

Chapter 4 細胞及環境的互動

4-1 細胞外環境

✓4-2 細胞間的溝通 (p.95-101)

4-3 物質通過細胞膜的運輸方式

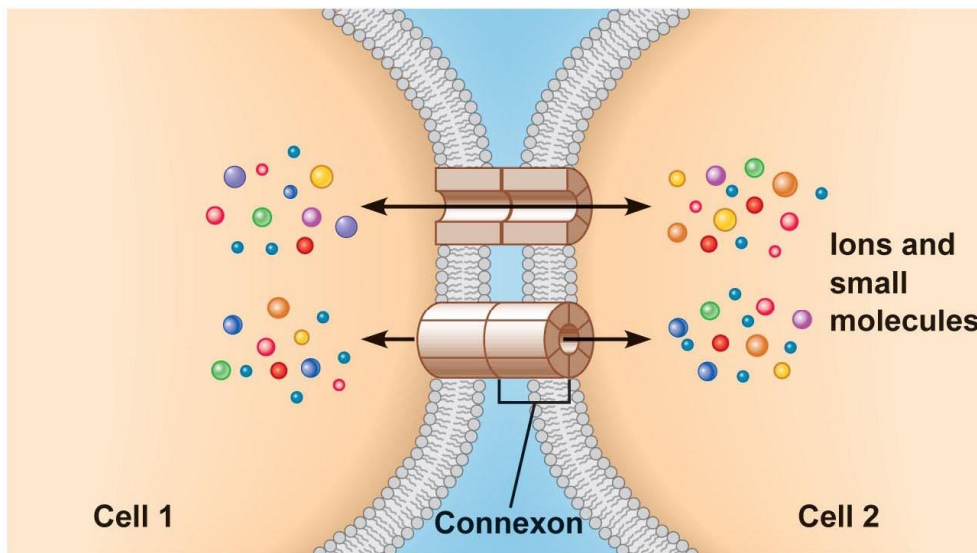
4-4 細胞的興奮性

Intercellular Communication: How Cells Talk to Each Other

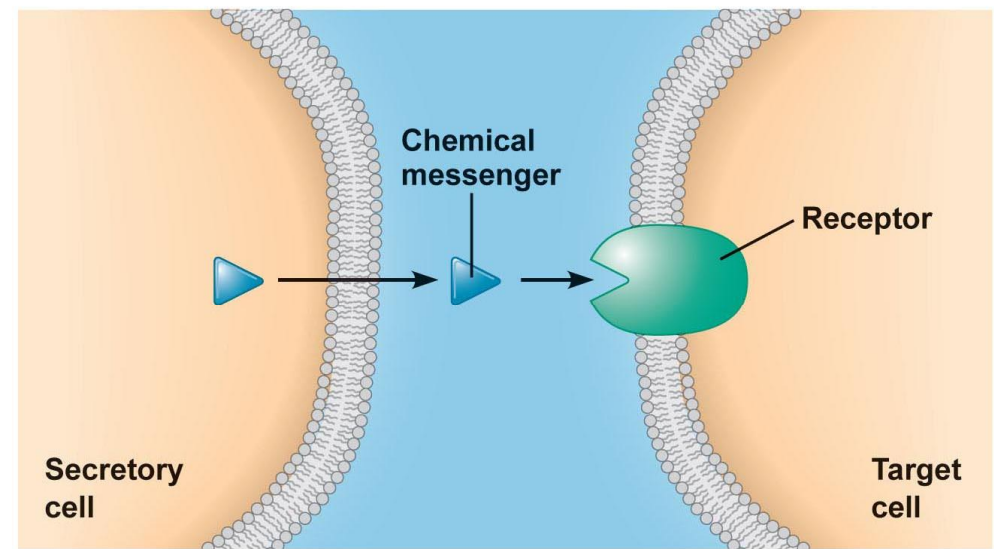
● General mechanisms

--Direct: **gap junctions**

--Indirect: **chemical messengers**



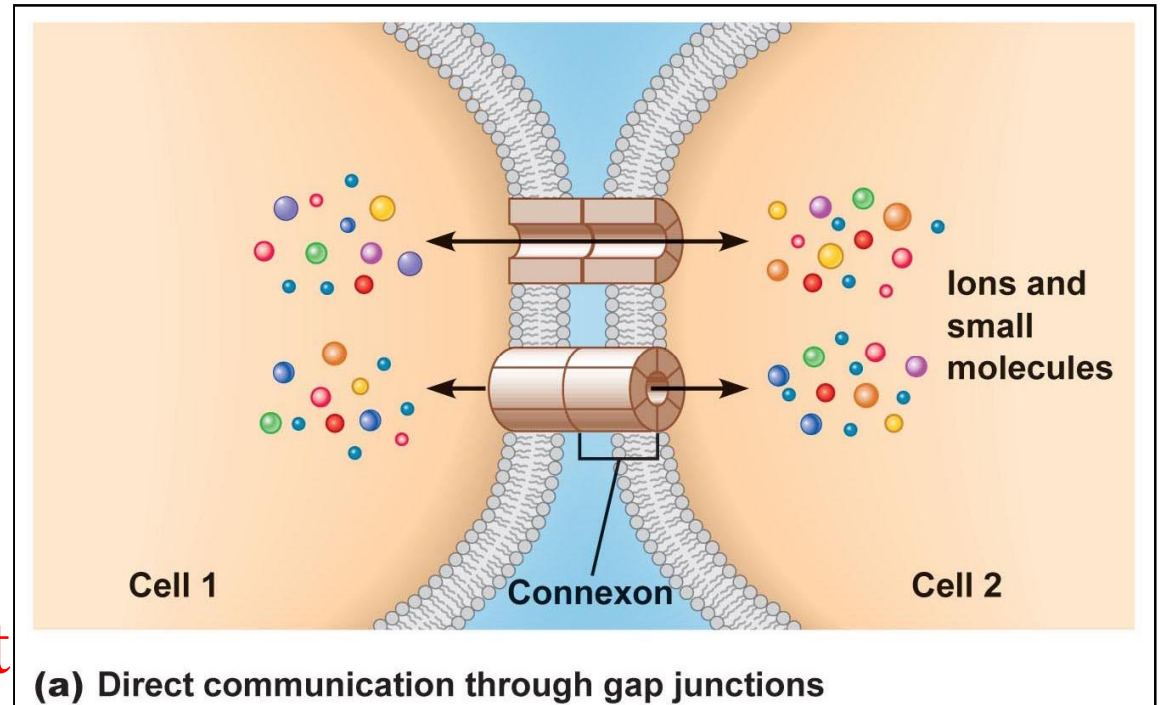
(a) Direct communication through gap junctions



(b) Communication via chemical messengers

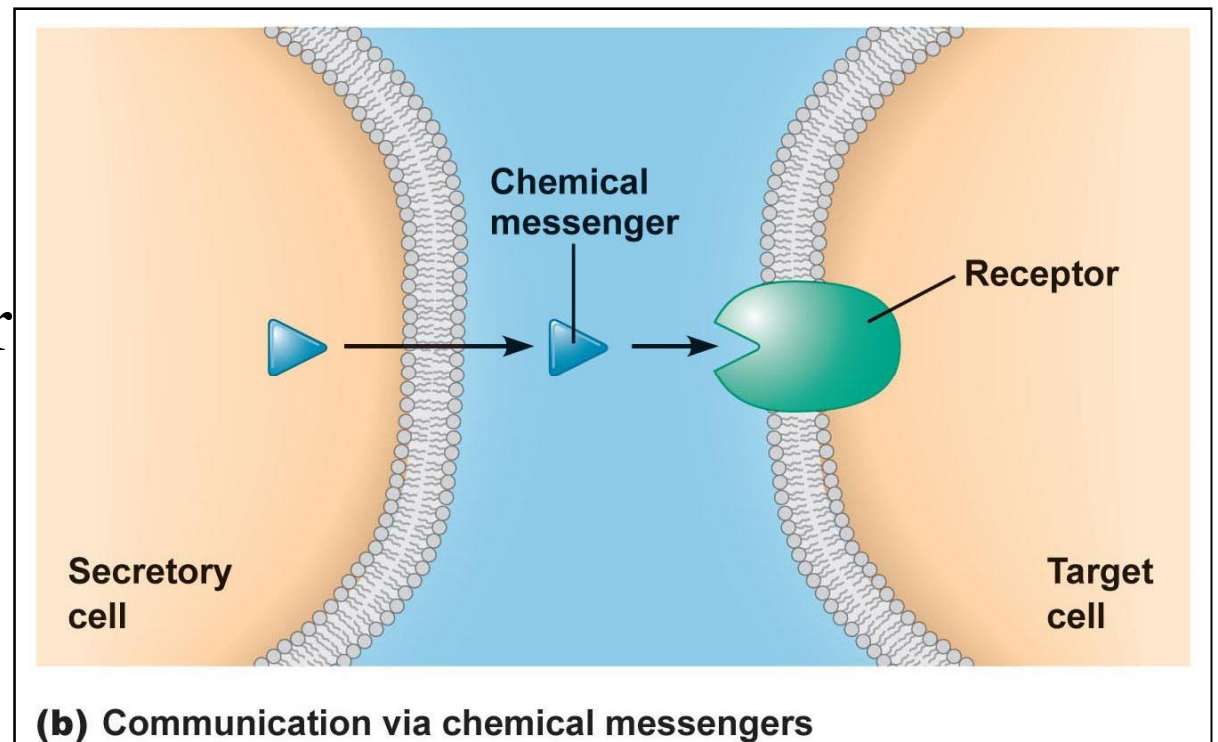
Gap Junctions

- Composed of **membrane proteins**
- Link **cytosol** of two adjacent cells
- Particles' movement between cells acts as **signal**
- Communication is **direct**
- Common in **smooth and cardiac muscle**



Chemical Messengers = Ligands

- Messenger is produced by **source cell**
- Messenger is transported to **target**
- Target cell has **receptors** for messenger
- Binding of messenger to receptor triggers a target cell response (**signal transduction**)
- Communication is **indirect**



Indirect

Intercellular Communication

- Terminology of chemical messenger

- **Ligand:** a chemical messenger

- **Source:** cells which produce the ligand

- **Target:** has receptors for and responds to messenger

Source → Ligand → Target

- Chemical messenger have **signaling functions**

Chemical Messenger Classification

- Classification by **function**
- Classification by **chemical properties**

--Solubility properties

- Hydrophobic/lipid-soluble
- Hydrophilic/lipid-insoluble

--Chemical class

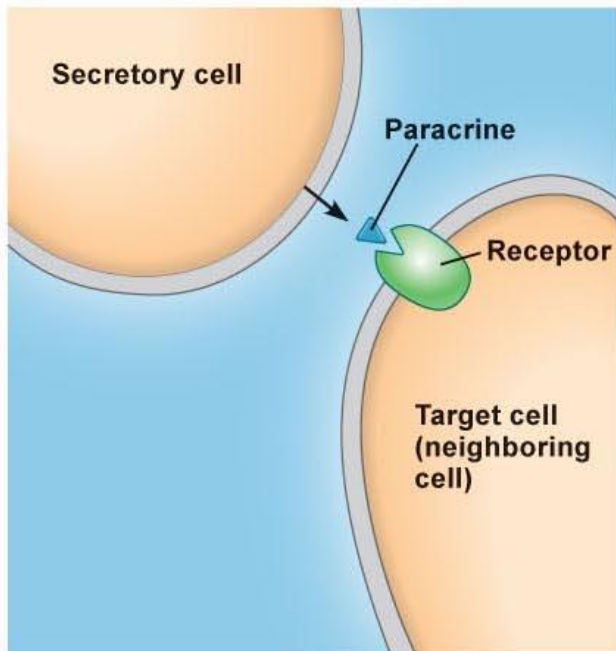
- Amino acid, Amine, Protein, Steroid and

Eicosanoid ligands

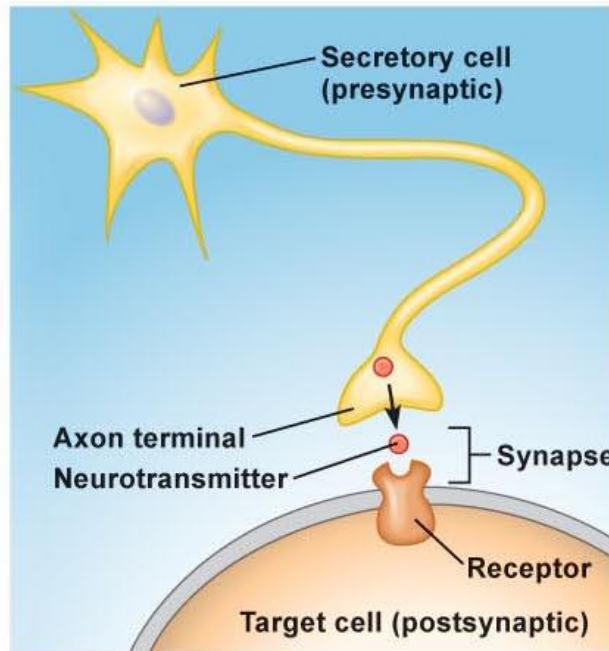
Messenger Classification by Function

Class	Secretory cell type	Distance to target cell	Mode of transport to target cell	Chemical classification of messenger
Paracrine	(Several)	Short	Diffusion	Amines, peptides/proteins, eicosanoids
Neurotransmitter	Neuron	Short*	Diffusion	Amino acids, amines, peptides/proteins
Hormone	Endocrine	Long	Blood	Amines, steroids, peptides/proteins

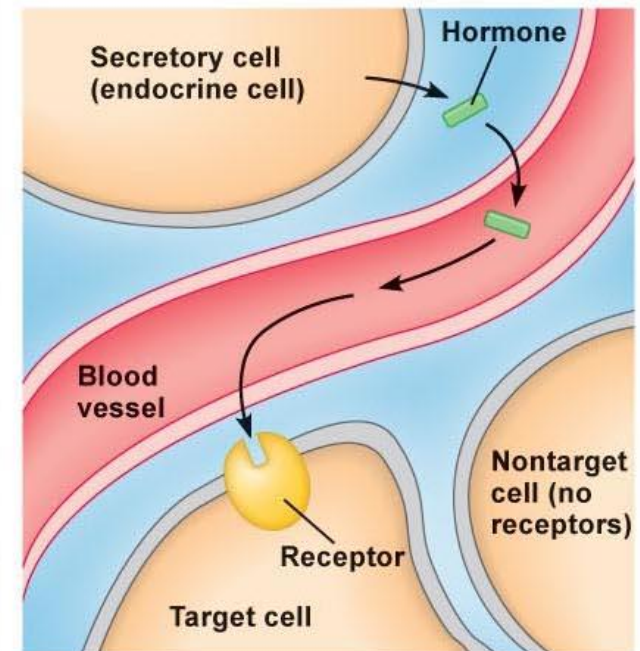
*Even though neurotransmitters diffuse over only a short distance to the postsynaptic cell, some neurons are involved in long-distance communication because the neuron that releases the neurotransmitter is often long (up to 1 meter).



