Receptors Functions and Signal Transduction L1- L2

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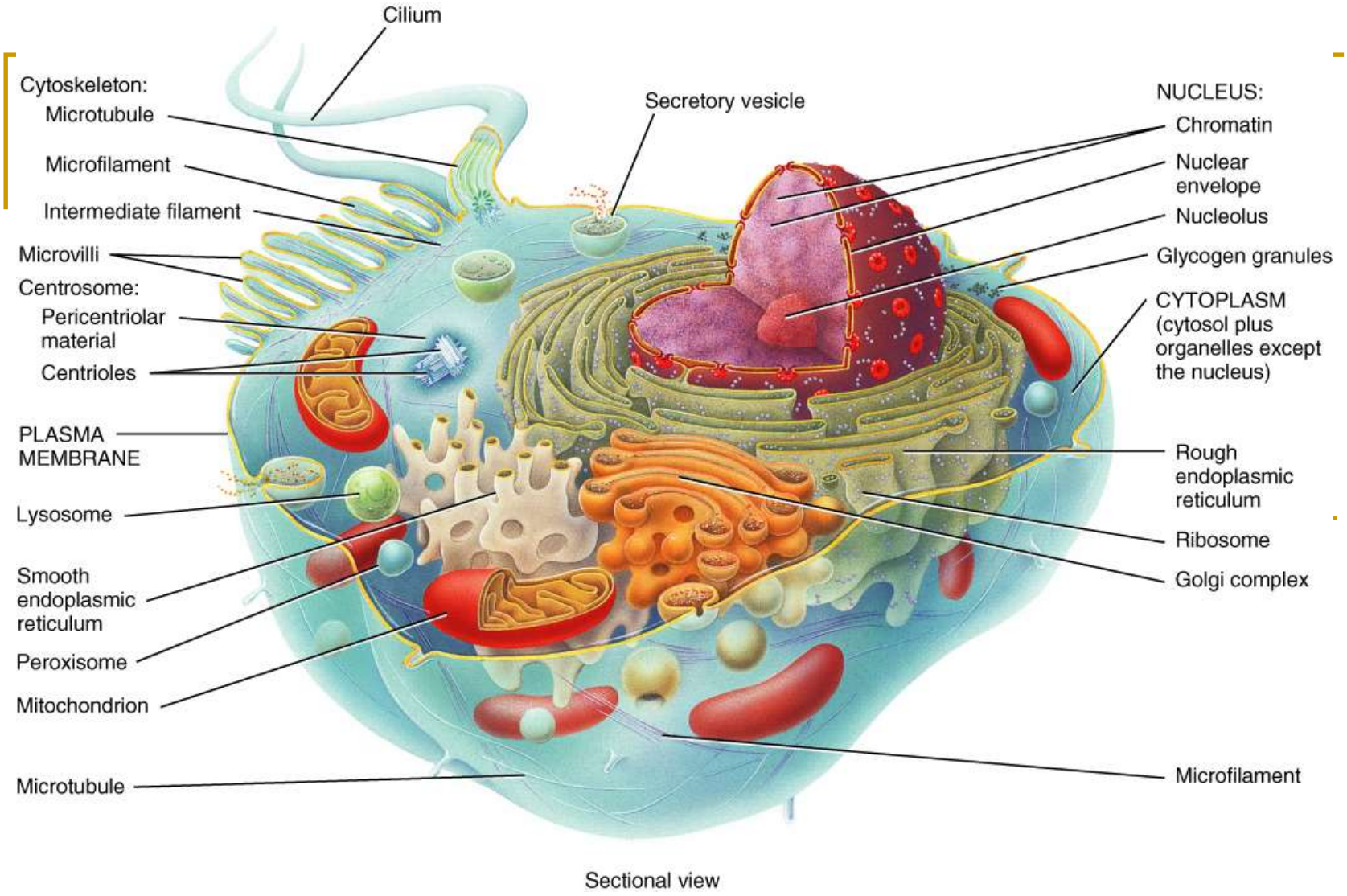
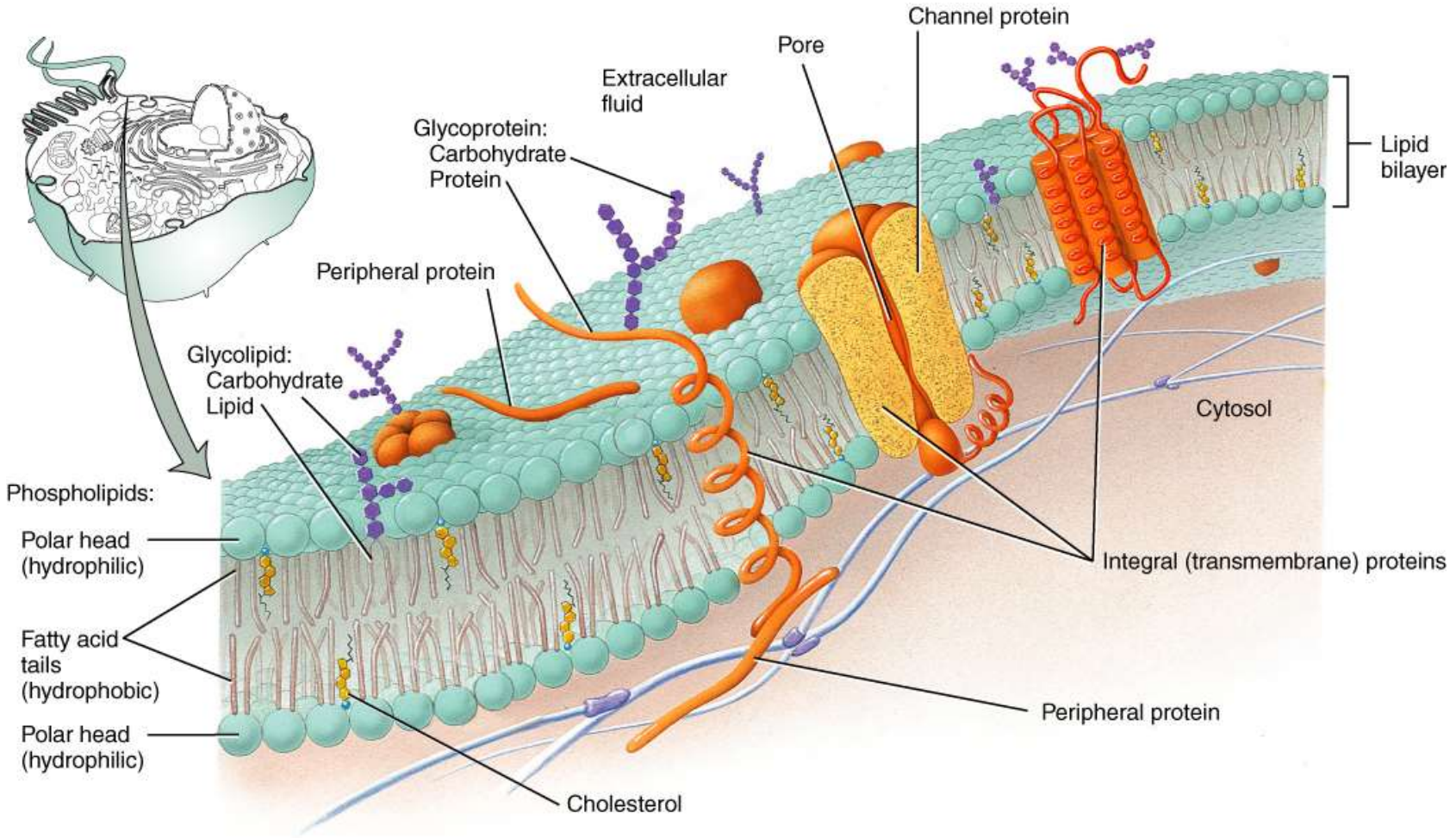
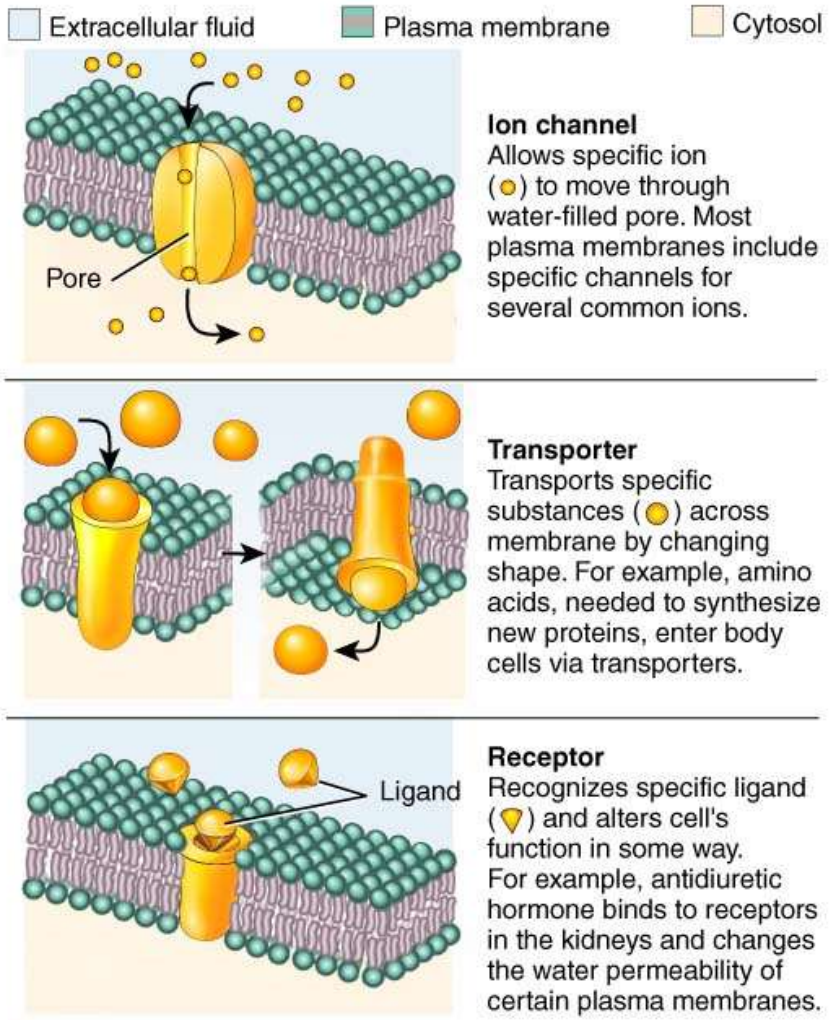
Objectives

- Define first messenger (Hormones)
- List hormone types
- Describe receptor types
- Outline the hormone receptors interactions
- Describe second messenger mechanism of action
- List second messengers



Sectional view

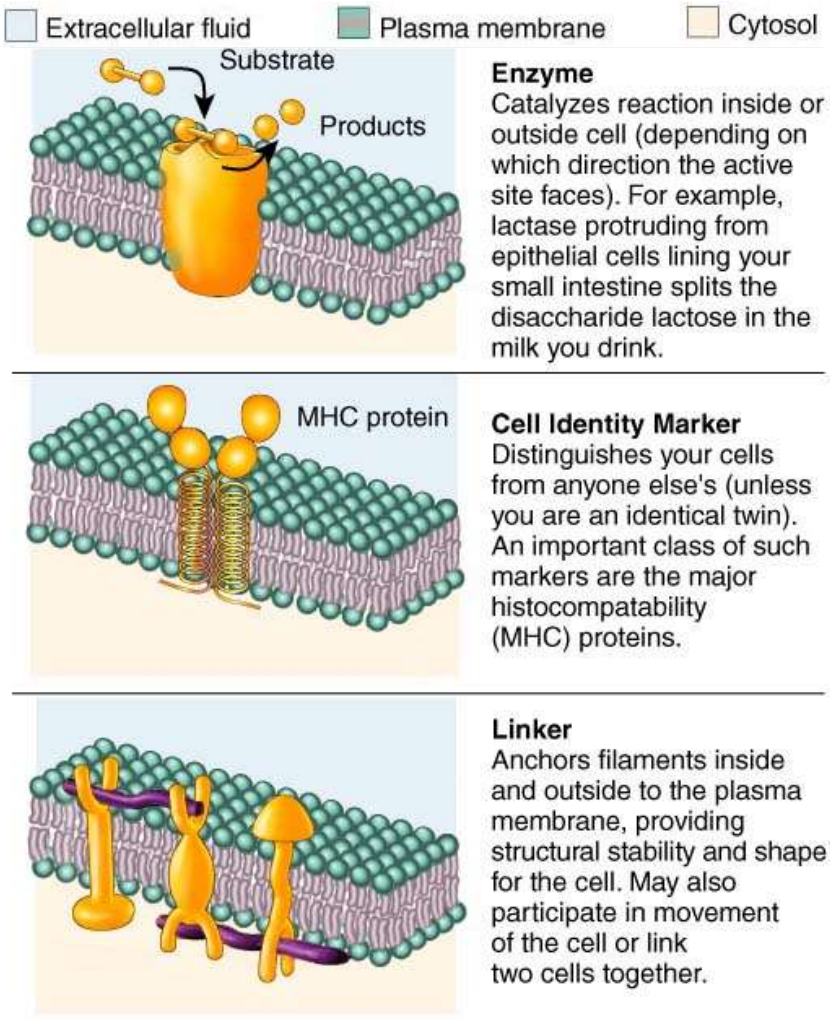

Channel protein
Pore
Extracellular fluid
Glycoprotein:
Carbohydrate
Protein
Lipid bilayer
Peripheral protein
Glycolipid:
Carbohydrate
Lipid
Cytosol
Phospholipids:
Polar head (hydrophilic)
Integral (transmembrane) proteins
Fatty acid tails (hydrophobic)
Peripheral protein
Polar head (hydrophilic)
Cholesterol



Ion channel
Allows specific ion (●) to move through water-filled pore. Most plasma membranes include specific channels for several common ions.

Transporter
Transports specific substances (●) across membrane by changing shape. For example, amino acids, needed to synthesize new proteins, enter body cells via transporters.

Receptor
Recognizes specific ligand (▼) and alters cell's function in some way. For example, antidiuretic hormone binds to receptors in the kidneys and changes the water permeability of certain plasma membranes.



Enzyme
Catalyzes reaction inside or outside cell (depending on which direction the active site faces). For example, lactase protruding from epithelial cells lining your small intestine splits the disaccharide lactose in the milk you drink.

Cell Identity Marker
Distinguishes your cells from anyone else's (unless you are an identical twin). An important class of such markers are the major histocompatability (MHC) proteins.

Linker
Anchors filaments inside and outside to the plasma membrane, providing structural stability and shape for the cell. May also participate in movement of the cell or link two cells together.

Overview of Signal Transduction

A. Definitions

Signaling: **Cell-cell communication via signals.**

Signal transduction: **Process of converting extracellular signals into intra-cellular responses.**

Ligand: **The signaling molecule.**

Receptors: **Bind specific ligands. Transmit signals to intracellular targets. Different receptors can respond differently to the same ligand.**

B. Components involved in signaling:

Ligands

Receptors

Intracellular Signaling Proteins

- ***Intermediary Proteins***
- ***Enzymes***
- ***Second Messengers***
- ***Target Proteins***
- ***Inactivating Proteins***

Overview of Signal Transduction

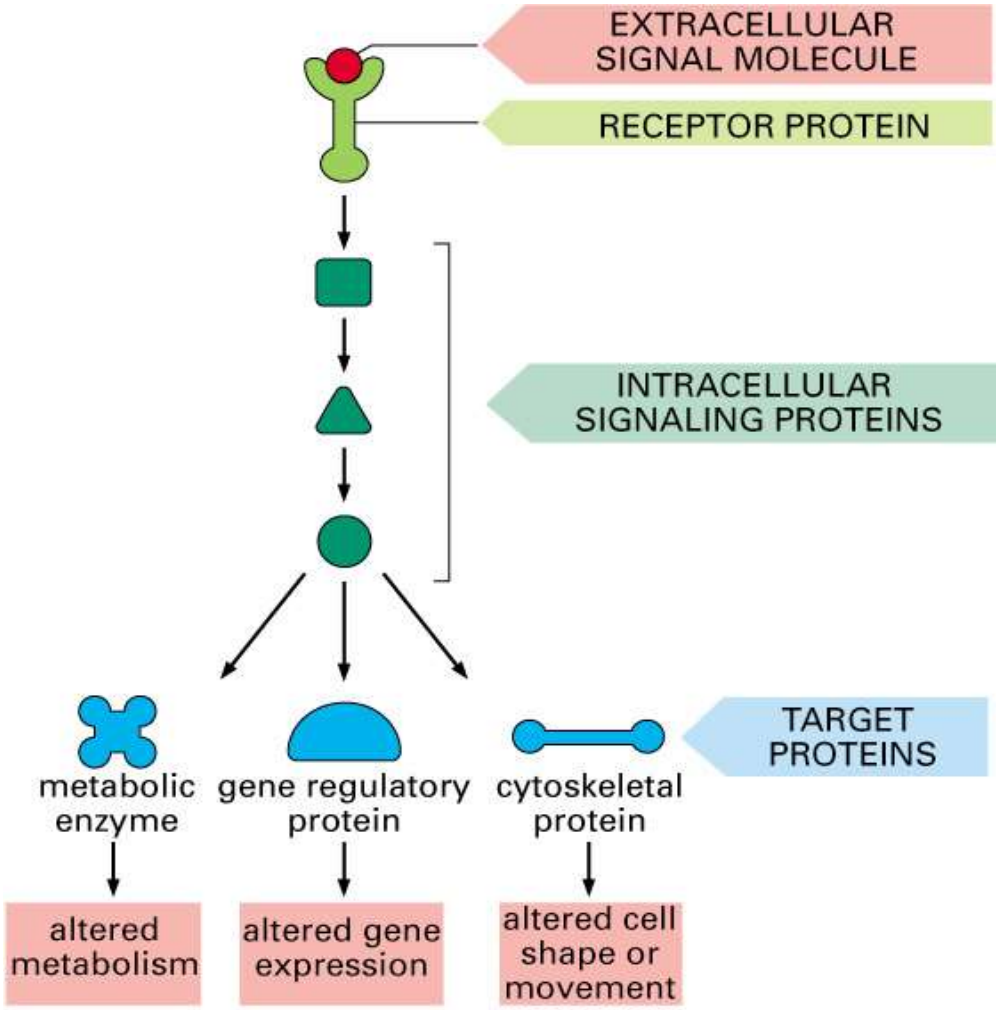
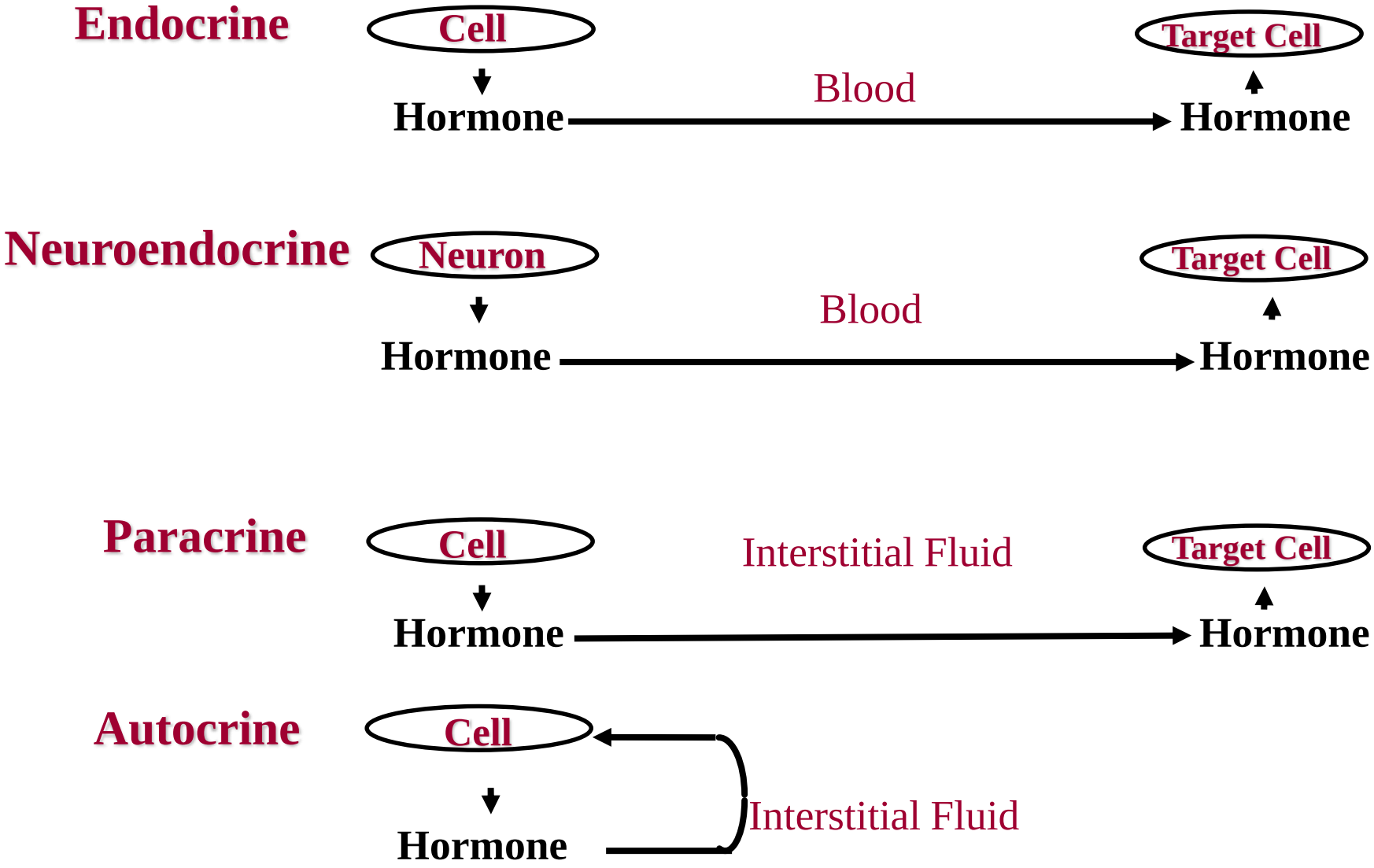


