⁺ Balance:**

- A. **Aldosterone** (secreted from cortex of adrenal gland) → increase Na⁺ intestinal absorption and reabsorption from tubule of the nephron
- B. **Renin** (secreted from juxta-glomerular cells in the kidney) → controls the production of Angiotensin, which stimulates the release of Aldosterone from adrenal gland

Reproduction

1. Brain level (Hypothalamus):

(GnRH) Gonadotropin releasing hormone

2. Pituitary Gland

- A. **Follicle stimulating hormone (FSH)** → stimulates production of gametes , spermatogenesis males and Oogenesis in females
- B. **Leutenizing hormones(LH)** → stimulate release of sex hormones , Affects release of oestrogen and progesterone, ovulation in females and increase release of testosterone in testis.
- C. **Prolactin** → affects production of milk after delivery
- D. **Oxytocin** → stimulate the release of milk during lactation and uterus contraction during delivery
- E. **Relaxin** → relaxation of cervix and vagina during delivery

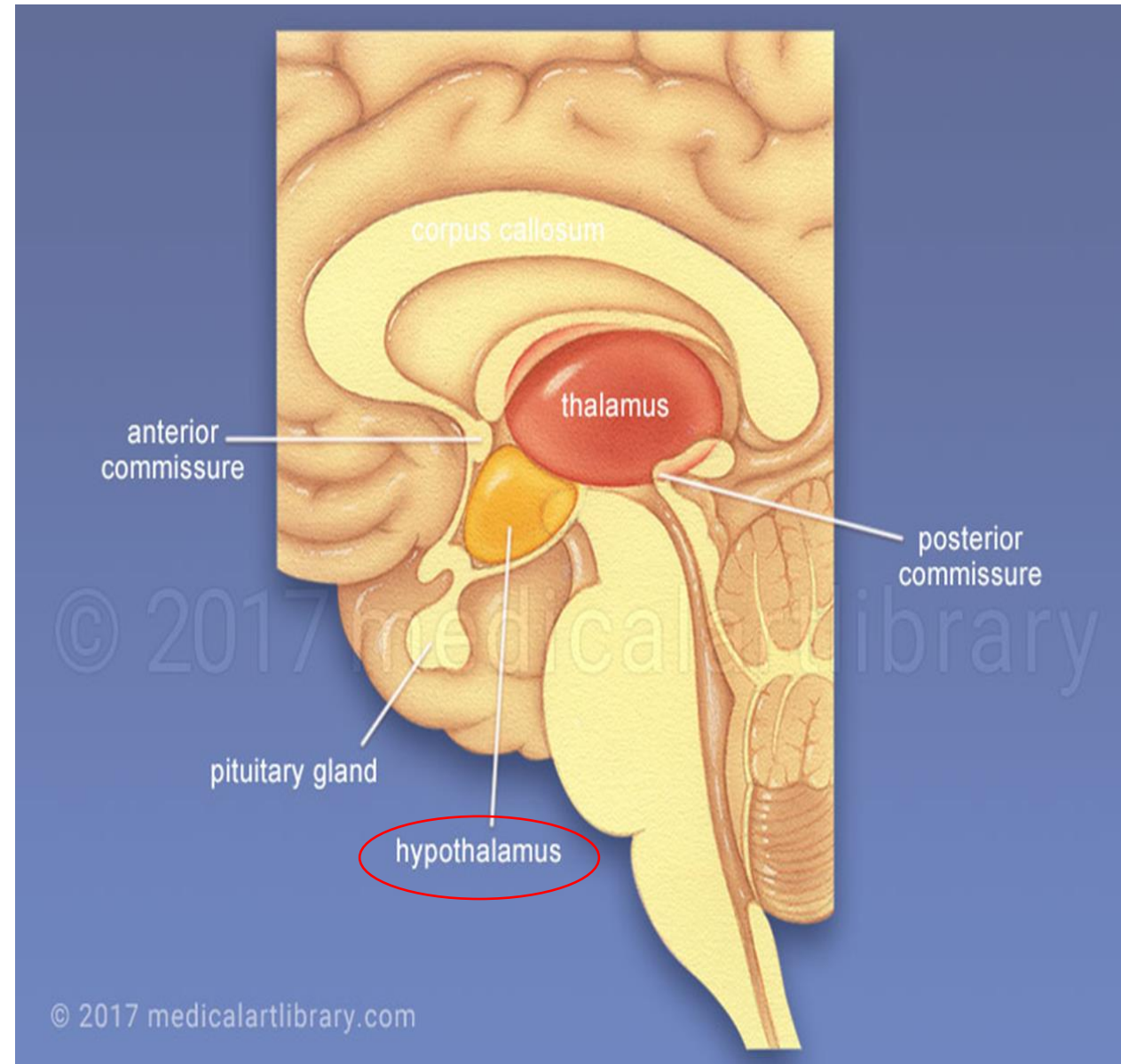
3. Gonads

- A. **Testosterone:** stimulate spermatogenesis , development of secondary sex organs
- B. **Estrogen:** secreted from the ovaries and essential for the development of Graffian follicle, development of endometrium for implantation of fertilized egg
- C. **Progesterone:** inhibition of FSH release to prevent the development of new Ova during pregnancy, prepare the uterus for implantation and prevent the production and release of prolactine, oxytocin and relaxin before delivery
- D. **Placental Hormones:** to keep pregnancy

Hypothalamus releasing factors
and neurohypophysis/
adenohypophysis of the
pituitary gland

HYPOTHALAMUS

- The portion of the brain that maintains the body's internal balance (homeostasis).
- The hypothalamus is the link between the endocrine and nervous systems.
- The hypothalamus produces releasing and inhibiting hormones, which stop and start the production of other hormones throughout the body.



Hypothalamus

- Temperature regulation
- Appetite centre and satiety centre to control food intake
- Thirst centre to control water intake
- Control water balance by having Osmoreceptor
 - I. Supra optic nucleus (SON) release ADH which controls water reabsorption in distal tubule of the nephron
 - II. Thirst centre which controls water intake
- **Control centre for endocrine system, control the release of tropic hormones from pituitary gland.**

Major Endocrine Organs: Pituitary (Hypophysis)

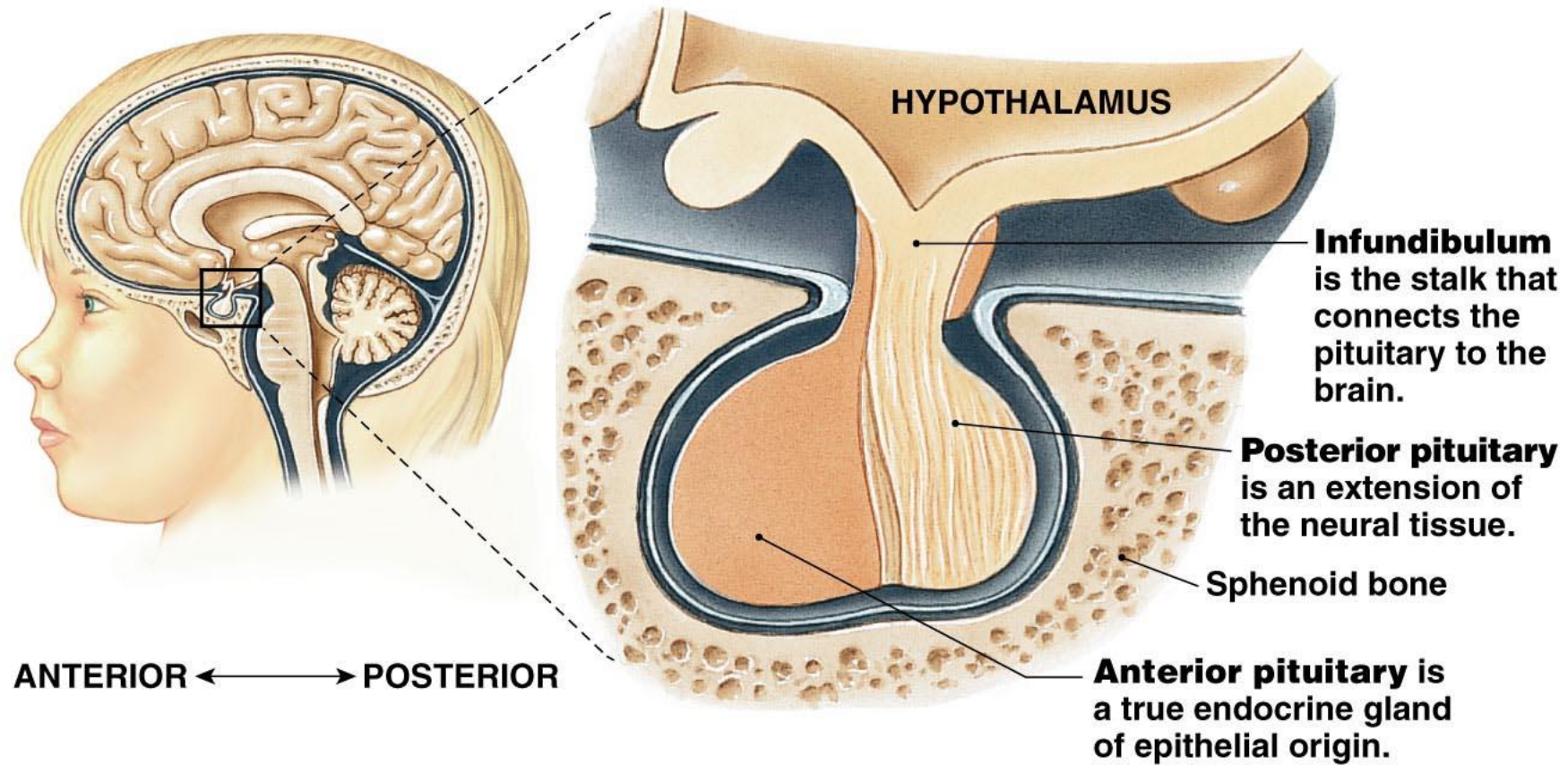
- Pituitary gland – two-lobed organ that have different embryonic origins, regulated separately and produce different hormones

- **Neurohypophysis** – posterior lobe (**neural tissue**)

Receives, stores, and releases hormones from the hypothalamus. Secretes neuroendocrine in response to changes in osmolality and volume or to mechanical sensation.

- **Adenohypophysis** – anterior lobe, made up of **glandular tissue**

- Synthesizes and secretes a number of hormones. Regulated by negative feedback via hormones from the target organ.



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- The hypothalamus sends a chemical stimulus to the anterior pituitary
 - **Releasing hormones** stimulate the synthesis and release of hormones
 - **Inhibiting hormones** shut off the synthesis and release of hormones

Figure 7-11

Major Endocrine Organs:
Pituitary (Hypophysis)

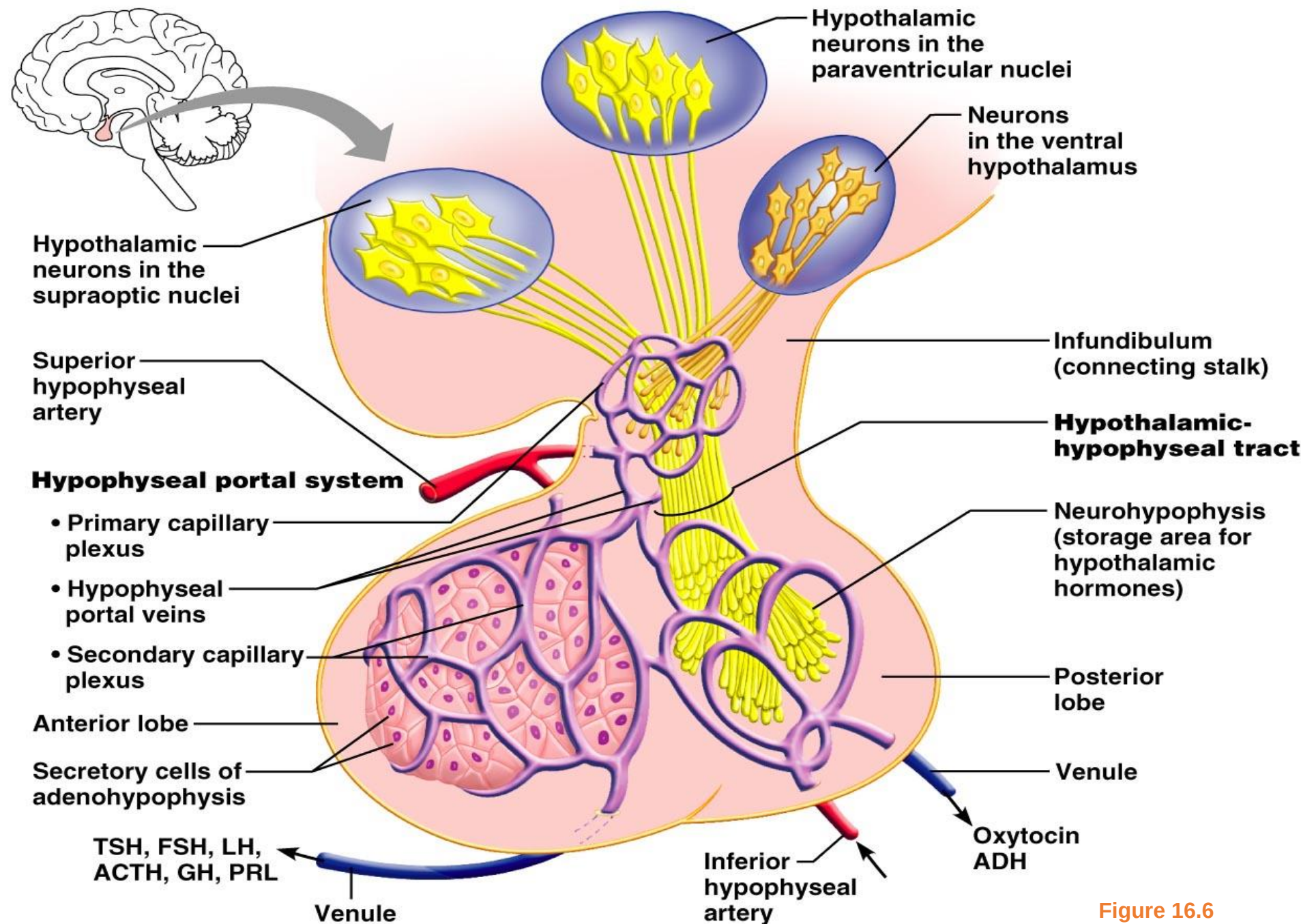
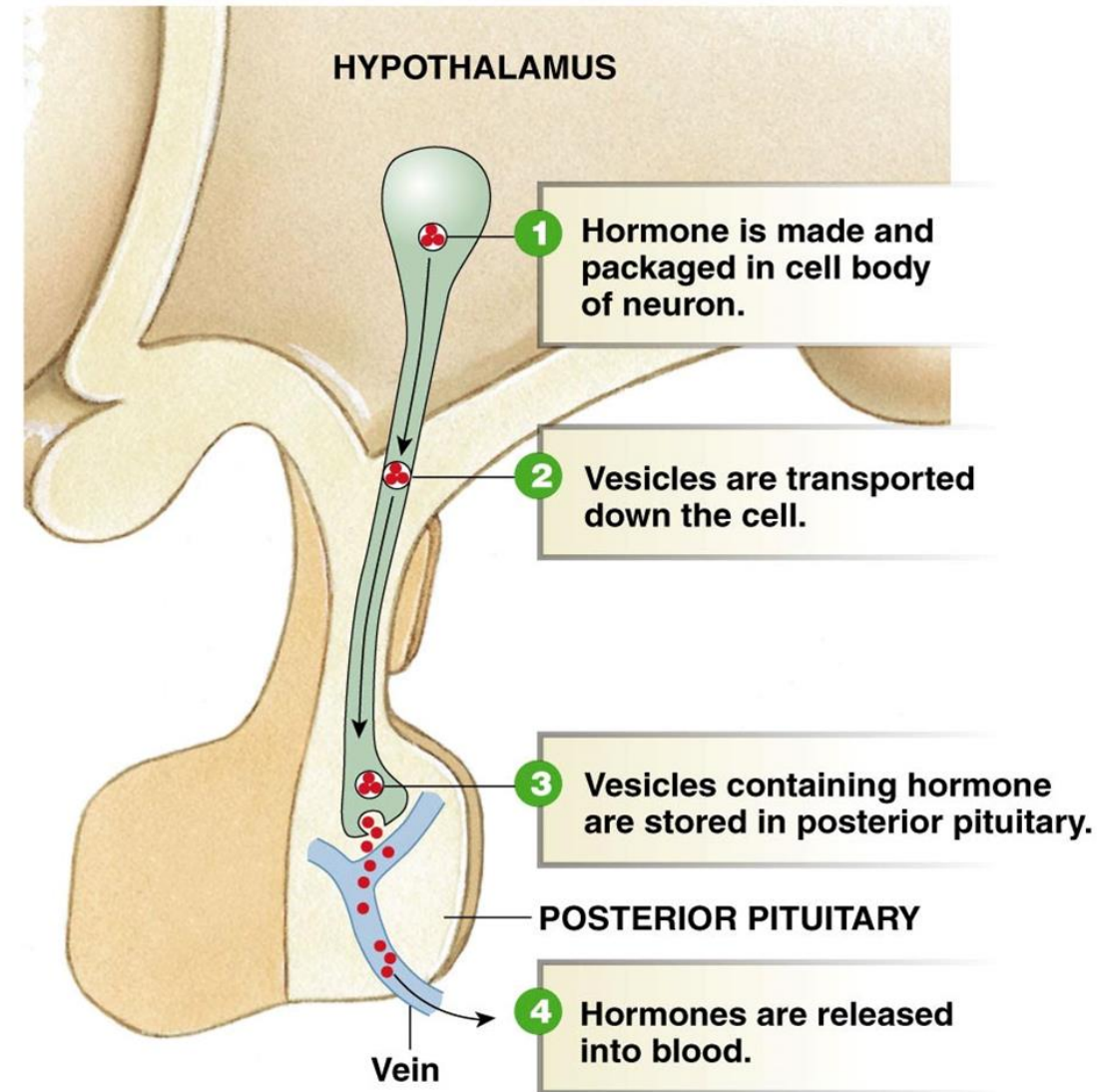


Figure 16.6

Pituitary-Hypothalamic Relationships:

Posterior Lobe

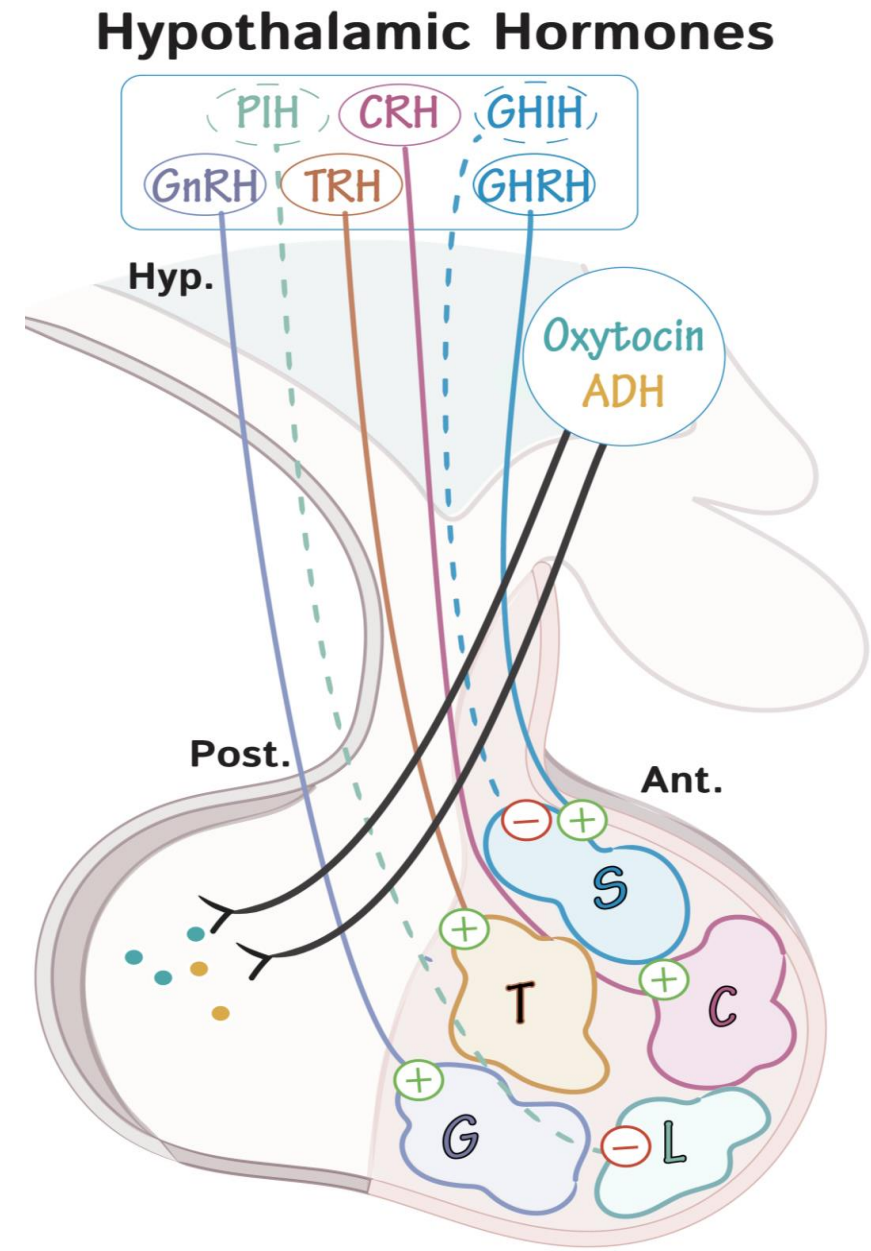
- The posterior lobe is a down growth of hypothalamic neural tissue
- Has a neural connection with the hypothalamus (**hypothalamic-hypophyseal tract**)
- Nuclei of the hypothalamus synthesize **oxytocin** and **antidiuretic hormone (ADH)**
- These hormones are transported to the posterior pituitary



Hypothalamic Hormone released and stored in the Posterior Pituitary Gland

Anti-diuretic hormone (ADH): increases water absorption into the blood by the kidneys.

Oxytocin: involved in a variety of processes, such as orgasm, the ability to trust, body temperature, sleep cycles, and the release of breast milk.



Neuropeptides

Oxytocin (OTC)

- *regulated by suckling and cry of infant*
- *increases contraction of myoepithelial cells in breast & smooth muscle in uterus*
- *“bonding hormone”*

Vasopressin (ADH)

- *regulated by osmotic and volume stimuli*
 - *rise in plasma osmolarity (plasma [Na])*
 - *decrease of ~10% or more in blood volume*
- *acts in kidney to move water from filtrate (urine) to blood to increase blood volume*

Oxytocin

- Oxytocin is a strong stimulant of uterine contraction
- Regulated by a positive feedback mechanism to oxytocin in the blood
- This leads to increased intensity of uterine contractions, ending in birth
- Oxytocin triggers milk ejection (“letdown” reflex) in women producing milk
- Synthetic and natural oxytocic drugs are used to induce or hasten labor
- Plays a role in sexual arousal and satisfaction in males and nonlactating females

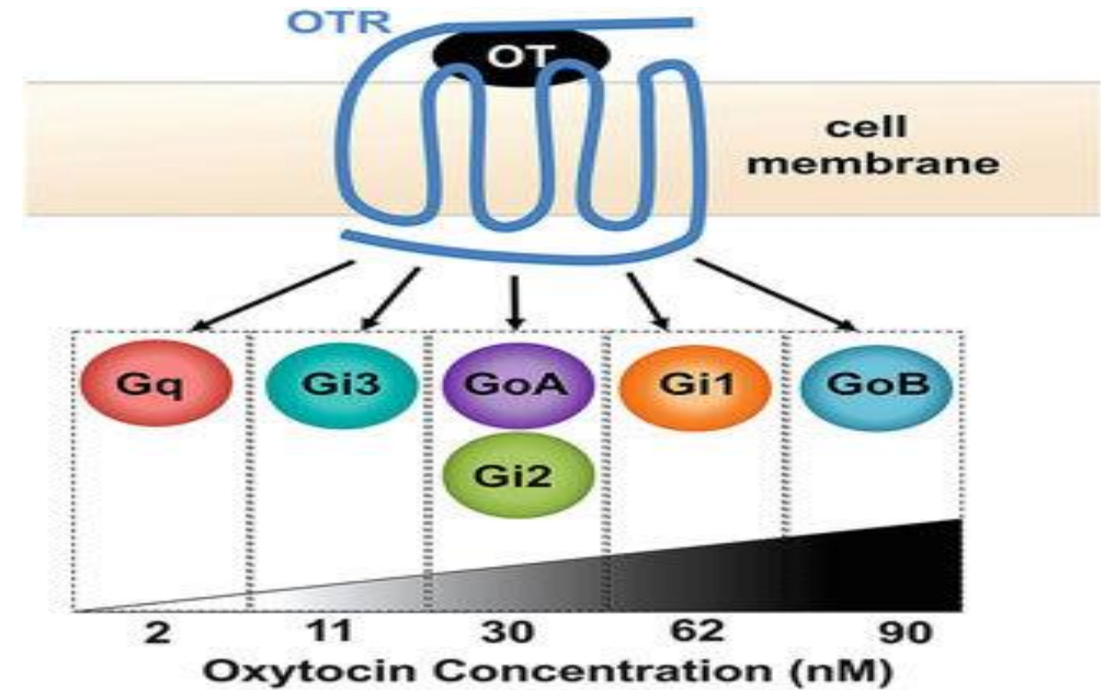
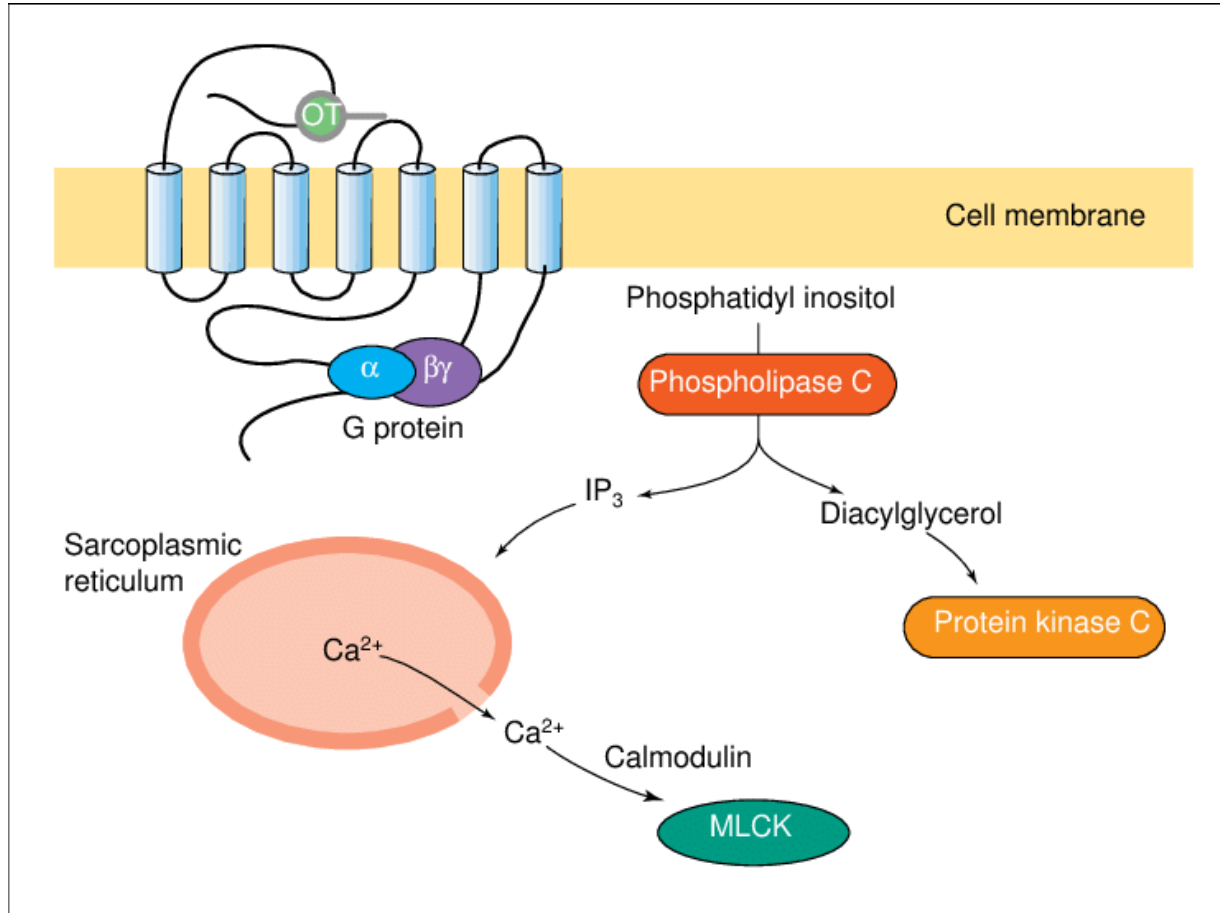
Antidiuretic Hormone (ADH)

- ADH helps to avoid dehydration or water overload
 - Prevents urine formation
- Osmoreceptors monitor the solute concentration of the blood
- With high solutes, ADH preserves water
- With low solutes, ADH is not released, thus causing water loss
- **Alcohol inhibits** ADH release

Subtype (Older Name)	Newer Name	Signaling Pathways	Location	Function
V1A	V1	G-protein coupled, phosphatidylinositol/calcium	vascular smooth muscle platelets hepatocytes myometrium	vasoconstriction, myocardialhypertrophy, platelet aggregation, glycogenolysis, uterine contraction
V1B	V3	G-protein coupled, phosphatidylinositol/calcium	anterior pituitary gland	releases ACTH, prolactin, endorphins
V2	V2	Adenylyl cyclase/c-AMP	basolateral membrane of renal collecting ducts	free water reabsorption from collecting ducts

ACTH: Adrenocorticotrophic hormone.

Oxytocin Receptor

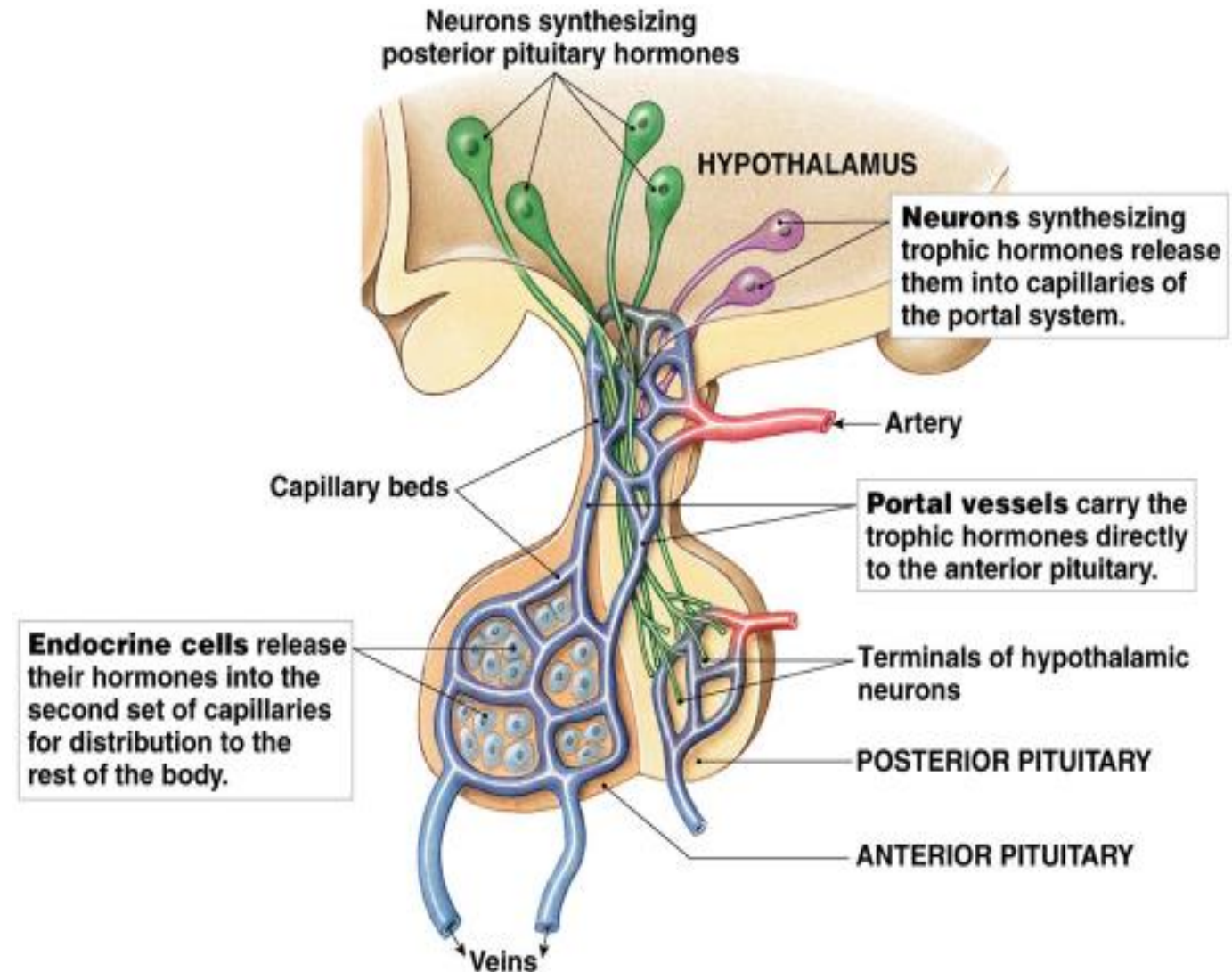


- oxytocin and vasopressin V1a, V1b and V2 receptors form a sub-family within the large superfamily of **G-protein-linked receptors**.
- **Renal V2 receptors** mediate vasopressin-induced water reabsorption via induction of intracellular **cAMP** production in collecting duct cells.
- Most remaining actions of vasopressin on blood vessel constriction, liver glycogenolysis, platelet adhesion, adrenal angiotensin II secretion and certain brain functions are mediated via **v1a-type receptors** that are coupled to a **Gq/11 protein**. V1 receptor activation leads to stimulation of phospholipases C, D and A2 and an increase in intracellular calcium.
- Vasopressin stimulates pituitary corticotrophin release via a third vasopressin receptor type (V1b) which is present on corticotrophs.
- Oxytocin induces myometrial contraction, endometrial prostaglandin F2 alpha production, mammary gland milk ejection, renal natriuresis and specific sexual, affiliative and maternal behaviours via oxytocin receptors which are also coupled to a Gq/11 protein

Pituitary-Hypothalamic Relationships:

Anterior Lobe

- There is no direct neural contact with the hypothalamus
- There is a **vascular connection**, the hypophyseal portal system, consisting of:
 - The primary capillary plexus
 - The hypophyseal **portal veins**
 - The secondary capillary plexus



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Figure 7-16

Adenohypophyseal Hormones

- The six hormones of the anterior pituitary gland:
 - Abbreviated as GH, TSH, ACTH, FSH, LH, and PRL
 - Regulate the activity of other endocrine glands
- In addition, pro-opiomelanocortin (POMC):
MSH melanocyte stimulating hormone
- The **tropic hormones** that are released are:
 - Thyroid-stimulating hormone (TSH)
 - Adrenocorticotrophic hormone (ACTH)
 - Follicle-stimulating hormone (FSH)
 - Luteinizing hormone (LH)

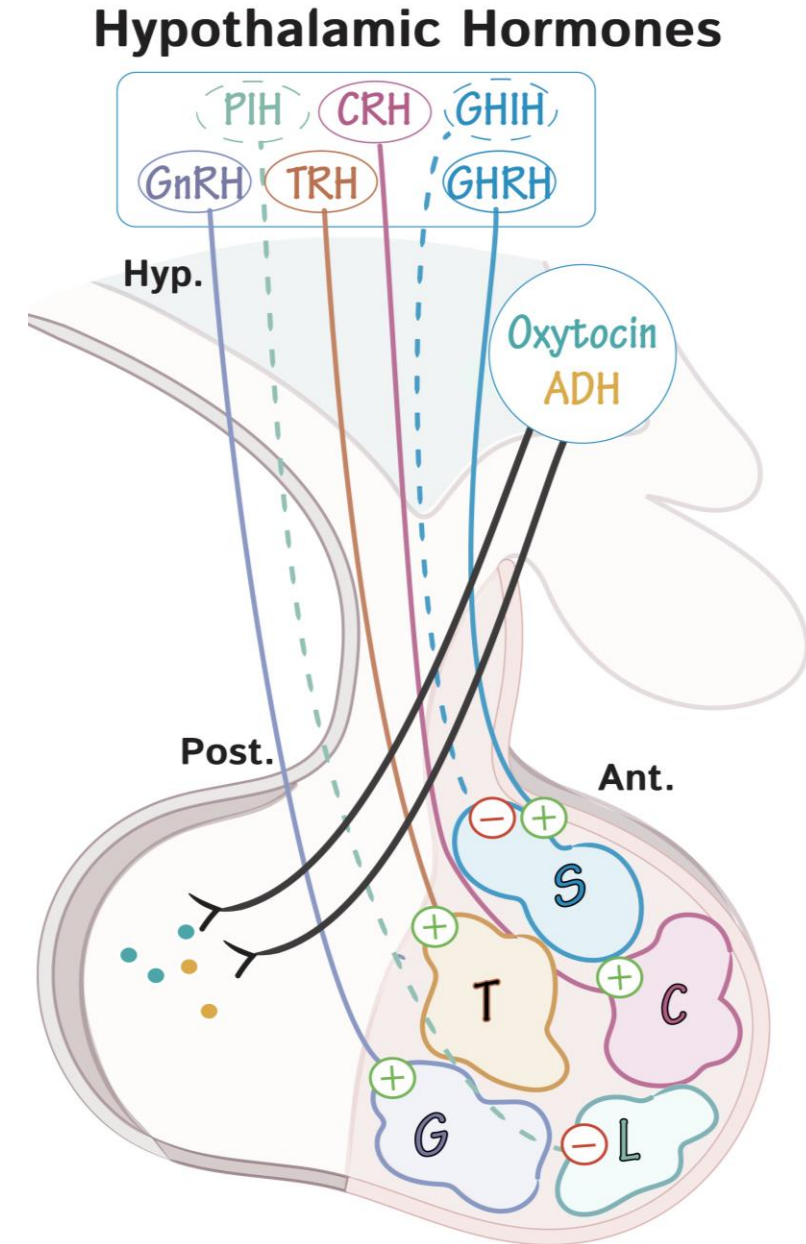
<u>Hormone</u>	<u>Other names</u>	<u>Symbol(s)</u>	<u>Structure</u>	<u>Target</u>	<u>Effect</u>
<u>Adrenocorticotrophic hormone</u>	Corticotropin	ACTH	<u>Polypeptide</u>	<u>Adrenal gland</u>	Secretion of <u>glucocorticoid</u> , <u>mineralocorticoid</u> and <u>androgens</u>
<u>Thyroid-stimulating hormone</u>	Thyrotropin	TSH	<u>Glycoprotein</u>	<u>Thyroid gland</u>	Secretion of <u>thyroid hormones</u>
<u>Follicle-stimulating hormone</u>	-	FSH	Glycoprotein	<u>Gonads</u>	Growth of <u>reproductive system</u>
<u>Luteinizing hormone</u>	Lutropin	LH, ICSH	Glycoprotein	<u>Gonads</u>	<u>Sex hormone</u> production
<u>Growth hormone</u>	Somatotropin	GH, STH	Polypeptide	<u>Liver, adipose tissue</u>	Promotes growth; <u>lipid</u> and <u>carbohydrate metabolism</u>
<u>Prolactin</u>	Lactotropin	PRL	Polypeptide	<u>Ovaries, mammary glands</u>	Secretion of <u>estrogens</u> / <u>progesterone</u> ; <u>milk</u> production

Primary hormones secreted by the hypothalamus include:

Corticotropin-releasing hormone (CRH): sends a message to the anterior pituitary gland to stimulate the adrenal glands to release corticosteroids, help regulate metabolism and immune response.

Gonadotropin-releasing hormone (GnRH): stimulates the anterior pituitary to release follicle stimulating hormone (FSH) and luteinizing hormone (LH), which ensure normal functioning of the ovaries and testes.

Growth hormone-releasing hormone (GHRH) or growth hormone-inhibiting hormone (GHIH) (somatostatin): GHRH prompts the anterior pituitary to release growth hormone (GH); GHIH has the opposite effect. In children, GH is essential to maintaining a healthy body composition. In adults, it aids healthy bone and muscle mass and affects fat distribution.

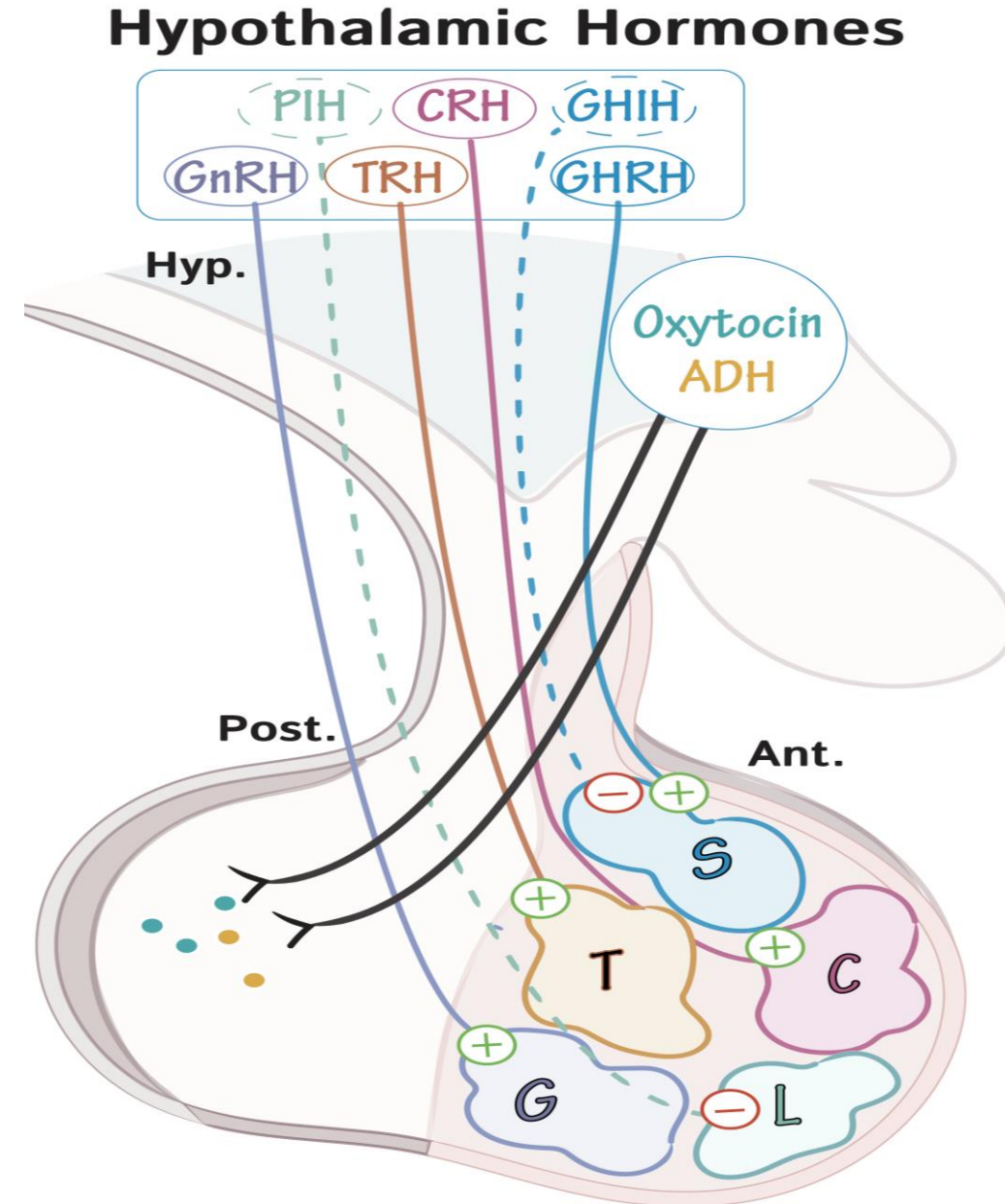


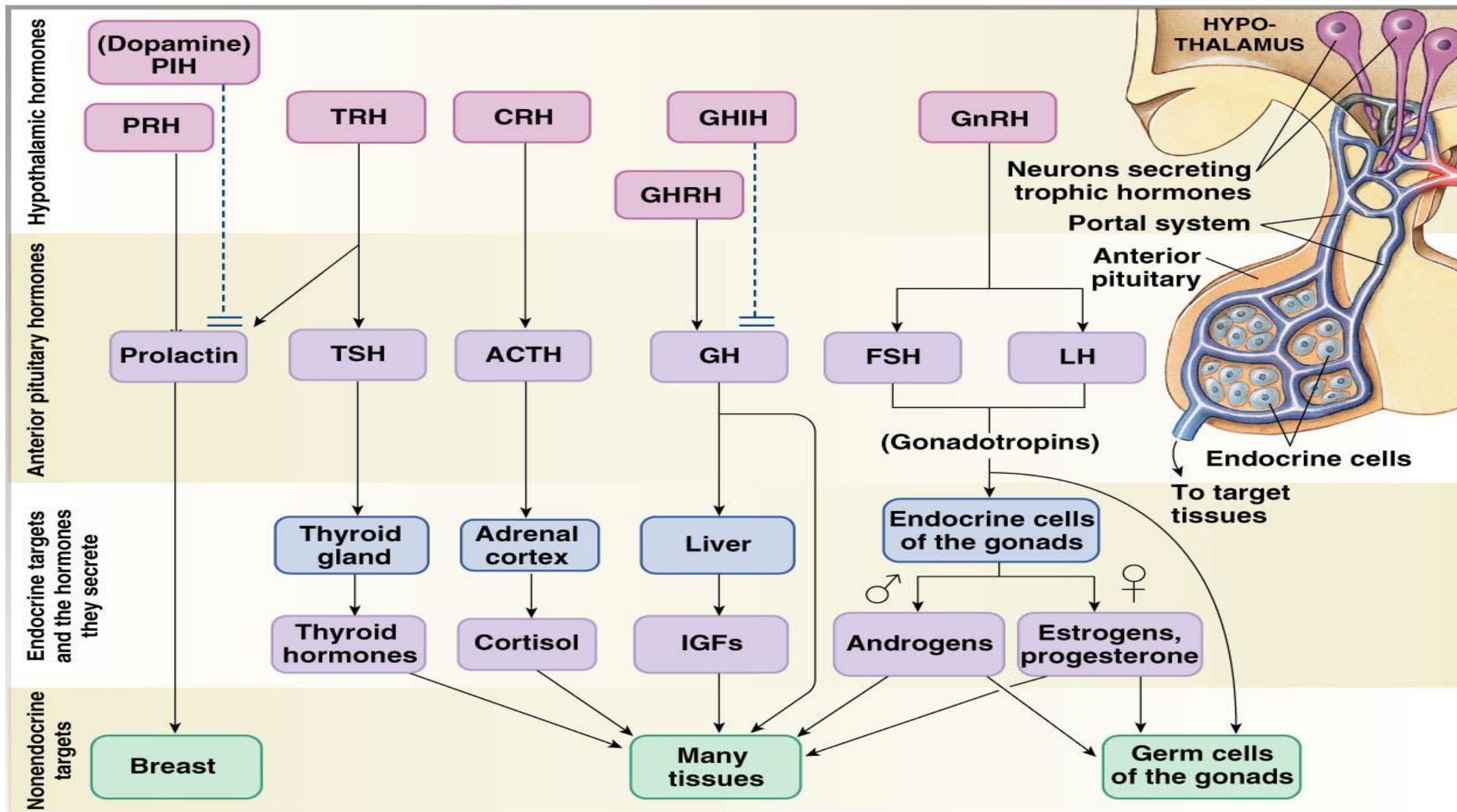
Primary hormones secreted by the hypothalamus include:

Prolactin-releasing hormone (PRH) or prolactin-inhibiting hormone (PIH) (dopamine): PRH prompts the anterior pituitary to stimulate breast milk production through the production of prolactin.

Conversely, PIH inhibits prolactin, and thereby, milk production.

Thyrotropin releasing hormone (TRH): TRH triggers the release of thyroid stimulating hormone (TSH), stimulates release of thyroid hormones, regulate metabolism, energy, and growth and development.



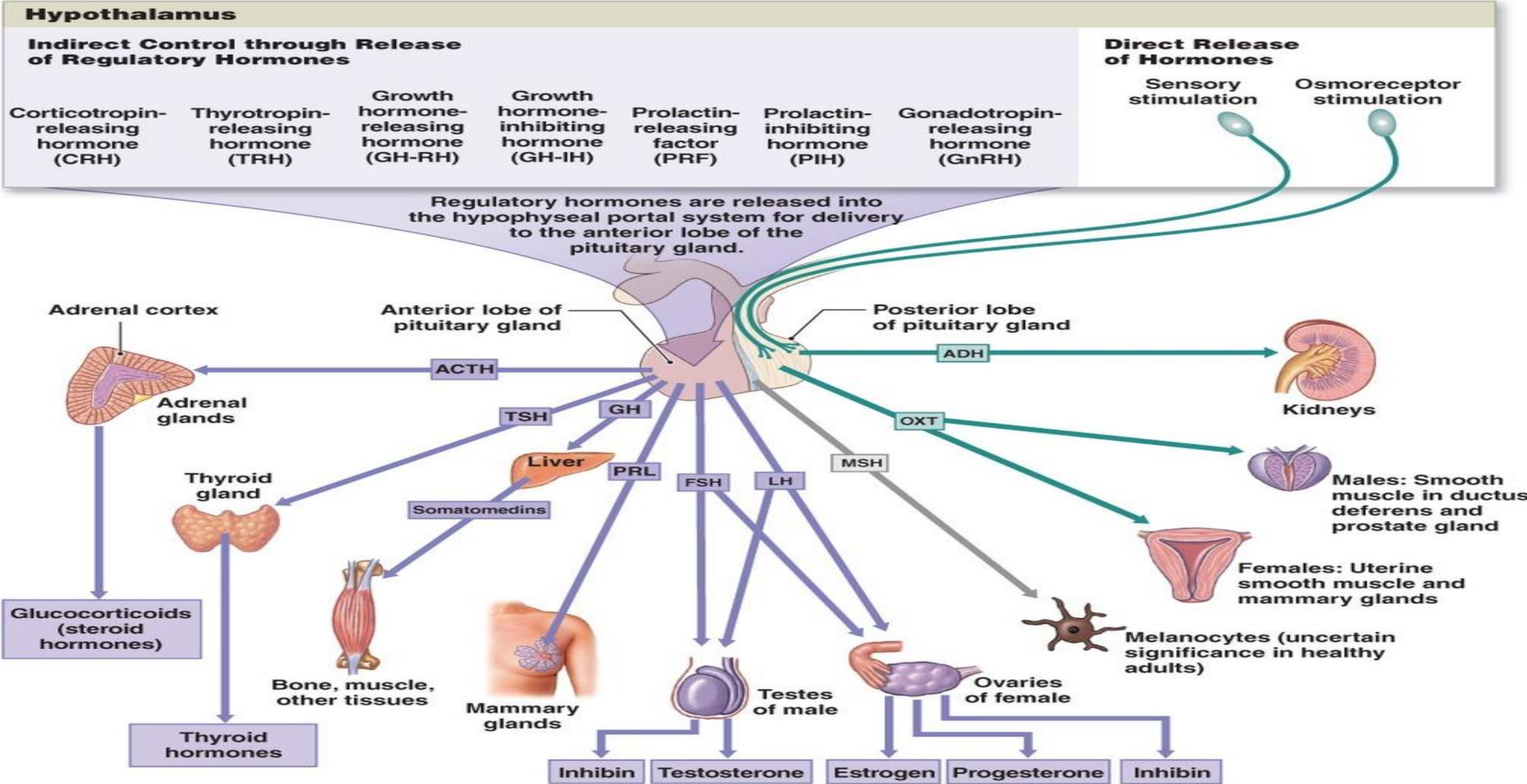


Cell types, hormones, and functions of the anterior pituitary

Name of cells	% of population	Hormone secreted	Functions
Somatotrophs	50	Somatotropin (Growth hormone, GH)	Stimulates IGF production by liver that promotes long bone growth
Lactotrophs	15-20	Prolactin (PRL)	Promotes milk secretion
Gonadotrophs	10	Follicle stimulating hormone (FSH), Luteinizing hormone (LH & Interstitial cell stimulating hormone, ICSH, in males)	FSH promotes ovarian follicle development, estrogen secretion in females & spermatogenesis in males. LH promotes follicle maturation & progesterone release in females. ICSH promotes androgen secretion from Leydig/interstitial cells in testes.
Thyrotrophs	5	Thyrotropin (TSH)	Promotes thyroid hormone production & secretion
Corticotrophs	15-20	Adrenal corticotrophic hormone (ACTH) & Lipotrophin (LPH)	Stimulates hormone secretion from the adrenal cortex Regulates lipid metabolism

IGF= insulin-like growth factor

An overview of the relationships between hypothalamic and pituitary hormones, and some effects of pituitary hormones on target tissues



Thyroid Stimulating Hormone (Thyrotropin)

- Stimulates the normal development and secretory activity of the thyroid
- Triggered by hypothalamic peptide thyrotropin-releasing hormone (TRH)
- Rising blood levels of thyroid hormones act on the pituitary and hypothalamus to block the release of TSH

Adrenocorticotrophic Hormone (Corticotropin)

- Stimulates the adrenal cortex to release corticosteroids
- Triggered by hypothalamic corticotropin-releasing hormone (CRH) in a daily rhythm
- Internal and external factors such as fever, hypoglycemia, and stressors can trigger the release of CRH

Gonadotropins

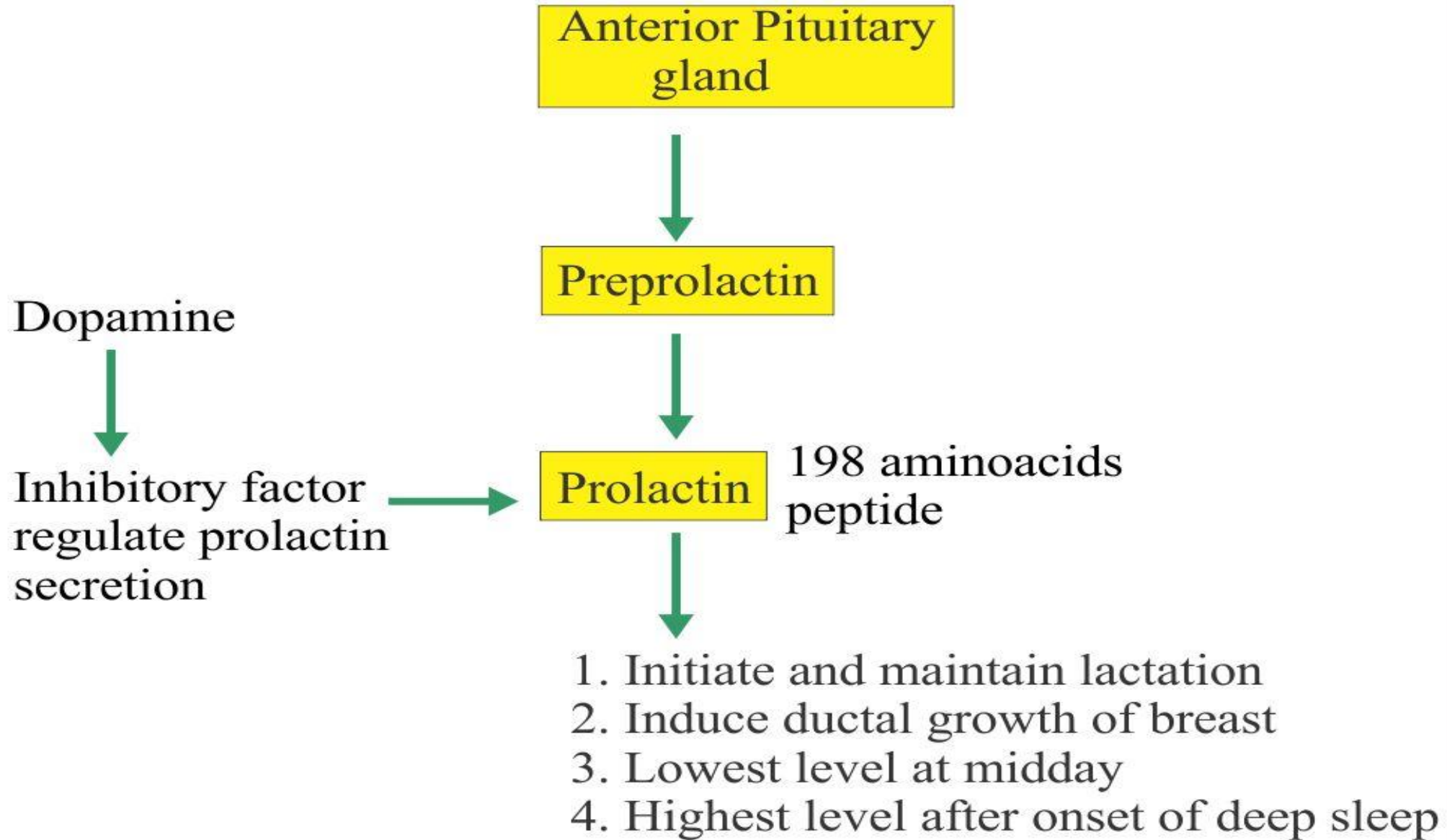
- Gonadotropins – follicle-stimulating hormone (FSH) and luteinizing hormone (LH)
 - Regulate the function of the ovaries and testes
 - FSH stimulates gamete (egg or sperm) production
 - **Absent from the blood in pre-pubertal** boys and girls
 - Triggered by the hypothalamic gonadotropin-releasing hormone (GnRH) during and after puberty

Functions of Gonadotropins

- In females
 - LH works with FSH to cause **maturation of the ovarian follicle**
 - LH works alone to trigger **ovulation** (expulsion of the egg from the follicle)
 - LH promotes synthesis and release of **estrogens and progesterone**
- In males
 - LH stimulates interstitial cells of the testes to **produce testosterone**
 - LH is also referred to as interstitial cell-stimulating hormone (ICSH)

Prolactin (PRL)

- In females, stimulates milk production by the breasts
- Triggered by the hypothalamic prolactin-releasing hormone (PRH)
- Inhibited by prolactin-inhibiting hormone (PIH) **dopamine**
- Blood levels rise toward the end of pregnancy
- **Suckling** stimulates PRH release and encourages continued milk production
- PRL receptor acts through JAK/STAT signaling pathway



Growth Hormone (GH)

somatotropic hormone

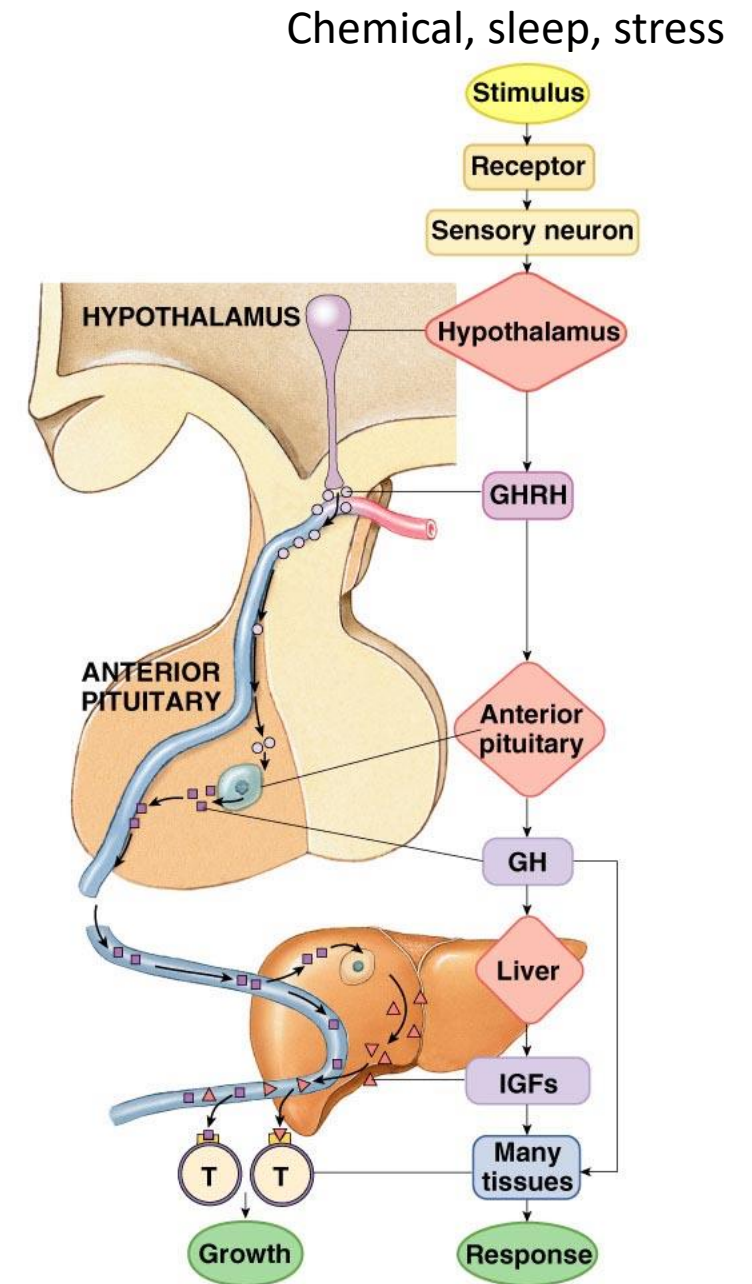
- Peptide hormone secreted by acidophils of the anterior pituitary gland that:
 - Stimulate most cells, but target bone and skeletal muscle
 - Promote protein synthesis and encourage the use of fats for fuel
 - The target tissues for GH include both endocrine and nonendocrine cells. GH acts as a **trophic hormone** to stimulate secretion of insulin-like growth factors
- **bound to a plasma growth hormone binding protein**
- Antagonistic hypothalamic hormones regulate GH
 - Growth hormone–releasing hormone (GHRH) stimulates GH release
 - Growth hormone–inhibiting hormone (GHIH) inhibits GH release (**somatostatin**)

- Affect the following tissue:

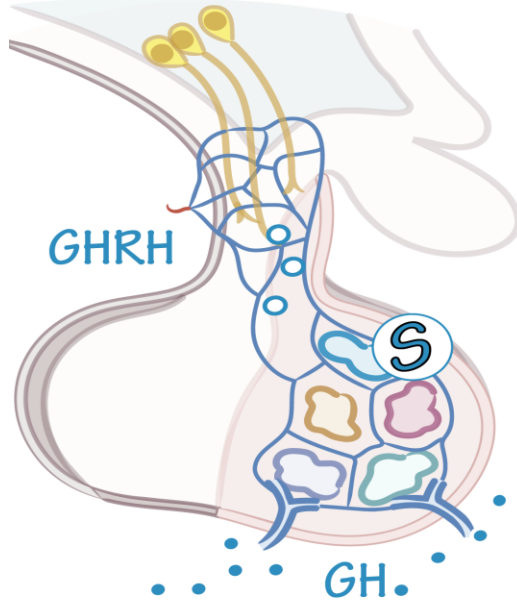
1. Bones: Increase protein and collagen synthesis and cell growth
2. Adipose tissue: Utilization of lipids as a source of energy for biosynthetic processes
3. Liver: Increase proteins and RNA synthesis, Gluconeogenesis. Causing the release of growth factors which stimulates linear growth of bones and tissue growth of many other organs.

There are two IGFs: [IGF-1](#) and [IGF-2](#)

The plasma half-life of IGF is much longer than that of GH.

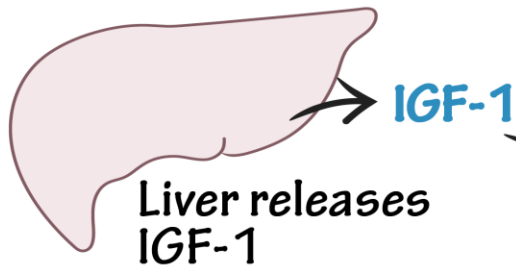


Growth Hormone (GH) Physiology



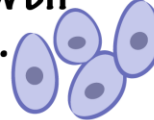
1. Hypothalamus secretes **Growth Hormone-Releasing Hormone (GHRH)**.
 - ⊕ Sleep, hypoglycemia, stress Fasting, exercise, grelin
 - ⊖ Age, obesity (Increase in FA)
 - Glucose
 - IGF-1
 - Growth Hormone
 - Negative feedback**
2. **GHRH stimulates Anterior Pituitary Somatotropes to release Growth Hormone.**
 - ⊖ GH Inhibitory Horm. (somatostatin)
 - IGF-1
 - Growth Hormone
 - Negative feedback**
3. **Growth hormone travels to target tissues throughout body.**

Diabetogenic Effects
Increases glycogen break-down to increase blood glucose.

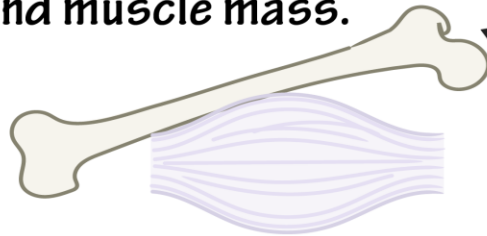


Growth Effects

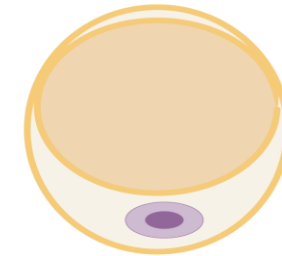
Increase cell growth and proliferation.