(a) Paracrines



(b) Neurotransmitters

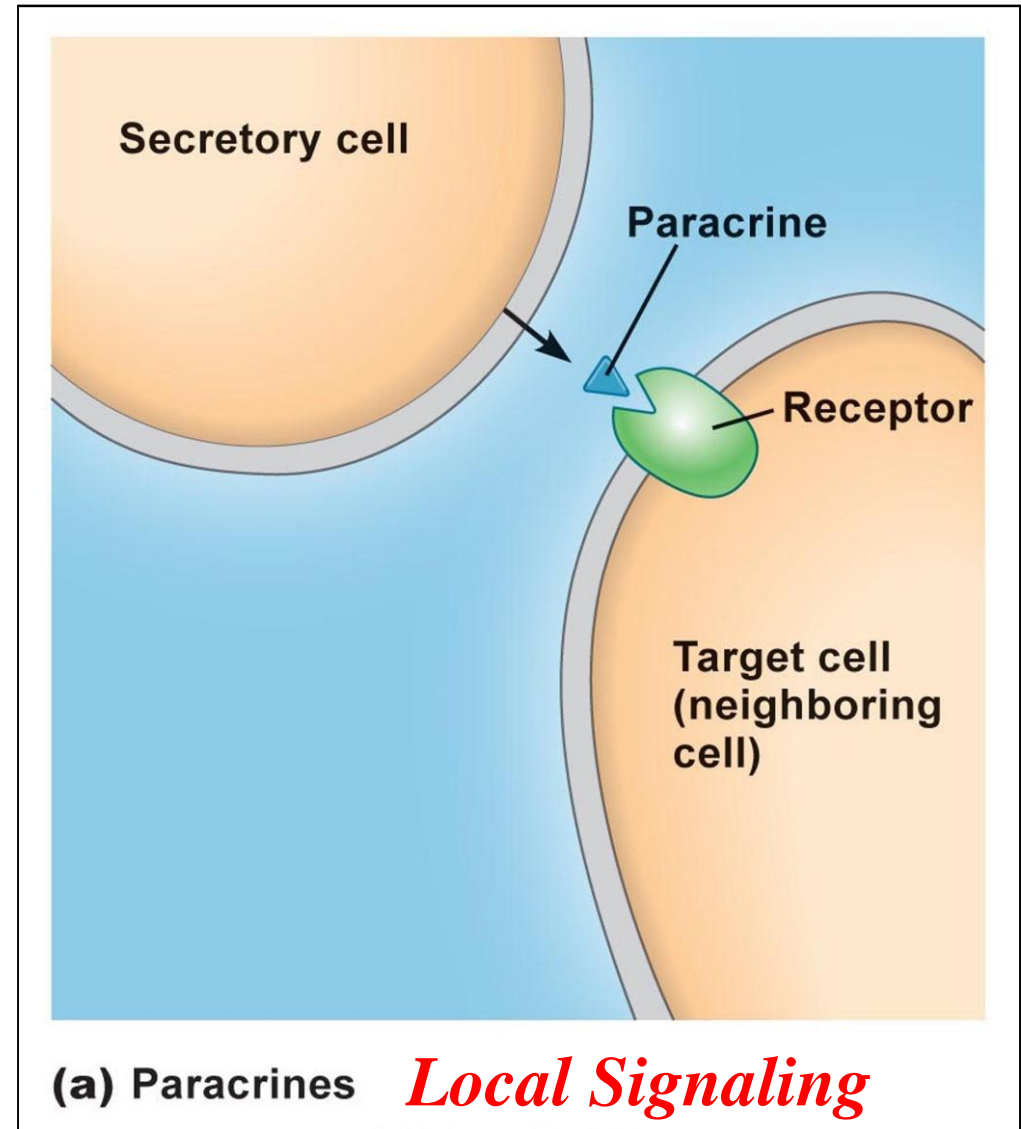


(c) Hormones

Messenger Classification by Function

● **Paracrine** chemical messenger

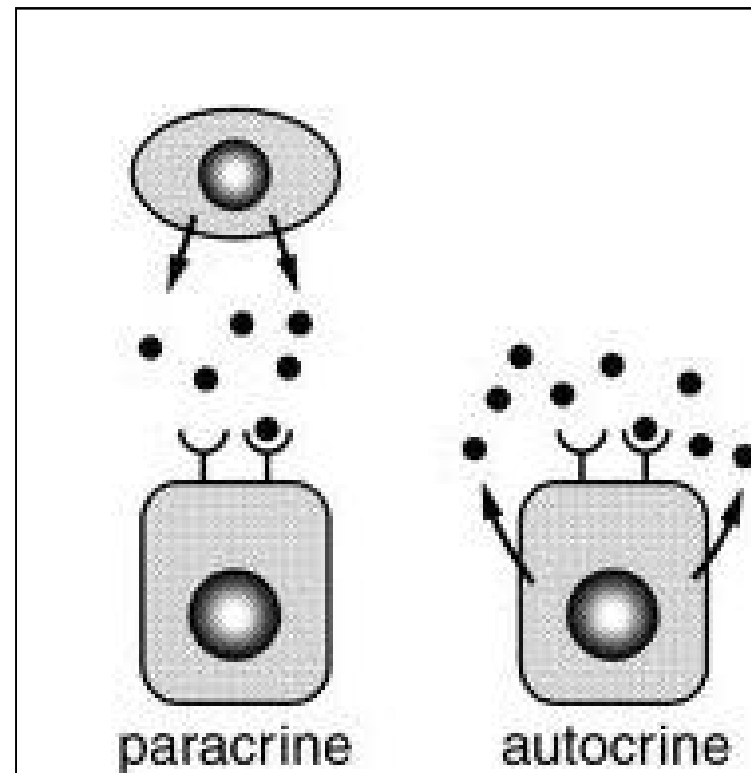
- Chemical that serves to signal a nearby cell
- Example: Histamine**, responsible for an inflammation response; **GH; clotting factor; cytokines**



Messenger Classification by Function

● Autocrine

- A subclass of paracrines
- Chemical that signals the same cell that secreted it
- Source and target are the **same**



Local Signaling

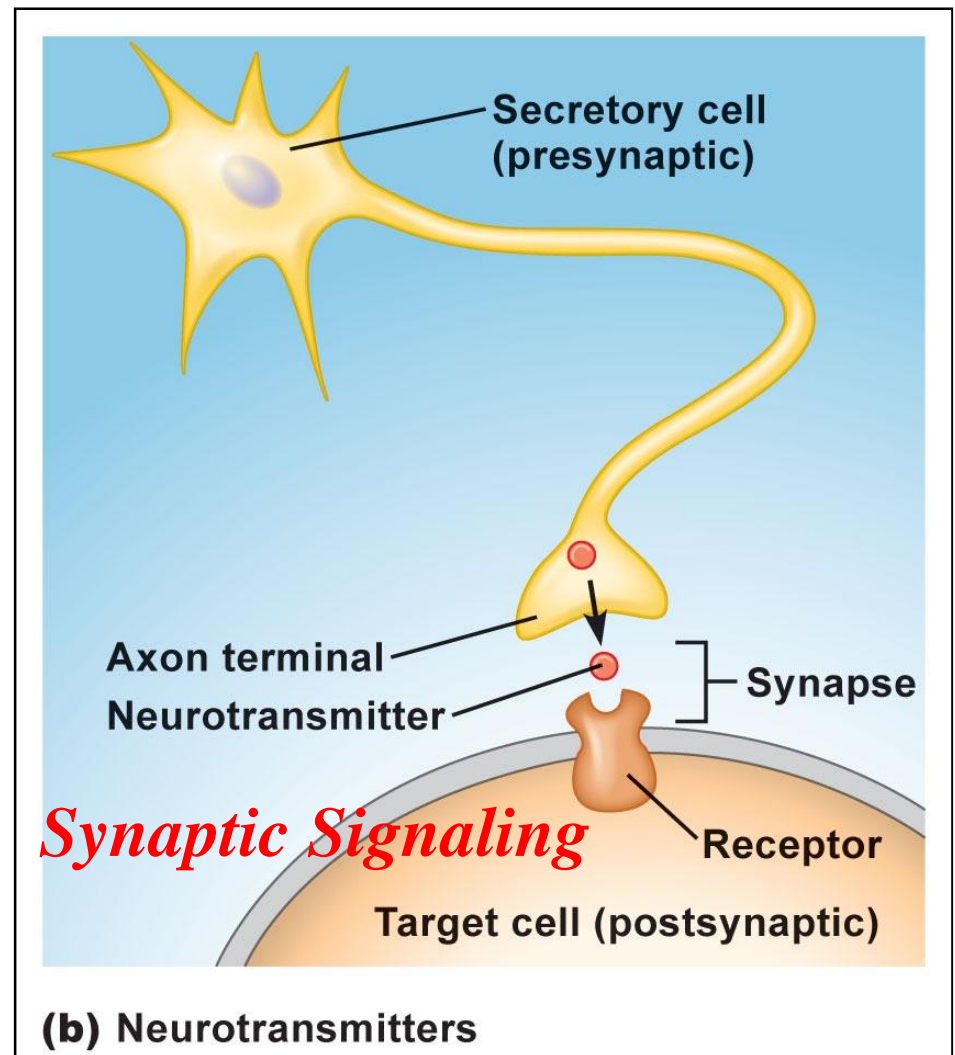
Paracrine & Autocrine Regulator

Autocrine or Paracrine Regulator	Major Sites of Production	Major Actions
Insulin-like growth factors (somatomedins)	Many organs, particularly the liver and cartilages	Growth and cell division
Nitric oxide	Endothelium of blood vessels; neurons; macrophages	Dilation of blood vessels; neural messenger; antibacterial agent
Endothelins	Endothelium of blood vessels; other organs	Constriction of blood vessels; other effects
Platelet-derived growth factor	Platelets; macrophages; vascular smooth muscle cells	Cell division within blood vessels
Epidermal growth factors	Epidermal tissues	Cell division in wound healing
Neurotrophins	Schwann cells; neurons	Regeneration of peripheral nerves
Bradykinin	Endothelium of blood vessels	Dilation of blood vessels
Interleukins (cytokines)	Macrophages; lymphocytes	Regulation of immune system
Prostaglandins	Many tissues	Wide variety (see text)
TNF α (tumor necrosis factor alpha)	Macrophages; adipocytes	Wide variety

Messenger Classification by Function

● Neurotransmitter (synaptic signaling)

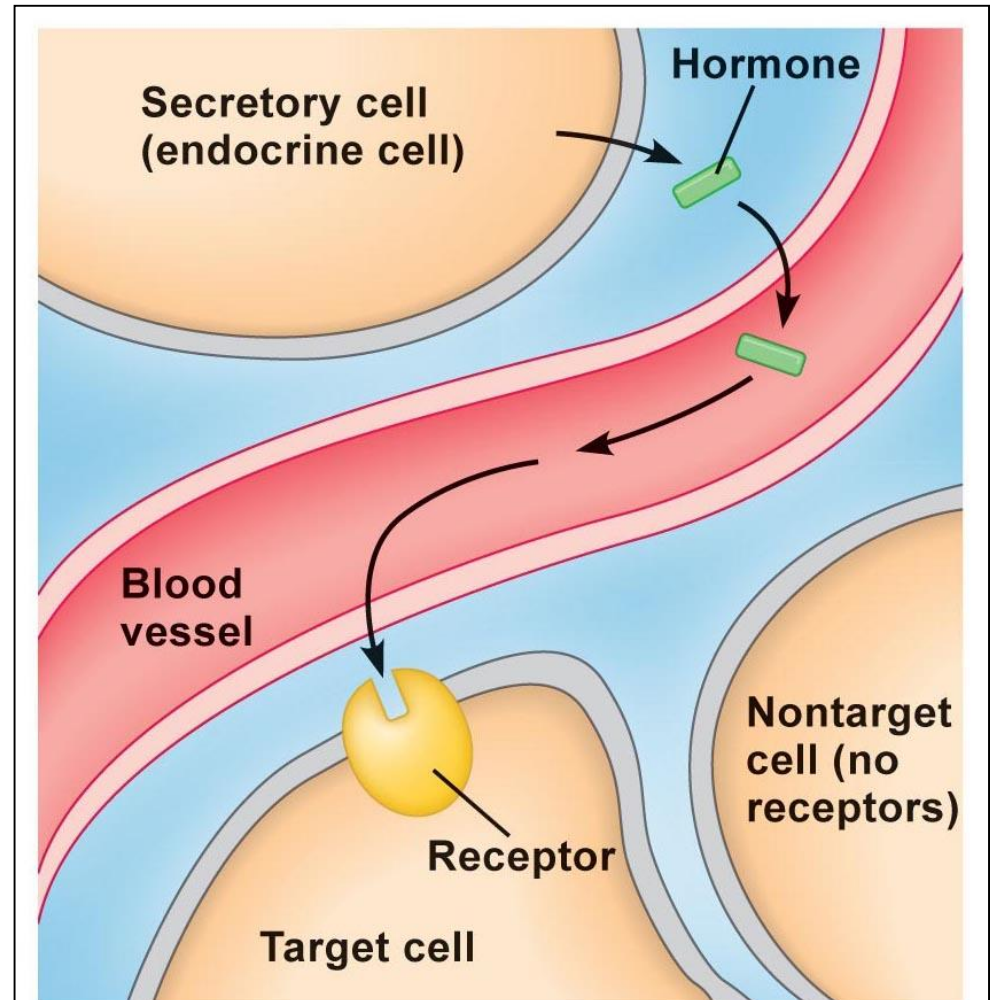
- Messenger produced by neurons
- Released into the **ECF** of **synaptic cleft**
- **Examples:** Acetylcholine, glycine, serotonin etc.



Messenger Classification by Function

● Hormone

- Messenger produced by endocrine cells
- Secreted into **blood** via interstitial fluid
- **Examples: Insulin, estrogen, thyroxin**

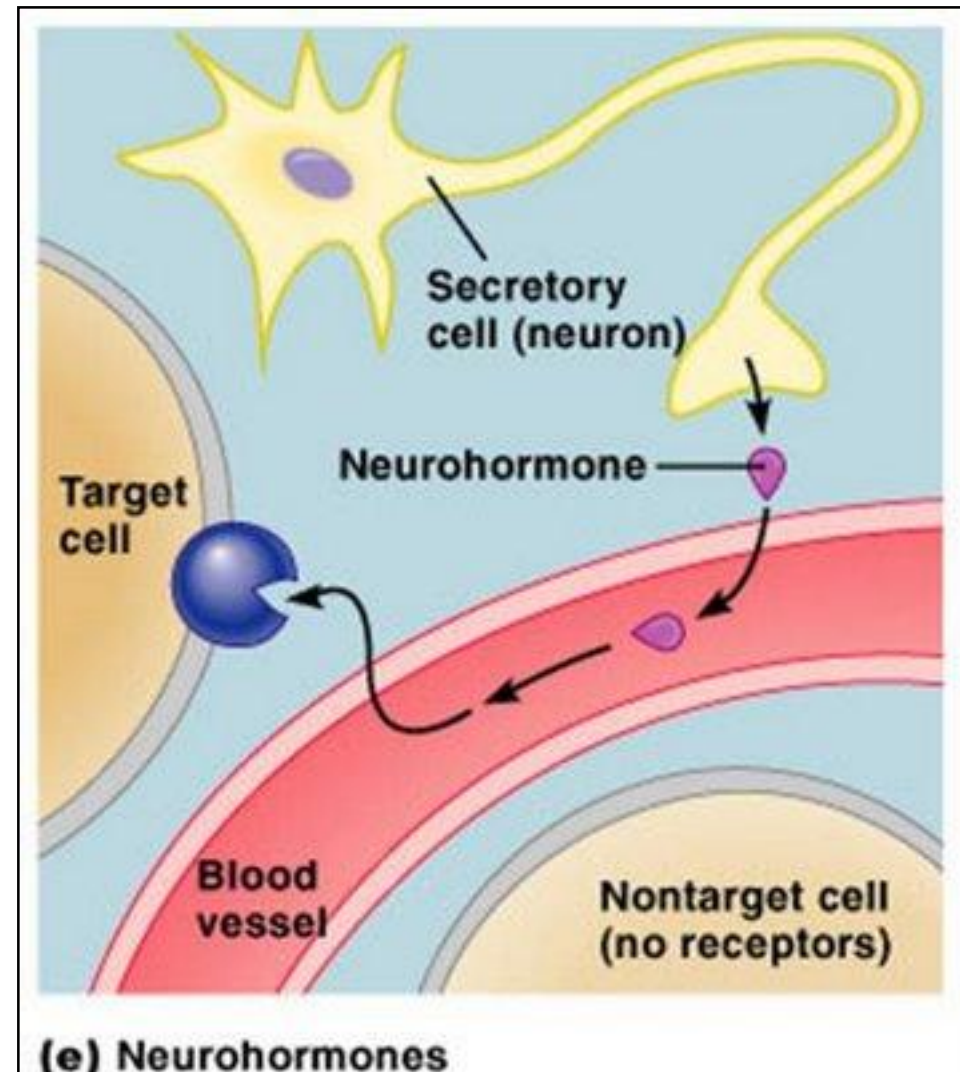


(c) Hormones *Endocrine signaling*

Messenger Classification by Function

● Neurohormone

- A special class of hormone
- Messenger produced by **neurons**
- Secreted into **blood** via interstitial fluid
- Examples: Antidiuretic hormone (ADH), oxytocin**



Messenger Classification by Solubility

● Lipid-insoluble ligand

- Not lipid soluble; is water soluble
- Does not easily cross cell membrane, which may require pumps or channels
- Receptors **on cell membrane**
- General action of target response
 - *Enzyme activation*
 - *Membrane permeability changes*
- Examples: epinephrine, insulin...