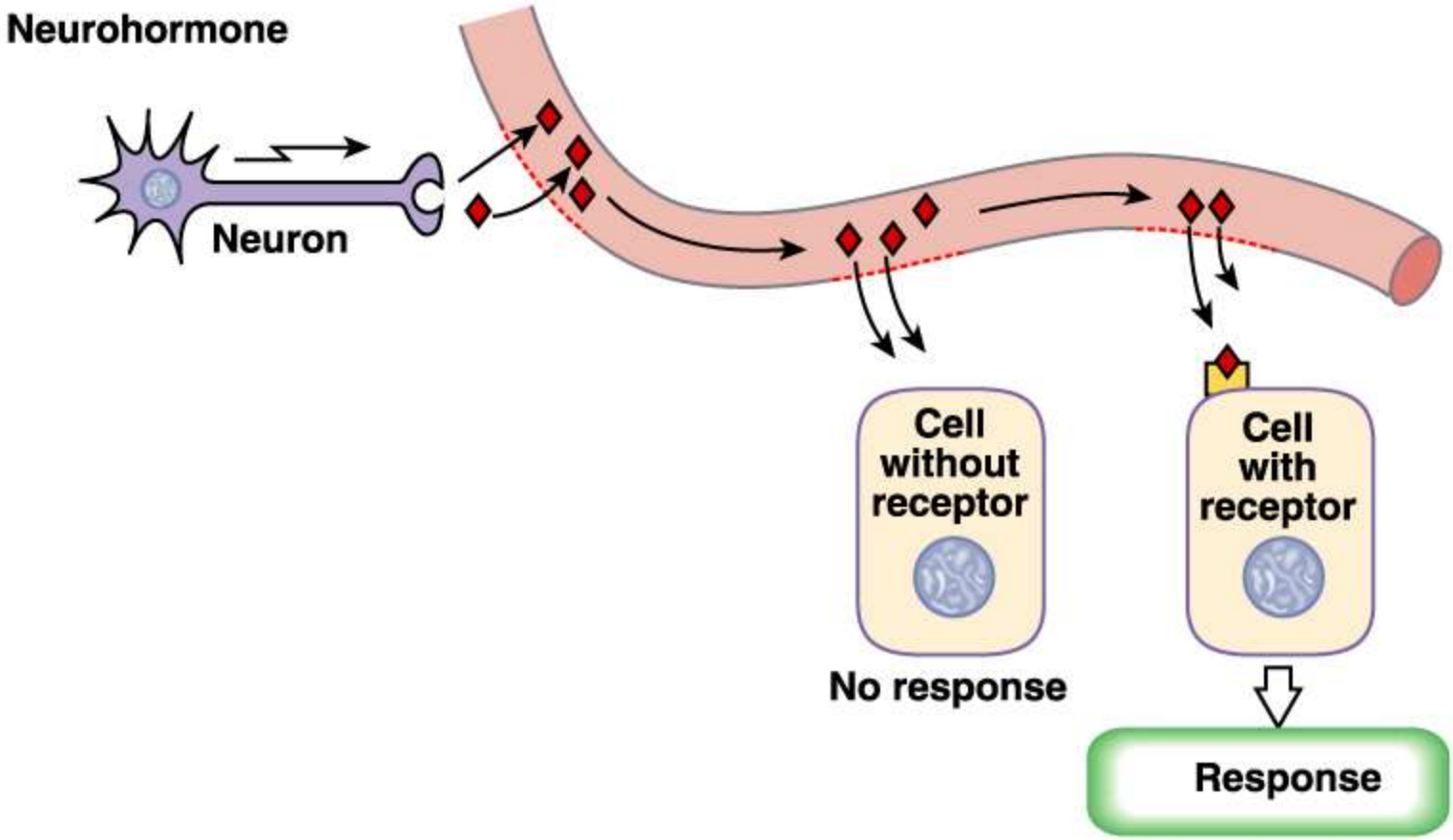
Figure 15–1. Molecular Biology of the Cell, 4th Edition.

Intercellular Communication



Endocrine Glands and Hormones

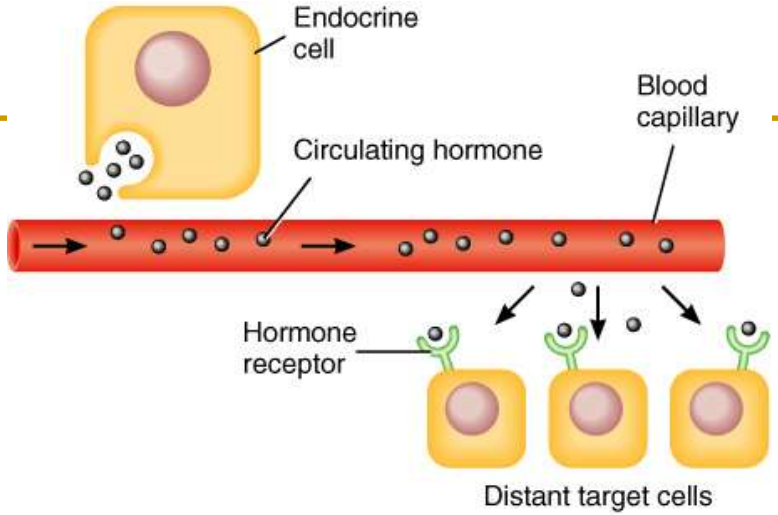
- Neurohormone:
  - Specialized neurons that secrete chemicals into the blood rather than synaptic cleft.
    - Chemical secreted is called neurohormone.
- Hormones:
  - Affect metabolism of target organs.
    - Help regulate total body metabolism, growth, and reproduction.


Neurohormone
Neuron
Cell without receptor
Cell with receptor
No response
Response

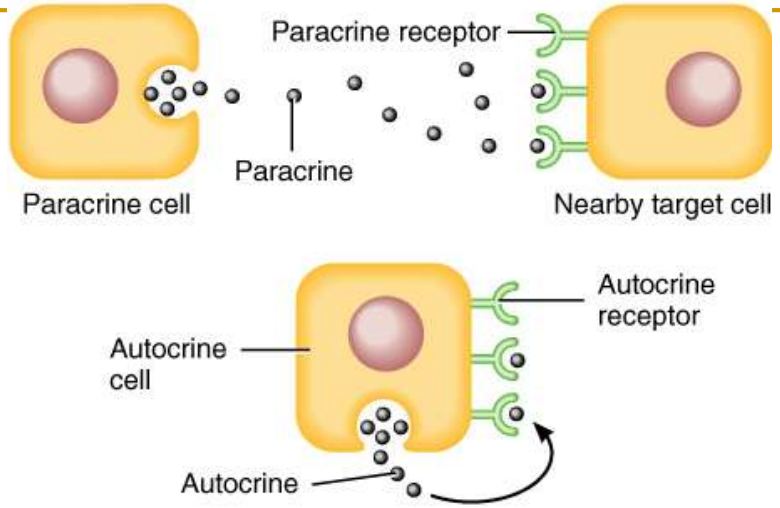
Classes of Hormones

- Peptide & Protein Hormones
- Steroid Hormones
- Amine Hormones
- Gas – Nitric Oxide (NO)

- Hormone types
  - Circulating – circulate in blood throughout body
  - Local hormones – act locally
    - Paracrine – act on neighboring cells
    - Autocrine – act on the same cell that secreted them

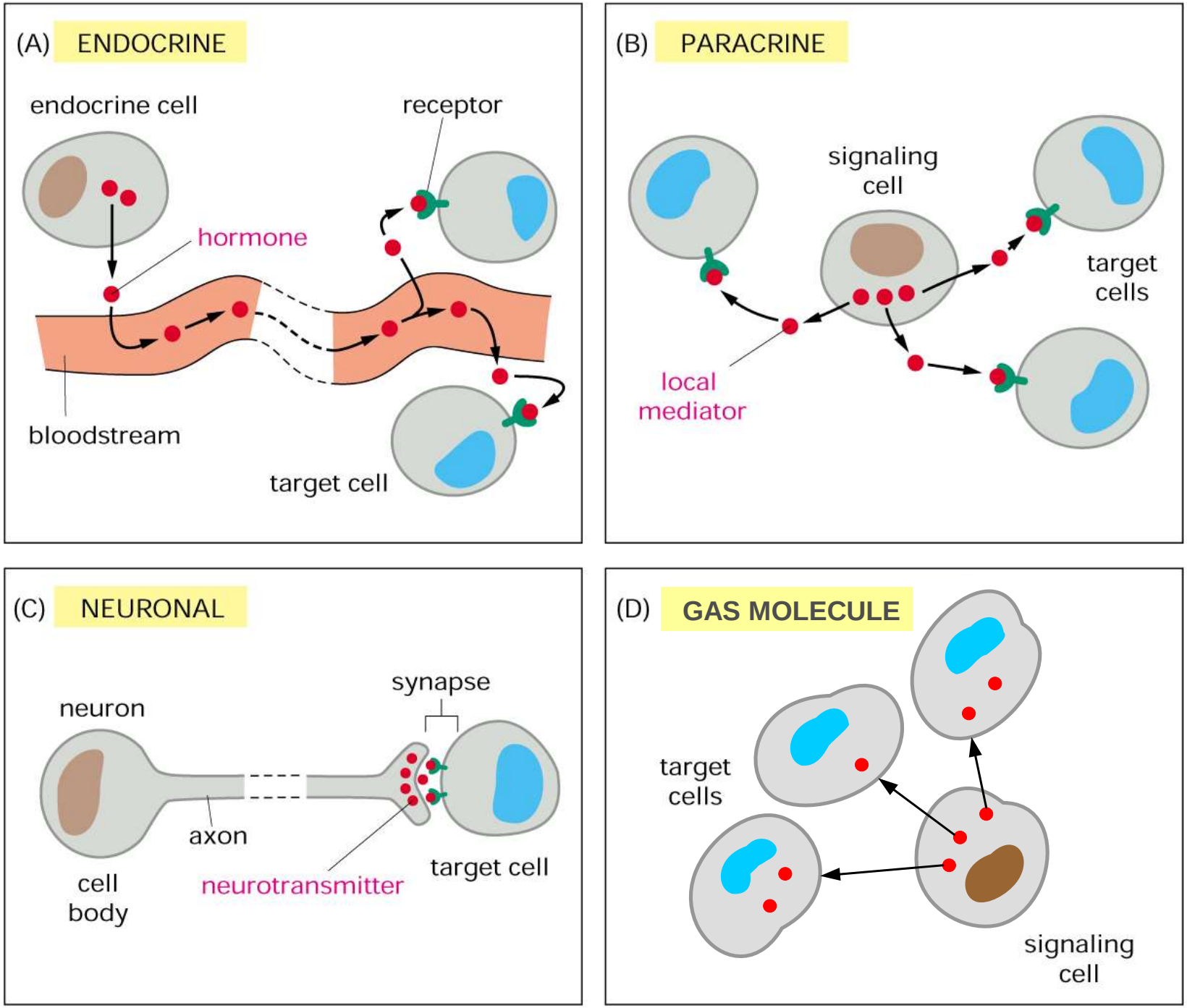


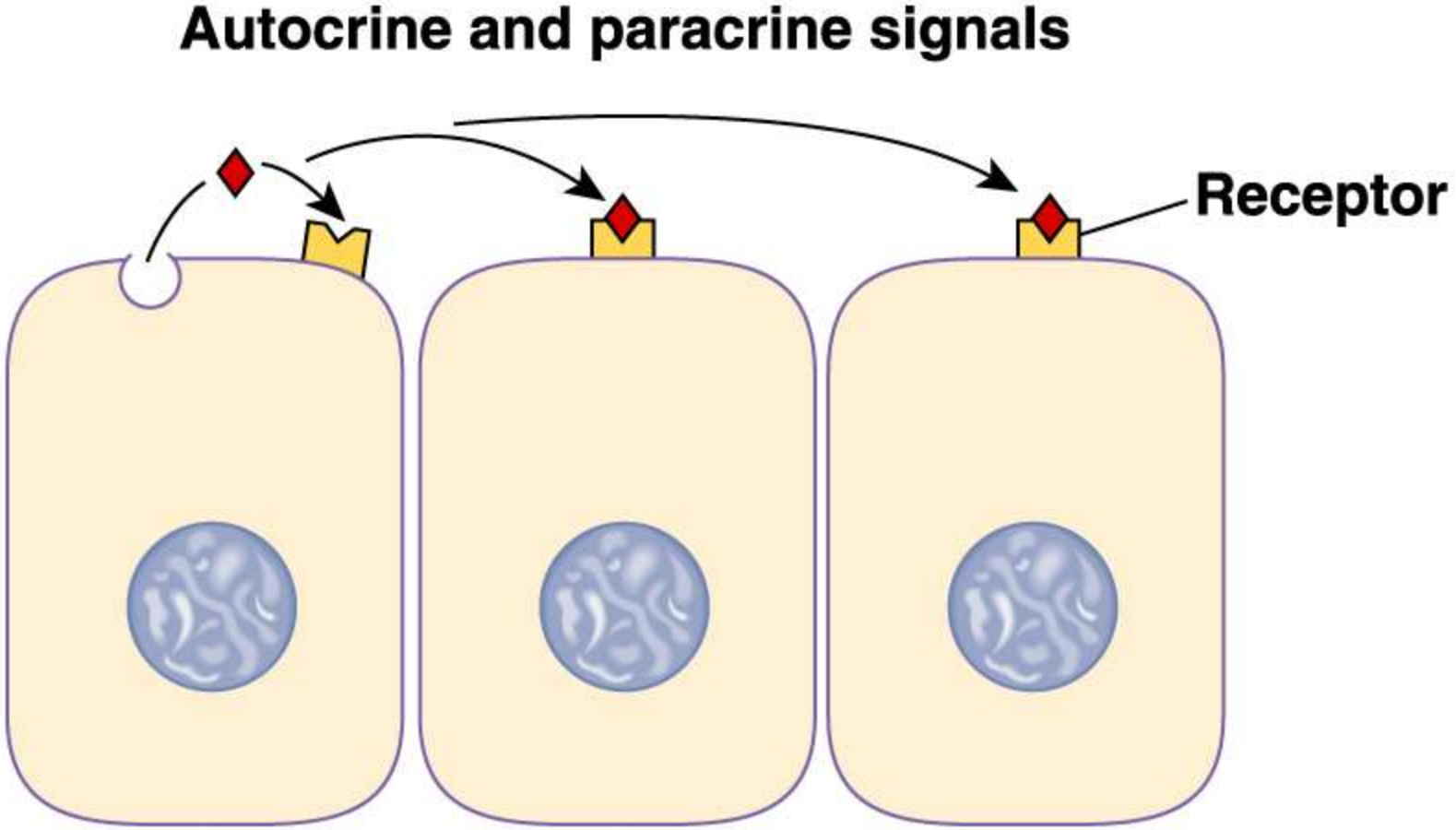
(a) Circulating hormones

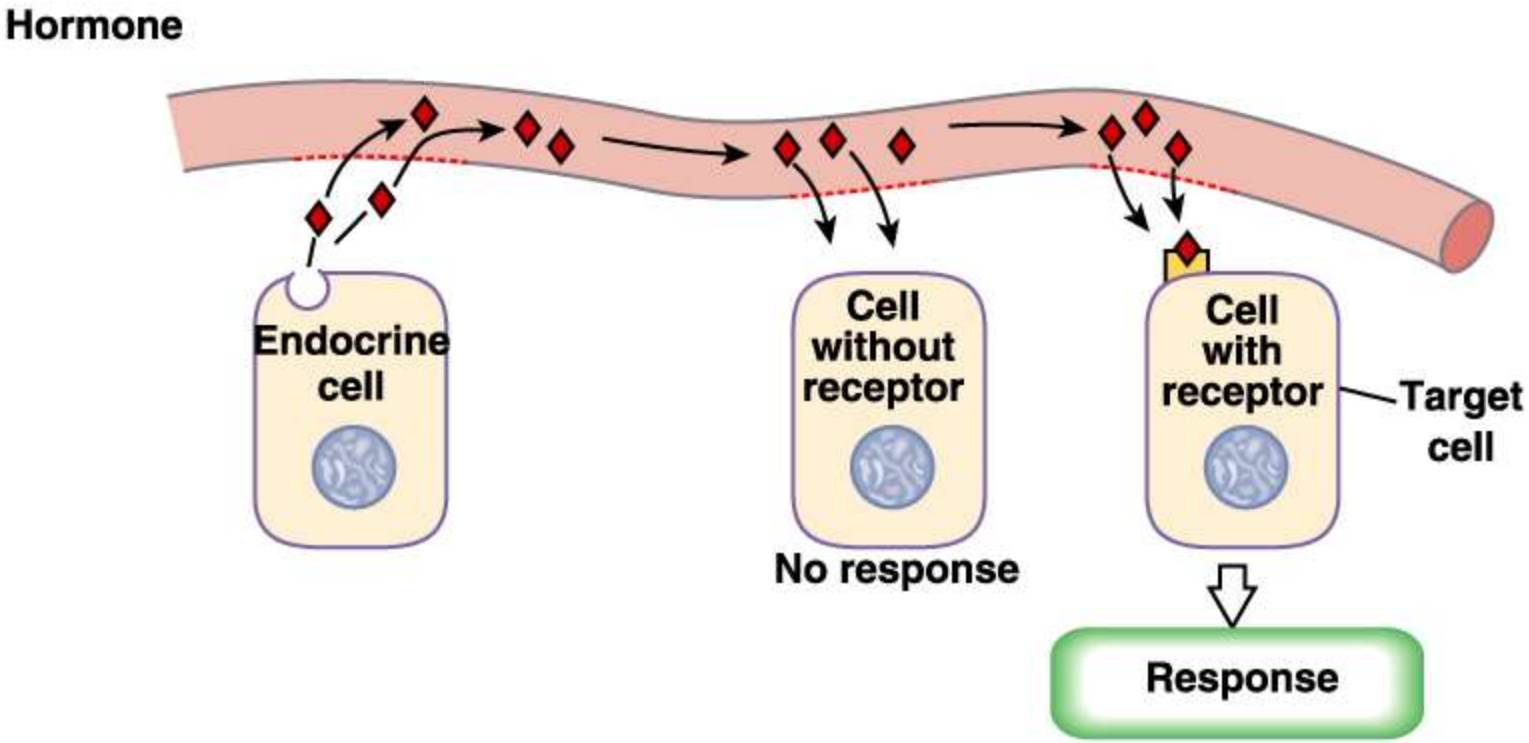


(b) Local hormones (paracrines and autocrines)

18.02


(A) ENDOCRINE
endocrine cell
receptor
hormone
bloodstream
target cell
(B) PARACRINE
signaling cell
target cells
local mediator
(C) NEURONAL
synapse
neuron
axon
cell body
neurotransmitter
target cell
(D) GAS MOLECULE
target cells
signaling cell


Autocrine and paracrine signals
Receptor


Hormone
Endocrine cell
Cell without receptor
No response
Cell with receptor
Target cell
Response

Chemical classes of hormones

- Lipid-soluble – use transport proteins
  - Steroid: Lipids derived from cholesterol.
    - Are lipophilic hormones.
      - Testosterone.
      - Estradiol.
      - Cortisol.
      - Progesterone.
  - Thyroid
  - Nitric oxide (NO)

Chemical classes of hormones …cont

- Water-soluble – circulate in "free" form
  - Amines:
    - Hormones derived from tyrosine and tryptophan.
    - NE, Epi, T_4 (lipid soluble)
  - Polypeptides and proteins:
    - Polypeptides:
      - Chains of < 100 amino acids in length.
        - ADH.
    - Protein hormones:
      - Polypeptide chains with > 100 amino acids.
      - Growth hormone.
  - Eicosanoid (prostaglandins)

Chemical Classification of Hormones …cont

- Glycoproteins:
  - Long polypeptides (>100) bound to 1 or more carbohydrate (CHO) groups.
    - FSH and LH, TSH and hCG (human chorionic gonadotropin)

      They have α and β subunits (α is common and β is specific)
- Hormones can also be divided into:
  - Polar:
    - H_20 soluble.
  - Nonpolar (lipophilic):
    - H_20 insoluble.
      - Can gain entry into target cells.
      - Steroid hormones and T_4.