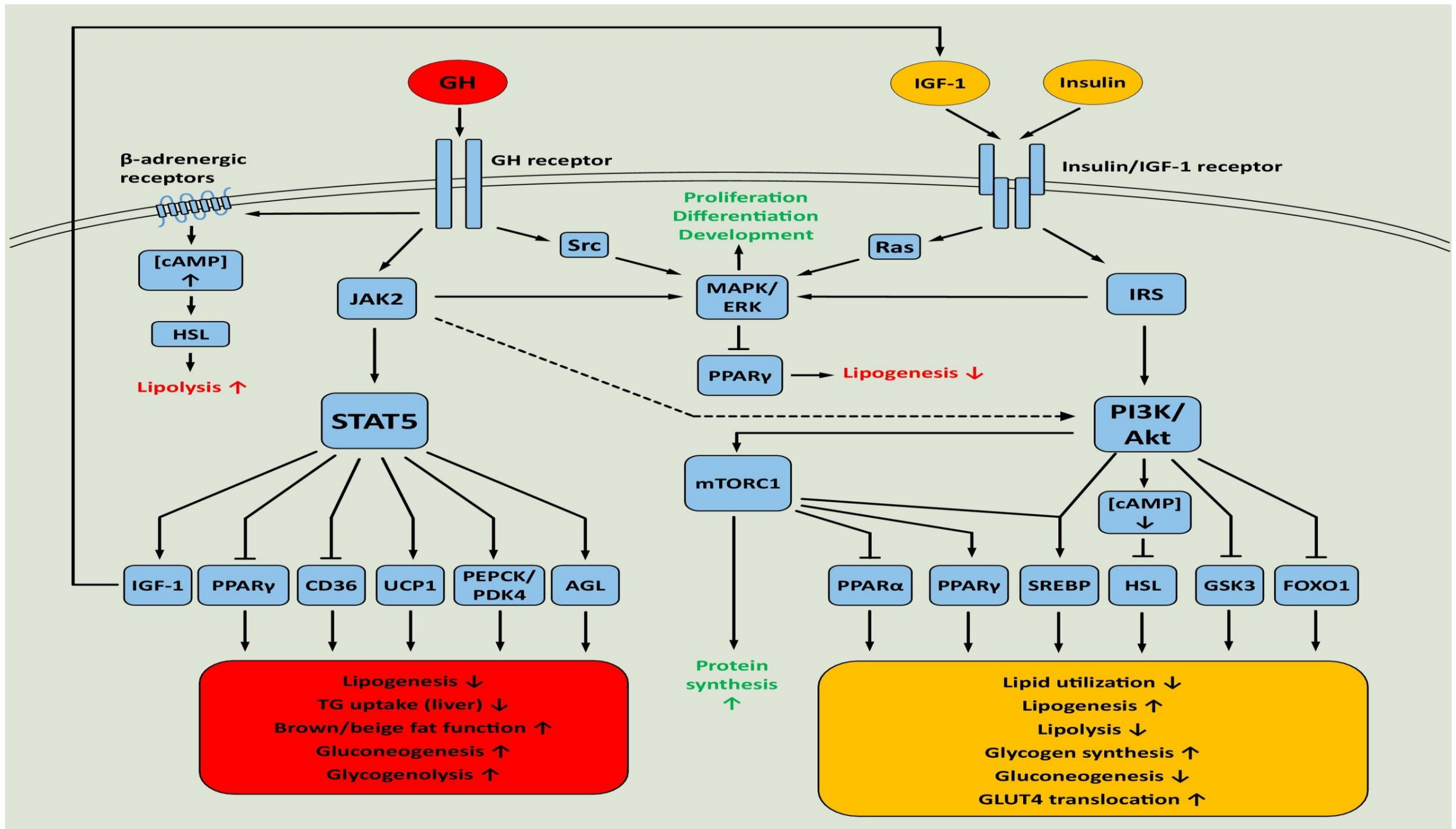
Increase bone length and muscle mass.



Glucose-Sparing Effects



Increases lipolysis;
Decreases glucose uptake.

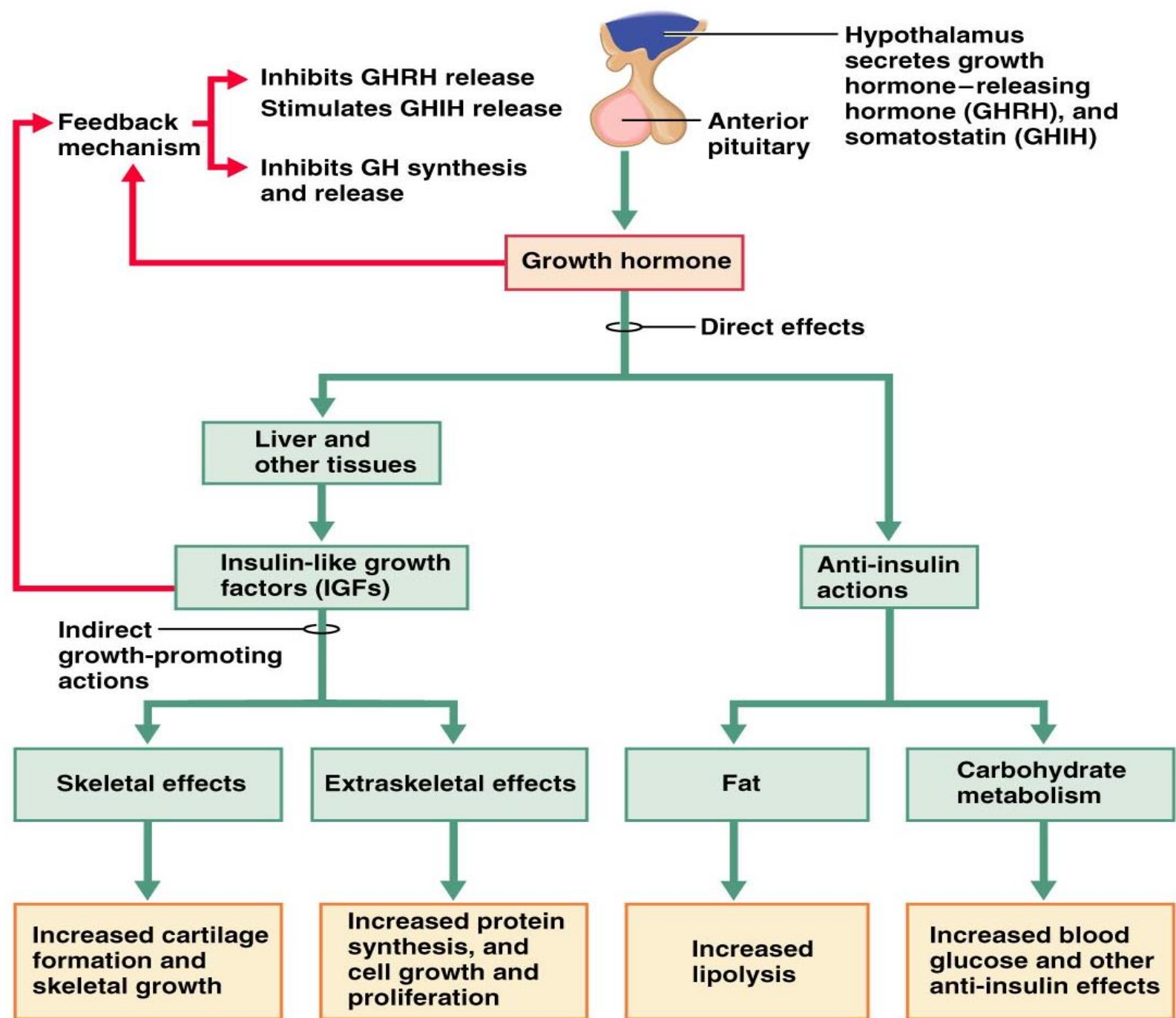


Metabolic Action of Growth Hormone

- GH stimulates liver, skeletal muscle, bone, and cartilage to produce **insulin-like growth factors (somatomedins)**
- Direct action promotes lipolysis and inhibits glucose uptake

Key:

- ← Increases, stimulates
- ← Reduces, inhibits
- Initial stimulus
- Physiological response
- Result



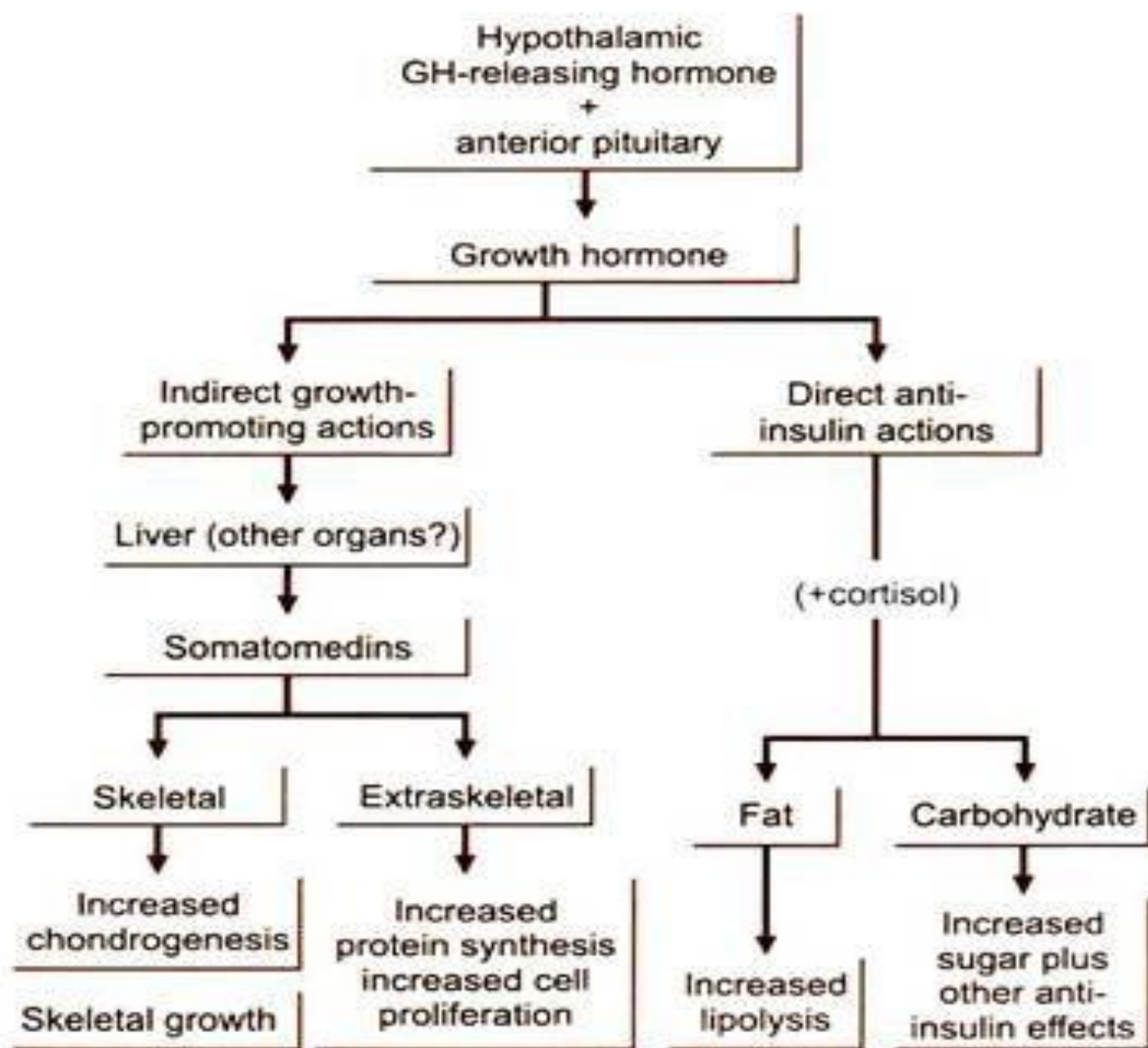


Fig. 6.9: Composite diagram showing actions of GH

Growth Hormone Functions

Growth Hormone (GH)

Promotes growth in

1. Soft tissue
2. Bone
3. Cartilage

1. Increase plasma P^+
2. Decrease BUN
3. Decrease AA concentration
4. Increase intestinal absorption of Ca^+
5. Decrease urinary excretion of Na^+ and K^+
6. Stimulate uptake of nonesterified fatty acid by muscle
7. Accelerate mobilization and metabolism of fats for adipose tissue in liver

Chronic increase of GH

1. Stimulate hepatic glycogenolysis
2. Antagonize the effect of insulin on glucose uptake by peripheral cells

laboedia.net

GH prevents the activation of Glut-4 by insulin, which stops the transport of glucose from blood into cells
A person with GH excess may suffer from ketoacidosis or diabetic ketoacidosis

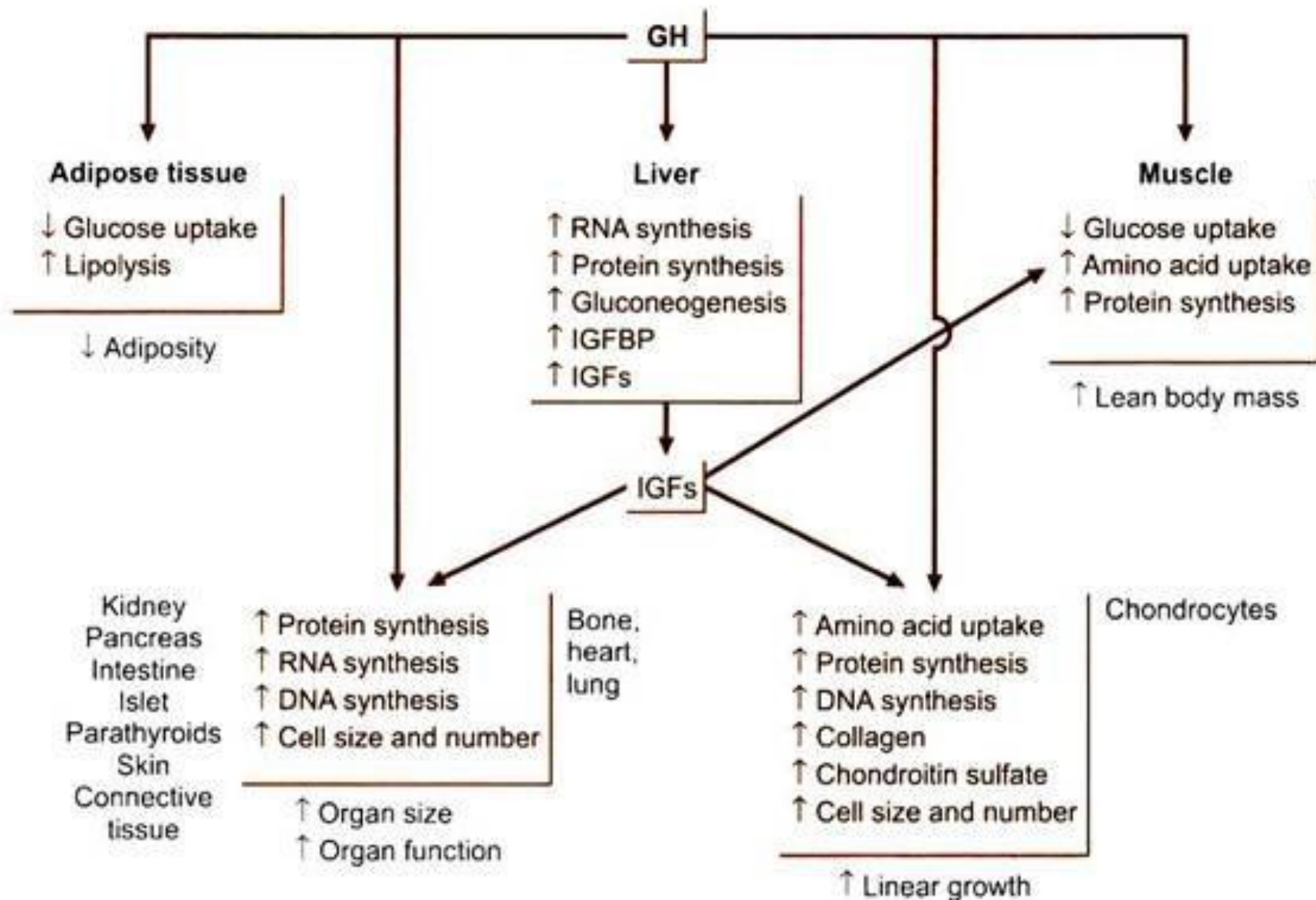


Fig. 6.10: Highlighting various intracellular actions of GH in the body

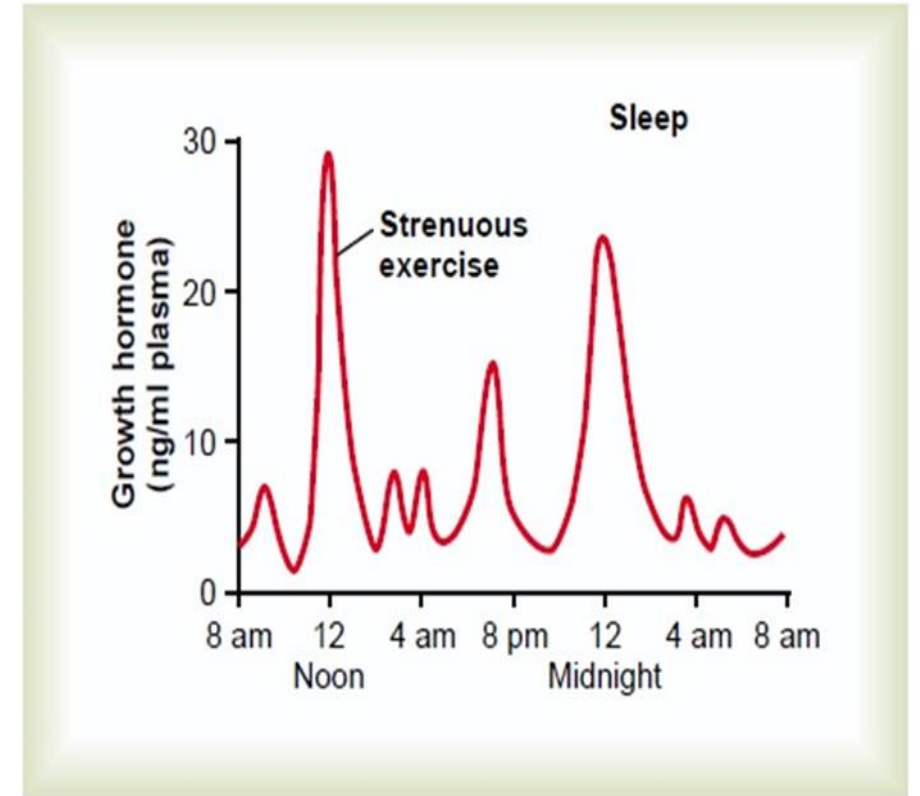
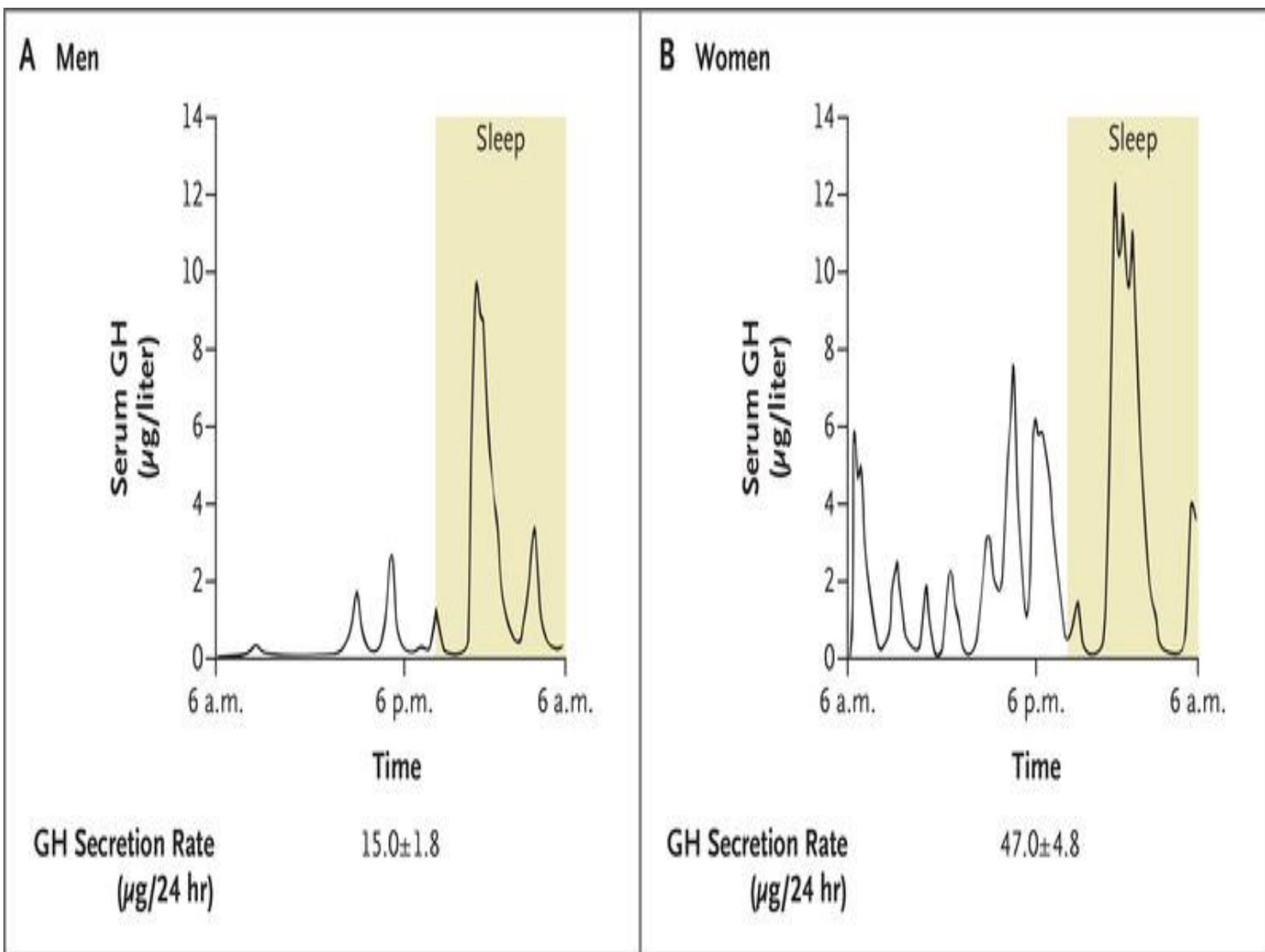
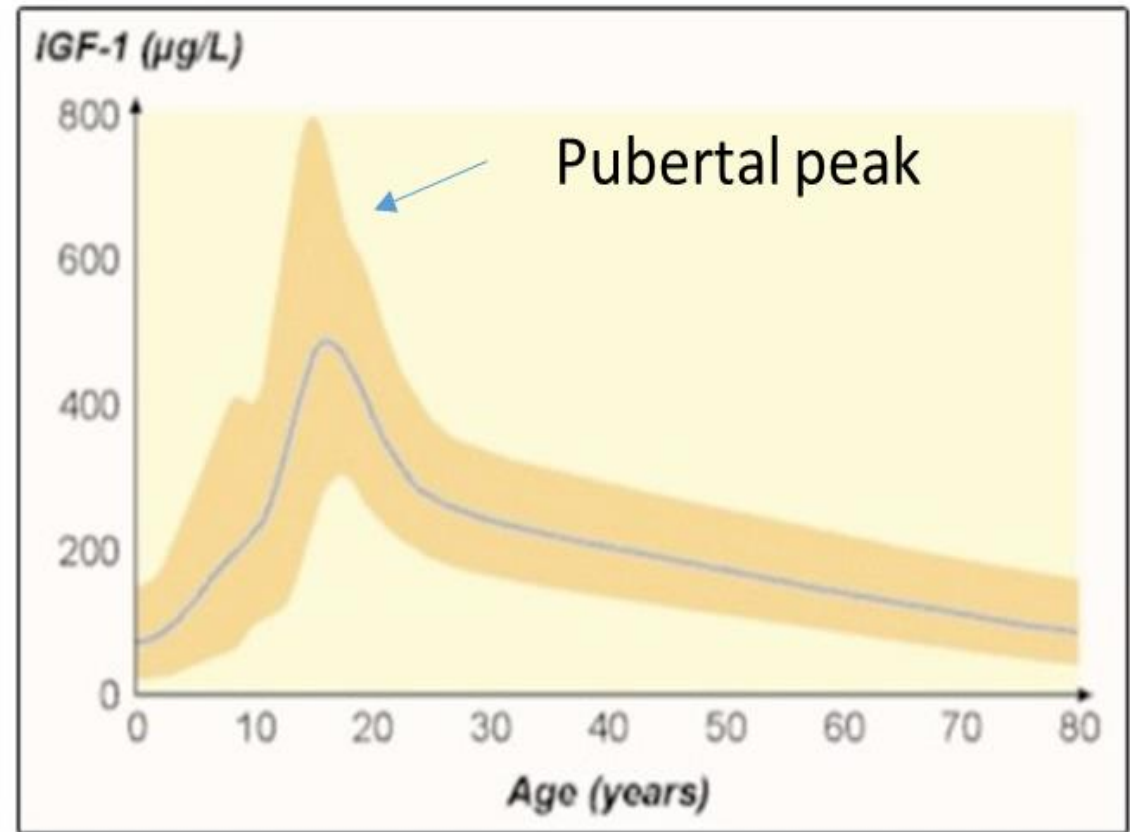


Figure 75-6

Typical variations in growth hormone secretion throughout the day, demonstrating the especially powerful effect of strenuous exercise and also the high rate of growth hormone secretion that occurs during the first few hours of deep sleep.

Secreted in pulsatile pattern
Secretion increases during the first 2 hours of deep sleep and during strenuous exercise

- Anabolic
- Secretion increase during puberty (decreased urea production during synthesis due to AA utilization)
- Decline with age may account for muscle wasting
- Measured via IGF-1 which has longer half life



- Severe growth hormone deficiency in childhood leads to **dwarfism**, which can result from: problem either with growth hormone synthesis or with defective GH receptors
- At the opposite extreme, oversecretion of growth hormone in children leads to **giantism**



Once **bone growth stops in late adolescence**, growth hormone cannot further increase height.

GH and IGFs can continue to act on cartilage and soft tissues.

Adults with excessive secretion of growth hormone develop a condition known as acromegaly

Acromegaly



Age 9



Age 16

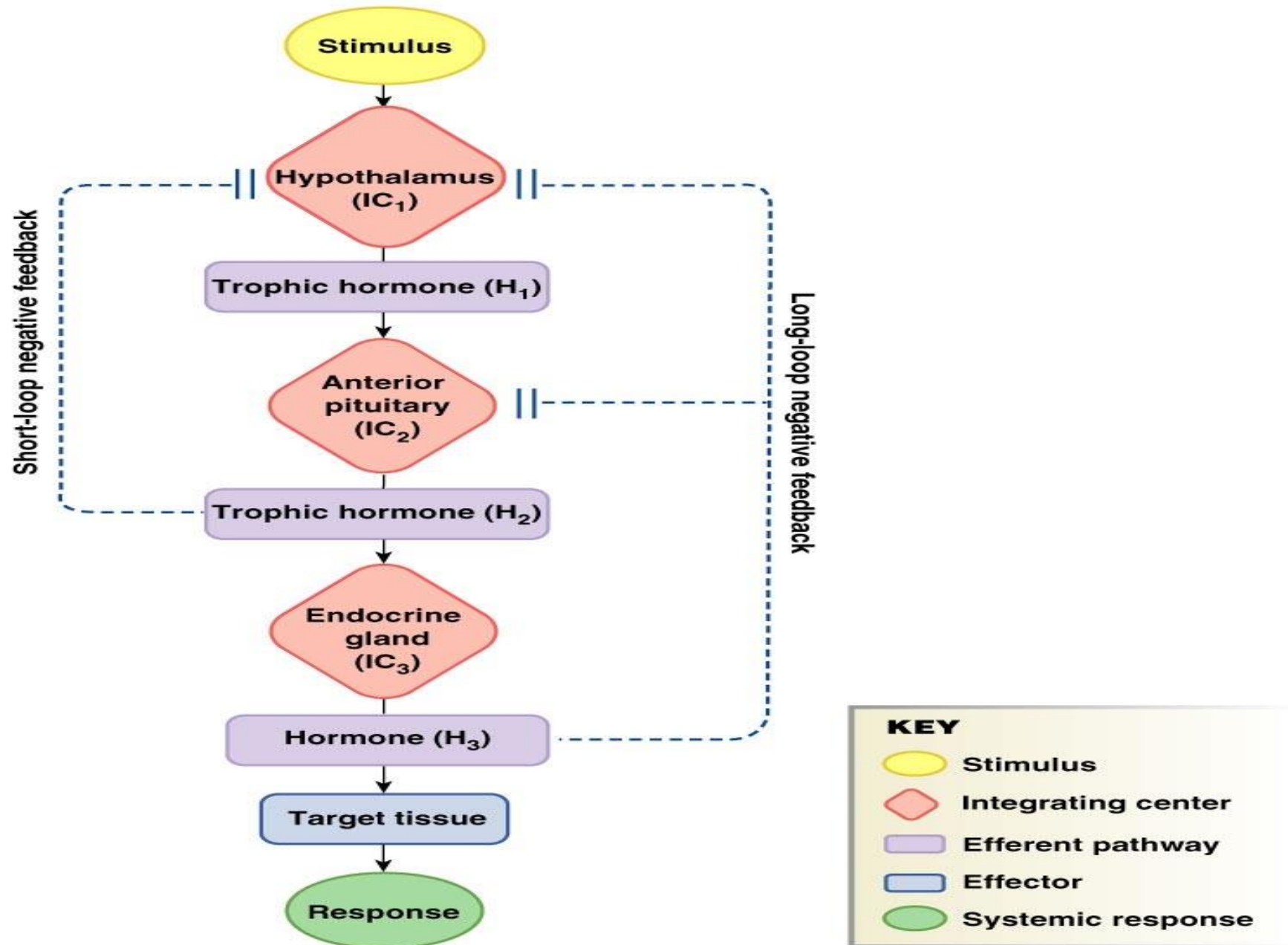


Age 33



Age 52

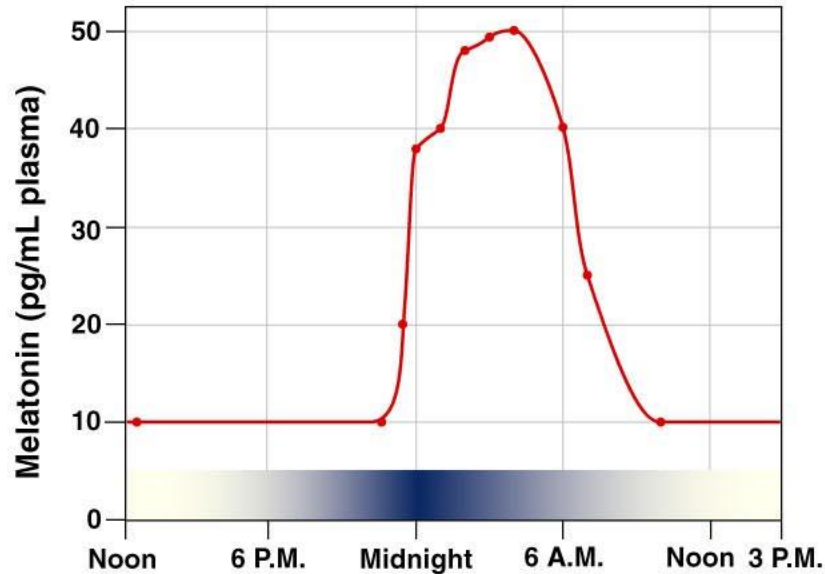
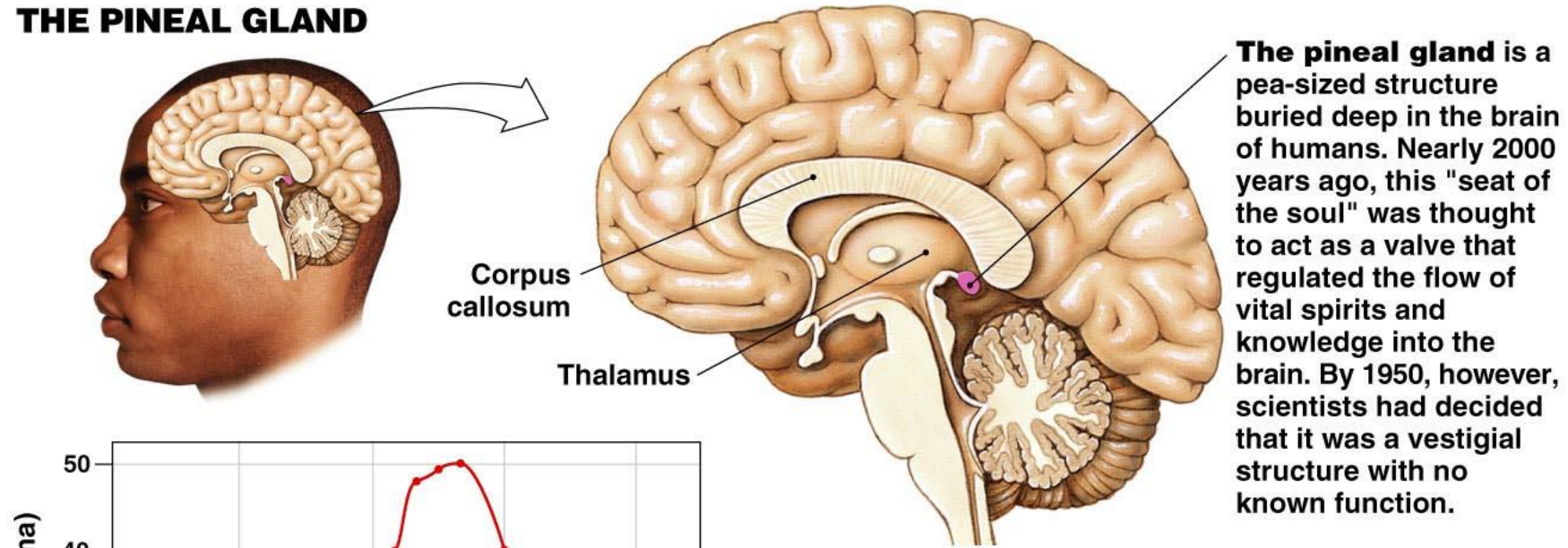
Progression of acromegaly in one woman. Excess growth hormone secretion in adults causes lengthening of the jaw, coarsening of the features, and growth in hands and feet.



Pineal Gland

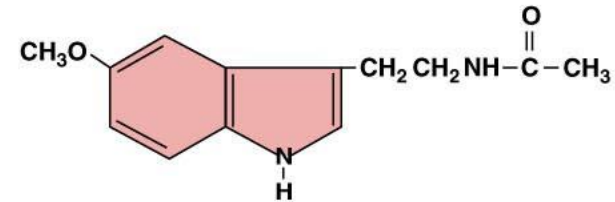
- Small gland hanging from the roof of the third ventricle of the brain
- Secretory product is melatonin
- Melatonin is involved with:
 - Day/night cycles
 - Physiological processes that show rhythmic variations (body temperature, sleep, appetite)

THE PINEAL GLAND



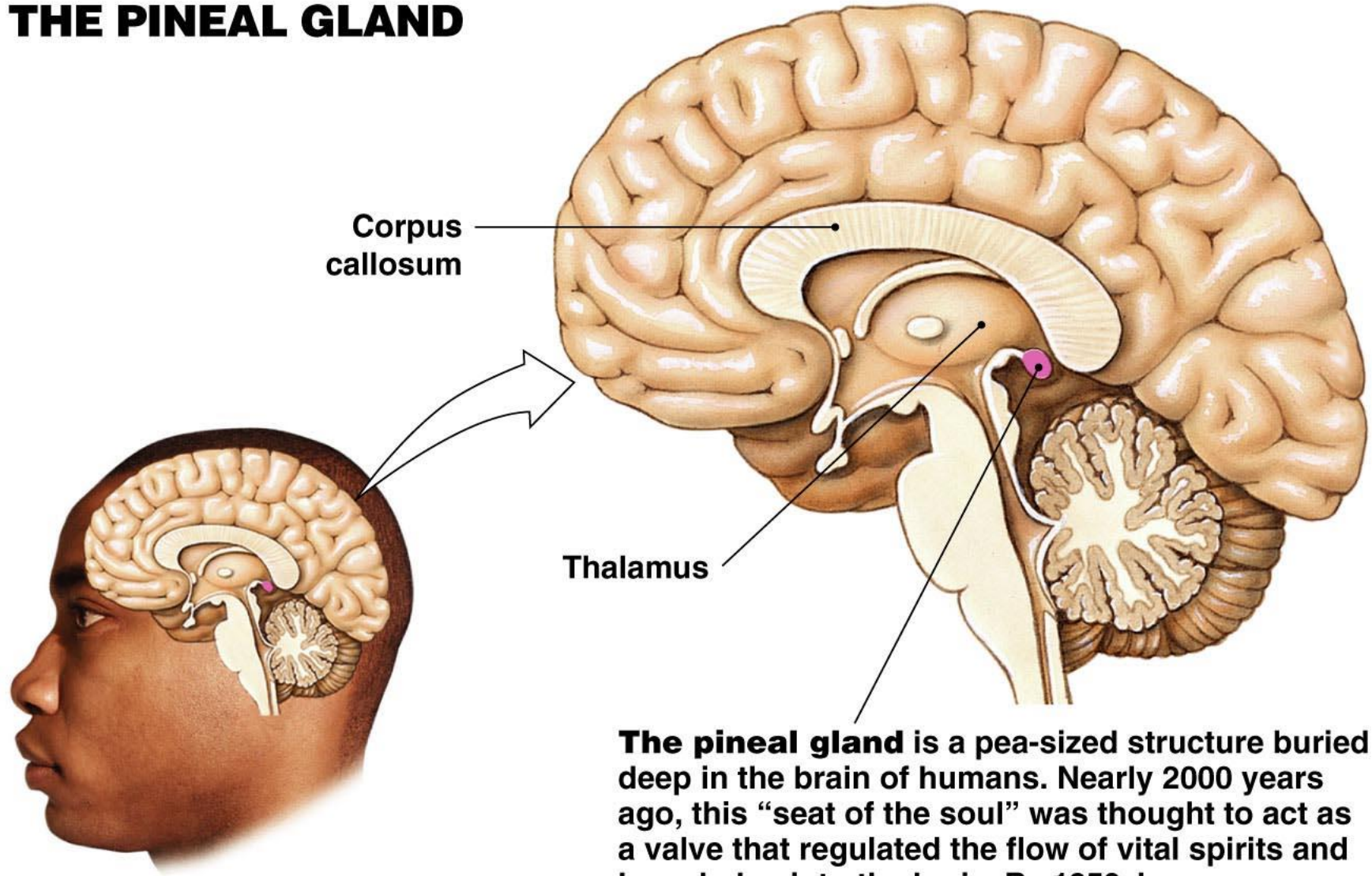
Melatonin is the "darkness hormone," secreted at night as we sleep. It is the chemical messenger that transmits information about light-dark cycles to the brain center that governs the body's biological clock.

(Adapted from J. Arendt, *Clin. Endocrinol.* 29: 205–229, 1988.)

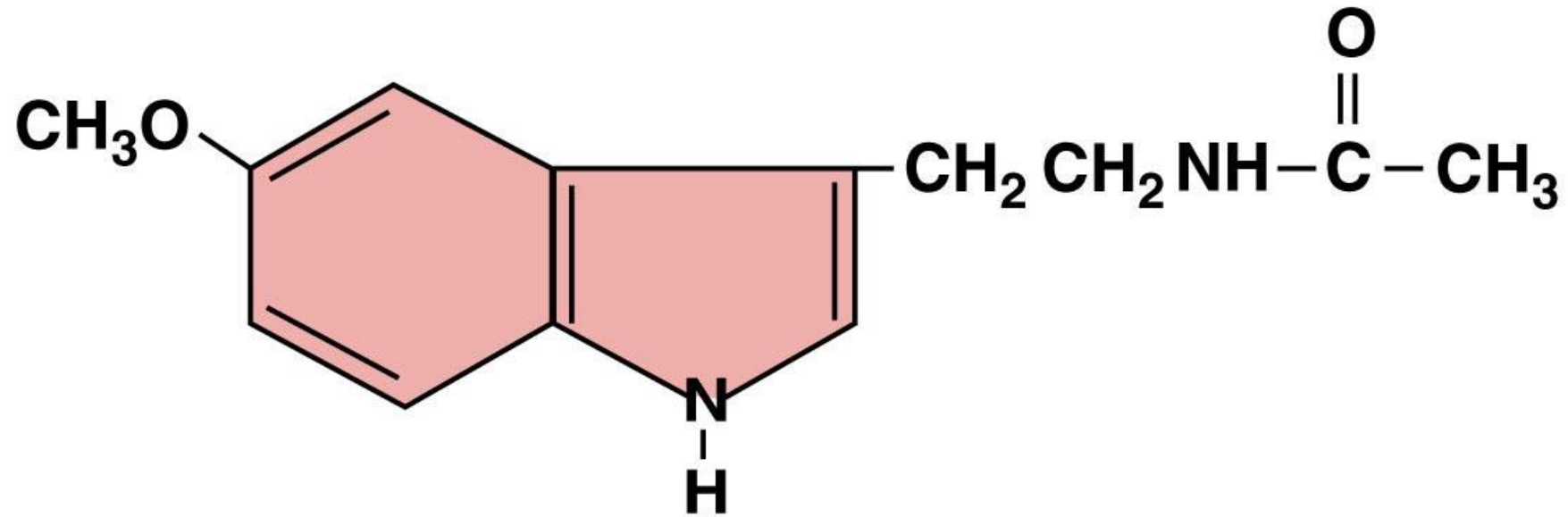


Melatonin is an amine hormone derived from the amino acid tryptophan.

THE PINEAL GLAND

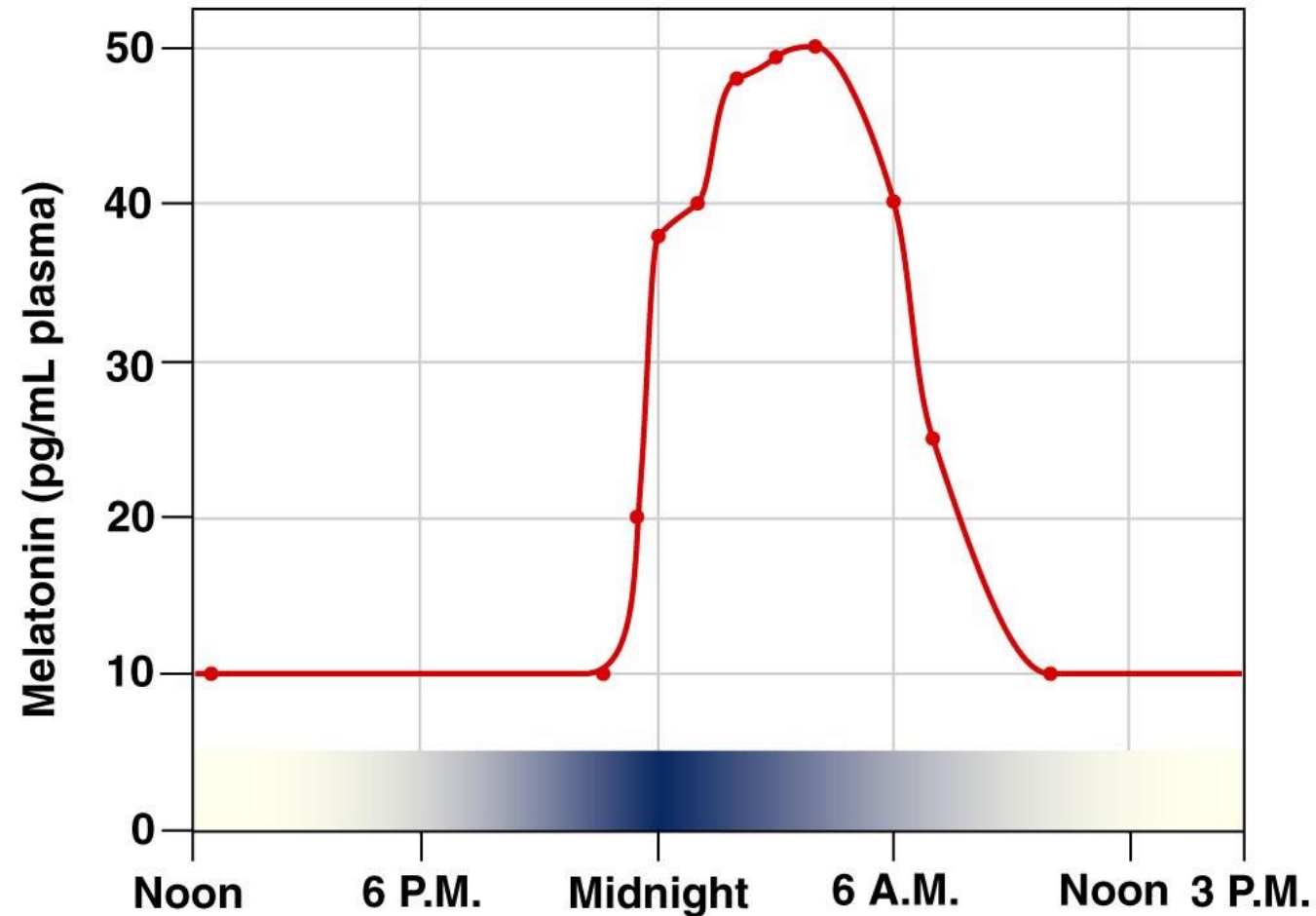


The pineal gland is a pea-sized structure buried deep in the brain of humans. Nearly 2000 years ago, this “seat of the soul” was thought to act as a valve that regulated the flow of vital spirits and knowledge into the brain. By 1950, however, scientists had decided that it was a vestigial structure with no known function.



Melatonin is an amine hormone
derived from the amino acid tryptophan.

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Melatonin is the “darkness hormone,” secreted at night as we sleep. It is the chemical messenger that transmits information about light-dark cycles to the brain center that governs the body’s biological clock.

(Adapted from J. Arendt, *Clin. Endocrinol.* 29: 205–229, 1988.)

Thymus

- Lobulated gland located deep to the sternum
- Major hormonal products are thymopoietins and thymosins
- These hormones are essential for the development of the T lymphocytes (T cells) of the immune system

Other Hormone-Producing Structures

- Heart – produces atrial natriuretic peptide (ANP), which reduces blood pressure, blood volume, and blood sodium concentration
- Gastrointestinal tract – enteroendocrine cells release local-acting digestive hormones
- Placenta – releases hormones that influence the course of pregnancy

Other Hormone-Producing Structures

- Kidneys – secrete erythropoietin, which signals the production of red blood cells
- Skin – produces cholecalciferol, the precursor of vitamin D
- Adipose tissue – releases leptin, which is involved in the sensation of satiety, and stimulates increased energy expenditure

Developmental Aspects

- Hormone-producing glands arise from all three germ layers
- Endocrine glands derived from mesoderm produce steroid hormones
- Endocrine organs operate smoothly throughout life
- Most endocrine glands show structural changes with age, but hormone production may or may not be affected

Developmental Aspects

- Exposure to pesticides, industrial chemicals, arsenic, dioxin, and soil and water pollutants disrupts hormone function
- Sex hormones, thyroid hormone, and glucocorticoids are vulnerable to the effects of pollutants
- Interference with glucocorticoids may help explain high cancer rates in certain areas

Developmental Aspects

- Ovaries undergo significant changes with age and become unresponsive to gonadotropins
- Female hormone production declines, the ability to bear children ends, and problems associated with estrogen deficiency (e.g., osteoporosis) begin to occur
- Testosterone also diminishes with age, but effect is not usually seen until very old age

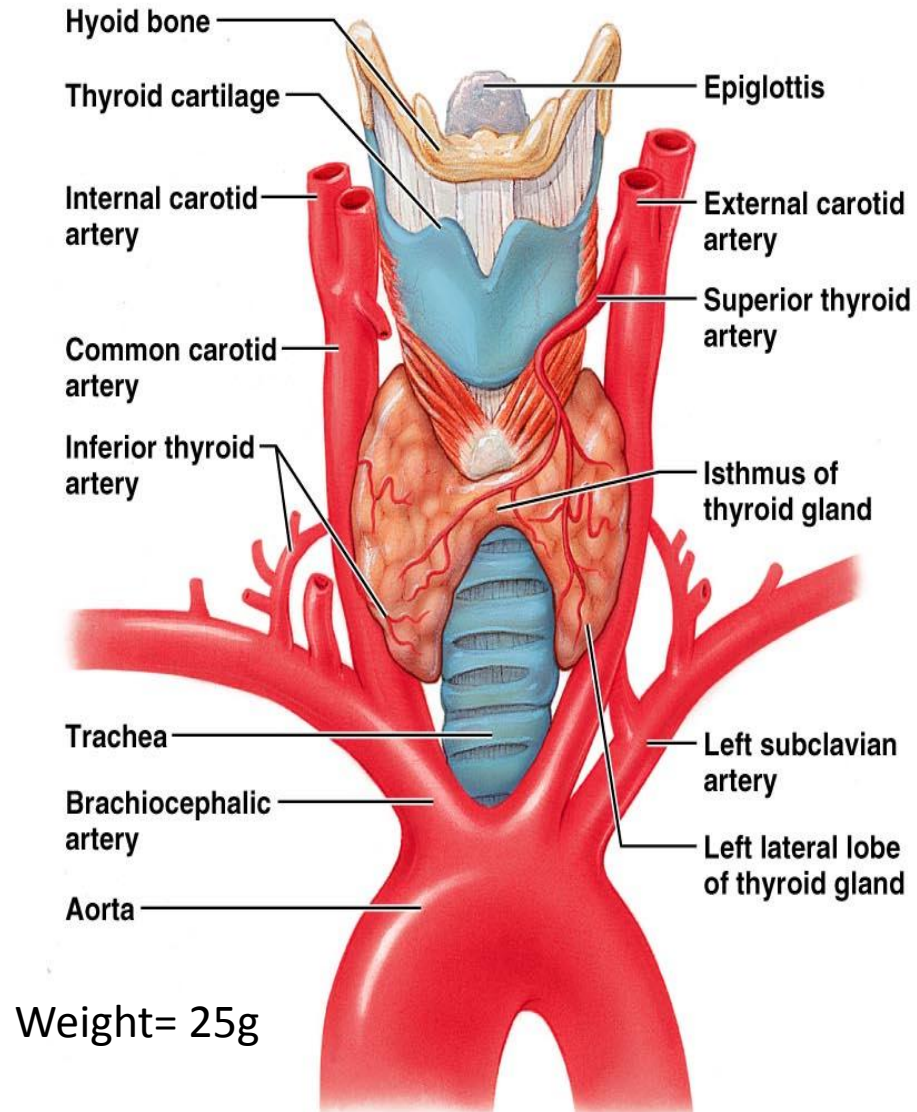
Developmental Aspects

- GH levels decline with age and this accounts for muscle atrophy with age
- Supplemental GH may spur muscle growth, reduce body fat, and help physique
- TH declines with age, causing lower basal metabolic rates
- PTH levels remain fairly constant with age, and lack of estrogen in women makes them more vulnerable to bone-demineralizing effects of PTH

Thyroid and Parathyroid Gland

Dr. Safa Abdul Ghani

Thyroid Gland



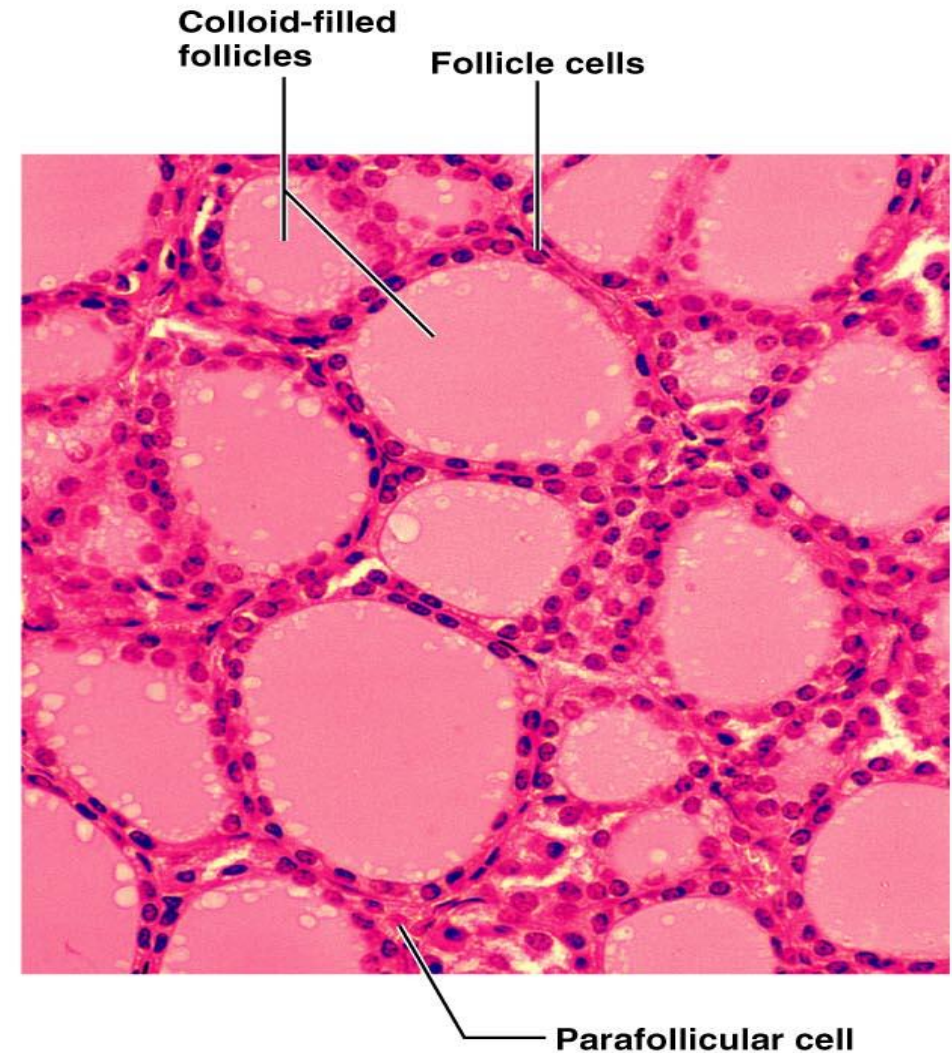
The thyroid gland is located below the larynx and consists of two broad lobes connected by an isthmus.



Figure 16.8

Thyroid Gland

- The largest endocrine gland, located in the anterior neck, consists of two lateral lobes connected by a median tissue mass called the isthmus
- Composed of **follicles** that produce the glycoprotein (thyroglobulin)
- **Colloid (thyroglobulin + iodine)** fills the lumen of the follicles and is the precursor of thyroid hormone
- Other endocrine cells, the **parafollicular** cells (C-cell), produce the hormone *calcitonin*



(b)

(b) Section of thyroid gland

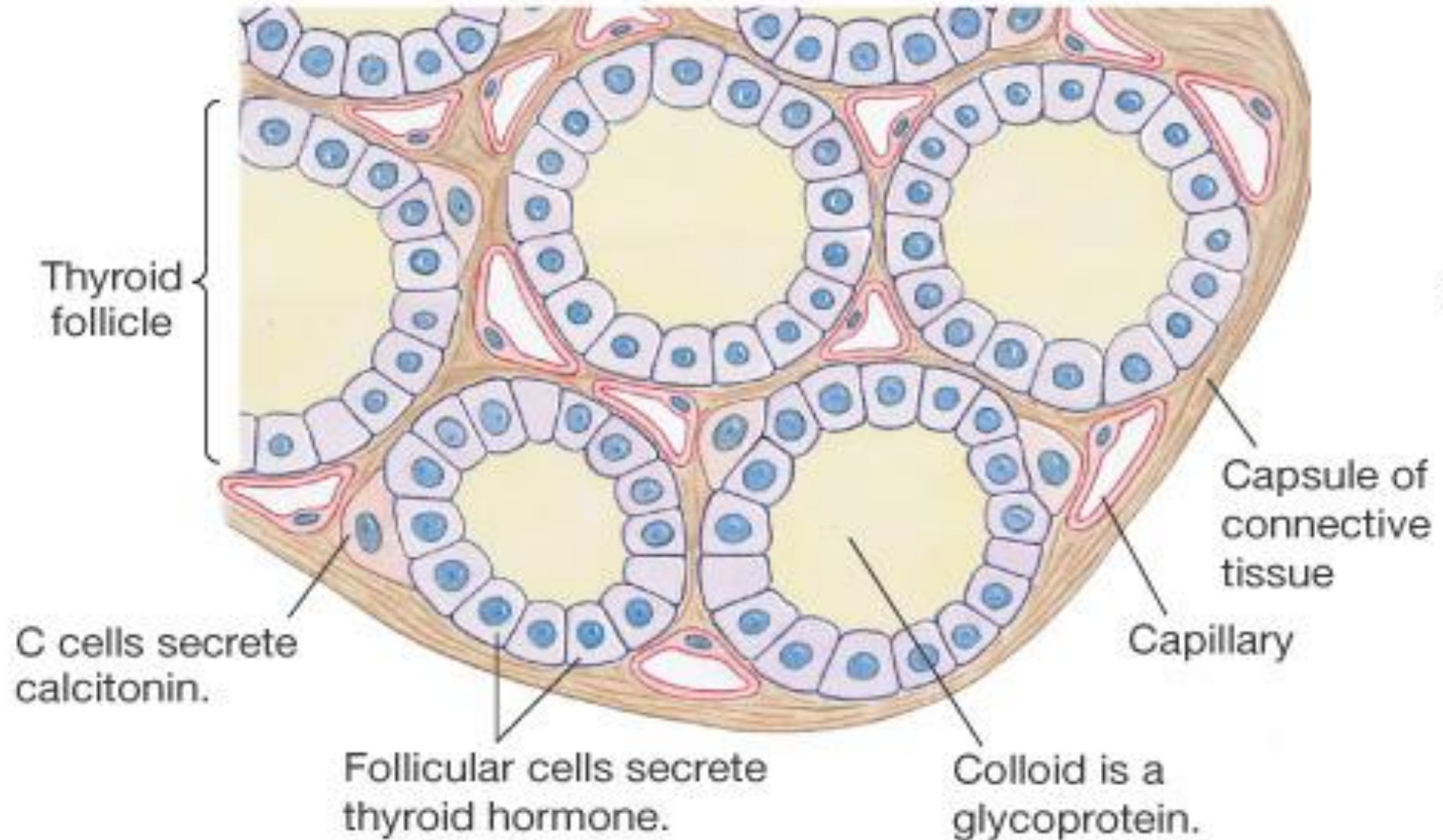
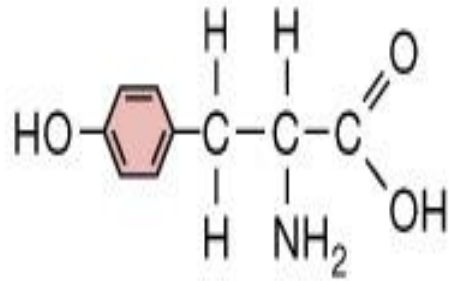


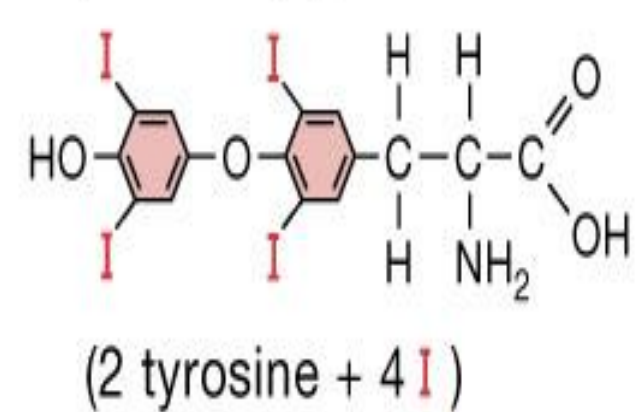
Figure 23-7b: **The thyroid gland**

Thyroxine and its Precursors: Structure & Synthesis

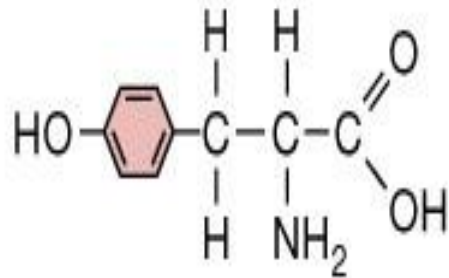
Tyrosine



Thyroxine (T₄)



Tyrosine



Triiodothyronine (T₃)

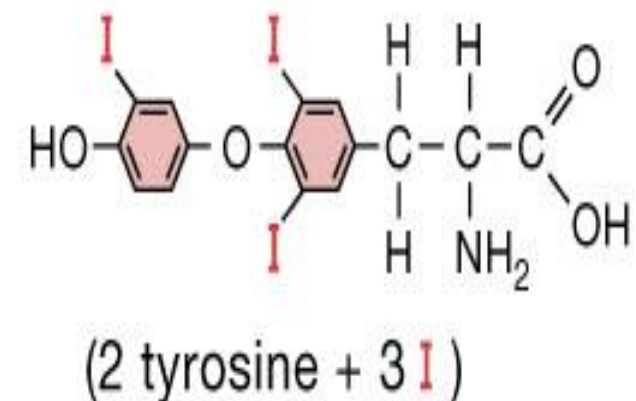


Figure 23-8: **Thyroid hormones are made from tyrosine and iodine**

Thyroid Hormone

- Thyroid hormone – major metabolic hormone
- Consists of two related iodine-containing compounds
 - T_4 – thyroxine; has two tyrosine molecules plus four bound iodine atoms
 - T_3 – triiodothyronine; has two tyrosines with three bound iodine atoms

TABLE 23-2 Thyroid Hormones	
Cell of origin	Thyroid follicle cells
Chemical nature	Iodinated amine
Biosynthesis	From iodine and tyrosine; formed and stored on parent protein thyroglobulin in follicle colloid
Transport in the circulation	Bound to thyroxine-binding globulin and albumins
Half-life	6–7 days for thyroxine (T ₄); about 1 day for triiodothyronine (T ₃)
Factors affecting release	Tonic release
Control pathway	TRH (hypothalamus) → TSH (anterior pituitary) → T ₃ + T ₄ (thyroid) → T ₄ deiodinates in tissues to form more T ₃
Target cells or tissues	Most cells of the body
Target receptor	Nuclear receptor
Whole body or tissue action	↑ Oxygen consumption (thermogenesis); protein catabolism in adults but anabolism in children; normal development of nervous system
Action at cellular level	Increases activity of metabolic enzymes and Na ⁺ -K ⁺ -ATPase
Action at molecular level	Production of new enzymes
Feedback regulation	T ₃ has negative feedback effect on anterior pituitary and hypothalamus

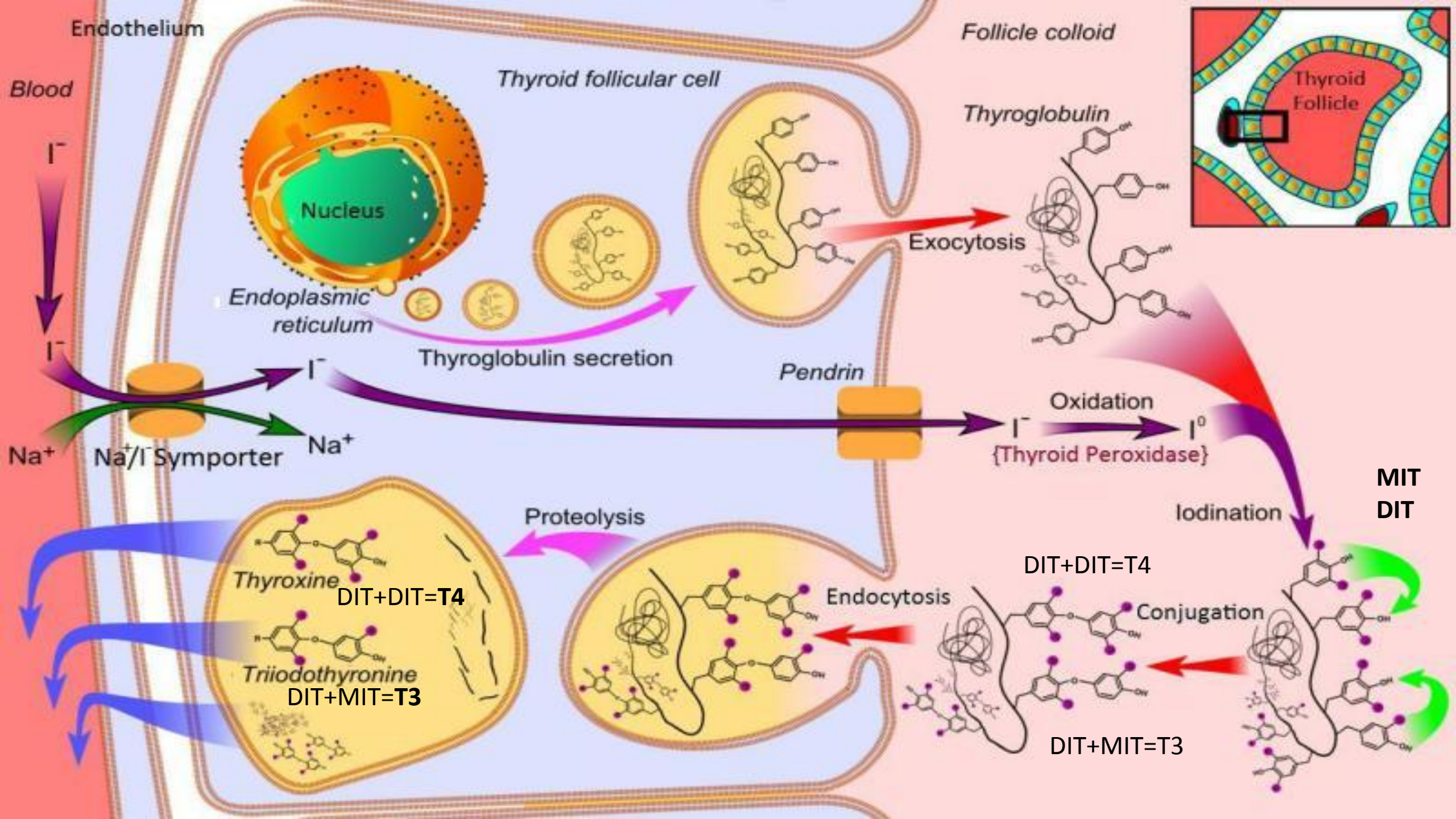
Effects of Thyroid Hormone

Effect basal metabolic rate: cellular respiration, protein synthesis and degradation. Also effect growth