Messenger Classification by Solubility

● Lipid-soluble ligand

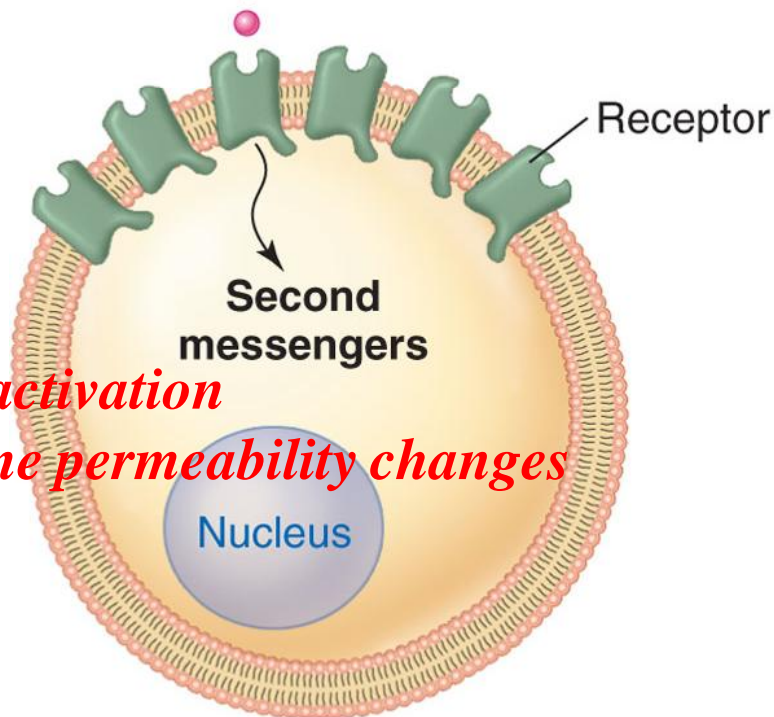
- Lipid soluble; not water soluble
- Easily crosses cell membrane
- Receptor location **within cell**
(intracellular location)
- General action of target response is via **gene activation**
- Examples: steroid hormones, thyroid hormones...

Messenger Classification by Solubility

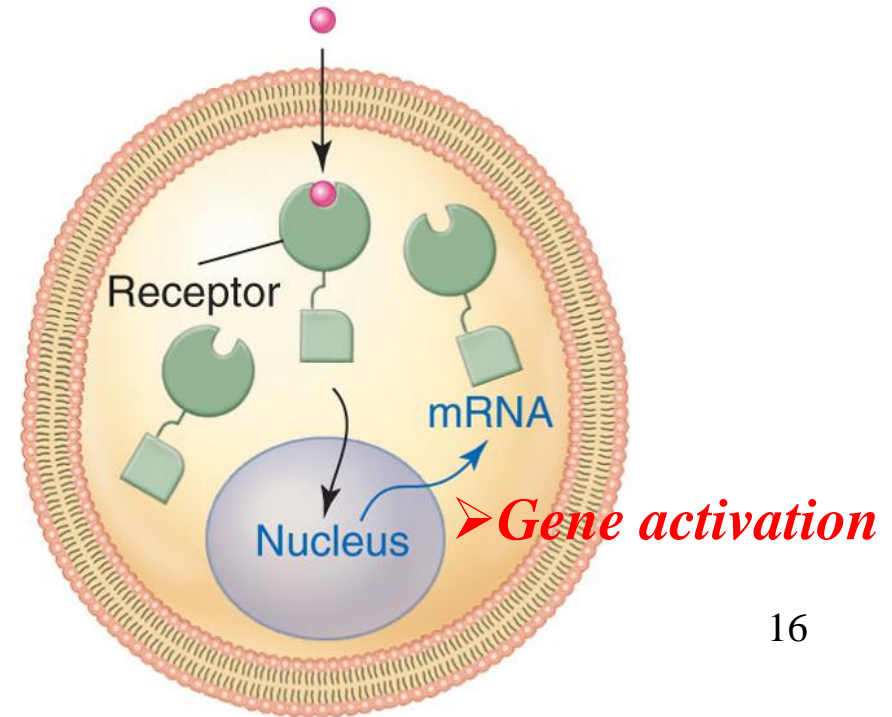
Regulatory molecule
(neurotransmitter, hormone,
or paracrine regulator)

If regulator is
polar (water-soluble)

If regulator is
nonpolar (lipid-soluble)



- *Enzyme activation*
- *Membrane permeability changes*



- *Gene activation*

Messenger Classification by Solubility

Property	Lipophobic messenger (hydrophilic)	Lipophilic messenger (hydrophobic)
Chemical classes	Amino acids, amines, peptides	Steroids, eicosanoids, thyroid hormones*
Storage in secretory cell	Secretory vesicles	None
Mechanism of secretion	Exocytosis	Diffusion
Transport in blood [†]	Dissolved	Bound to carrier protein
Location of receptor	Plasma membrane	Cytosol or nucleus
Signal transduction mechanism	Open/close ion channels [‡] Activate membrane-bound enzymes G proteins and second messenger systems	Alter transcription of mRNA (alter protein synthesis)
Relative time to onset of response	Fast	Slow
Relative duration of response	Short	Long
Relative half-life	Short	Long

*Thyroid hormones are amines but are lipophilic.
[†]Refers to hormones and certain cytokines only.
[‡]Some of these effects are mediated by G proteins.

Messenger Classification by Chemical Class

Class	Chemical property	Location of receptors on target cell	Functional classification
Amino acids	Lipophobic	Plasma membrane	Neurotransmitters
Amines*	Lipophobic	Plasma membrane	Paracrines, neurotransmitters, hormones
Peptides/proteins	Lipophobic	Plasma membrane	Paracrines, neurotransmitters, hormones
Steroids	Lipophilic	Cytosol [†]	Hormones
Eicosanoids	Lipophilic	Cytosol	Paracrines

*One exception is the thyroid hormones, which, although amines, are lipophilic and have receptors in the nucleus of target cells.
[†]A few steroid hormones have receptors on the plasma membrane.

Messenger Classification by Chemical Class

1. Amino acids

- Lipophobic
- Target cell receptors on cell membrane
- Only four amino acids function as messengers, all as neurotransmitters
- Examples:** Glutamate, aspartate, glycine, GABA

Synthesis and Release of Amino Acids

- Made from glucose
 - Glutamate
 - Aspartate
- Made from 3-phosphoglycerate (glycolytic intermediate)
 - Glycine
- From glutamate (glutamic acid decarboxylase)
 - GABA
- Synthesized within neuron (source)
- Stored in vesicle until needed
- Released by exocytosis

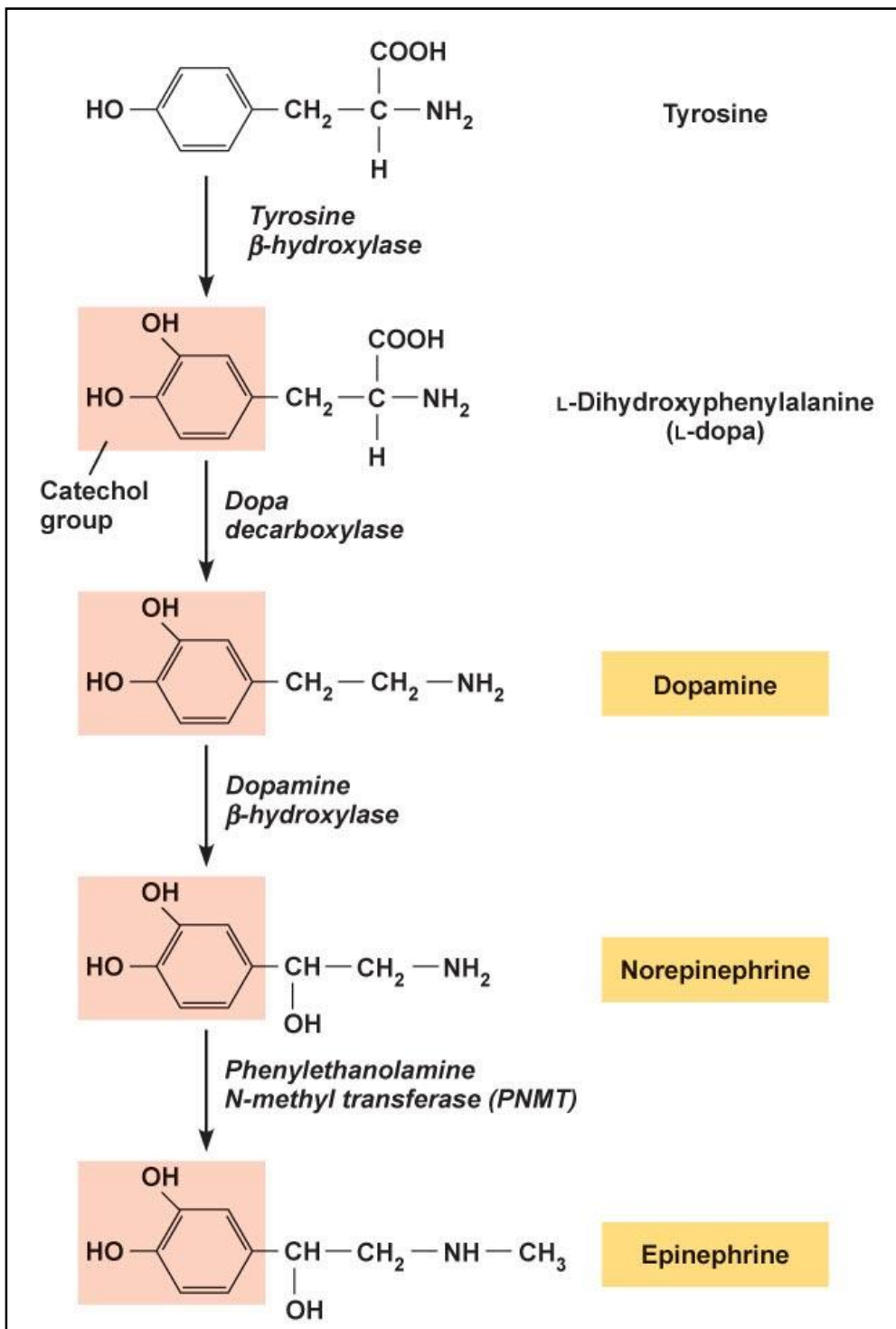
Messenger Classification by Chemical Class

2.Amines

- Most are lipophobic, except **thyroid hormones**
- Target receptors on cell membrane
- Made or derived from an amino acid
- Contains an amine group (-NH₂)
- Examples: catecholamines, serotonin, histamine**

Synthesis and Release of **Amines**

- Produced in cytosol of source
- Stored in vesicles of source
- Release is by exocytosis
- The amine produced is determined by which **enzymes** are present in source cell



Synthesis and Release of Catecholamines

--Derived from **tyrosine**

- *Dopamine (DA)*
- *Norepinephrine (NE)*
= *noradrenaline*
- *Epinephrine (Epi)*
= *adrenaline*

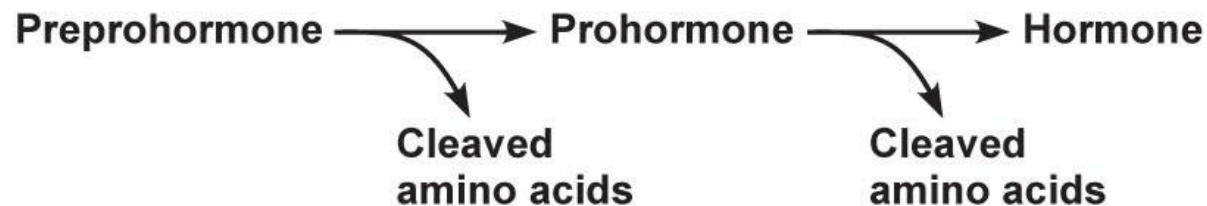
Messenger Classification by Chemical Class

3. Peptide and protein messengers

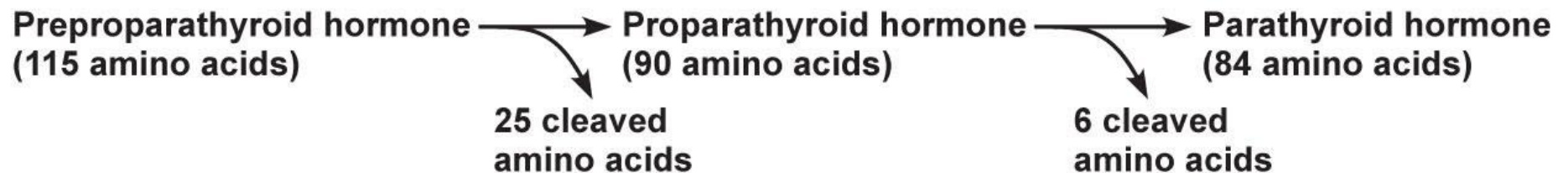
- Most abundant type of ligand
- Lipophobic
- Target receptors on cell membrane
- Made of chains of amino acids
 - *Peptide ligand (<50 amino acids)*
 - *Protein ligand (>50 amino acids)*

Synthesis and Release of Peptide and Protein

- Formed by cleaving larger proteins
- Stored in secretory vesicles
- Released by exocytosis
- General terminology

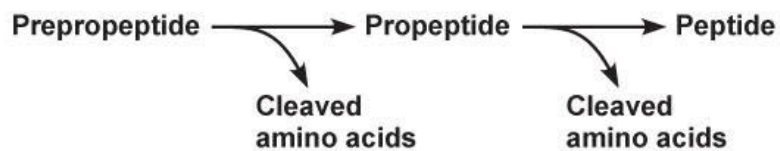
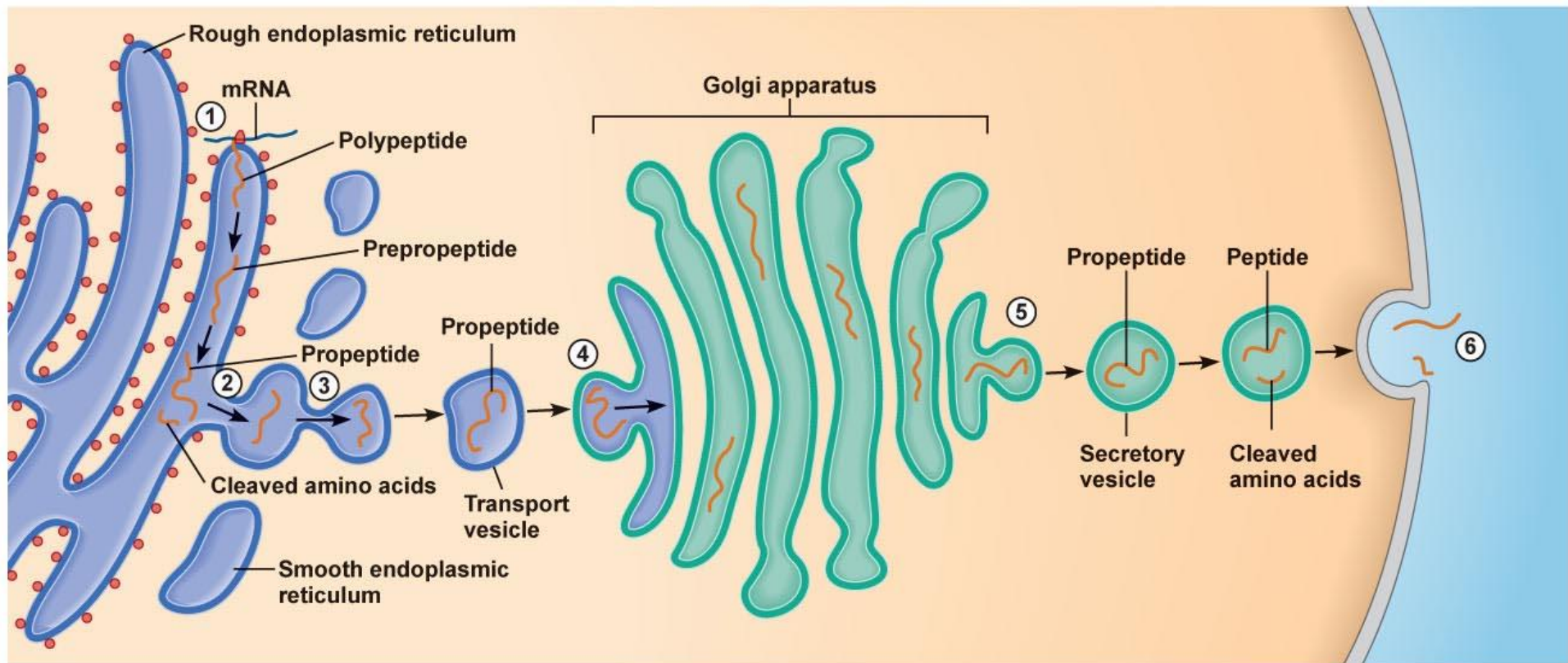