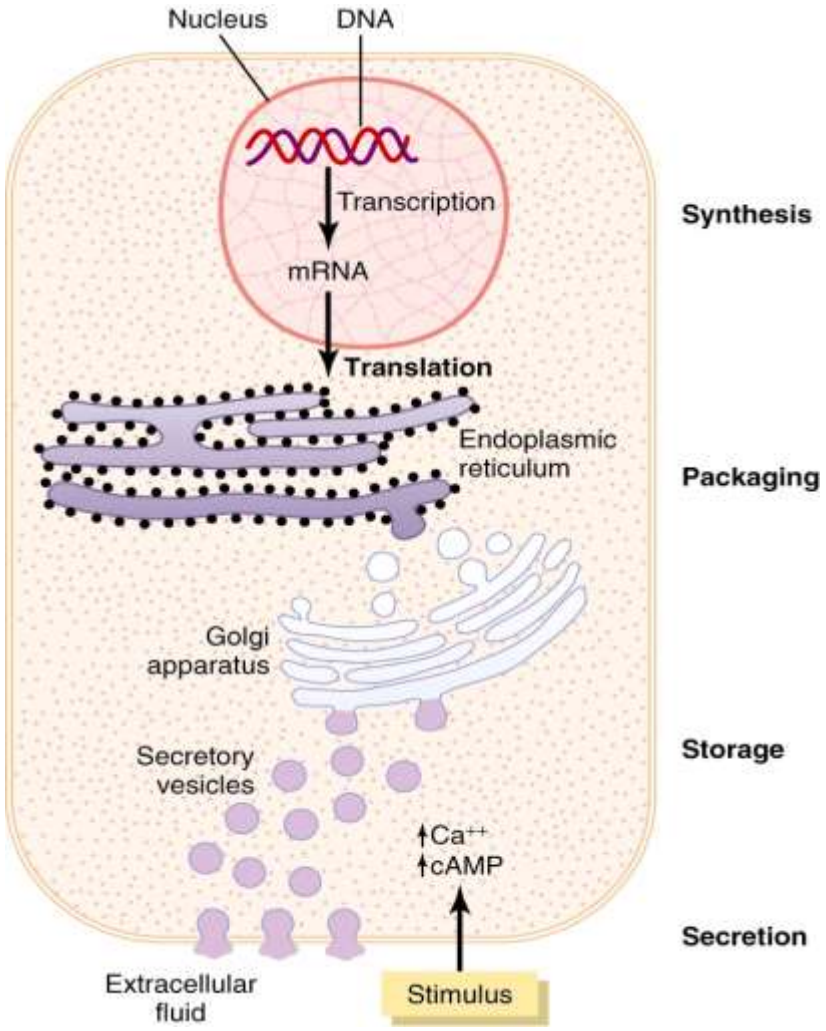
Prohormones and Prehormones

- Prohormone:
  - Precursor is a longer chained polypeptide that is cut and spliced together to make the hormone.
    - Proinsulin.
- Preprohormone:
  - Prohormone derived from larger precursor molecule.
    - Preproinsulin.
- Prehormone:
  - Molecules secreted by endocrine glands that are inactive until changed into hormones by target cells.
    - T_4 converted to T_3.

Peptide & Protein Hormones

Gland/Tissue	Hormones	Gland/Tissue	Hormones
Hypothalamus	▪ TRH, GnRH, CRH GHRH, Somatostatin,	Placenta	▪ HCG, HCS or HPL
Anterior pituitary	▪ ACTH, TSH, FSH, LH, PRL, GH	Kidney	▪ Renin
Posterior pituitary	▪ Oxytocin, ADH	Heart	▪ ANP
Thyroid	▪ Calcitonin	G.I. tract	▪ Gastrin, CCK, Secretin, GIP, Somatostatin
Pancreas	▪ Insulin,Glucagon, Somatostatin		
Liver	▪ Somatomedin C (IGF-1)	Adipocyte	▪ Leptin
Parathyroid	▪ PTH	Adrenal medulla	▪ Norepinephrine, epinephrine

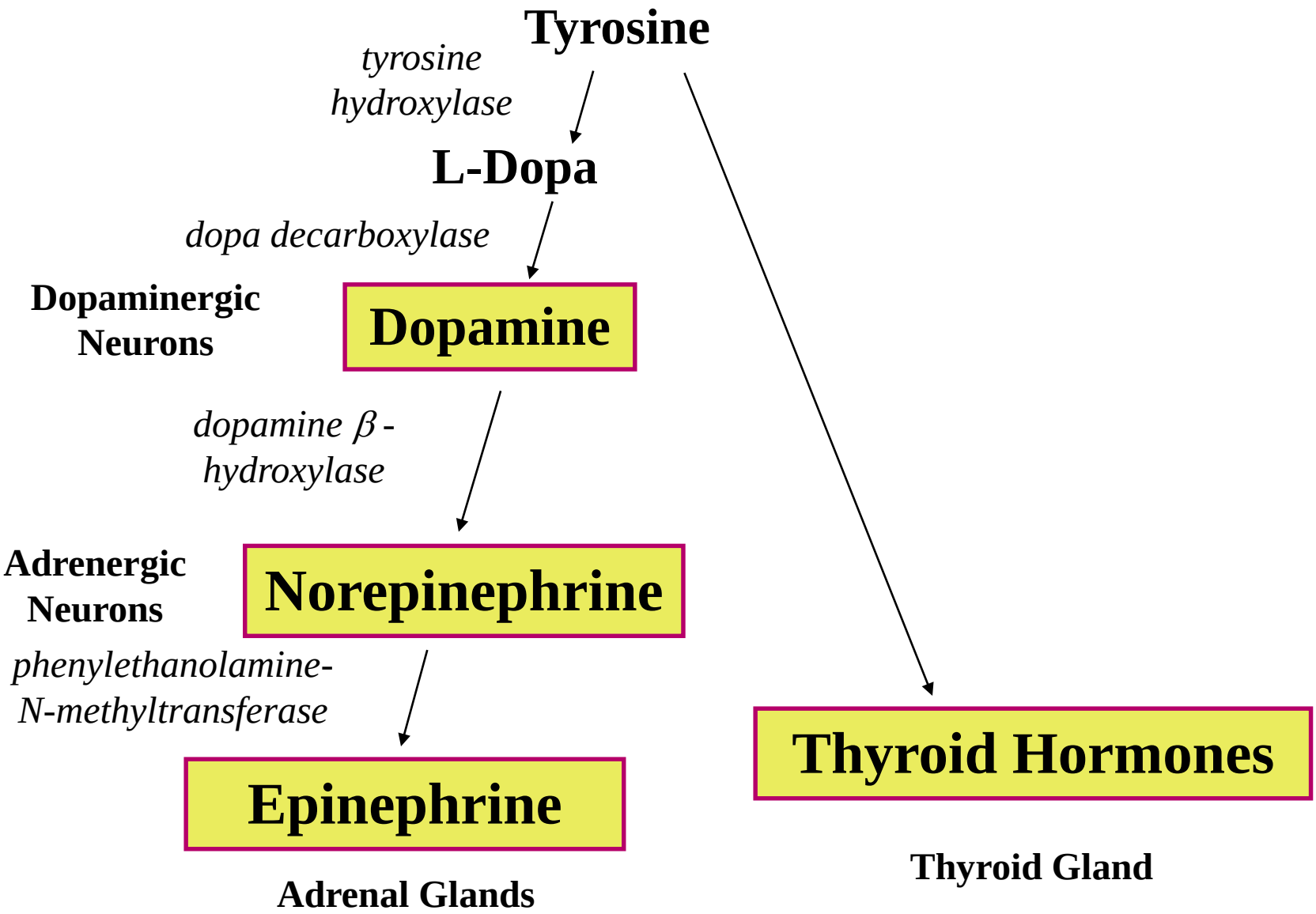
Synthesis and secretion of peptide hormones



Amine Hormones

Gland/Tissue	Hormones
Hypothalamus	▪ Dopamine
Thyroid	▪ T_3, T_4
Adrenal medulla	▪ NE, EPI

Synthesis of Amine Hormones



Steroid Hormones

Gland/Tissue	Hormones
Adrenal Cortex	▪ Cortisol, Aldosterone, Androgens
Testes	▪ Testosterone
Ovaries	▪ Estrogens, Progesterone
Corpus Luteum	▪ Estrogens, Progesterone
Placenta	▪ Estrogens, Progesterone
Kidney	▪ 1,25-Dihydroxycholecalciferol (calcitriol)

Chemical classification of hormones

Table 10-4 Chemical Classification and Function of Hormones

Chemical Classification	Examples	Regulated Function
Endocrine Hormones		
Amino acid derivatives	Epinephrine (adrenaline) and norepinephrine (both derived from tyrosine)	Stress responses: regulation of heart rate and blood pressure; release of glucose and fatty acids from storage sites
	Thyroxine (derived from tyrosine)	Regulation of metabolic rate
Peptides	Antidiuretic hormone (vasopressin)	Regulation of body water and blood pressure
	Hypothalamic hormones (releasing factors)	Regulation of tropic hormone release from pituitary gland
Proteins	Anterior pituitary hormones	Regulation of other endocrine systems
Steroids	Sex hormones (androgens and estrogens)	Development and control of reproductive capacity
	Corticosteroids	Stress responses; control of blood electrolytes
Paracrine Hormones		
Amino acid derivative	Histamine	Local responses to stress and injury
Arachidonic acid derivatives	Prostaglandins	Local responses to stress and injury

Hormone Activity

- Hormones affect only specific target tissues with specific receptors
- Receptors are dynamic and constantly synthesized and broken down
  - Down-regulation
  - Up-regulation

Effects of [Hormone] on Tissue Response

- Priming effect (upregulation):
  - Increase number of receptors formed on target cells in response to particular hormone.
  - Greater response by the target cell.
- Desensitization (downregulation):
  - Prolonged exposure to high [polypeptide hormone].
    - Subsequent exposure to the same [hormone] produces less response.
      - Decrease in number of receptors on target cells.
        - Insulin in adipose cells.
  - Pulsatile secretion may prevent downregulation.

Effects of [Hormone] on Tissue Response

- [Hormone] in blood reflects the rate of secretion.
- Half-life:
  - Time required for the blood [hormone] to be reduced to ½ reference level.
    - Minutes to days.
- Normal tissue responses are produced only when [hormone] are present within physiological range.
- Varying [hormone] within normal, physiological range can affect the responsiveness of target cells.

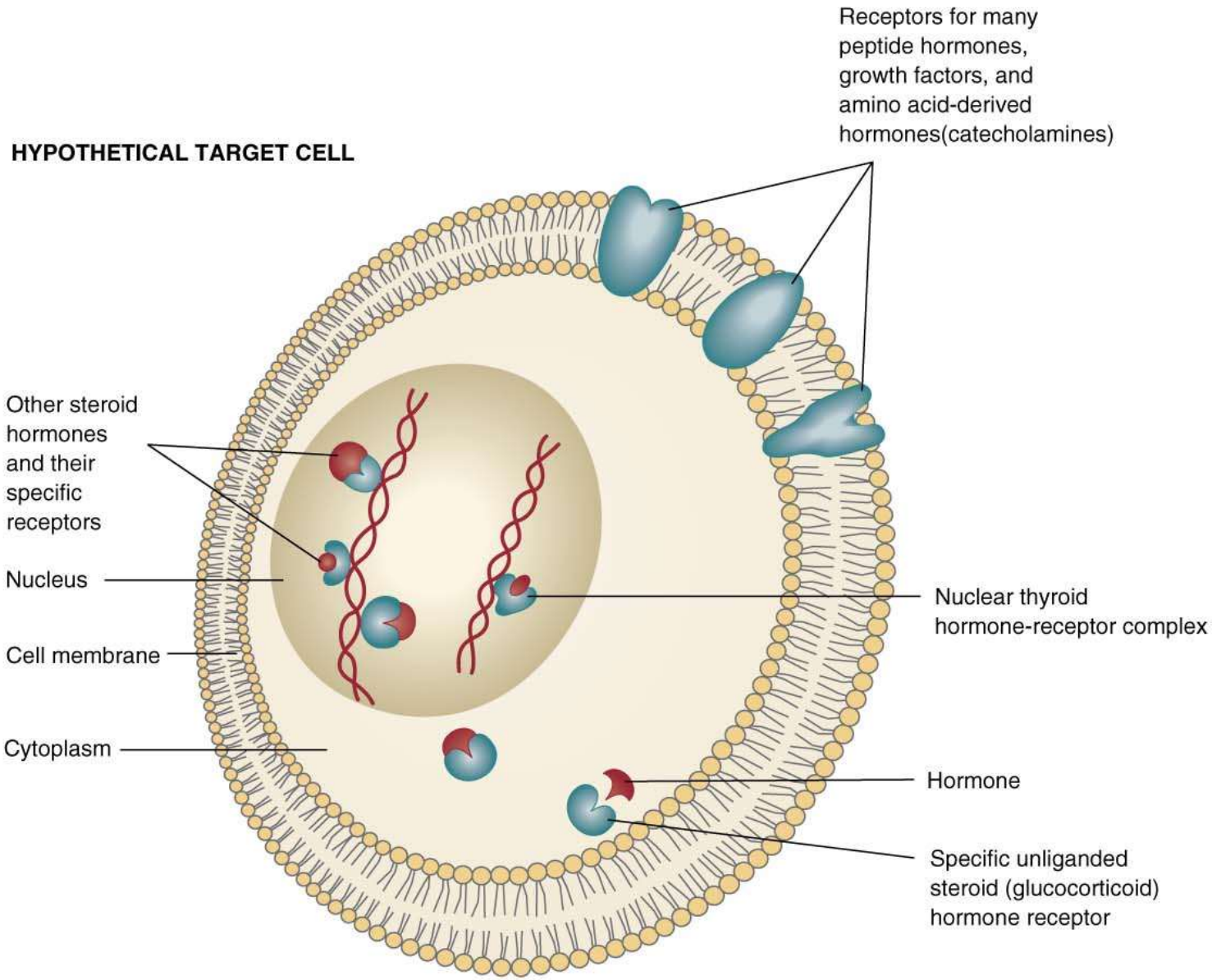
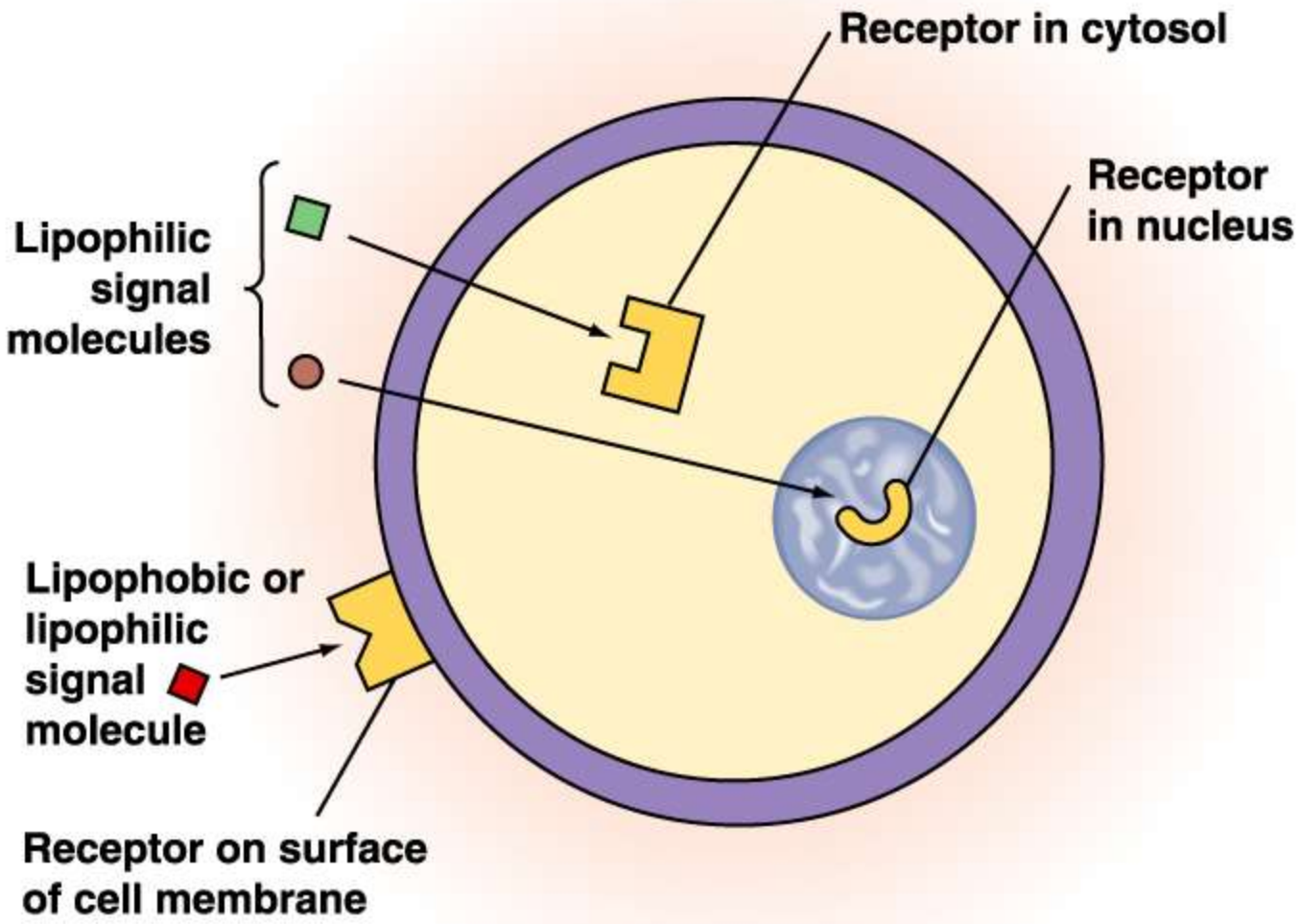
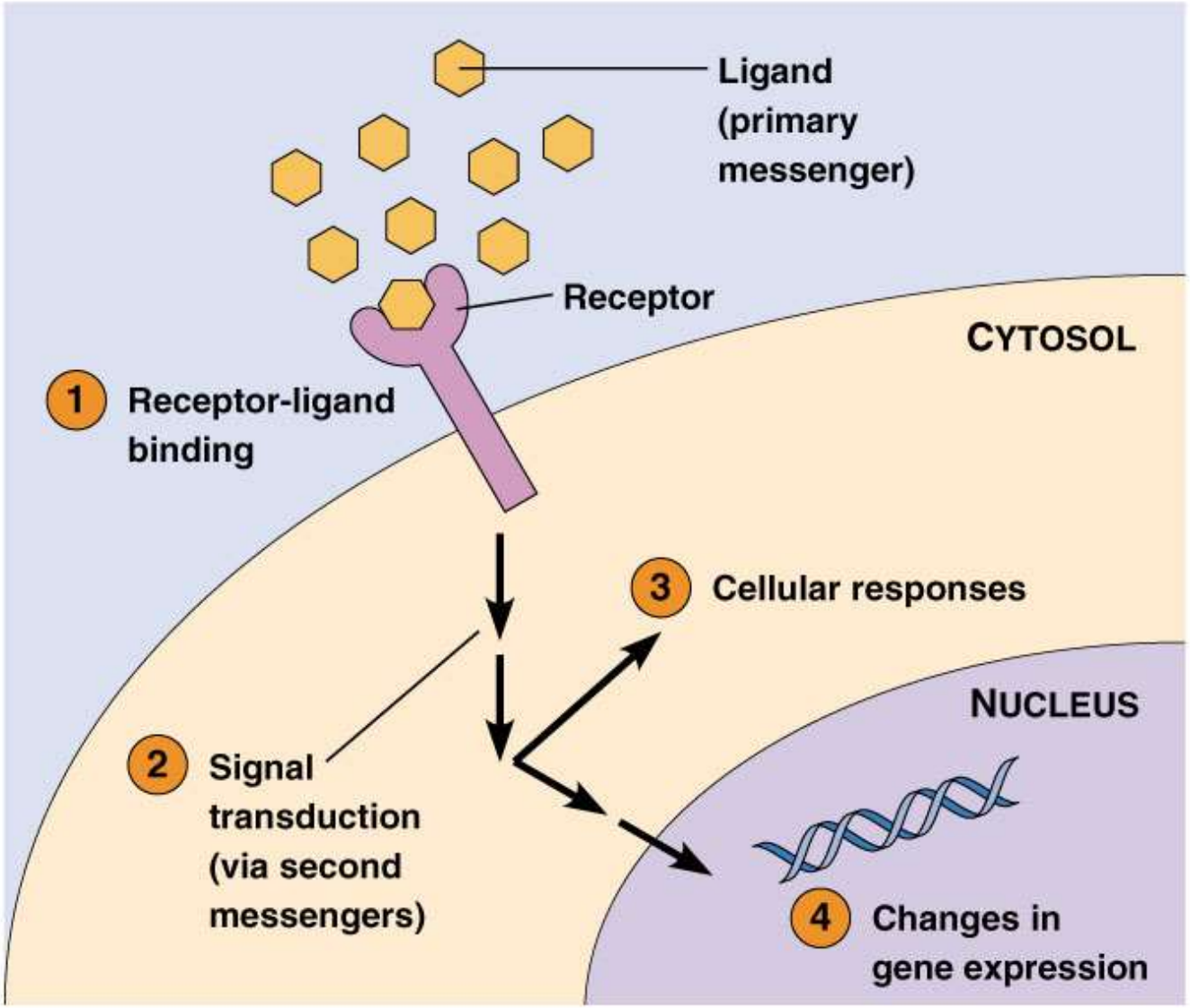


Figure 23.1. Diagram showing the different locations of classes of hormone receptors expressed by a target cell.


Receptor in cytosol
Receptor in nucleus
Lipophilic signal molecules
Lipophobic or lipophilic signal molecule
Receptor on surface of cell membrane

Signals get translated into cellular responses or changes in gene expression



Mechanisms of Hormone Action

- Hormones of same chemical class have similar mechanisms of action.
  - Similarities include:
    - Location of cellular receptor proteins depends on the chemical nature of the hormone.
    - Events that occur in the target cells.
- To respond to a hormone:
  - Target cell must have specific receptors for that hormone (specificity).
    - Hormones exhibit:
      - Affinity (bind to receptors with high bond strength).
      - Saturation (low capacity of receptors).

Mechanisms of Hormone Action

- Response depends on both hormone and target cell
- Lipid-soluble hormones bind to receptors inside target cells
- Water-soluble hormones bind to receptors on the plasma membrane
  - Activates second messenger system
  - Amplification of original small signal
- Responsiveness of target cell depends on
  - Hormone's concentration
  - Abundance of target cell receptors

Receptor

Receptors are specific membrane proteins, which are able to recognize and bind to corresponding ligand molecules, become activated, and transduce signal to next signaling molecules.

Glycoprotein or Lipoprotein

ligand

A small molecule that binds specifically to a larger one; for example, a hormone is the ligand for its specific protein receptor.