- TH is concerned with:
 - Glucose oxidation
 - Increasing metabolic rate
 - Heat production
 - TH plays a role in:
 - Maintaining blood pressure
 - Regulating tissue growth
 - Developing skeletal and nervous systems
 - Maturation and reproductive capabilities
- In children: thyroid hormones are necessary for full expression of growth hormone, which means they are essential for normal growth and development, especially of the nervous system. In the first few years after birth, myelin and synapse formation requires T3 and T4

Synthesis of Thyroid Hormone

- **Thyroglobulin** is synthesized and discharged into the lumen. It's a glycoprotein rich with tyrosine (precursor)
- Iodides (I^-) are actively taken into the cell, oxidized to iodine (I_2) by **peroxidase enzymes**, and released into the lumen. This process is stimulated by TSH
- Iodine attaches to tyrosine, forming T_1 (monoiodotyrosine, or MIT), and T_2 (diiodotyrosine, or DIT)
- Iodinated tyrosines link together to form T_3 and T_4
- Colloid is then endocytosed and combined with a lysosome, where T_3 and T_4 are cleaved and diffuse into the bloodstream
- T_4 is larger than T_3 , slower in turnover and could be stored in liver and kidney



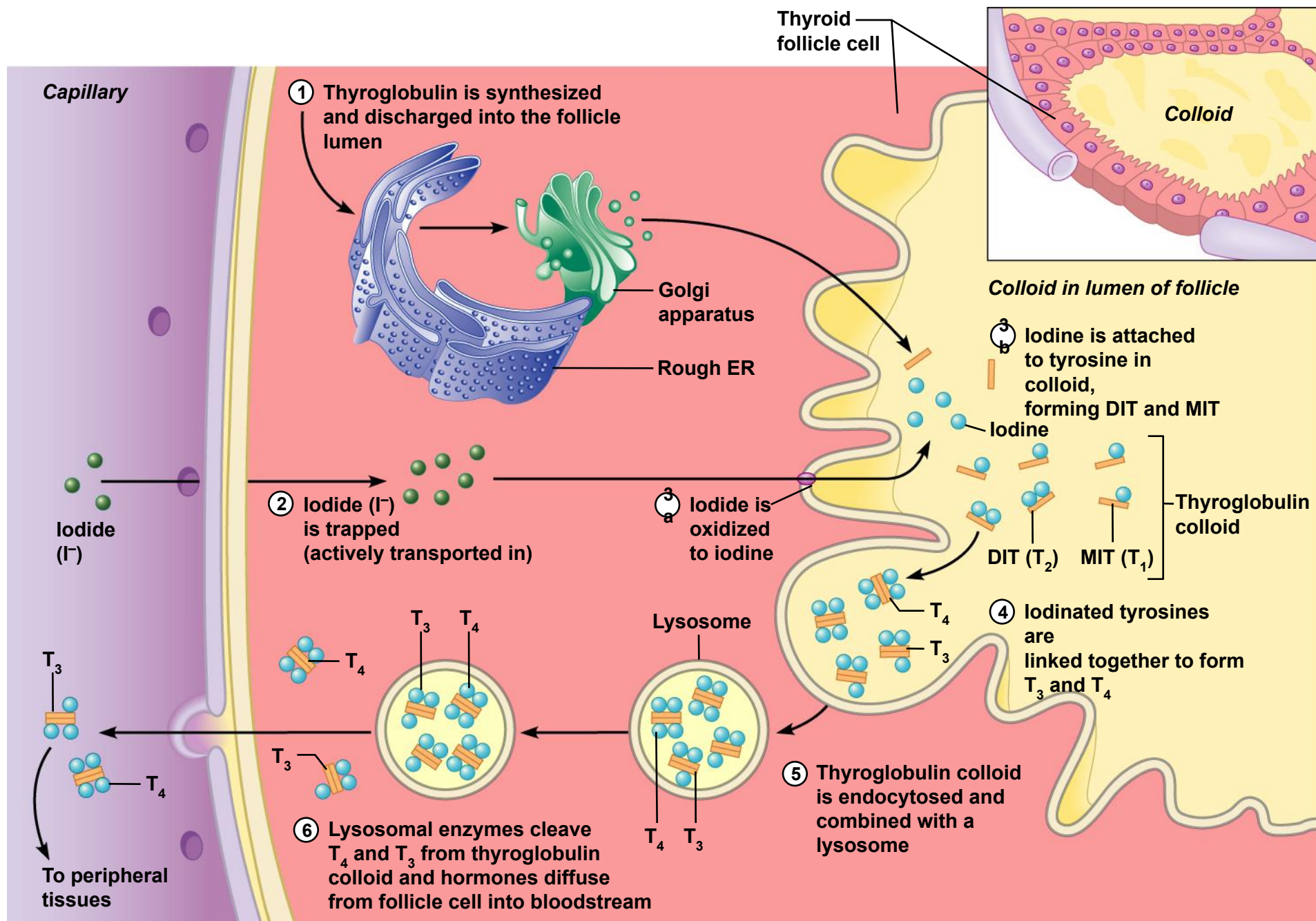


Figure 16.9

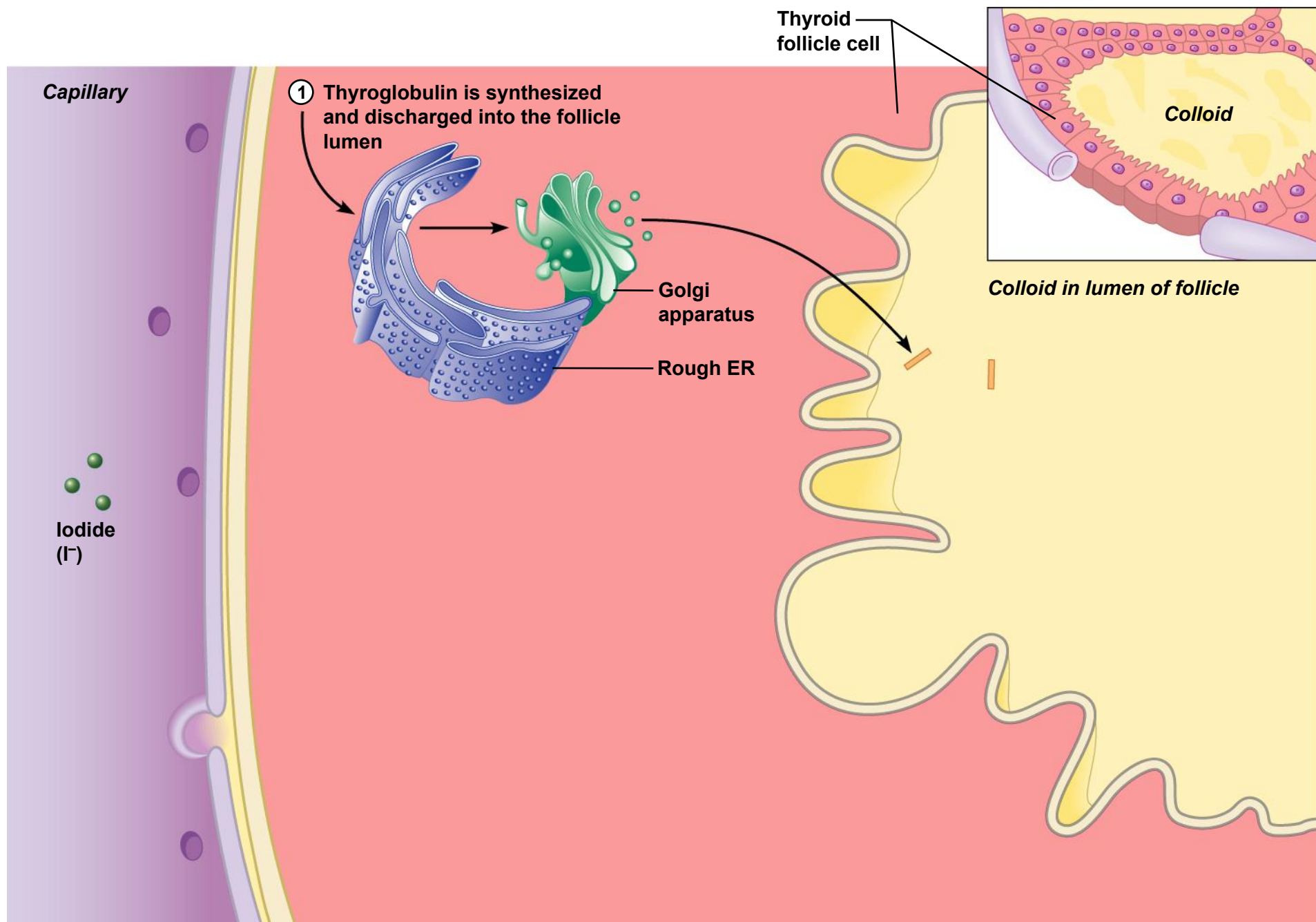


Figure 16.9

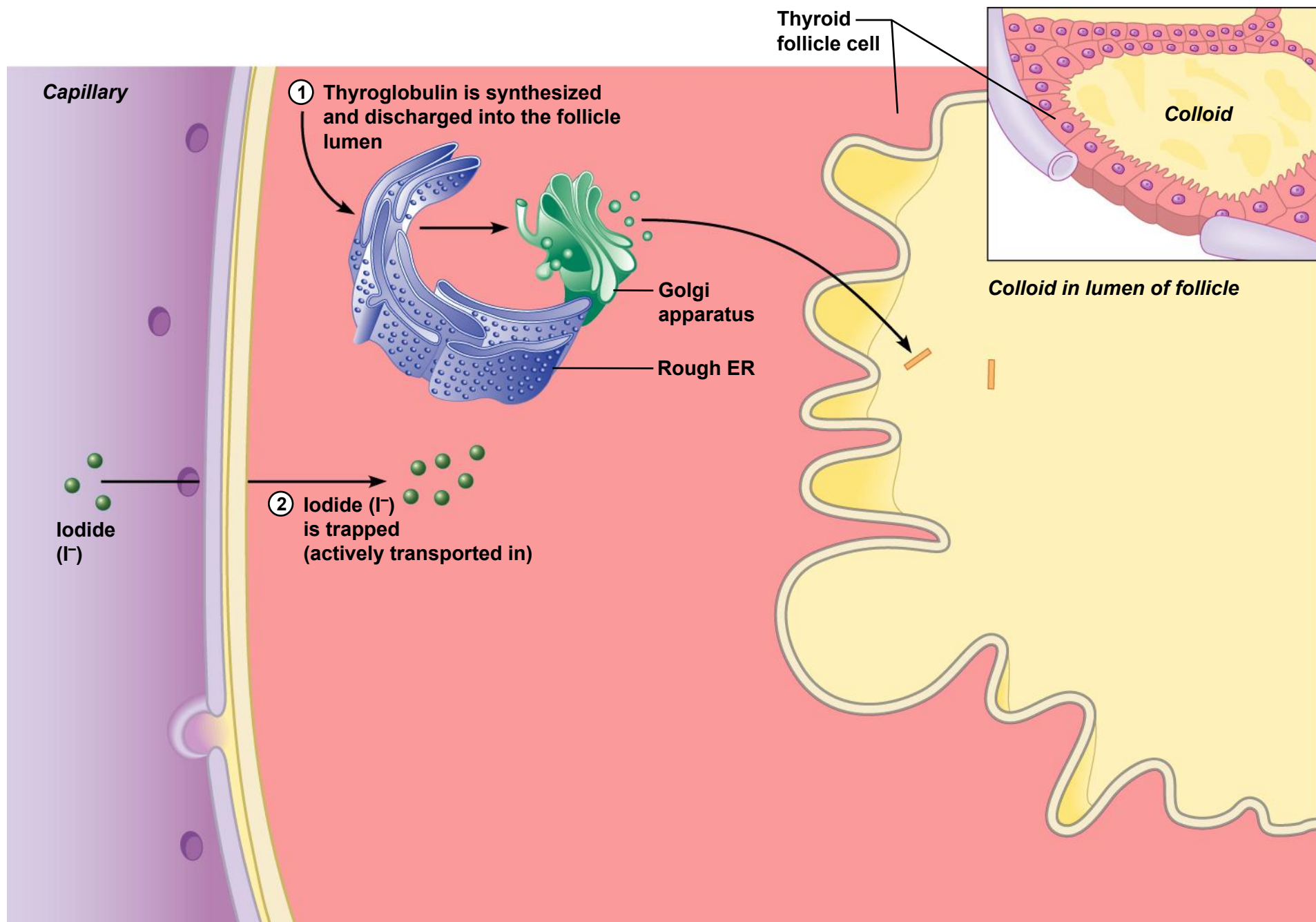


Figure 16.9

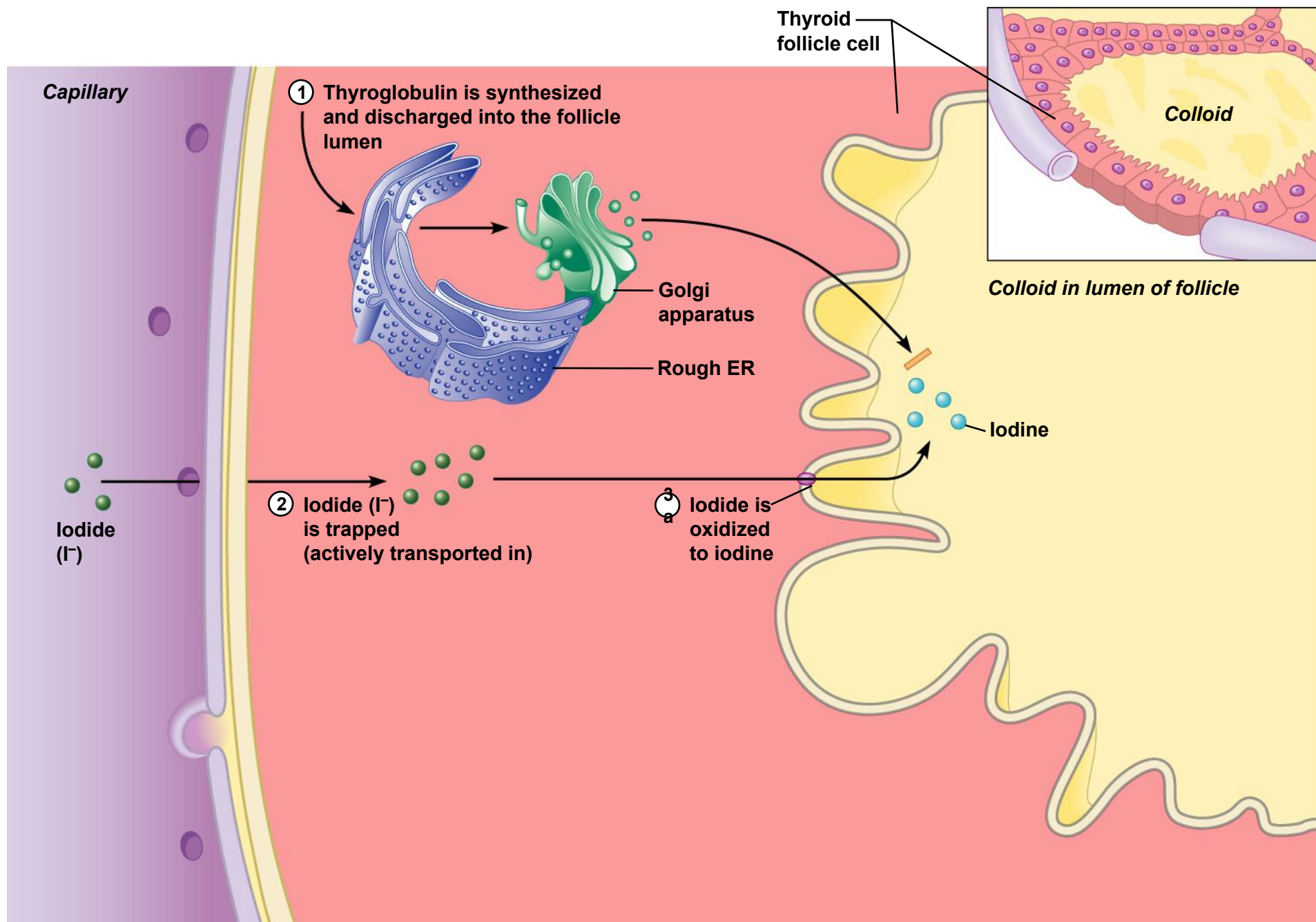


Figure 16.9

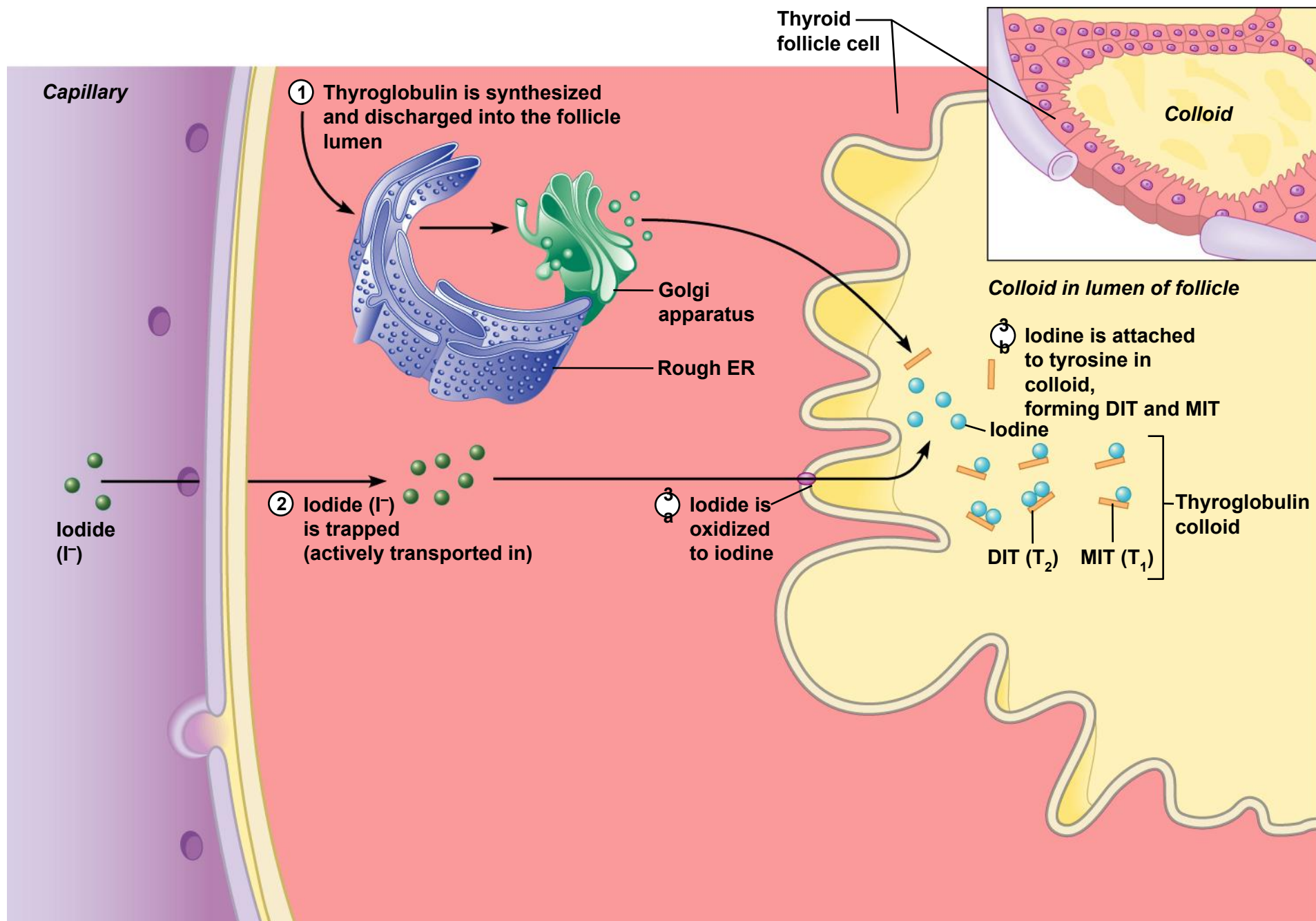


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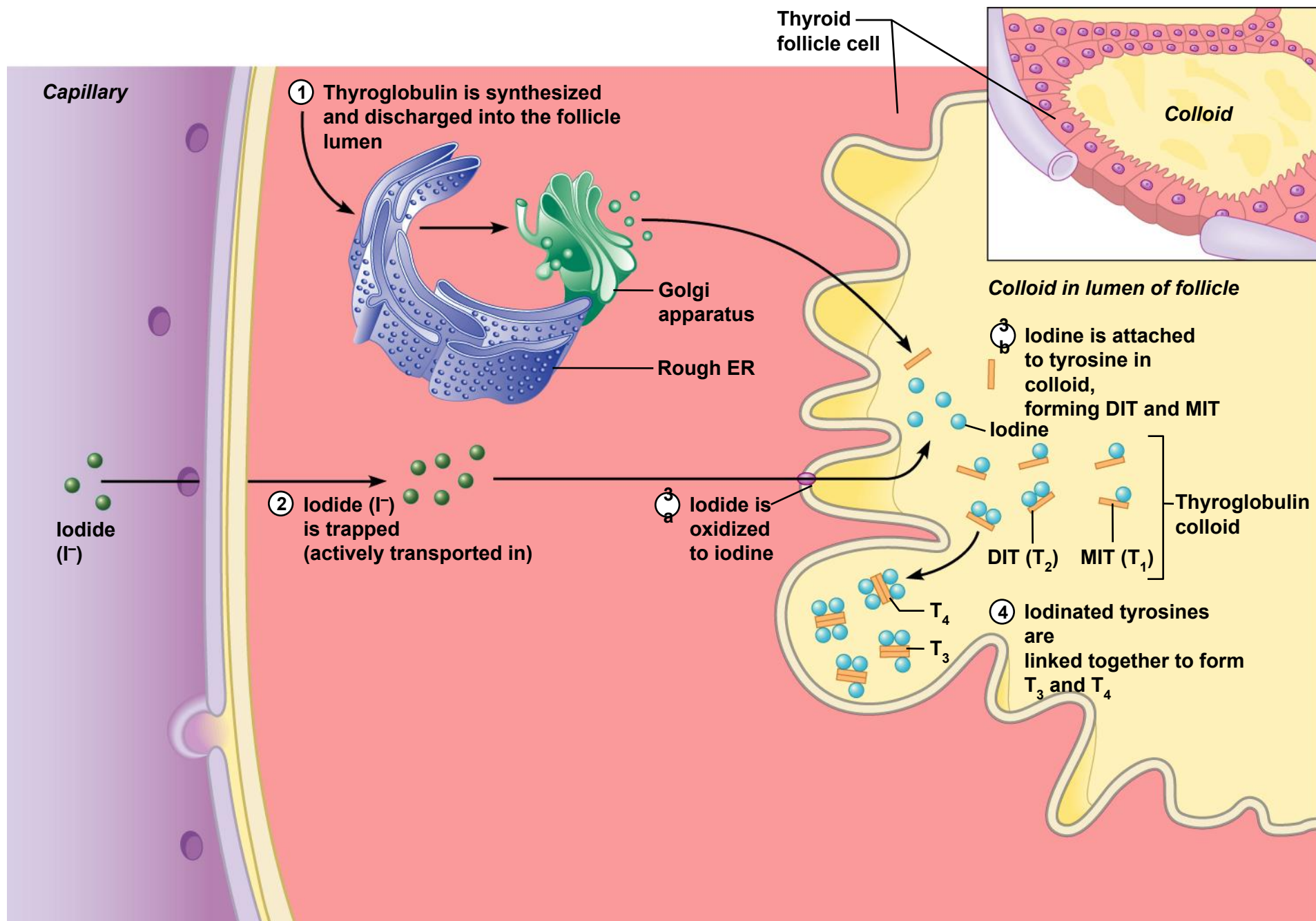


Figure 16.9

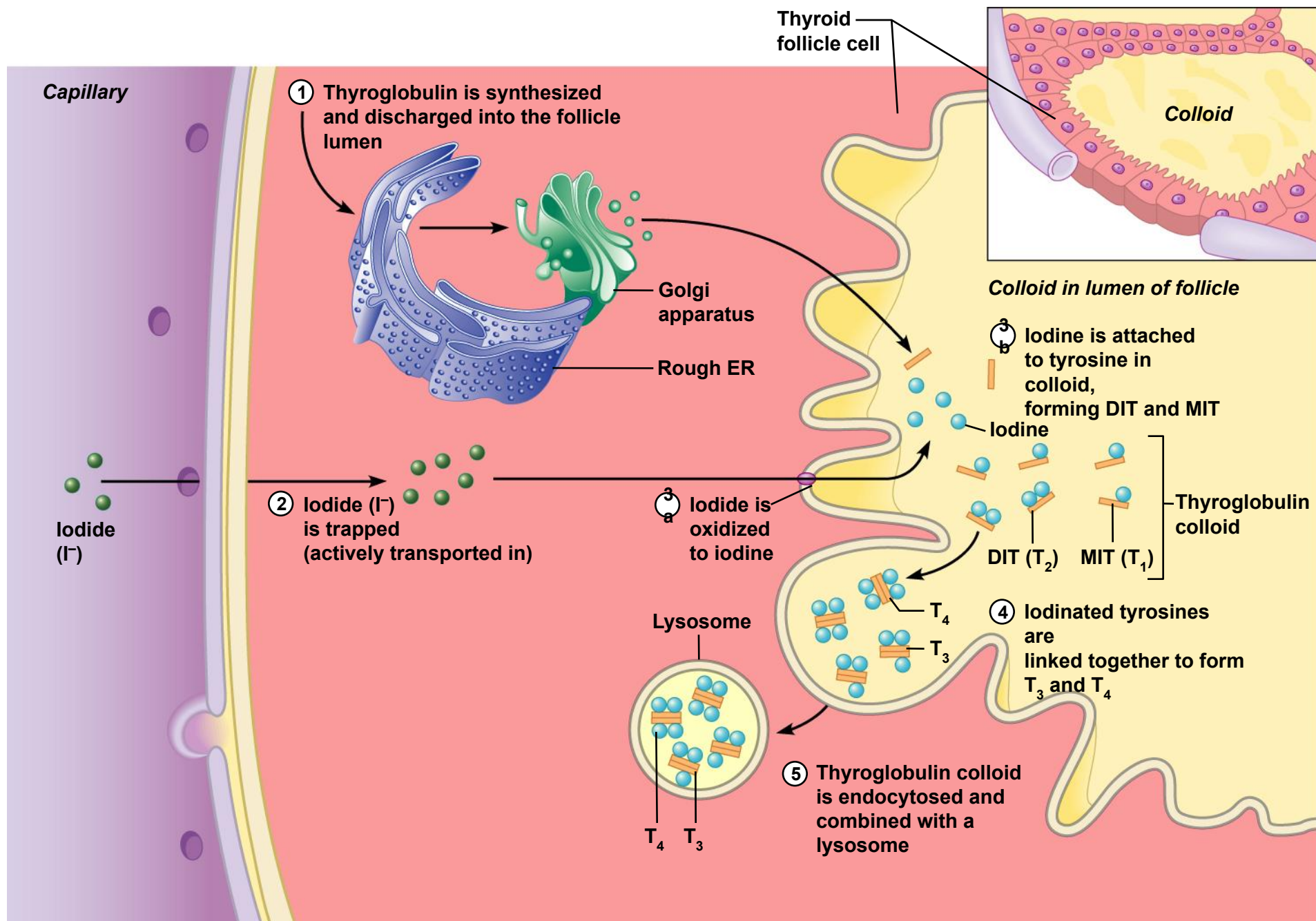


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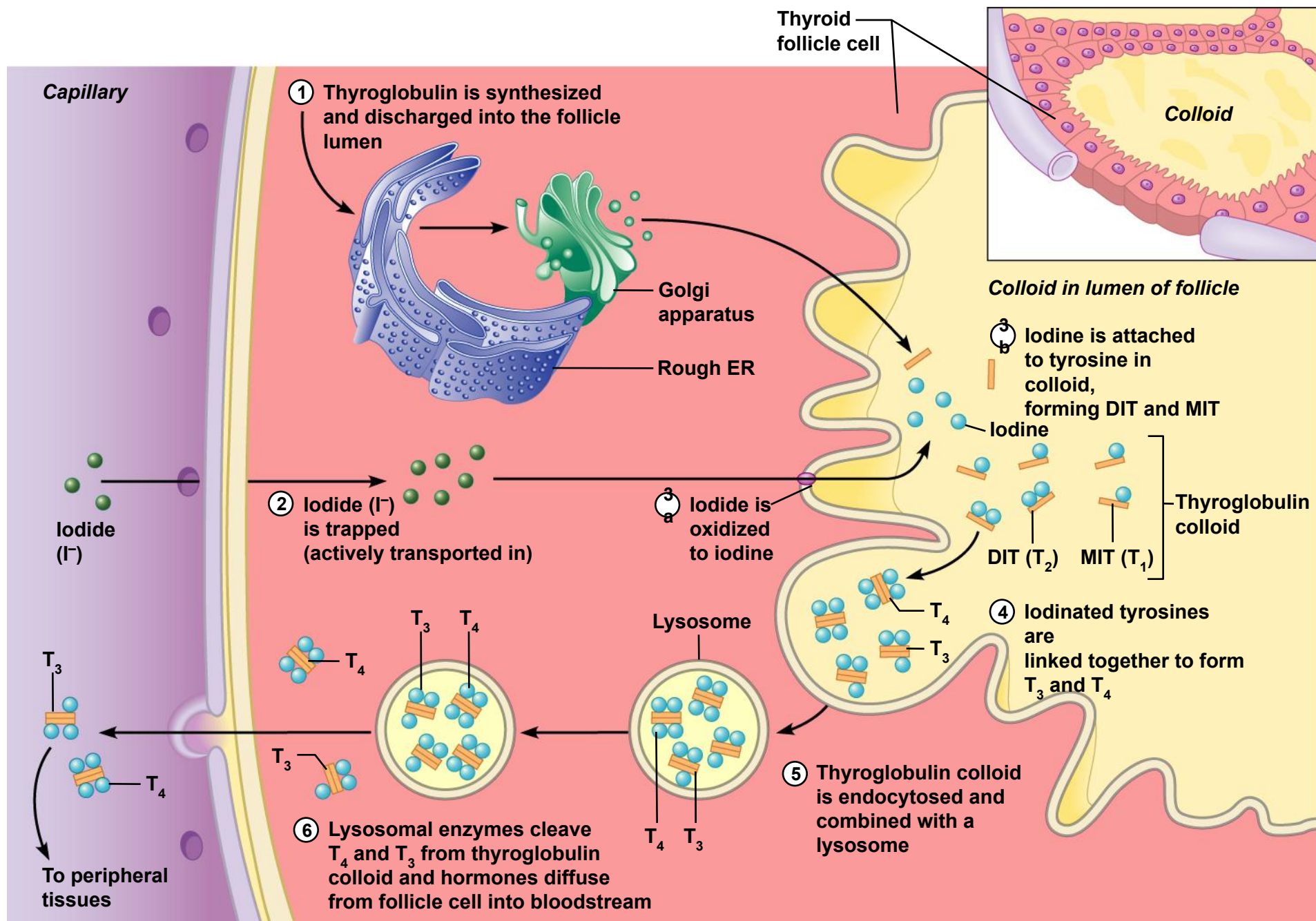


Figure 16.9

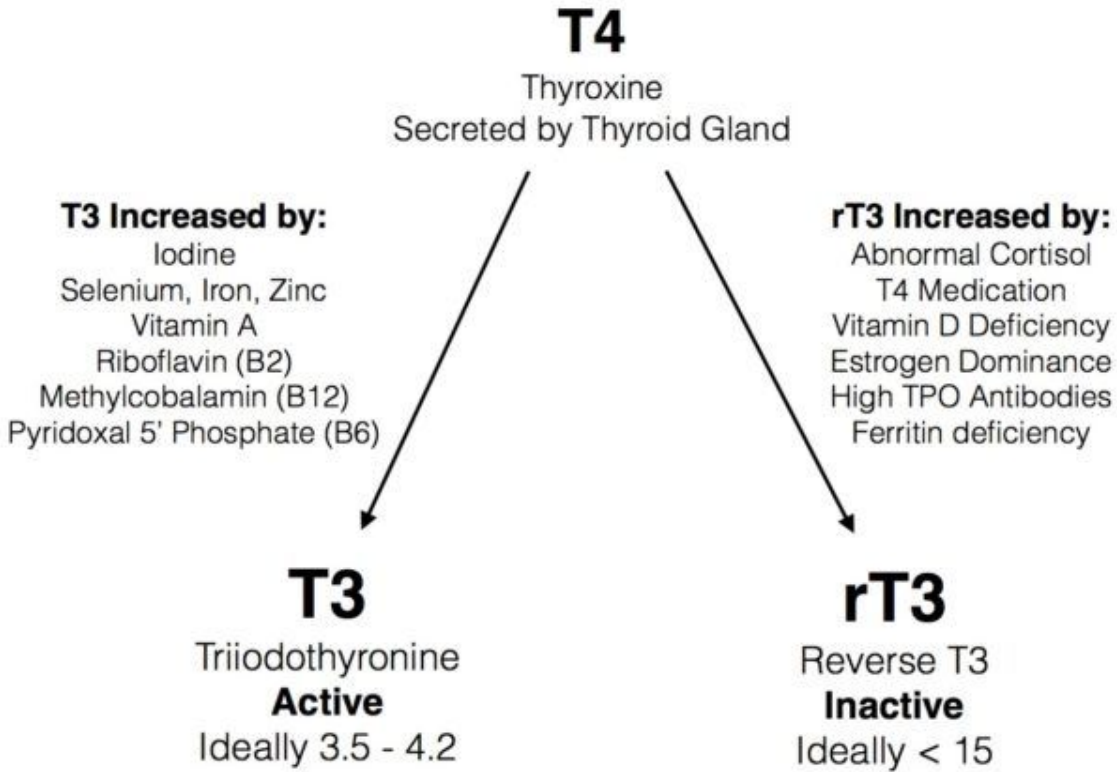
Transport and Regulation of TH

- T_4 and T_3 bind to **thyroxine-binding globulins (TBGs)** produced by the liver. It can be transported also by transthyretin and albumin
- Both bind to target receptors, but T_3 is ten times more active than T_4
- Peripheral tissues convert T_4 to T_3
- Target cells make about 85% of active T3 by using the enzyme **deiodinase** to remove an iodine from T4
- Mechanisms of activity are similar to steroids
- Regulation is by negative feedback
- Hypothalamic thyrotropin-releasing hormone (TRH) can overcome the negative feedback

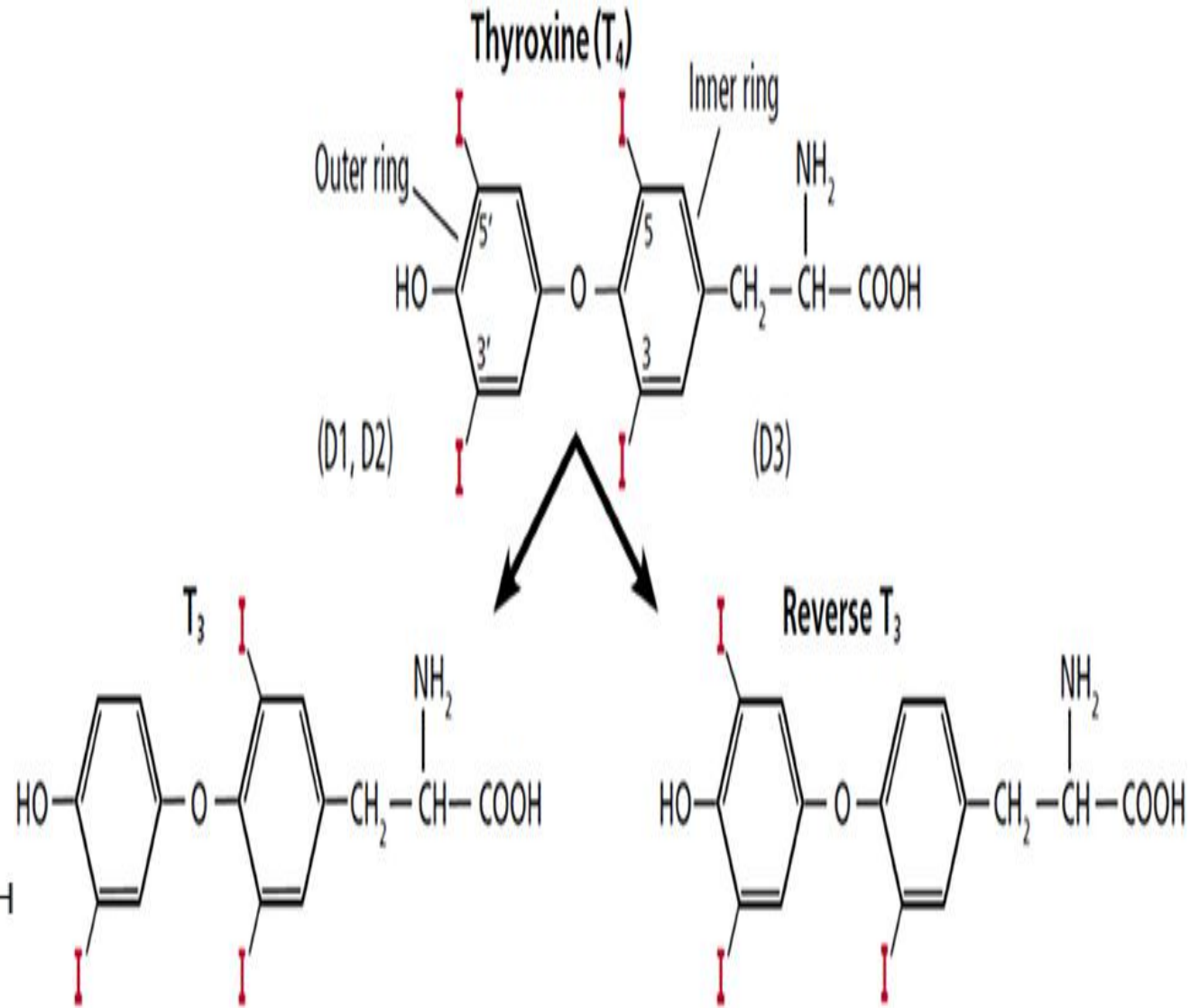
Differences between T3 and T4

	T3	T4
Secretion	30 microgram /day	80 microgram /day
Source	20 – 25% by gland 75 - 80% by conversion	Solely by gland
Half-life	1 day	7 days
Potency	3-4 times more potent than T4	Potent
Binding	0.2% in unbound	0.02% in unbound

Thyroid Hormone Conversion



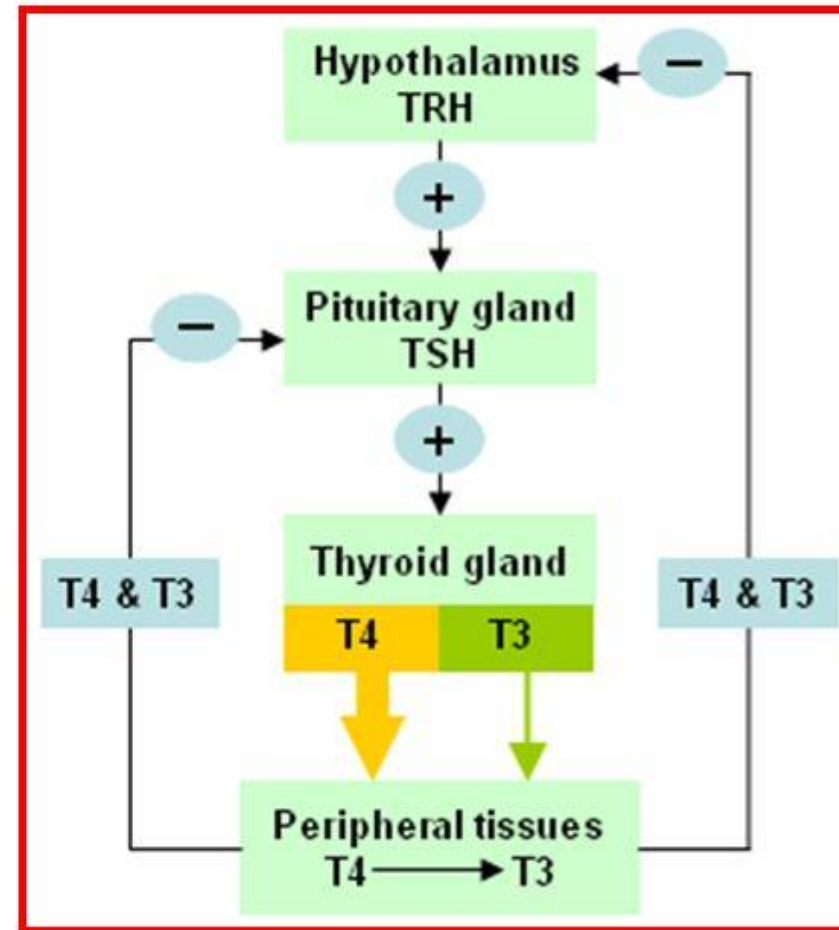
T4 has 2 choices, it either converts to T3 or rT3
What you create determines your well-being, not your TSH
The more rT3 you make, the more hypothyroid you are

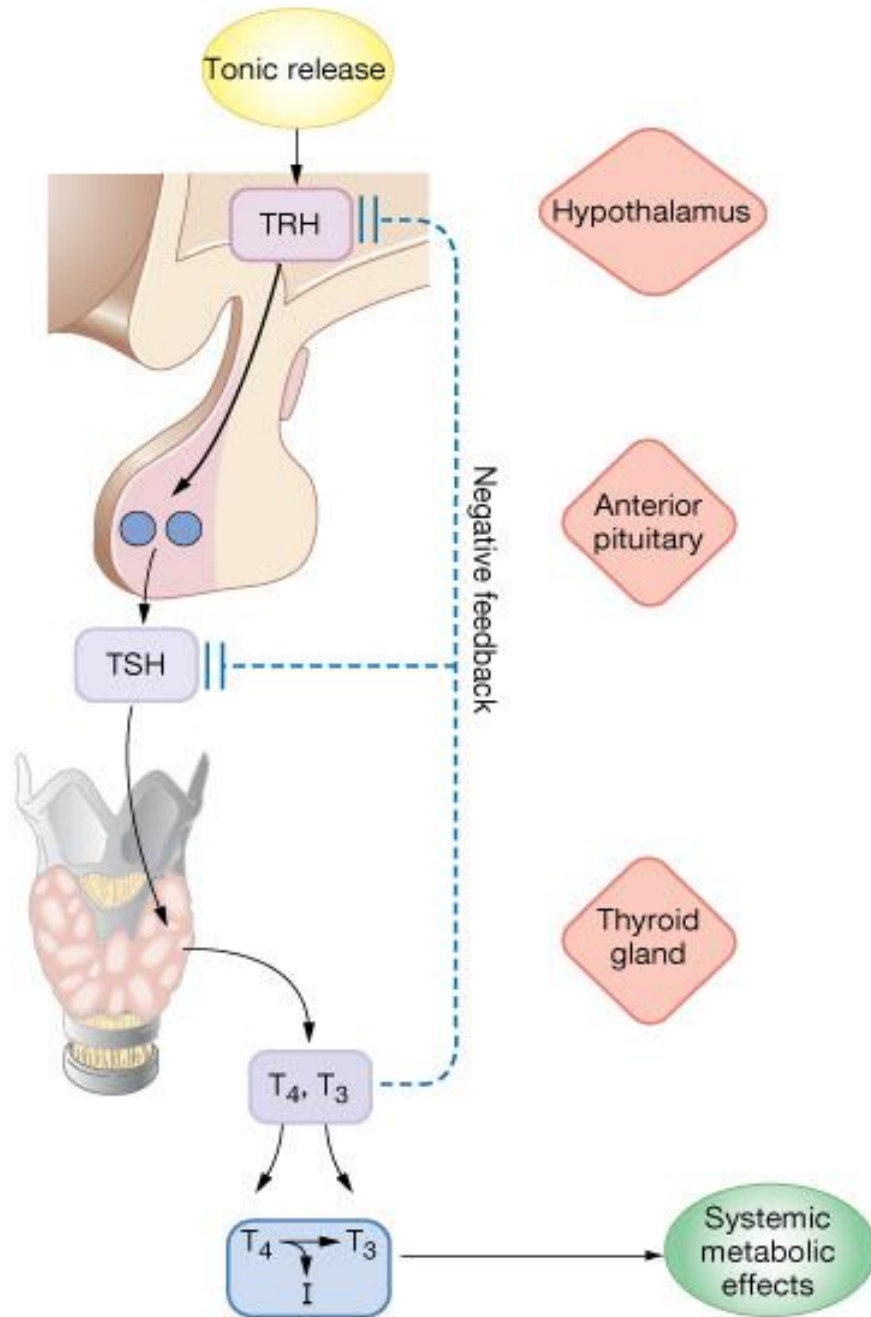


Regulation of Thyroid Hormone Secretion

High thyroid hormone levels
suppress TRH & TSH

Low thyroid hormone levels
stimulate TRH & TSH to produce
more hormone



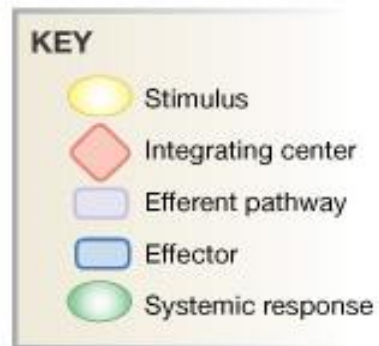


TRH is released from hypothalamus due to:

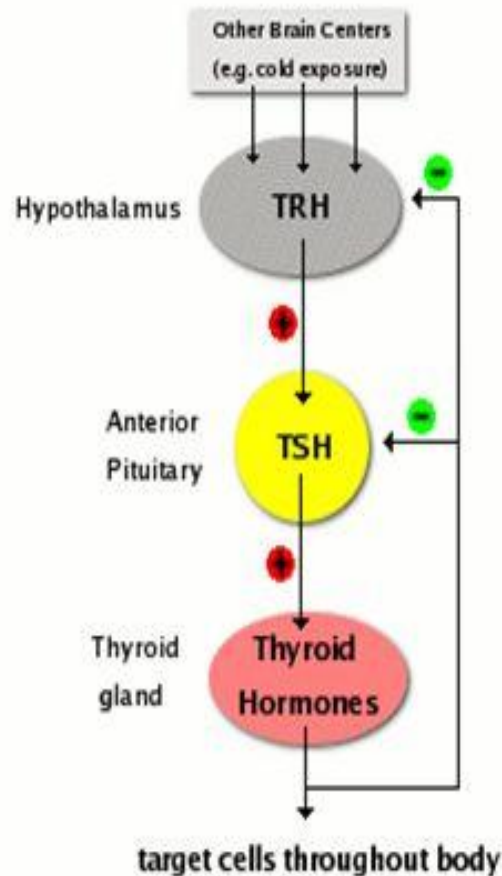
- Low thyroid hormones levels
- Low metabolic rate
- Cold
- Pregnancy
- High altitudes

TRH is inhibited in response to:

- High thyroid hormones levels
- High metabolic rate
- High levels of estrogen and androgen
- Aging



Regulation of Thyroid Hormone Secretion



Hypothalamic-pituitary-thyroid axis

- Control of thyroid hormone secretion is a **NEGATIVE FEEDBACK LOOP**
- Binding of TSH on thyroid epithelia enhances all the processes for hormone synthesis of
 1. Iodide transporter
 2. Thyroid peroxidase
 3. Thyroglobulin
- Magnitude of the TSH signal sets the rate for endocytosis of colloid
 - ↑ TSH → Faster rates of colloid synthesis **hence more hormone in circulation**
 - ↓ TSH → Decrease in colloid synthesis **hence less hormone in circulation**

COLD Exposure can increase TRH release → enhanced thyroid hormone release

Physiologic effects of thyroid hormones

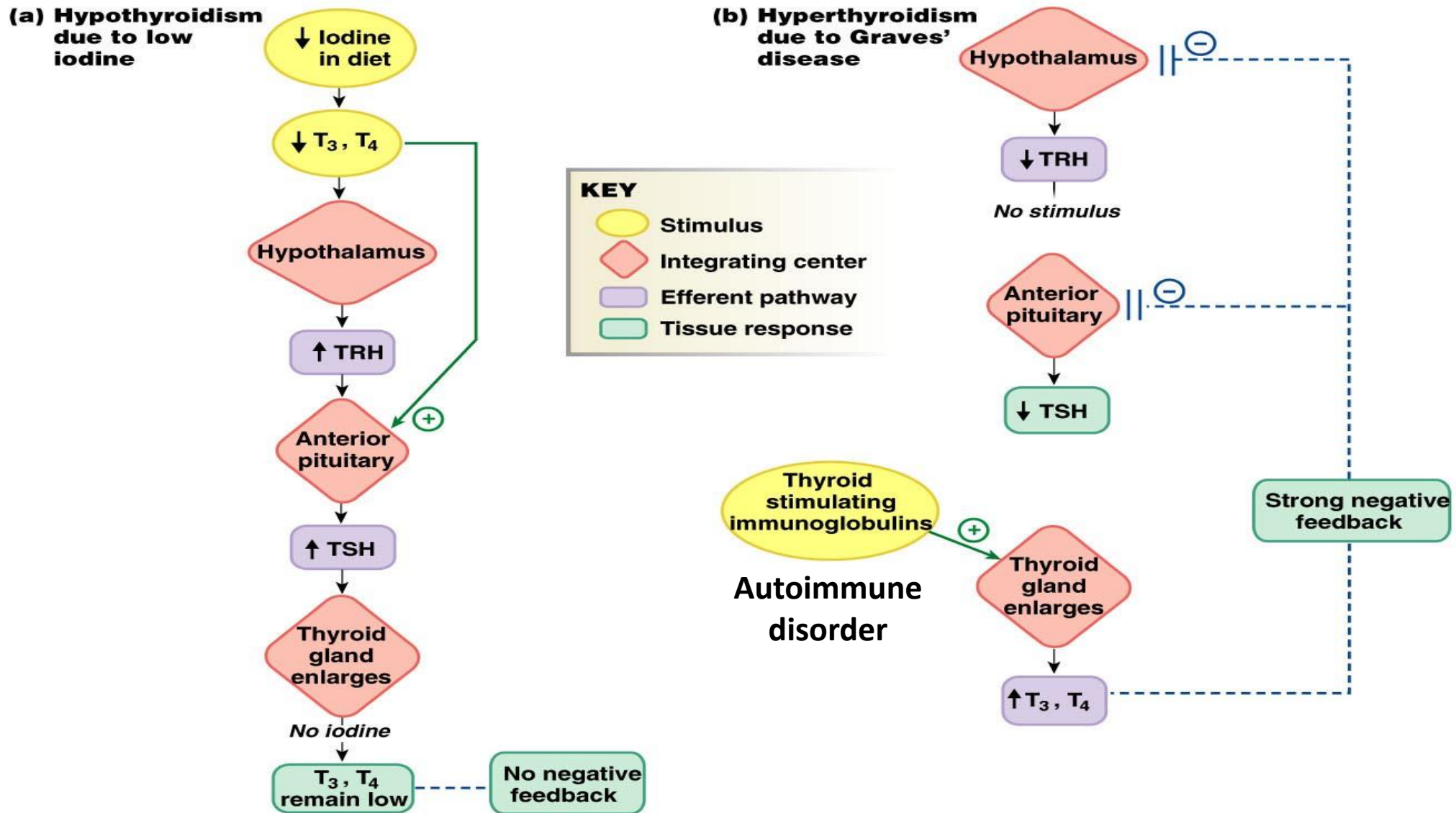
Target Tissue	Effect	Mechanism
Heart	Chronotropic	Increase number and affinity of beta-adrenergic receptors.
	Inotropic	Enhance responses to circulating catecholamines. Increase proportion of alpha myosin heavy chain (with higher ATPase activity).
Adipose tissue	Catabolic	Stimulate lipolysis.
Muscle	Catabolic	Increase protein breakdown.
Bone	Developmental	Promote normal growth and skeletal development.
Nervous system	Developmental	Promote normal brain development.
Gut	Metabolic	Increase rate of carbohydrate absorption.
Lipoprotein	Metabolic	Stimulate formation of LDL receptors.
Other	Calorigenic	Stimulate oxygen consumption by metabolically active tissues (exceptions: adult brain, testes, uterus, lymph nodes, spleen, anterior pituitary). Increase metabolic rate.

Goiter



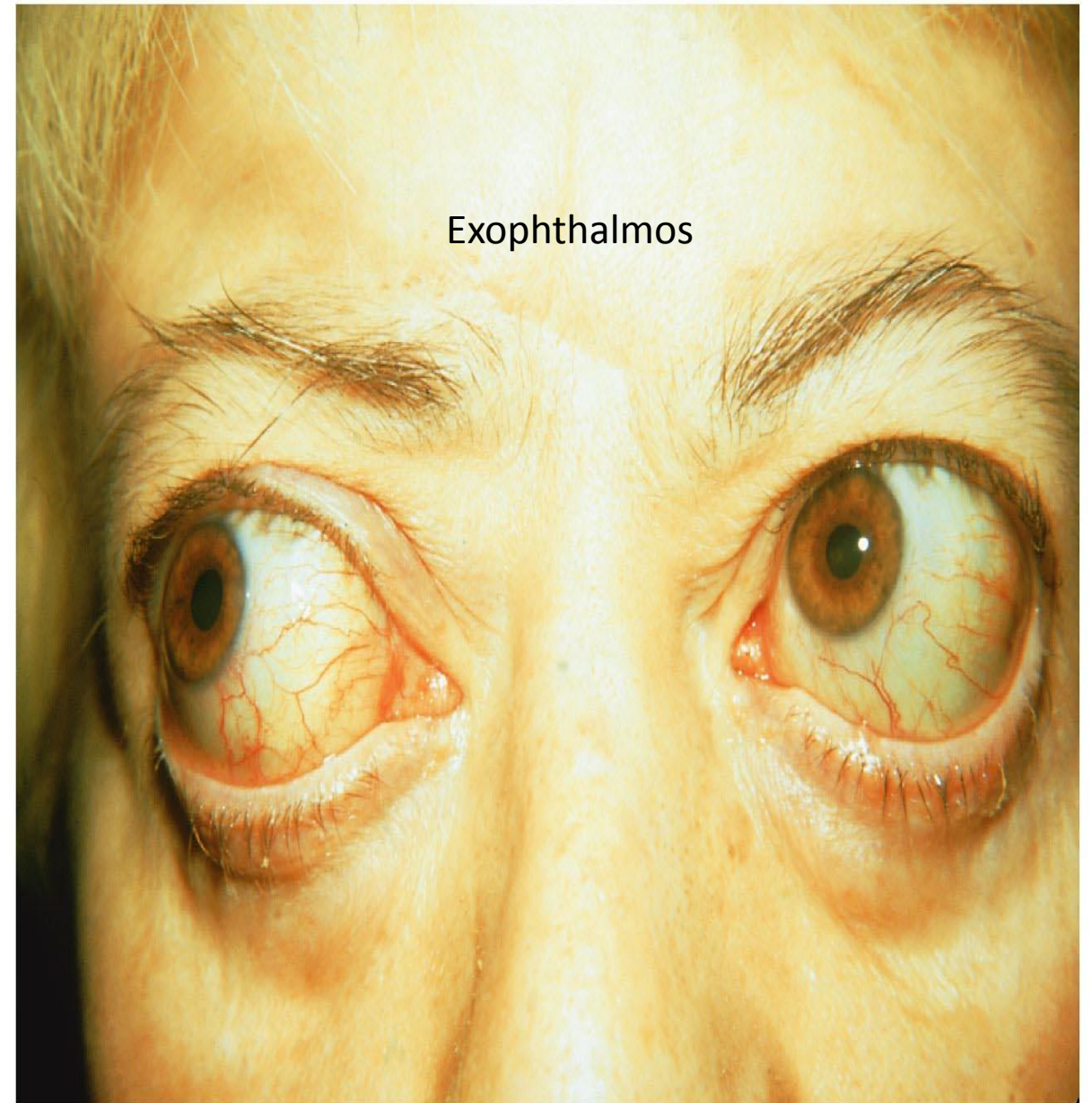
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Figure 23-13



Goiter can occur in both hypothyroidism and hyperthyroidism. (a) In hypothyroidism caused by iodine deficiency, absence of negative feedback increases TSH secretion and results in goiter. (b) In Graves disease, thyroid stimulating immune proteins (TSI) bind to thyroid gland TSH receptors and cause the gland to hypertrophy.

Figure 23-14 - Overview



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Figure 23-15

Calcitonin

- A peptide hormone produced by the parafollicular, or C-cells
- Lowers blood calcium levels in children
- Antagonist to parathyroid hormone (PTH)

TABLE 23-7 Calcitonin	
Cell of origin	C cells of thyroid gland (parafollicular cells)
Chemical nature	32-amino acid peptide
Biosynthesis	Typical peptide
Transport in the circulation	Dissolved in plasma
Half-life	<10 minutes
Factors affecting release	↑ Plasma $[Ca^{2+}]$
Target cells or tissues	Bone and kidney
Target receptor	G protein-coupled membrane receptor
Whole body or tissue action	Prevents bone resorption; enhances kidney excretion
Action at molecular level	Signal transduction pathways appear to vary during cell cycle
Other information	Experimentally decreases plasma $[Ca^{2+}]$ but has little apparent physiological effect in adult humans; possible effect on skeletal development; possible protection of bone Ca^{2+} stores during pregnancy and lactation

Calcitonin

- Calcitonin targets the skeleton, where it:
 - Activate **osteoblasts** (form bone tissue) □ transfer calcium from blood to bone tissue.
 - Inhibits **osteoclast** (breakdown bone tissue) activity.
 - Stimulates calcium uptake and incorporation into the bone matrix
- Regulated by a humoral (calcium ion concentration in the blood) negative feedback mechanism

Calcitonin apparently plays only a minor role in daily calcium balance in adult humans. Patients whose thyroid glands have been removed show no disturbance in calcium balance.

Parathyroid Glands

- Tiny glands embedded in the posterior aspect of the thyroid
- Cells are arranged in cords containing **oxyphil** and **chief cells**
- Chief (principal) cells secrete PTH
- PTH (parathormone) **regulates calcium balance in the blood**

Parathyroid Glands

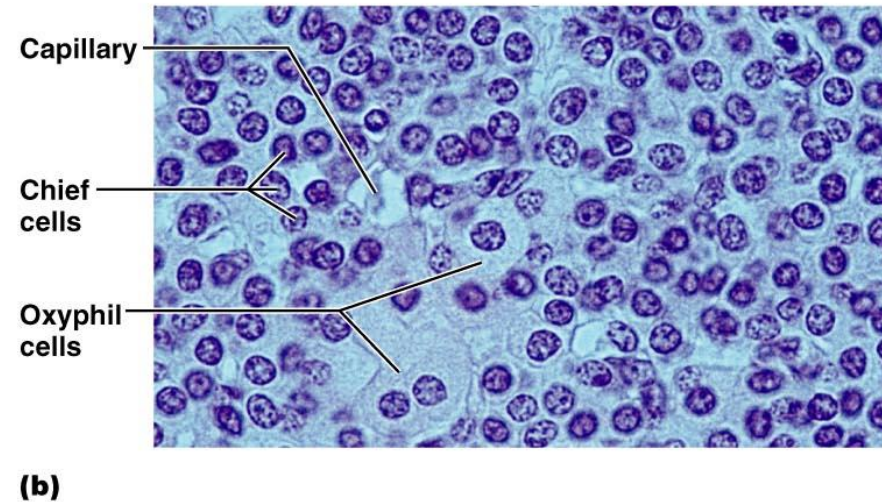
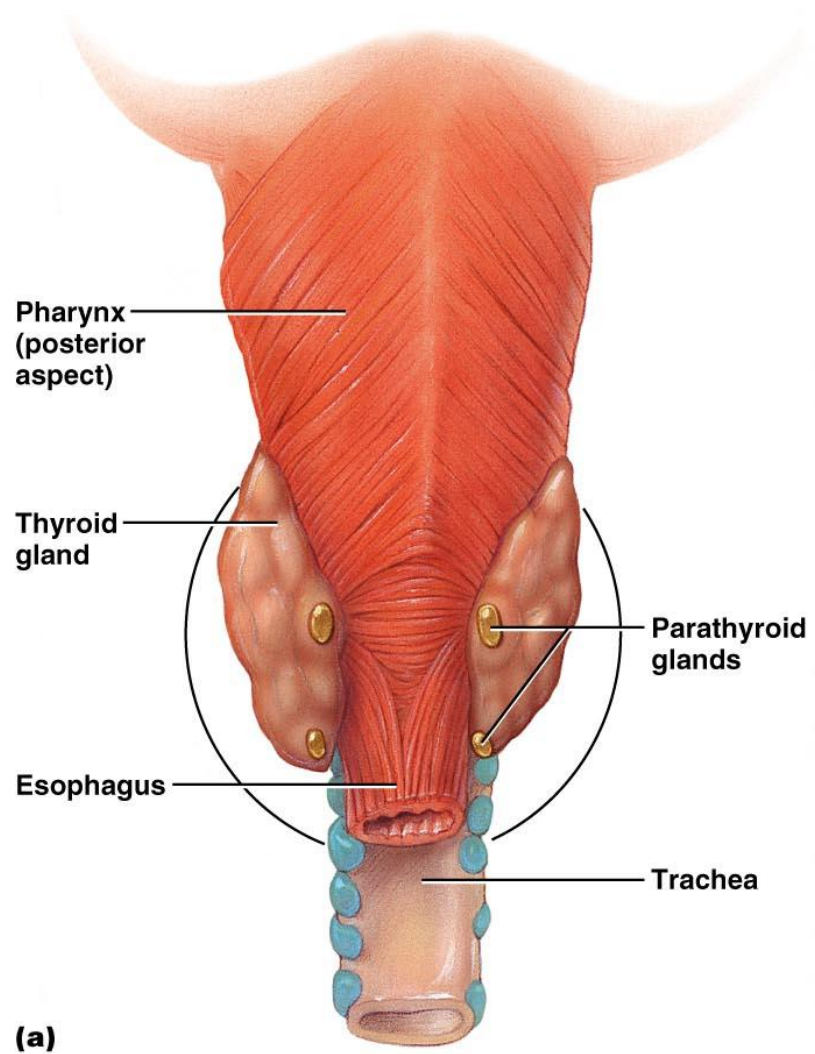


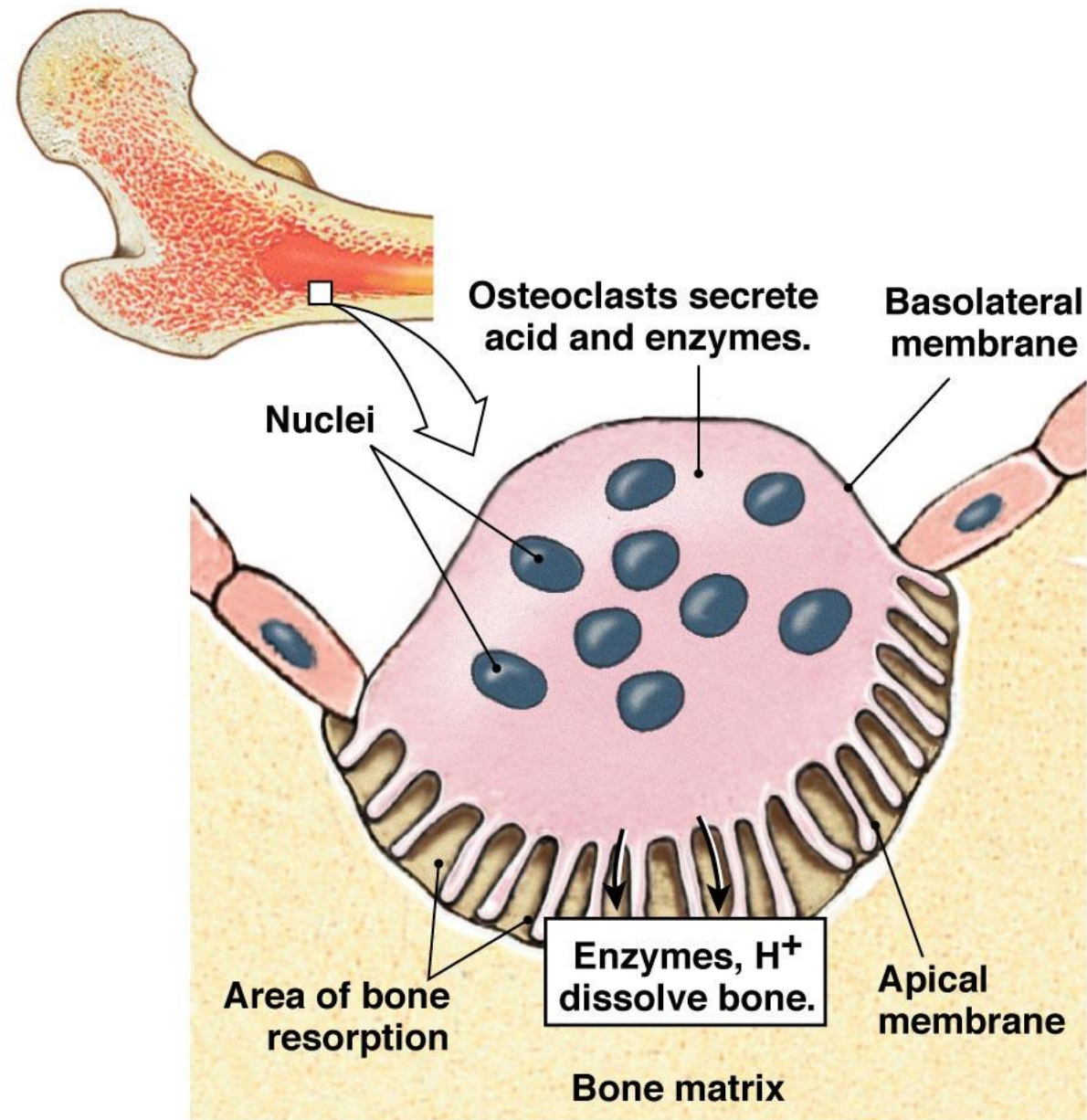
Figure 16.11

TABLE 23-5	Parathyroid Hormone (PTH)
Cell of origin	Parathyroid glands
Chemical nature	84-amino acid peptide
Biosynthesis	Continuous production, little stored
Transport in the circulation	Dissolved in plasma
Half-life	Less than 20 minutes
Factors affecting release	↓ Plasma Ca^{2+}
Target cells or tissues	Kidney, bone, intestine
Target receptor	Membrane receptor acts via cAMP
Whole body or tissue action	↑ Plasma Ca^{2+}
Action at cellular level	↑ Vitamin D synthesis; ↑ renal reabsorption of Ca^{2+} ; ↑ bone resorption
Action at molecular level	Rapidly alters Ca^{2+} transport but also initiates protein synthesis in osteoclasts
Onset of action	2–3 hours for bone, with increased osteoclast activity requiring 1–2 hours; 1–2 days for intestinal absorption; within minutes for kidney transport
Feedback regulation	Negative feedback by ↑ plasma Ca^{2+}
Other information	Osteoclasts have no PTH receptors, so are affected by PTH-induced paracrines. PTH is essential for life; absence causes hypocalcemic tetany.