(b) Generalized scheme of hormone synthesis



(c) Parathyroid hormone synthesis

Synthesis and Release of Peptide and Protein



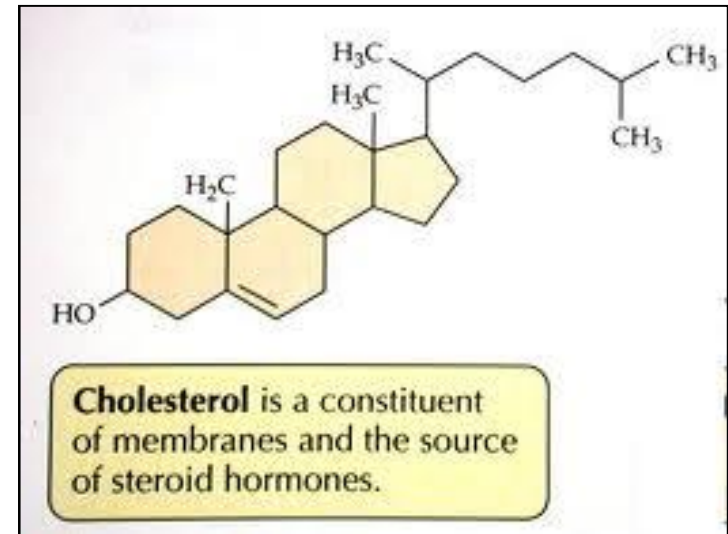
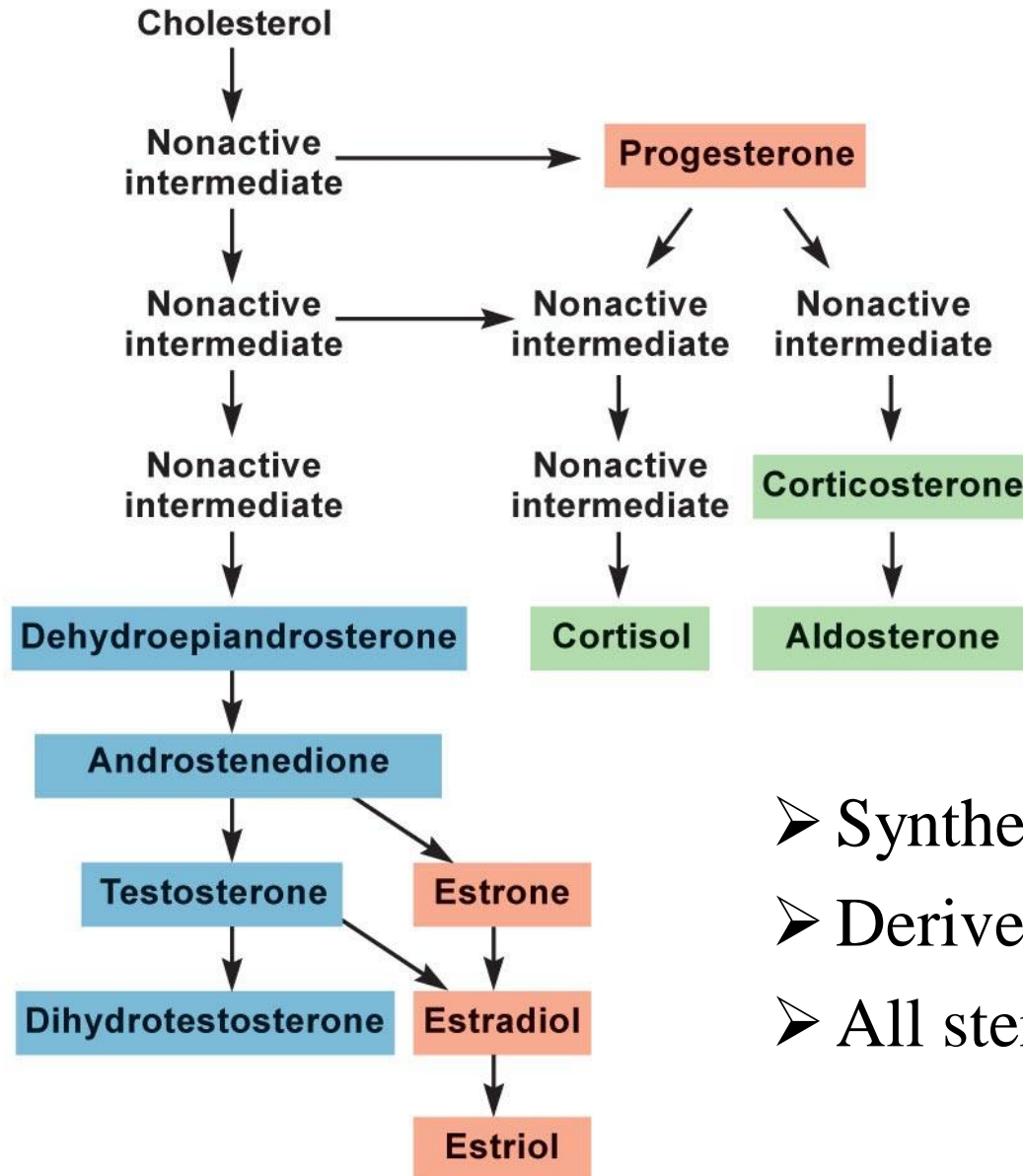
(a) Peptide synthesis

Messenger Classification by Chemical Class

4. Steroid ligands

- Lipophilic
- Target has intracellular receptors
- Derived from **cholesterol**
- All steroid messengers (ligands) function as **hormones**

Synthesis and Release of Steroid



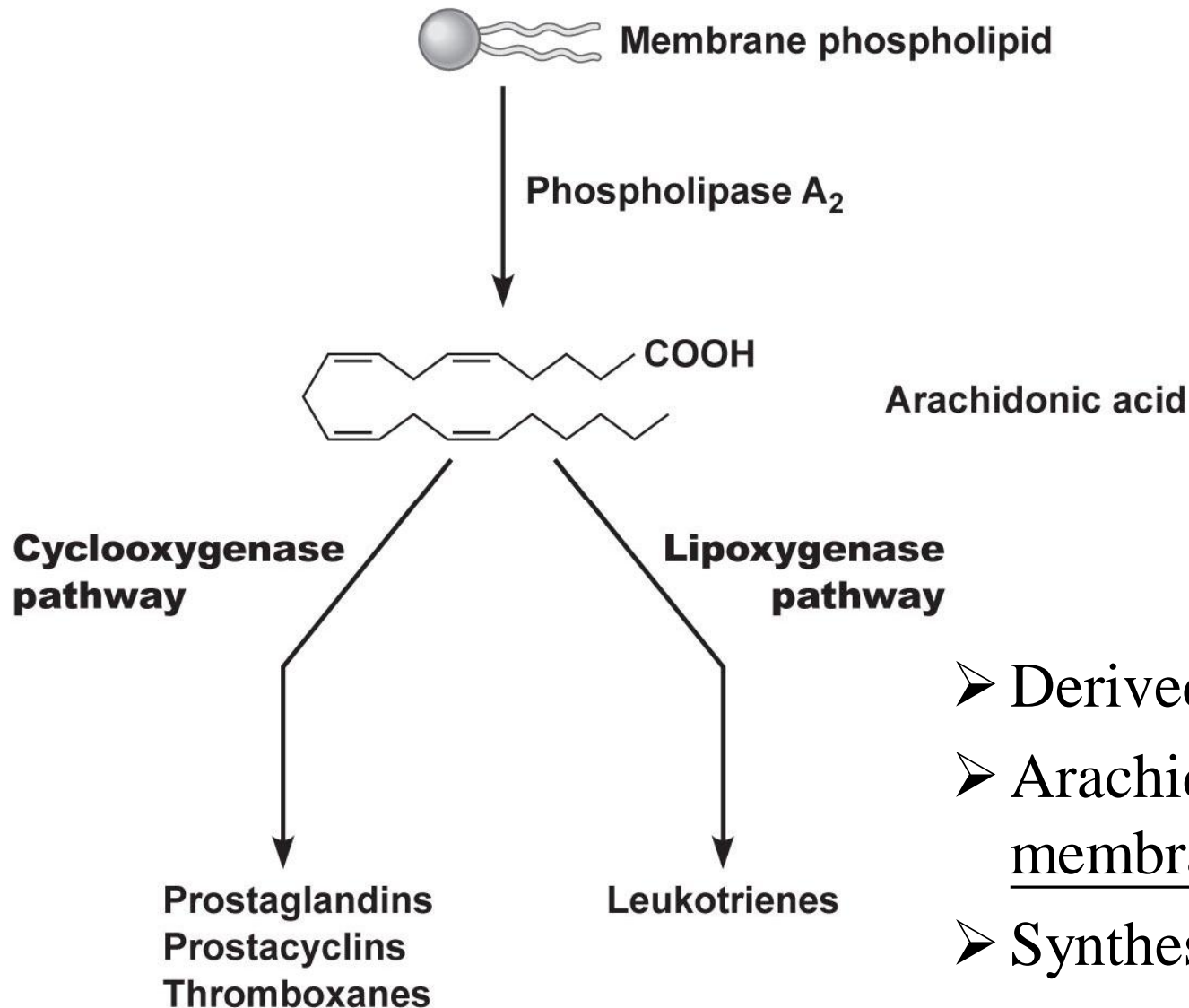
- Synthesized on **demand**
- Derived from **cholesterol** molecule
- All steroid ligands are similar

Messenger Classification by Chemical Class

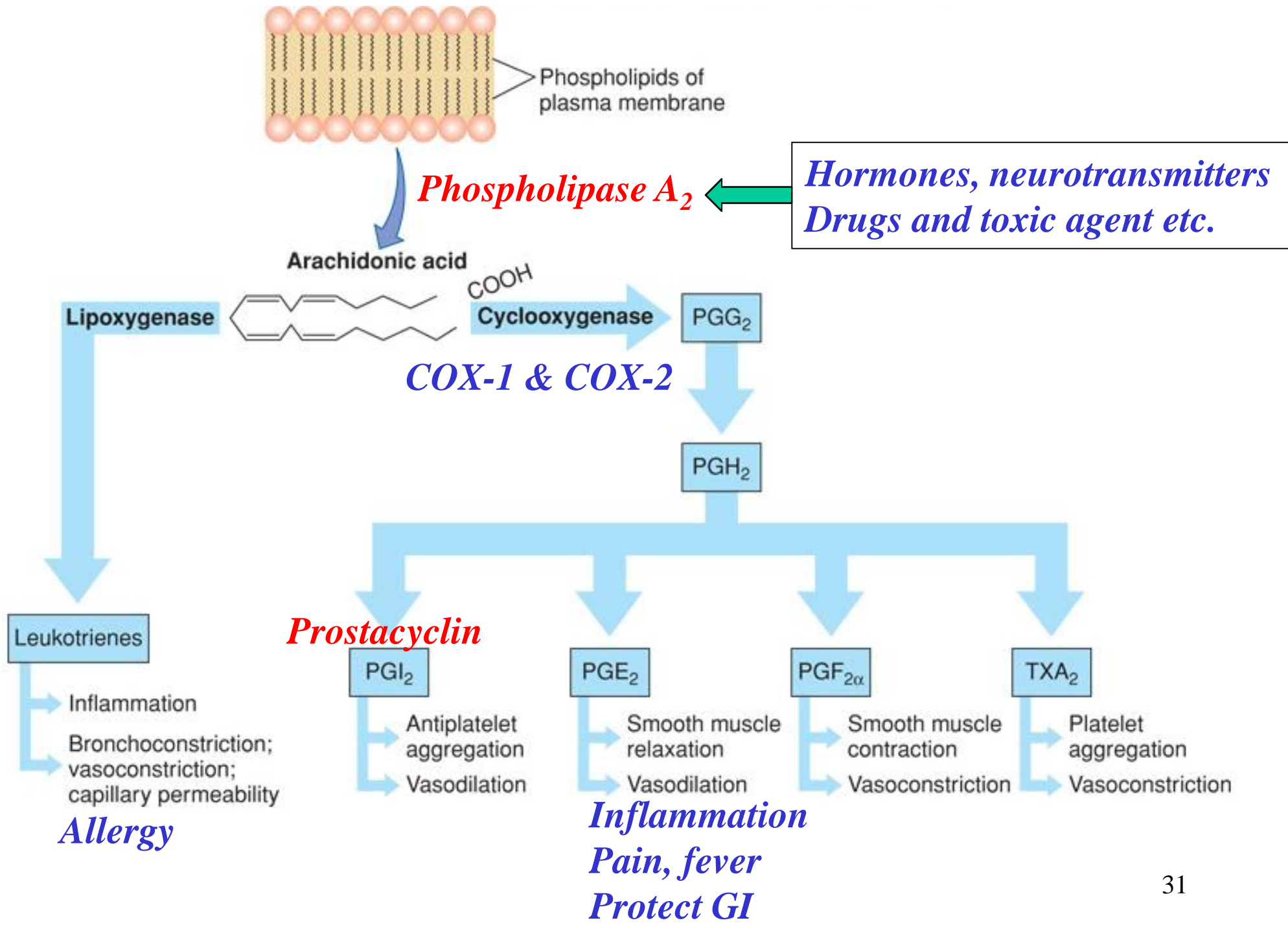
5. Eicosanoid ligands

- Lipophilic
- Intracellular target receptors
- Derived from **arachidonic acid (AA)**,
a cell membrane phospholipid
- Examples:** **prostaglandin (PG)**,
leukotrienes (LT), **thromboxanes (TX)**

Synthesis and Release of Eicosanoid



- Derived from **arachidonic acid**
- Arachidonic acid is a membrane phospholipid
- Synthesized on **demand**





1936年，Goldblatt和von Euler分別發現人體精液中含有一種使平滑肌興奮和血壓降低的液體成分，當時誤以為是由前列腺所分泌，故命名為**前列腺素** (prostaglandin, PG)。實際上，前列腺素廣泛存在於人體和動物體的各种組織和器官中，透過旁分泌和自分泌產生作用。

前列腺素主要分為A~I型，還有多種亞型。其分布廣泛，作用複雜，代謝快，半衰期 (half life) 為1~2分鐘，為典型之組織激素。其中PGA₂和PGI₂經血液循環系統產生作用；PGE和PGF類衍生物可使婦女子宮強烈收縮，可用於終止妊娠和催產；PGE₁或PGE₂和PGA能抑制胃液的分泌，保護胃壁細胞，可以用於治療胃潰瘍、出血性胃炎及腸炎。

Messenger Transport

● **Diffusion** through interstitial fluid

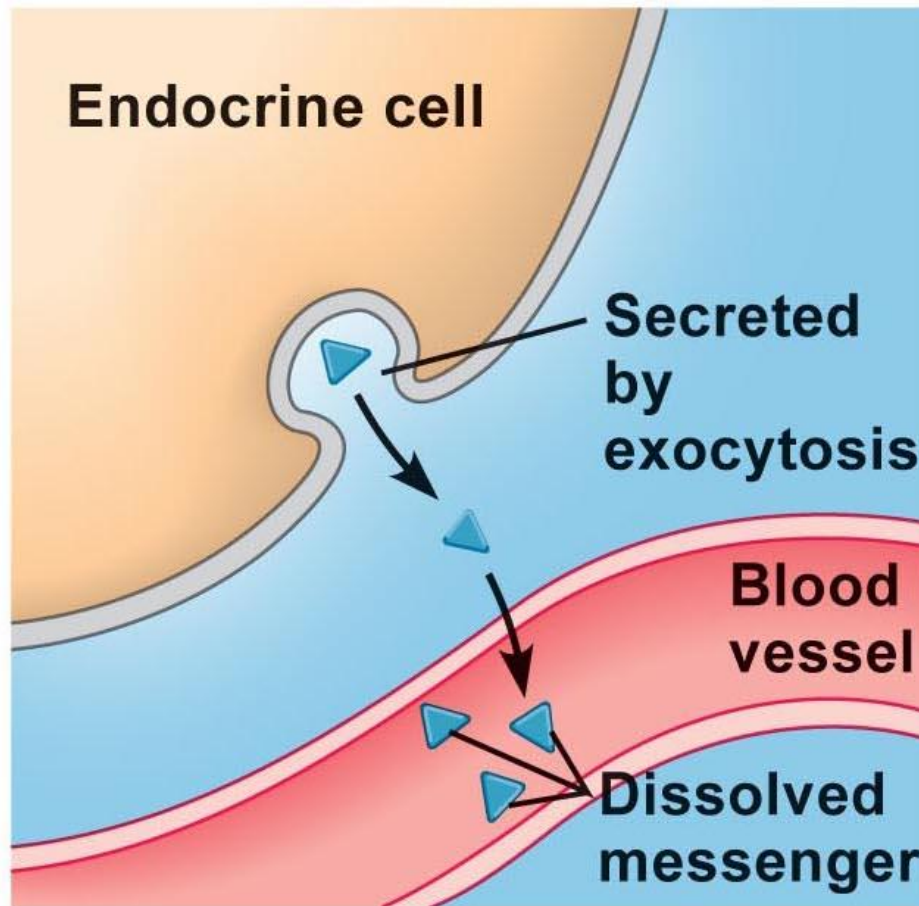
- Source and target are close
- Ligand is quickly degraded
- Examples:** Paracrines, autocrines, neurotransmitters, and most cytokines