- **Membrane receptors**

  membrane

  Glycoprotein

- **Intracellular receptors**

  Cytosol or nuclei

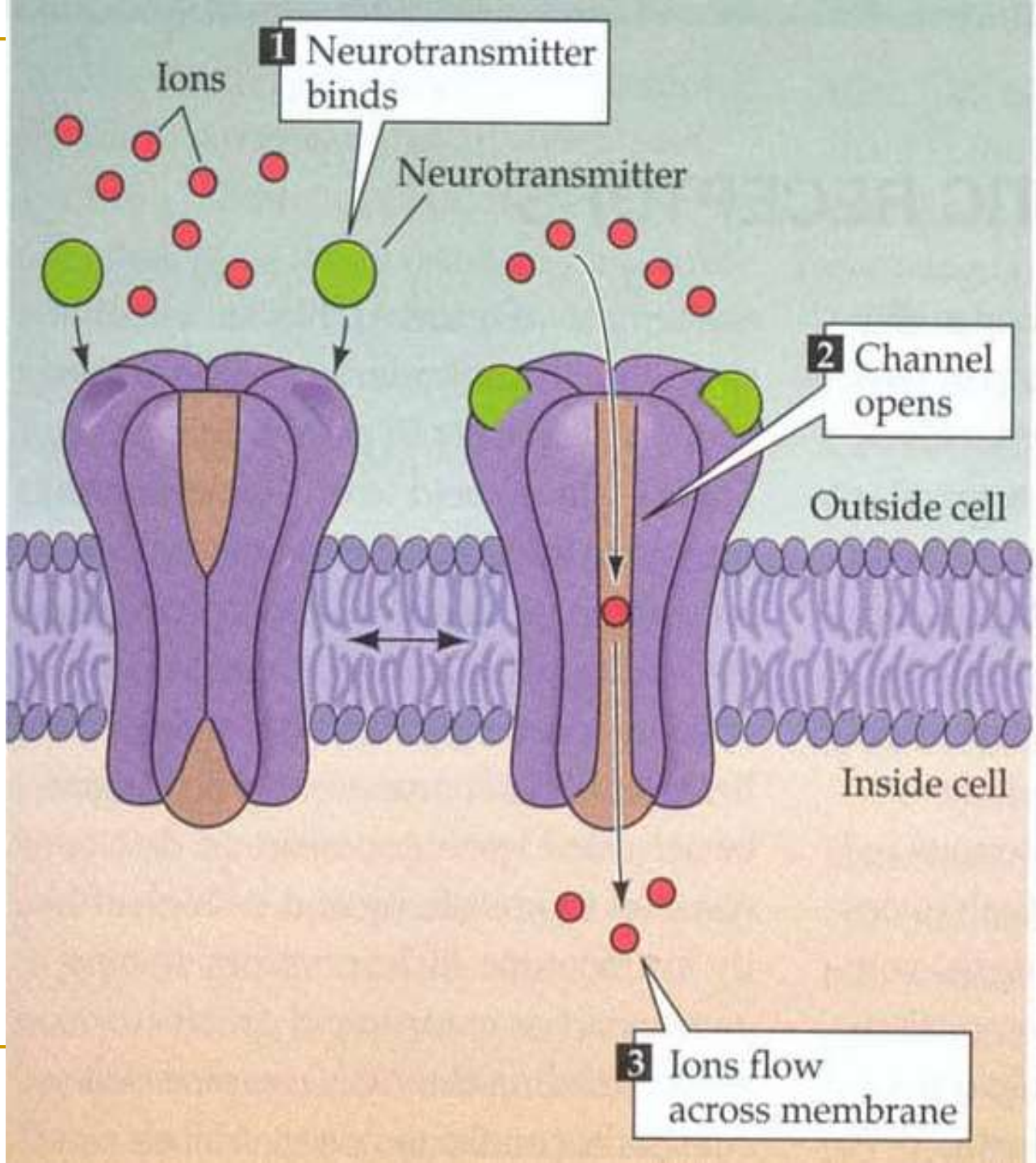
  DNA binding protein

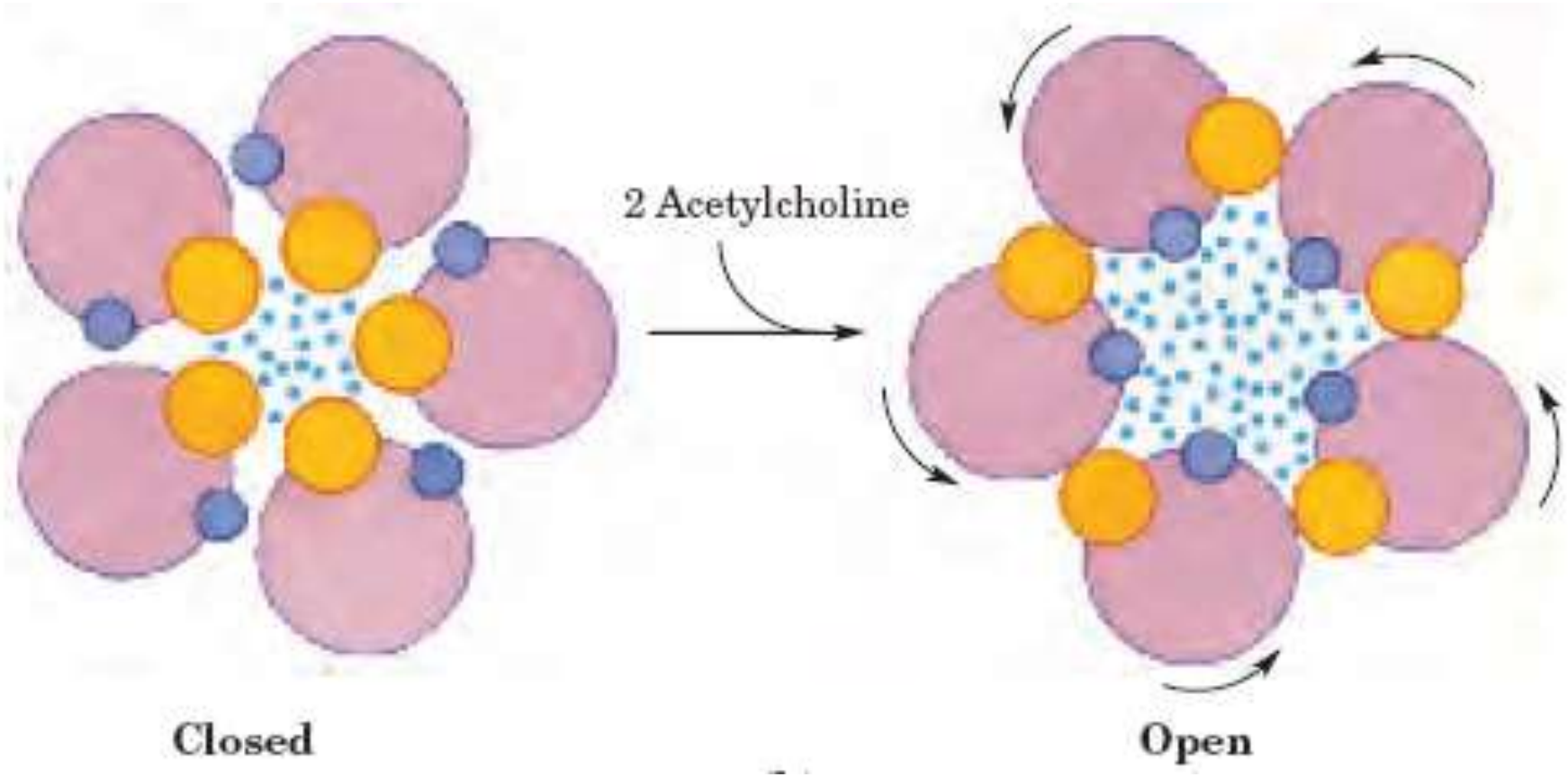
1. membrane receptors

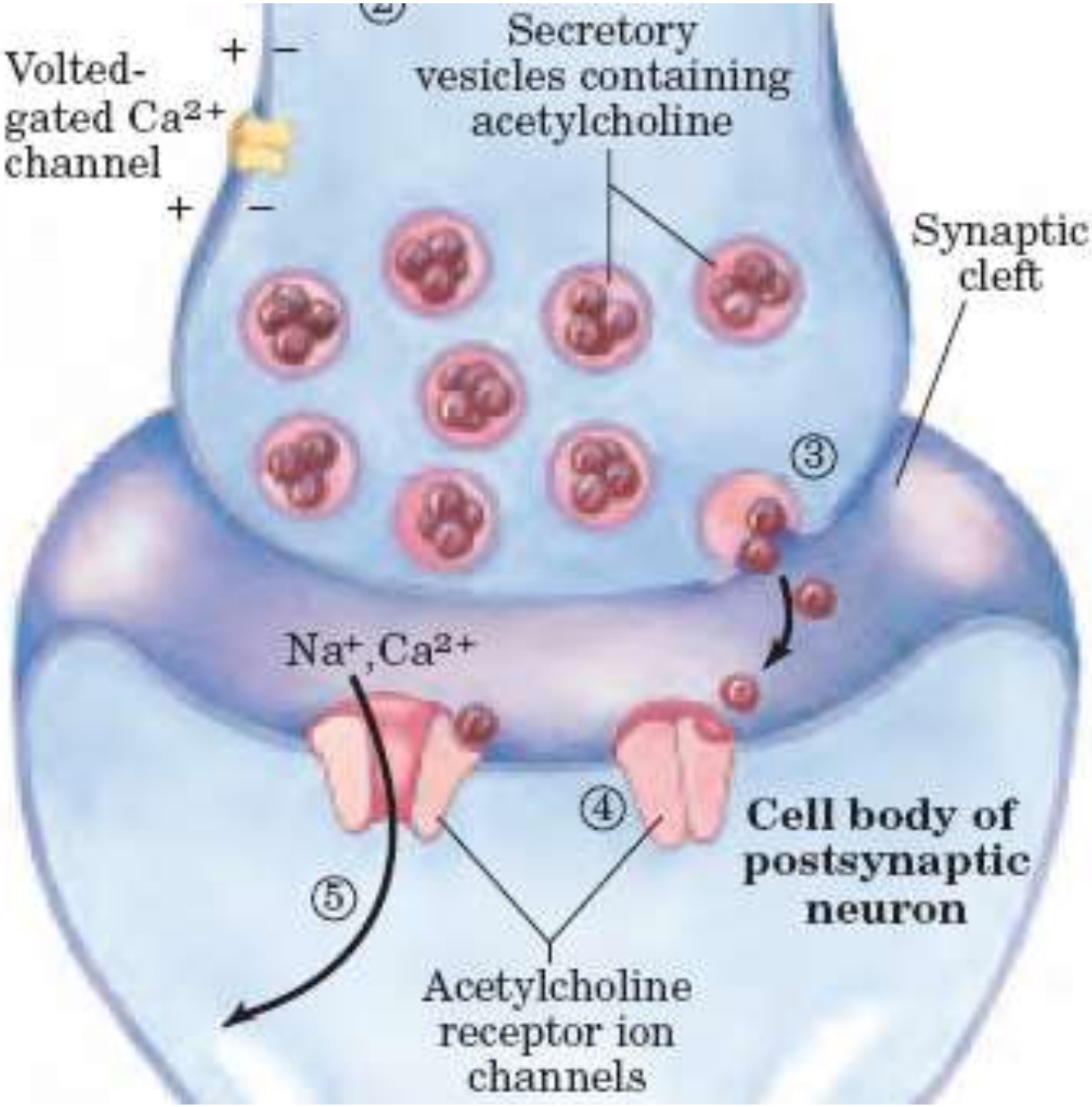
(1) Ligand-gate ion channels type

(cyclic receptor)

ligand→receptor→ion channel open or close

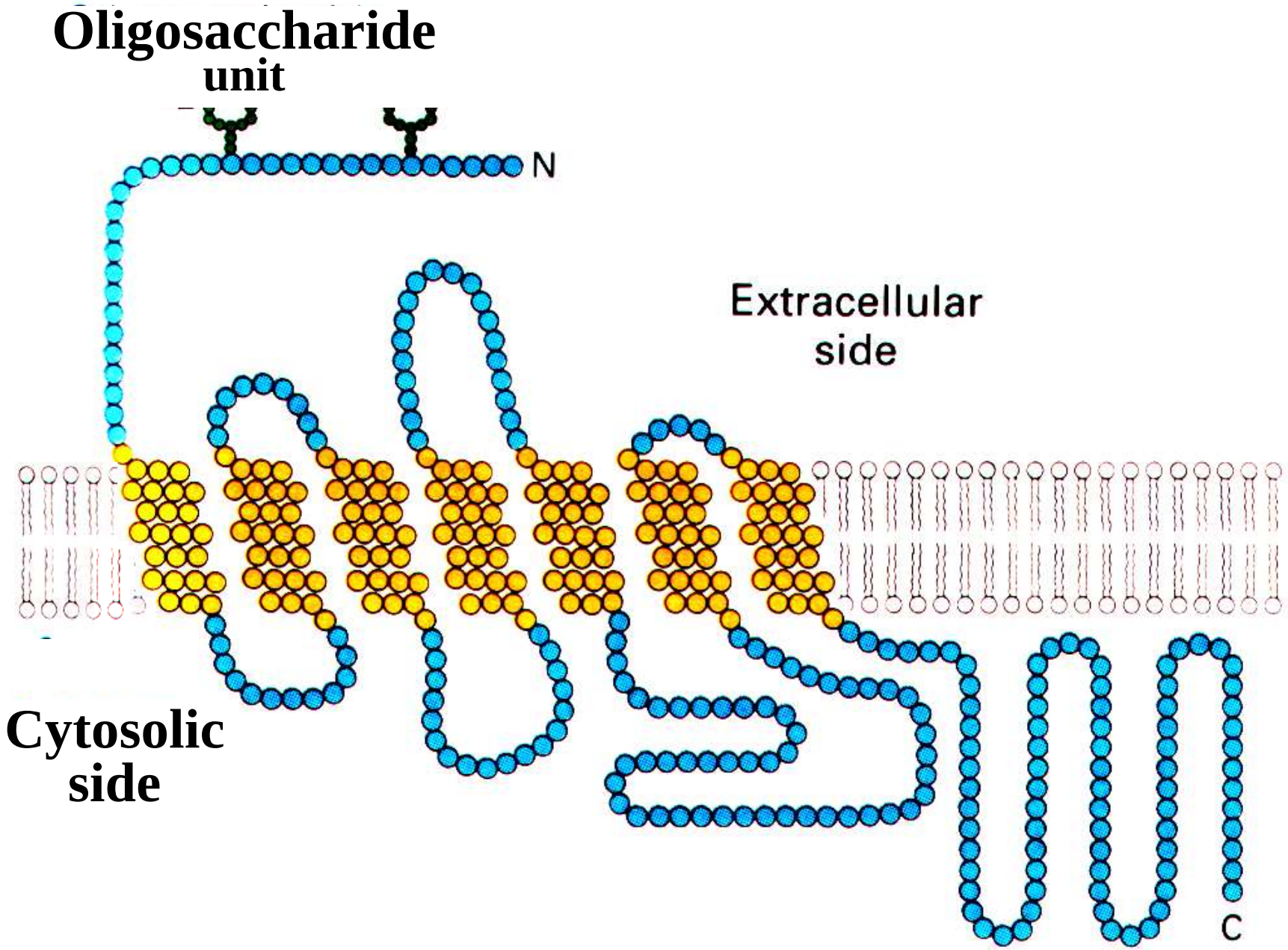

Ions
1 Neurotransmitter binds
Neurotransmitter
2 Channel opens
Outside cell
Inside cell
3 Ions flow across membrane


2 Acetylcholine
Closed
Open


Volted-gated Ca^{2+} channel
+ −
+ −
Secretory vesicles containing acetylcholine
Synaptic cleft
③
Na^+, Ca^{2+}
④
Cell body of postsynaptic neuron
⑤
Acetylcholine receptor ion channels