Effects of Parathyroid Hormone

- PTH release increases Ca^{2+} in the blood as it:
 - Increases absorption of Ca^{2+} by **intestinal mucosal**
 - Enhances the reabsorption of Ca^{2+} and the secretion of phosphate by the **kidneys**
 - **Stimulates osteoclasts** to digest **bone matrix**
- Rising Ca^{2+} in the blood inhibits PTH release

Osteoclasts are responsible for bone resorption. Osteoclasts secrete acid that dissolves calcium phosphate in bone



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Figure 23-24

Effects of Parathyroid Hormone

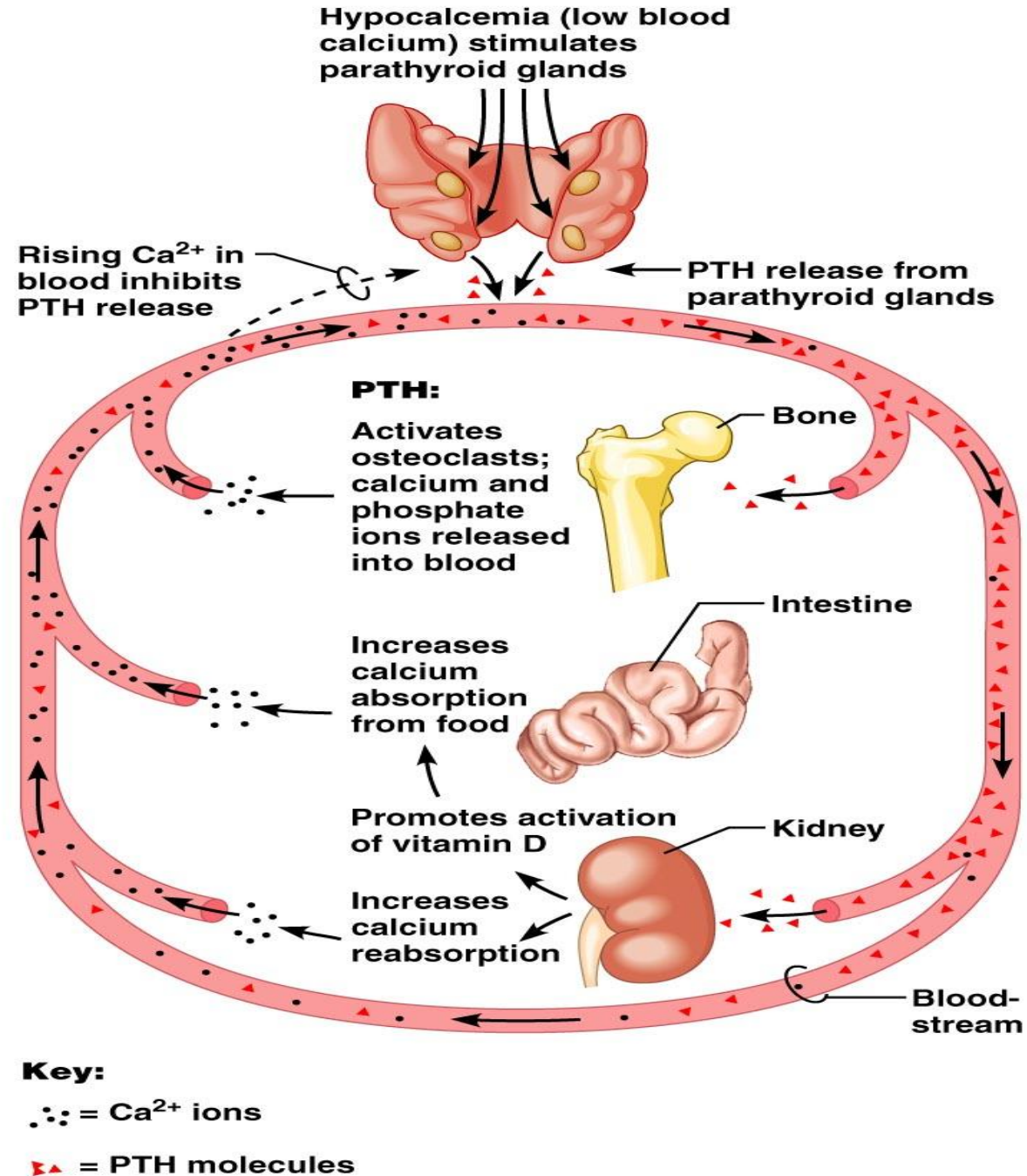
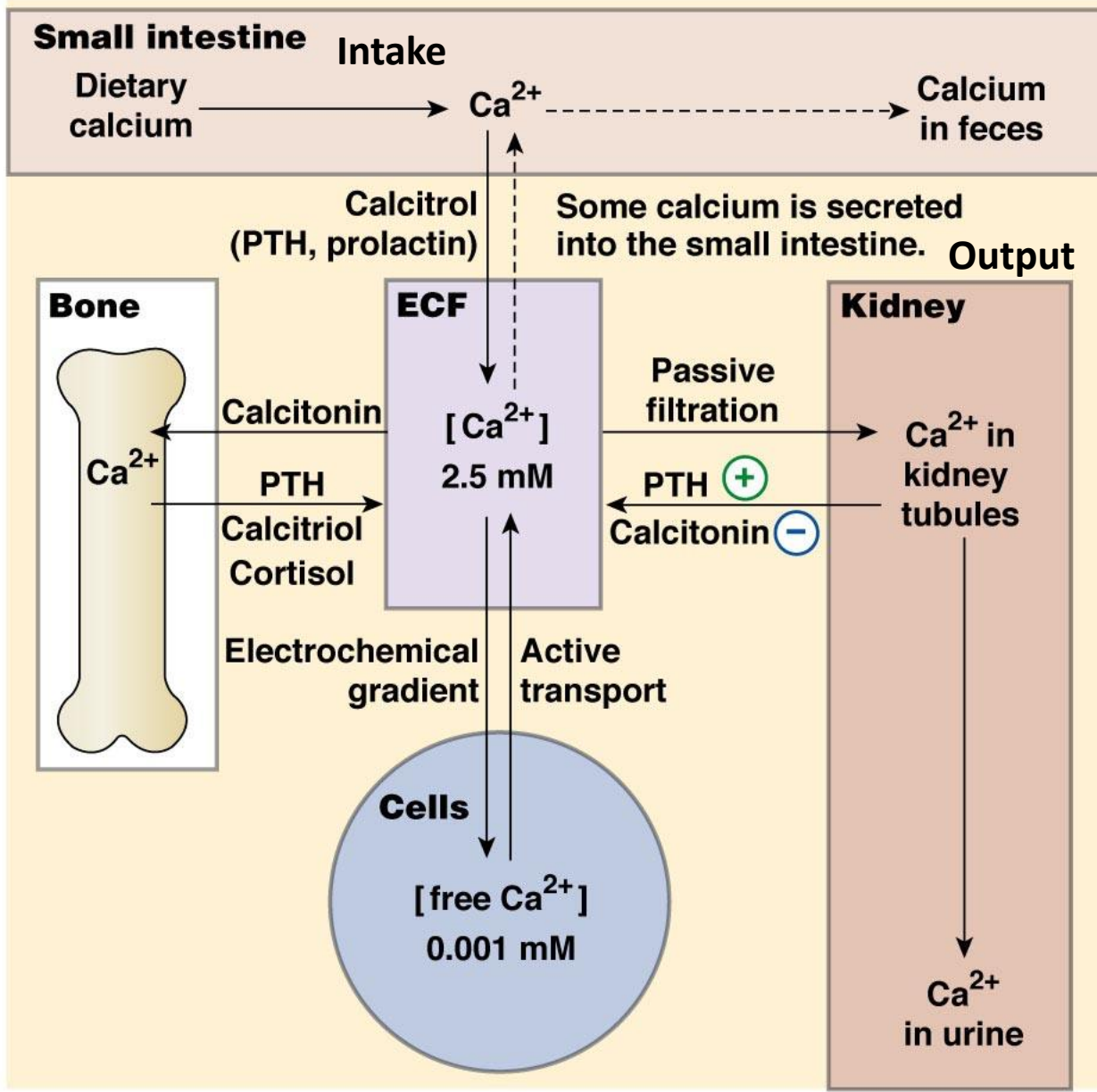


Figure 16.12

Ca2+ has several physiological functions:

- 1. Ca2+ is an important **signal molecule**.
Calcium entering the cytoplasm initiates exocytosis of synaptic and secretory vesicles, contraction in muscle fibers, or altered activity of enzymes and transporters. Removal of Ca2+ from the cytoplasm requires active transport.
- 2. Ca2+ is part of the **intercellular cement** that holds cells together at tight junctions.
- 3. Ca2+ is a **cofactor in the coagulation** cascade
- 4. Plasma Ca2+ concentrations affect the **excitability of neurons**
If plasma Ca2+ falls too low (hypocalcemia), neuronal permeability to Na2+ increases, neurons depolarize, and the nervous system becomes hyperexcitable. Hypercalcemia has the opposite effect, depressing neuromuscular activity

TABLE 23-4 Functions of Calcium in the Body		
COMPARTMENT	PERCENTAGE OF BODY CALCIUM	FUNCTION
Extracellular matrix	99%	Calcified matrix of bone
Extracellular fluid	0.1%	“Cement” for tight junctions; role in myocardial and smooth muscle contraction; neurotransmitter release at synapses; role in excitability of neurons; cofactor in coagulation cascade
Intracellular	0.9%	Signal in second messenger pathways; role in muscle contraction



Ca^{2+} absorption is hormonally regulated.

PTH :

1. Mobilizes calcium from bone. Increased bone resorption by osteoclasts
2. Enhances renal reabsorption of calcium
3. Indirectly increases intestinal absorption of calcium (Calcitriol)

KEY

PTH = parathyroid hormone

TABLE 23-6	Vitamin D₃ (Calcitriol, 1,25-Dihydroxy-cholecalciferol)
Cell of origin	Complex biosynthesis; see below
Chemical nature	Steroid
Biosynthesis	Vitamin D formed by sunlight on precursor molecules or ingested in food; converted in two steps (liver and kidney) to 1,25(OH) ₂ D ₃
Transport in the circulation	Bound to plasma proteins
Stimulus for synthesis	↓ Ca ²⁺ ; indirectly via PTH; prolactin also stimulates synthesis
Target cells or tissues	Intestine, bone, and kidney
Target receptor	Nuclear
Whole body or tissue action	↑ Plasma Ca ²⁺
Action at molecular level	Stimulates production of calbindin, a Ca ²⁺ -binding protein, and of CaSR in parathyroid gland; associated with intestinal transport by unknown mechanism
Feedback regulation	Plasma Ca ²⁺ shuts off PTH secretion

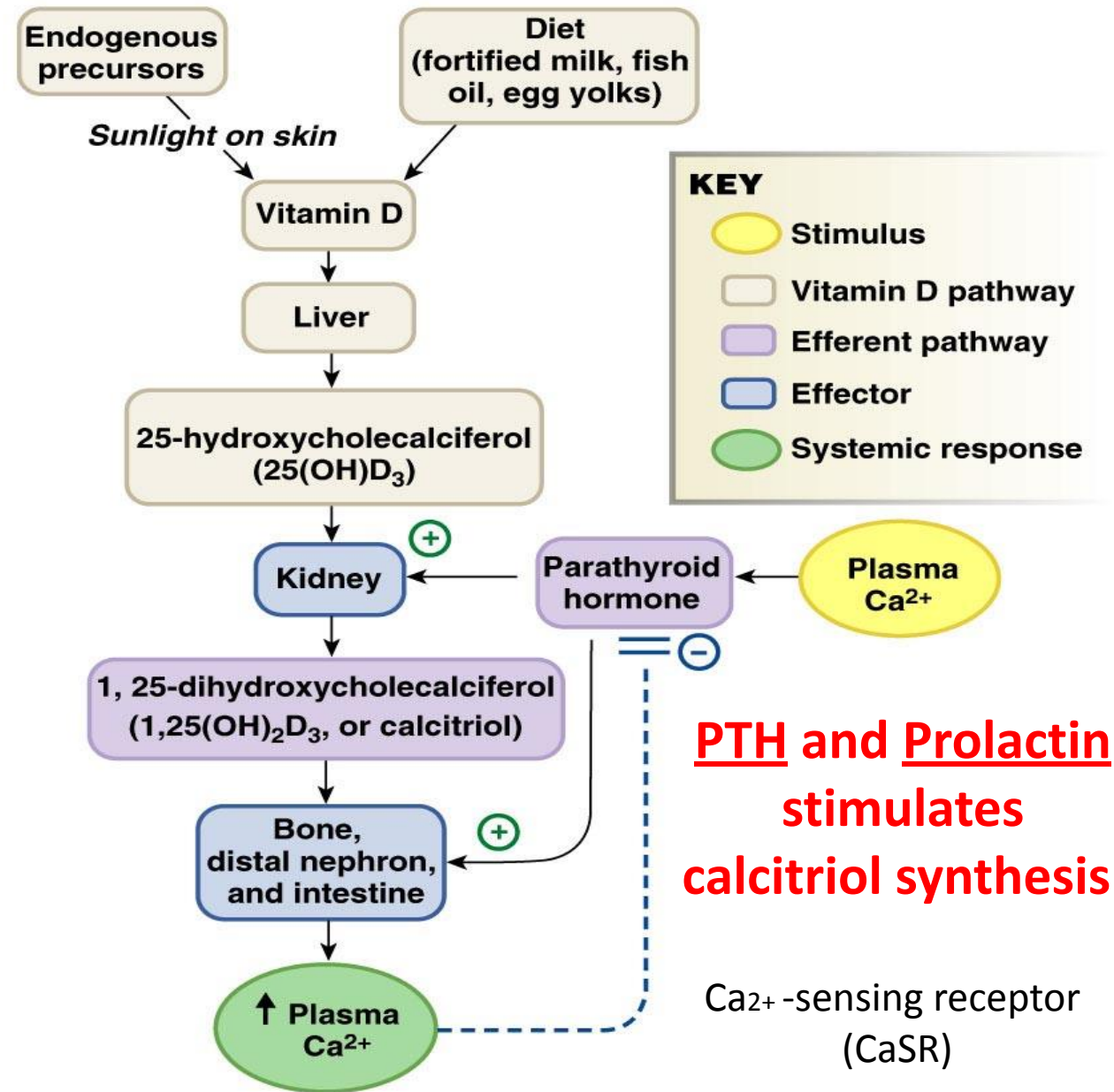
Calcitriol (Vit D3)

Intestinal absorption of Ca^{2+} is enhanced by the action of a hormone known as 1,25-dihydroxycholecalciferol ($1,25(\text{OH})_2\text{D}_3$) = **vitamin D3**

The body makes calcitriol from vitamin D that has been obtained through diet or made in the skin by the action of sunlight

Vitamin D is modified in two steps first in the liver, then in the kidneys to make calcitriol

- Enhance calcium uptake from small intestine and facilitates renal reabsorption
- Help mobilize Ca^{2+} out of the bone



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Figure 23-23

Calcium and Phosphate Homeostasis Are Linked

- Phosphate homeostasis is closely linked to calcium homeostasis.
- most phosphate in the body is found in bone.
- physiological roles: **energy transfer and storage in high-energy phosphate bonds, activation or deactivation of enzymes, transporters, and ion channels and form part of the DNA and RNA backbone.**

□ Phosphate homeostasis parallels that of Ca_{2+}

- Phosphate is absorbed in the intestines, filtered and reabsorbed in the kidneys, and divided between bone, ECF, and intracellular compartments. Vitamin D3 enhances intestinal absorption of phosphate. Renal excretion is affected by both PTH and vitamin D3

Osteoporosis: Disease of Bone Growth & Calcium Metabolism

Bone Reabsorption Exceeds Deposition

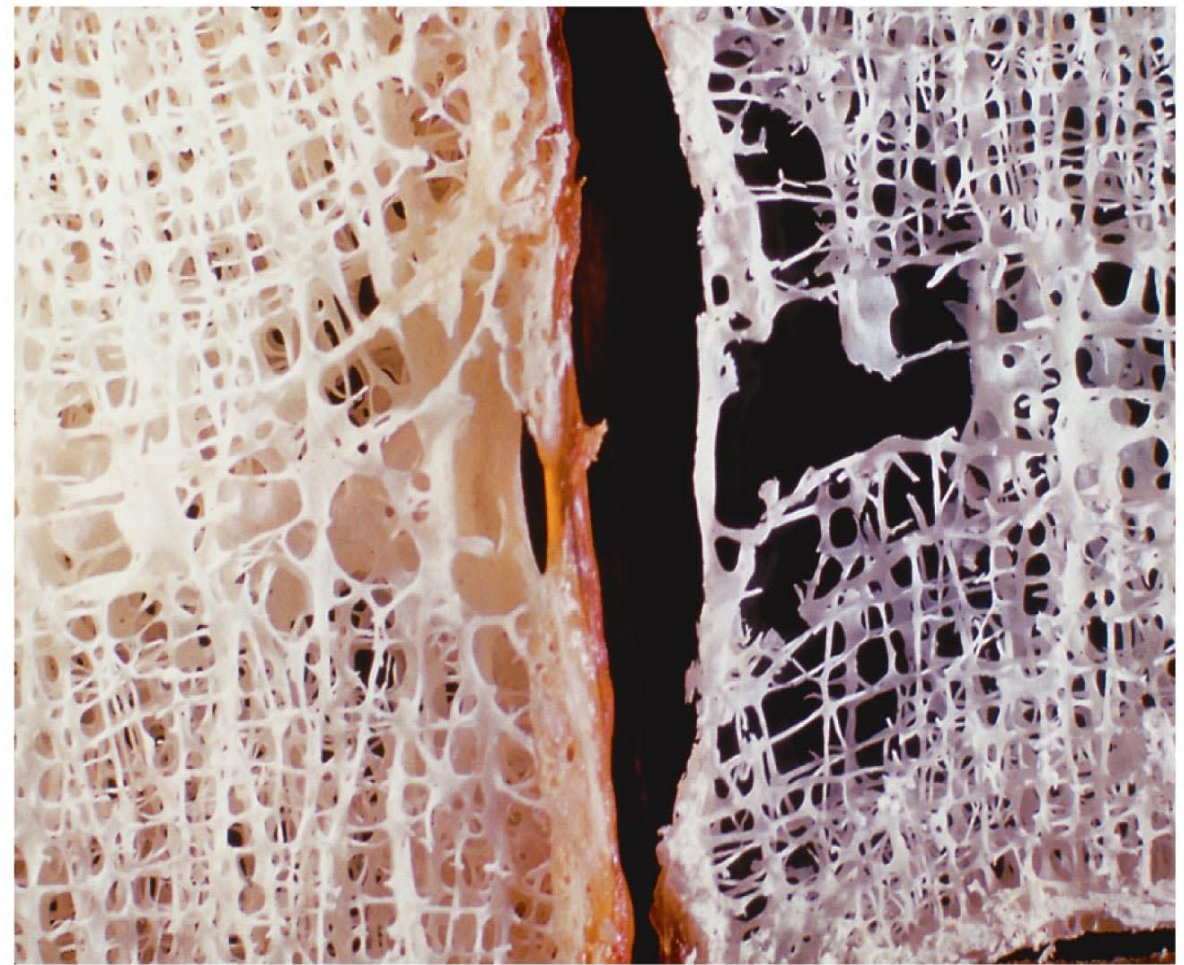
Osteoclasts mobilize Ca^{++} to Plasma

Factors:

Inadequate Ca^{++} Intake, Genes

Hormones (after menopause,
decrease estrogen)

Smoking



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Normal bone (left) and bone loss in osteoporosis (right).
These photographs dramatically illustrate why people with
osteoporosis have a high incidence of bone fractures

Figure 23-21

Intestinal and pancreas hormones

Hormonal control of GI system

Previously we mentioned glands and the fact they are under local control via the enteric nervous system and also higher control from the autonomic nervous system

Glands can be controlled by hormones also

Hormones are released in response to **food in the GI tract** and are carried in the **blood** to the **glands** to **increase or decrease secretion**

The hormones affect the **volume** of secretions

Gastrin:

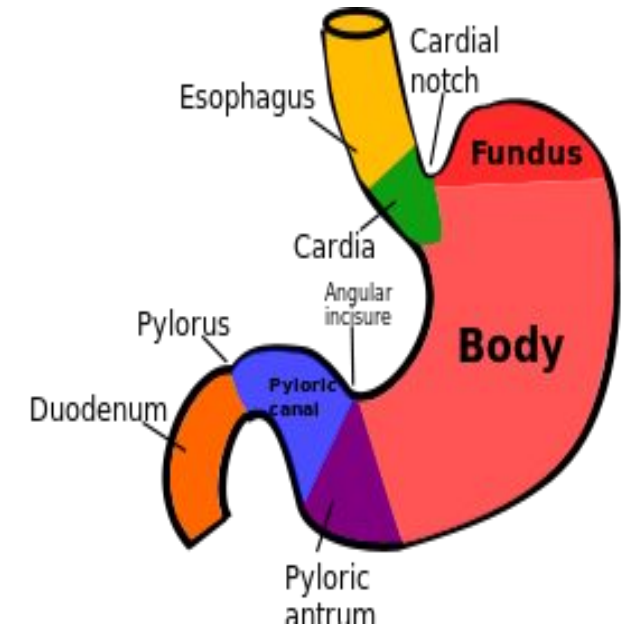
Released from the **antrum** of the stomach

Released when there is **stretch** of the stomach - after a **meal**

This stimulates:

- **Gastric acid secretion from parietal cells in the stomach**
- **Pepsinogen from chief cells in the stomach (inactive form of pepsin)**
 - **Pepsin is used to digest protein**

Low pH decreases gastrin secretion (pH less than 3)



Cholecystikinin - secreted from I cells

Secreted from the **duodenum** and **jejunum**

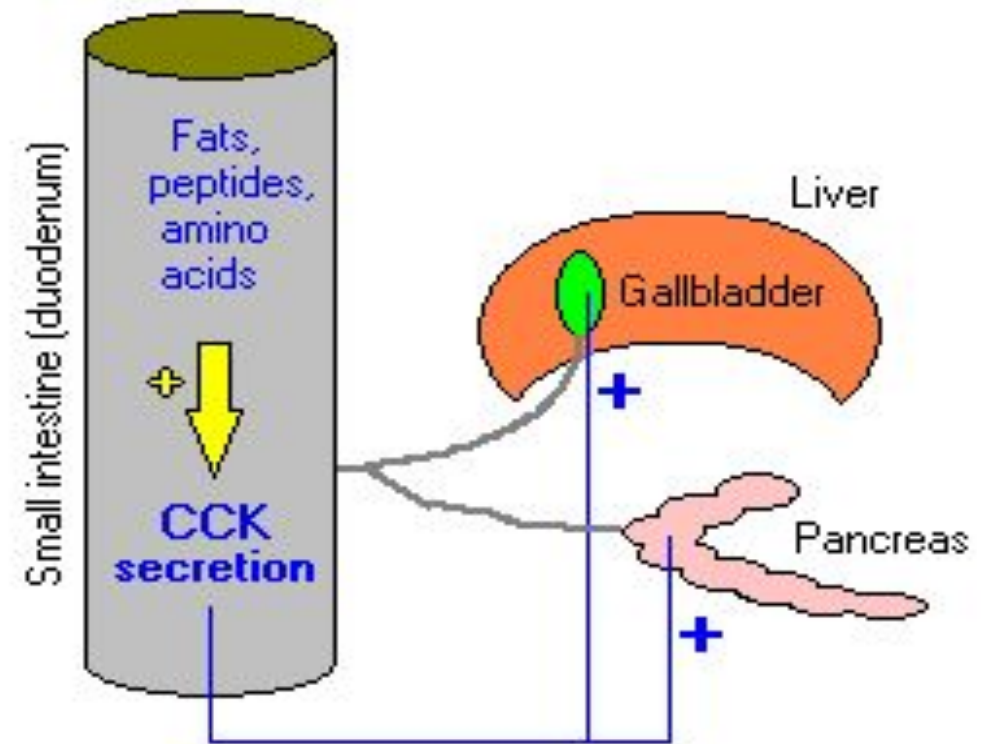
Released in response to digestive products of digestion specifically **fats**

Causes **contraction of the gallbladder** which releases **bile**

Bile breaks down fat which allows them to be absorbed

Moves to the pancreas through the blood to cause an **increase on pancreatic digestive enzymes** e.g. lipase used to break down lipids

It also **inhibits stomach contraction** - so can allow adequate time for digestion in the upper part of the GI tract



Secretin - secreted from S cells

Secreted from the **duodenum**

Released in response to **gastric acid** entering the duodenum from the stomach (pH less than 4.5)

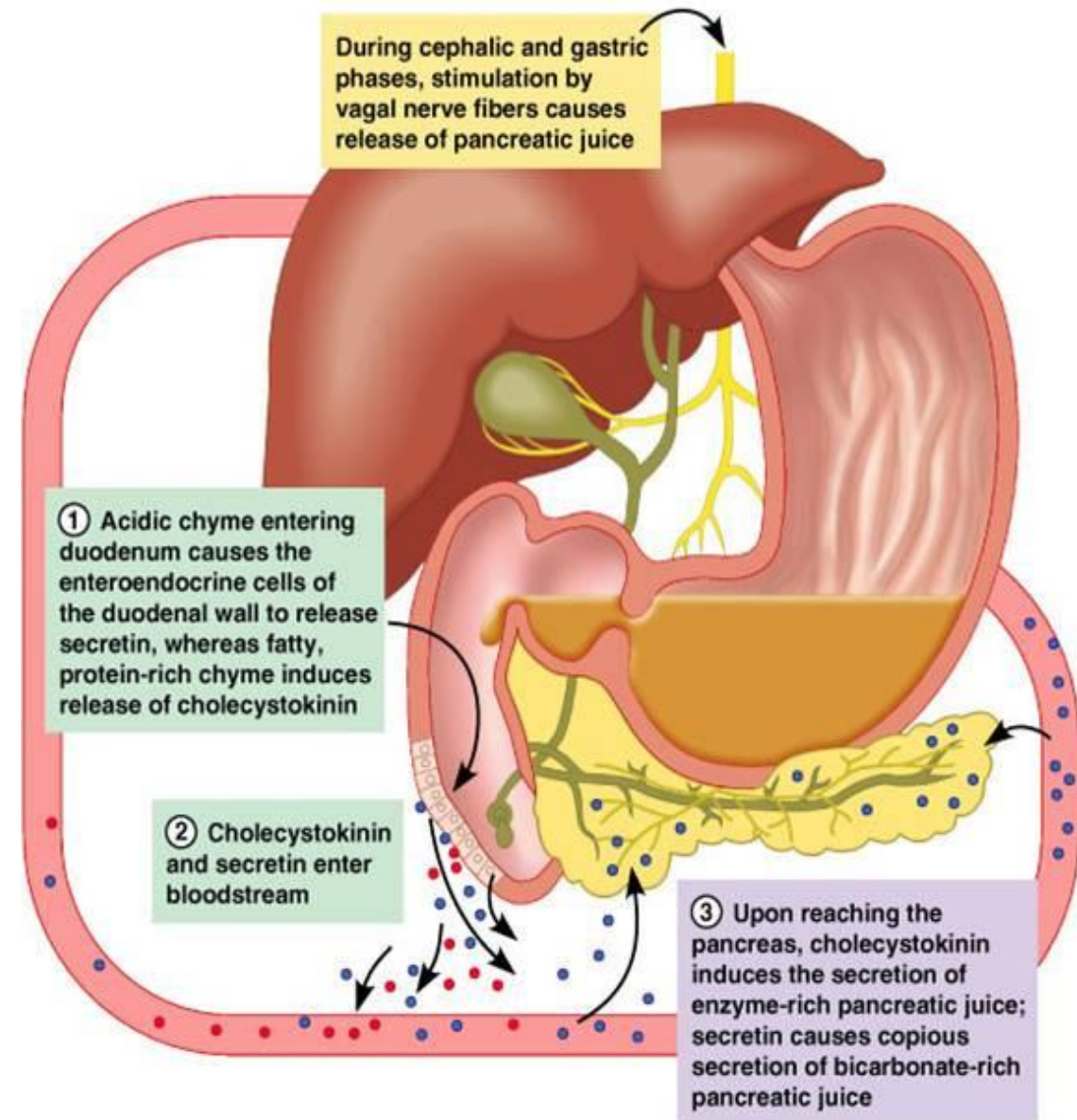
Stimulates the release of **bicarbonate from the pancreas** - to neutralise the pH in the intestine

Causes hydrochloric acid to combine with sodium bicarbonate to form NaCl (salt) and H_2CO_3 (carbonic acid)

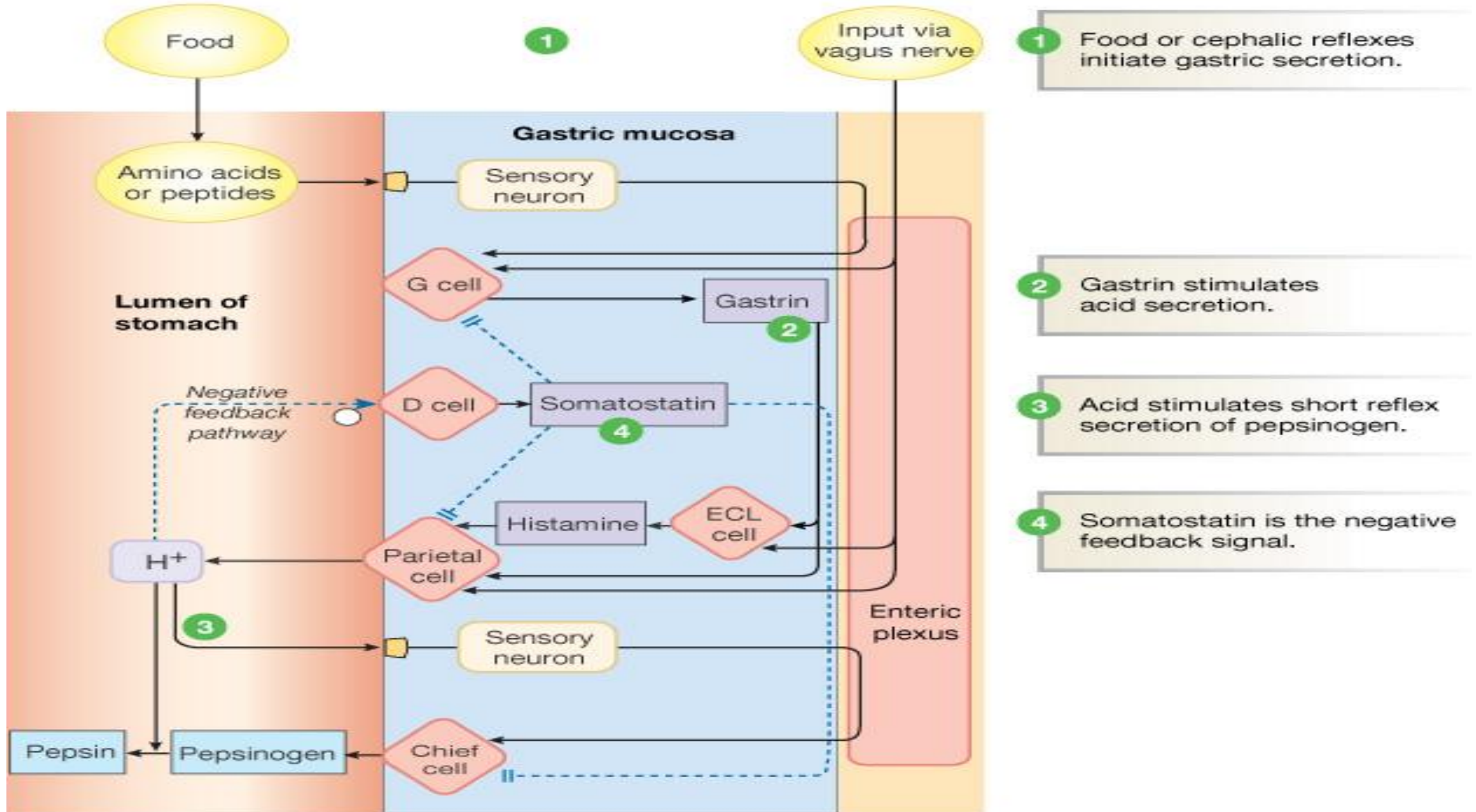
The carbonic acid $\rightarrow \text{CO}_2$ and H_2O

The carbon dioxide is absorbed into the blood and expired

Secretin also **inhibits** stomach motility and **acid release**



Regulation of the Stomach Digestive Activities



Intestinal Phase: Pancreatic Secretions

- Enzymes

- HCO_3^-

- Insulin

- Glucagon

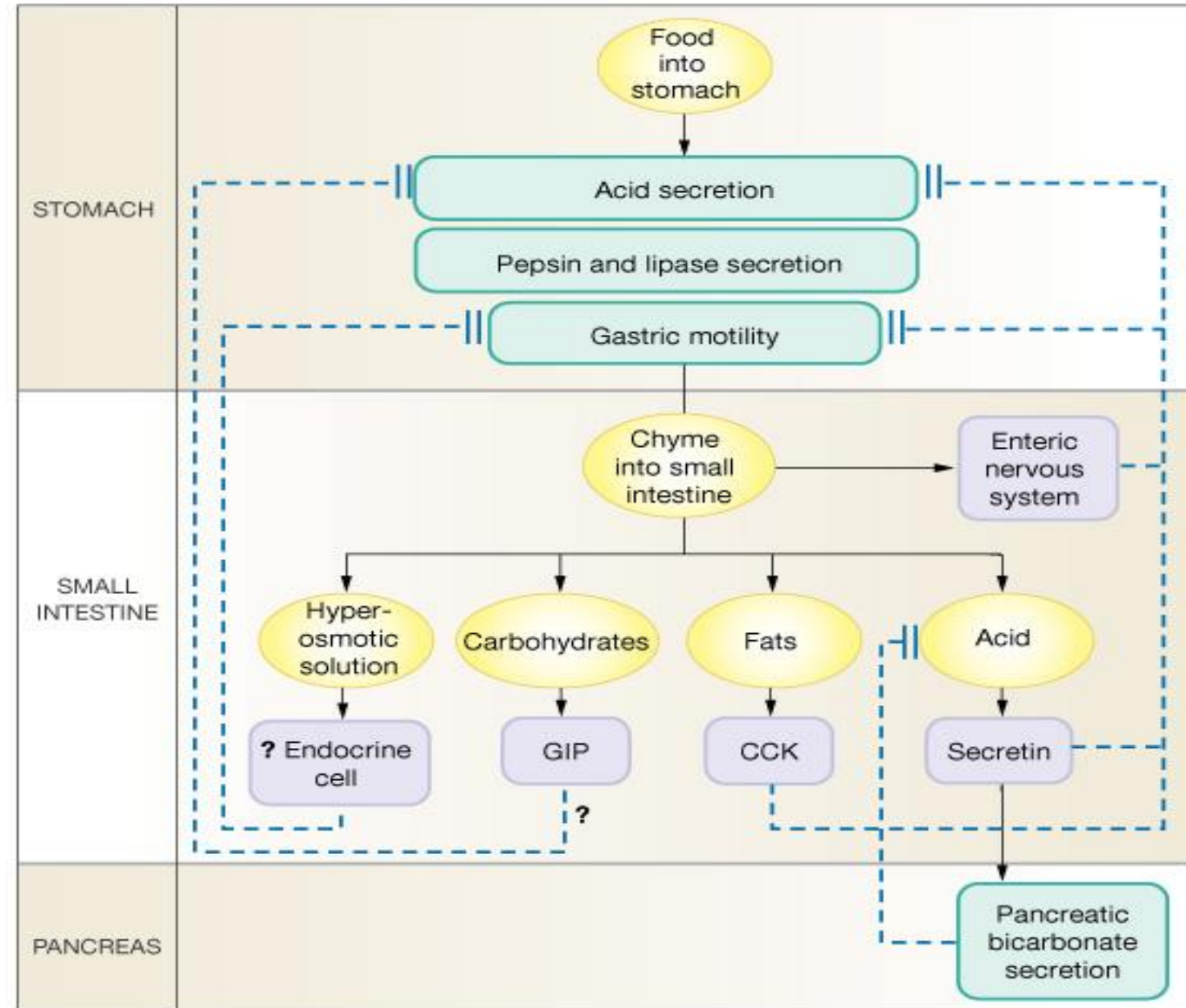


Figure 21-18: The intestinal phase of gastric function

Gastric inhibitory peptide

Secreted by the **mucosa of the upper part of the intestine**

Released in response to **fatty acids and amino acids**

Reduces the motility of the stomach → slows to emptying of the stomach into the duodenum and allows more time for digestion

Motilin

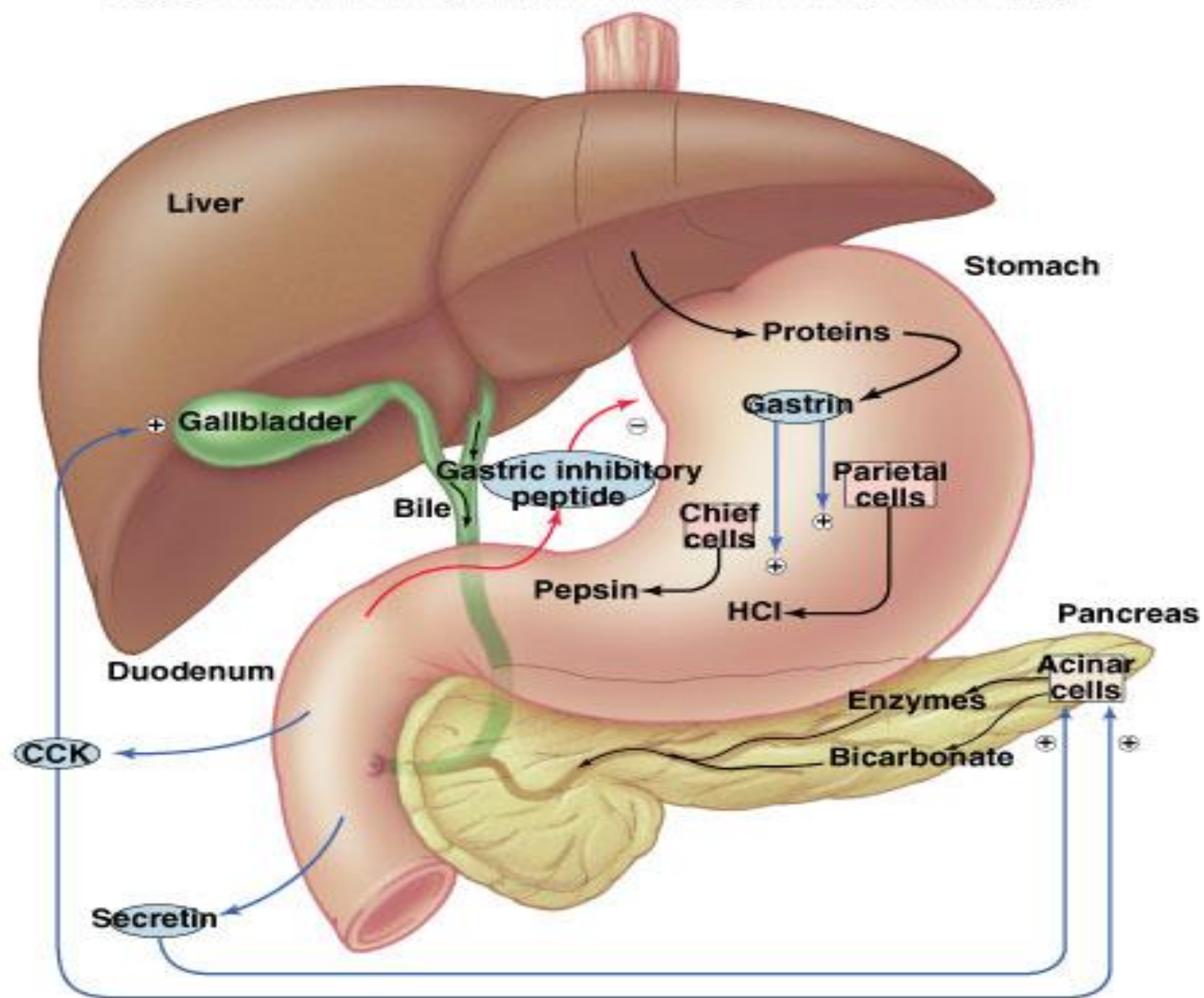
Released during **FASTING**!

Released from the **duodenum**

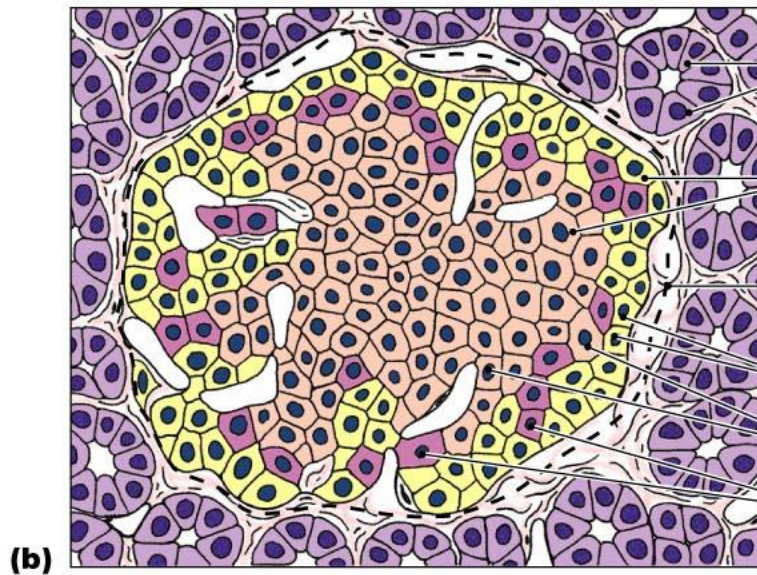
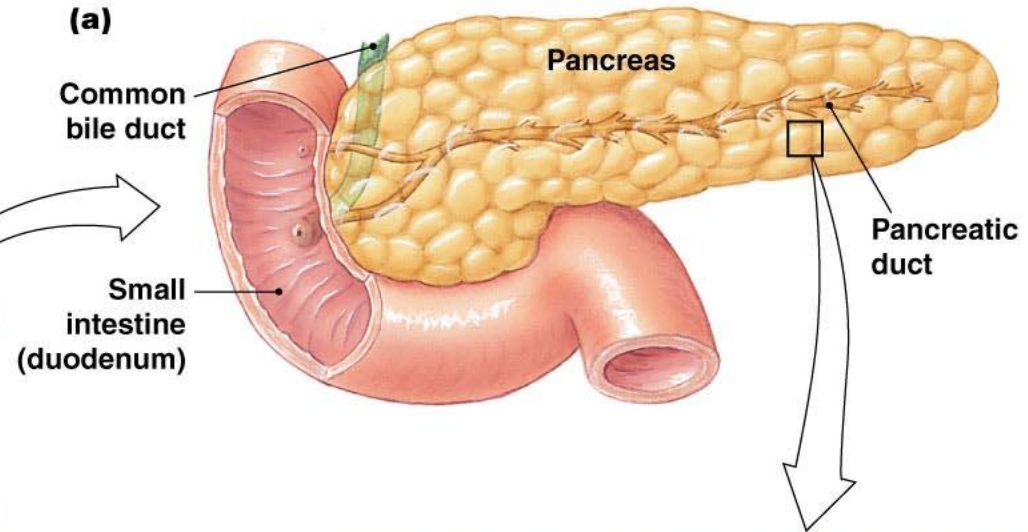
INCREASES gastric motility - causes waves of contracting even 90 minutes in a fasting person

Inhibited after **ingestion of food**

- *Gut hormones work by signalling to the brain which causes nerve stimulation of the parasympathetic or sympathetic nerve to cause a response*



CELL	SECRETES:
Alpha cells	Glucagon
D cells	Somatostatin
Beta cells	Insulin, amylin



Exocrine cells

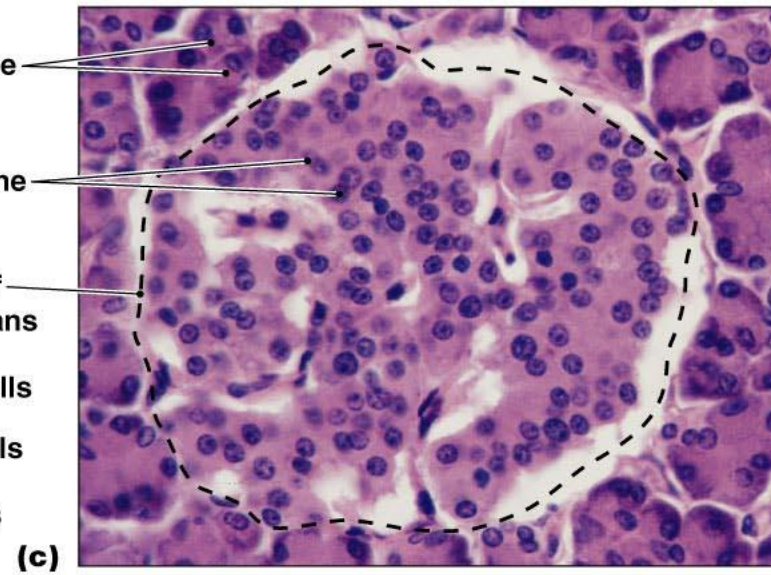
Endocrine cells

Islet of Langerhans

Alpha cells

Beta cells

D cells



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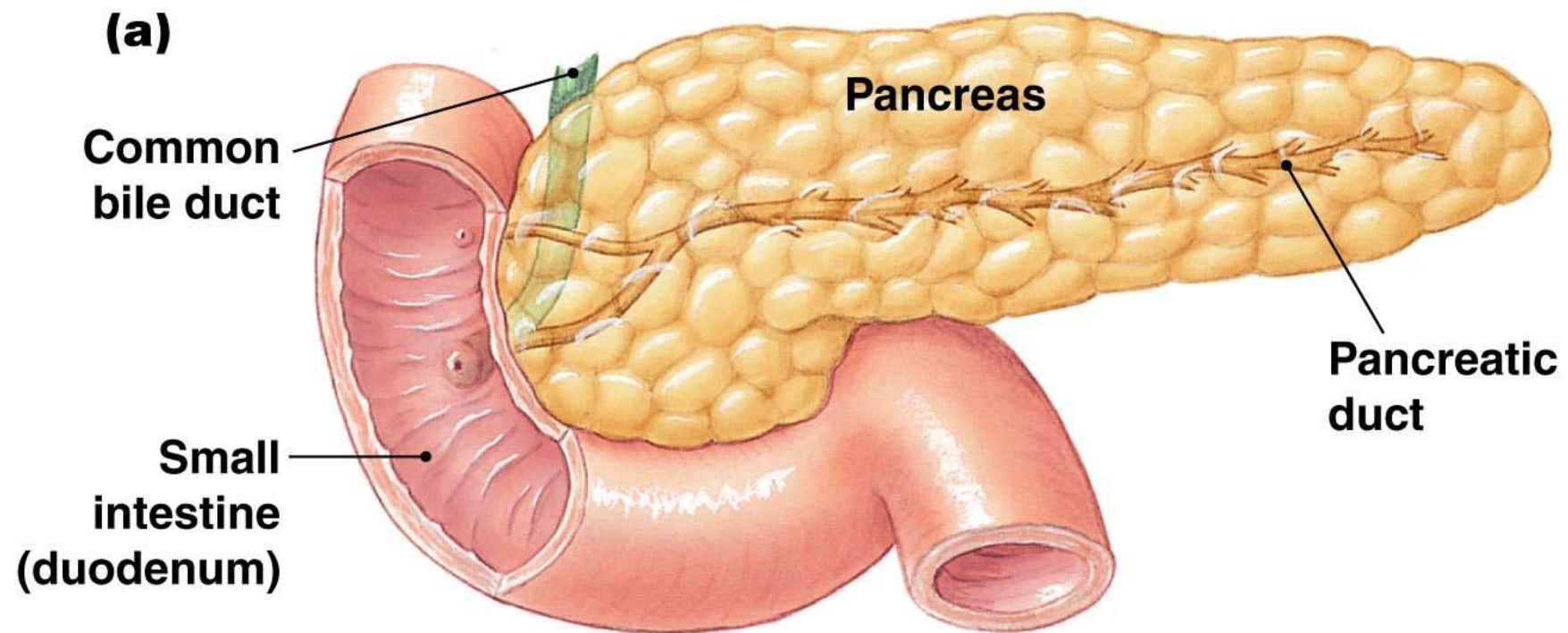
Figure 22-8 - Overview

Pancreas

- A triangular gland, which has both exocrine and endocrine cells, located behind the stomach
- Acinar cells produce an enzyme-rich juice used for digestion (exocrine product)
- Pancreatic islets (islets of Langerhans) produce hormones (endocrine products)
- The islets contain two major cell types:
 - Alpha (α) cells that produce glucagon
 - Beta (β) cells that produce insulin

Physiologic Anatomy of the Pancreas

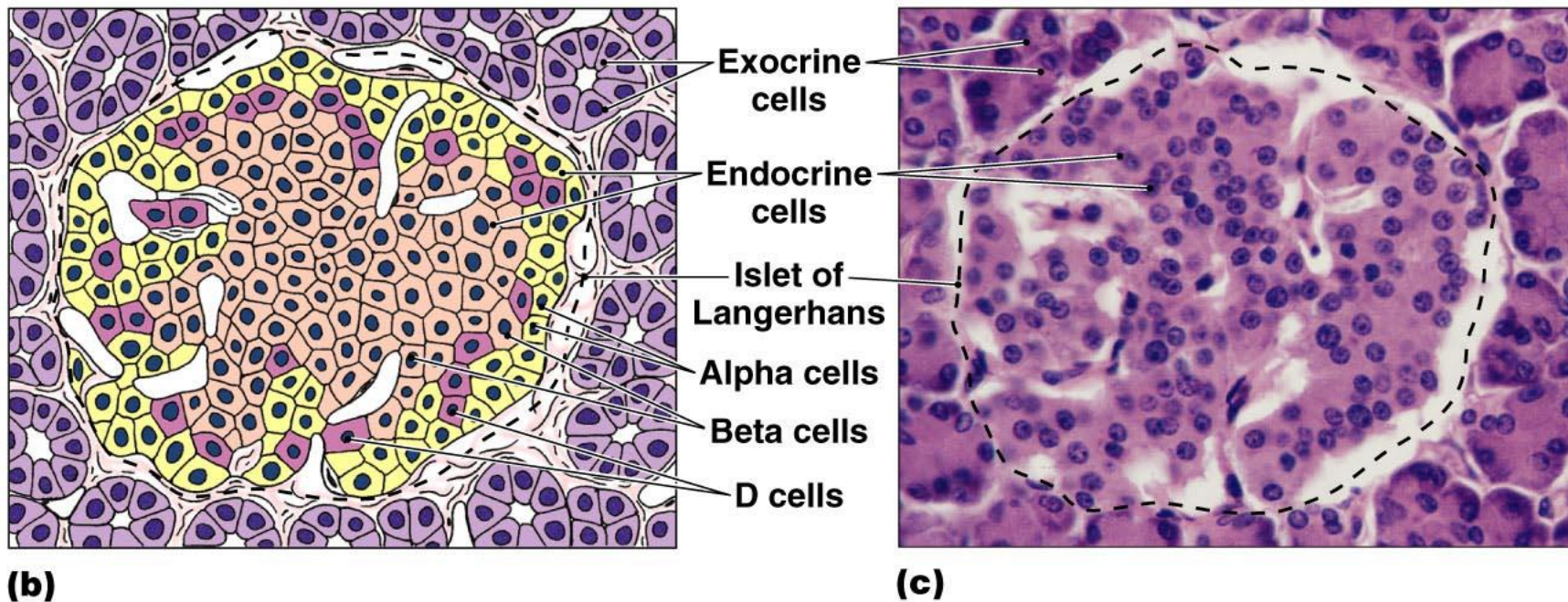
- Two major types of tissues
 - 1) The **acini**, which secrete digestive juices into duodenum
 - 2) The **islets of Langerhans**, which secrete insulin and glucagon into blood. (Two antagonistic hormones)
- 1 to 2 million islets of Langerhans, organized around small capillaries into which its cells secrete their hormones.
- The islets contain three major types of cells alpha, beta, delta cell
- The **beta cells** 60 % of all the cells of the islets, lie mainly in the middle of each islet and secrete insulin and amylin,
- The **alpha cells**, 25 % of the total, secrete glucagon
- The **delta cells**, about 10 %, secrete somatostatin.
- One other type of cell, the PP cell, is present in small numbers in the islets and secretes pancreatic polypeptide.



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Figure 22-8a

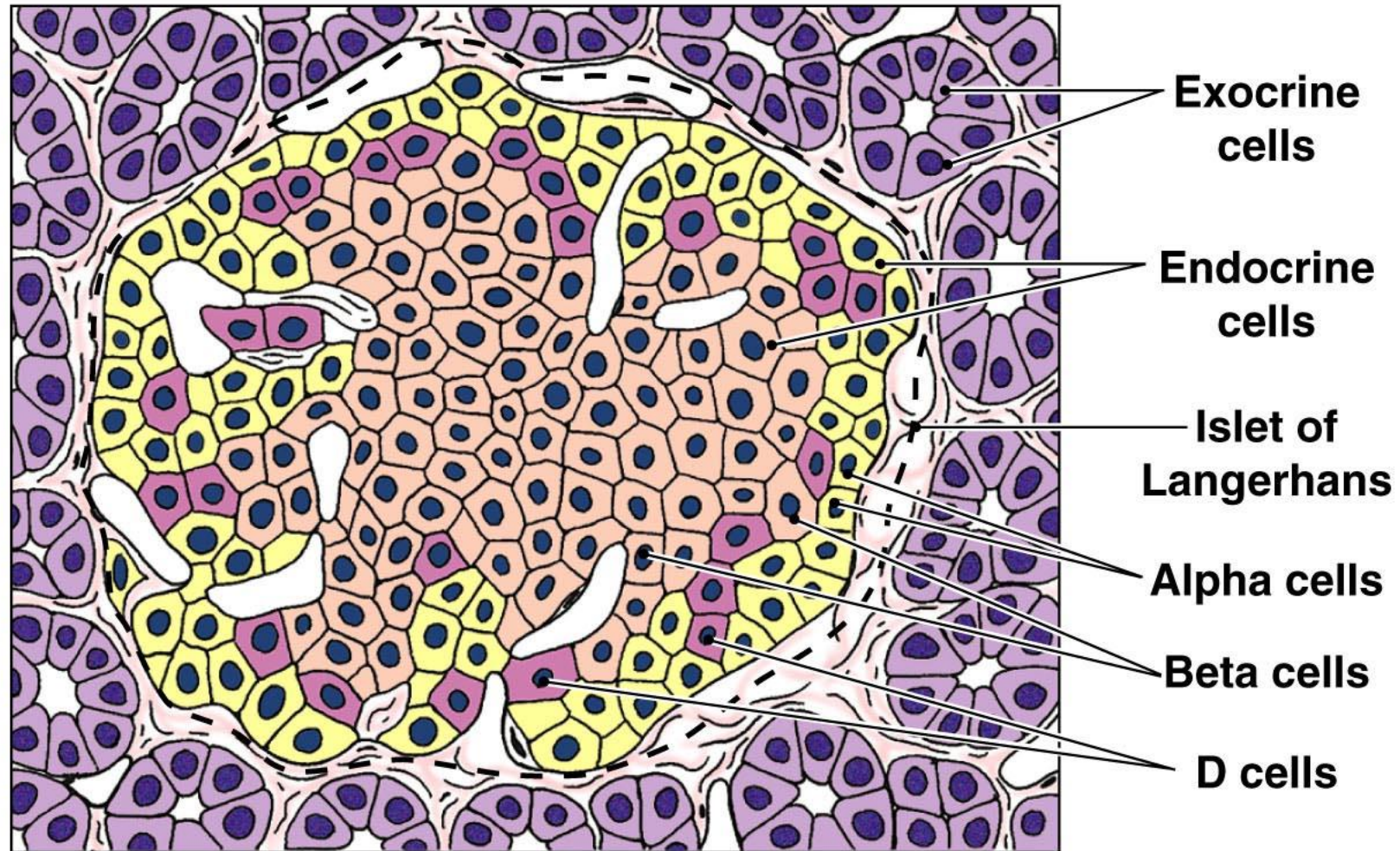
CELL	SECRETES:
Alpha cells 	Glucagon
D cells 	Somatostatin
Beta cells 	Insulin, amylin



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Figure 22-8b–c

(b)



CELL	SECRETES:
Alpha cells	Glucagon
D cells	Somatostatin
Beta cells	Insulin, amylin

Insulin

- A 51-amino-acid protein consisting of two amino acid chains linked by disulfide bonds
- Synthesized as part of proinsulin and then excised by enzymes, releasing functional insulin
- Insulin:
 - Lowers blood glucose levels
 - Enhances transport of glucose into body cells
 - Counters metabolic activity that would enhance blood glucose levels

TABLE 22-3 Insulin	
Cell of origin	Beta cells of pancreas
Chemical nature	51-amino acid peptide
Biosynthesis	Typical peptide
Transport in the circulation	Dissolved in plasma
Half-life	5 minutes
Factors affecting release	Plasma [glucose] > 100 mg/dL; ↑ blood amino acids; GLP-1 (feedforward reflex); and parasympathetic activity amplifies. Sympathetic activity inhibits.
Target cells or tissues	Liver, muscle, and adipose tissue primarily; brain, kidney, and intestine not insulin dependent
Target receptor	Membrane receptor with tyrosine kinase activity; pathway with insulin-receptor substrates
Whole body or tissue action	↓ Plasma [glucose] by ↑ transport into cells or ↑ metabolic use of glucose
Action at cellular level	↑ Glycogen synthesis; ↑ aerobic metabolism of glucose; ↑ protein and triglyceride synthesis
Action at molecular level	Inserts GLUT transporters in muscle and adipose cells; alters enzyme activity. Complex signal transduction pathway involved.
Feedback regulation	↓ Plasma [glucose] shuts off insulin release.
Other information	Growth hormone and cortisol are antagonistic.