● **Blood-borne transport**

- Source and target at distance
- Lipophobic ligands dissolve in plasma
- Lipophilic ligands bind to carrier protein
- Examples:** Hormones, neurohormones, and some cytokines

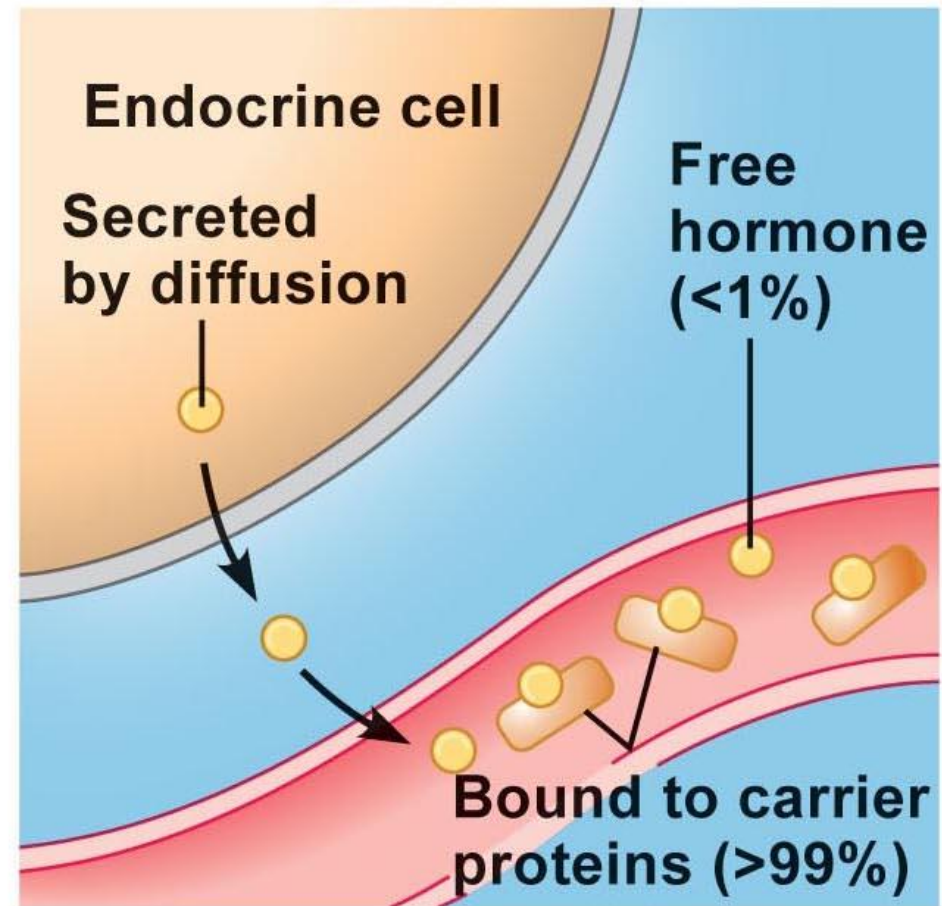
Messenger Transport

Blood-borne transport



Lipid-insoluble ligand

- *Have relative short half-life*
- *Example: Half-life insulin is <10 min*



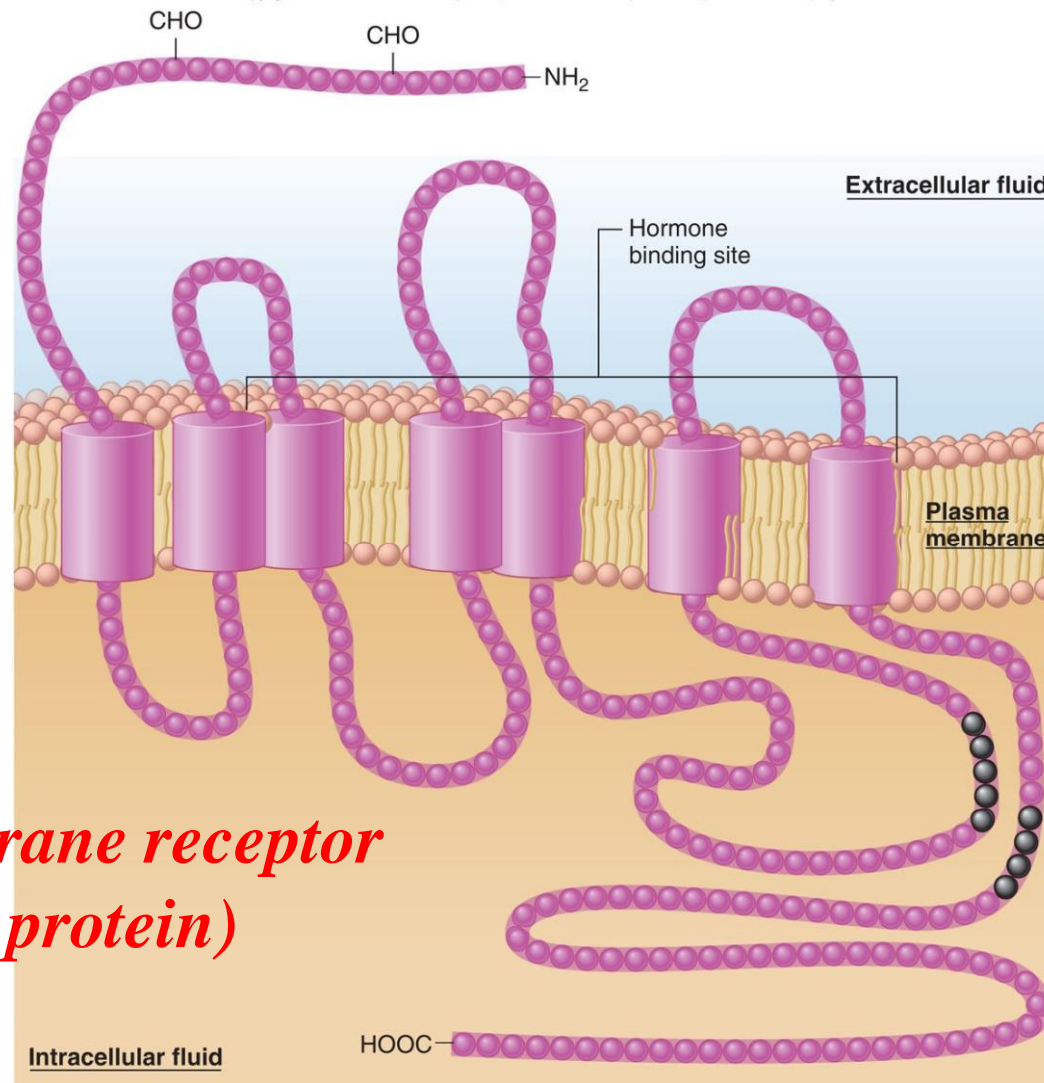
Lipid-soluble ligand

- *Have relative long half-life*
- *Example: Half-life of cortisol = 90 min*

Signal Transduction

How a chemical signal is translated into a cell action

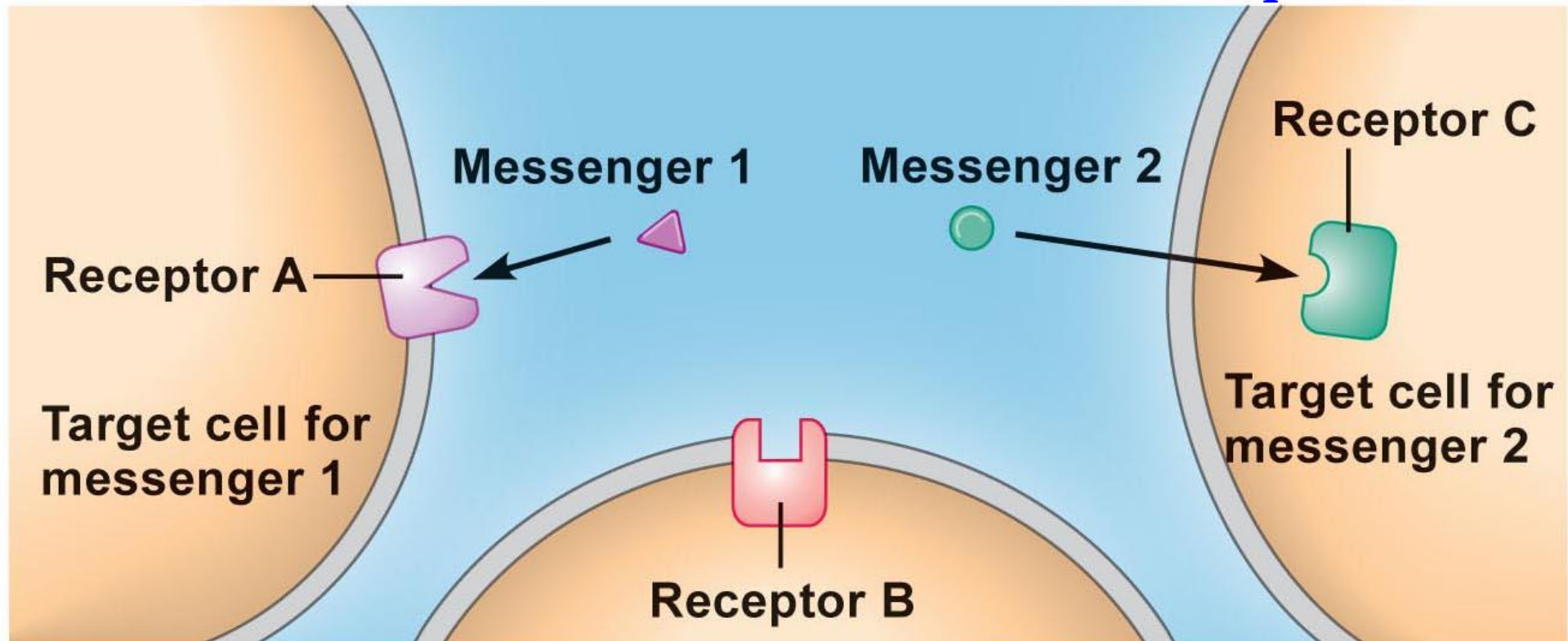
Source → Ligand → Target (receptor) → Response



*Typical membrane receptor
(integral protein)*

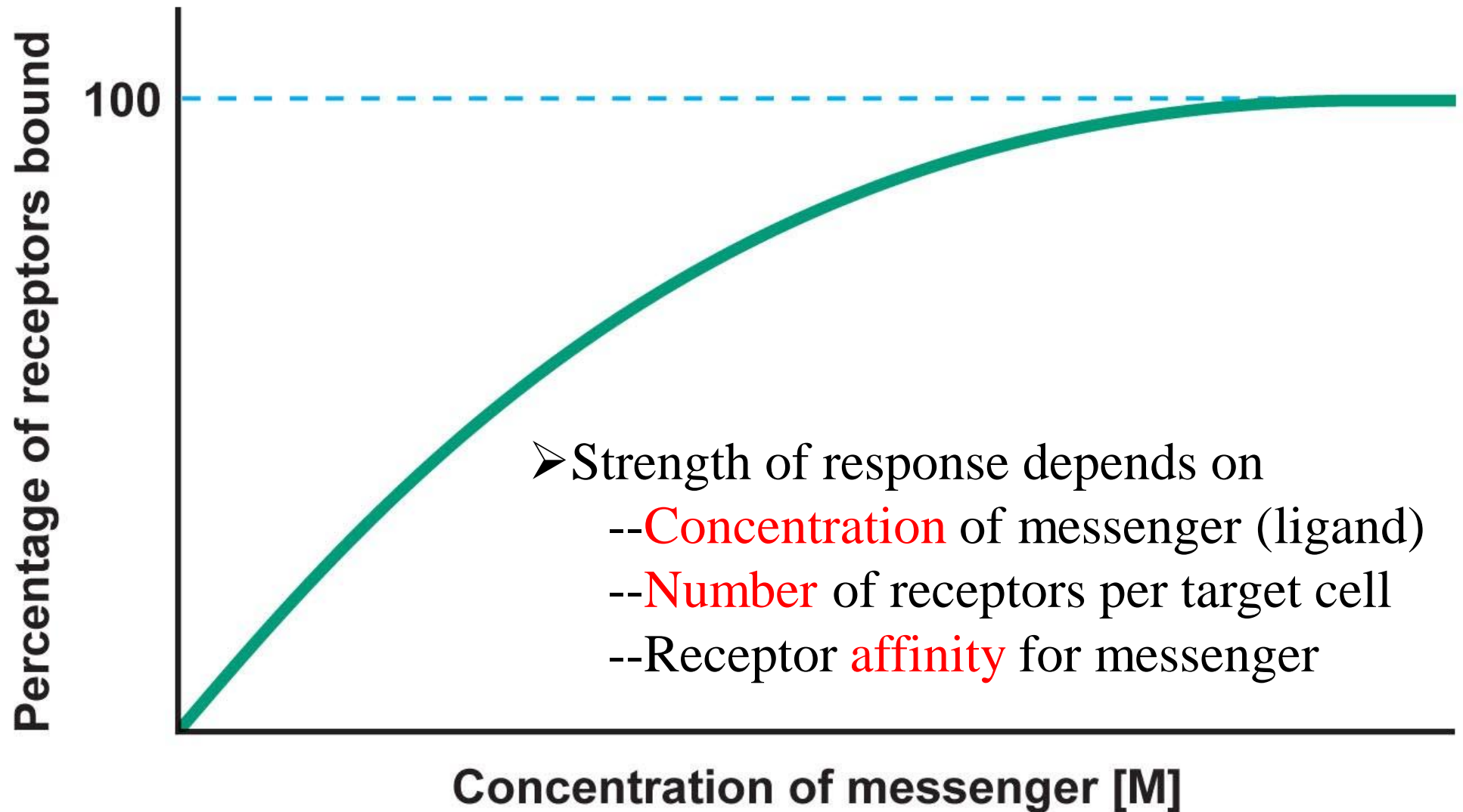
Receptor Properties

- ✓ *Specificity*
- ✓ *Affinity*
- ✓ *Saturation*
- ✓ *Reverse*
- ✓ *Competition*



- One messenger may bind many receptor types
- One target may have many types of receptors
- Number of receptors per cell varies and is dynamic ³⁶

Magnitude of Target Response



名稱	定義
Receptor	A specific protein in either the plasma membrane or interior of a target cell with which a chemical messenger combines.
Specificity	The ability of a receptor to bind only one type or a limited number of structurally related types of chemical messengers.
Saturation	The degree to which receptors are occupied by a messengers.If all are occupied, the receptors are fully saturated; if half are occupied, the saturation is 50 percent, and so on.
Affinity	The strength with a chemical messenger binds to its receptor.
Competition	The ability of different molecules very similar in structure to its receptor.
Antagonist	A molecule that competes for a receptor with a chemical messenger normally present in the body. The antagonist binds to the receptor but does not trigger the cell's response.
Agonist	A chemical messenger that binds to a receptor and triggers the cell's response; often refers to a drug that mimics a normal messenger's action.
Down-regulation	A decrease in the <u>total number of target-cell receptors</u> for a given messenger in response to chronic high extracellular concentration of the messenger.
Up-regulation	An increase in the <u>total number of target-cell receptors</u> for a given messenger in response to a chronic low extracellular concentration of the messenger.
Supersensitivity	The increased responsiveness of a target cell to a given messenger, resulting from <u>up-regulation</u> .