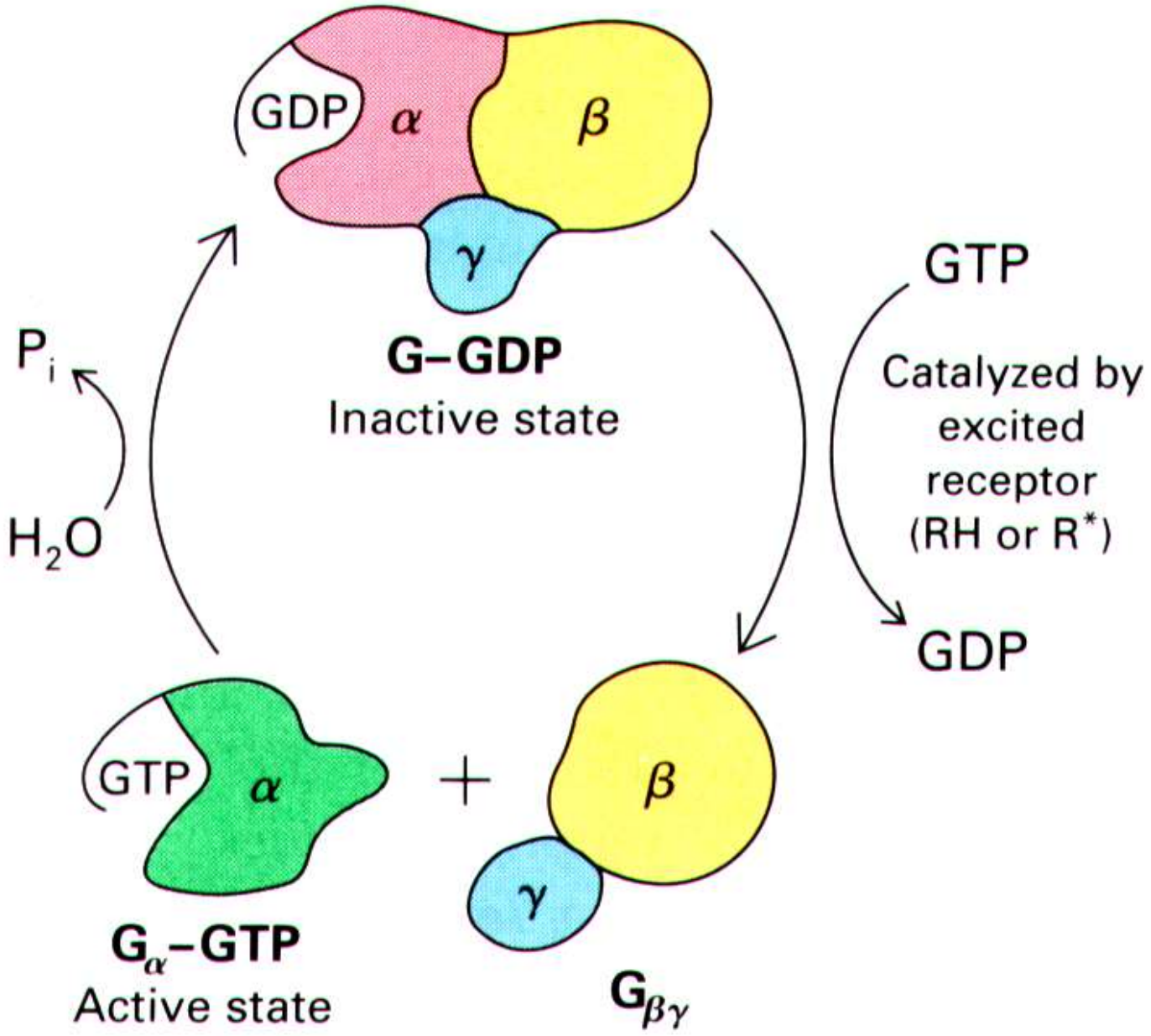
(2) G Protein-Coupled Receptors

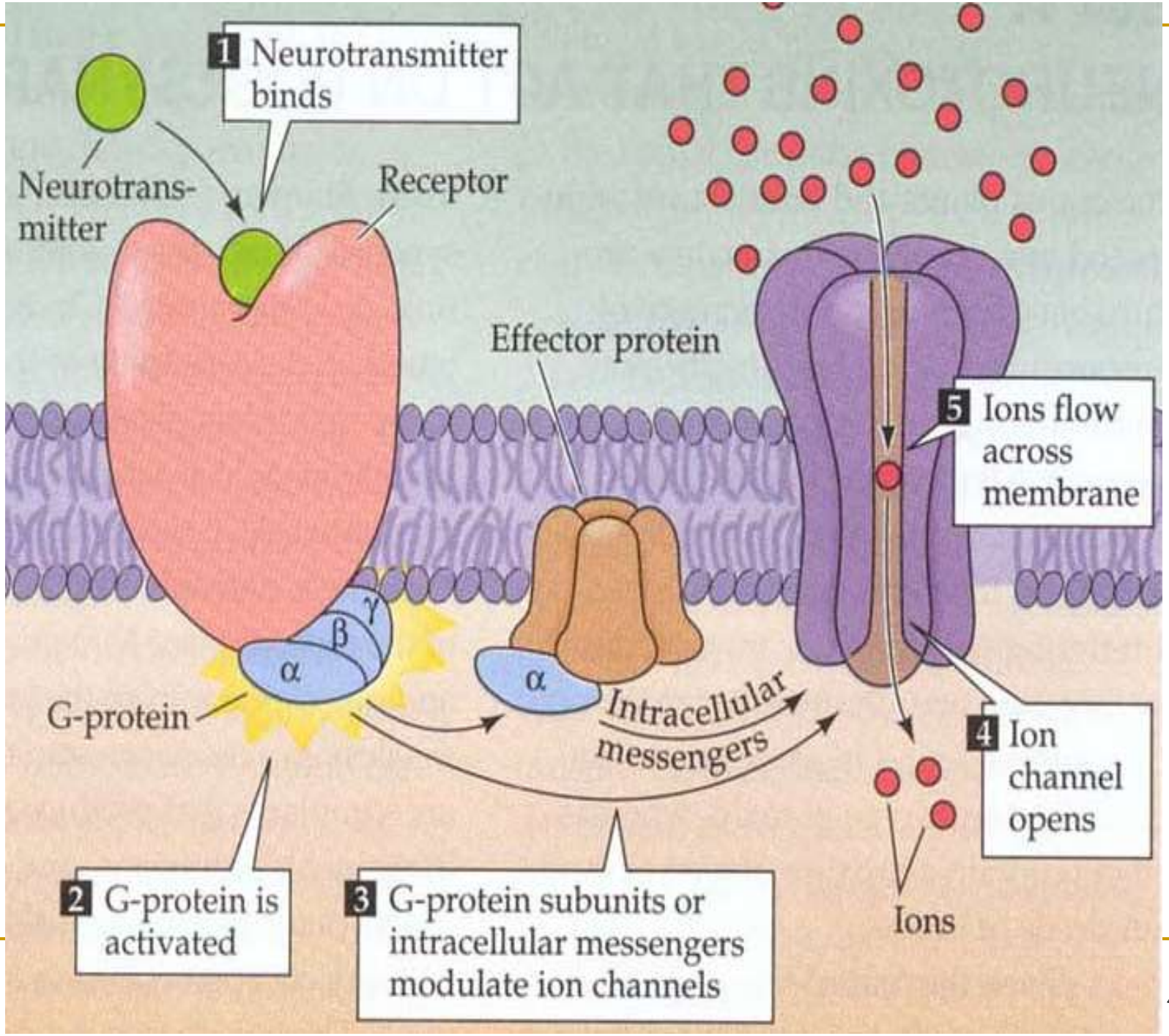
1) 7-helices transmembrane receptor

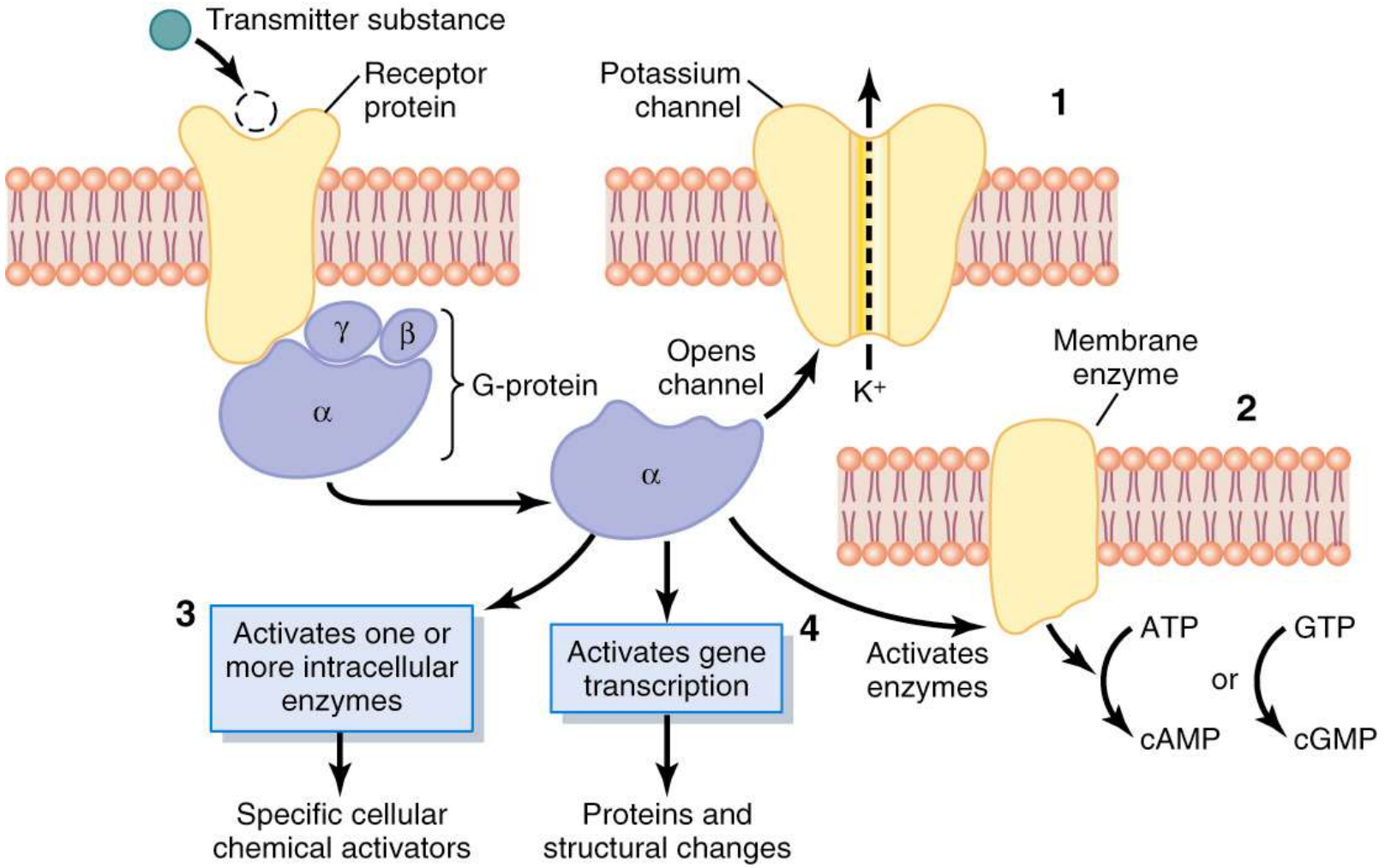

Oligosaccharide unit
N
Extracellular side
Cytosolic side
C

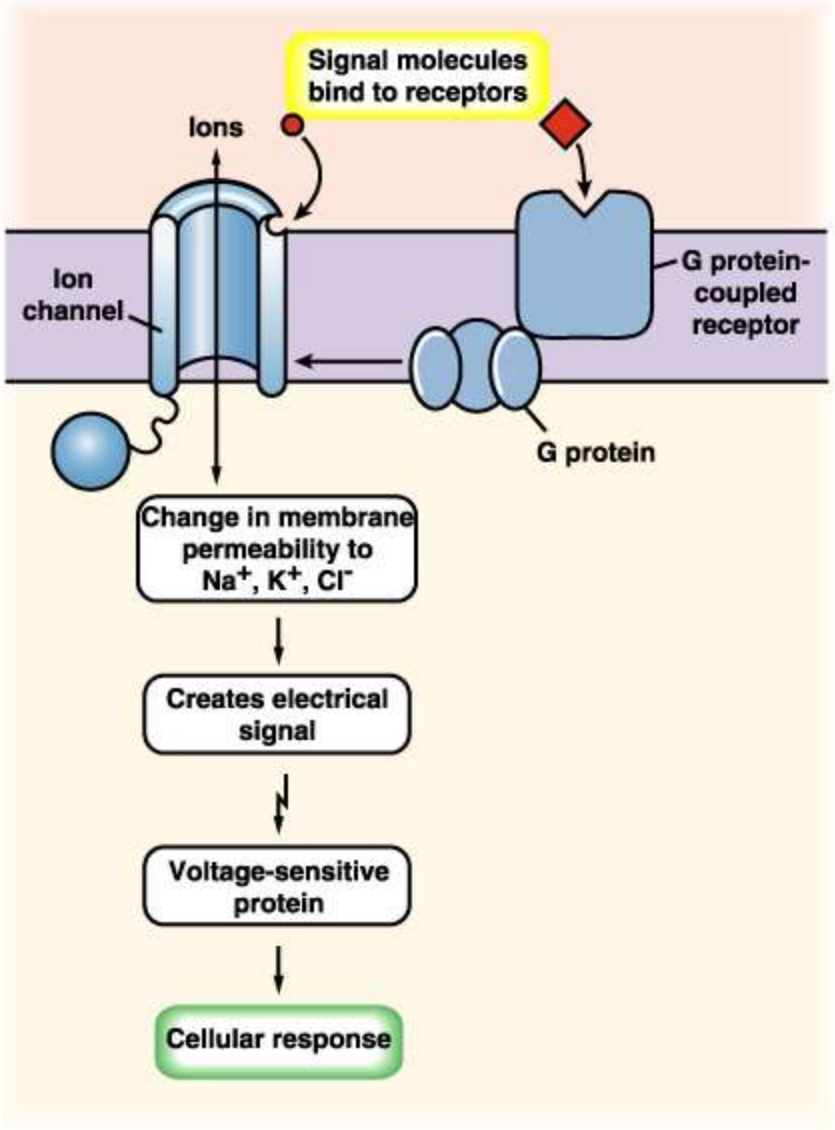
2) G protein (Guanylate binding protein)

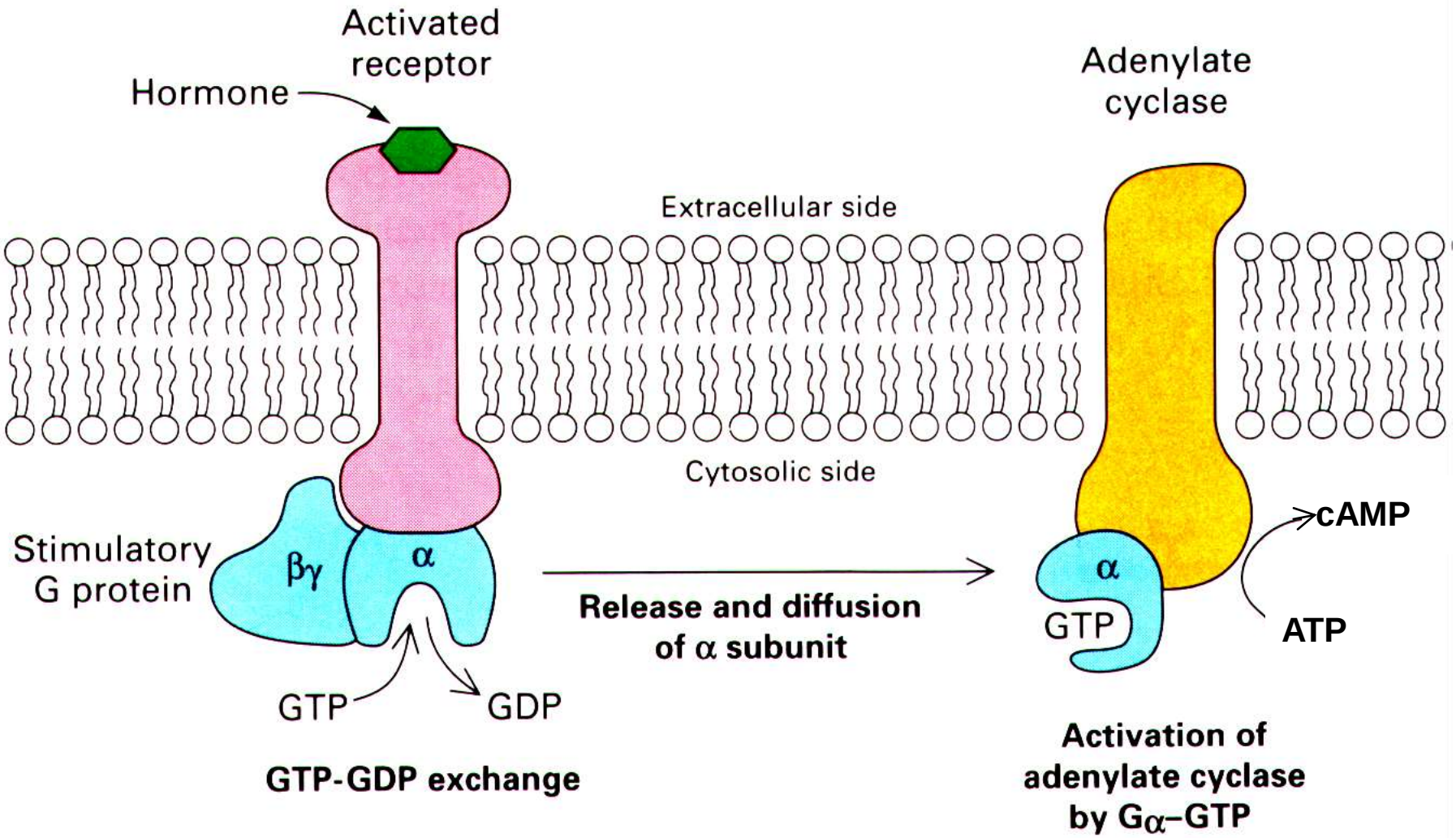
- G protein refers to any protein which binds to GDP or GTP and act as signal transduction.
- G proteins consist of three different subunits (α, β, γ-subunit) bound to GDP when exchanged to GTP activate α-subunit
- α-subunit carries GTPase activity, binding and hydrolysis of GTP.


GDP
α
β
γ
G–GDP
Inactive state
GTP
Catalyzed by
excited
receptor
(RH or R*)
GDP
Pi
H2O
GTP
α
β
γ
Gα–GTP
Active state
Gβγ

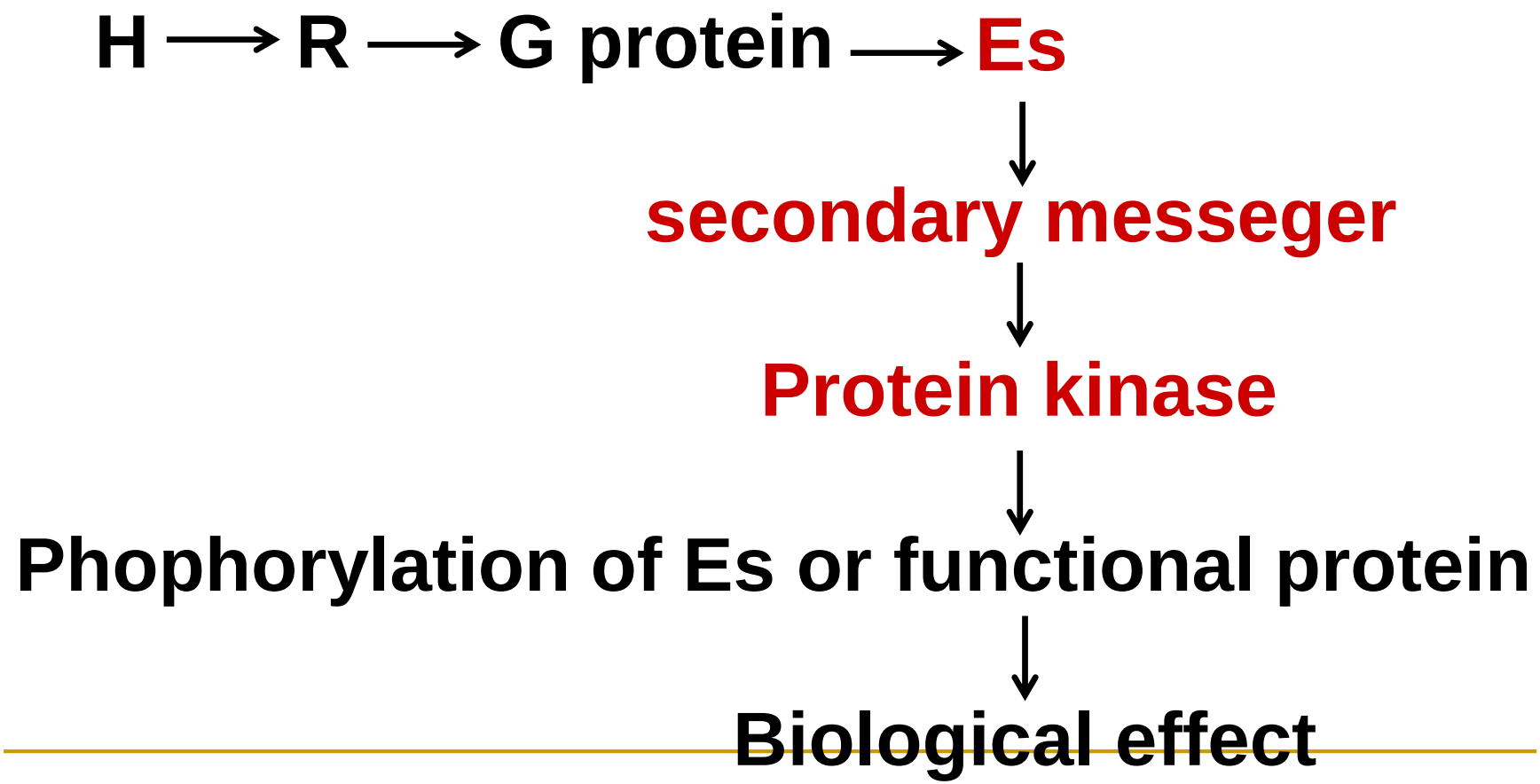

1 Neurotransmitter binds
Neurotrans-
mitter
Receptor
Effector protein
5 Ions flow across membrane
γ
β
α
α
G-protein
Intracellular messengers
4 Ion channel opens
2 G-protein is activated
3 G-protein subunits or intracellular messengers modulate ion channels
Ions


Transmitter substance
Receptor protein
Potassium channel
1
γ
β
α
G-protein
Opens channel
K+
Membrane enzyme
2
α
3
Activates one or more intracellular enzymes
Specific cellular chemical activators
4
Activates gene transcription
Proteins and structural changes
Activates enzymes
ATP
or
GTP
cAMP
cGMP


Signal molecules bind to receptors
Ions
Ion channel
G protein-coupled receptor
G protein
Change in membrane permeability to Na^+, K^+, Cl^-
Creates electrical signal
Voltage-sensitive protein
Cellular response


Activated
receptor
Hormone
Adenylate
cyclase
Extracellular side
Cytosolic side
Stimulatory
G protein
βγ
α
GTP
GDP
GTP-GDP exchange
Release and diffusion
of α subunit
α
GTP
cAMP
ATP
Activation of
adenylate cyclase
by Gα–GTP

- Pathway of G protein linked receptor



Properties of binding of H and R

- highly specificity
- highly affinity
- saturation
- reversible binding
- special function model

Receptor Types

- Channel-linked receptors
  - Ionotropic
- Enzyme-linked receptors
  - Protein kinases → phosphorylation
  - Neurotrophins
- G-protein-coupled receptors
  - Metabotropic
- Intracellular receptors
  - Activation by cell-permeant signals ~

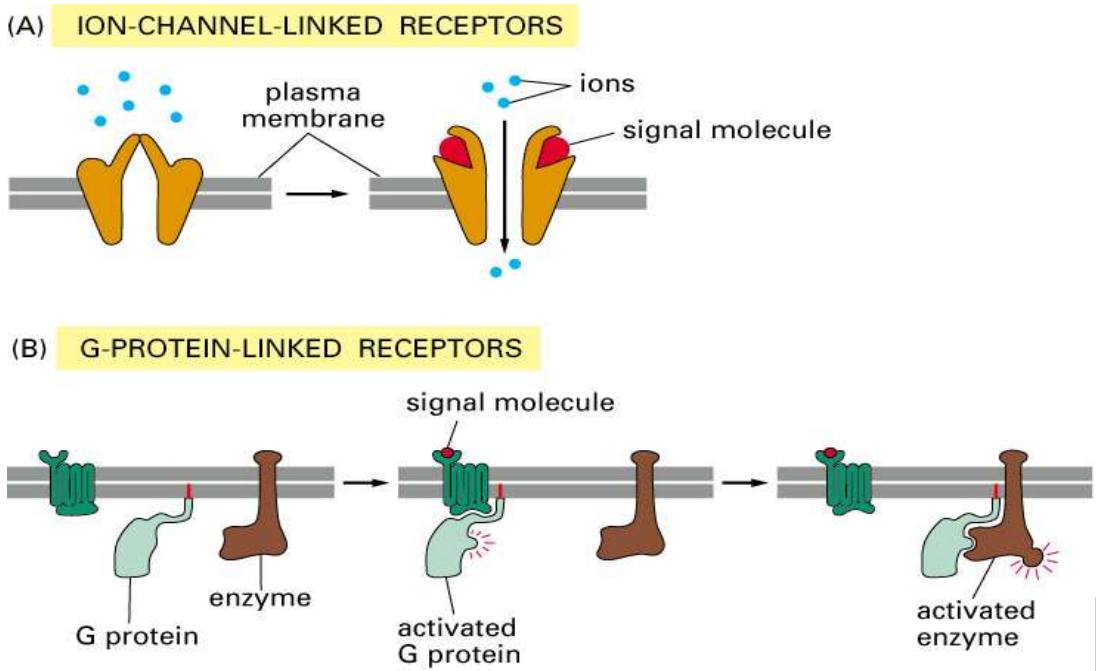
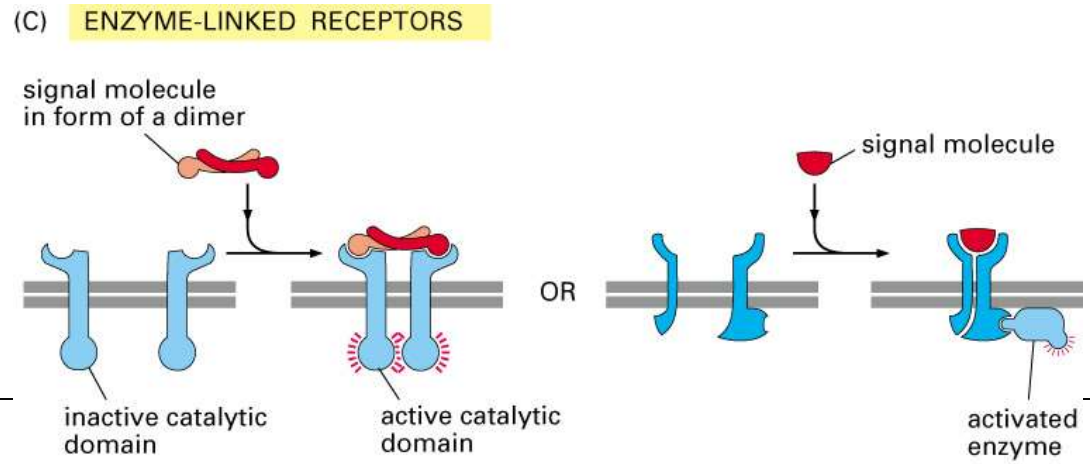
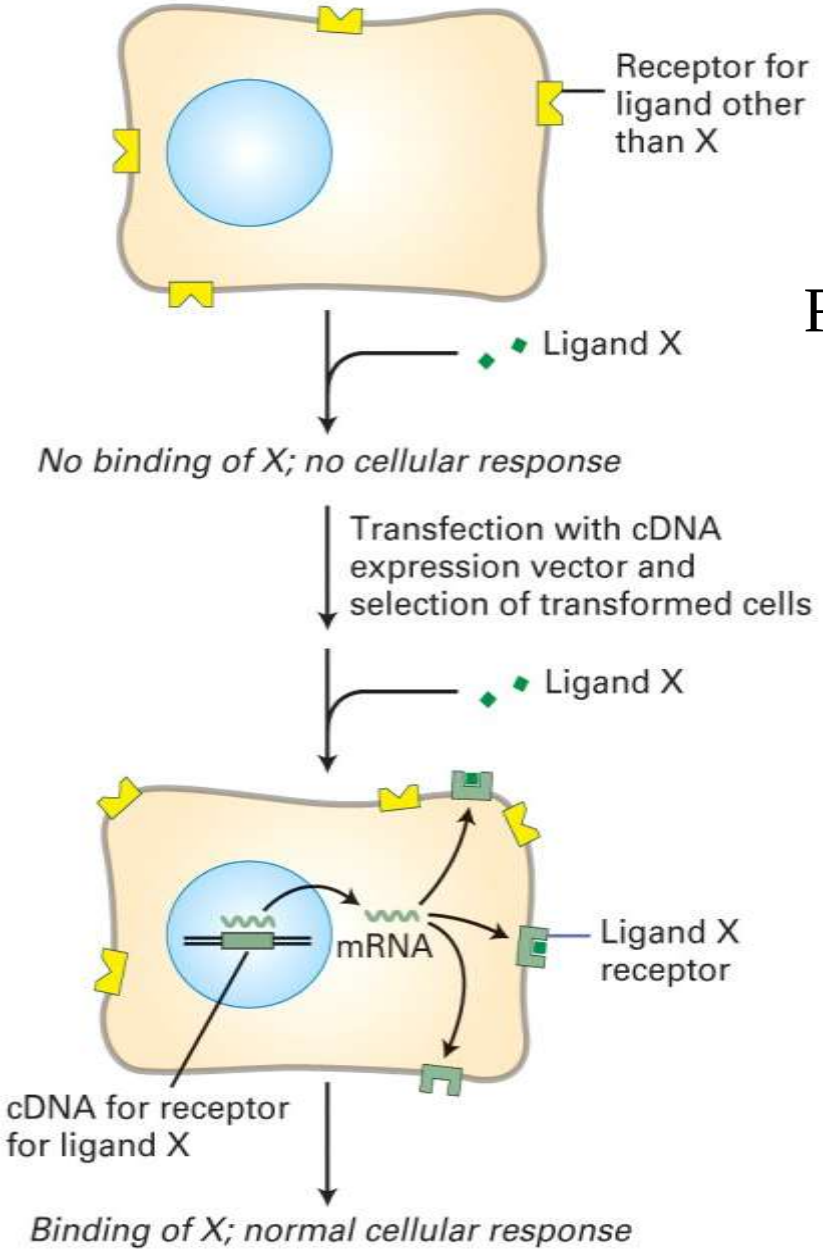


Figure 15–15 part 1 of 2. Molecular Biology of the Cell, 4th Edition.