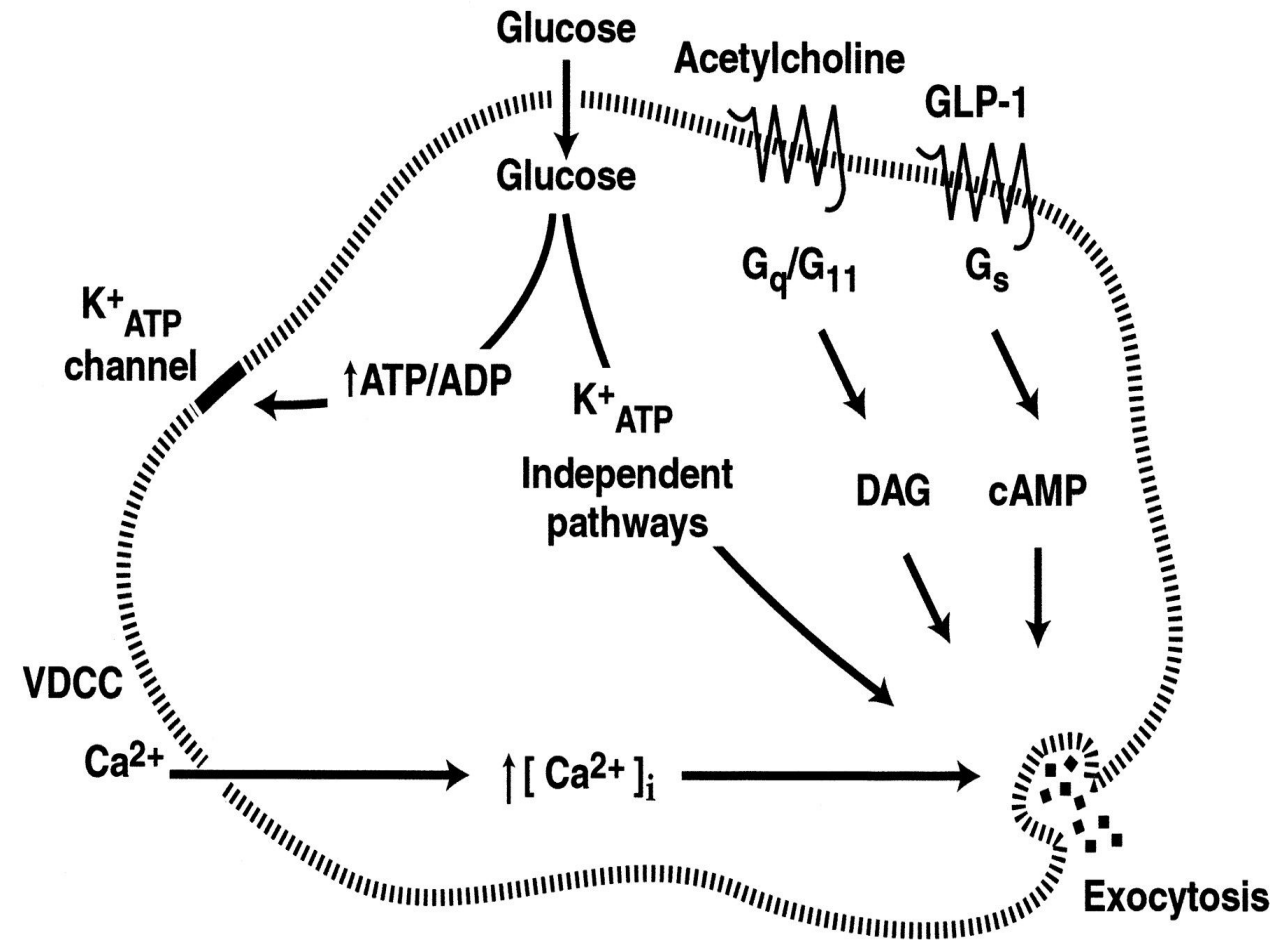
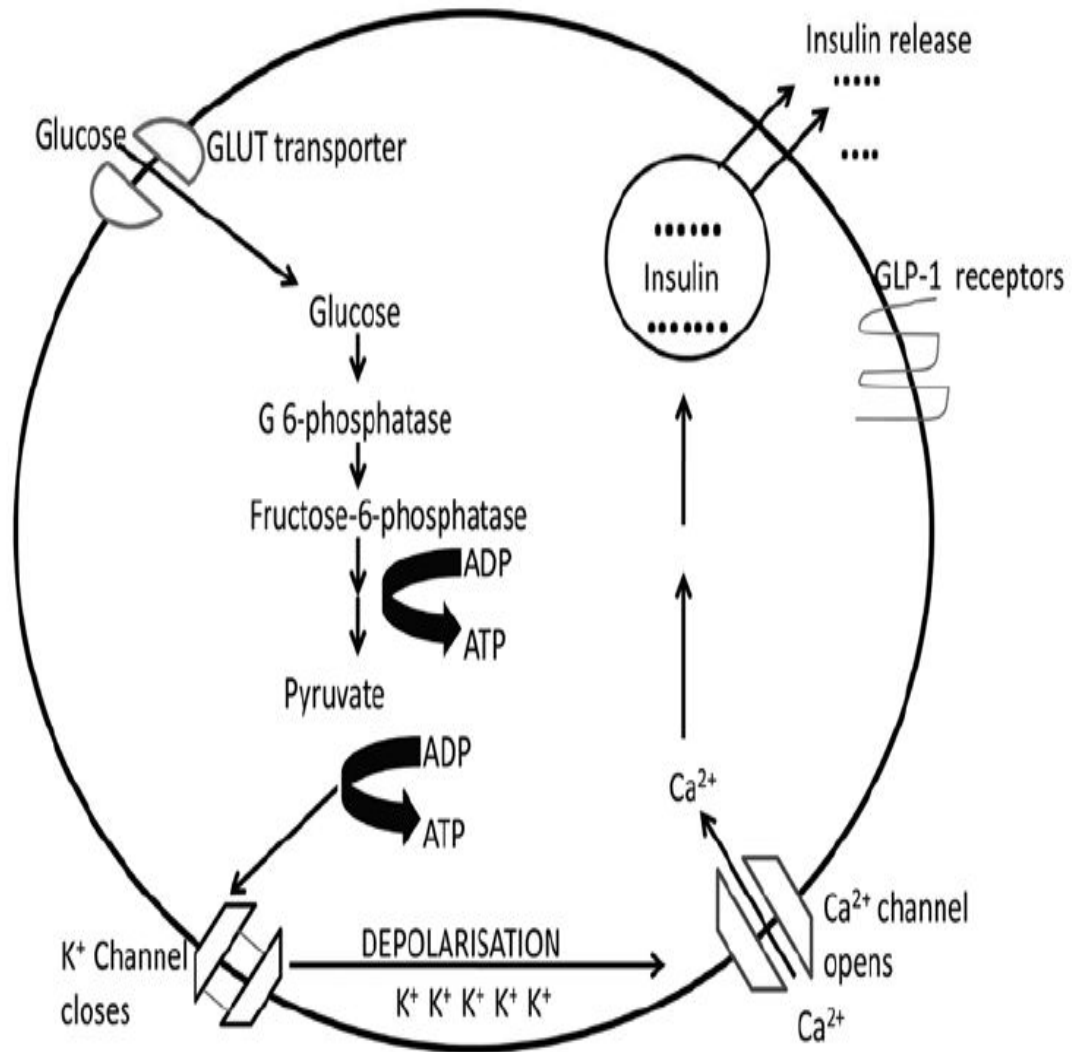
Glucagon

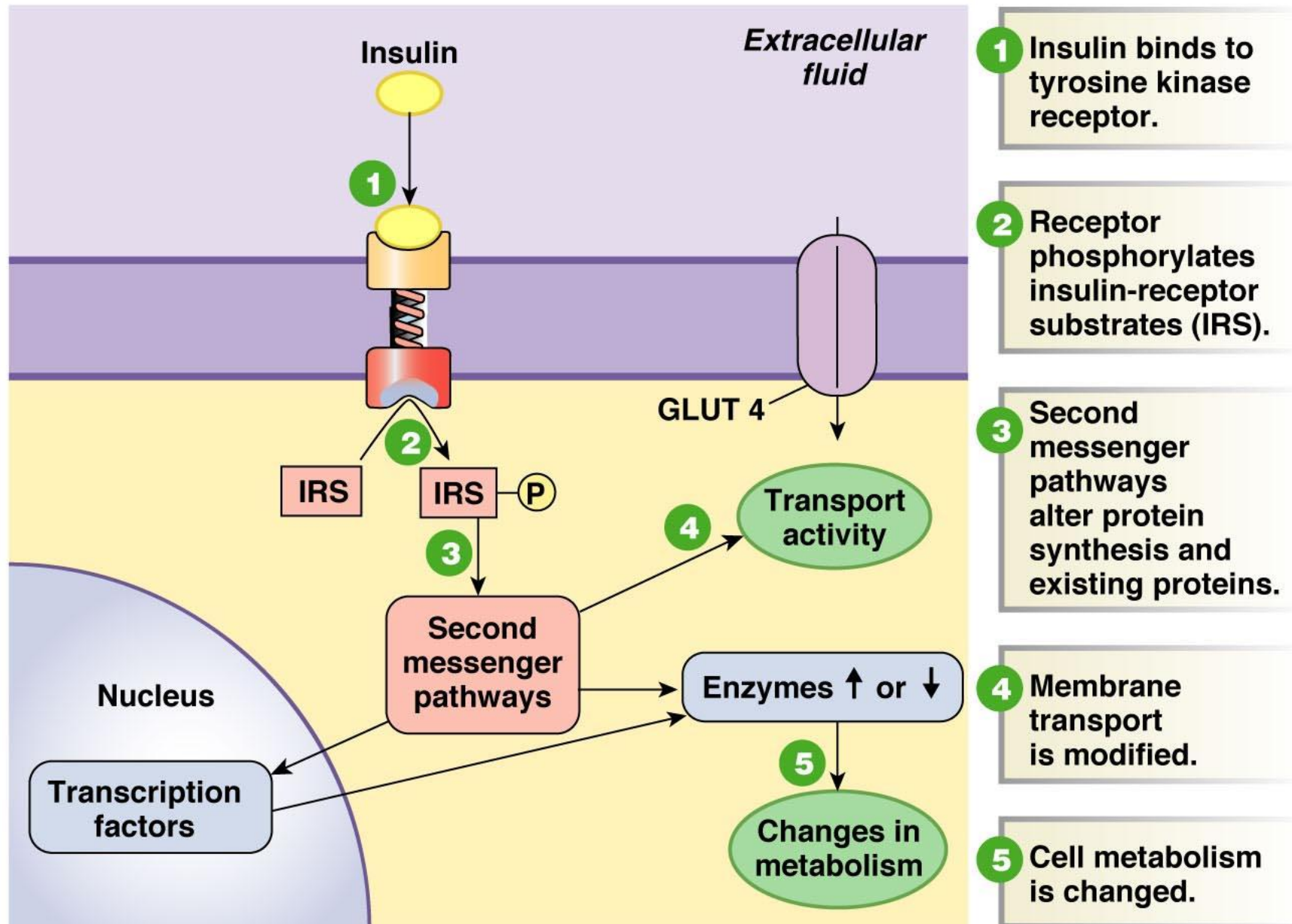
- A 29-amino-acid polypeptide hormone that is a potent hyperglycemic agent
- Its major target is the liver, where it promotes:
 - Glycogenolysis – the breakdown of glycogen to glucose
 - Gluconeogenesis – synthesis of glucose from lactic acid and noncarbohydrates
 - Release of glucose to the blood from liver cells

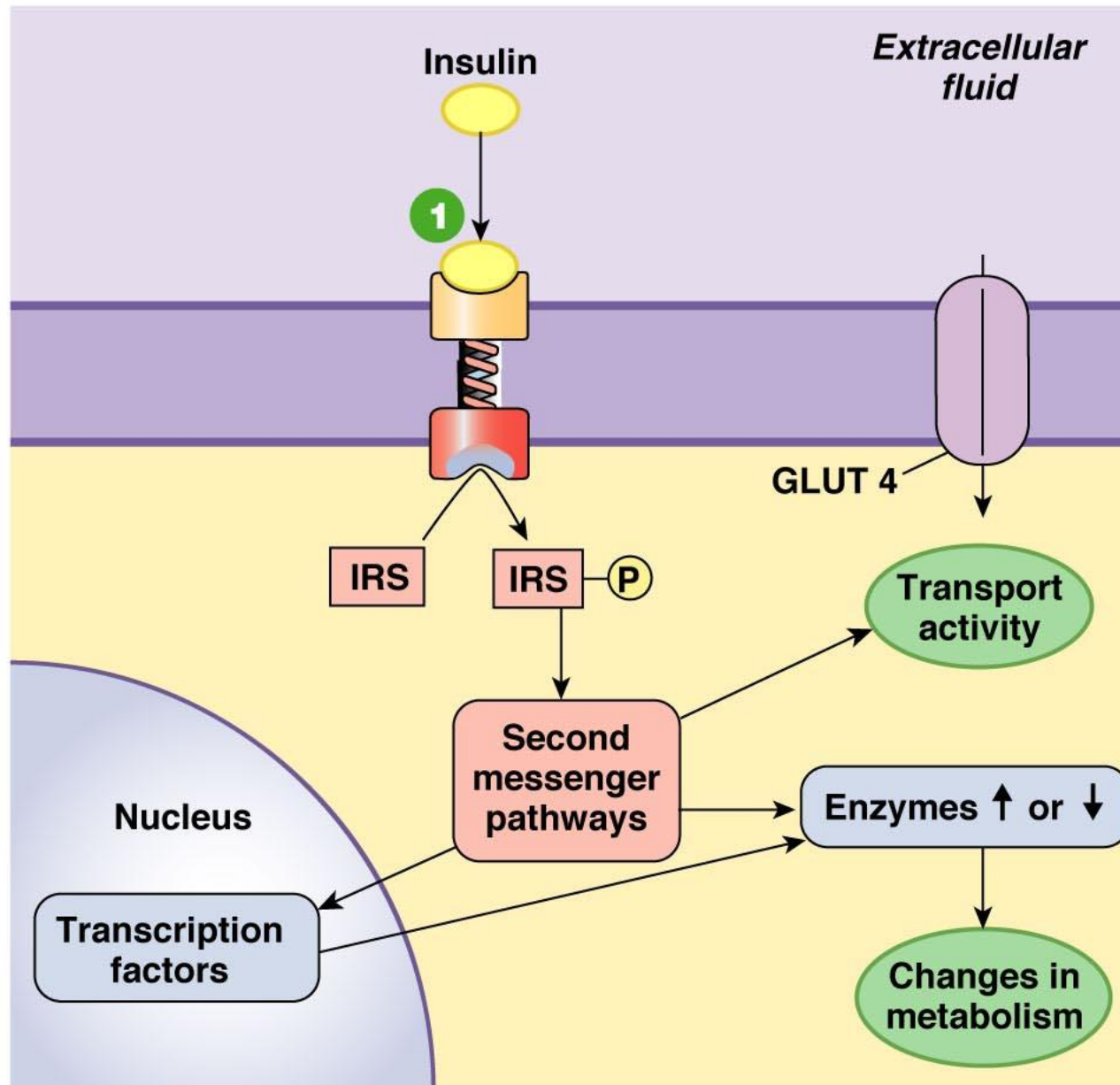
TABLE 22-5 Glucagon	
Cell of origin	Alpha cells of pancreas
Chemical nature	29-amino acid peptide
Biosynthesis	Typical peptide
Transport in the circulation	Dissolved in plasma
Half-life	4–6 minutes
Factors affecting release	Stimulated by plasma [glucose] < 200 mg/dL, with maximum secretion below 50 mg/dL; ↑ blood amino acids
Target cells or tissues	Liver primarily
Target receptor/second messenger	G protein-coupled receptor linked to cAMP
Whole body or tissue action	↑ Plasma [glucose] by glycogenolysis and gluconeogenesis; ↑ lipolysis leads to ketogenesis in liver
Action at molecular level	Alters existing enzymes and stimulates synthesis of new enzymes
Feedback regulation	↑ Plasma [glucose] shuts off glucagon secretion
Other information	Member of secretin family (along with VIP, GIP, and GLP-1)

Effects of Insulin Binding

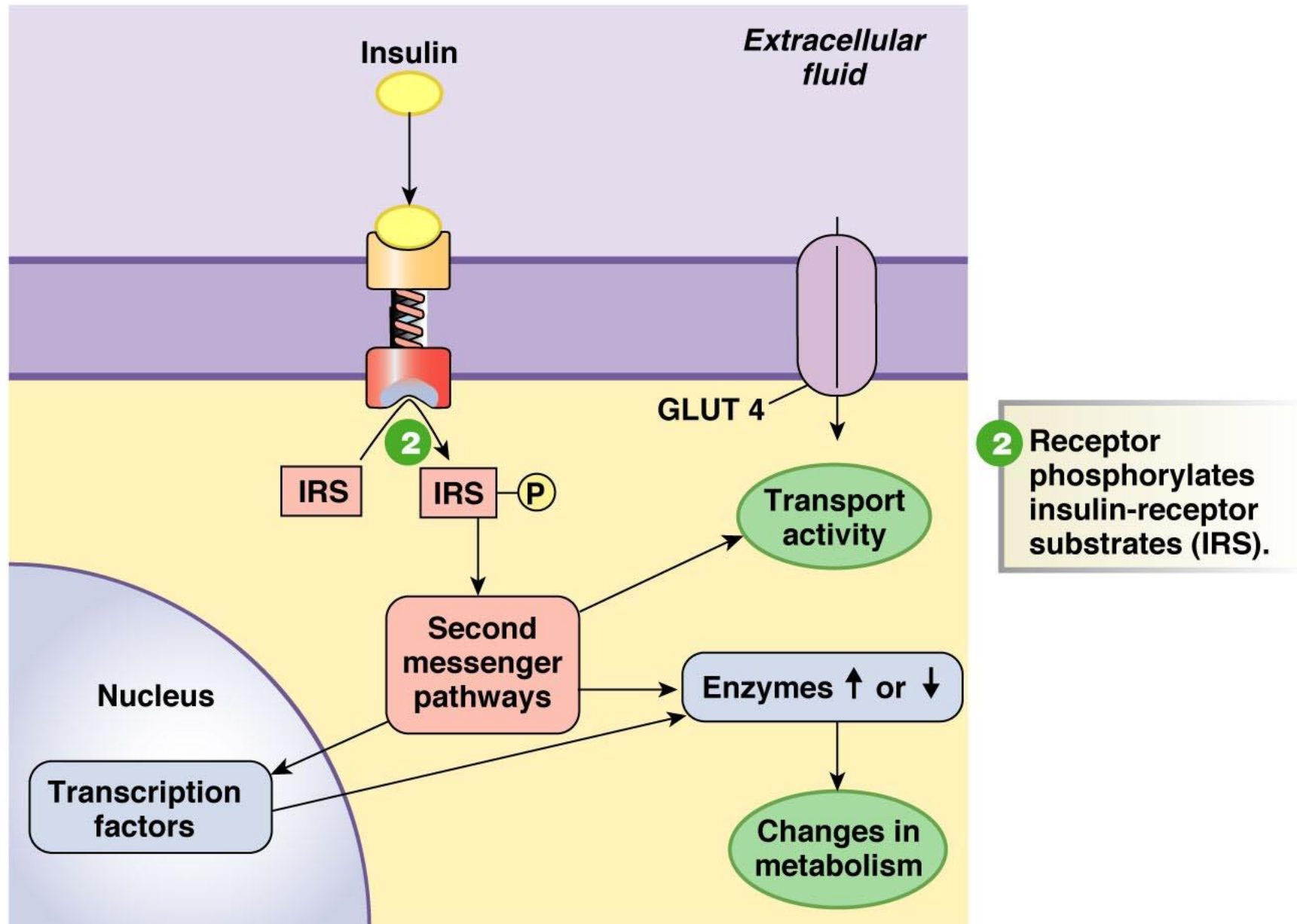
- The insulin receptor is a tyrosine kinase enzyme
- After glucose enters a cell, insulin binding triggers enzymatic activity that:
 - Catalyzes the oxidation of glucose for ATP production
 - Polymerizes glucose to form glycogen
 - Converts glucose to fat (particularly in adipose tissue)

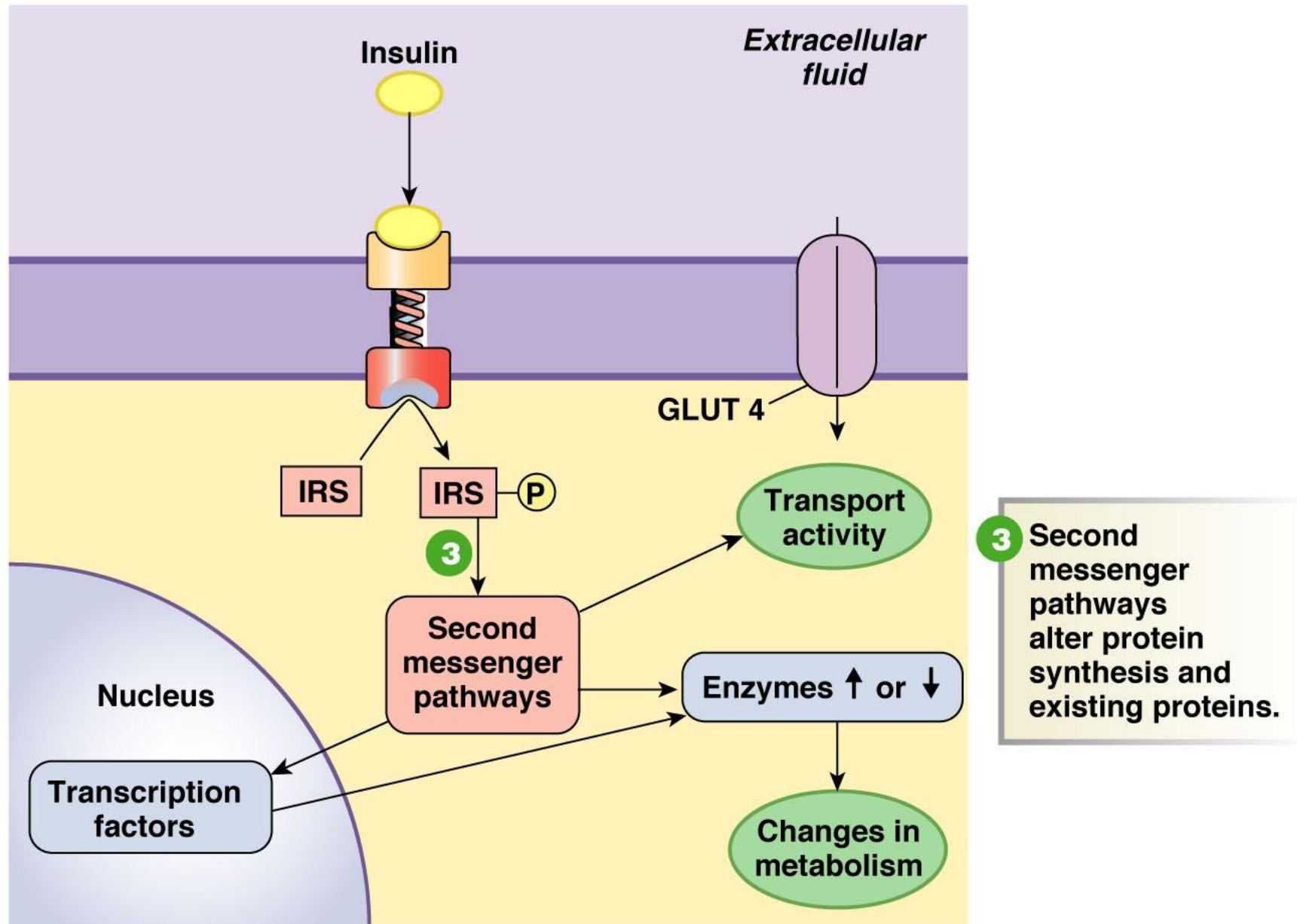


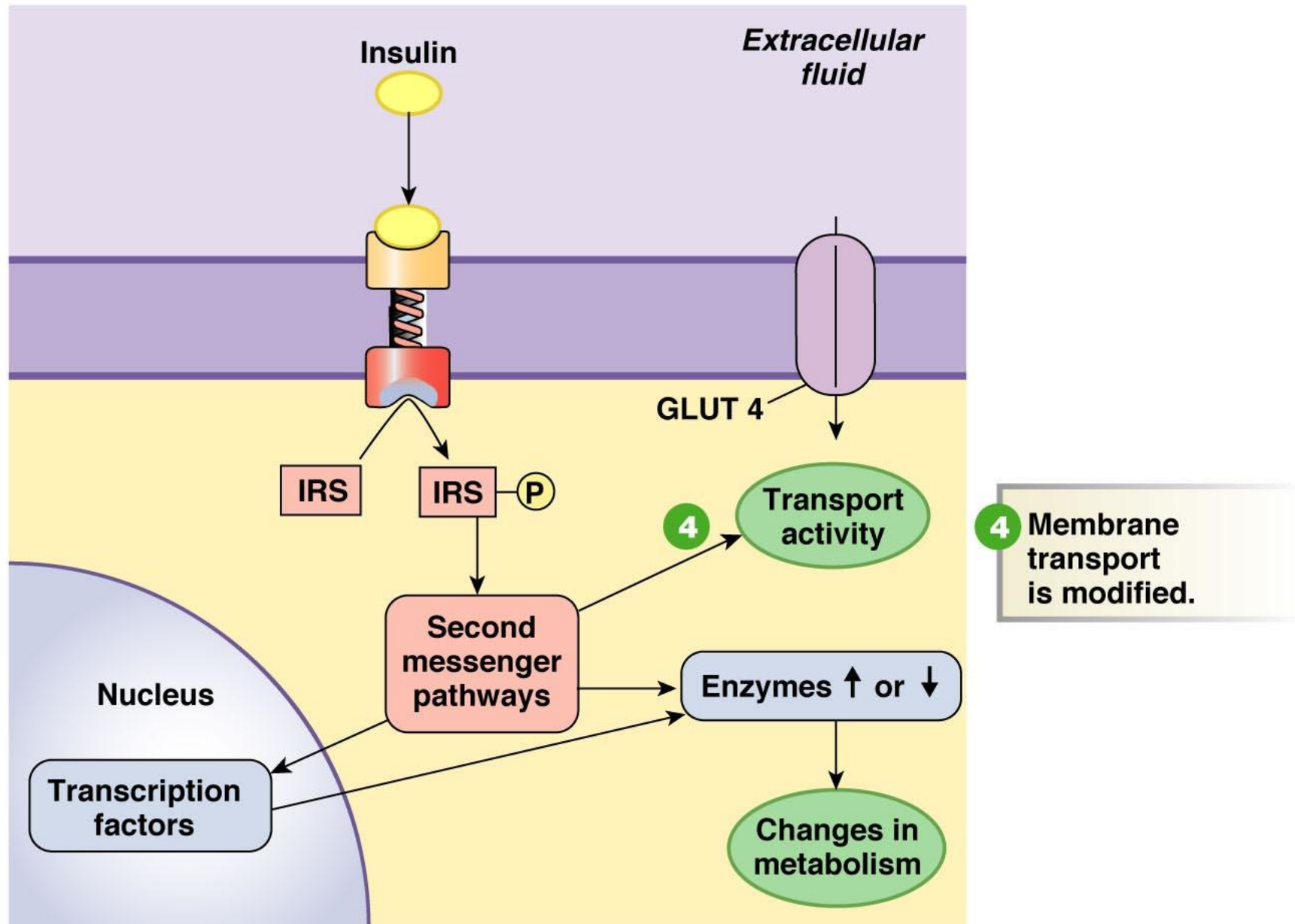


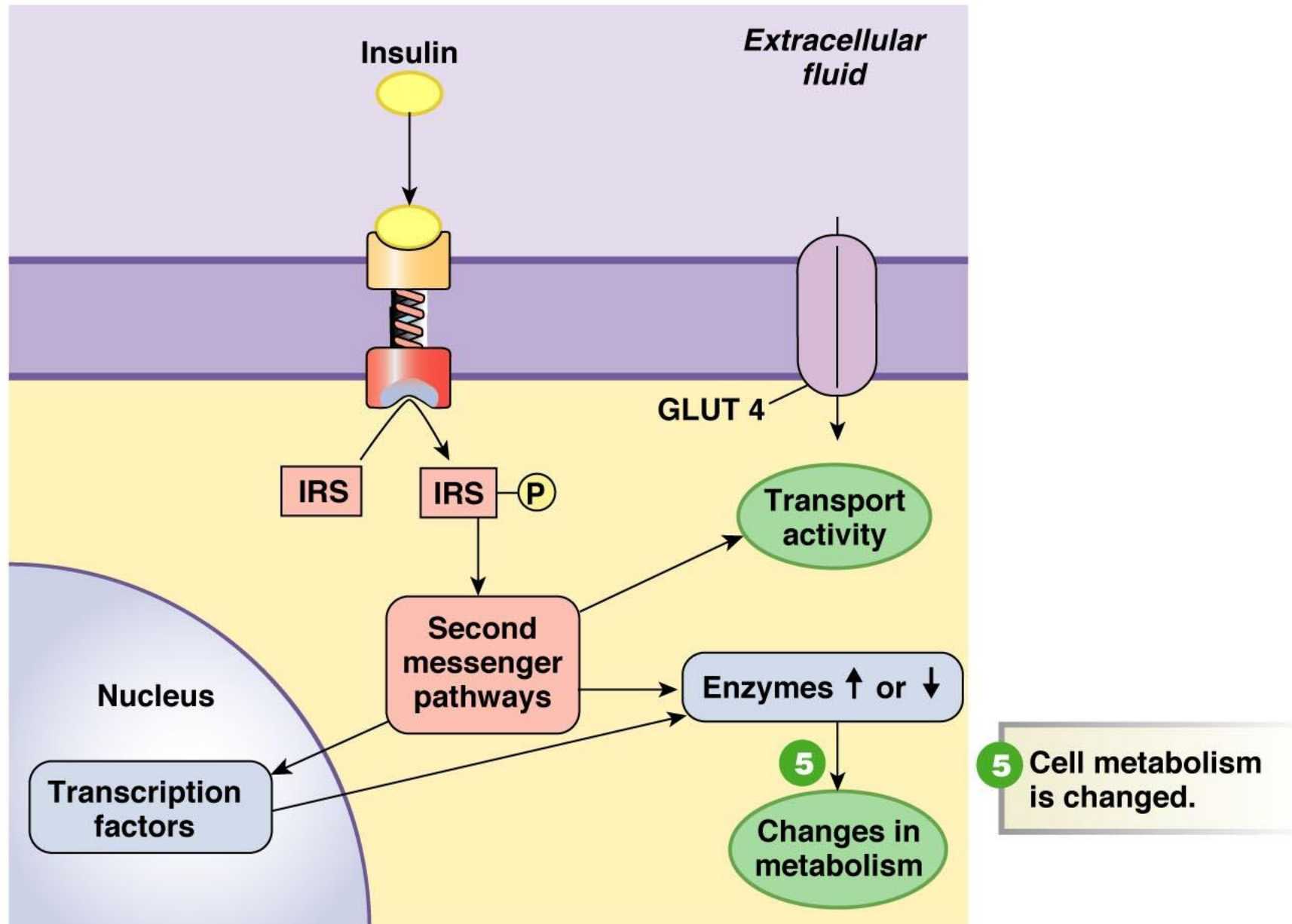


1 Insulin binds to tyrosine kinase receptor.

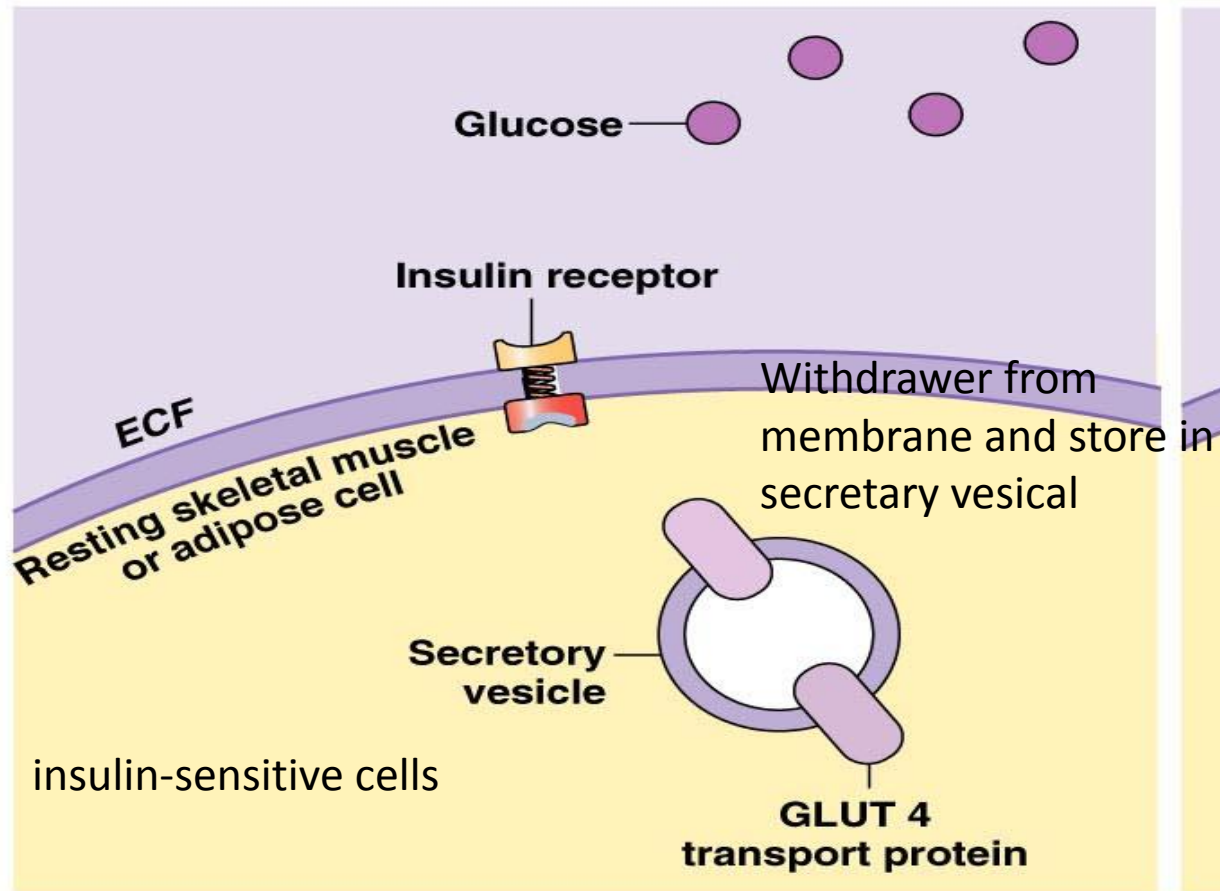




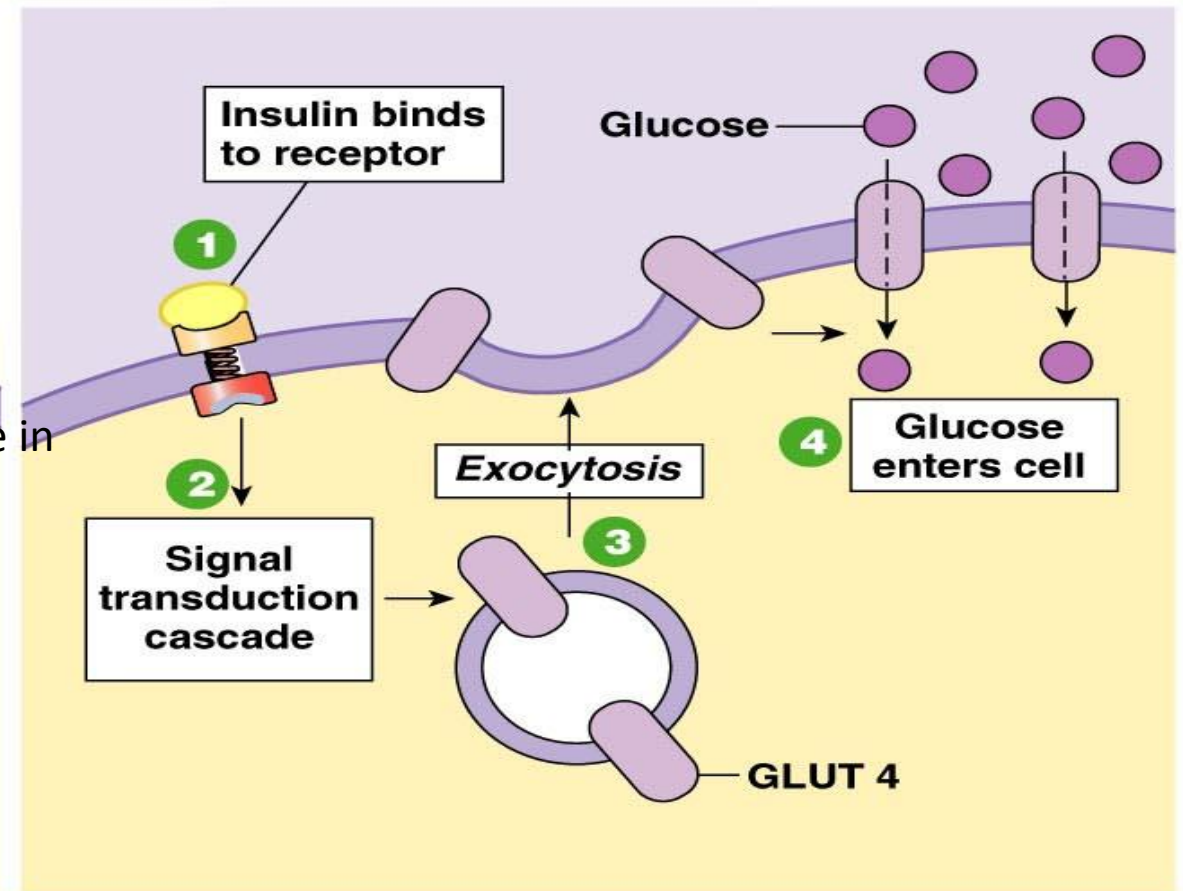




(a) In the absence of insulin, glucose cannot enter the cell.



(b) Insulin signals the cell to insert GLUT 4 transporters into the membrane, allowing glucose to enter cell.

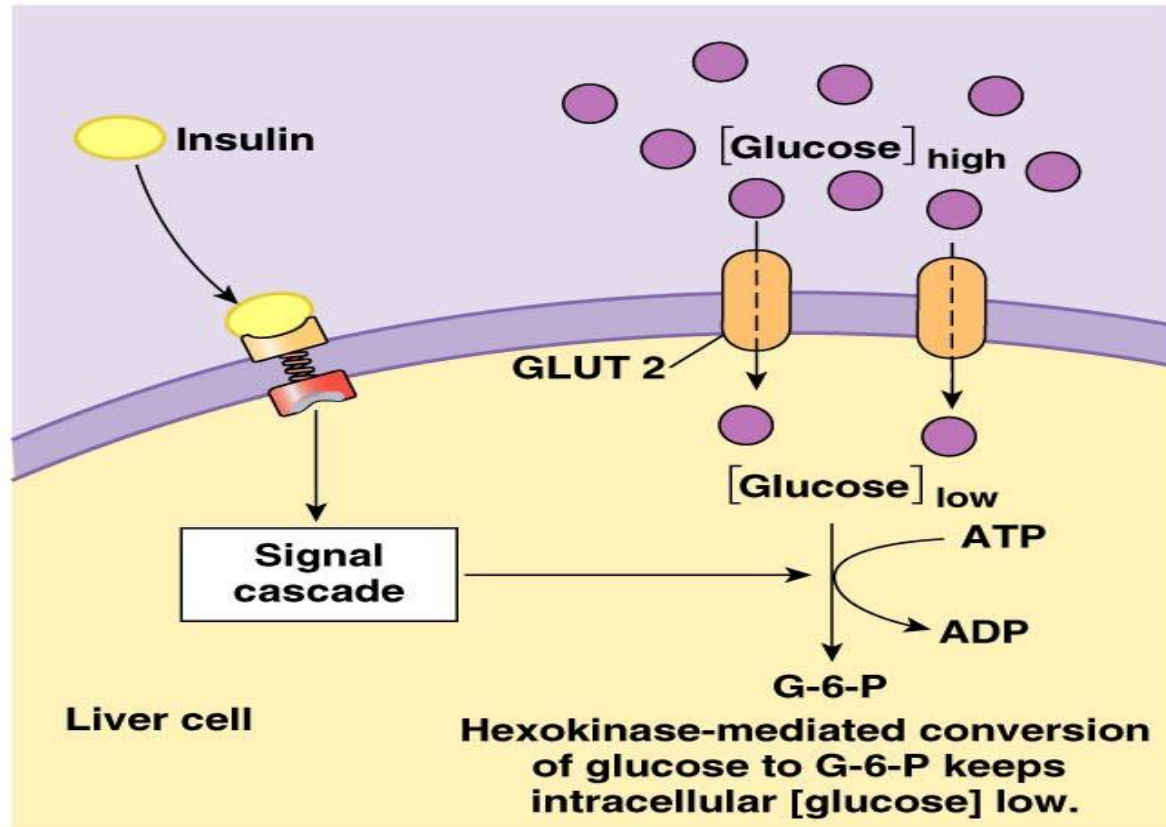


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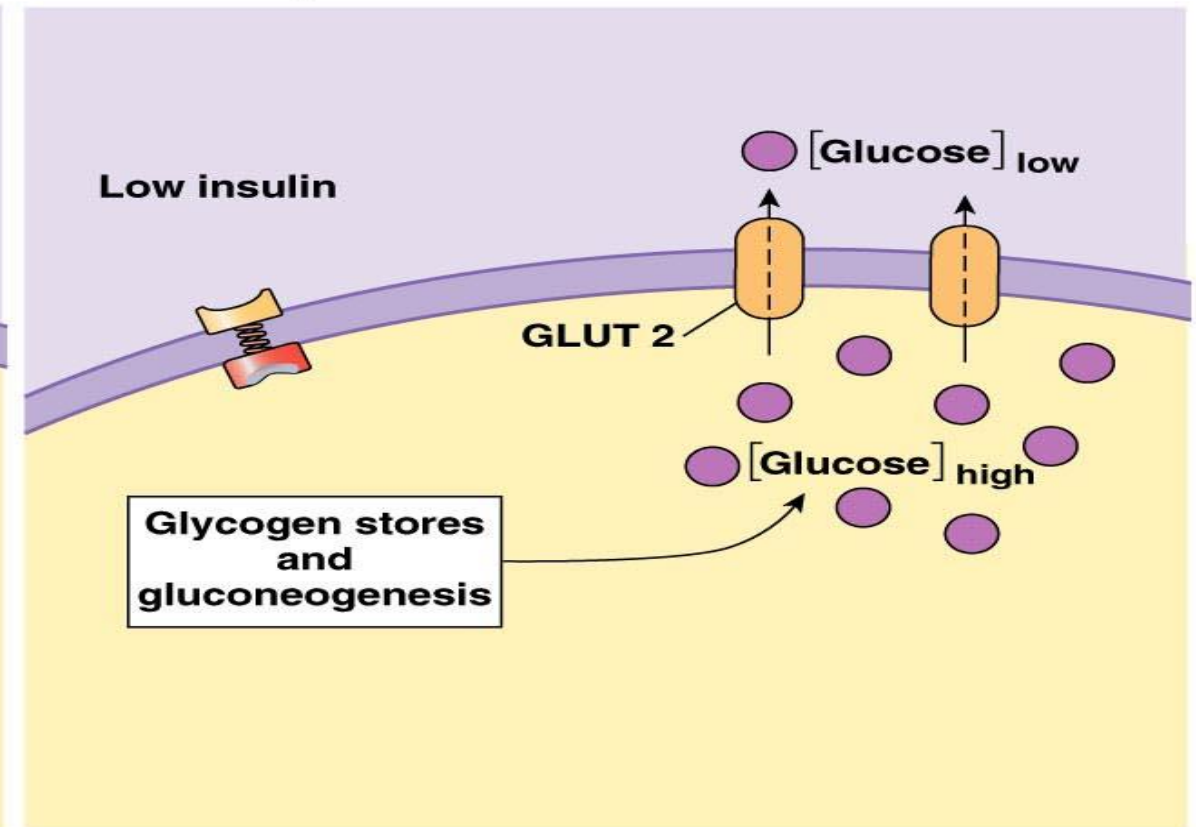
Other tissues, including the brain, kidney and intestine ☐ do not require insulin for glucose uptake and metabolism.

Figure 22-12 - Overview

(a) Hepatocyte in fed state: liver cell takes up glucose.



(b) Hepatocyte in fasted state: liver cell makes glucose and transports it out into the blood.



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Hepatocytes have GLUT2 transporters that are always present in the cell membrane. Hepatocyte not directly insulin dependent but it is influenced by the presence or absence of insulin.

Figure 22-13 - Overview

Regulation of Blood Glucose Levels

The Insulin-to-Glucagon Ratio Regulates Metabolism

- The hyperglycemic effects of glucagon and the hypoglycemic effects of insulin

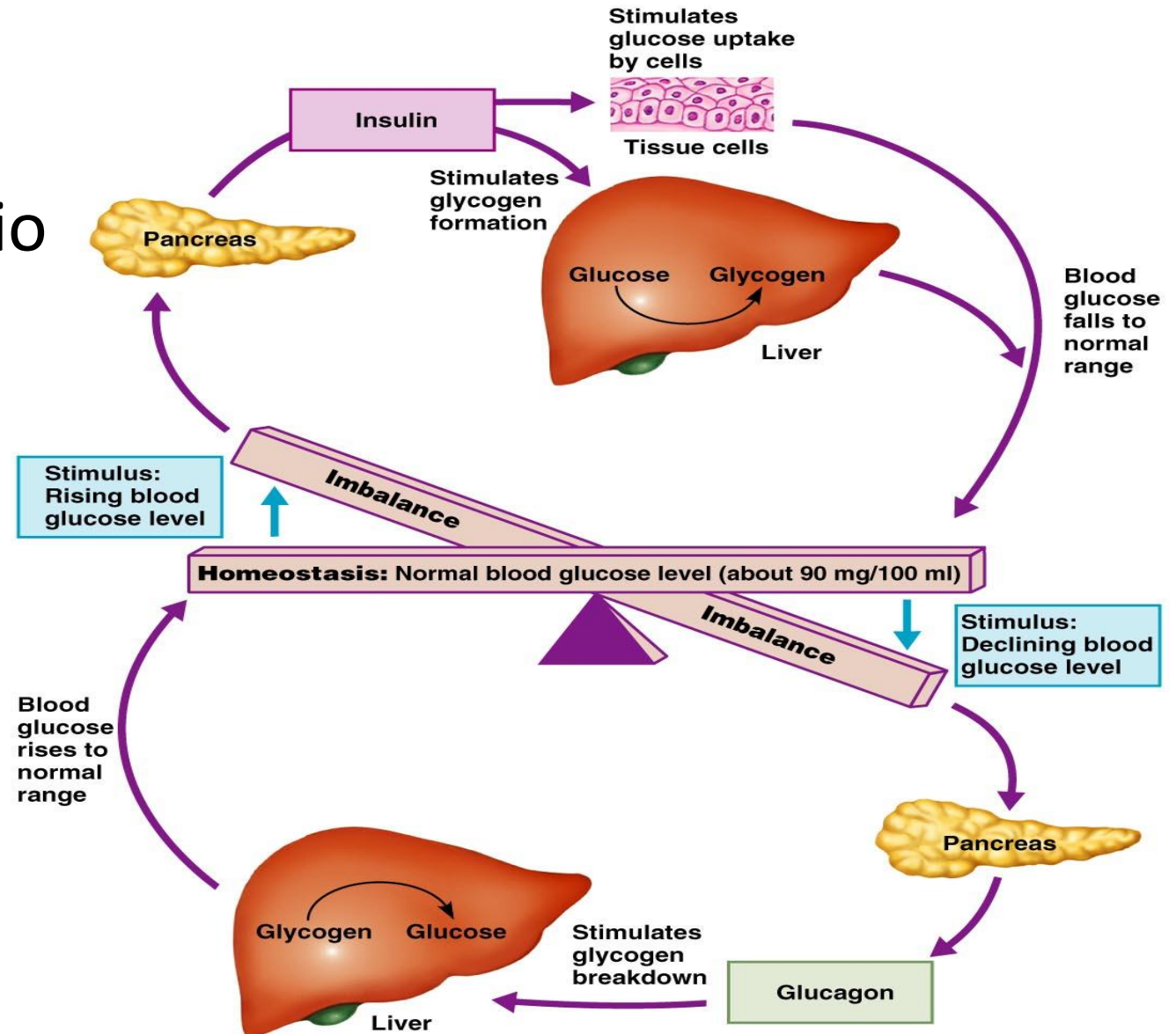
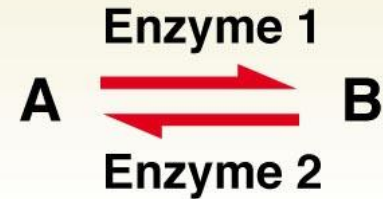


Figure 16.18

(a) Without regulation of enzymatic activity, the pathway will simply cycle back and forth.



No net synthesis
of substance A or B

(b) Fed-state metabolism under the influence of insulin



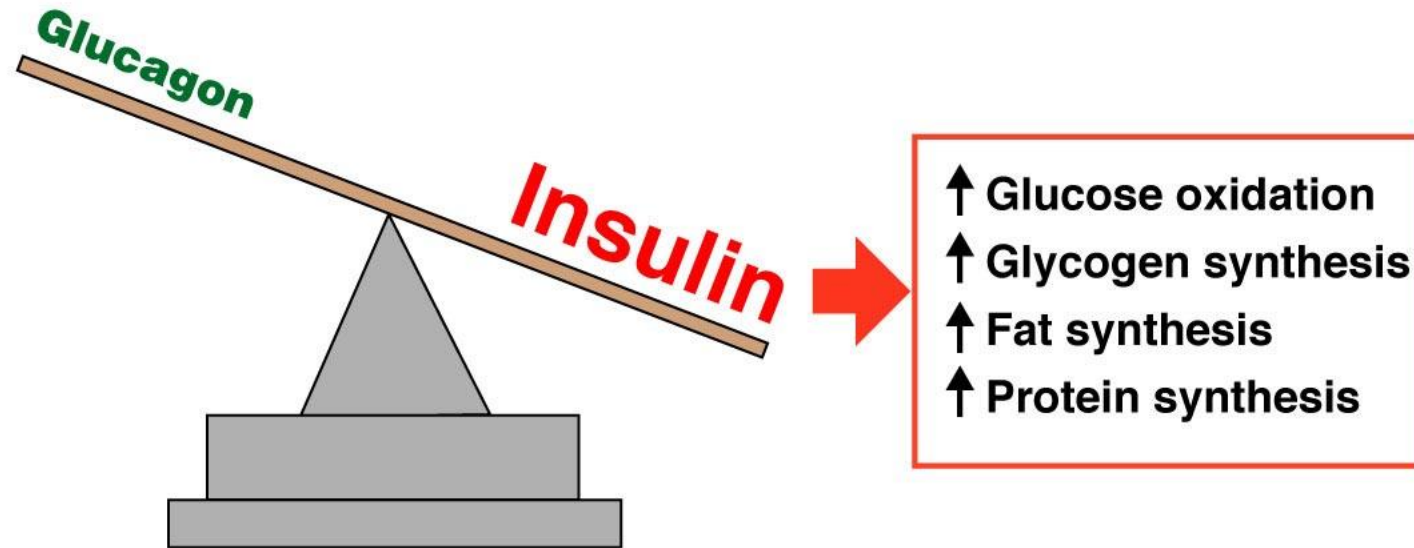
Net glycogen
synthesis

(c) Fasted-state metabolism under the influence of glucagon

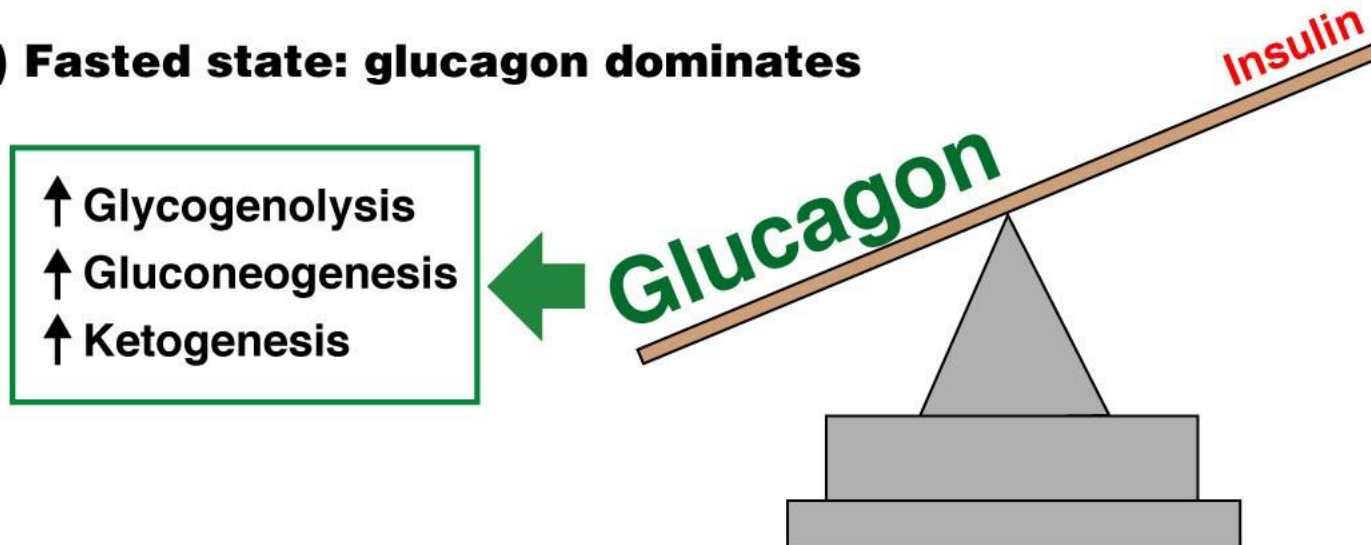


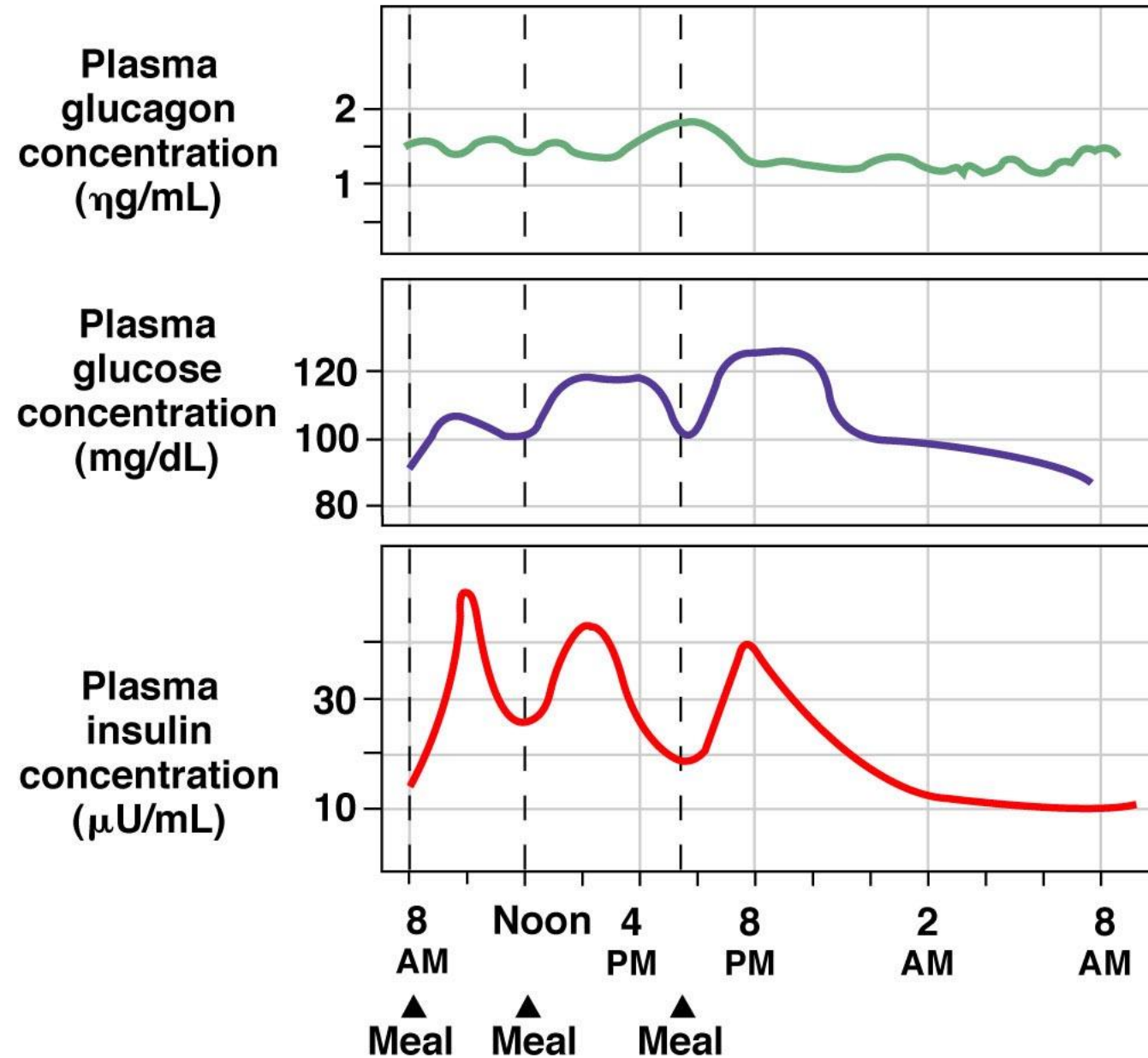
Net glucose
synthesis

(a) Fed state: insulin dominates



(b) Fasted state: glucagon dominates



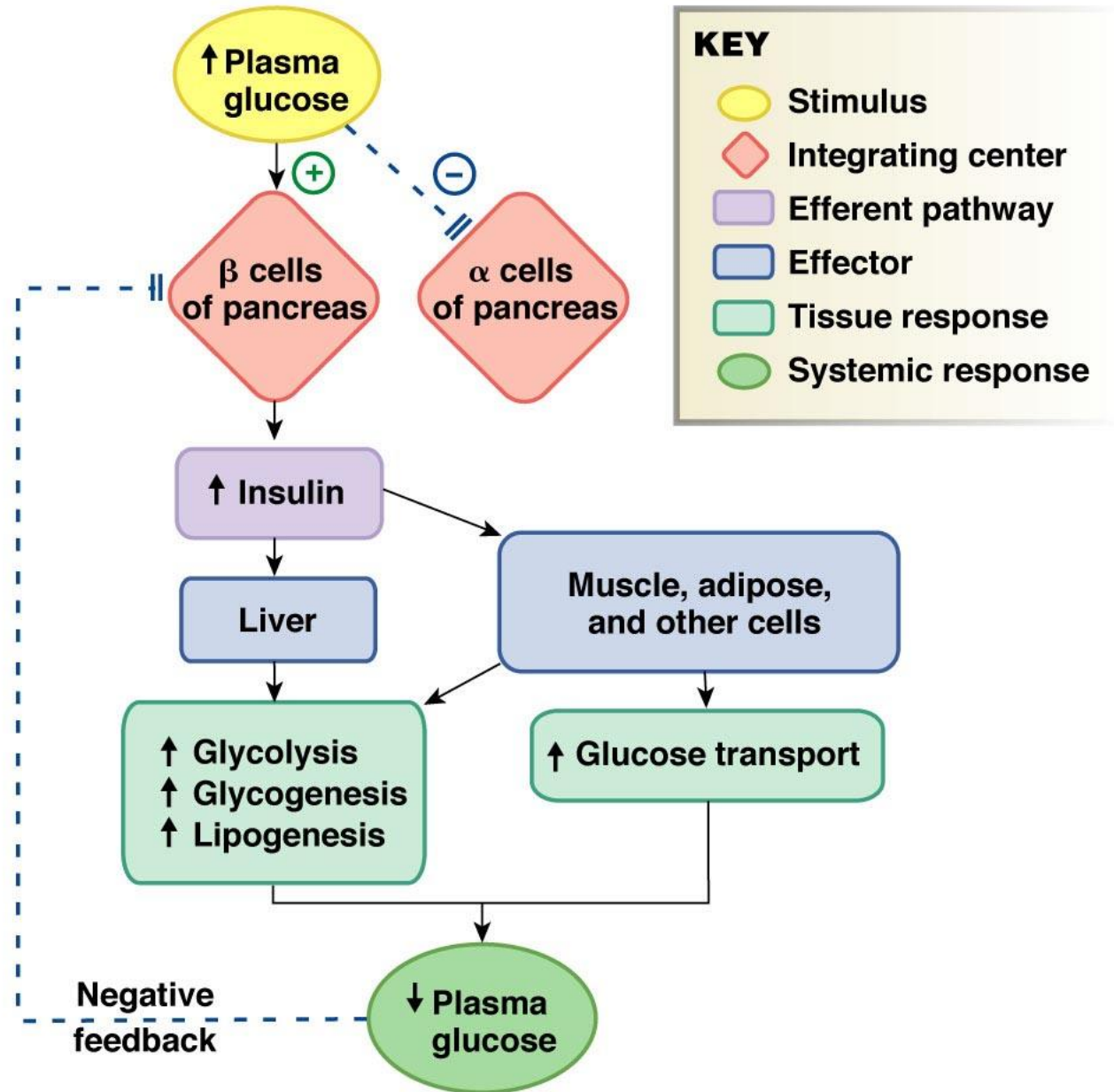


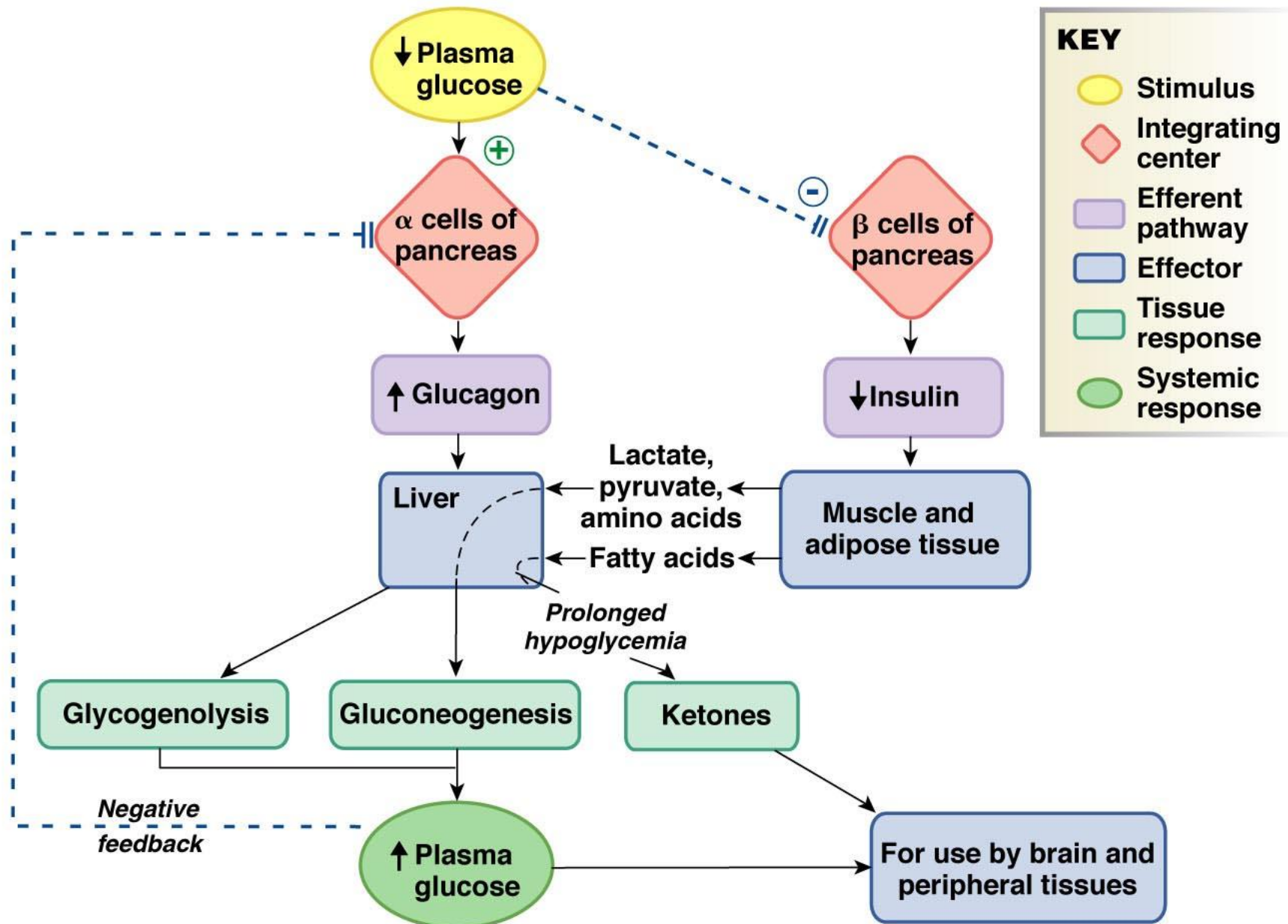
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Figure 22-10

TABLE 22-4	Adrenal Catecholamines (Epinephrine and Norepinephrine)
Origin	Adrenal medulla (90% epinephrine and 10% norepinephrine)
Chemical nature	Amines made from tyrosine
Biosynthesis	Typical peptide
Transport in the circulation	Some bound to sulfate
Half-life	2 minutes
Factors affecting release	Primarily fight-or-flight reaction through CNS and autonomic nervous system; hypoglycemia
Target cells or tissues	Mainly neurons, pancreatic endocrine cells, heart, blood vessels, adipose tissue
Target receptor	G protein-coupled receptors; α and β subtypes
Second messenger	cAMP (α_2 and all β receptors); IP ₃ (α_1 receptors)
Whole body or tissue action	↑ Plasma [glucose]; activate fight-or-flight and stress reactions; ↑ glucagon and ↓ insulin secretion
Onset and duration of action	Rapid and brief

- Increased plasma **glucose**
- Increased plasma **amino acids**
- Feedforward effects of **GI hormones** such as CCK and gastrin, amplify insulin secretion
- **Parasympathetic** activity
- Epinephrine and norepinephrine inhibit insulin secretion and switch metabolism to gluconeogenesis

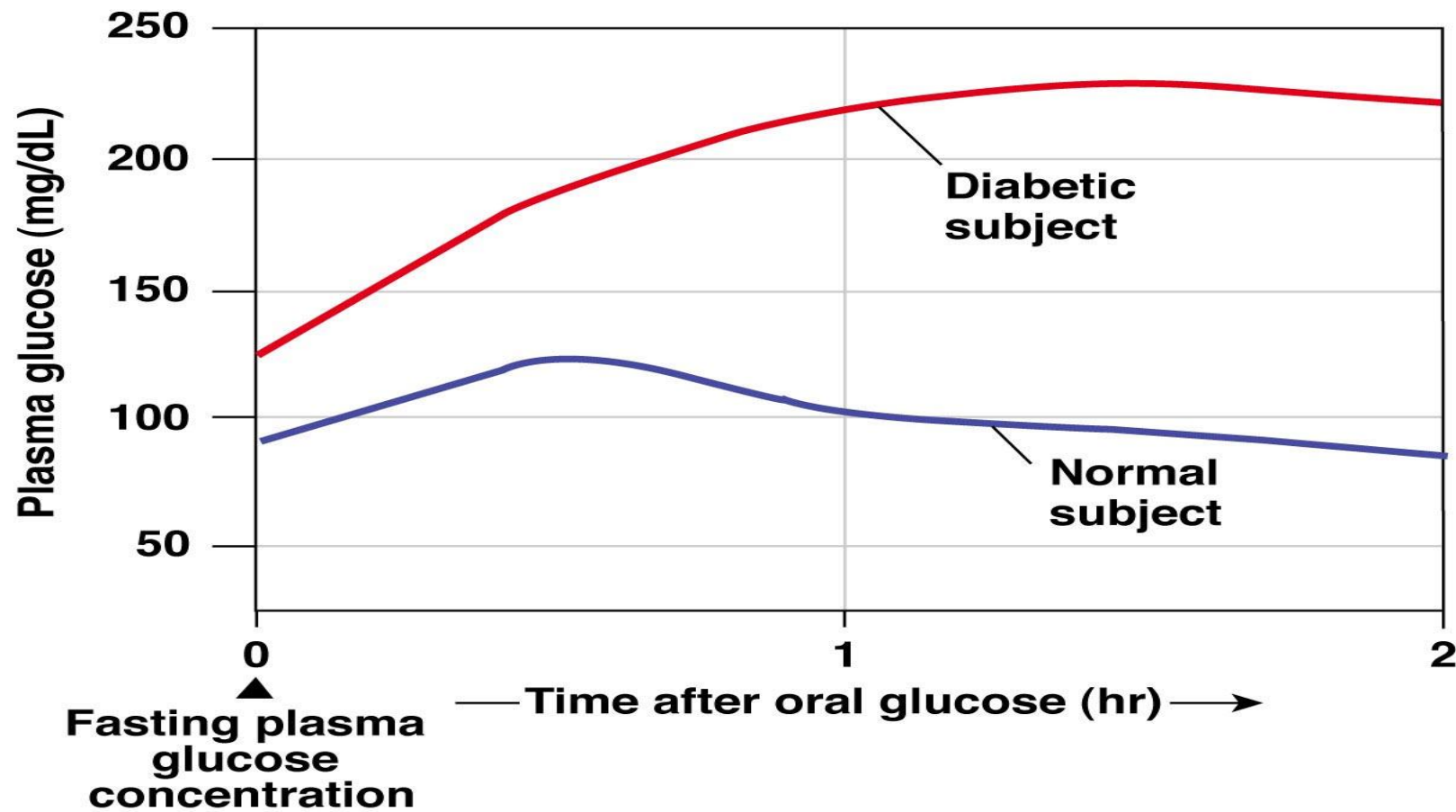




Diabetes Mellitus (DM)

- Results from hyposecretion or hypoactivity of insulin
- The three signs of DM are:
 - Polyuria – huge urine output
 - Polydipsia – excessive thirst
 - Polyphagia – excessive hunger and food consumption
- Hyperinsulinism – excessive insulin secretion, resulting in hypoglycemia

- type 1 diabetes mellitus: insulin deficiency resulting from **beta cell destruction**. most commonly an autoimmune disease in which the body fails to recognize the beta cells as self and destroys them with antibodies and white blood cells.
- type 2 diabetes. This type of diabetes is also known as insulin-resistant diabetes



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Normal and abnormal glucose tolerance tests.

At time 0, the subject consumes a glucose drink or a meal. In diabetic individuals, the plasma glucose concentration remains above 200 mg/dL after two hours. Individuals with plasma glucose of 140–199 mg/dL after two hours have impaired glucose tolerance. Normal people have glucose concentrations below 140 mg/dL at the two-hour mark.