Agonist and Antagonist

● Agonist

- Chemical which binds to receptor
- Action mimics normal response

● Antagonist

- Chemical which binds to receptor
- Binding does not result in response
- Competes with normal ligand
- Response is opposite of the agonist

Agonist and Antagonist

- **Beta-endorphin = endogenous opiate**

- Beta-endorphin binds to mu opiate receptors producing analgesia

- **Morphine = mu receptor agonist**

- Administration of morphine produces analgesia

- **Naloxone = mu receptor antagonist**

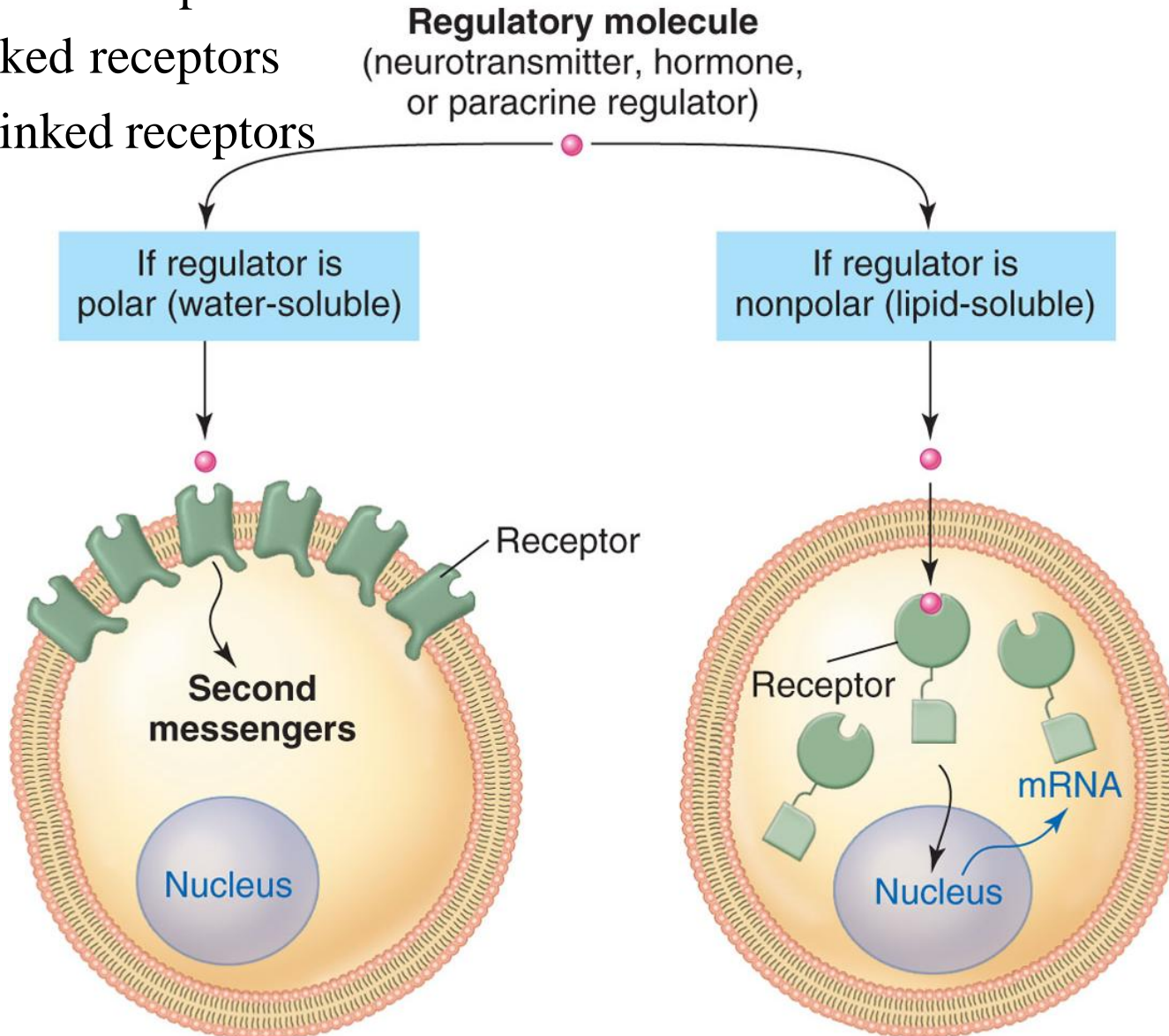
- Administration of naloxone blocks morphine- or beta-endorphin–produced analgesia

Mechanisms of Signal Transduction

Membrane receptor-mediated responses

- **Channel**-linked receptors
- **Enzyme**-linked receptors
- **G protein**-linked receptors

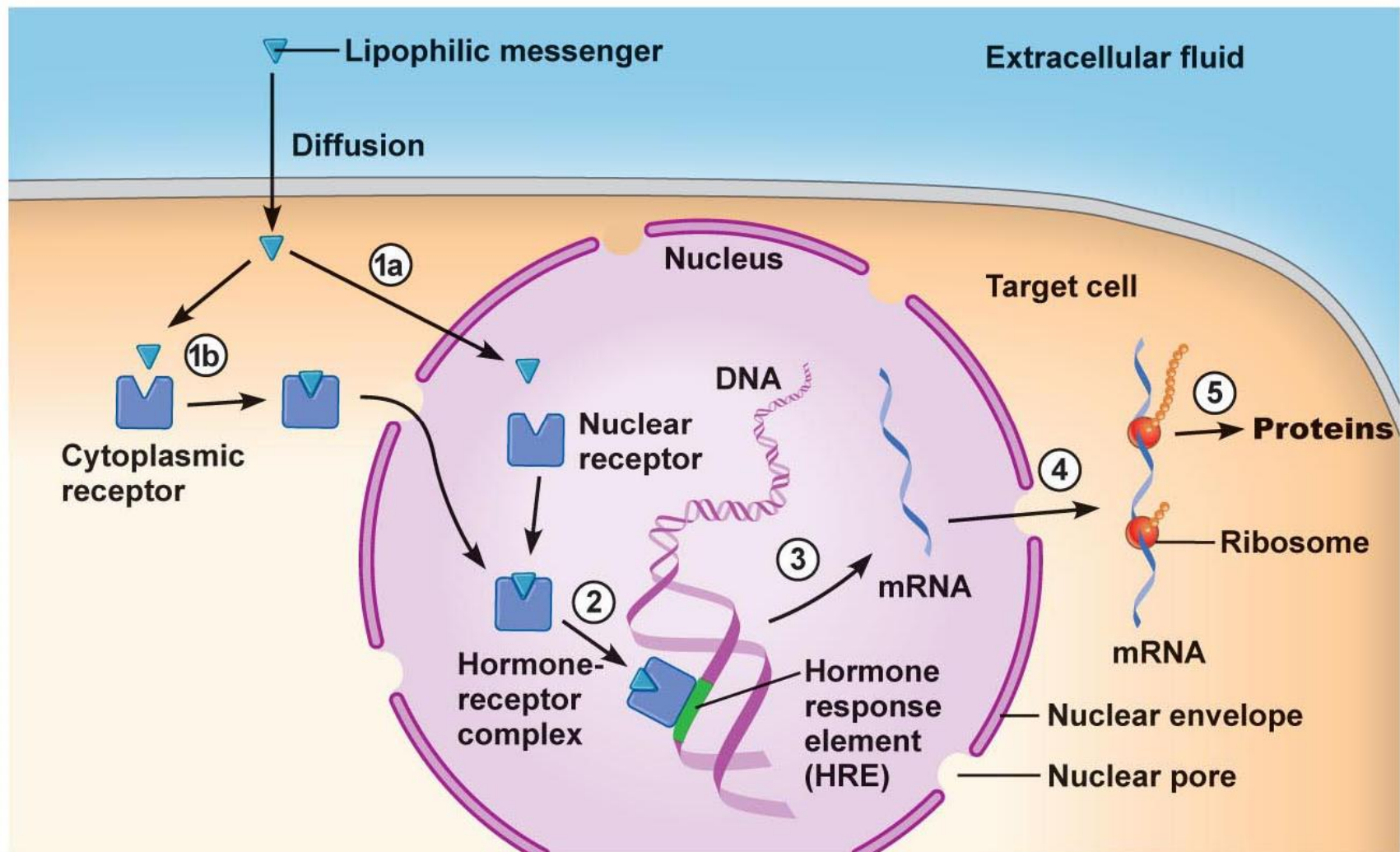
Intracellular-mediated responses



Mechanisms of Signal Transduction

1. Intracellular-Mediated Response

Characteristic of **lipid-soluble messengers**, receptors are in cytosol or nucleus and cell response is via gene activation



Mechanisms of Signal Transduction

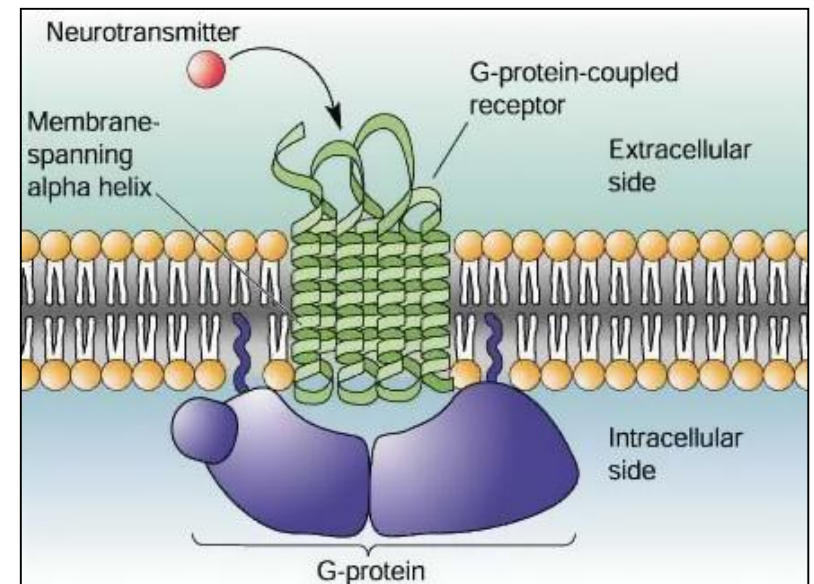
2. Membrane Receptor-Mediated Responses

- Characteristic of **lipid-insoluble messengers**
- Receptors are on cell membrane
- Response of the target is either by
Movement of **ions**, or phosphorylation of
enzymes (enzyme activation)
- Overview of mechanisms