Receptors determine response

No receptor - no response

G Protein Signal Cascade

The **signal** is usually passed from a **7-helix receptor** to an intracellular **G-protein**.

- Seven-helix receptors are thus called **GPCR**, or **G-P**rotein-**C**oupled **R**eceptors.
- Approx. 800 different GPCRs are encoded in the human genome.

G Protein Signal Cascade

G-protein-Coupled Receptors may **dimerize** or form oligomeric complexes within the membrane.

Ligand binding may promote oligomerization, which may in turn affect activity of the receptor.

Various **GPCR-interacting proteins** (**GIPs**) modulate receptor function. Effects of GIPs may include:

- altered **ligand affinity**
- receptor **dimerization** or oligomerization
- control of receptor **localization**, including transfer to or removal from the plasma membrane
- promoting close **association** with other signal proteins

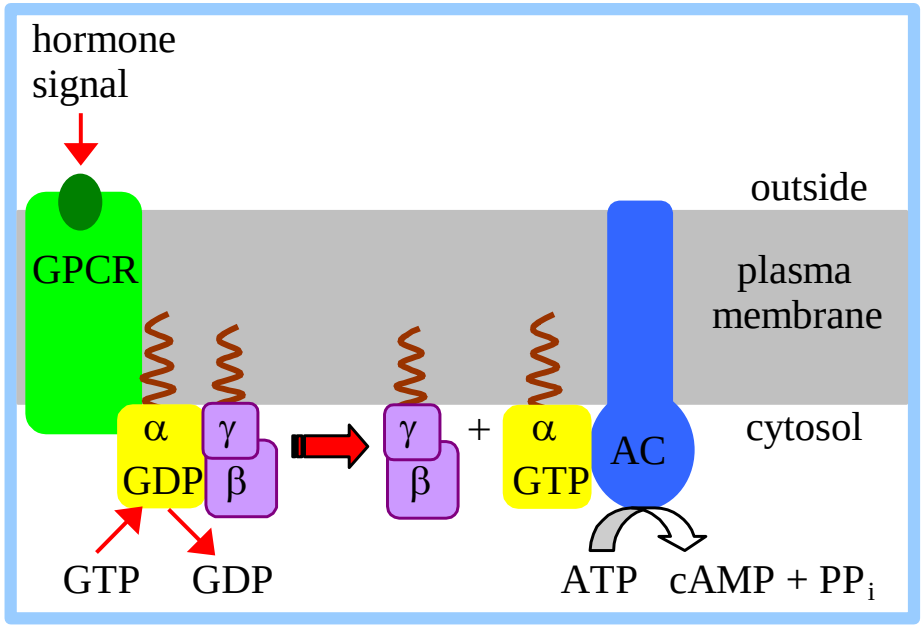
G Protein Signal Cascade

- **G-proteins** are **heterotrimeric**, with 3 subunits **α**, **β**, **γ**.
- A G-protein that activates cyclic-AMP formation within a cell is called a **stimulatory G-protein**, designated $\mathbf{G_s}$ with alpha subunit $\mathbf{G_{s\alpha}}$.
- $\mathbf{G_s}$ is activated, e.g., by receptors for the hormones **epinephrine** and **glucagon**.

  The **β-adrenergic receptor** is the **GPCR** for epinephrine.

G Protein Signal Cascade

- The **α** subunit of a G-protein (G_α) binds **GTP**, and can hydrolyze it to GDP + P_i.



- **α** & **γ** subunits have covalently attached **lipid anchors** that bind a G-protein to the plasma membrane cytosolic surface.
- **Adenylate Cyclase** (AC) is a transmembrane protein, with cytosolic domains forming the catalytic site.

Adenylate Cyclase

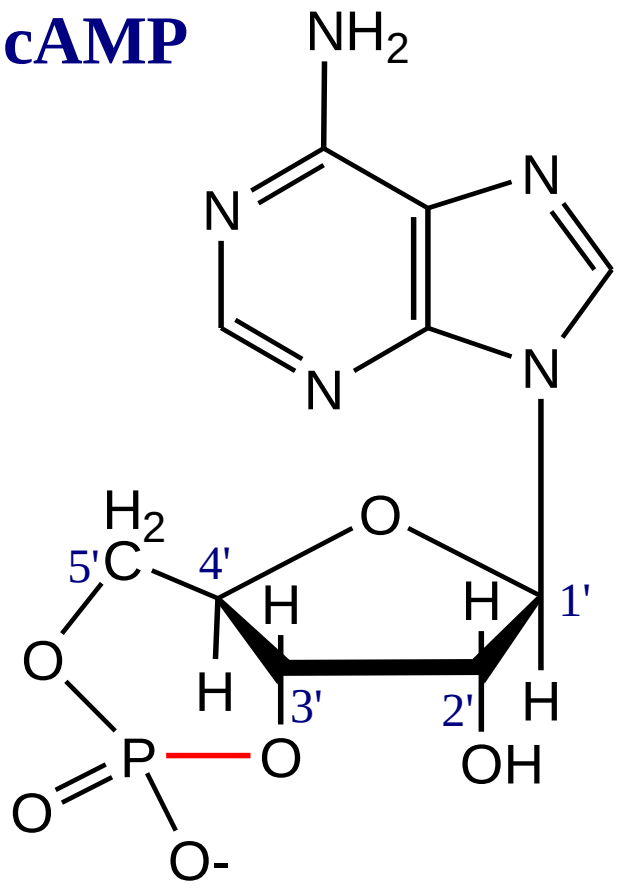
Adenylate Cyclase (Adenylyl Cyclase) catalyzes:

ATP à **cAMP + PP_i**

Binding of certain **hormones** (e.g., epinephrine) to the outer surface of a cell activates Adenylate Cyclase to form cAMP within the cell.

Cyclic AMP is thus considered to be a **second messenger**.

cAMP



G Protein Signal Cascade

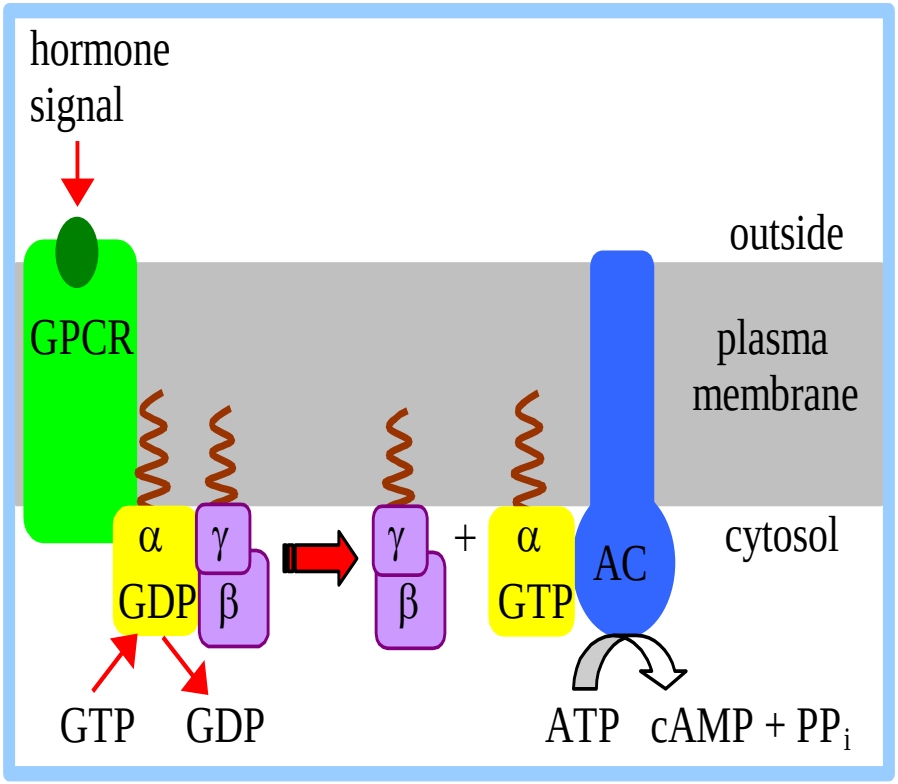
The **sequence of events** by

which a hormone activates

cAMP signaling:

1. Initially **G_α** has bound **GDP**, and **α**, **β**, & **γ** subunits are complexed together.

$G_{\beta,\gamma}$, the complex of **β**, & **γ** subunits, **inhibits G_α**.

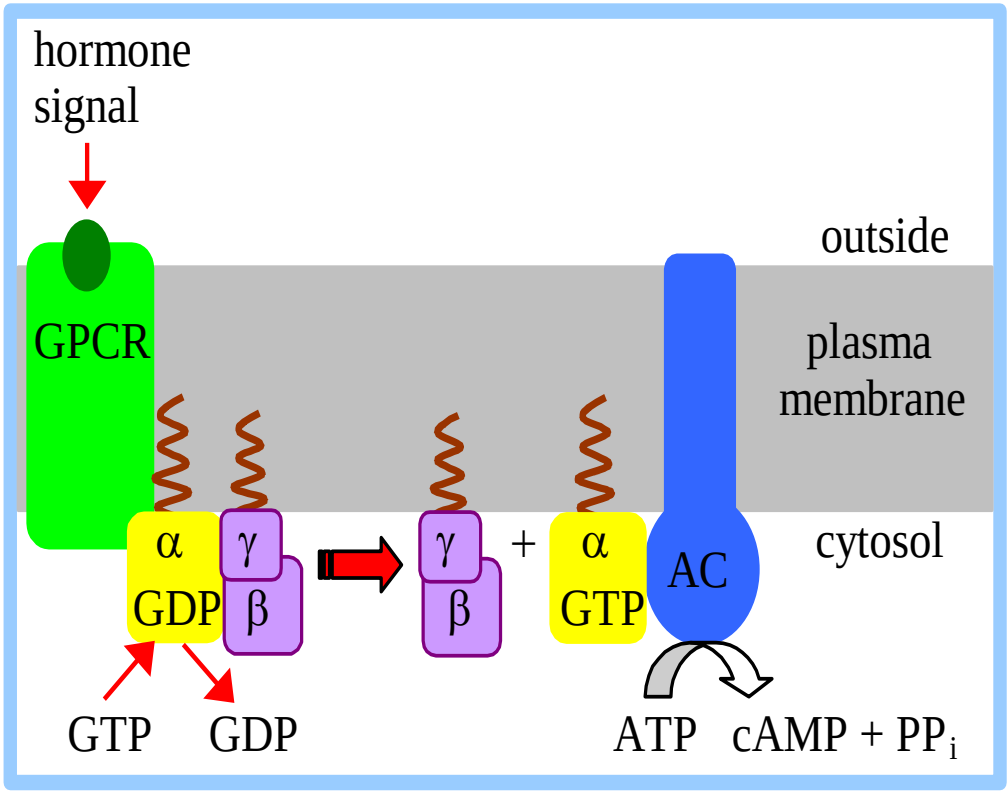


G Protein Signal Cascade

2. **Hormone binding**, usually to an extracellular domain of a 7-helix receptor (GPCR), causes a **conformational change** in the receptor that is transmitted to a **G-protein** on the cytosolic side of the membrane.

The nucleotide-binding site on **G α** becomes more accessible to the cytosol, where [GTP] > [GDP].

G_α releases GDP & binds GTP (**GDP-GTP exchange**).

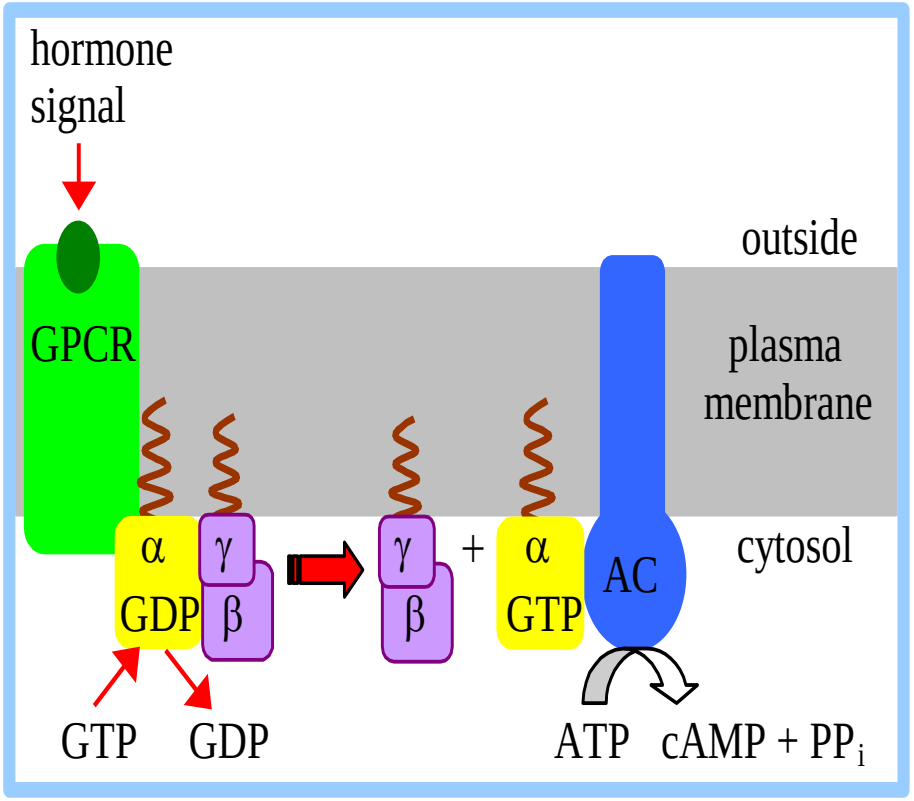


G Protein Signal Cascade

3. Substitution of **GTP** for GDP causes another conformational change in

G_α.

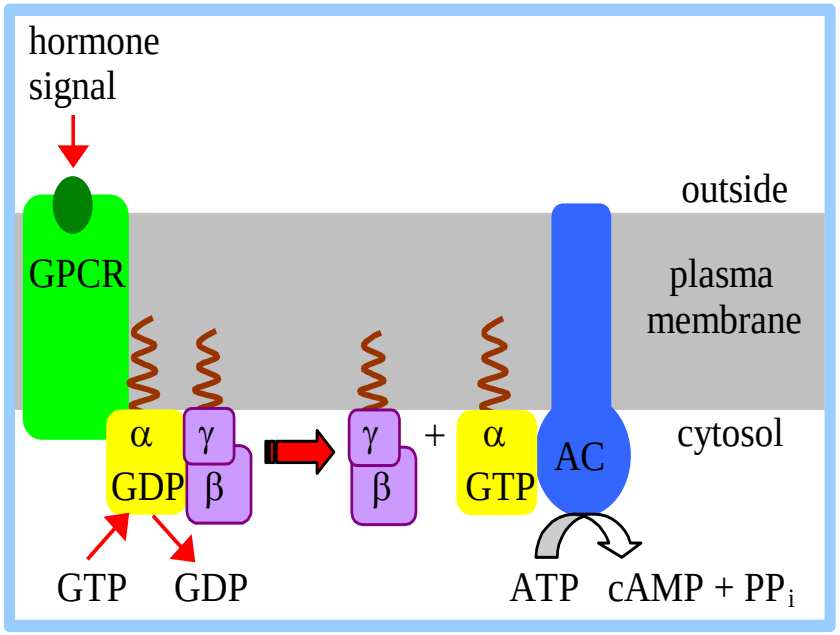
G_α -GTP dissociates from the inhibitory **β**, **γ** complex & can now bind to and activate **Adenylate Cyclase**.



G Protein Signal Cascade

4. **Adenylate Cyclase**, activated by the stimulatory G_α-GTP, catalyzes synthesis of **cAMP**.

5. **Protein Kinase A** (cAMP Dependent Protein Kinase) catalyzes transfer of phosphate from ATP to serine or threonine residues of various cellular proteins, altering their activity.



Turn off of the signal:

1. **G_{α}** hydrolyzes GTP to GDP + P_i. (**GTPase**).

   The presence of **GDP** on G_{α} causes it to rebind to the inhibitory **βγ** complex.

   Adenylate Cyclase is no longer activated.

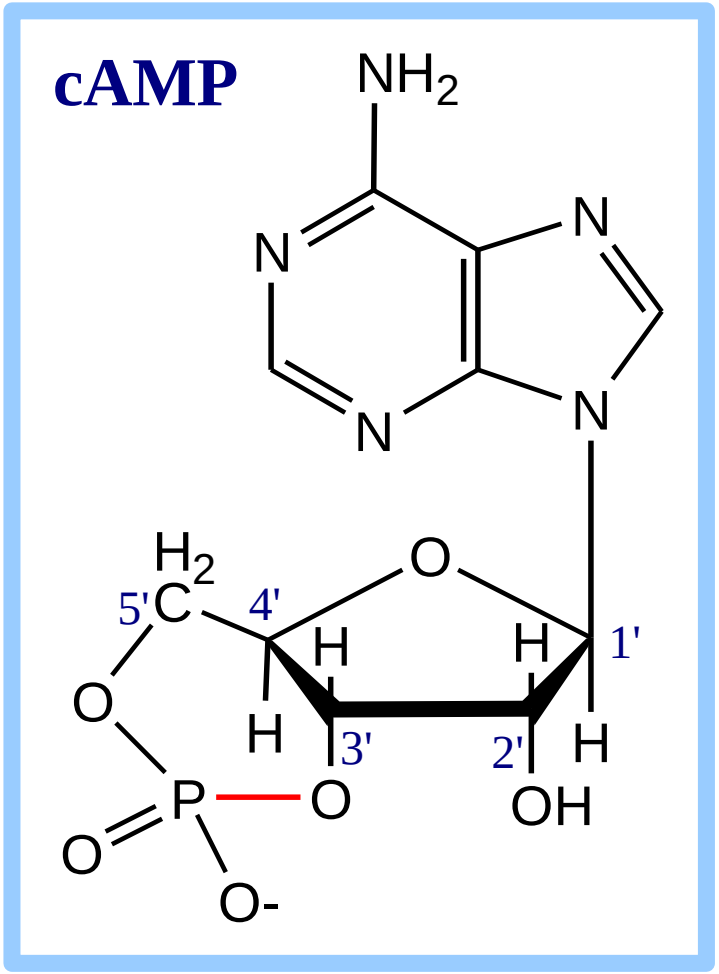
2. **Phosphodiesterases** catalyze hydrolysis of **cAMP → AMP**.

Phosphodiesterase enzymes catalyze:

cAMP + H_2O → AMP

The phosphodiesterase that cleaves cAMP is activated by phosphorylation catalyzed by Protein Kinase A.

Thus **cAMP stimulates its own degradation**, leading to rapid turnoff of a cAMP signal.