Figure 22-17

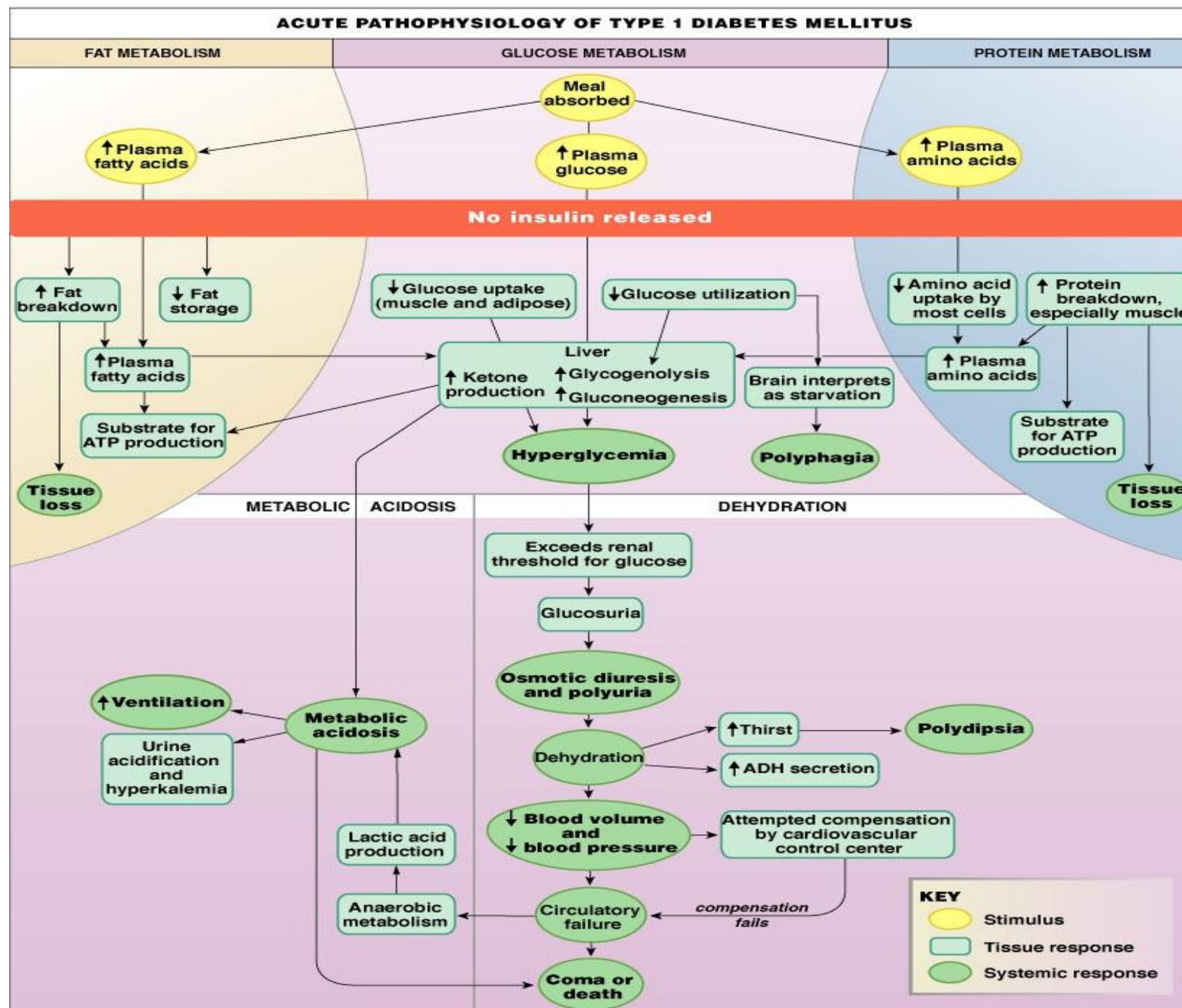


Figure 22-16

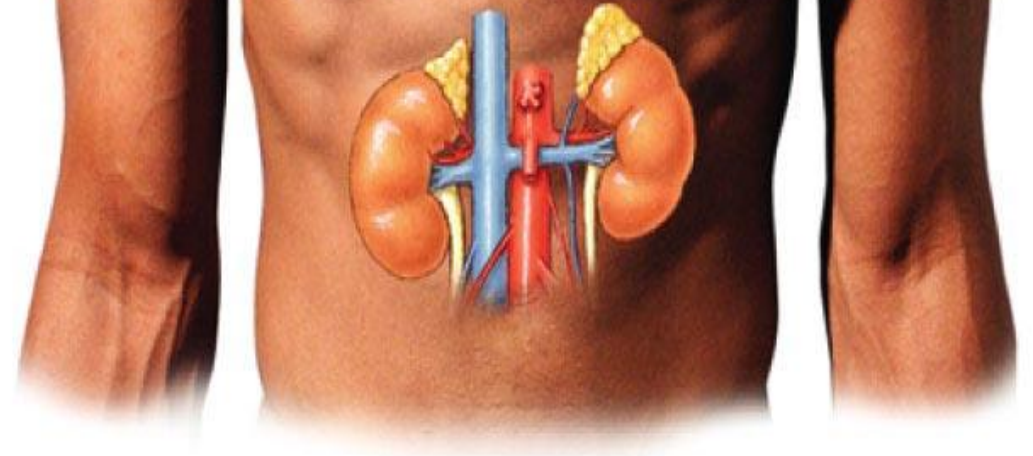
Adrenal gland Sex Hormones

Dr Safa Abdul Ghani

Adrenal Gland

- Adrenal glands – paired, pyramid-shaped organs atop the kidneys
- Structurally and functionally, they are two glands in one
 - **Adrenal medulla** – **neural tissue** that acts as part of the SNS
 - **Adrenal cortex** – **glandular tissue** derived from embryonic mesoderm

(a)



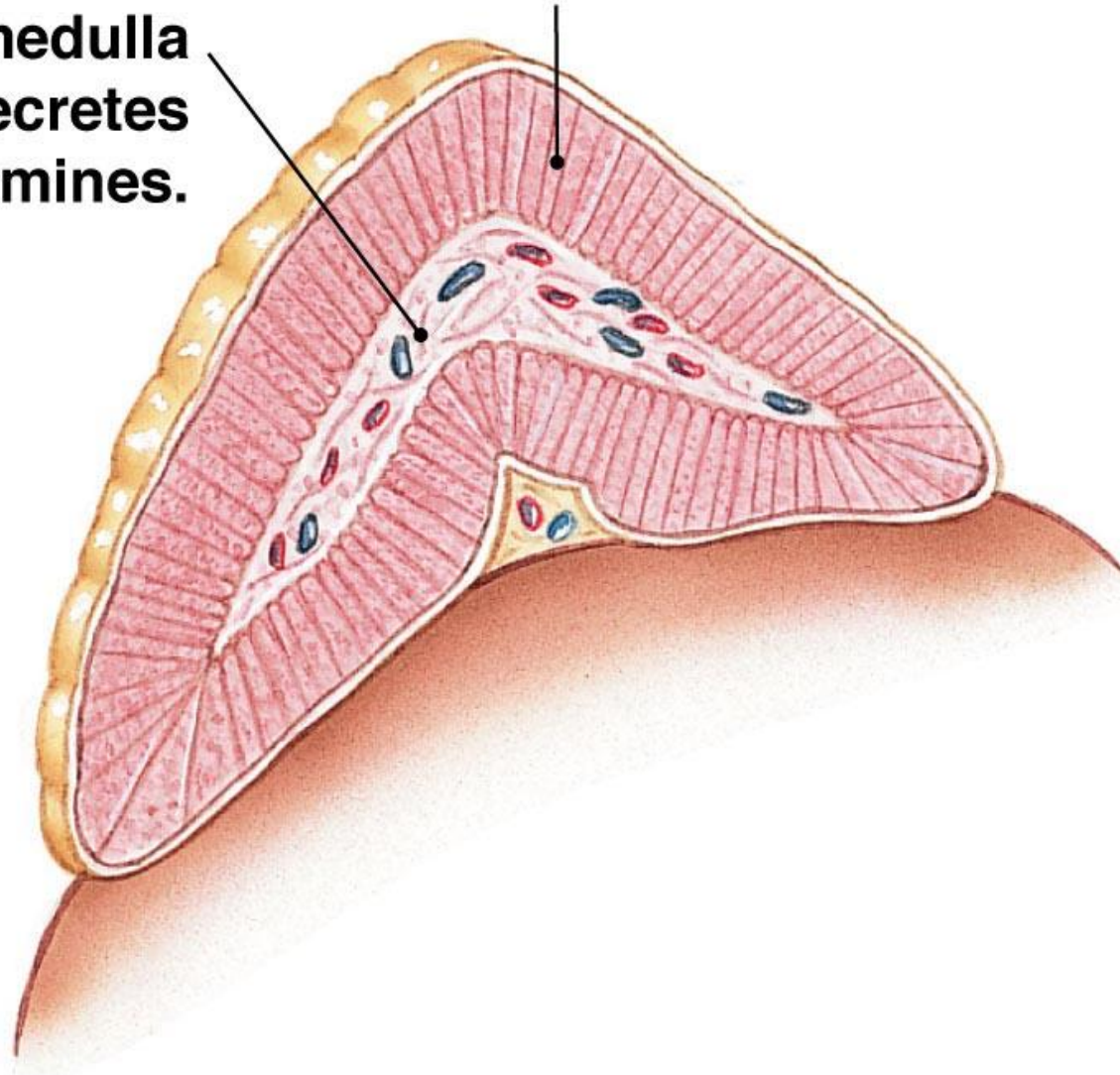
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Figure 23-1a

(b)

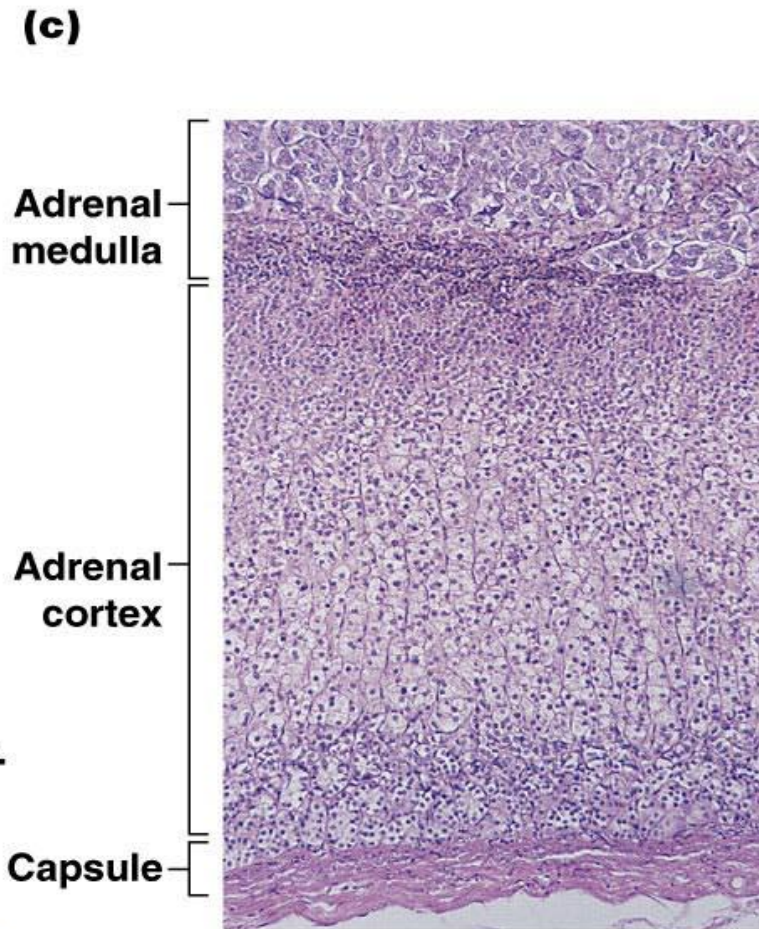
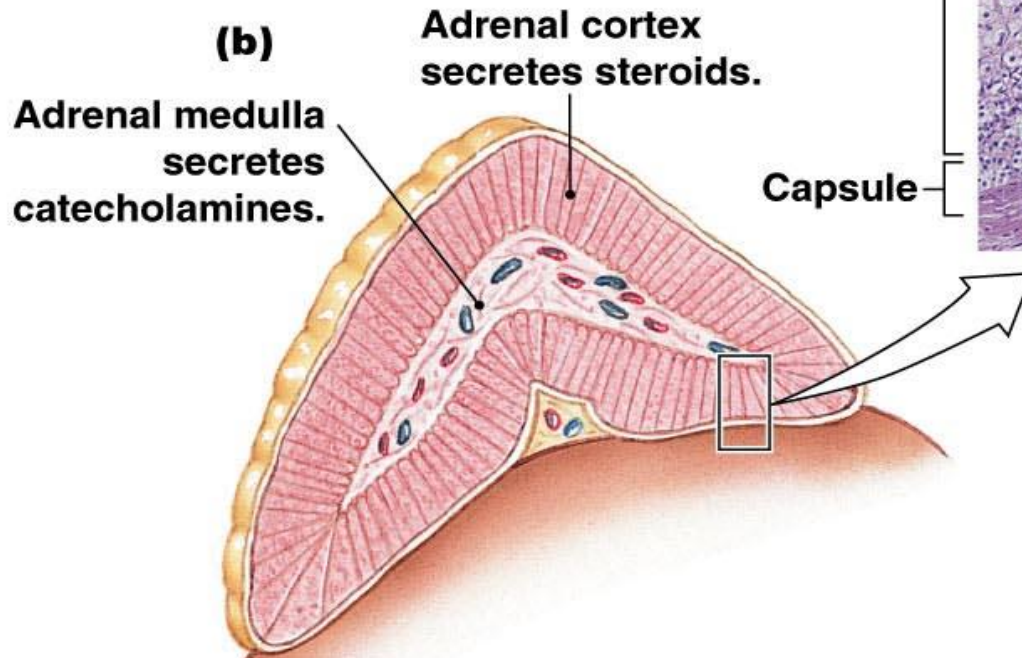
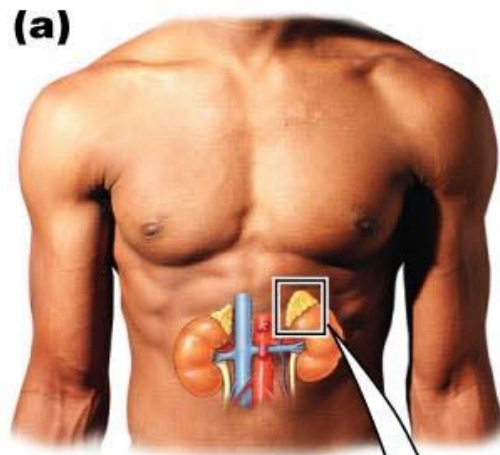
**Adrenal medulla
secretes
catecholamines.**

**Adrenal cortex
secretes steroids.**



Adrenal Cortex

- Synthesizes and releases steroid hormones called **corticosteroids**
- Different corticosteroids are produced in each of the three layers
 - Zona glomerulosa – **mineralocorticoids** (chiefly aldosterone)
 - Zona fasciculate – **glucocorticoids** (chiefly cortisol)
 - Zona reticularis – **gonadocorticoids** (chiefly adrenal androgens)



Region of adrenal gland	Secretes
Adrenal medulla	Catecholamines
Zona reticularis	Sex hormones gonadocorticoids
Zona fasciculata	Glucocorticoids
Zona glomerulosa	Aldosterone mineralocorticoids

Figure 23-1 - Overview

Adrenal Cortex

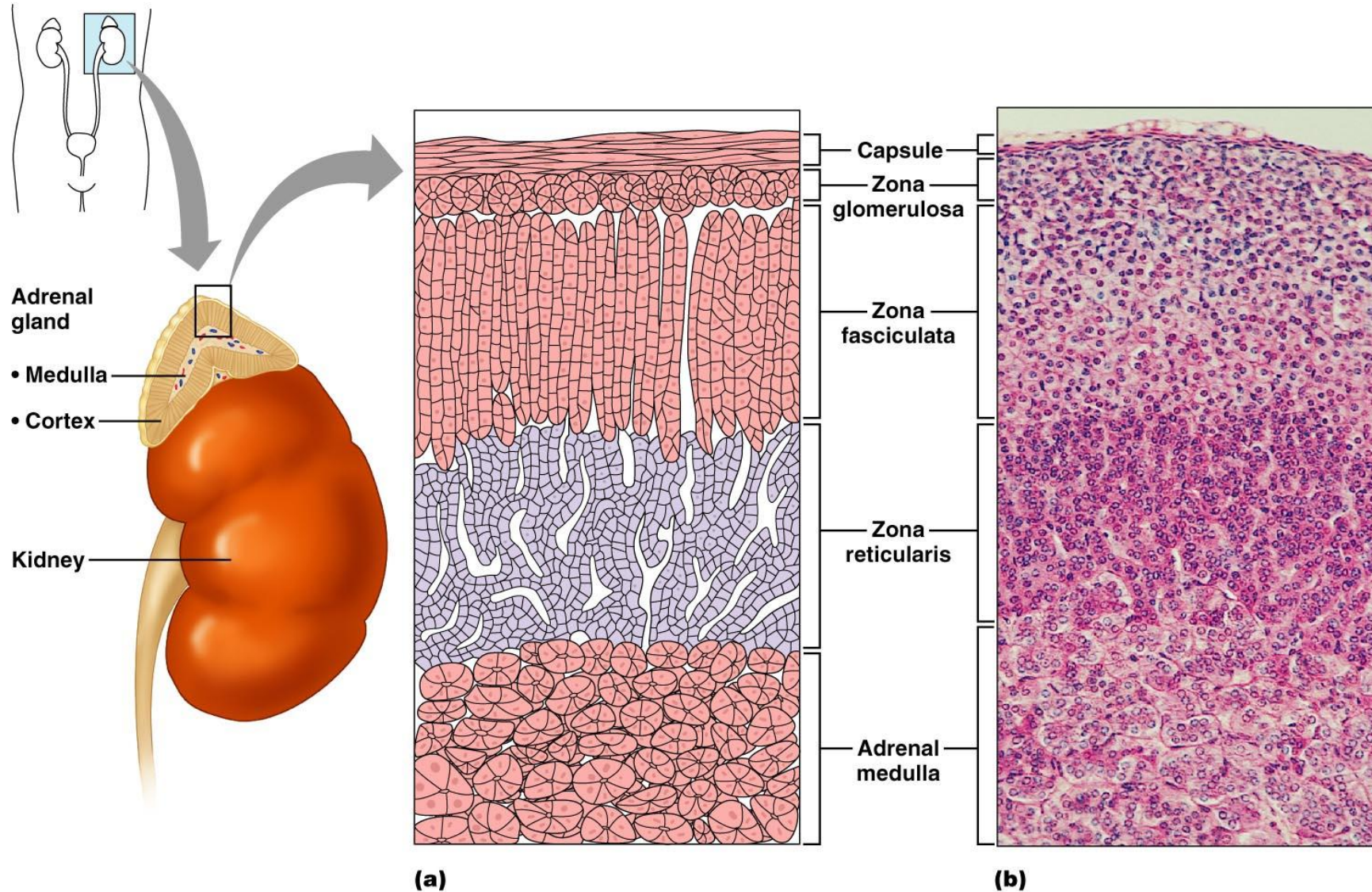
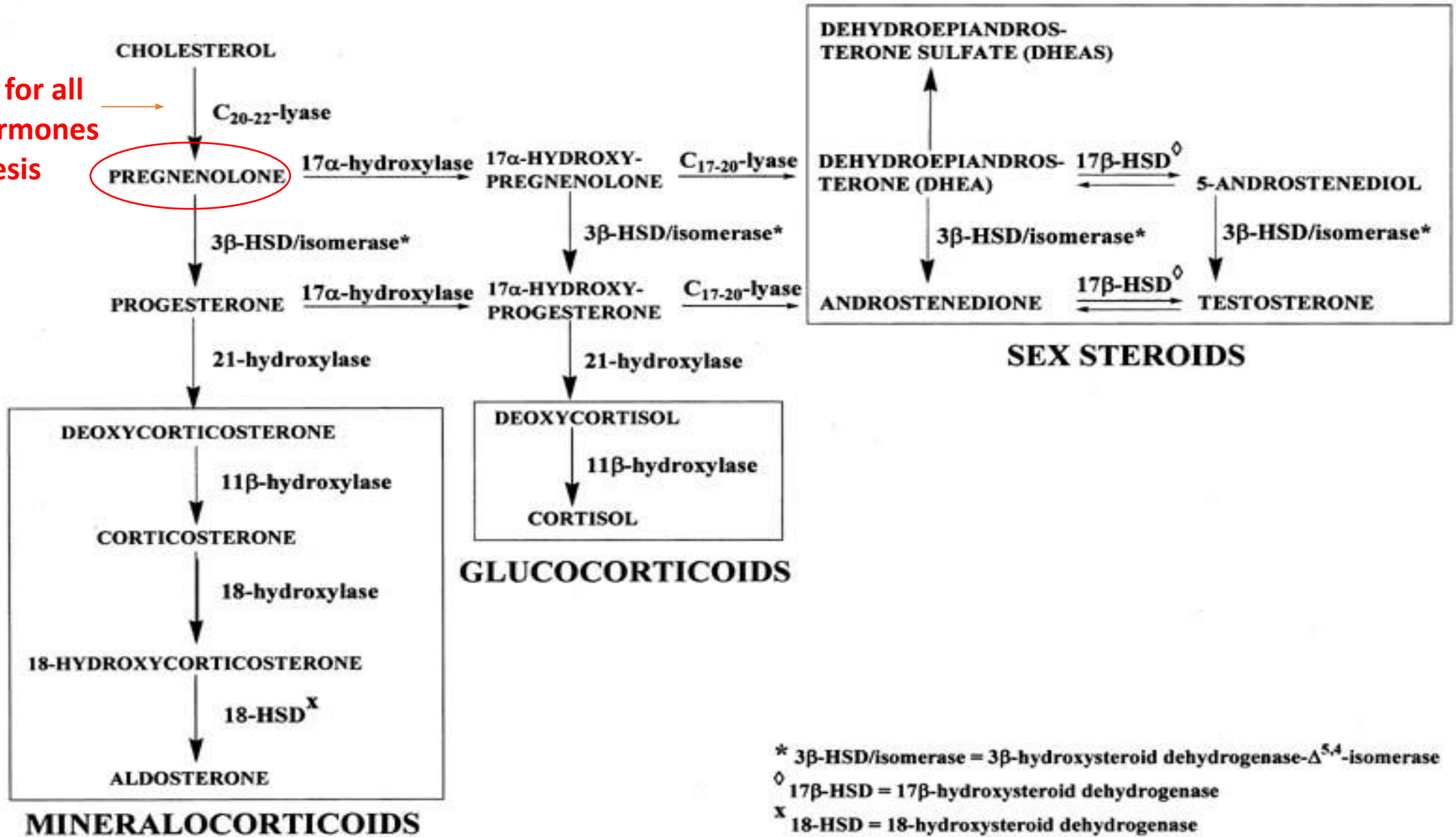
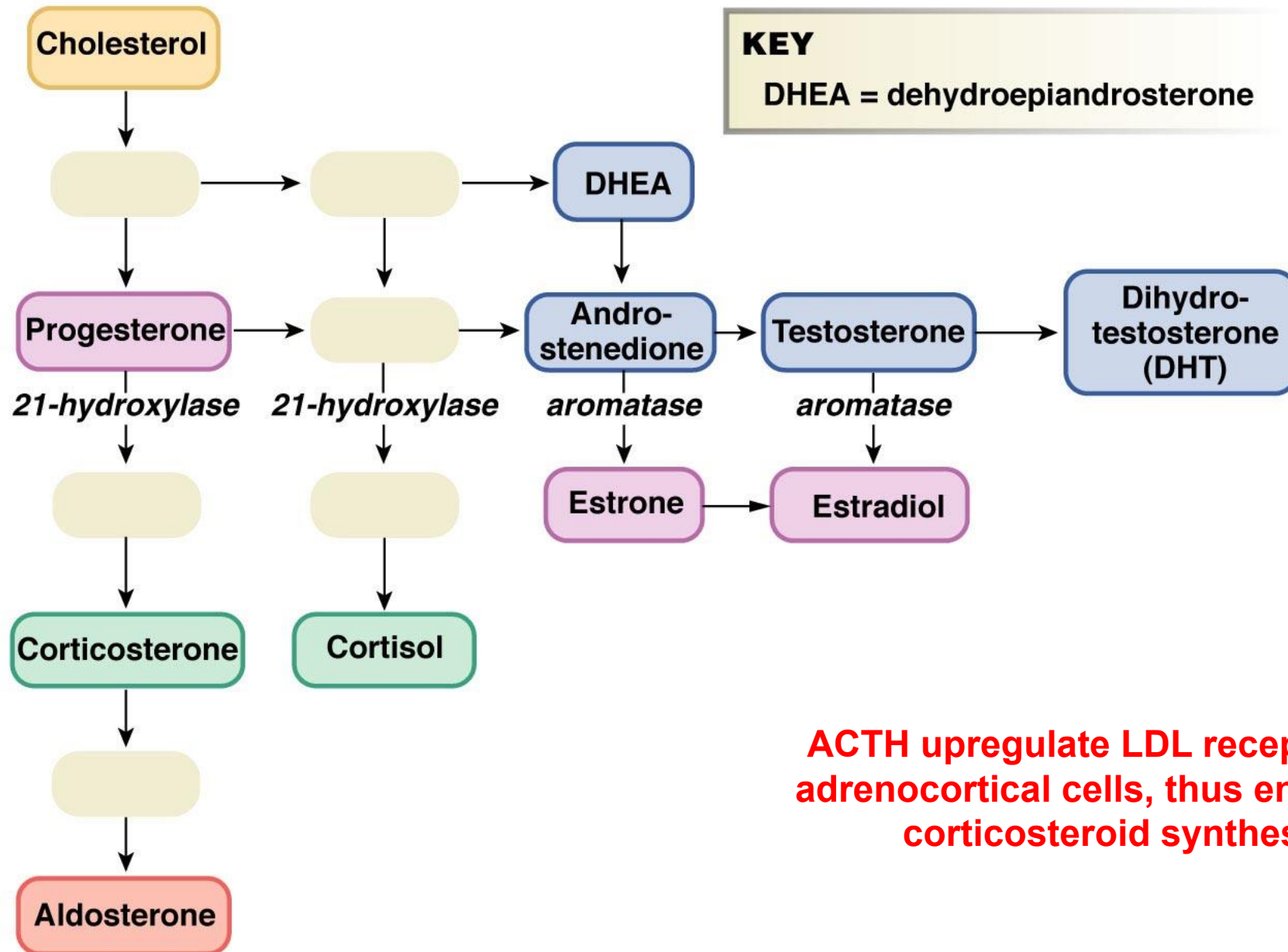


Figure 16.13a, b

First step for all
steroid hormones
synthesis



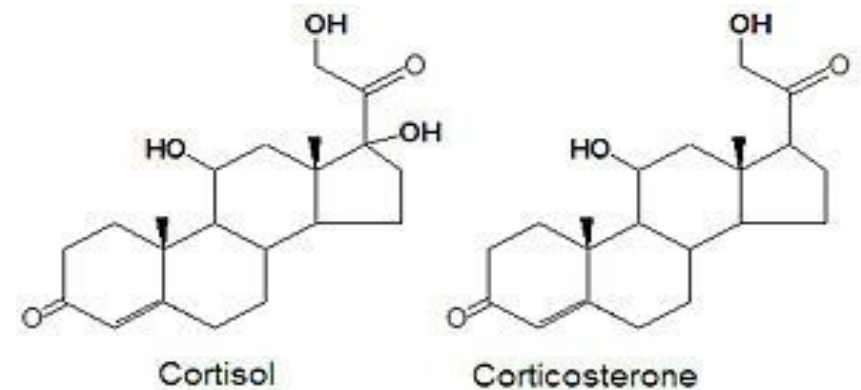


ACTH upregulate LDL receptors on adrenocortical cells, thus enhancing corticosteroid synthesis

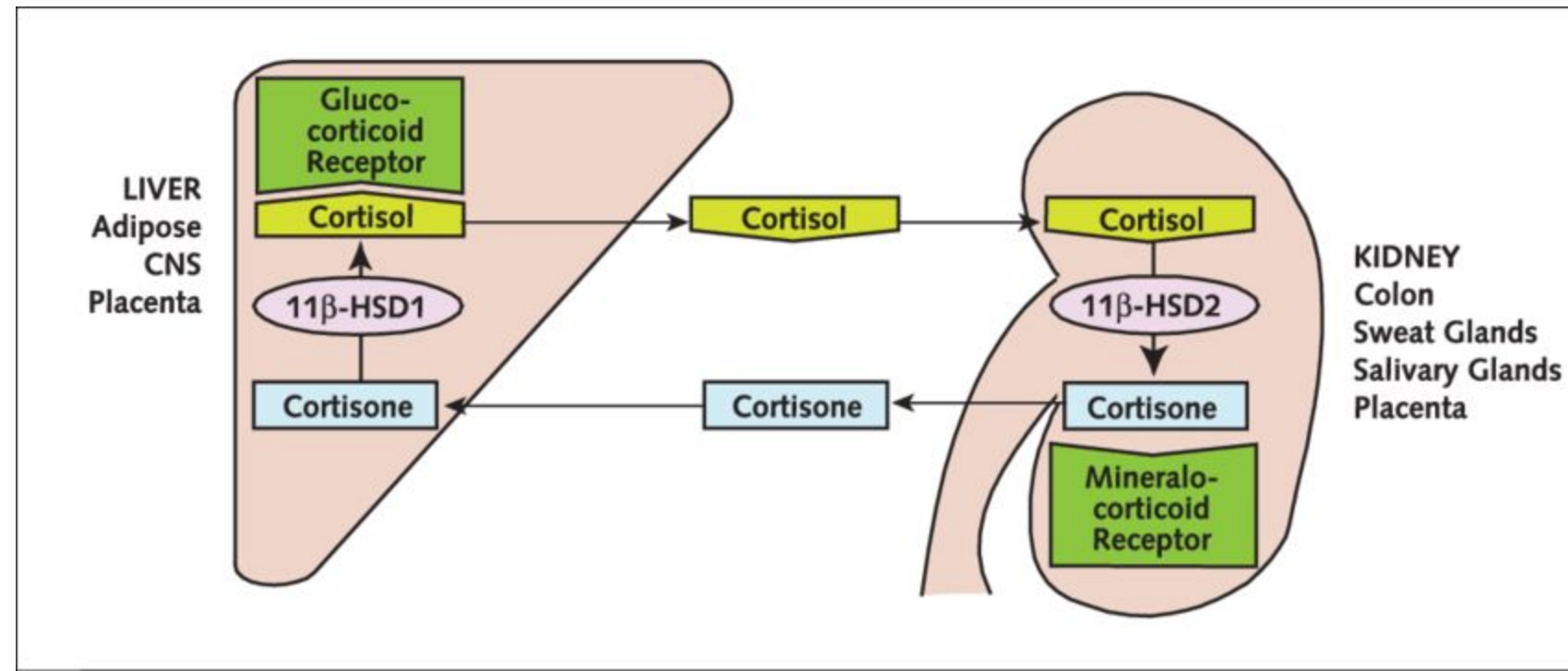
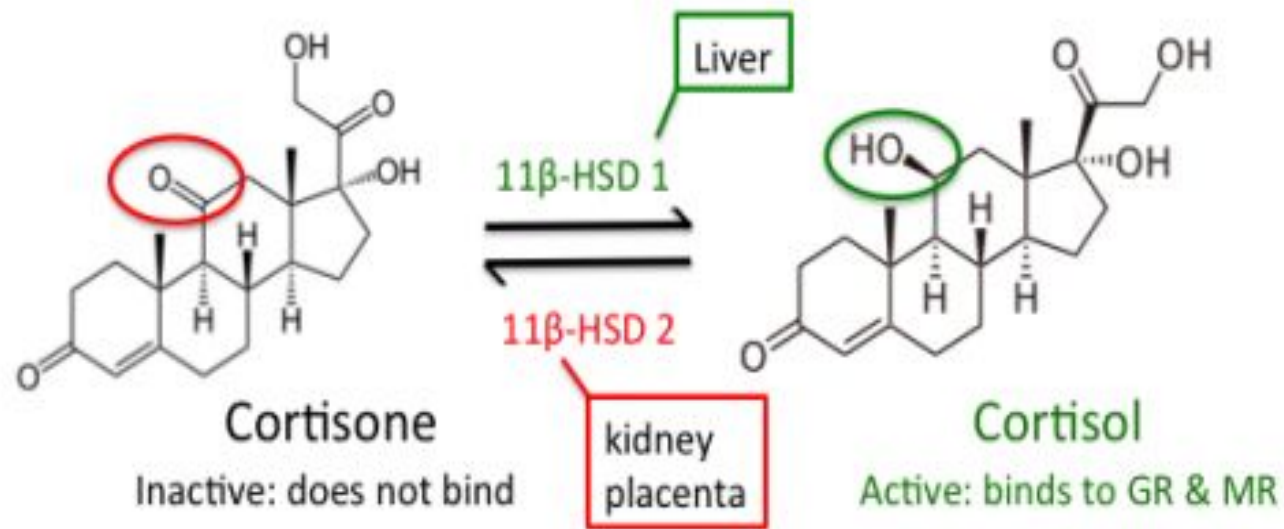
TABLE 23-1 Cortisol	
Origin	Adrenal cortex
Chemical nature	Steroid
Biosynthesis	From cholesterol; made on demand, not stored
Transport in the circulation	On corticosteroid-binding globulin (made in liver)
Half-life	60–90 minutes
Factors affecting release	Circadian rhythm of tonic secretion; stress enhances release
Control pathway	CRH (hypothalamus) → ACTH (anterior pituitary) → cortisol (adrenal cortex)
Target cells or tissues	Most tissues
Target receptor	Intracellular
Whole body or tissue action	↑ Plasma [glucose]; ↓ immune activity; permissive for glucagon and catecholamines
Action at cellular level	↑ Gluconeogenesis and glycogenolysis; ↑ protein catabolism; blocks cytokine production by immune cells
Action at molecular level	Initiates transcription, translation, and new protein synthesis
Feedback regulation	Negative feedback to anterior pituitary and hypothalamus

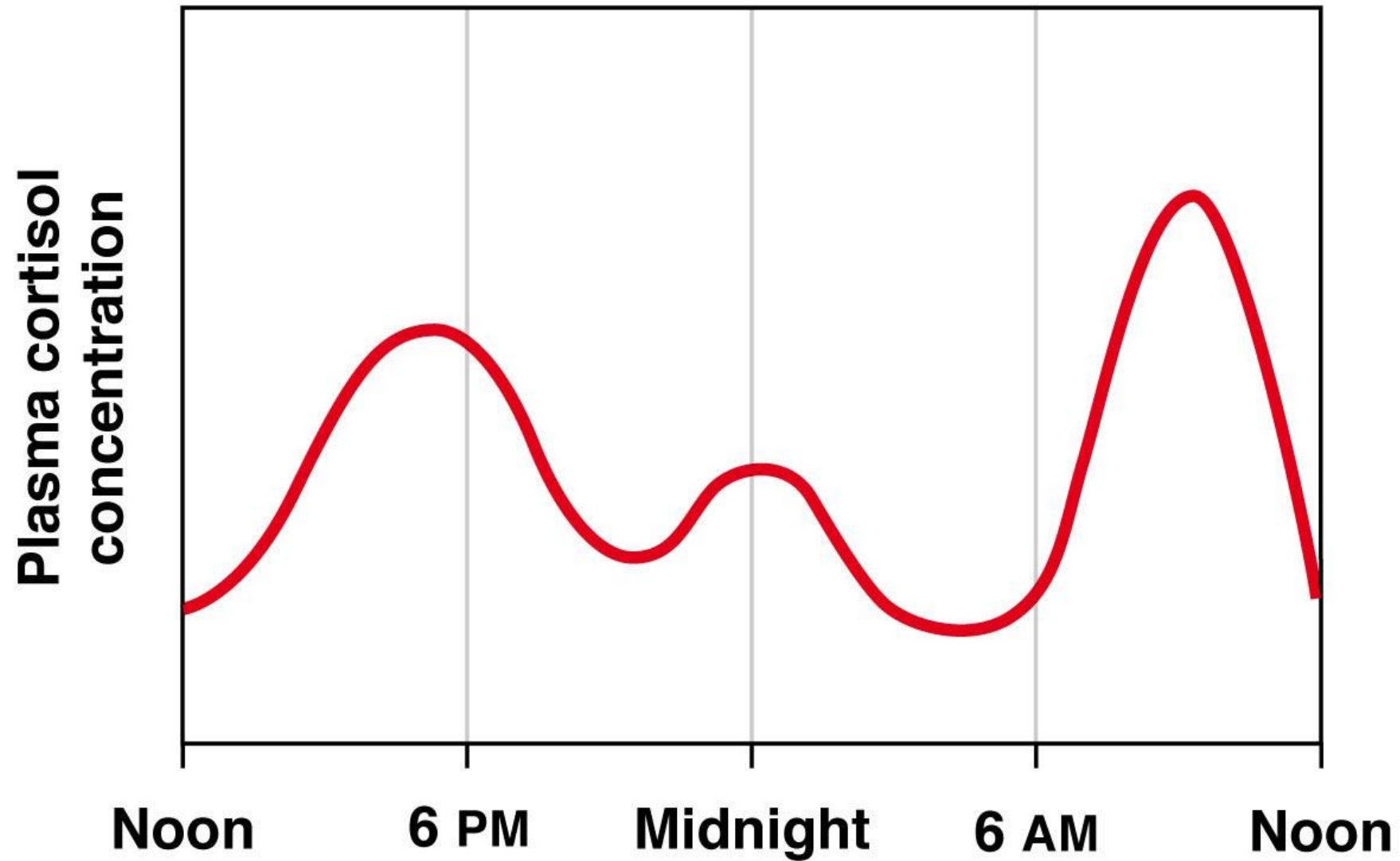
Cortisol: Very potent, account for 95% of glucocorticoid activity

Corticosterone: account for 4% of total glucocorticoid , less potent than cortisol in a ratio of 10:1



Modulation by 11 β -hydroxysteroid dehydrogenase (HSD)





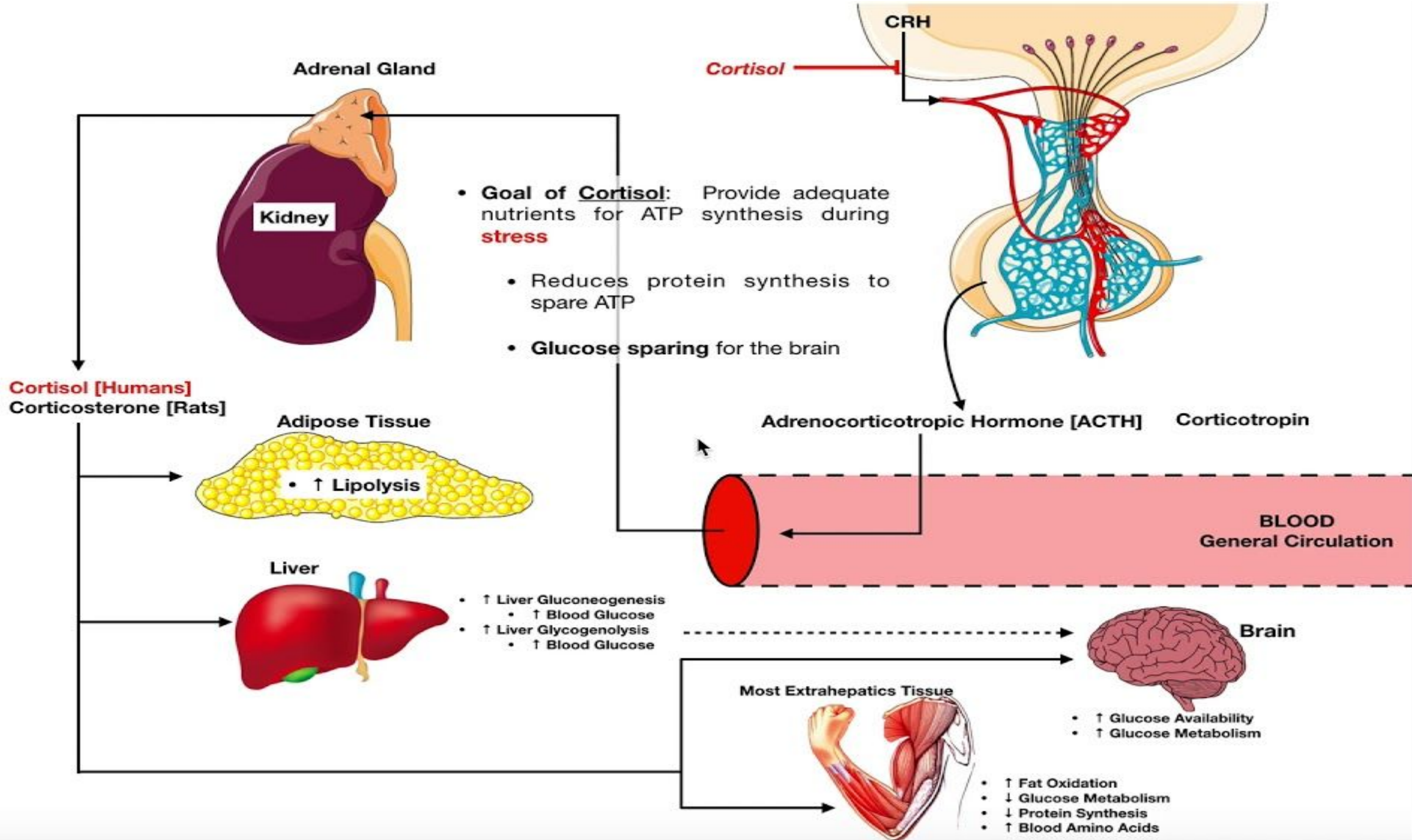
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Secretion normally peaks in the morning and diminishes during the night.

Figure 23-4

Glucocorticoids (Cortisol)

- transported by a carrier protein, corticosteroid-binding globulin (CBG or transcortin).
- Cortisol secretion also increases with stress (body stress hormone).
- Help the body resist stress by :
 - Keeping blood sugar levels relatively constant
 - Maintaining blood volume and preventing water shift into tissue
- Cortisol provokes:
 - Gluconeogenesis (formation of glucose from noncarbohydrates)
 - Rises in blood glucose, fatty acids, and amino acids
- Because cortisol is required for full glucagon and catecholamine activity, it is said to have a permissive effect on those hormones



- 1. **Cortisol promotes gluconeogenesis in the liver.** Some glucose produced in the liver is released into the blood, and the rest is stored as glycogen. As a result, cortisol **increases blood glucose** concentrations.
- 2. **Cortisol causes the breakdown of skeletal muscle proteins** to provide a substrate for gluconeogenesis. Decrease protein synthesis and transport into extrahepatic tissue while it has Proteoanabolic effect in the liver
- 3. **Cortisol enhances lipolysis** so that fatty acids are available to peripheral tissues for energy use. The glycerol from fatty acids can be used for gluconeogenesis. Increase FA concentration in blood
- 4. **Cortisol suppresses the immune system** by preventing cytokine release and antibody production by white blood cells. Reduce lymphocyte
REDUCE INFLAMMATION
- 5. Cortisol causes **negative calcium balance**, increase HCL secretion, decrease GLUT4 mediated glucose uptake
- 6. Cortisol **influences brain function**, increase awake time



VISUAL SYSTEM

Anti-inflammatory
Anti-angiogenesis
Photoreceptor survival



NERVOUS SYSTEM

Physiological homeostasis
Responses to stressors



CARDIOVASCULAR SYSTEM

Anti-inflammatory
Cardiomyocyte survival
Increment of blood pressure
and vascular tone
Anti-angiogenesis



RESPIRATORY SYSTEM

Suppression of cytokines,
chemokines, and
cell adhesion molecules



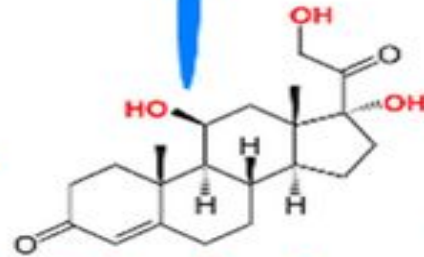
GLUCOSE AND LIVER METABOLISM

Glucose regulation
Lipid homeostasis



REPRODUCTIVE SYSTEM

Gonadal function
Fetal organ development
and maturation



Cortisol



MUSCULOSKELETAL SYSTEM

Anti-inflammatory
Muscle catabolism and anabolism
Insulin resistance
Osteoblast apoptosis
Osteoclastogenesis



IMMUNE SYSTEM

Suppression of pro-
inflammatory cytokines
Regulation of immune cell
maturation, migration
and apoptosis



INTEGUMENTARY SYSTEM

Anti-inflammatory
Delayed wound healing
Epithelial integrity

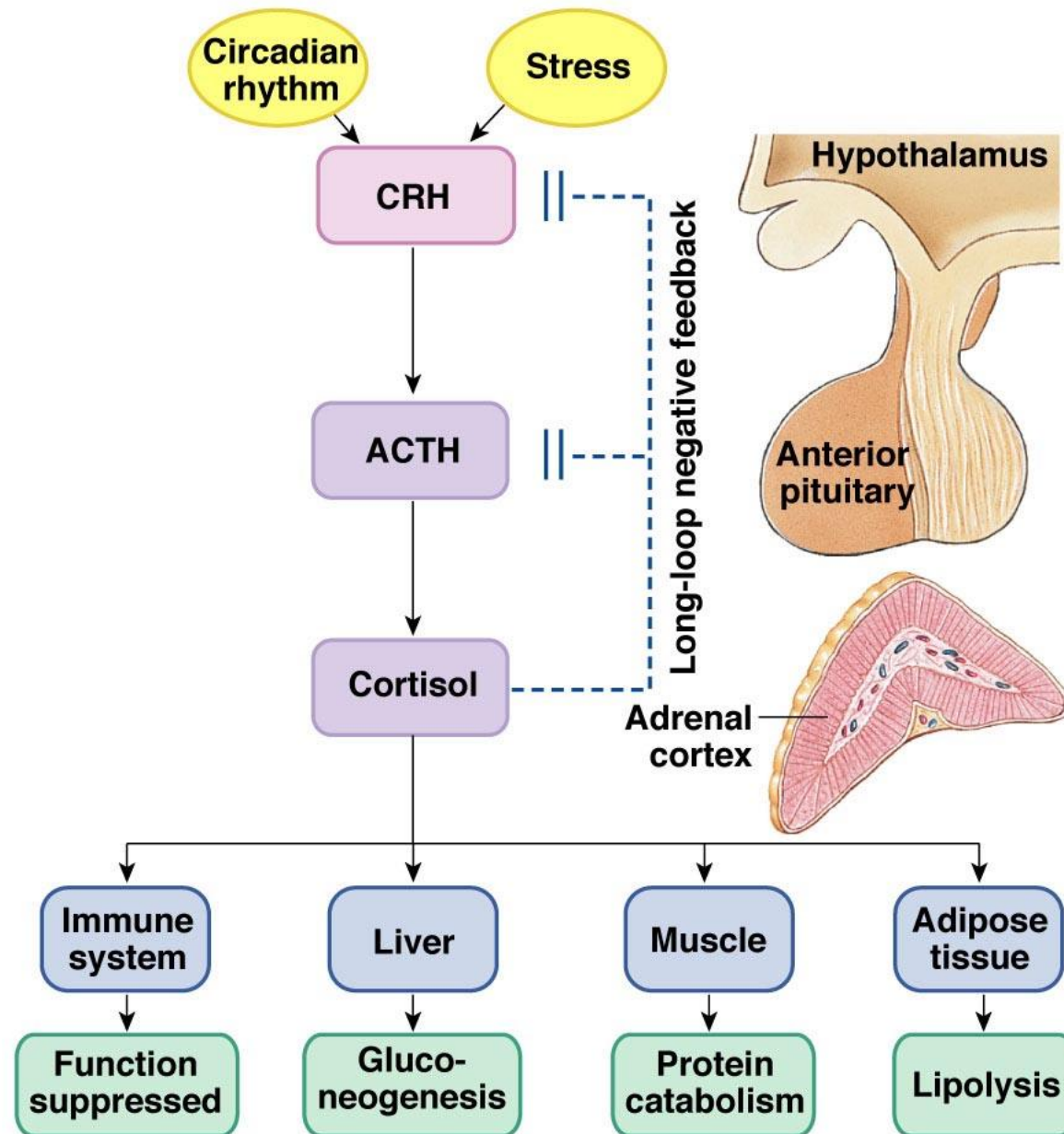


Figure 23-3

Excessive Levels of Glucocorticoids (at high concentrations)

- Excessive levels of glucocorticoids:
 - hyperglycemia
 - Depress cartilage and bone formation (**Cortisol** indirectly acts on bone by blocking **calcium** absorption which decreases bone cell growth)
 - Muscle protein breakdown and lipolysis cause tissue wasting (muscle atrophy)
 - Inhibit inflammation
 - Depress the immune system
 - Promote changes in cardiovascular, neural, and gastrointestinal function
 - mood elevation followed by depression, as well as difficulty with learning and memory.

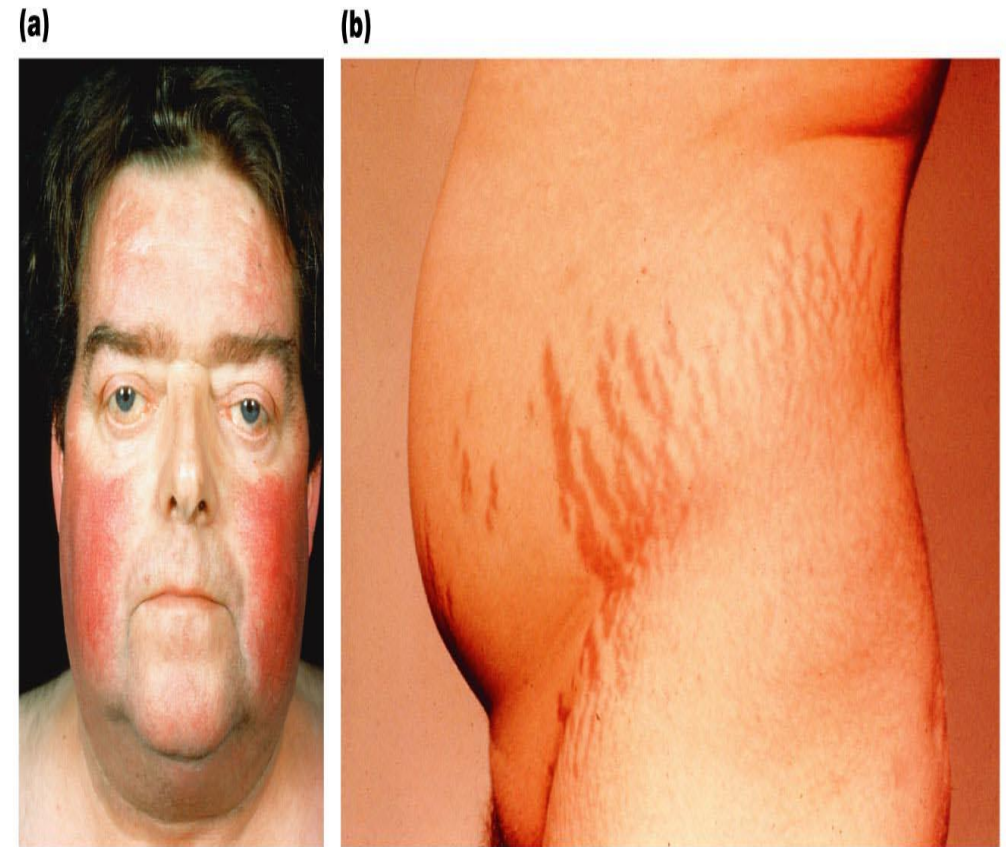
Hypercortisolism : Cushings syndrome

Excess cortisol in the body

Tumour or Cortisol therapy (for organ transplant) with high doses for more than a week has the potential to cause hypercortisolism

Hypocortisolism : Addison's disease

- less common than Cushing s syndrome.
- Hyposecretion of all adrenal steroid hormones, usually following **autoimmune destruction** of the adrenal cortex.
- Hereditary defects in the enzymes needed for production



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Figure 23-5

Stress and the Adrenal Gland

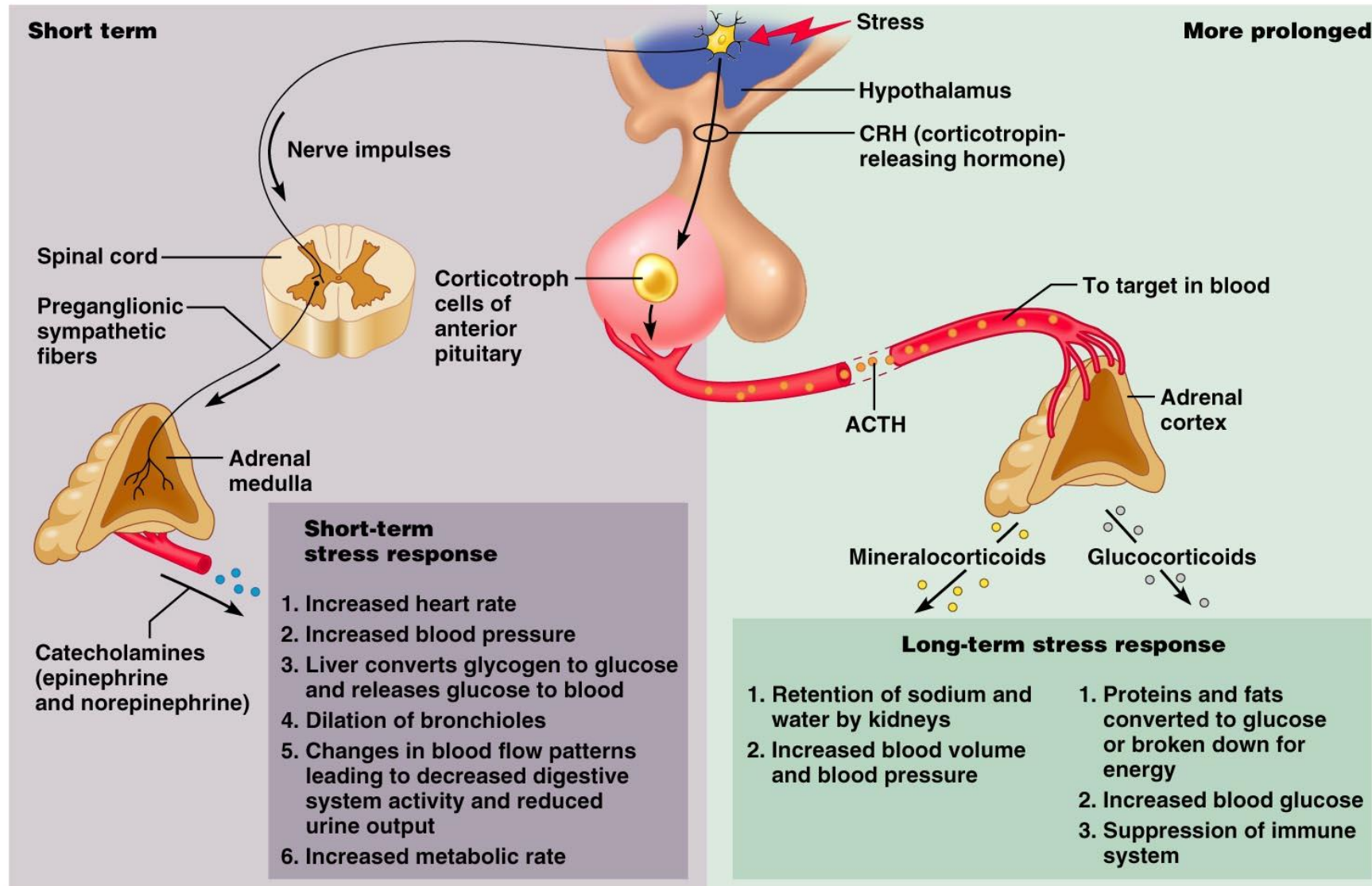


Figure 16.16

Mineralocorticoids

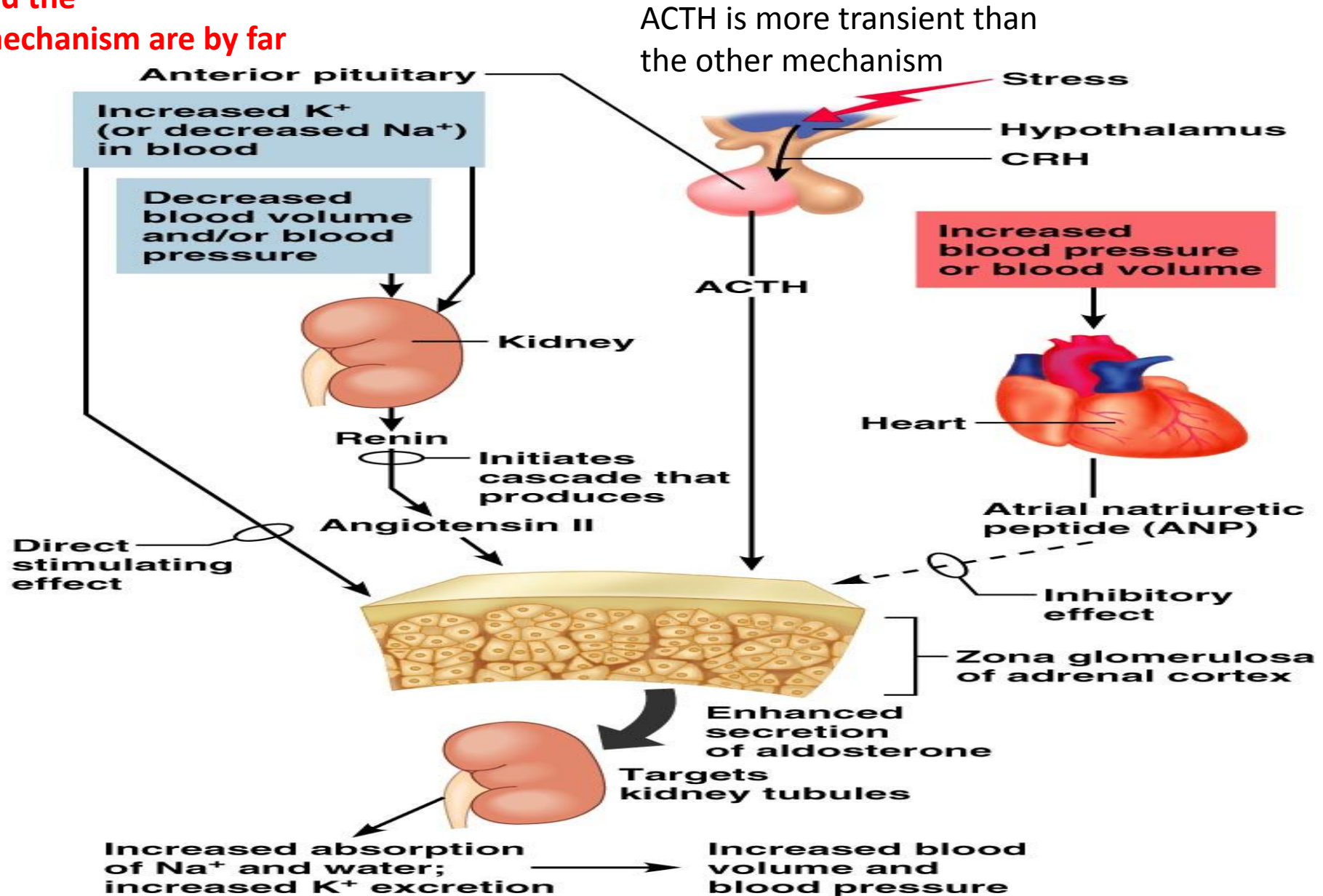
- Regulate electrolytes in extracellular fluids
- Aldosterone – most important mineralocorticoid
 - Maintains Na^+ balance by reducing excretion of sodium from the body
 - Stimulates reabsorption of Na^+ by the kidneys
 - 60% bound to plasma protein , 40% is free
 - Half life 20min
- Aldosterone secretion is stimulated by:
 - Rising blood levels of K^+
 - Low blood Na^+
 - Decreasing blood volume or pressure

The Four Mechanisms of Aldosterone Secretion

- Renin-angiotensin mechanism – kidneys release renin, which is converted into angiotensin II that in turn stimulates aldosterone release
- Plasma concentration of sodium and potassium – directly influences the zona glomerulosa cells
- ACTH – causes small increases of aldosterone during stress
- Atrial natriuretic peptide (ANP) – inhibits activity of the zona glomerulosa

Major Mechanisms of Aldosterone Secretion

K⁺ concentration and the renin-angiotensin mechanism are by far the most potent



Hormonal control of tubular mechanisms

1. **Aldosterone**: increase Na^+ reabsorption and K^+ , H^+ secretion
2. **ADH**: increase water reabsorption
3. **Angiotensin 2**: increase NaCl and water reabsorption
4. **Parathyroid hormones**: increase Ca^{+2} , Mg^{+2} reabsorption and decrease phosphate reabsorption

Mechanism of Na⁺ Selective Reabsorption in Collecting Duct

- Aldosterone: Steroid H from Adrenal Cortex
 - Stimulates Na⁺ Uptake (& K⁺ Secretion)
 - ↑ Channel Synthesis

Mechanism of Na^+ Selective Reabsorption in Collecting Duct

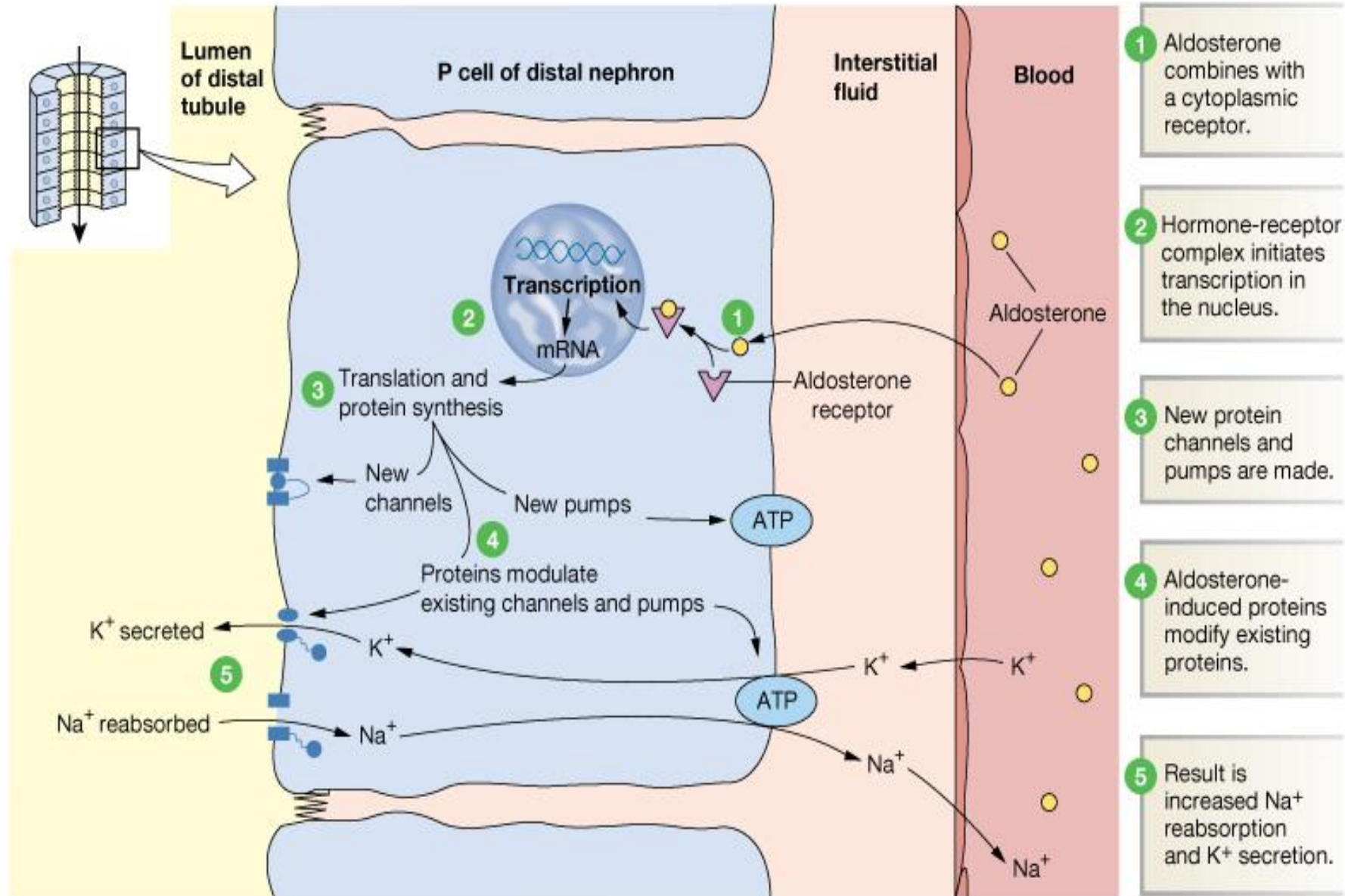


Figure 20-12: Aldosterone action in principal cells

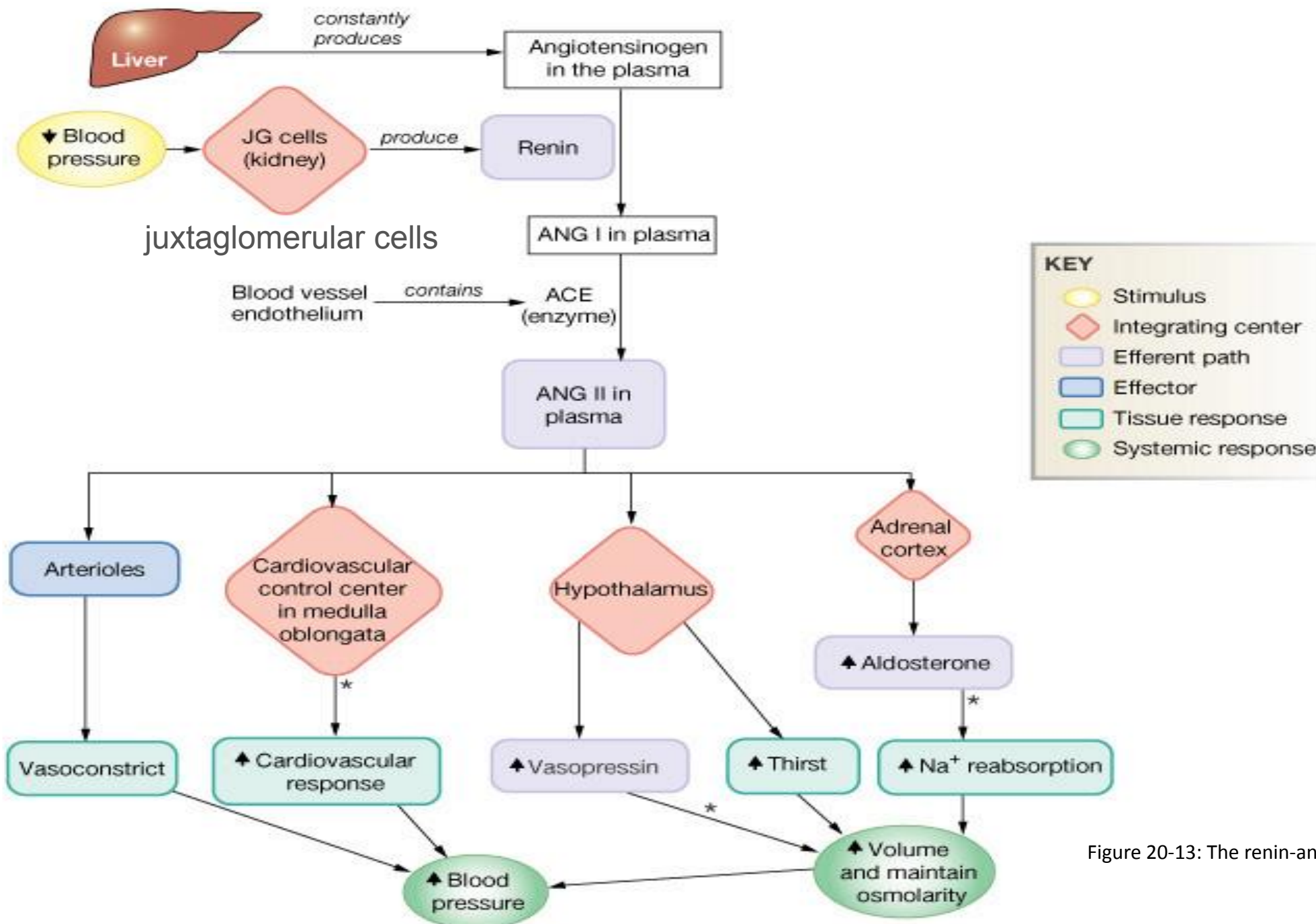


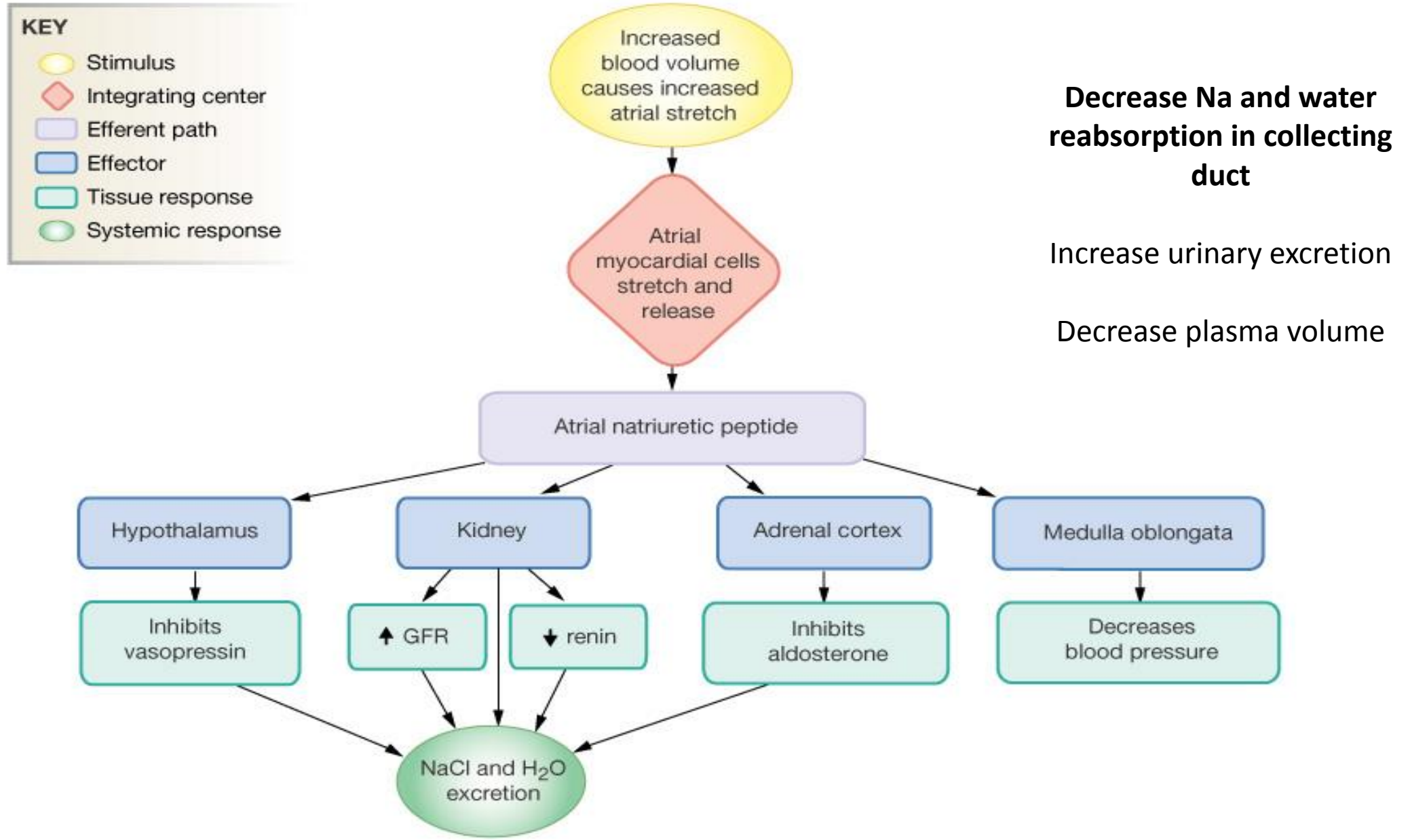
Figure 20-13: The renin-angiotensin-aldosterone pathway