Channel-linked receptors

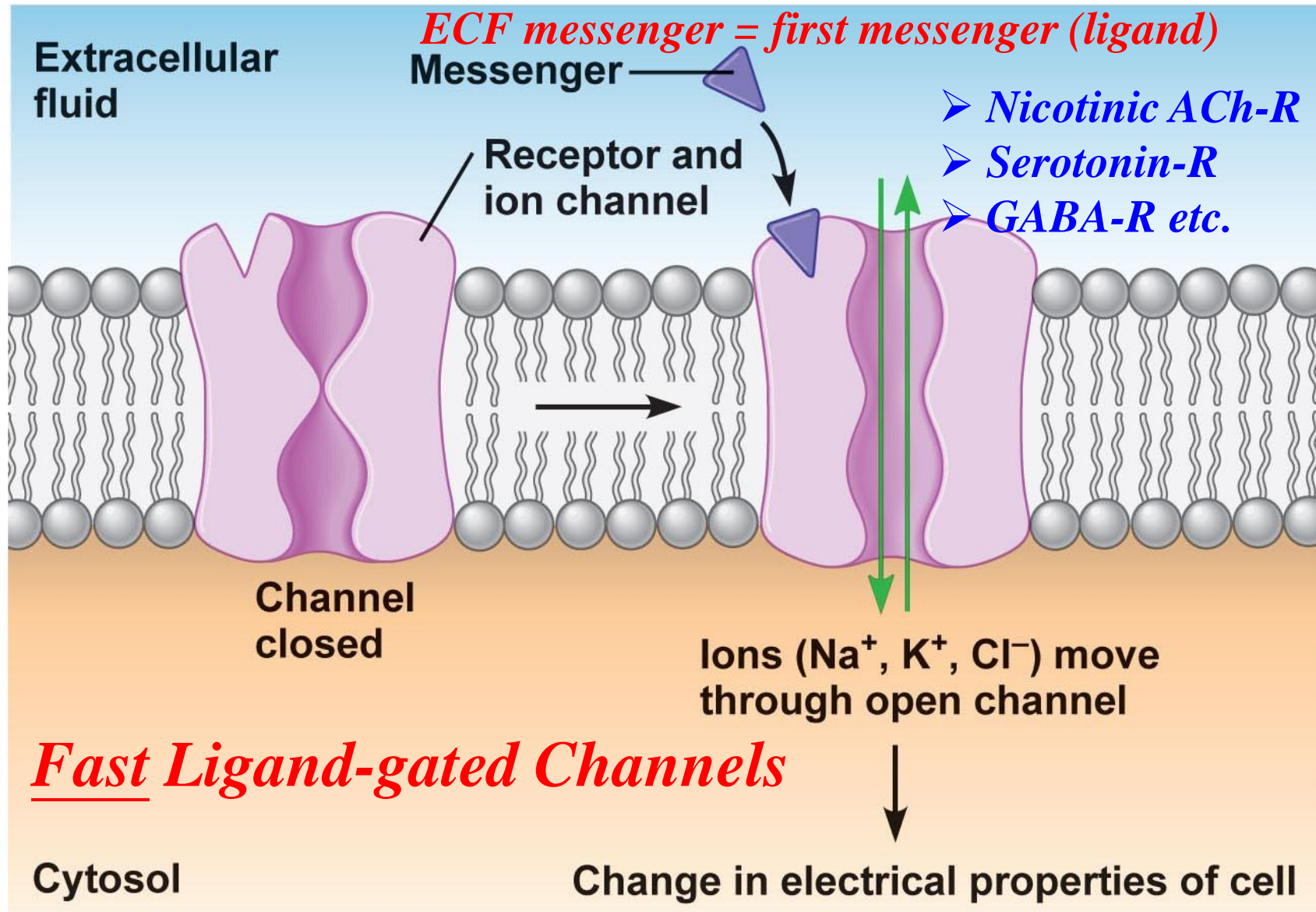
Enzyme-linked receptors

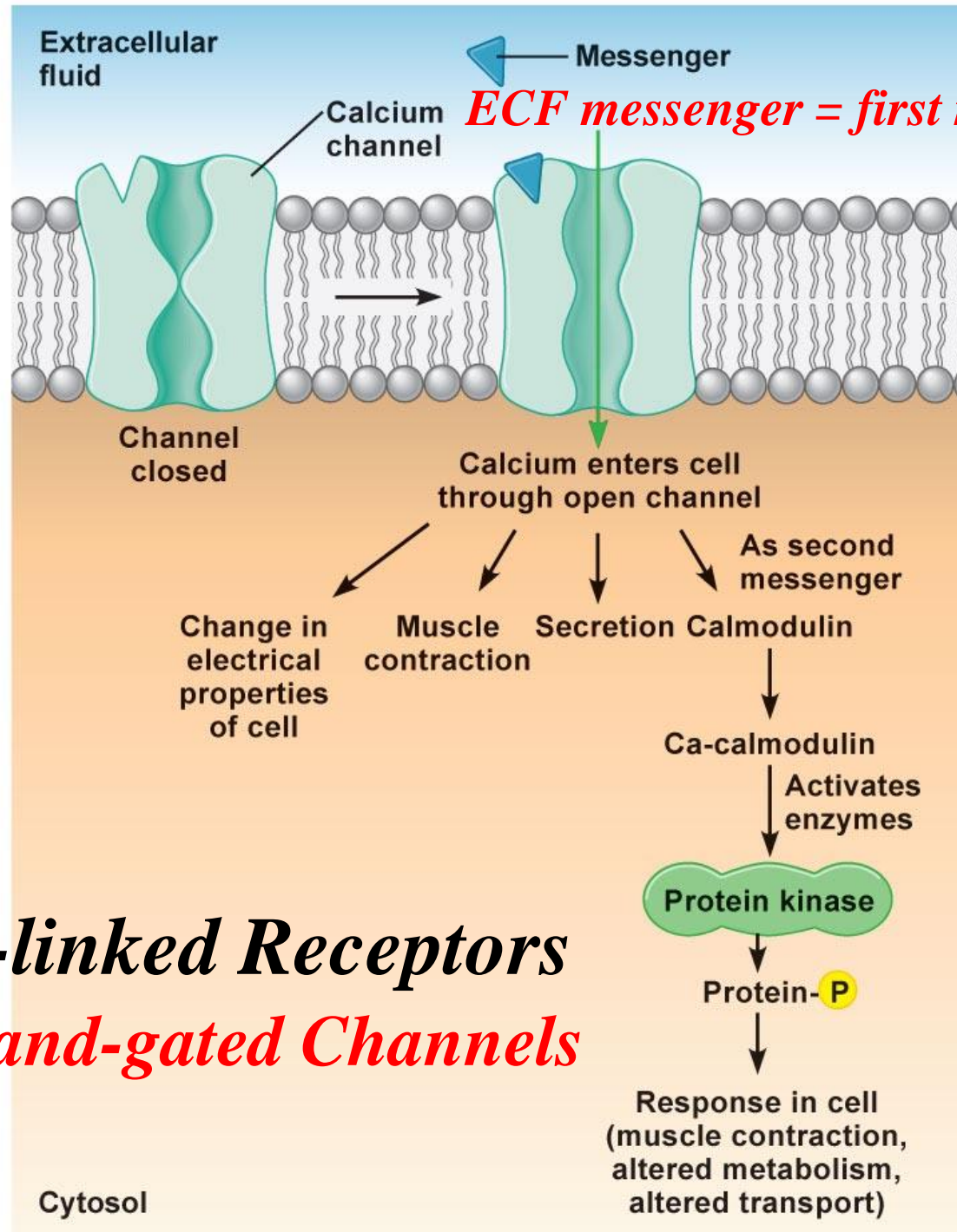
G protein-linked receptors



Membrane Receptor-Mediated Responses

Channel-linked Receptors



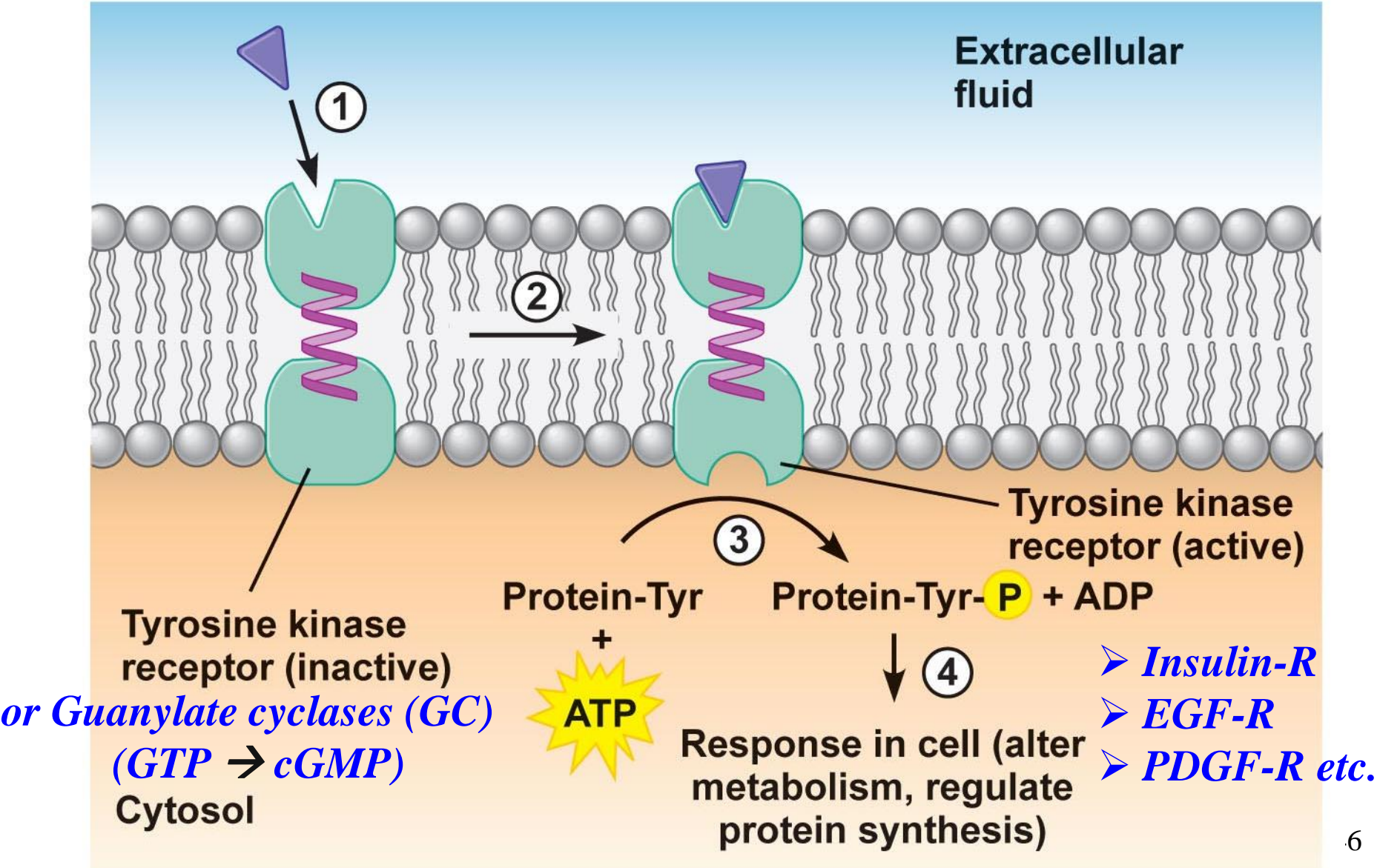


ECF messenger = first messenger (ligand)

*Channel-linked Receptors
= Fast Ligand-gated Channels*

Membrane Receptor-Mediated Responses

Enzyme-linked Receptors



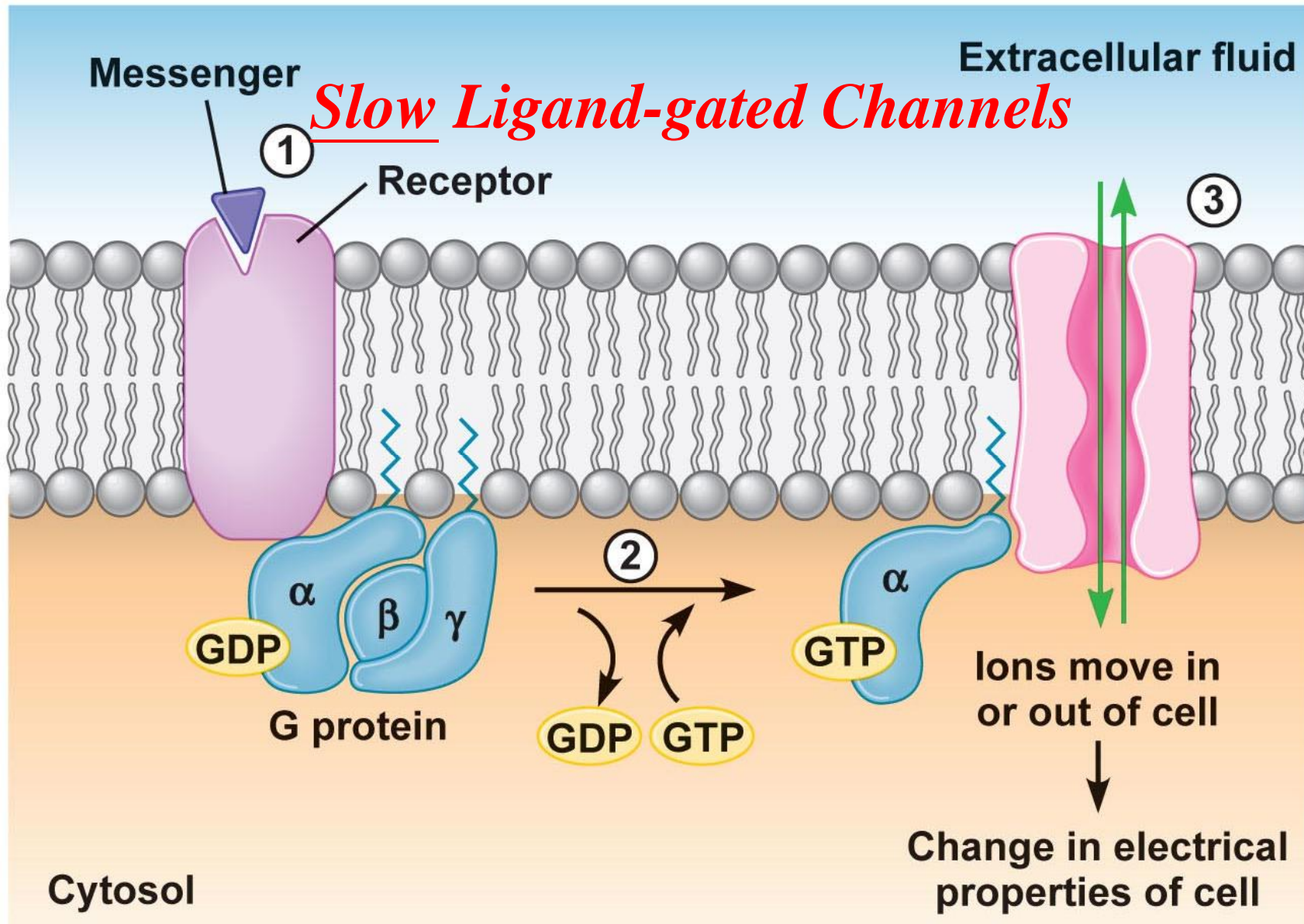
Membrane Receptor-Mediated Responses

G Protein-linked Receptors

- G proteins are regulatory proteins
- G proteins link ECF messenger to effectors
 - Ion channels, or enzymes (→ *second messenger*)
- Slow ligand-gated channels
 - Receptor and channel—different proteins
 - Receptor and channel linked by G protein
 - Binding of ligand activates G protein, which activates channel
 - Action is indirect (slow)
 - Change in transport of ions through channel causes target response
- **Second messenger**

Membrane Receptor-Mediated Responses

G Protein-linked Receptors



Membrane Receptor-Mediated Responses

G Protein-linked Receptors

- **Second messengers**

- Intracellular messenger

- Triggered by first messenger (ligand) activating G protein

- G protein activates amplifier enzyme

- Amplifier enzyme activates second messenger production

- **Binding of first messenger to receptor leads to production of second messenger**

- **Involves G proteins**

- **G_s** (Activates amplifier enzyme)

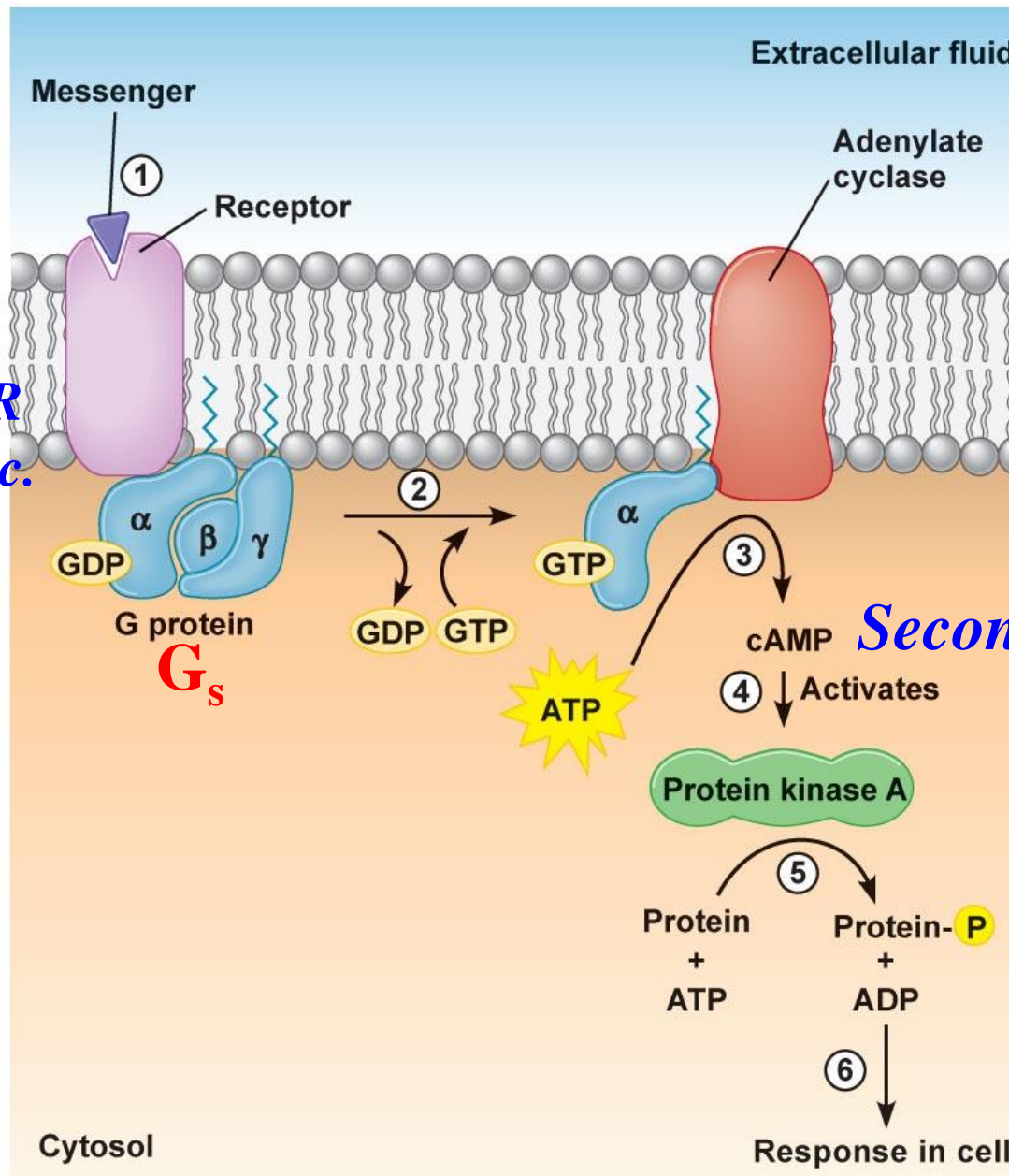
- **G_i** (Inhibits amplifier enzyme)