Enzyme-linked receptors:

1. Tyrosine kinase-linked receptors (TKRs).

A. **Overview of TKRs:**

1. **Cell surface receptors that are directly linked to intracellular enzymes (kinases).**

2. **Includes receptors for most growth factors (NGF, EGF. PDGF), insulin, and Src.**

3. **Common structure: N terminal extracellular ligand-binding domain, single TM domain, cytosolic C-terminal domain with tyrosine kinase activity.**

4. **Can be single polypeptide or dimer.**

Examples of tyrosine kinase-linked receptors (TKRs):

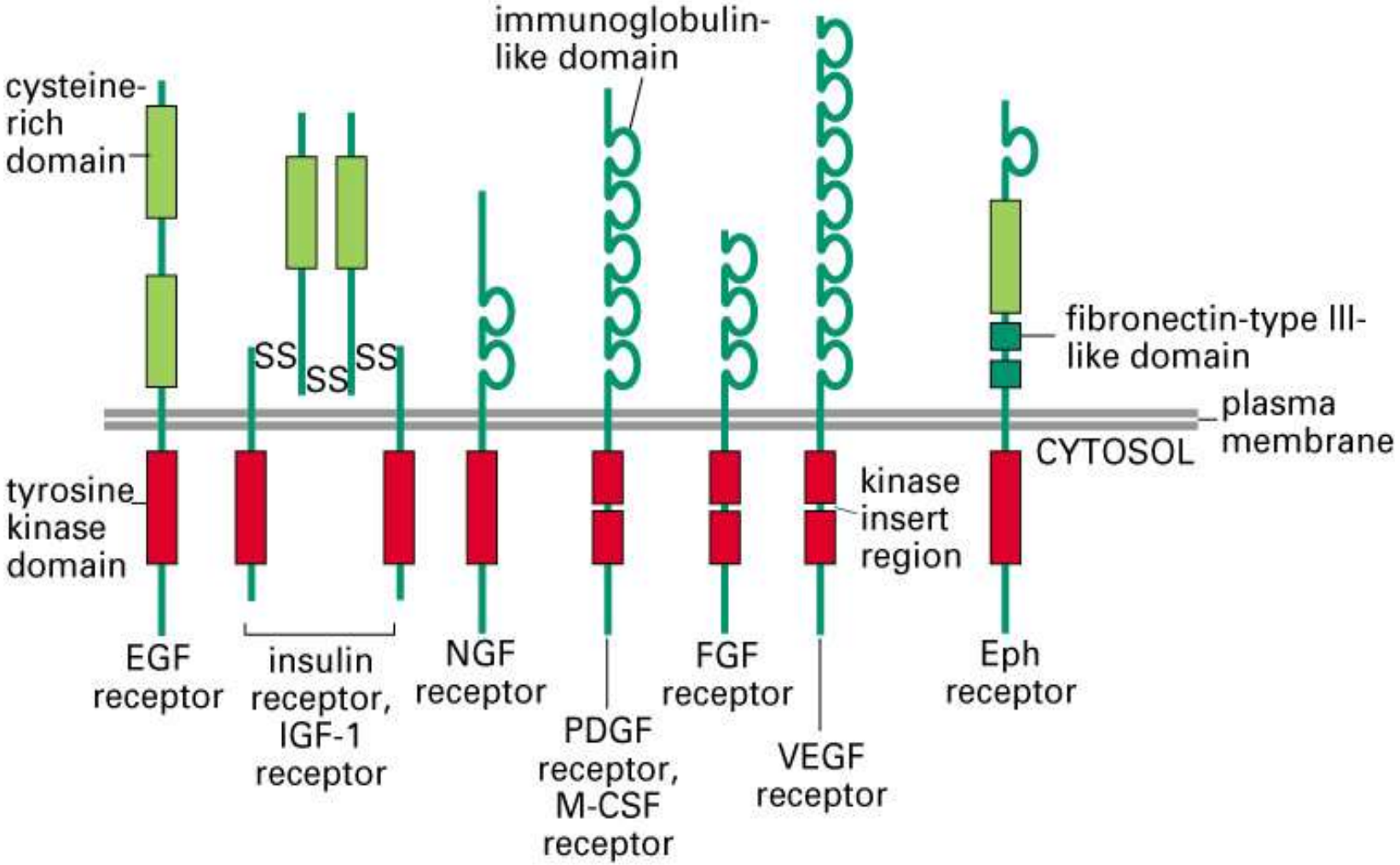


Figure 15–49. Molecular Biology of the Cell, 4th Edition.

C. Enzyme-linked receptors, cont.:

1. Tyrosine kinase-linked receptors (TKRs)

B. Mechanism of activation of TKRs:

i. ligand binding induces receptor dimerization (receptor crosslinking).

ii. dimerization leads to autophosphorylation of the receptor (cross-phosphorylation).

iii. phosphorylation increases kinase activity & also creates specific new binding sites.

iv. proteins that bind to these new binding sites transmit intracellular signals.

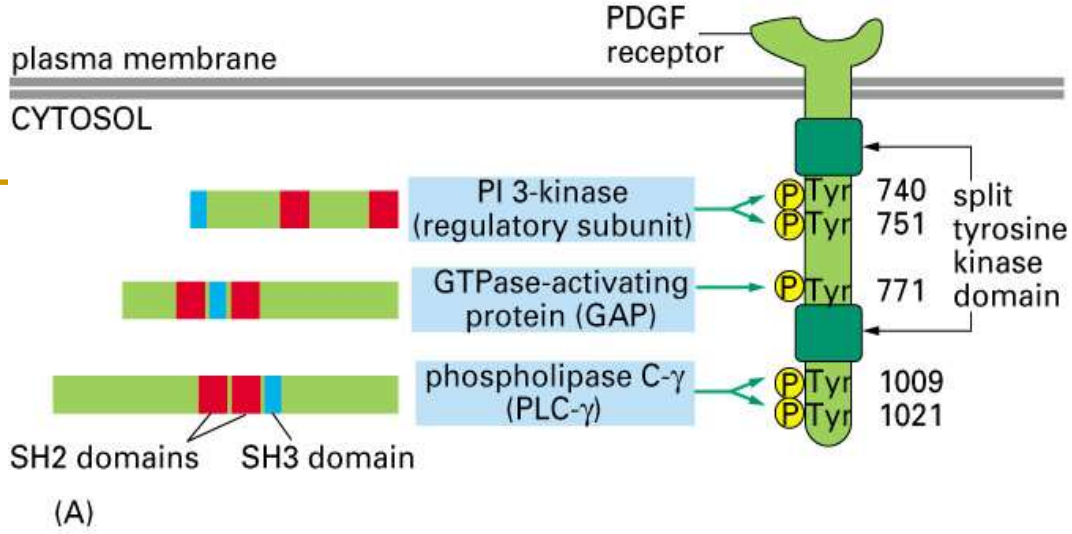


Figure 15–53 part 1 of 2. Molecular Biology of the Cell, 4th Edition.

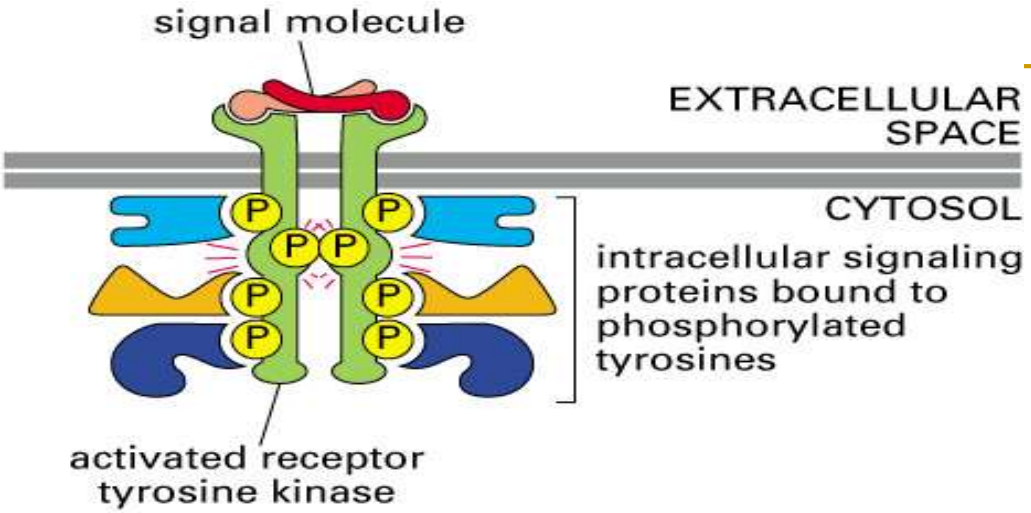


Figure 15–52. Molecular Biology of the Cell, 4th Edition.

How receptor tyrosine kinases work together with monomeric GTPases:

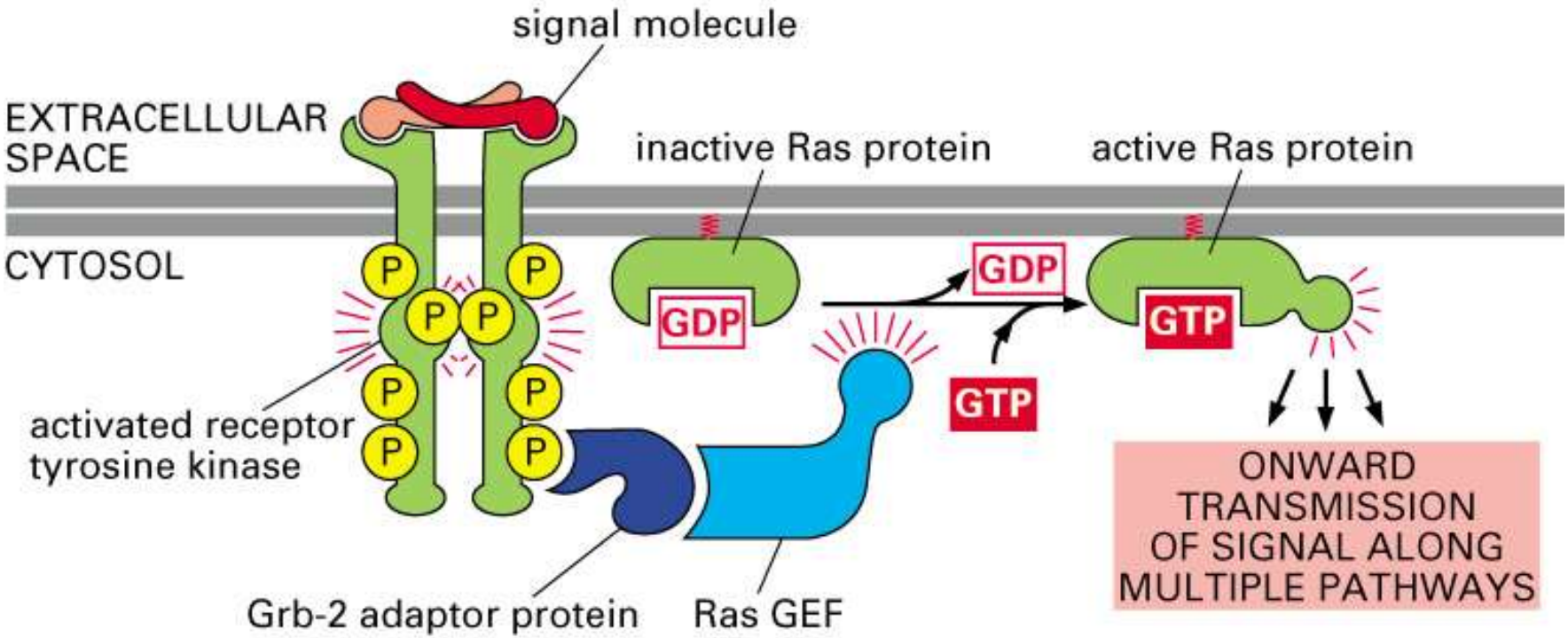


Figure 15–55. Molecular Biology of the Cell, 4th Edition.

C. Enzyme-linked receptors, cont.:

1. **Tyrosine kinase-linked receptors (TKRs)**
   - ***C.*** **Different ways that TKRs can be activated:**
     - **i. Ligand dimerization**
     - **ii. Monomeric ligand binds to a crosslinking protein**
     - **iii. Clustered monomeric cell-surface ligand**

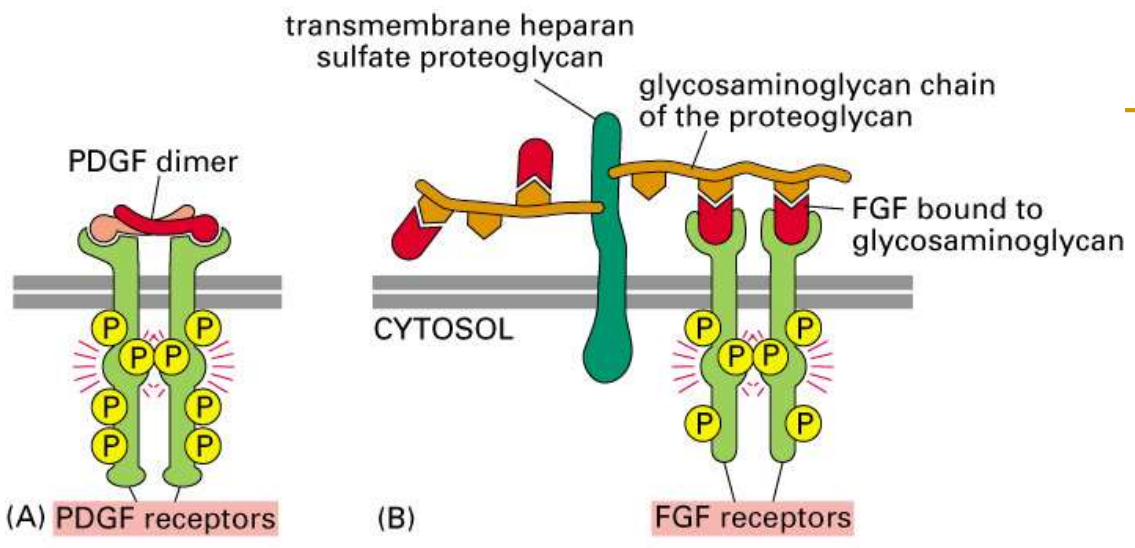


Figure 15–50 part 1 of 2. Molecular Biology of the Cell, 4th Edition.

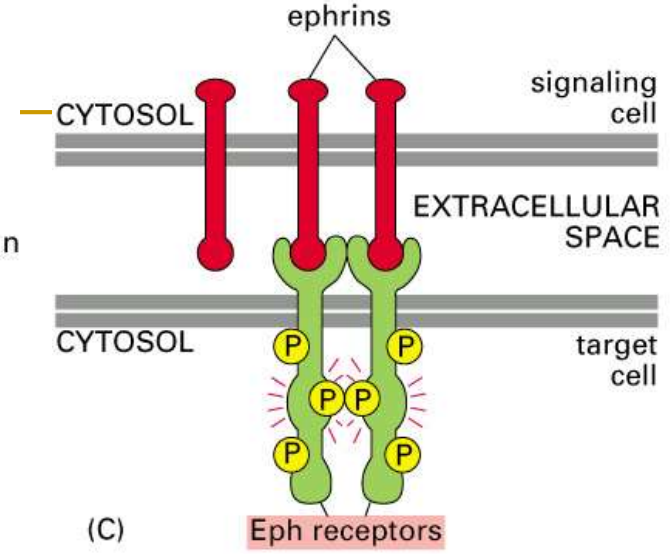


Figure 15–50 part 2 of 2. Molecular Biology of the Cel


THANKYOU

Receptors Functions and Signal Transduction- L3

Faisal I. Mohammed, MD, PhD

Second Messenger Targets

- Enzymes
  - Modulate phosphorylation
  - Phosphorylation → activation or inactivation
- Protein Kinases
  - Increase phosphorylation
- Protein Phosphatases
  - activated by Ca^{2+}/calmodulin
  - Decrease phosphorylation ~

Second Messengers

- Calcium (Ca^{2+})
  - Target: calmodulin
  - Calmodulin → protein kinases (protein kinas B)
- Cyclic nucleotides
  - cAMP & cGMP
  - Target: protein kinases ~

Second Messengers

- Diacylglycerol (DAG) & inositol triphosphate (IP_3)
  - From membrane lipids
  - DAG and calcium → Protein Kinase C (membrane)
  - IP_3 → Ca^{2+} (endoplasmic reticulum) ~

Hormones That Use 2nd Messengers

- Hormones cannot pass through plasma membrane use 2nd messengers.
  - Catecholamine, polypeptide, and glycoprotein hormones bind to receptor proteins on the target plasma membrane.
- Actions are mediated by 2nd messengers (signal-transduction mechanisms).
  - Extracellular hormones are transduced into intracellular 2nd messengers.

Adenylate Cyclase-cAMP

- **4. Second Messengers: for Hormones that can't cross PM**
- **A. cAMP:**

i. **Production:**

ATP converted to cAMP by adenylate cyclase (a large multipass TM protein). Degraded by cAMP phosphodiesterase

ii. **Action:**

a. cAMP-dependent protein kinase (protein kinase A (PKA)). PKA is a tetramer of catalytic and regulatory subunits. cAMP binding leads to dissociation of regulatory subunits and release of catalytic subunits which then phosphorylate target proteins in cytoplasm:

Adenylate Cyclase-cAMP

iii. **Action:**

b. **PKA enters the nucleus and phosphorylates CREB (CRE binding protein), which binds to the cAMP response element (CRE), a regulatory DNA sequence associated with specific genes. This results in activation of transcription of those genes.**

iv. **Rapid turn on and rapid turn off of cAMP and activation by cAMP :**

Question: what turns off proteins activated by protein kinases?

v. **Amplification of signal at each step of signaling pathway - characteristic feature of signal transduction.**

Second messenger -cAMP

A. cAMP, cont.:

vi. **Regulation of adenylate cyclase: Receptors that cause increase in cAMP do so by activating G_s, a stimulatory protein that activates adenylyl cyclase. Adenylyl cyclase is turned off by G_i, an inhibitory protein.**

vii. **Pathogens alter cAMP production: Cholera toxin active subunit catalyzes transfer of ADP ribose from intracellular NAD to the α subunit of G_s, causing it to be continuously active, stimulating adenylyl cyclase indefinitely. This causes ion channels that export chloride to produce a net effux of Cl- and water, leading to severe diarrhea characteristic of cholera.**

B. cGMP:

1. **produced from GTP by guanylyl cyclase;**

2. **activates cGMP-dependent kinases or other targets**

3. **example: G-prot. Coupled rhodopsin photoreceptor in rod cells of retina**

cAMP production:

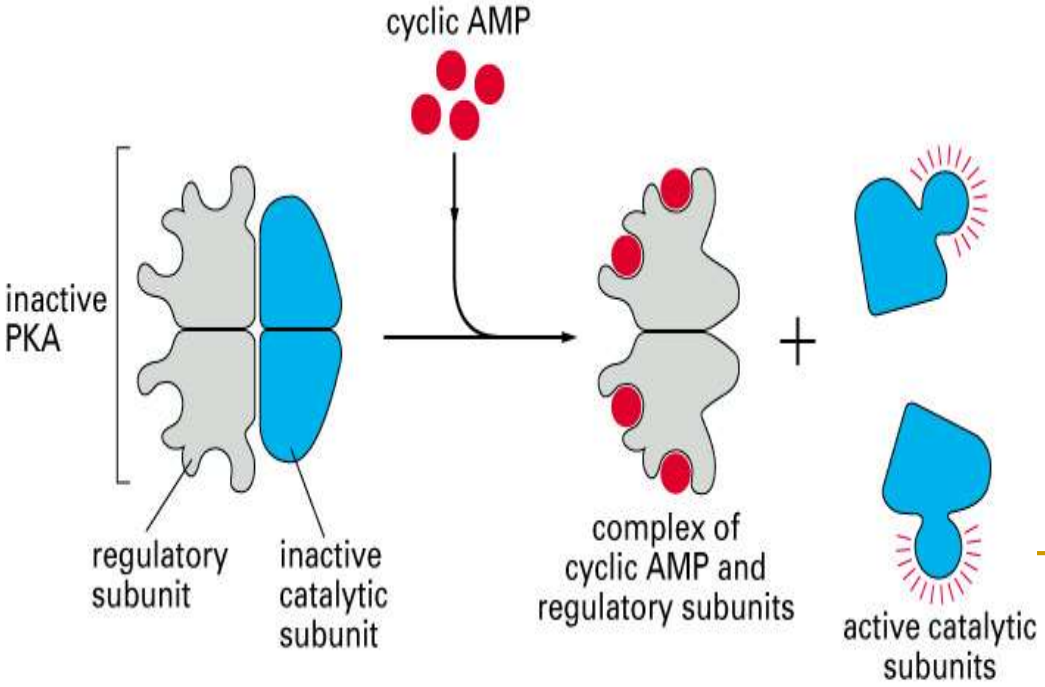


Figure 15–32. Molecular Biology of the Cell, 4th Edition.