Artial Natruretic Peptide (ANP): Regulates Na⁺ & H₂O Excretion

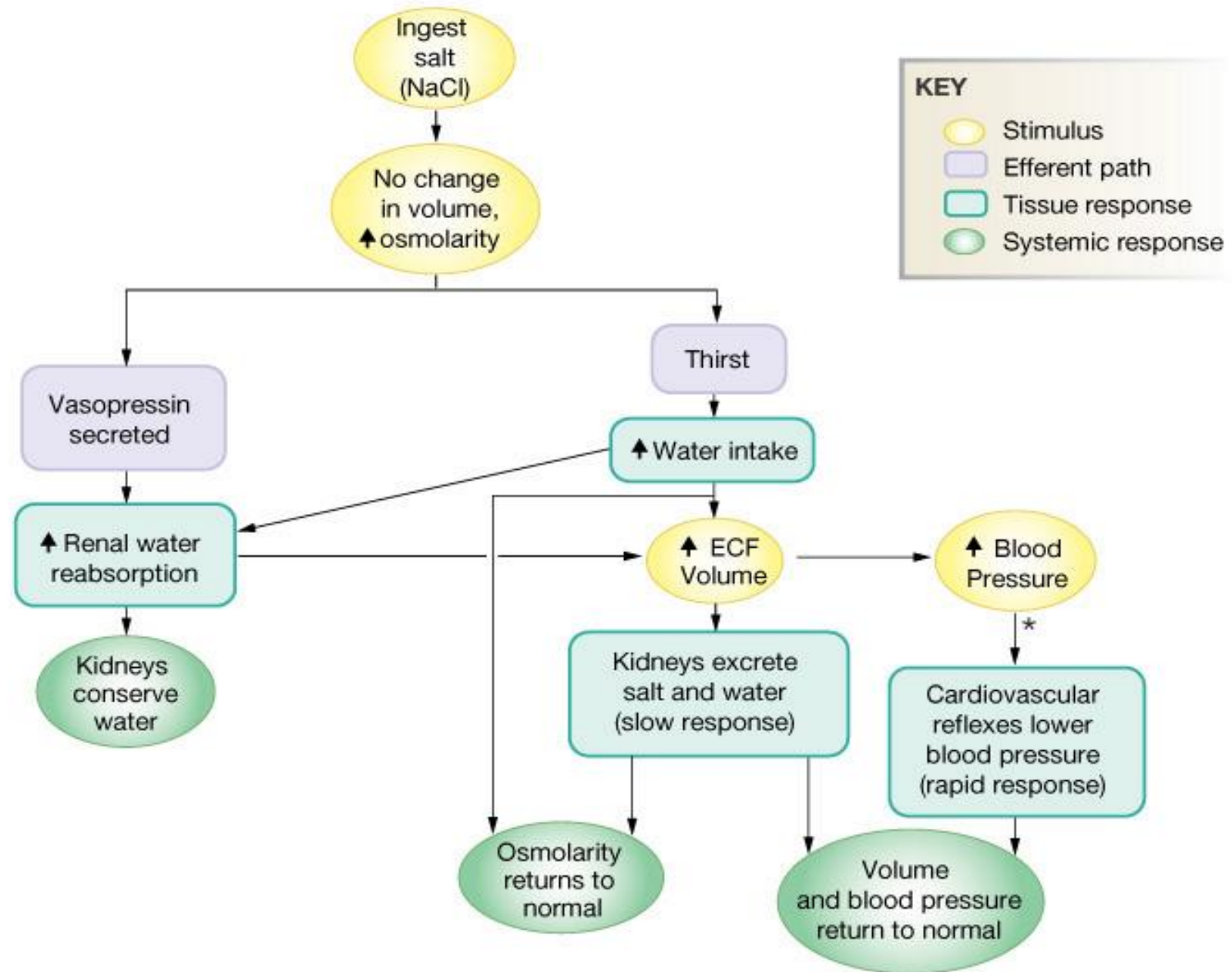
- Hormone from Myocardial cells
- Stimulates: Hypothalamus, Kidney
Adrenal, & medulla

Atrial Natriuretic Peptide: ANP

Regulates Na^+ & H_2O Excretion



Sodium Balance: Intake & Excretion



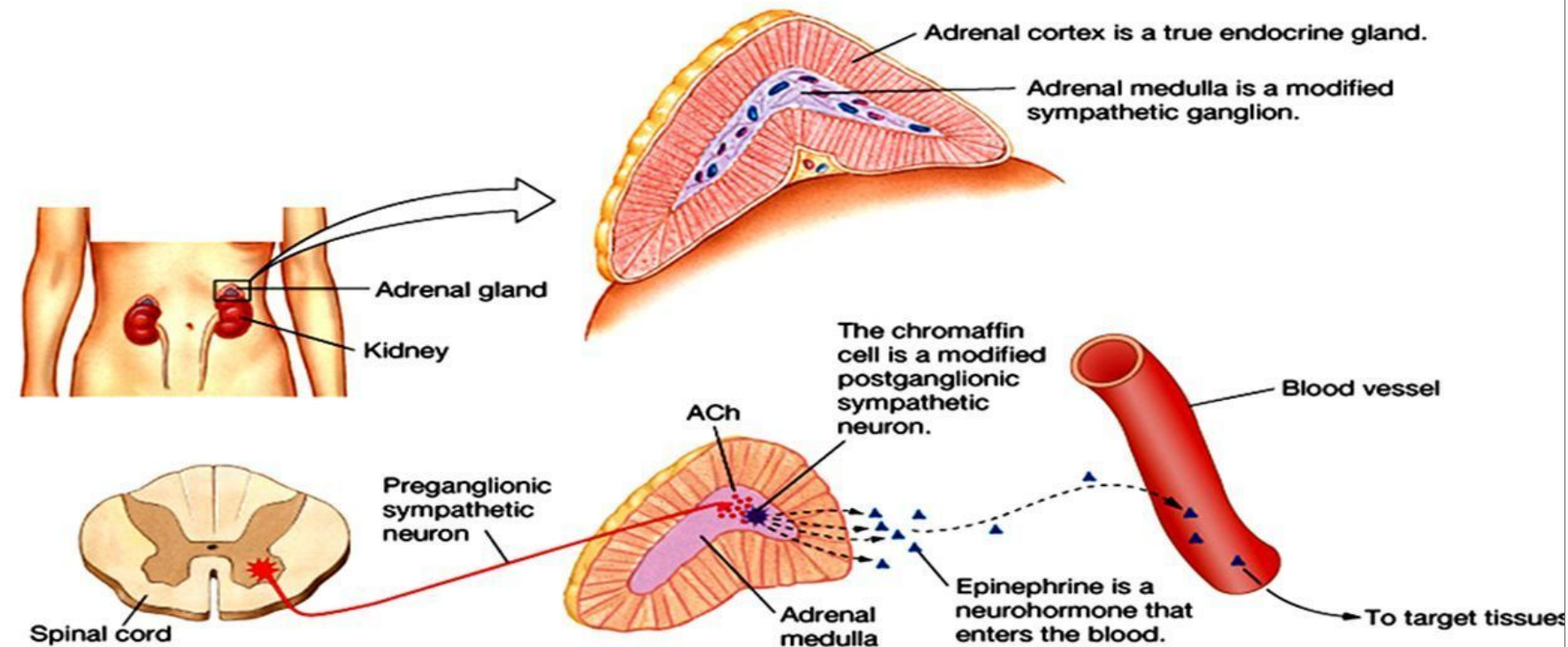
Gonadocorticoids (Sex Hormones)

- Most gonadocorticoids secreted are androgens (male sex hormones), and the most important one is testosterone
- Androgens contribute to:
 - The onset of puberty
 - The appearance of secondary sex characteristics
 - Sex drive in females
- Androgens can be converted into estrogens after menopause

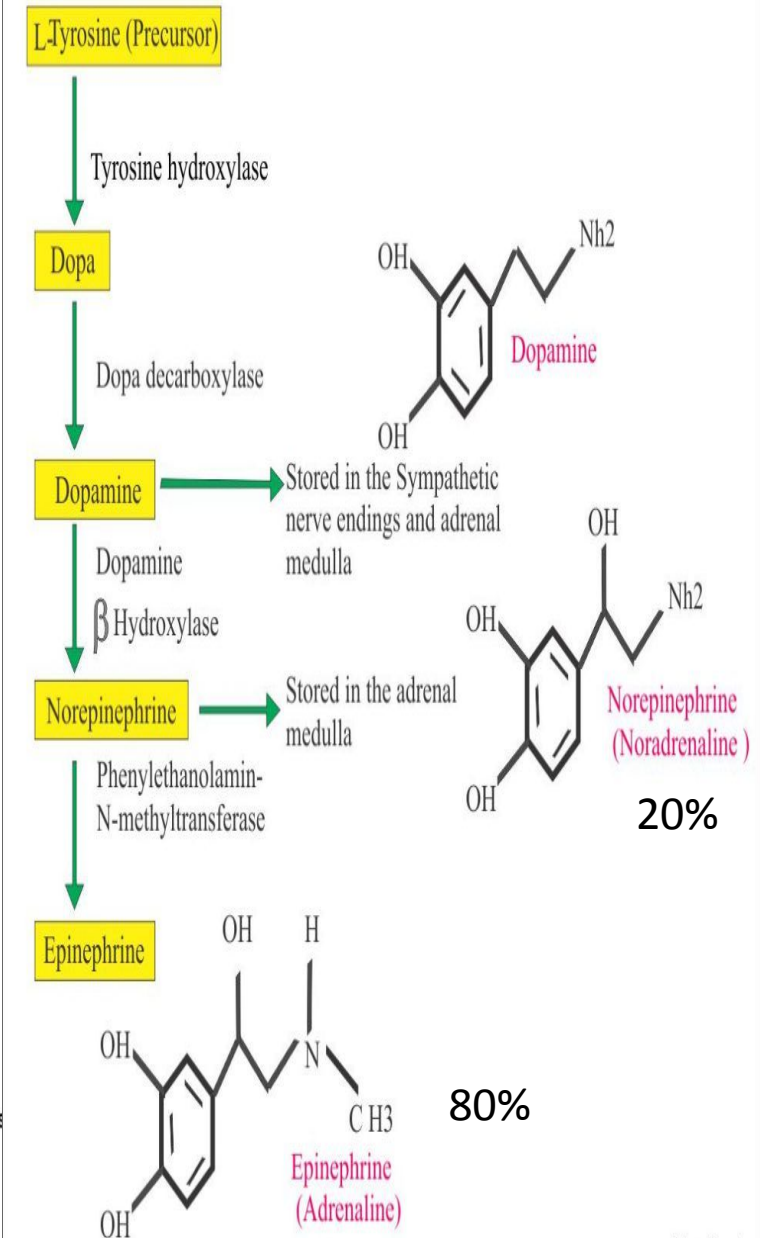
Adrenal Medulla

- Made up of chromaffin cells that secrete epinephrine and norepinephrine
- Secretion of these hormones causes:
 - Blood glucose levels to rise
 - Blood vessels to constrict
 - The heart to beat faster
 - Blood to be diverted to the brain, heart, and skeletal muscle
- Epinephrine is the more potent stimulator of the heart and metabolic activities
- Norepinephrine is more influential on peripheral vasoconstriction and blood pressure

- Its secretions are derived from tyrosine :
- Tyrosine $\longrightarrow$ Dopamine $\longrightarrow$ Norepinephrine $\longrightarrow$ Epinephrine
- Phenylethanolamine N-methyltransferase (PNMT) is an enzyme found in the adrenal medulla that converts norepinephrine (noradrenaline) to epinephrine (adrenaline).



Catecholamines



Classification of Adrenergic Hormone Receptors

Receptor	Agonists	Second Messenger	G protein
α_1 (α_1)	NE > E	IP ₃ /Ca ²⁺ ; DAG	G _q
α_2 (α_2)	E > NE	↓ cyclic AMP	G _i
β_1 (β_1)	E = NE	↑ cyclic AMP	G _s
β_2 (β_2)	E >> NE	↑ cyclic AMP	G _s

E = epinephrine; NE = norepinephrine

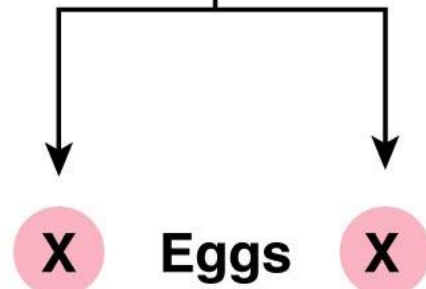
Reproduction Hormones

Reproduction Hormones

- A. Control of sexual differentiation
- B. Hormones affecting **Male** sex organs
- C. Hormones affecting **Female** sex organs
- D. Pregnancy hormones

Female parent

XX



Male parent

XY

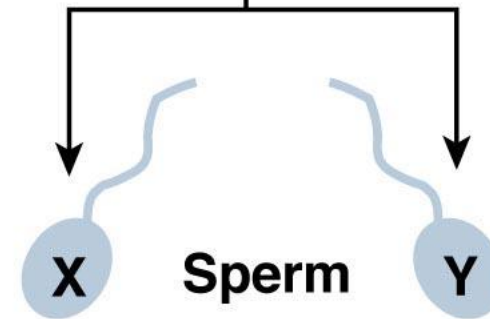
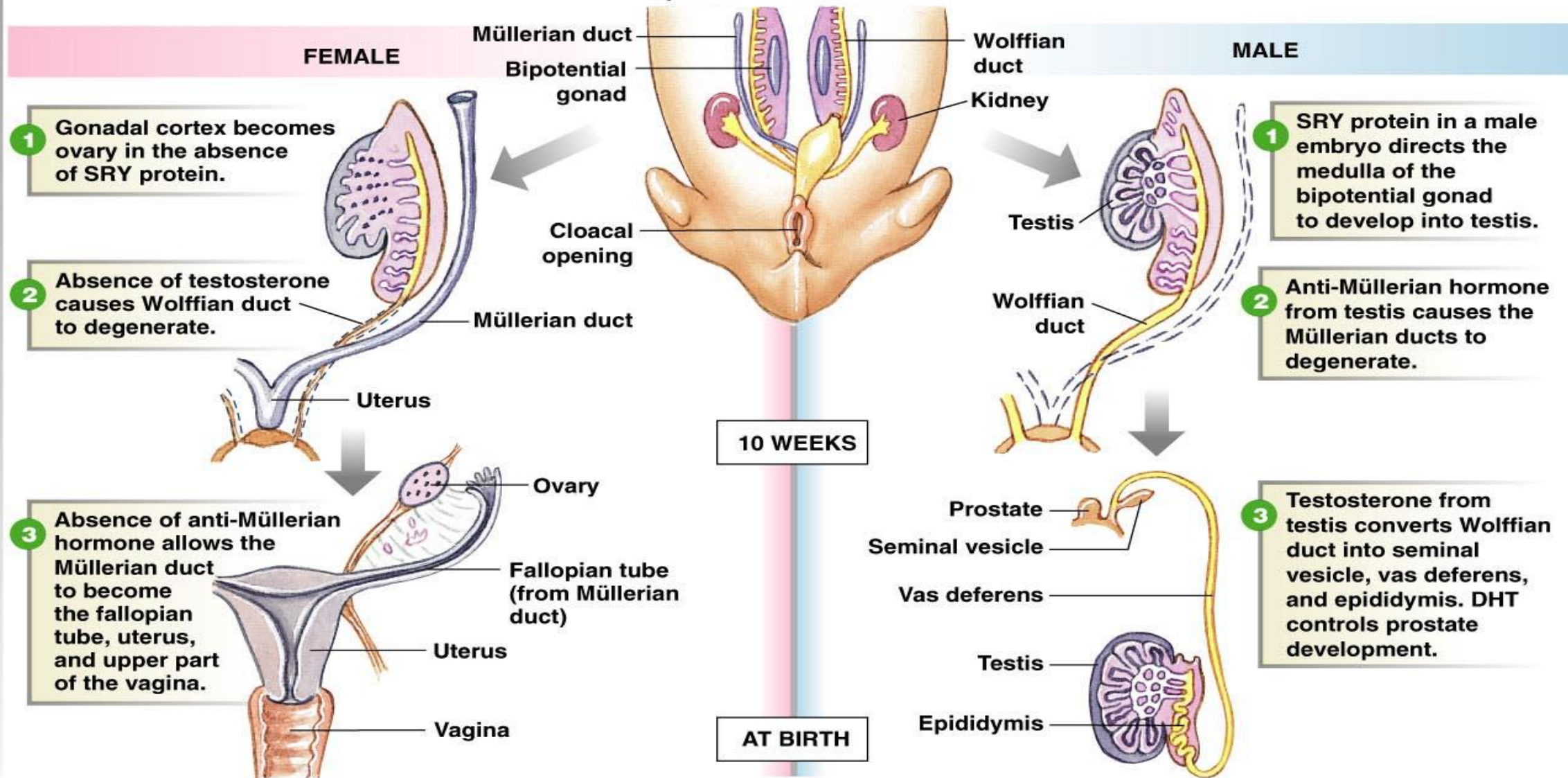


Figure 26-2

(a) Development of internal organs

Bipotential stage: 6 weeks of fetal development

The internal reproductive organs have the potential to develop into male or female structures.



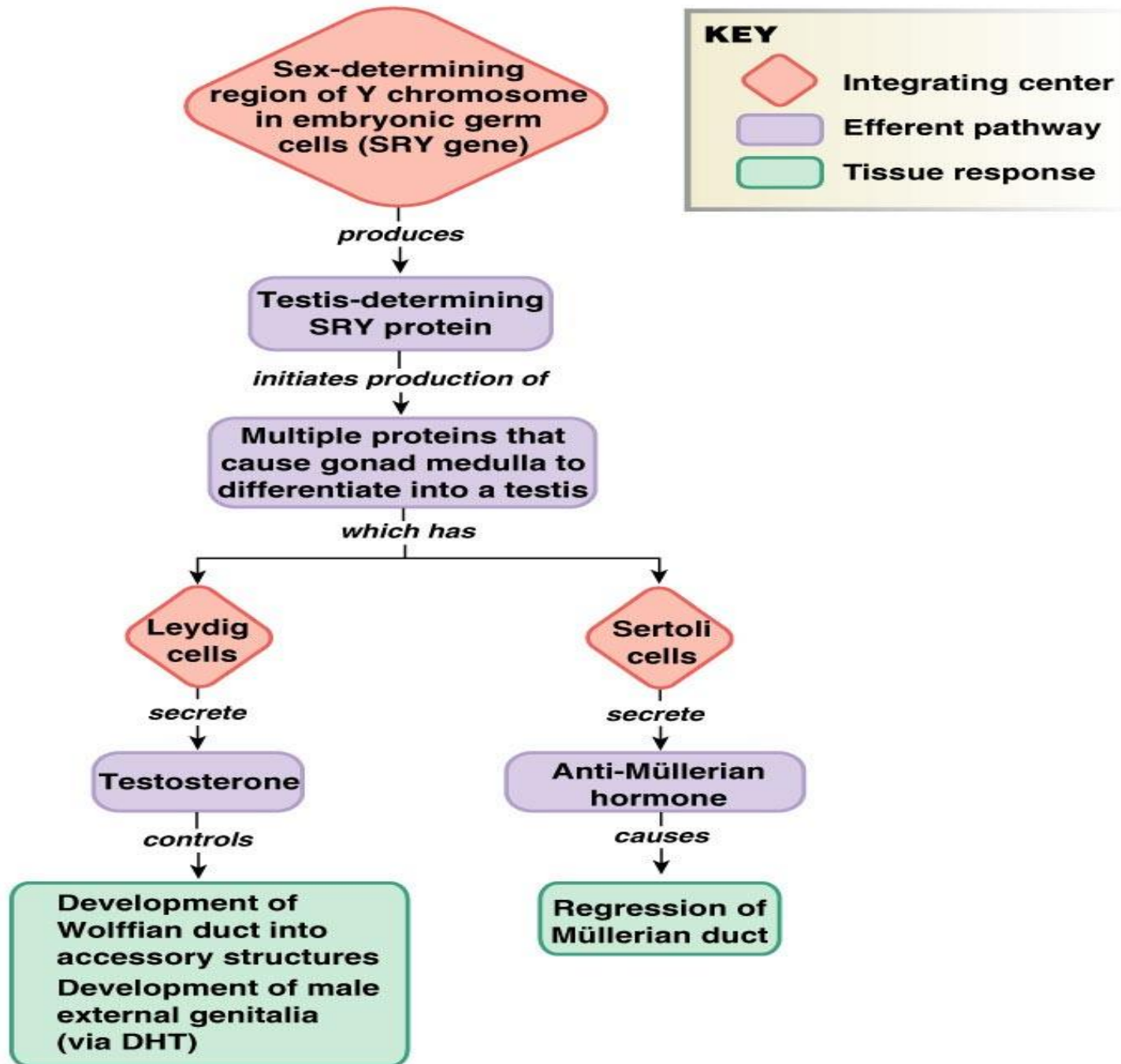
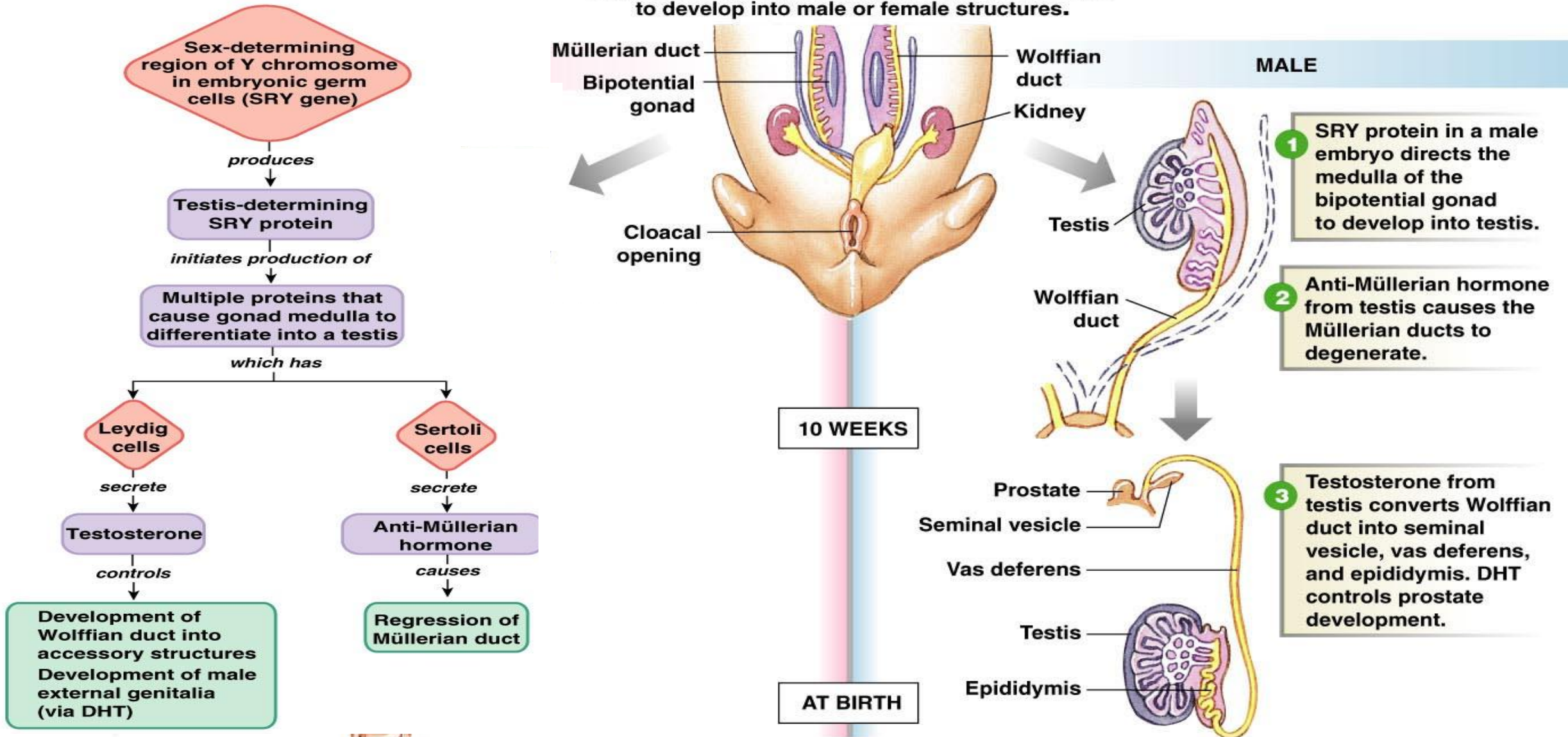


Figure 26-4

(a) Development of internal organs

Bipotential stage: 6 weeks of fetal development

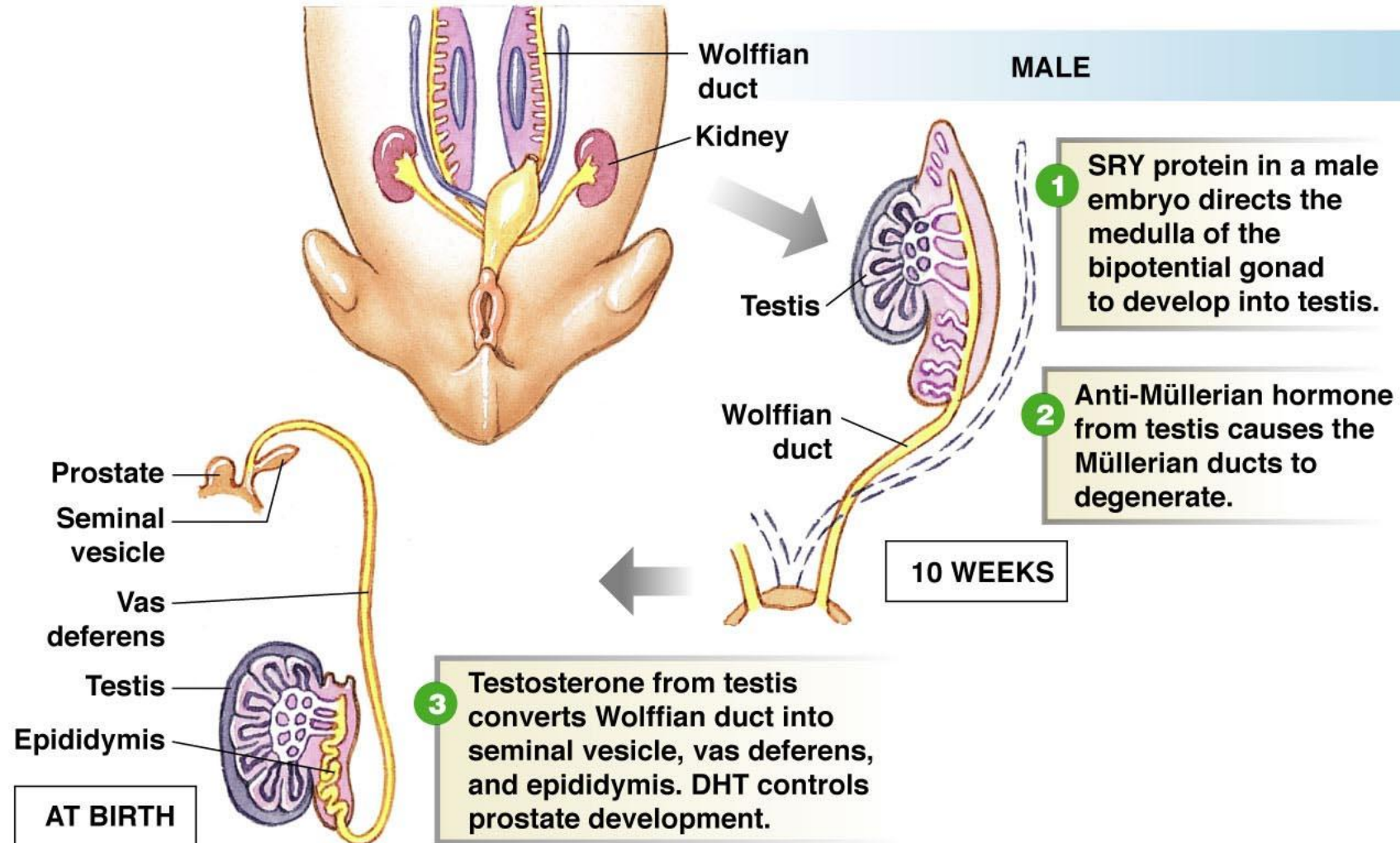
The internal reproductive organs have the potential to develop into male or female structures.



(a) Development of internal organs

Bipotential stage: 6 weeks of fetal development

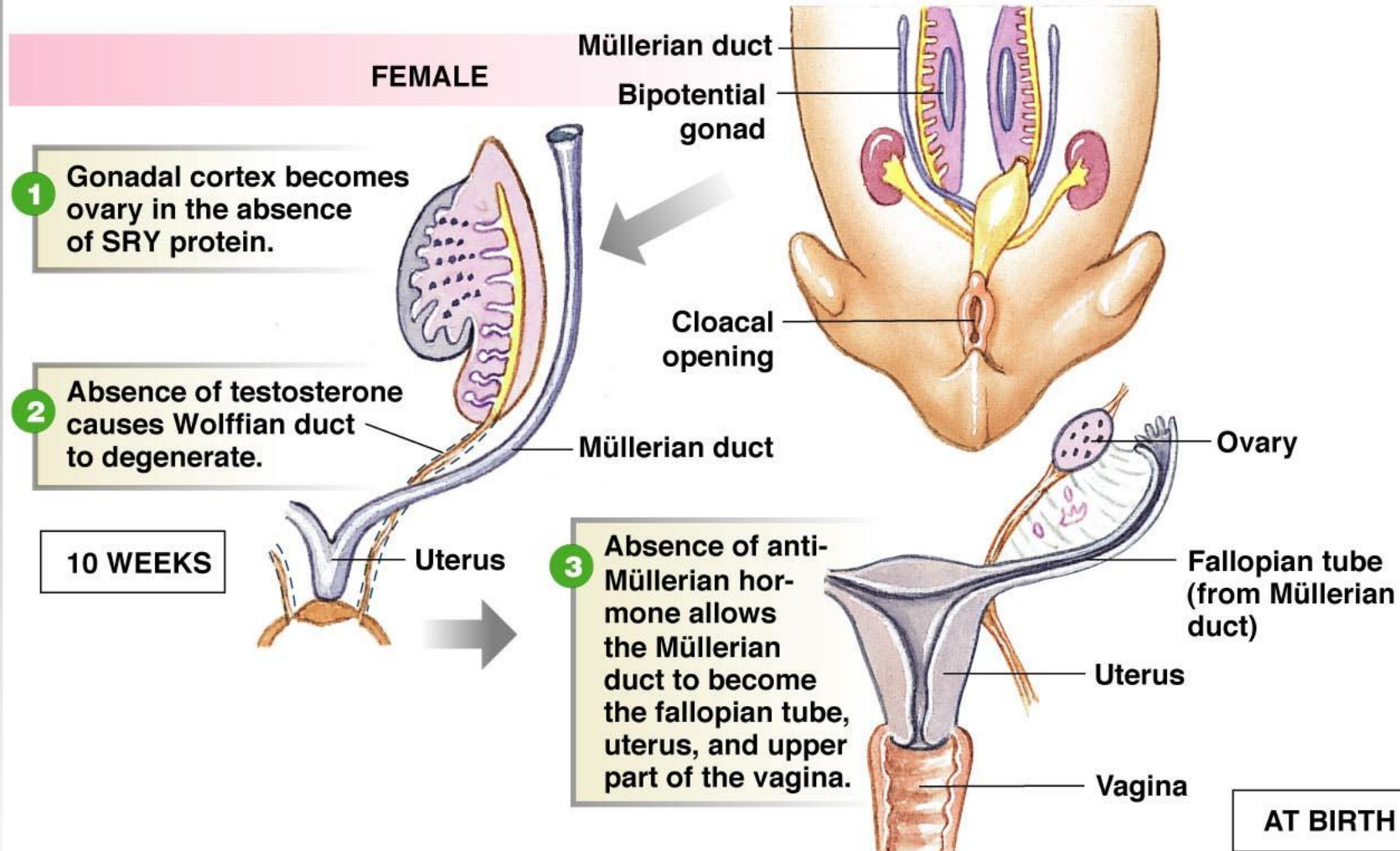
The internal reproductive organs have the potential to develop into male or female structures.



(a) Development of internal organs

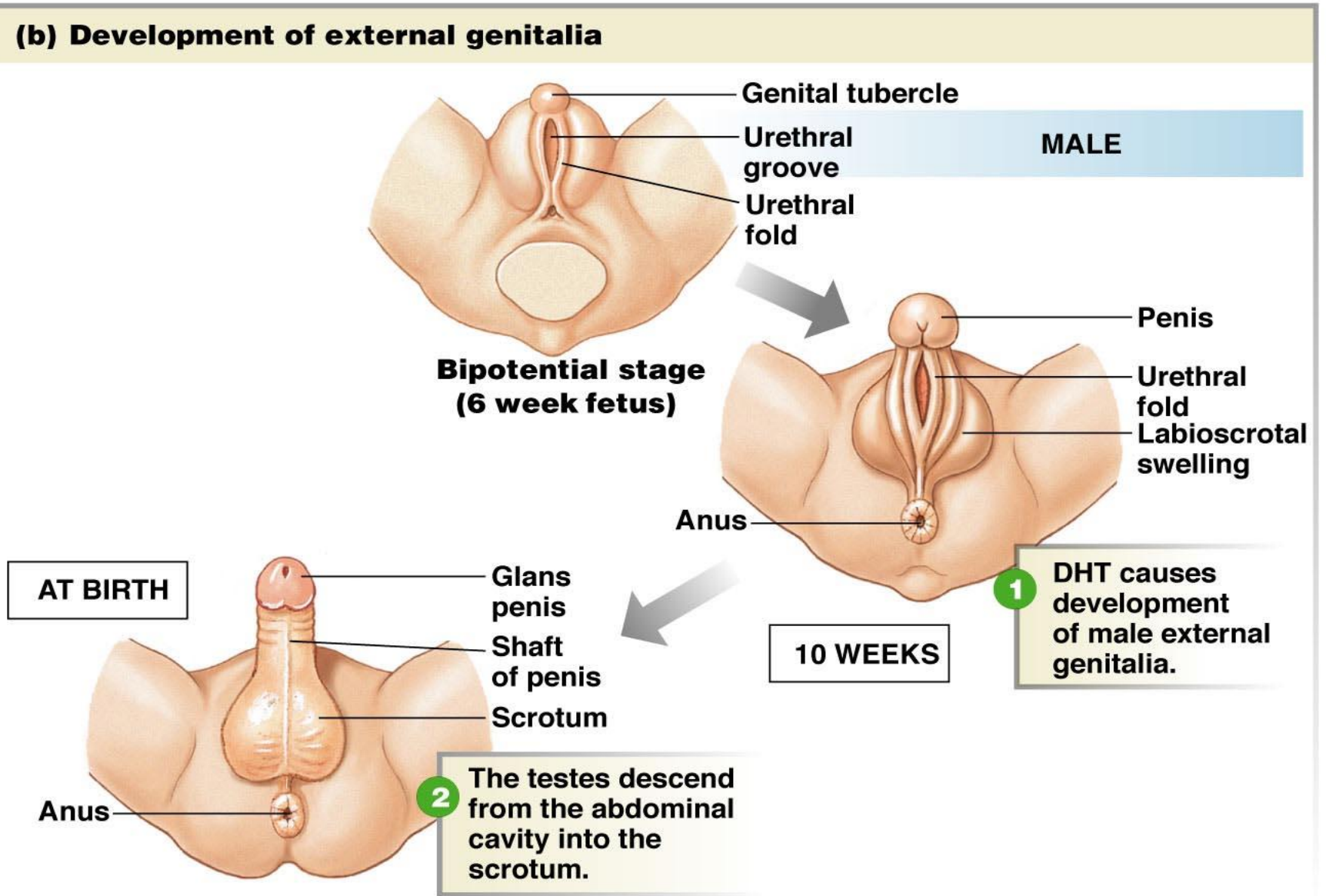
Bipotential stage: 6 weeks of fetal development

The internal reproductive organs have the potential to develop into male or female structures.



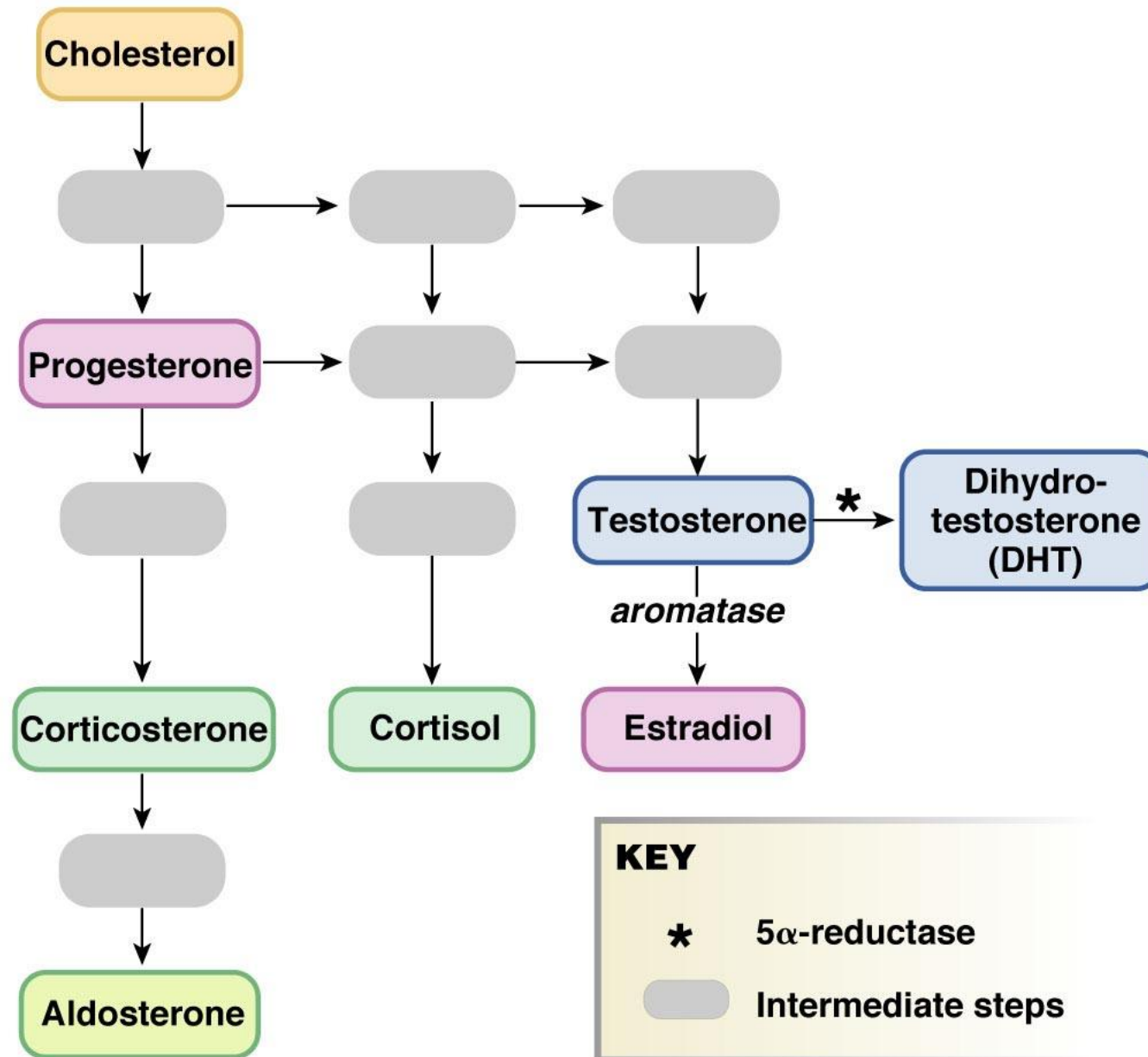
DHT (dihydrotestosterone)

5 alpha reductase

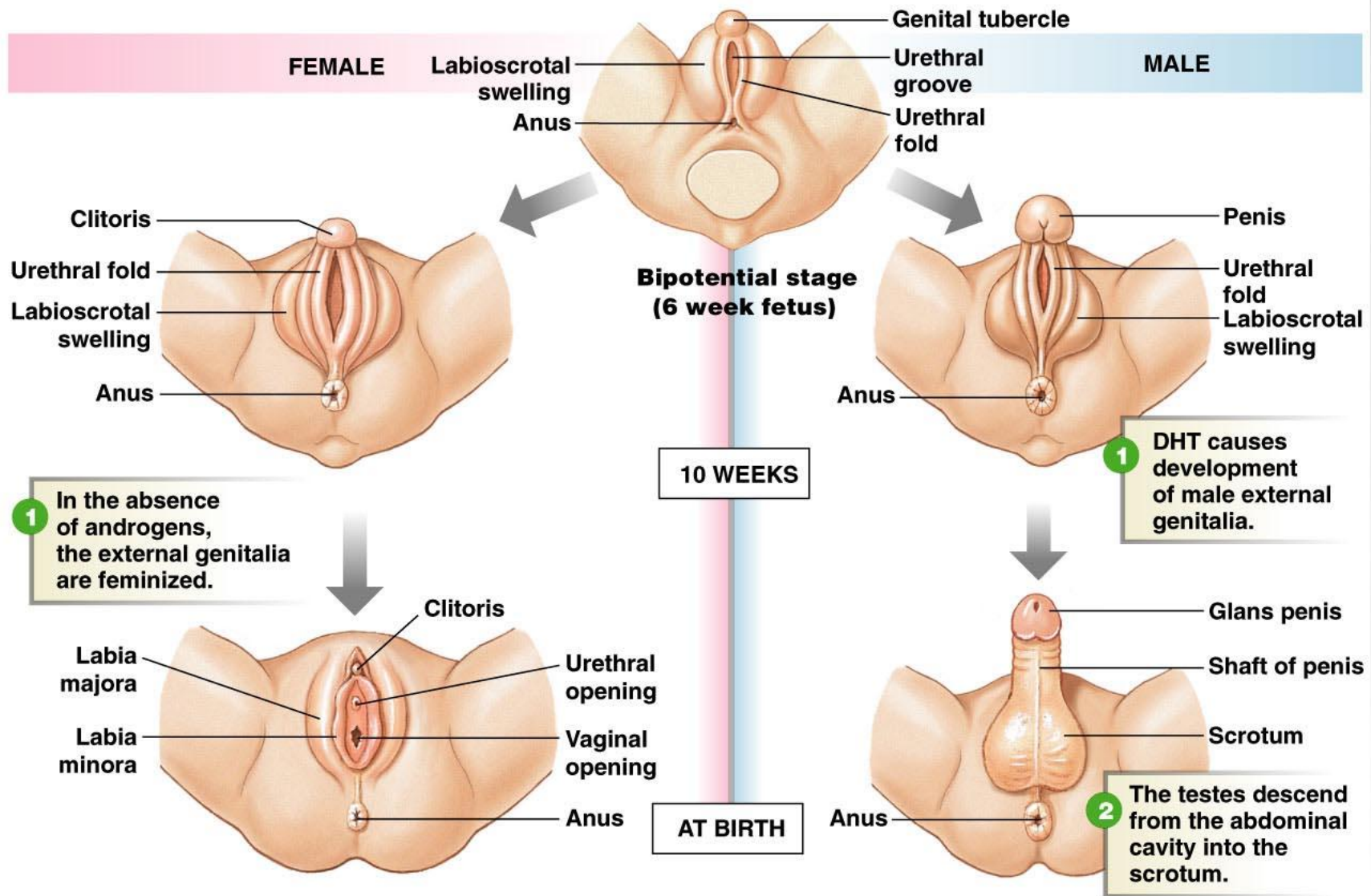


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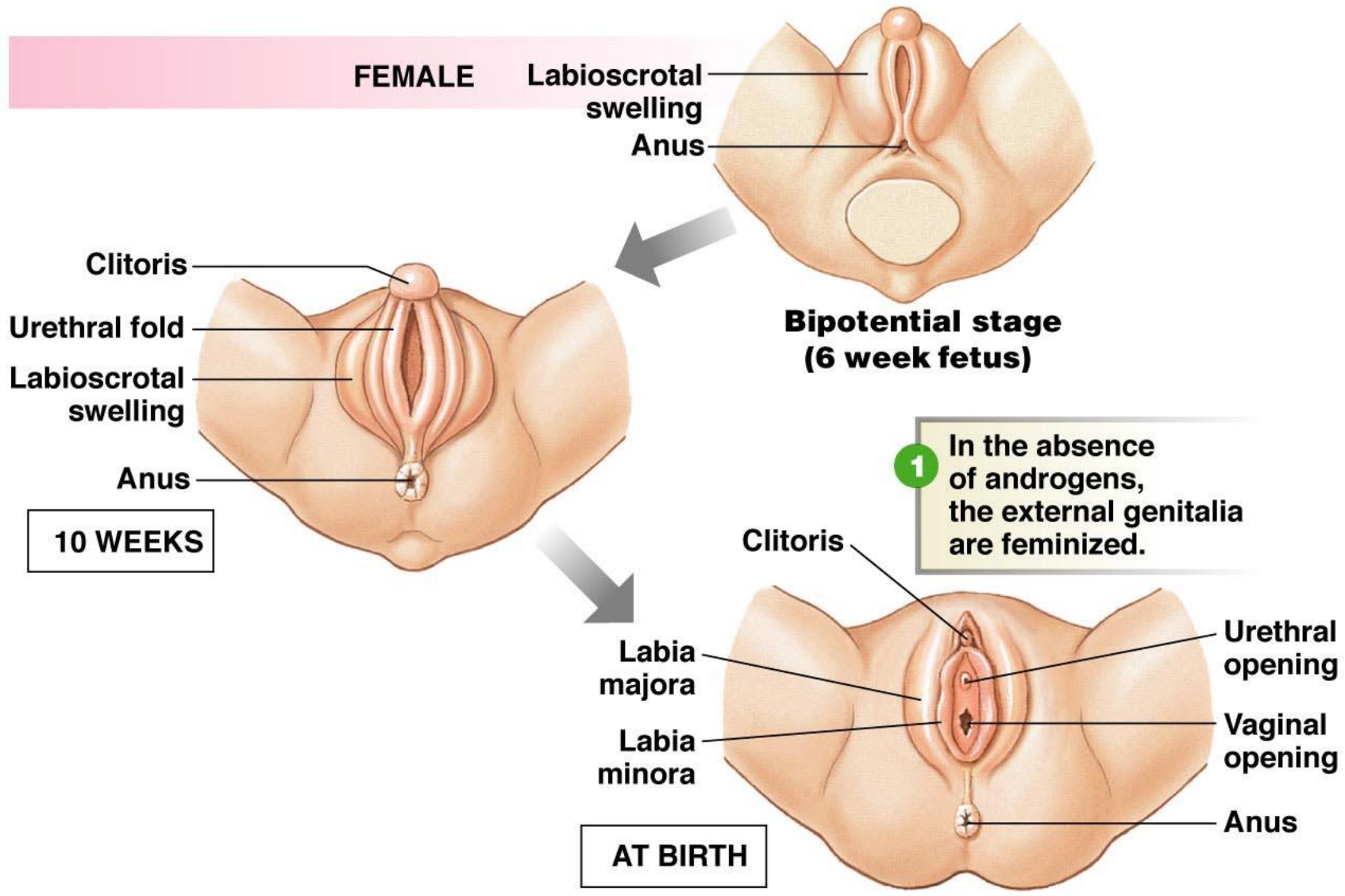
Figure 26-3b (2 of 2)

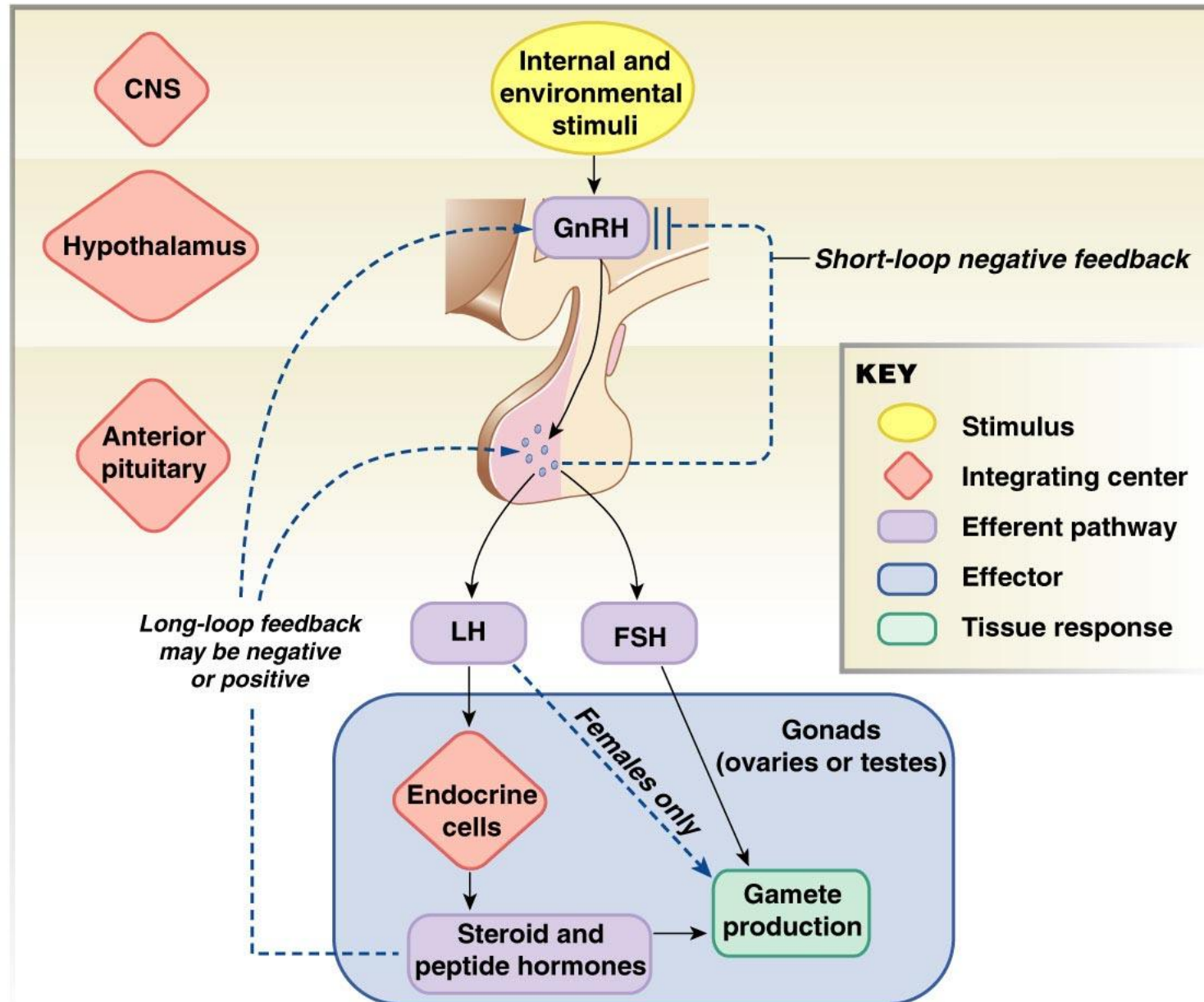


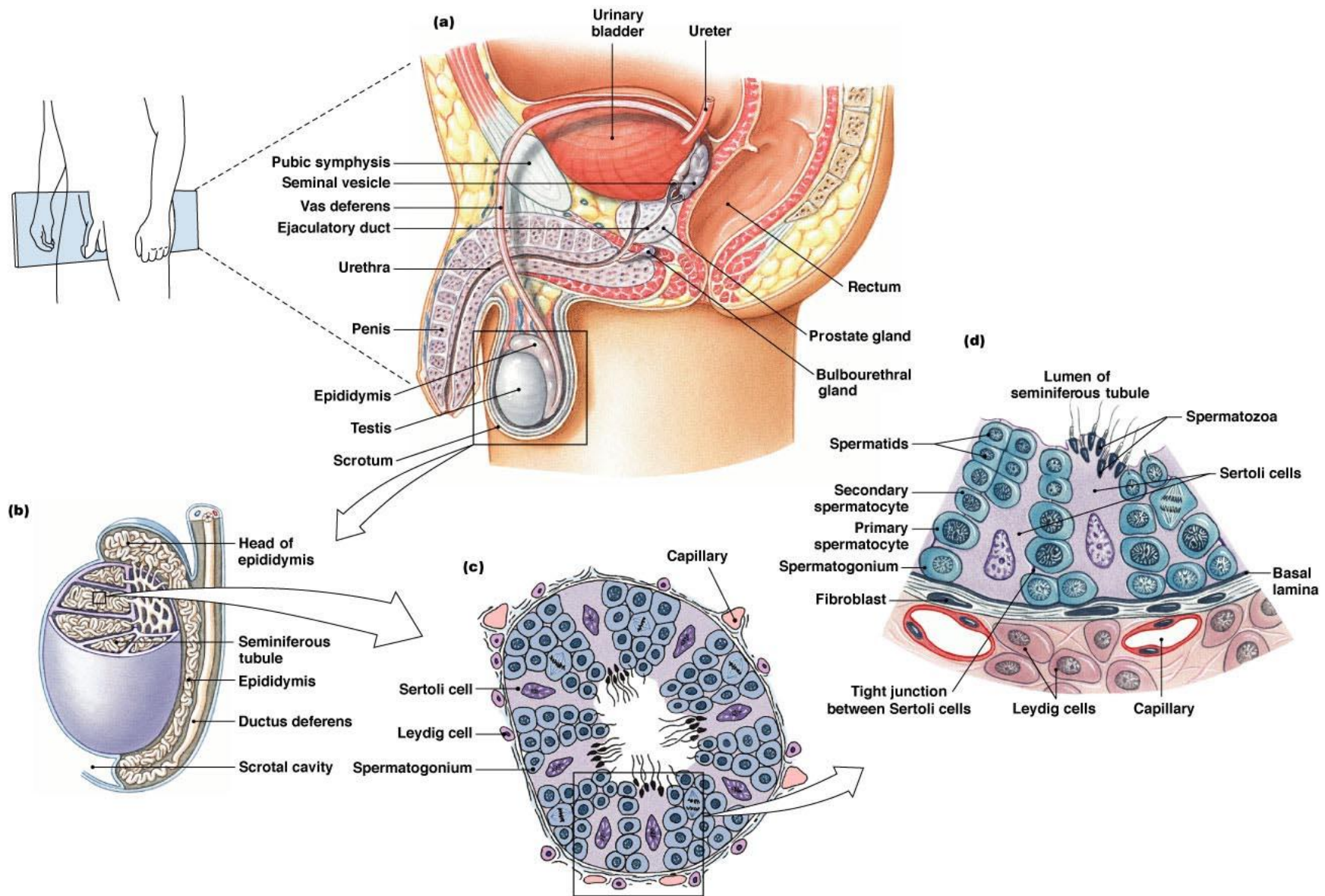
(b) Development of external genitalia



(b) Development of external genitalia

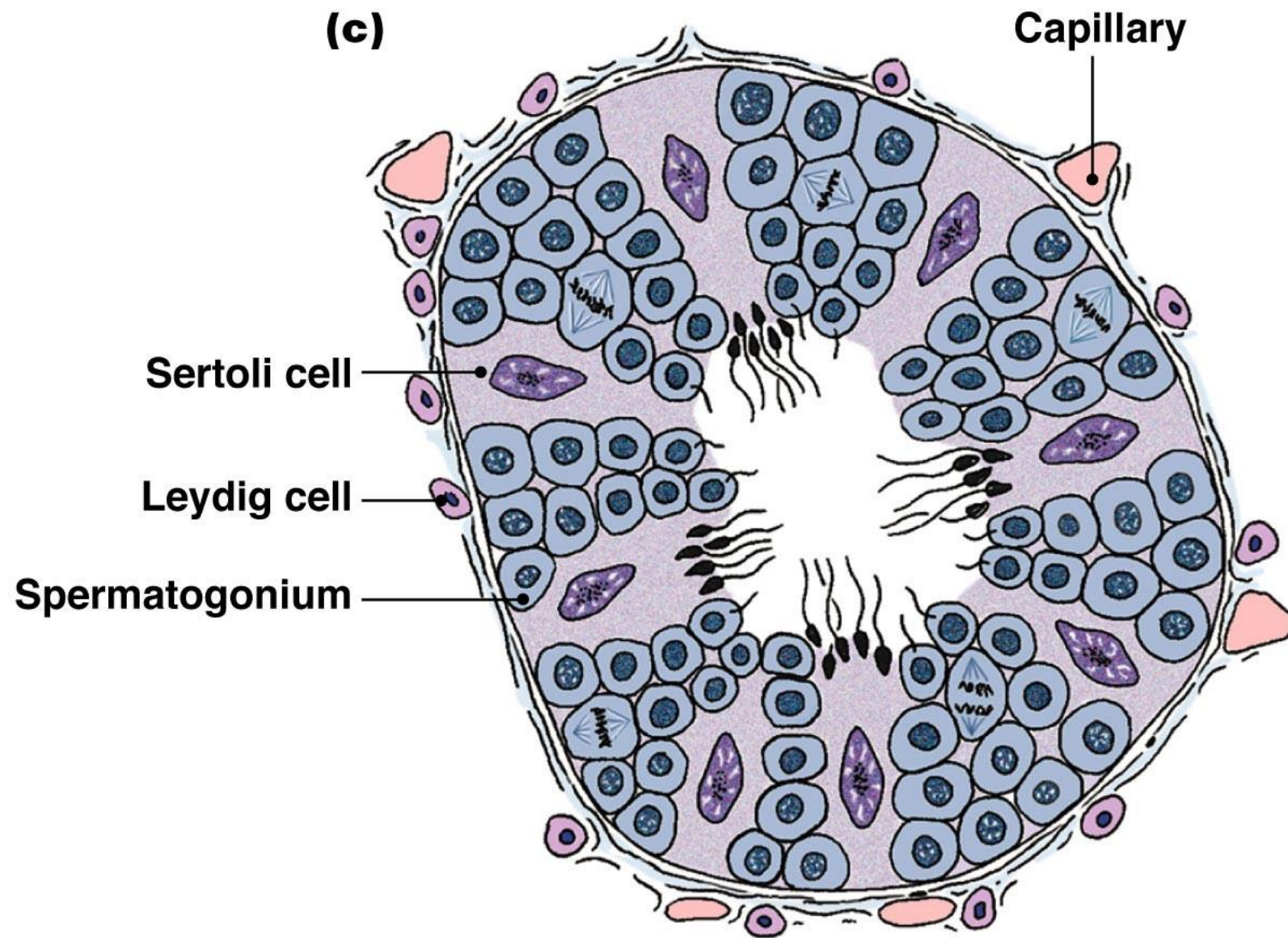




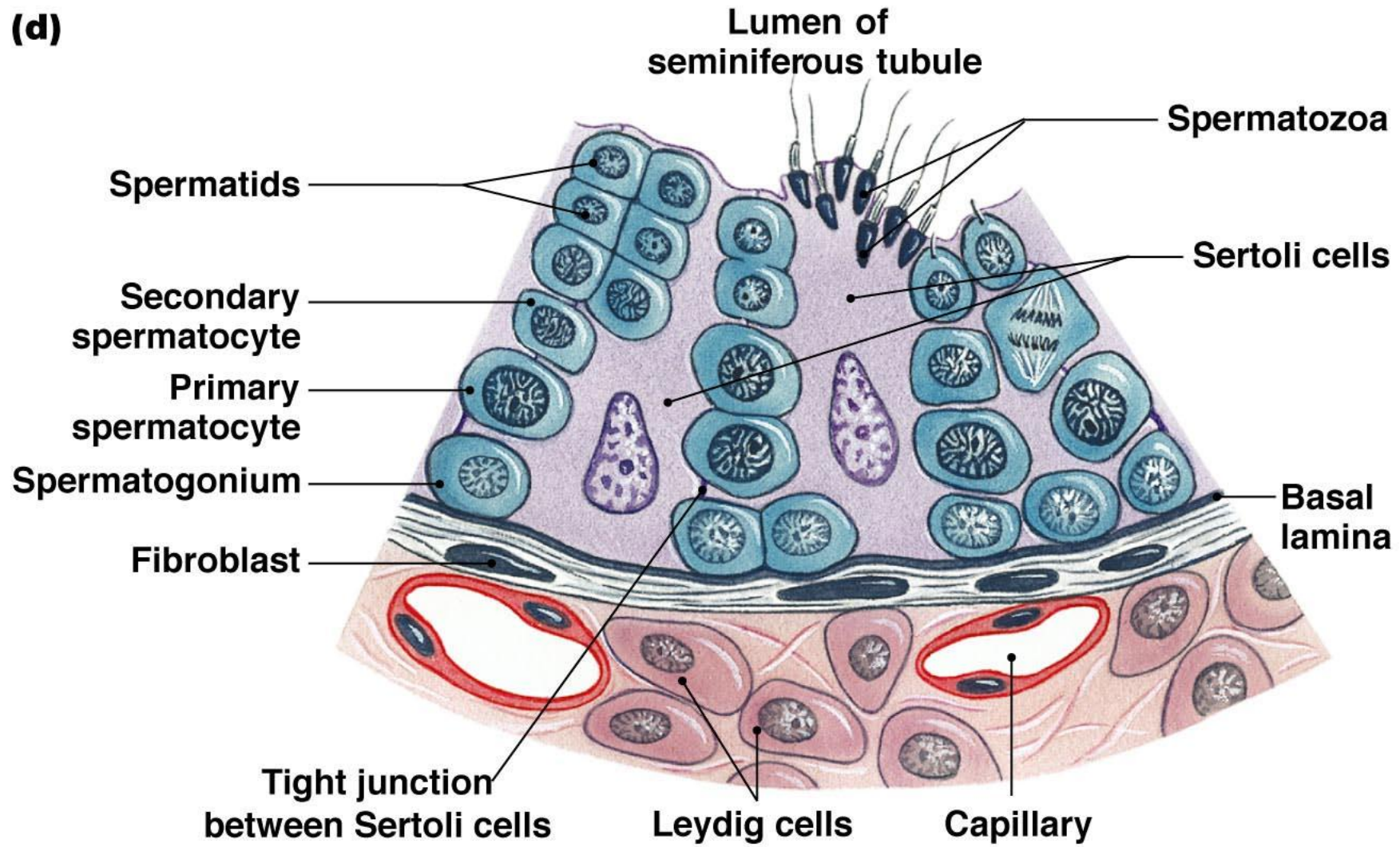


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Figure 26-9 - Overview



(d)