- **Purpose is **signal amplification****

G Protein-linked Receptors

Adenylyl Cyclase - cAMP

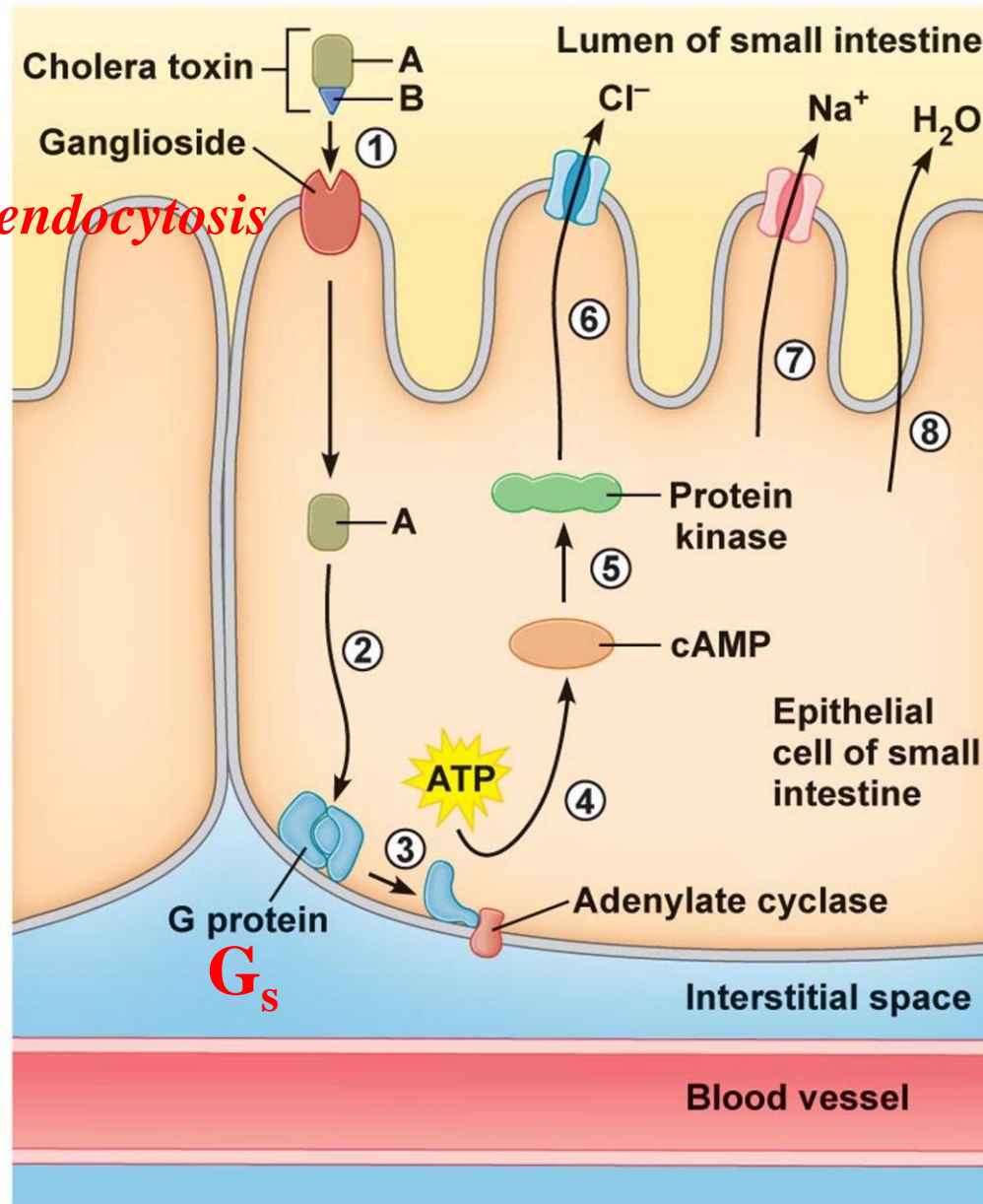
- *Epinephrine-R*
- *AVP (V₂)-R etc.*

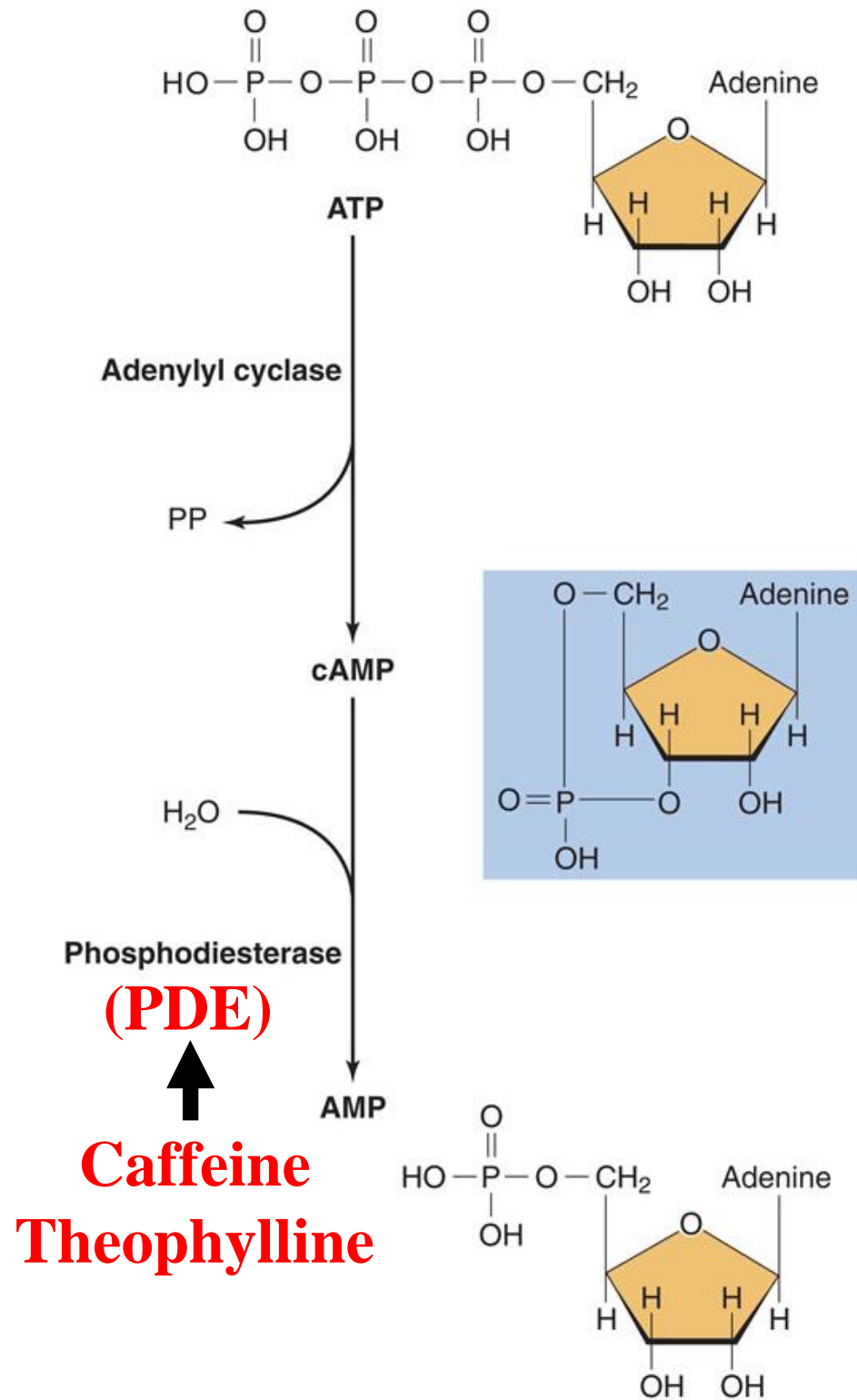


Second messenger

Clinical Application: Cholera Toxin → Watery Diarrhea

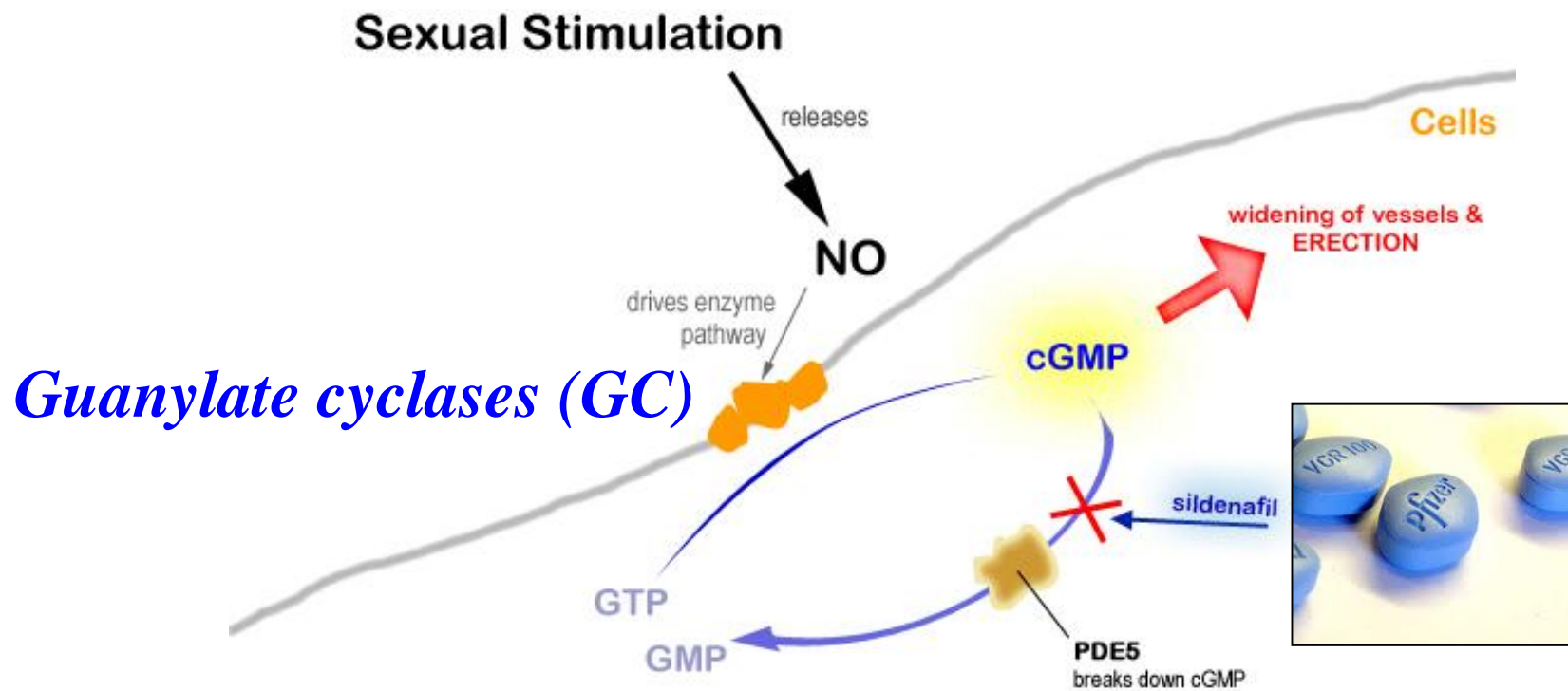
Receptor-mediated endocytosis





Clinical Application: *Viagra*[®] (sildenafil citrate)

- a potent and selective inhibitor of *cGMP-specific phosphodiesterase type 5 (PDE5)*, which is responsible for degradation of cGMP in the *corpus cavernosum in the penis*



Penile vascular smooth-muscle cell

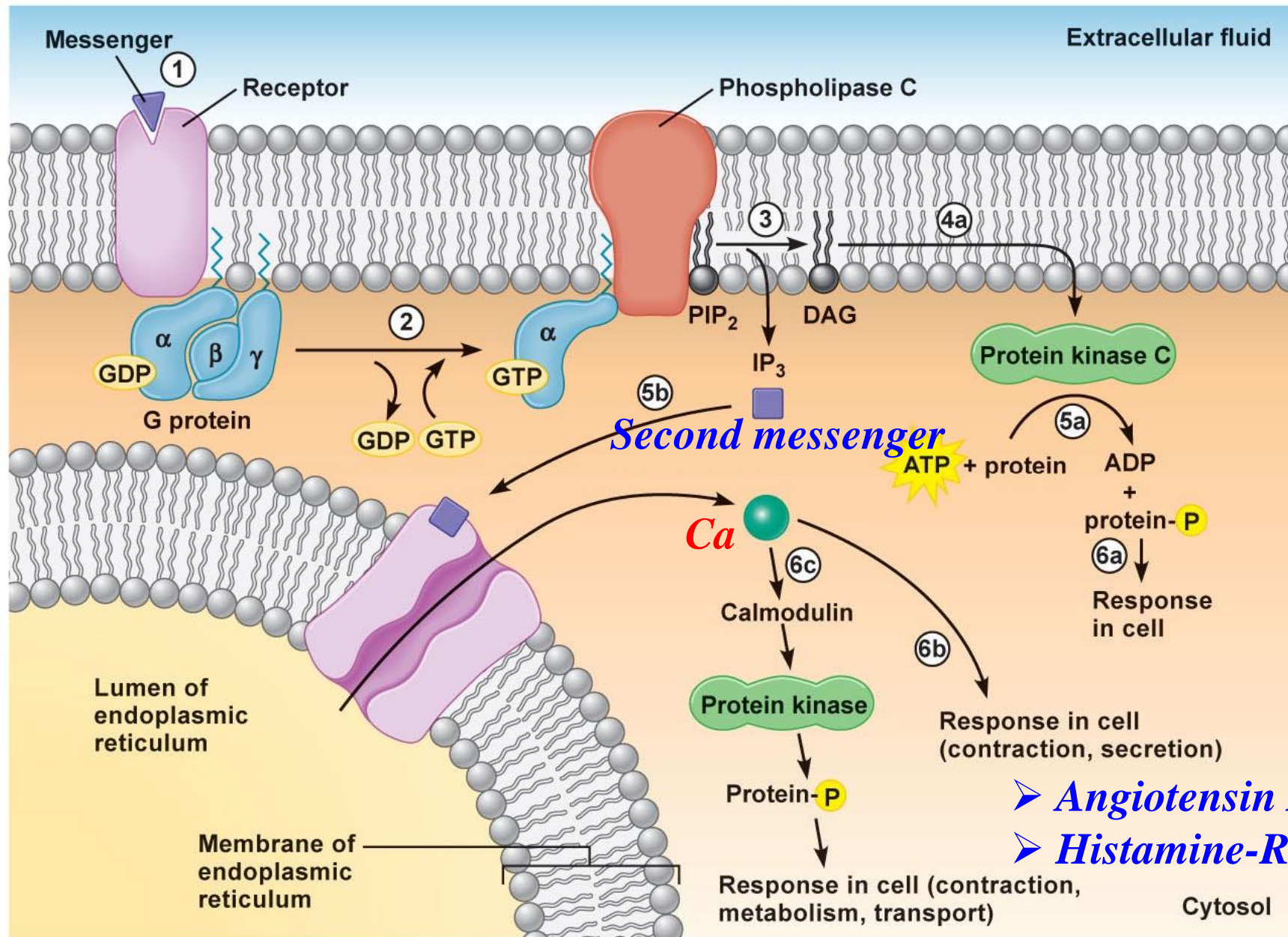
Types of Second Messengers

Second messenger	Precursor	Amplifier enzyme	Usual action	Examples of first messengers in the system
Cyclic adenosine monophosphate (cAMP)	ATP	Adenylate cyclase	Activates protein kinase A PKA	Epinephrine, vasopressin, ACTH, glucagon
Cyclic guanosine monophosphate (cGMP)	GTP	Guanylate cyclase	Activates protein kinase G PKG	Atrial natriuretic peptide, endothelins
Diacylglycerol (DAG)	Inositol-4,5-biphosphate (PIP ₂)	Phospholipase C	Activates protein kinase C PKC	Angiotensin II, histamine, vasopressin
Inositol triphosphate (IP ₃)	Inositol-4,5-biphosphate (PIP ₂)	Phospholipase C	Stimulates calcium release from intracellular stores	Angiotensin II, histamine, vasopressin
Calcium*	None	None	Binds to calmodulin, then activates a protein kinase	Angiotensin II, histamine, vasopressin

*Calcium increases in the cytosol in response to opening of ion channels either in the plasma membrane or in certain organelles.

G Protein-linked Receptors

Phospholipase C - IP₃ & DAG



Heterotrimeric G Proteins

TABLE 5–1. SELECTED MAMMALIAN HETEROTRIMERIC G PROTEINS CLASSIFIED ON THE BASIS OF THEIR α SUBUNITS*

G Protein	Activated by Receptors for	Effectors	Signaling Pathways
G_s	Epinephrine, norepinephrine, histamine, glucagon, adrenocorticotrophic hormone, luteinizing hormone, follicle-stimulating hormone, thyroid-stimulating hormone, others	Adenylyl cyclase Ca^{++} channels	\uparrow cAMP \uparrow Ca^{++} influx
G_{olf}	Odorants	Adenylyl cyclase	\uparrow AMP (olfaction)
G_{t1} (rods)	Photons	cGMP phosphodiesterase	\downarrow cGMP (vision)
G_{t2} (cones)	Photons	cGMP phosphodiesterase	\downarrow cGMP (color vision)
G_{i1}, G_{i2}, G_{i3}	Norepinephrine, prostaglandins, opiates, angiotensin, many peptides	Adenylyl cyclase Phospholipase C Phospholipase A_2 K^+ channels	\downarrow cAMP \uparrow InsP3, diacylglycerol, Ca^{++}
G_q	Acetylcholine, epinephrine	Phospholipase $C\beta$	Membrane polarization \uparrow InsP3, diacylglycerol, Ca^{++}

*There is more than one isoform of each class of α subunit; more than 20 distinct α subunits have been identified.

Ligands & Signal Transduction Mechanisms

Messenger	Functional class	Chemical class	Signal transduction mechanism
Epinephrine	Hormone, neurotransmitter	Amine	G protein–coupled receptors
Thyroid hormones	Hormone	Amine (lipophilic)	Altered transcription of mRNA
Vasopressin (ADH)	Hormone, neurotransmitter	Peptide	G protein–coupled receptors
Insulin	Hormone, neurotransmitter	Peptide	Enzyme-linked receptors
Estrogen	Hormone	Steroid	Altered transcription of mRNA
Glutamate	Neurotransmitter	Amino acid	Channel-linked receptor, G protein–coupled receptors
Serotonin	Neurotransmitter, paracrine	Amine	Channel-linked receptor, G protein–coupled receptors
Prostaglandins	Paracrine	Eicosanoid	G proteins, unknown for many
Interleukins	Cytokine	Peptide	Enzyme-linked receptors
GABA	Neurotransmitter	Amino acid	Channel-linked receptor

自己

當你能飛的時候就不要放棄飛

當你能夢的時候就不要放棄夢

當你能愛的時候就不要放棄愛

用最少的悔恨面對過去

用最少的浪費面對現在

用最多的夢面對未來

你不能左右天氣，但你能轉變你的心情
好好扮演自己的角色，做自己該做的事，

活出你的生命，作自己的主角