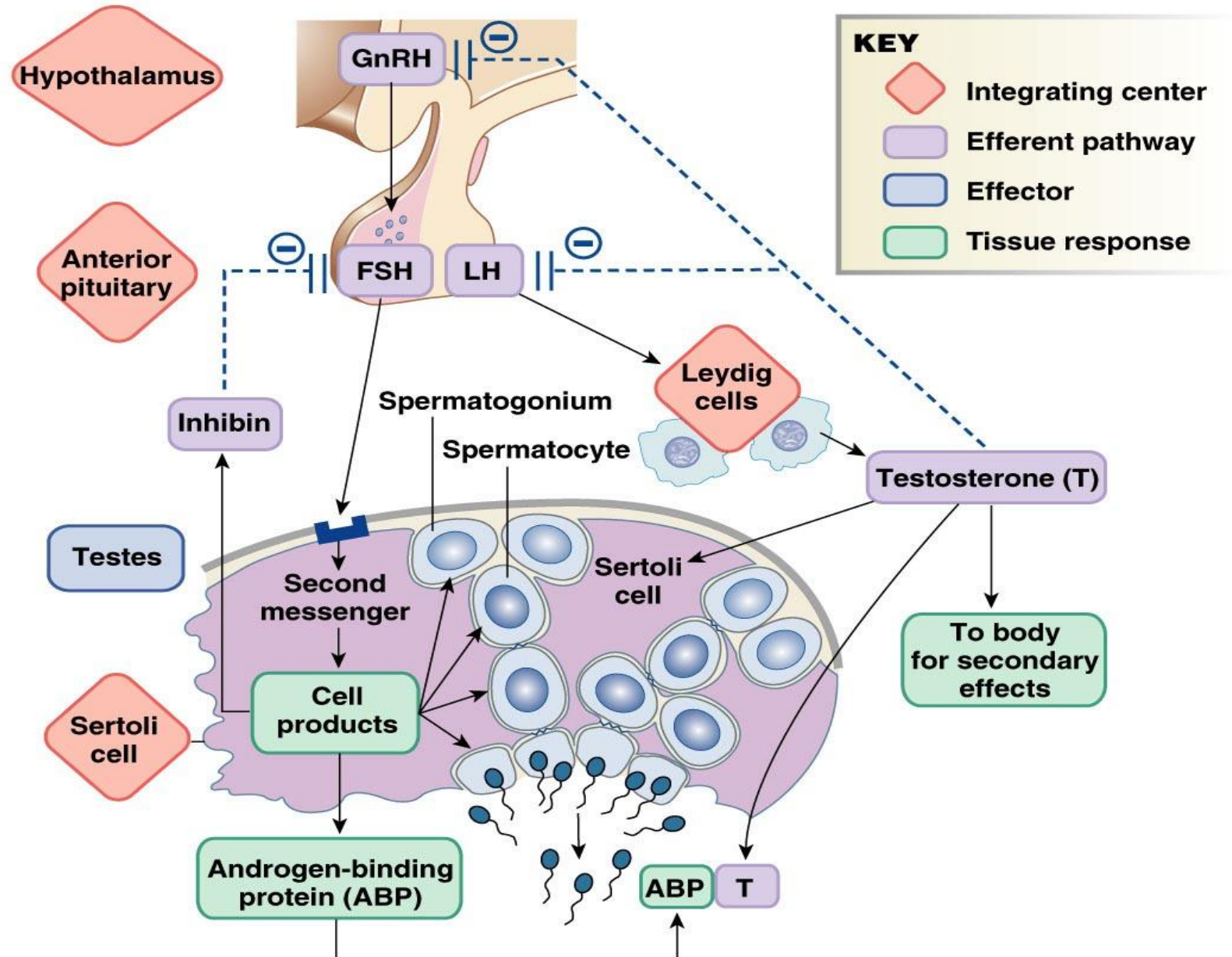


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Figure 26-9d

- Hypothalamus releases GnRH which stimulates

- LH to produce testosterone
- FSH to stimulate sperm cell formation
- Inhibin inhibits FSH secretion from anterior pituitary



Hormonal factors affecting spermatogenesis

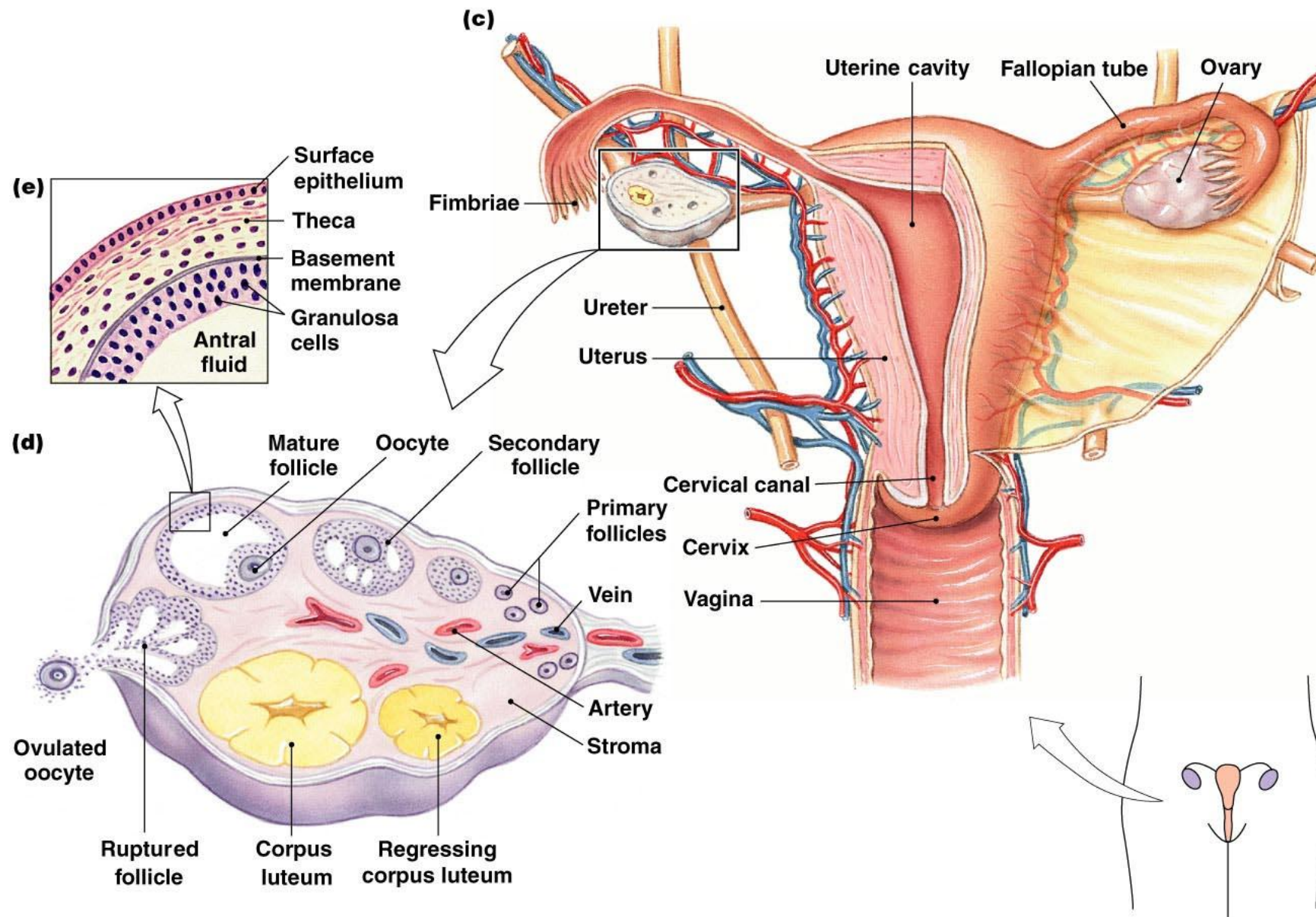
- Testosterone (secreted from Leydig cells in testis): essential for growth and division of germ cells
- LH (Ant. Pituitary gland): stimulate the release of testosterone from Leydig cells
- FSH (Ant. Pituitary gland): stimulate the Sertoli cells, essential for the conversion of spermatids to sperm
- Estrogens (formed by Sertoli cells from testosterone): Sertoli cells secrete androgen binding proteins which bind to estrogen and testosterone and transfer them for **maturation of sperms**
- Growth hormones: essential for metabolic function of the testis and promote early division of spermatogonia

Androgens

- anabolic and/or masculinizing effects in both males and females
- *Testosterone*
 - the most important
 - synthesized mainly by Leydig cells in the testes
 - in smaller amounts by thecal cells in the ovary of the female and by the adrenal gland in both sexes.
 - Other androgens secreted by the testes are 5α -dihydrotestosterone (DHT), androstenedione, and dehydroepiandrosterone (DHEA) in small amounts.
- Secretion controlled by GnRH from the hypothalamus
 - which stimulates the anterior pituitary gland to secrete FSH and LH.
 - LH stimulates testosterone synthesis in the Leydig cells,
 - FSH is necessary for spermatogenesis
 - Testosterone (or its active metabolite, DHT) inhibits production GnRH and FSH/LH by a negative feedback loop

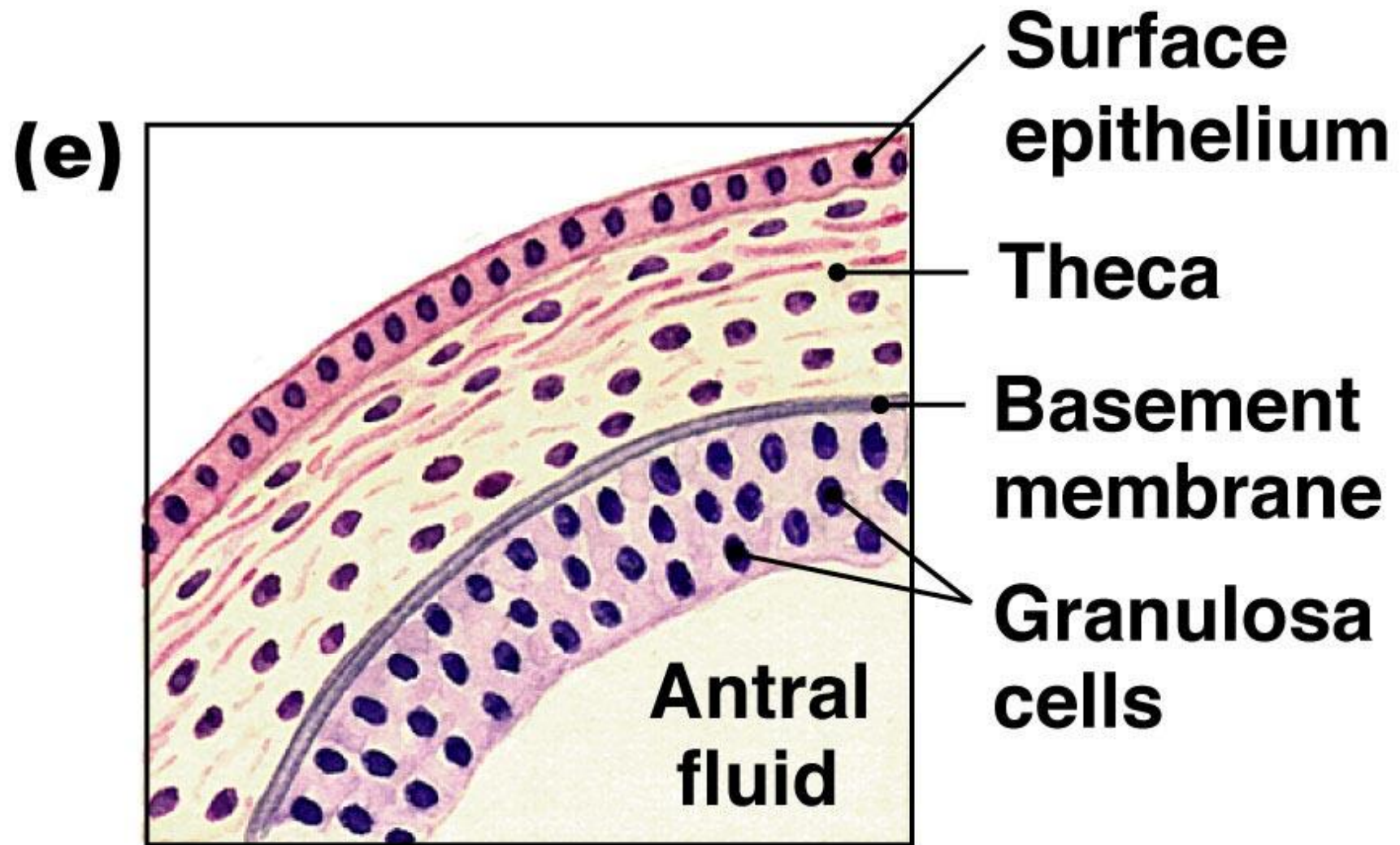
Functions of Androgens

1. Regulation of differentiation of male internal and external genitalia
2. Stimulation of growth development and function of male genitalia
3. Stimulation of sexual hair development
4. Stimulation of bone growth
5. Stimulation of erythropoietin synthesis
6. Stimulation of protein anabolic effects (muscles)
7. Initiation and maintenance of spermatogenesis
8. Stimulation of androgen binding protein synthesis
9. Maintenance of secretion of sex glands
10. Regulation of behavioural effects
11. Growth of larynx



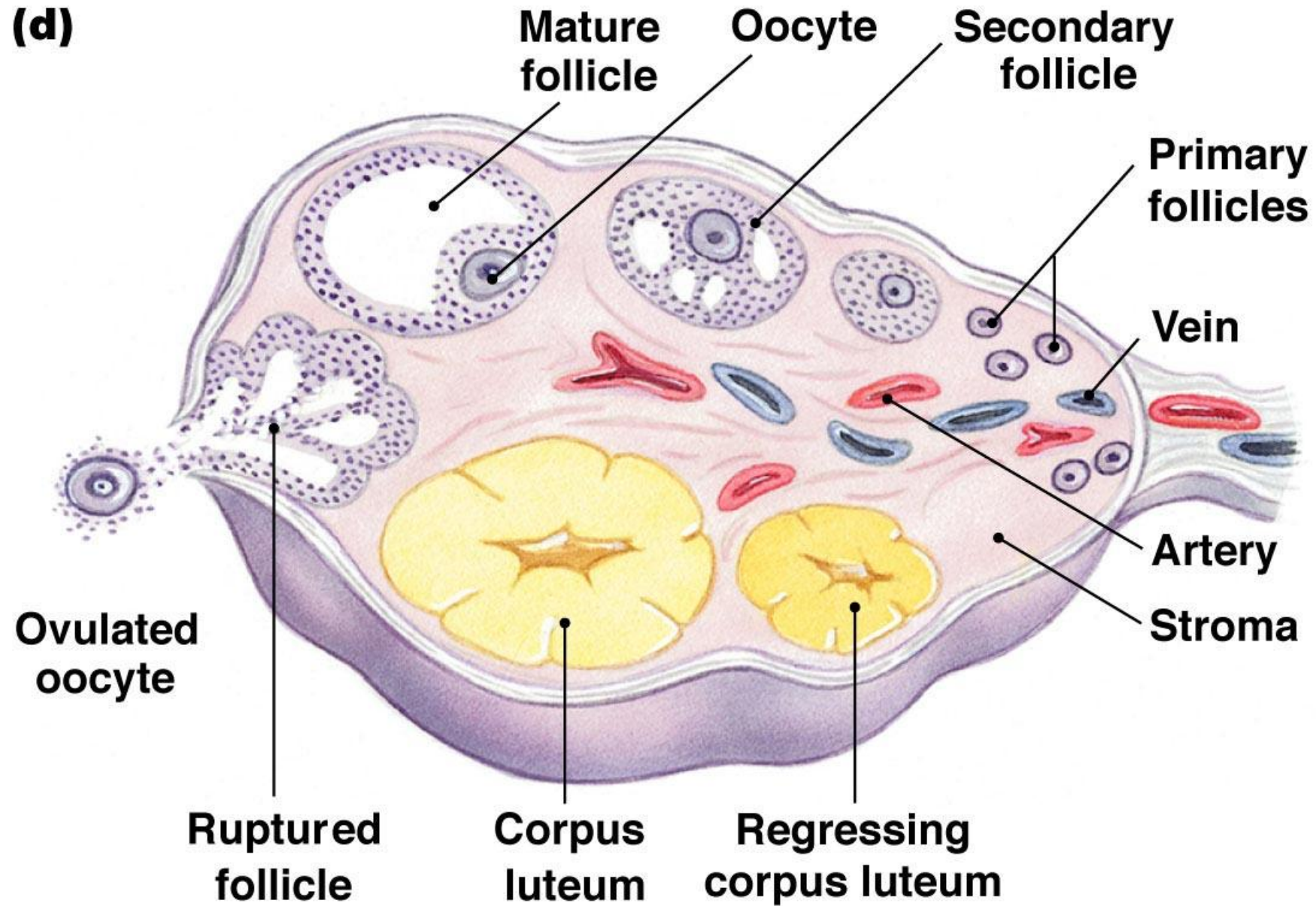
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Figure 26-12c-e



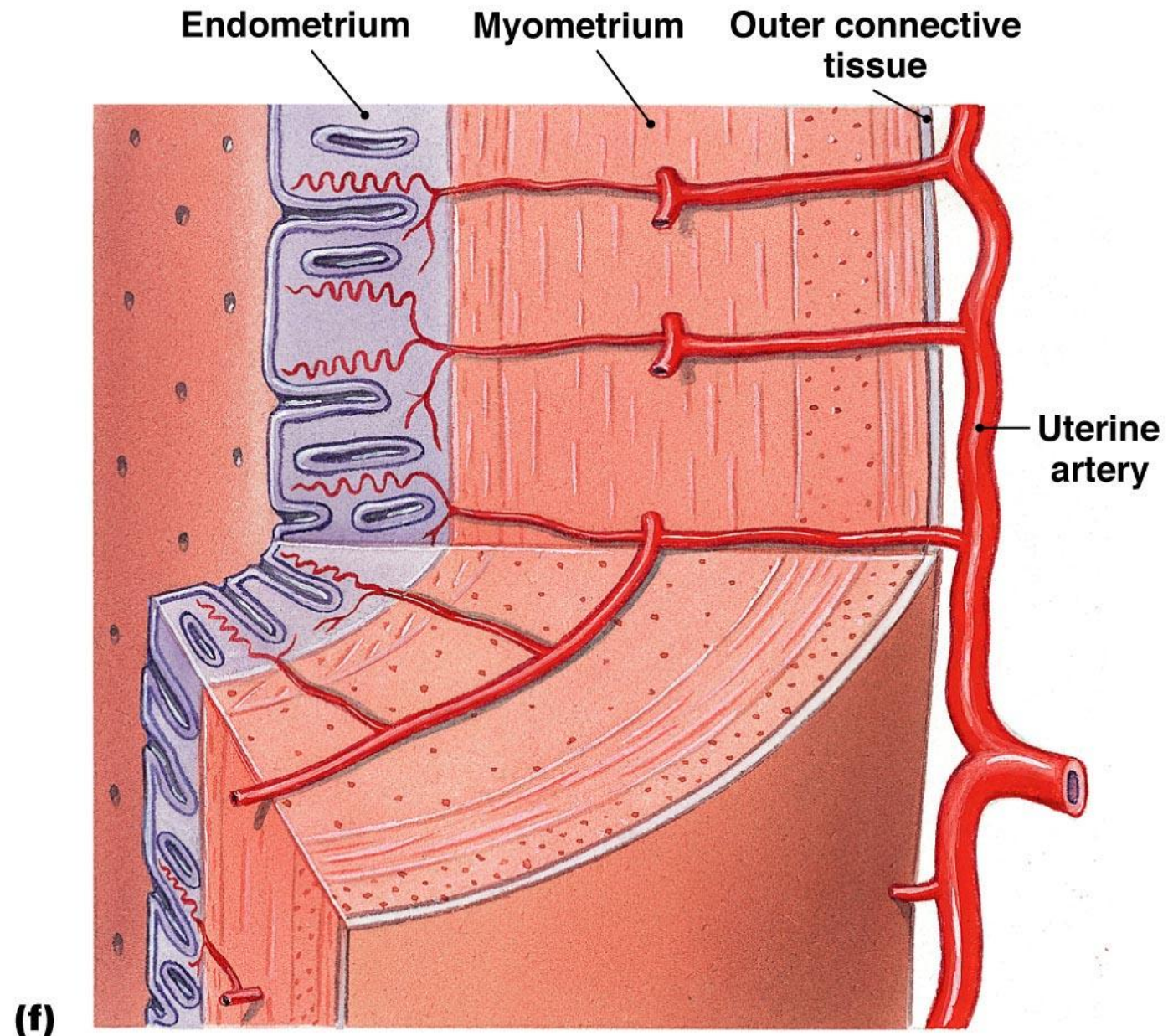
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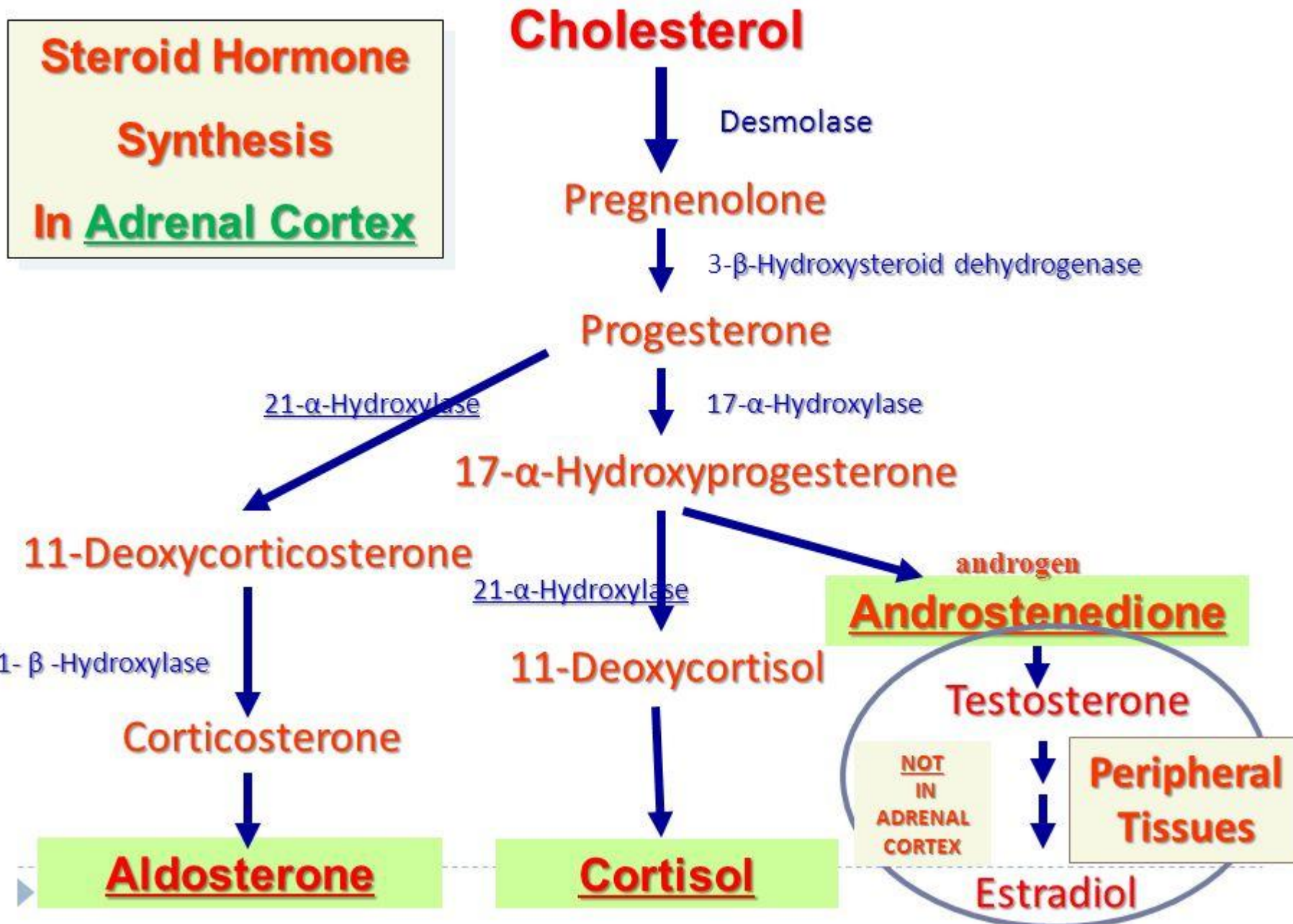
Figure 26-12e



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Figure 26-12d



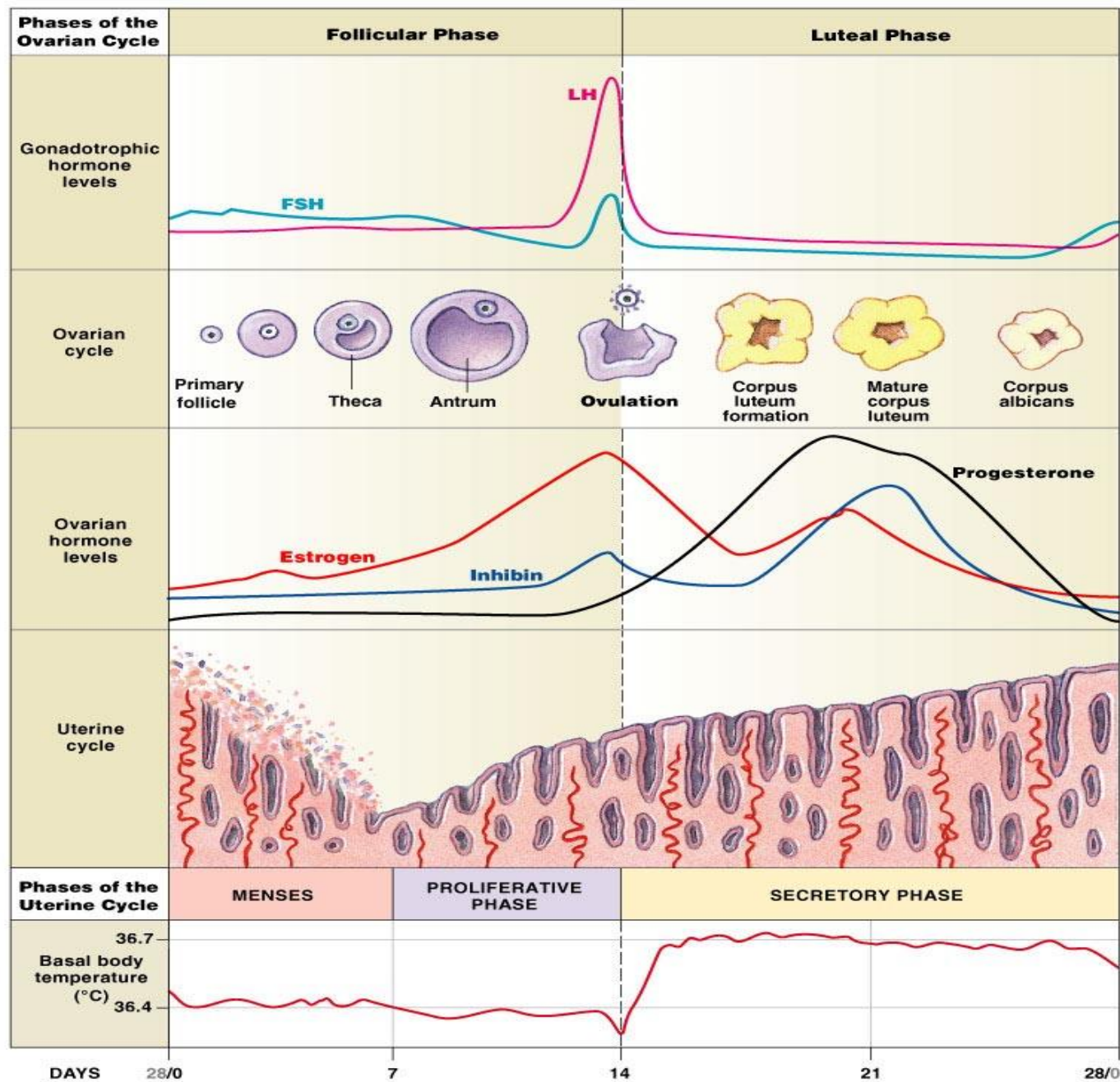


Action of Estrogens

1. Stimulation of growth of uterus, vagina, fallopian tubes
2. Growth of Mammary glands
3. Secretion of thin cervical mucus
4. Stimulation of Follicular growth
5. Stimulation of Granulosa cell-LH receptor formation
6. Stimulation of endometrial proliferation
7. Stimulation of bone growth
8. Delay of bone loss during menopause
9. Increase progesterone receptor
10. Decrease serum cholesterol and glucose tolerance
11. Increase high density lipoprotein
12. Increase production of clotting factors
13. Increase Thyroxin binding globulin

TABLE 26-2 **Effects of Sex Steroids
on Gonadotropin Release**

STEROID HORMONE	EFFECT	GONADOTROPIN LEVEL
Low estrogen or androgen	Absence of negative feedback	Increases
Moderate estrogen or androgen	Negative feedback	Decreases
High androgen	Negative feedback	Decreases
Sustained high estrogen	Positive feedback	Increases



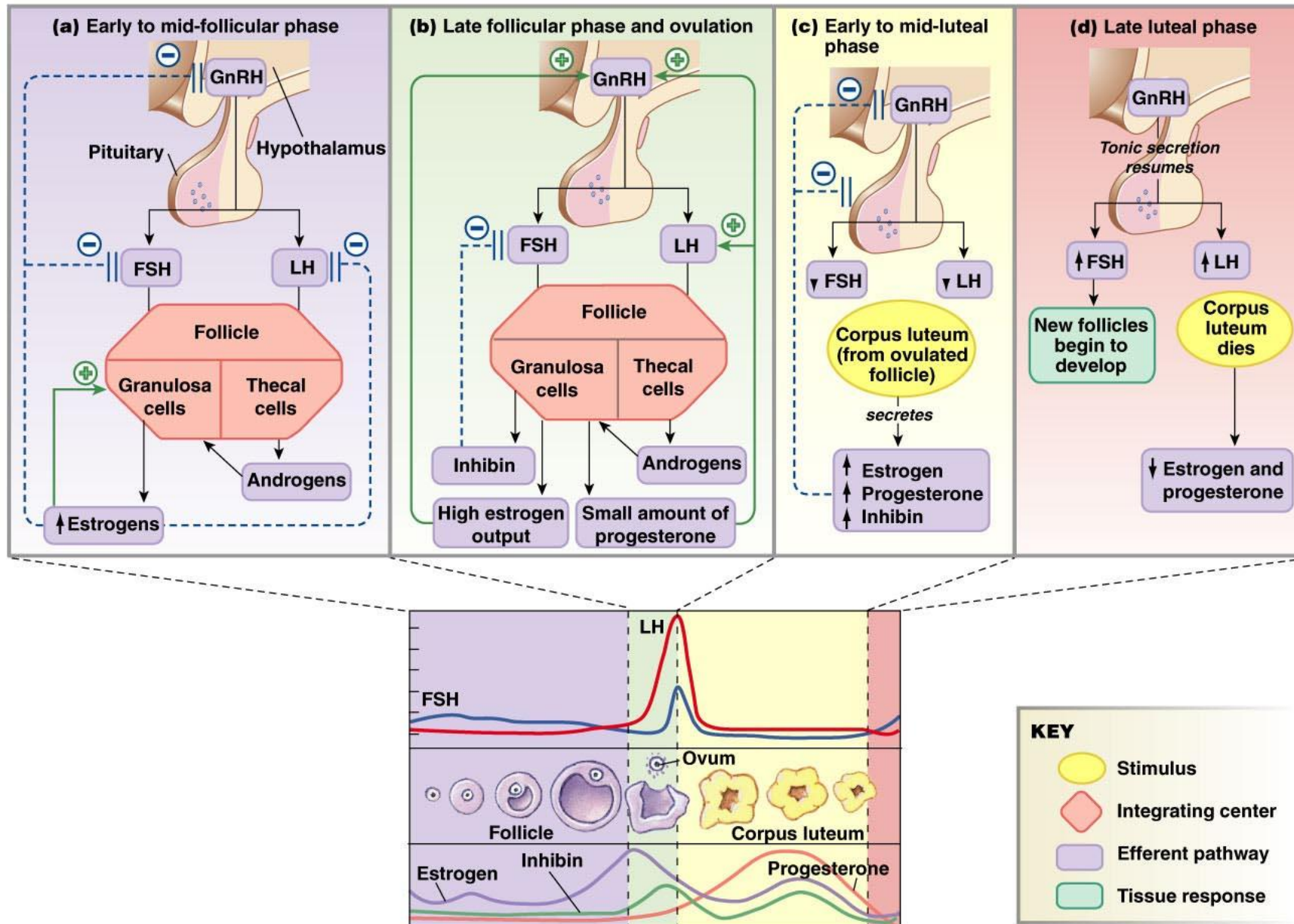
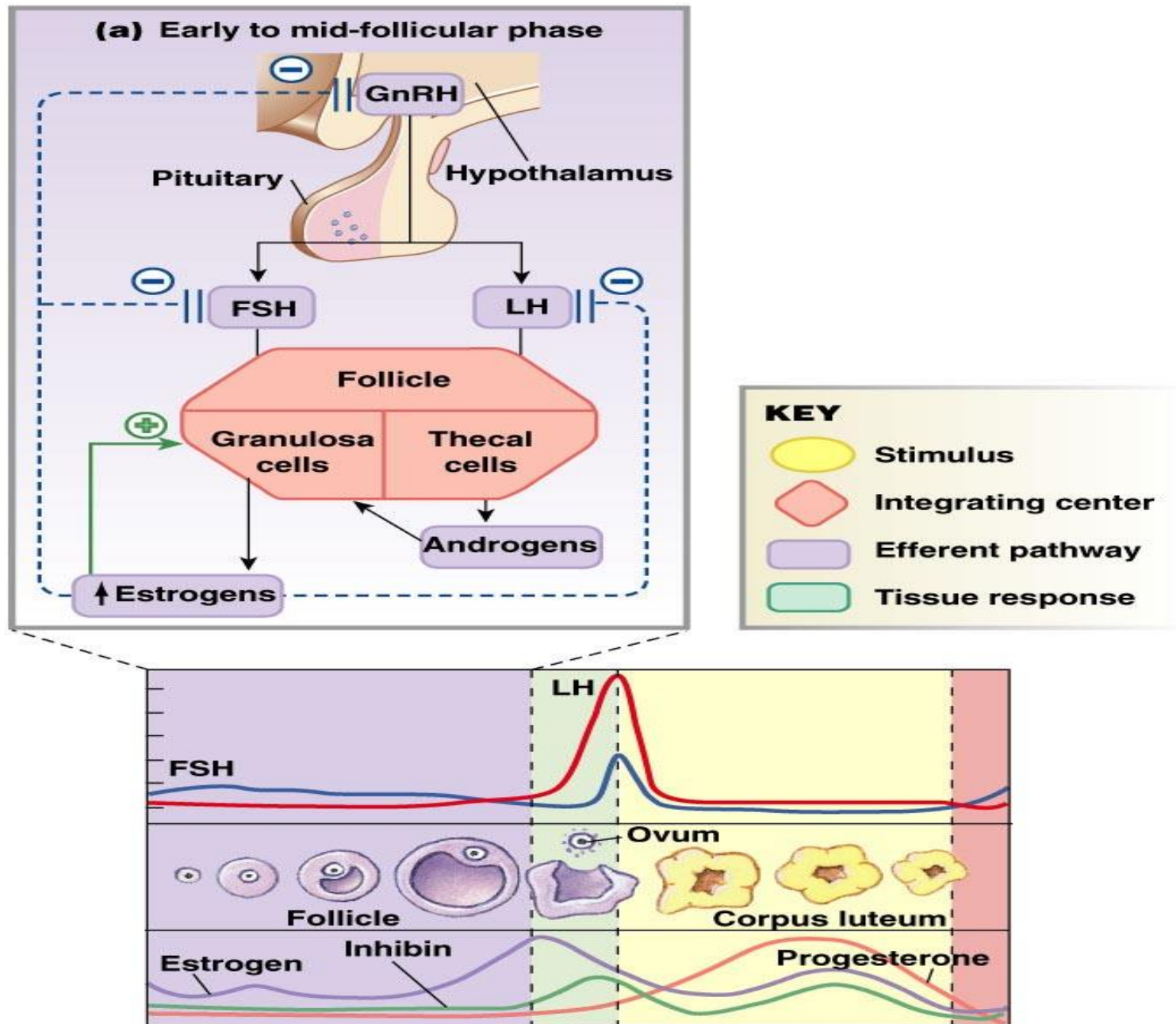
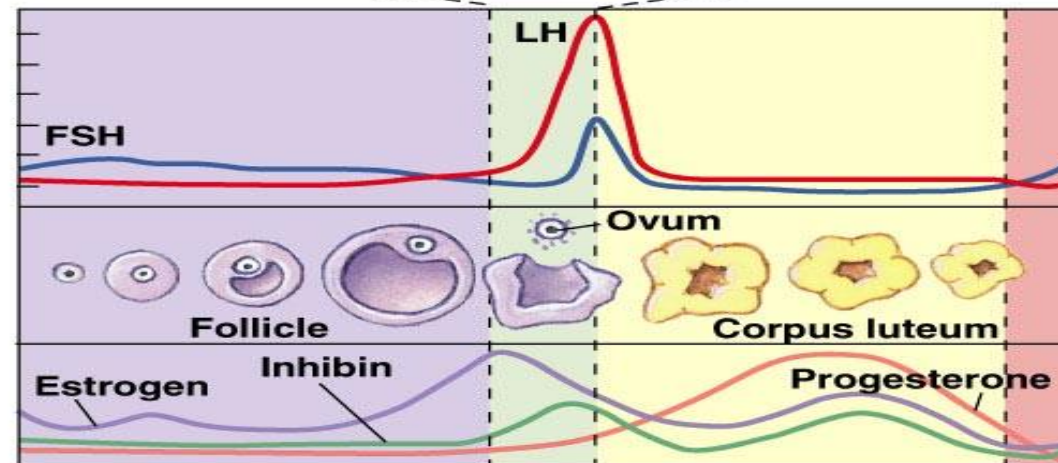
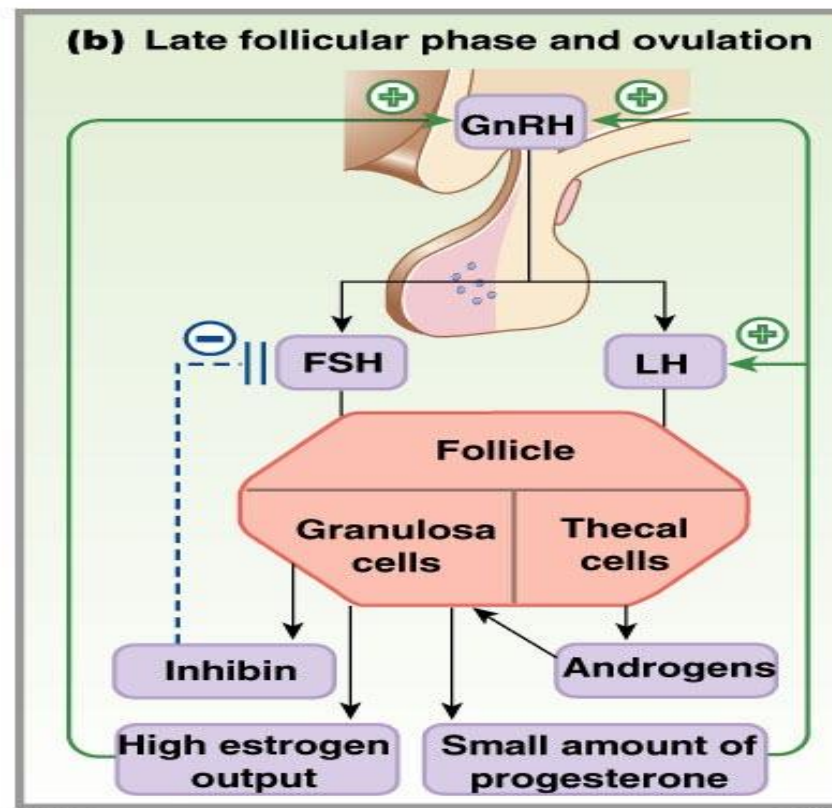
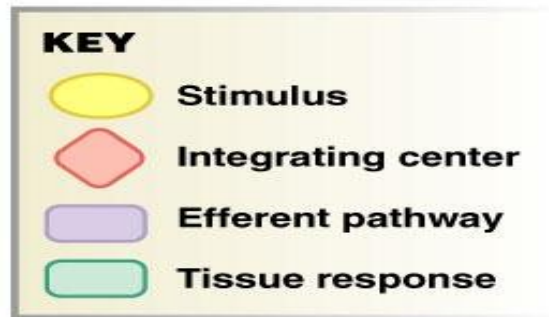
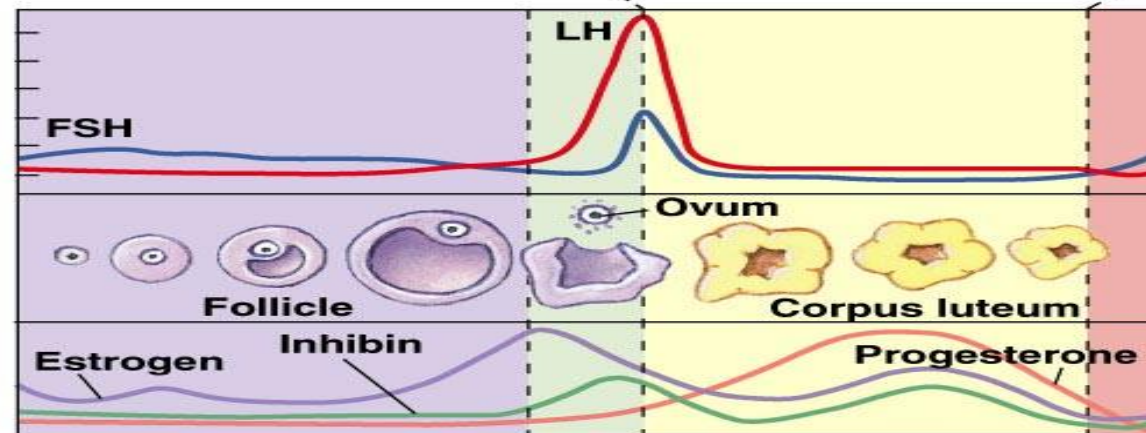
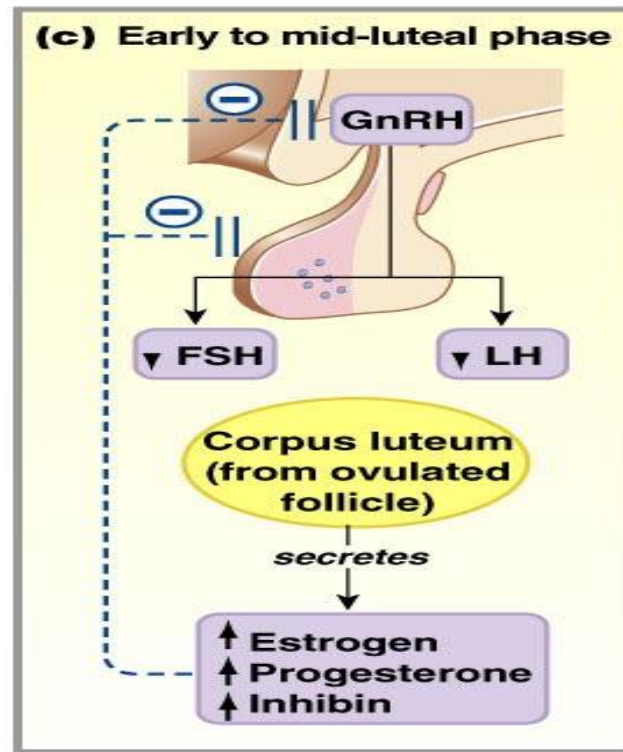
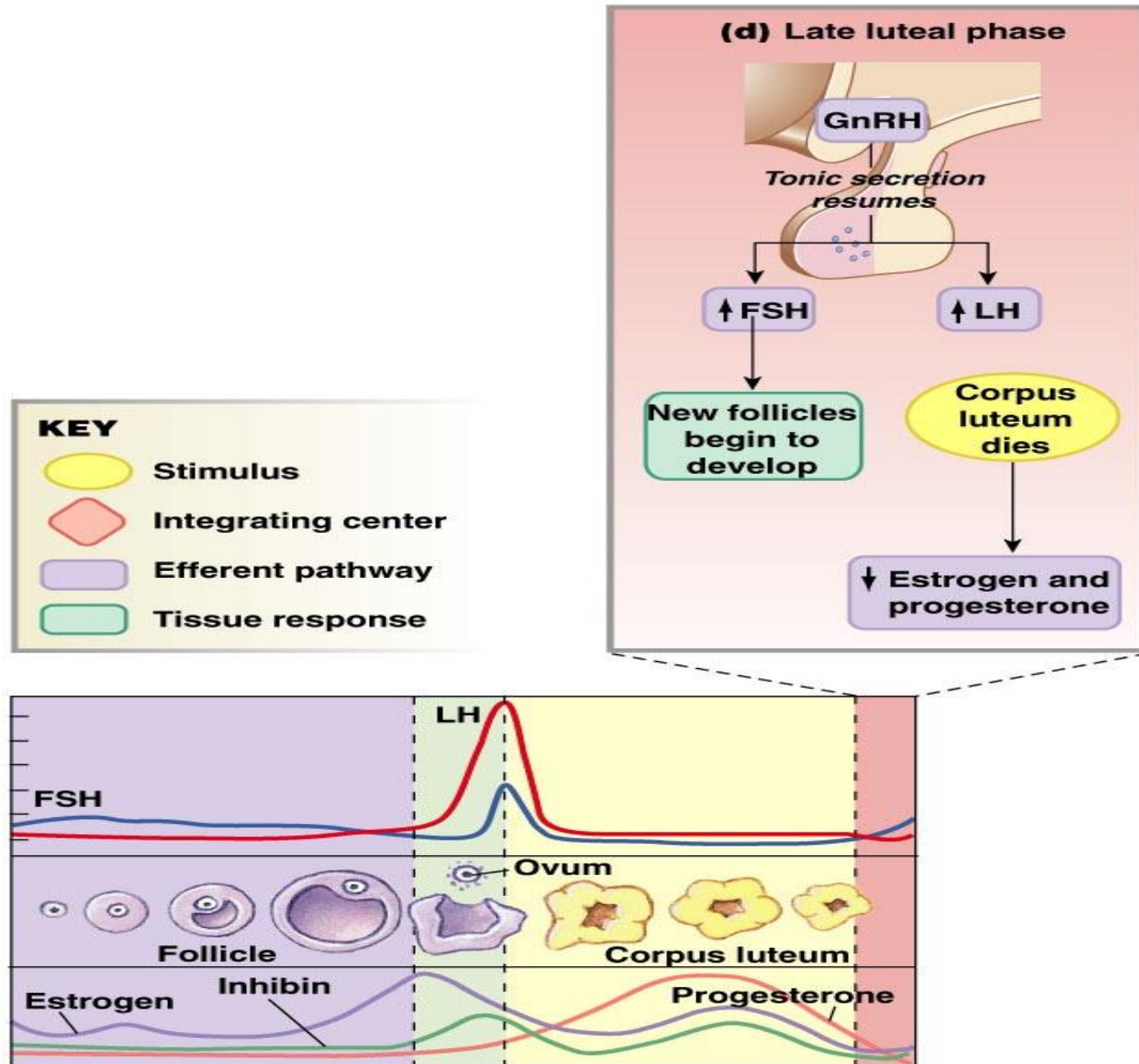


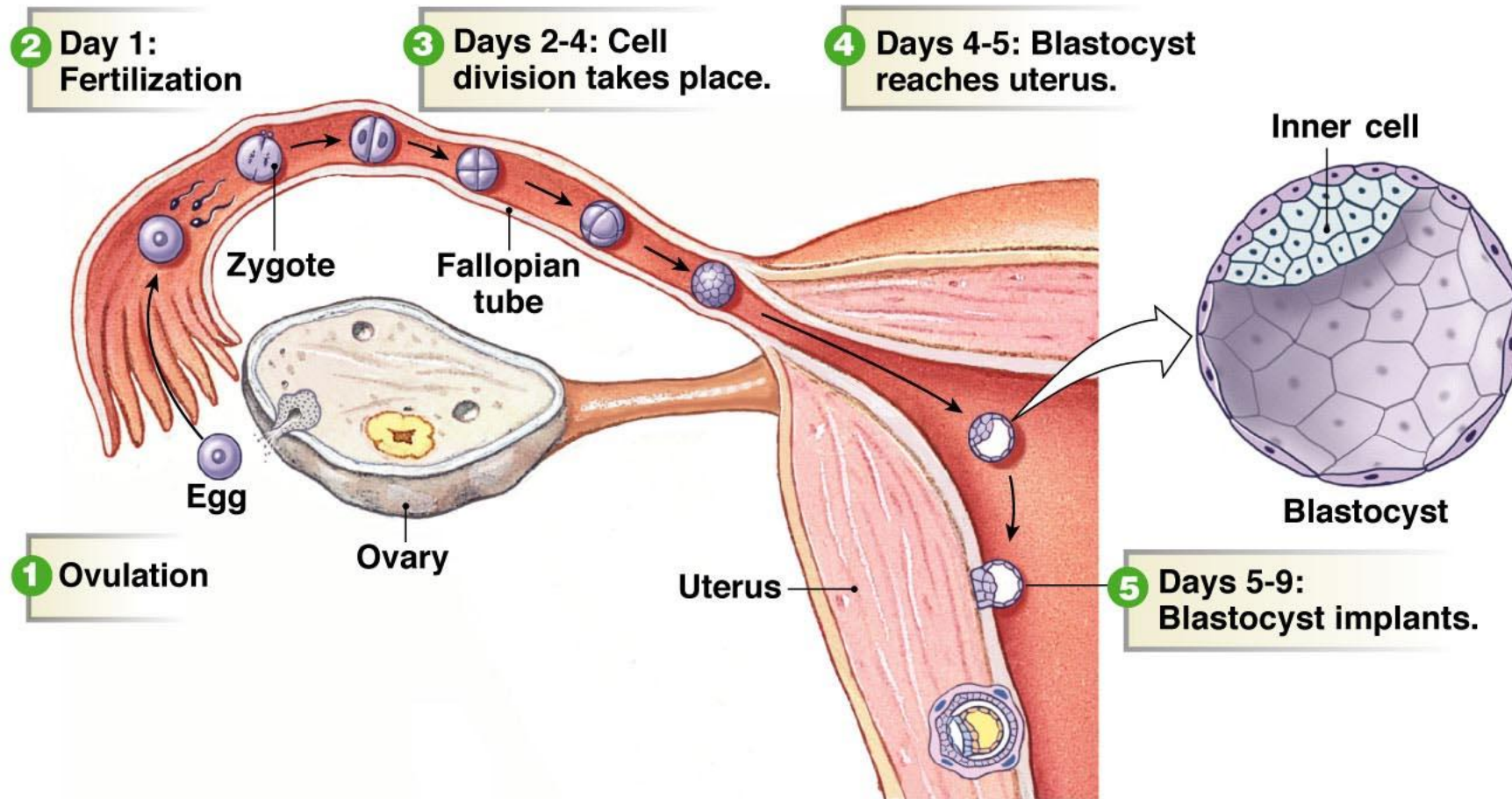
Figure 26-14 - Overview











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Figure 26-18 - Overview

Endocrine Control of Menstrual Cycle:

Late Luteal phase

- **Pregnancy:**

Maintain ↑ Progesterone, Estrogen & Inhibin

- **No Pregnancy:**

↓ Progesterone, Estrogen & Inhibin

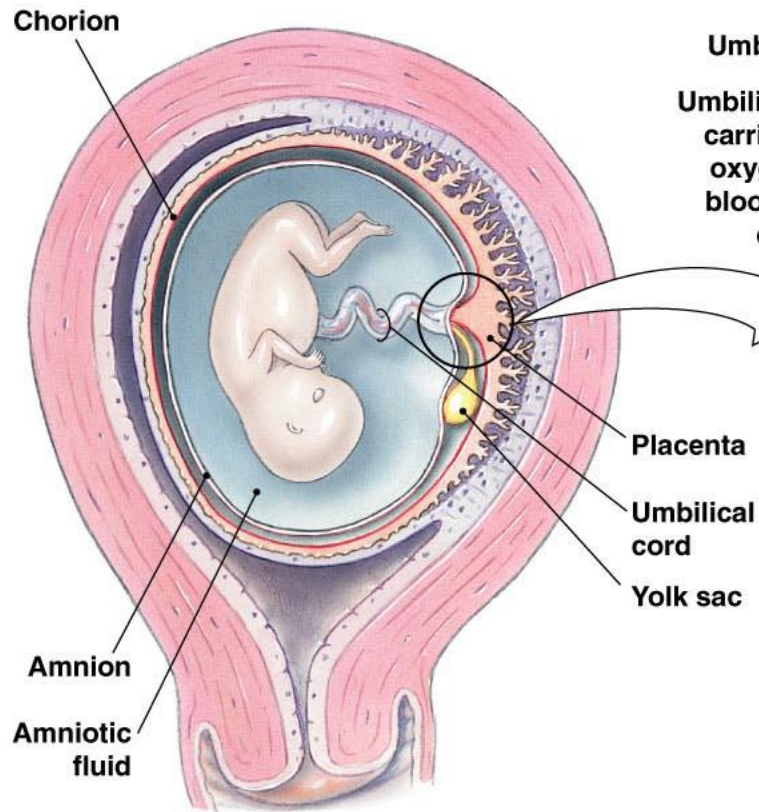
Menses, ↑ FSH & LH → new follicle development

Female Reproductive Physiology

Fertilization Effects

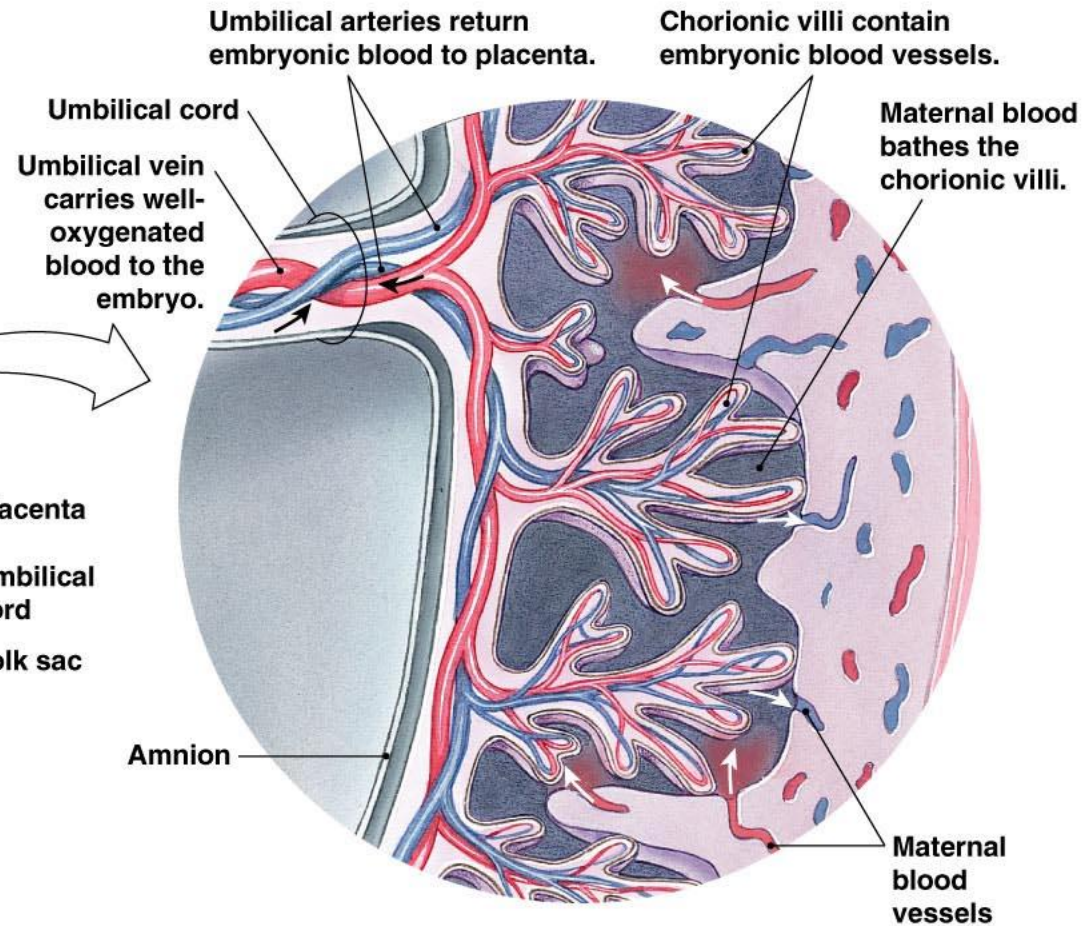
- What happens if fertilization occurs?
 - Uterine endometrium is maintained by
 - First the release of **progesterone from the corpus luteum**,
 - then the release of **hCG (human chorionic gonadotropin)** which maintains the corpus luteum until the **7th week**,
 - From 7th week on, the **placenta produces progesterone** which continues to maintain the endometrium & the corpus luteum degenerates
 - Placenta also produces estrogen and progesterone which at high levels blocks GnRH
 - Estrogen is also involved in breast development
 - Progesterone is also involved in uterine maintenance and relaxation (prevents premature contractions)
 - Placenta also produces hPL (human placental lactogen)
 - Implicated in breast development and milk production

(a) The developing embryo floats in amniotic fluid. It obtains oxygen and nutrients from the mother through the placenta and umbilical cord.



WEEK 10

(b) Some material is exchanged across placental membranes by diffusion, but other material must be transported.



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Figure 26-19 - Overview

Pregnancy Hormones

- Follicular Phase: LH+FSH

LH stimulate Androgen release from Thecal cells to the ovary and granulosa cells

FSH stimulate Granulosa cells to produce estrogen

- Ovulation: Triggered by LH (10 folds increase), FSH only 3 fold

- Luteal Phase: Corpus Luteum produce large amount of progesterone and estrogen

- Maintenance of pregnancy:

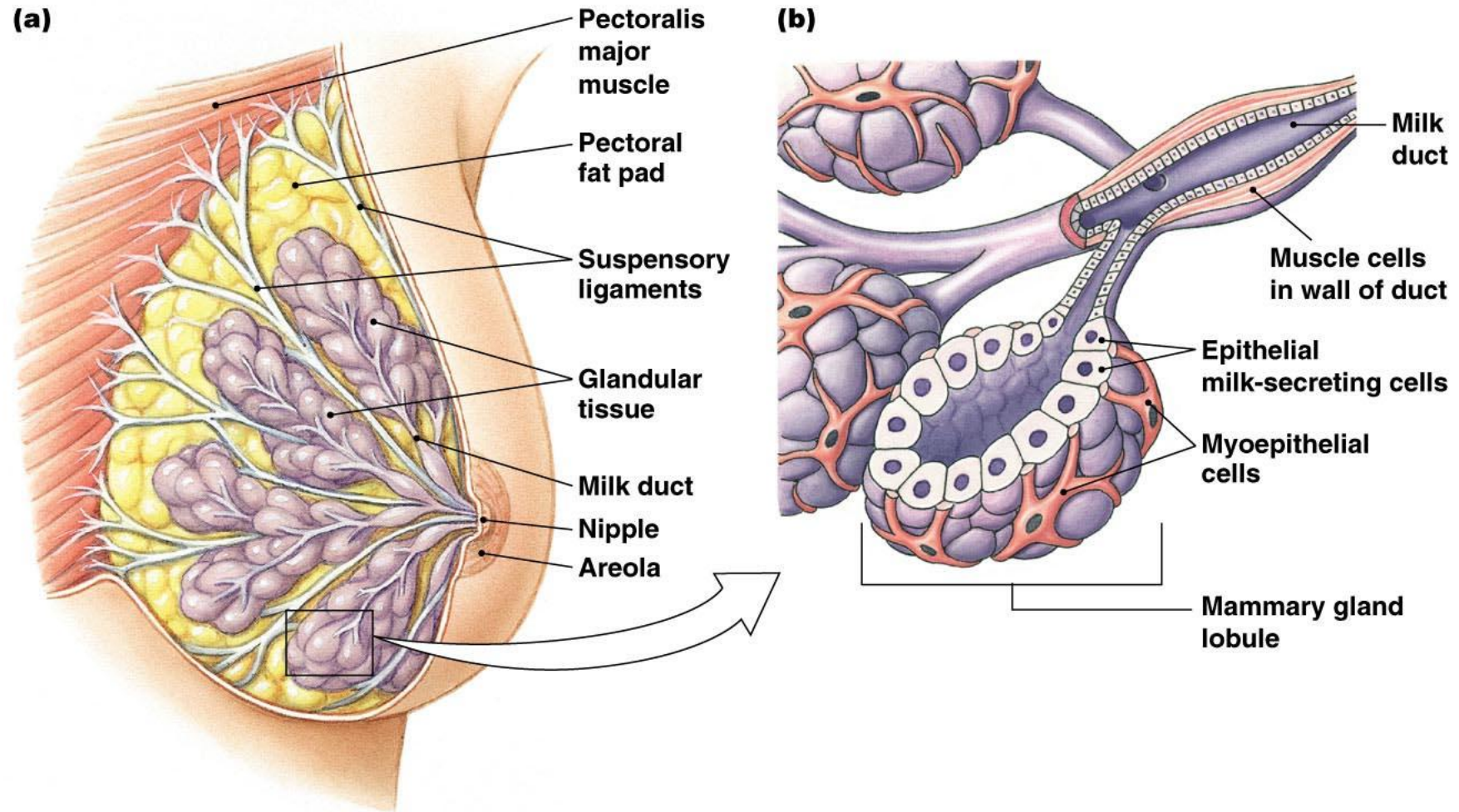
1. Continuous production of progesterone from corpus luteum first then placenta
2. Inhibition of FSH and LH
3. Inhibition of Prolactin, Oxytocine and Relaxin

- Delivery

1. Decrease of Progesterone
2. Increase in FSH
3. Increase in Oxytocine, relaxin and prostaglandins

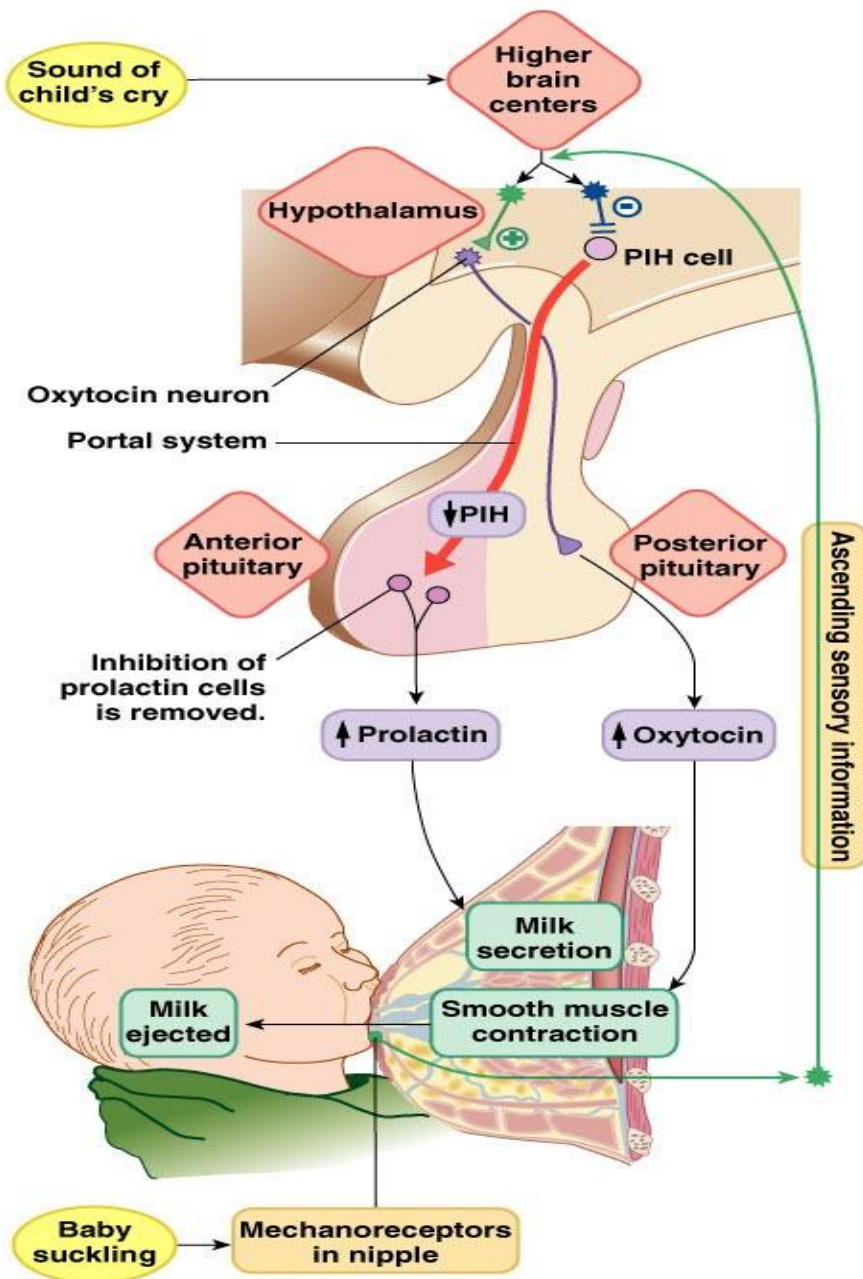
Action of Progesterone

1. Production of secretory Endometrium
2. Stimulation of viscous cervical mucus
3. Suppression of milk synthesis and FSH release
4. Prevent development of new Ova
5. Increase body temperature
6. Decrease uterine motility
7. Increase ventilation
8. Decrease sodium retention, antagonism of Aldosterone action



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Figure 26-22 - Overview



Role of Prolactin (males)

- Hyperprolactinemia inhibits male reproductive function
- May cause Infertility
- Decreases Gonadotropin secretion and action on the testis
- Decrease testicular Androgen production, decrease spermatogenesis

□ 5 alpha reductase deficiency:

Cause decrease in DHT (dihydrotestosterone), normal development of male internal genitalia but in complete external genitalia (incomplete male hermaphroditism)