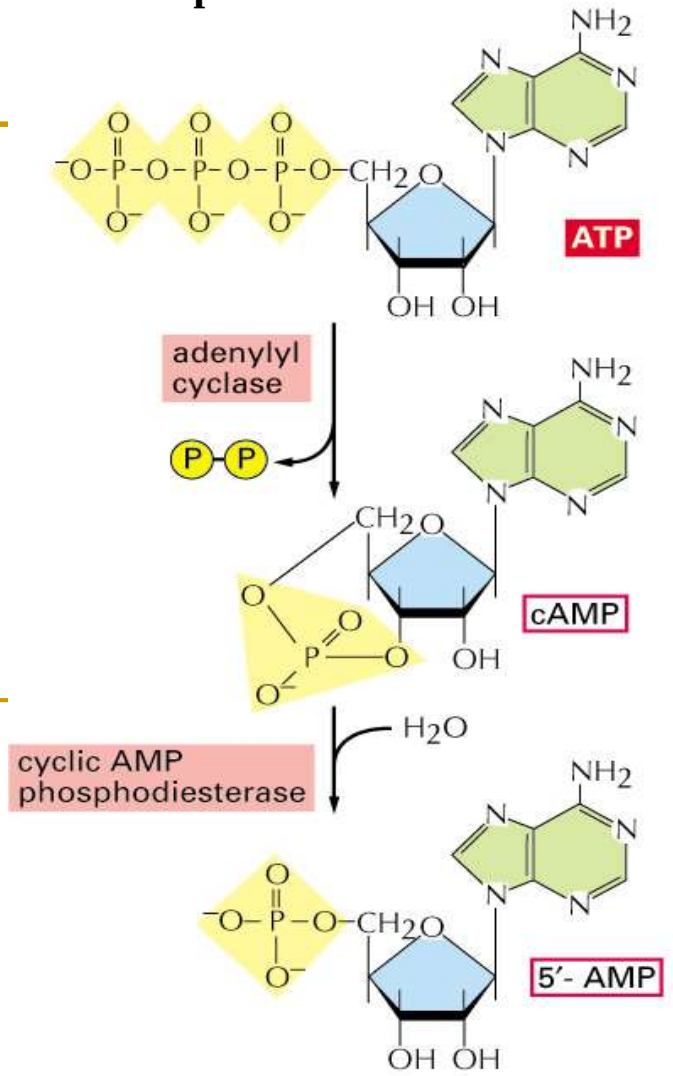


Figure 15–31. Molecular Biology of the Cell, 4th Edition.

Adenylate Cyclase-cAMP

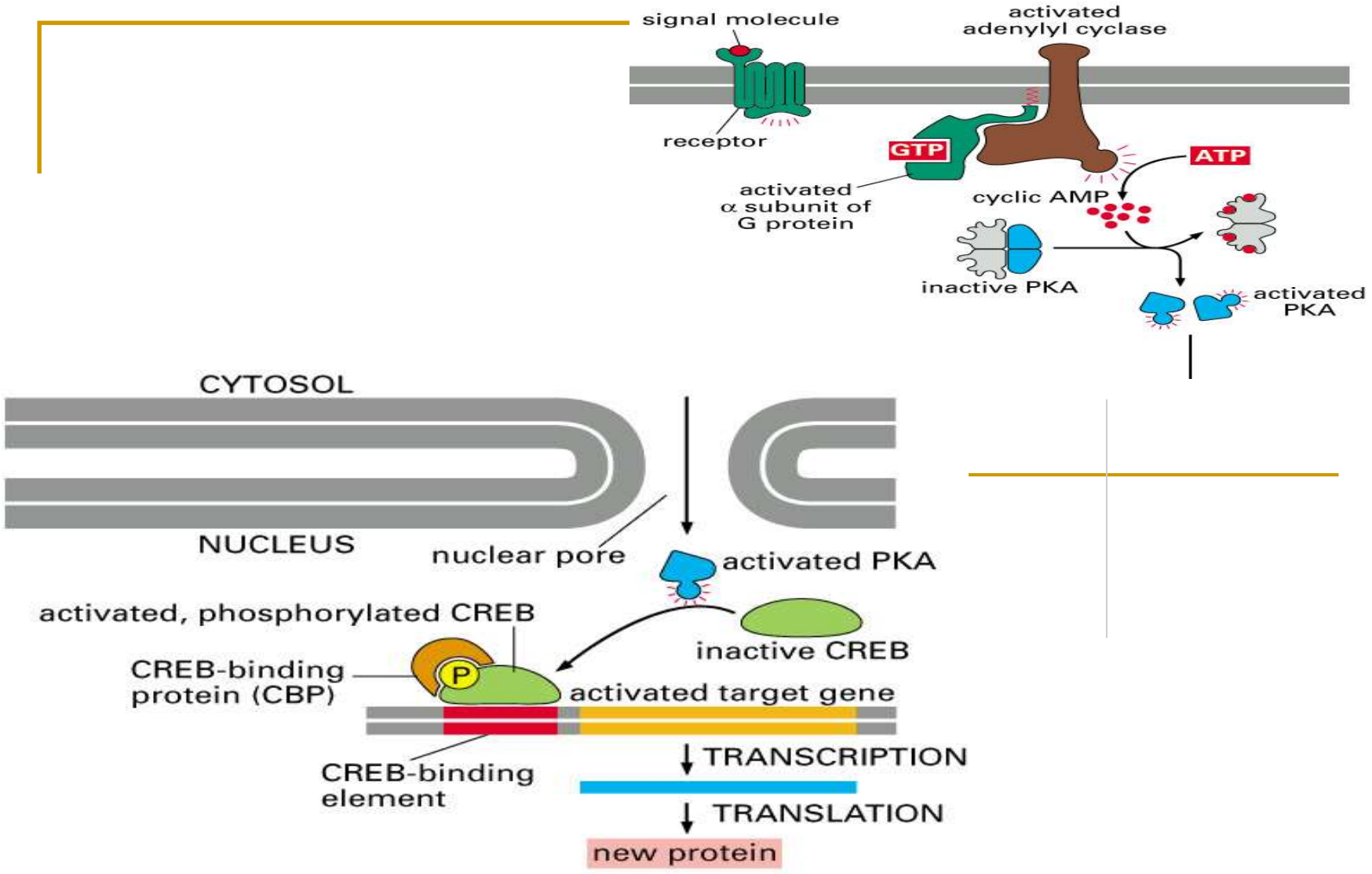


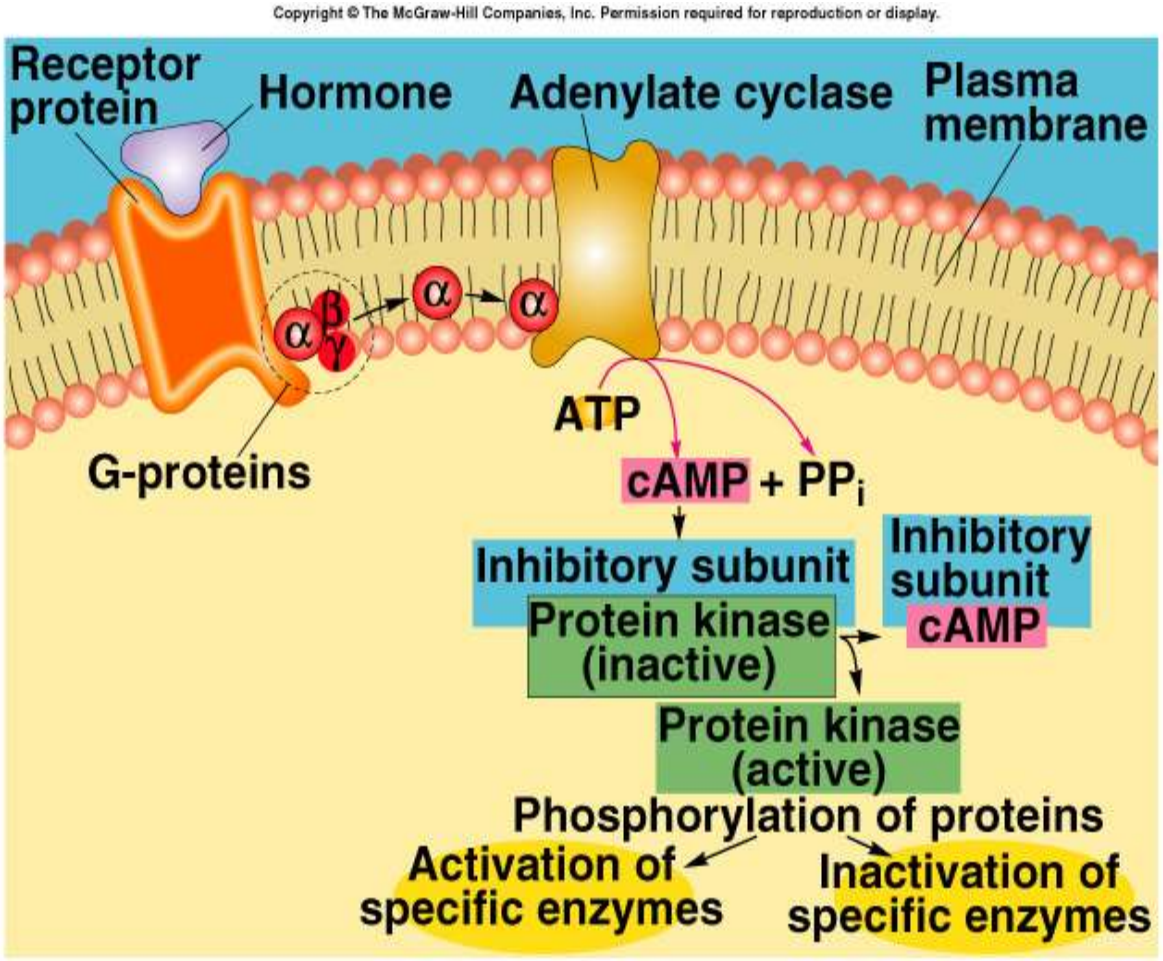
Figure 15–33 part 2 of 2. Molecular Biology of the Cell, 4th Edition.

Adenylate Cyclase-cAMP

- Polypeptide or glycoprotein hormone binds to receptor protein causing dissociation of α subunit of G-protein.
- G-protein α subunit binds to and activates adenylate cyclase.
- ATP → cAMP + PP_i
- cAMP attaches to inhibitory subunit of protein kinase.
- Inhibitory subunit dissociates and activates cAMP dependent protein kinase (protein kinase A)

Adenylate Cyclase-cAMP (continued)

- Phosphorylates enzymes within the cell to produce hormone's effects.
- Modulates activity of enzymes present in the cell.
- Alters metabolism of the cell.
- cAMP inactivated by phosphodiesterase.
  - Hydrolyzes cAMP to inactive fragments.



A. cAMP:

i. Production:

ATP converted to cAMP by adenylate cyclase.

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ii. Action:

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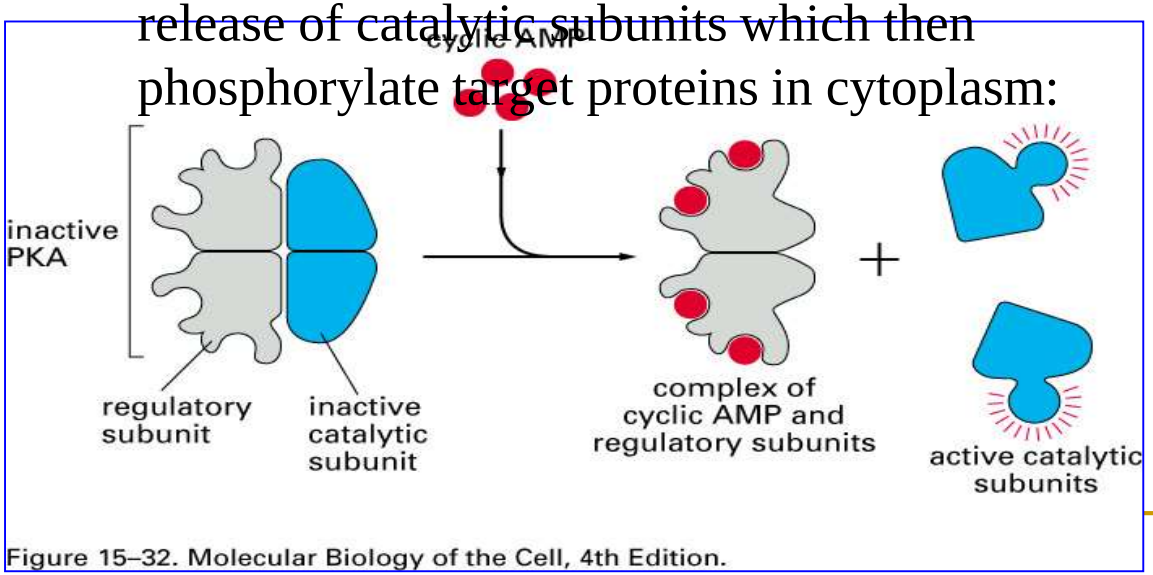


Figure 15–32. Molecular Biology of the Cell, 4th Edition.

cAMP production:

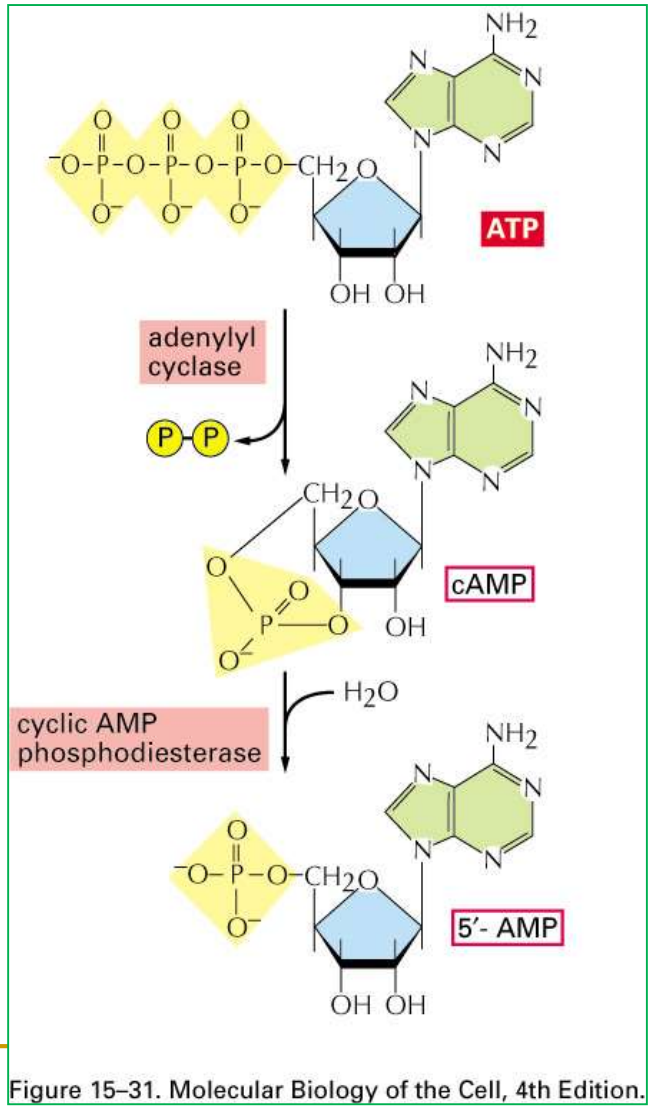
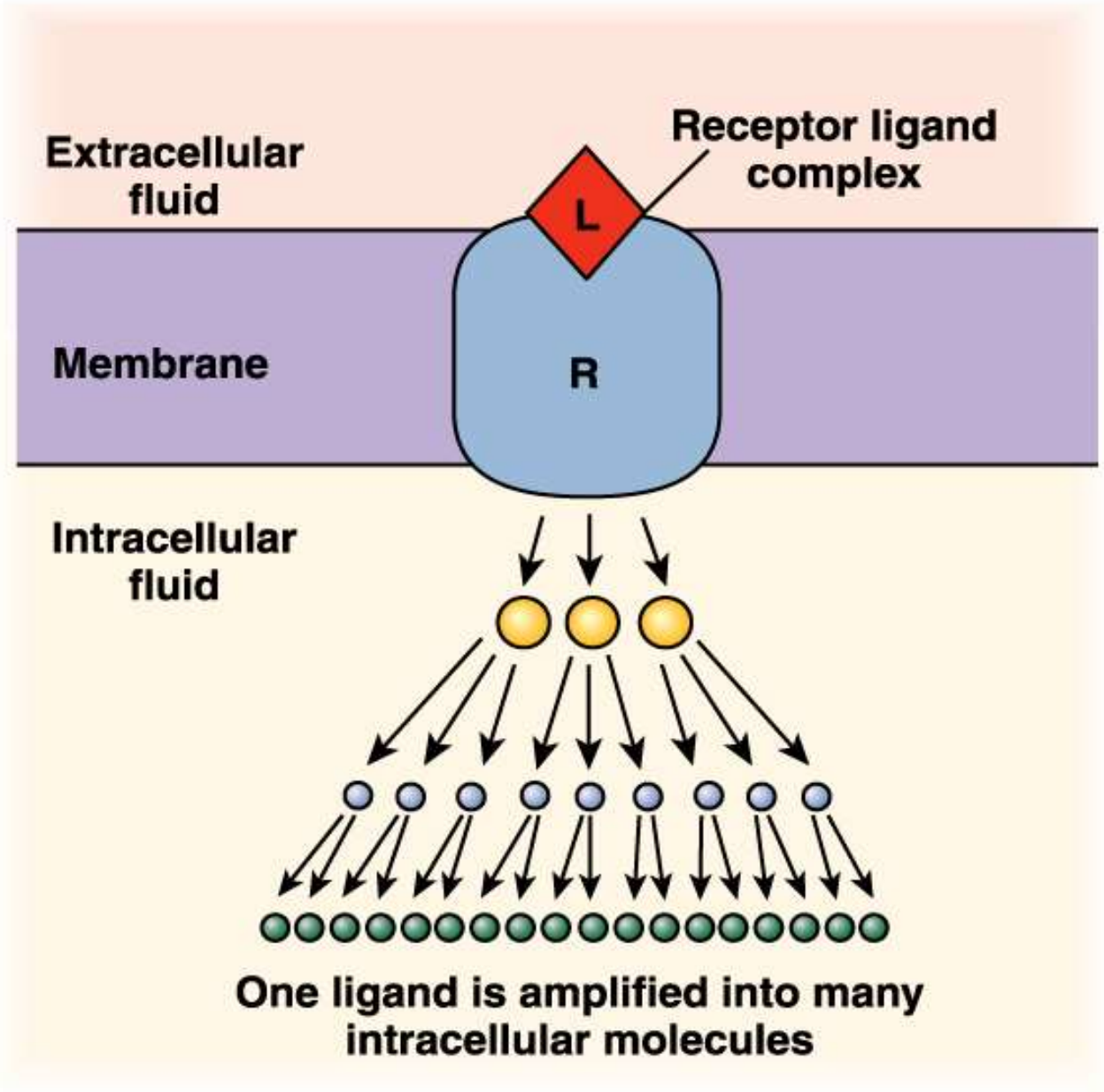
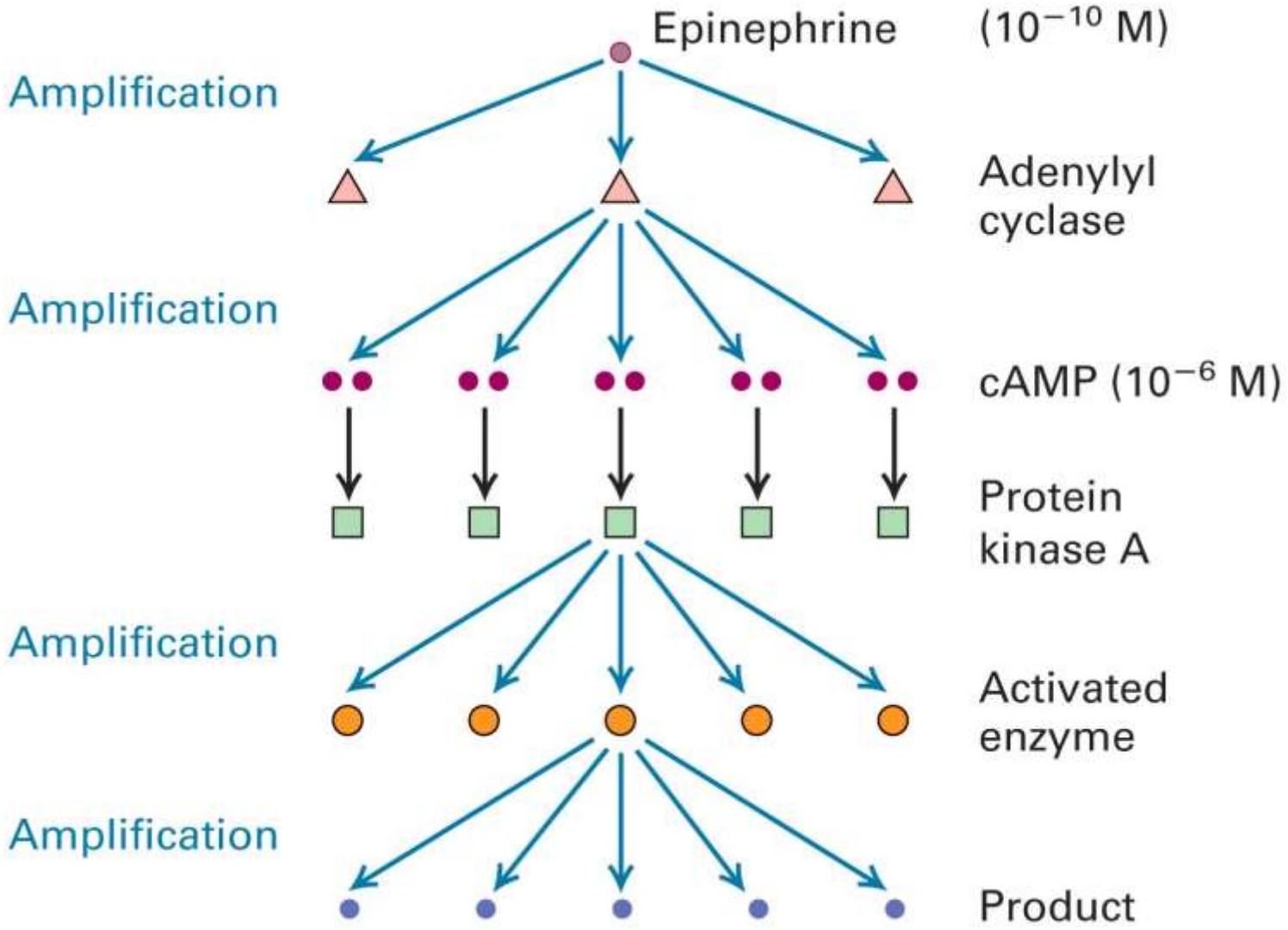


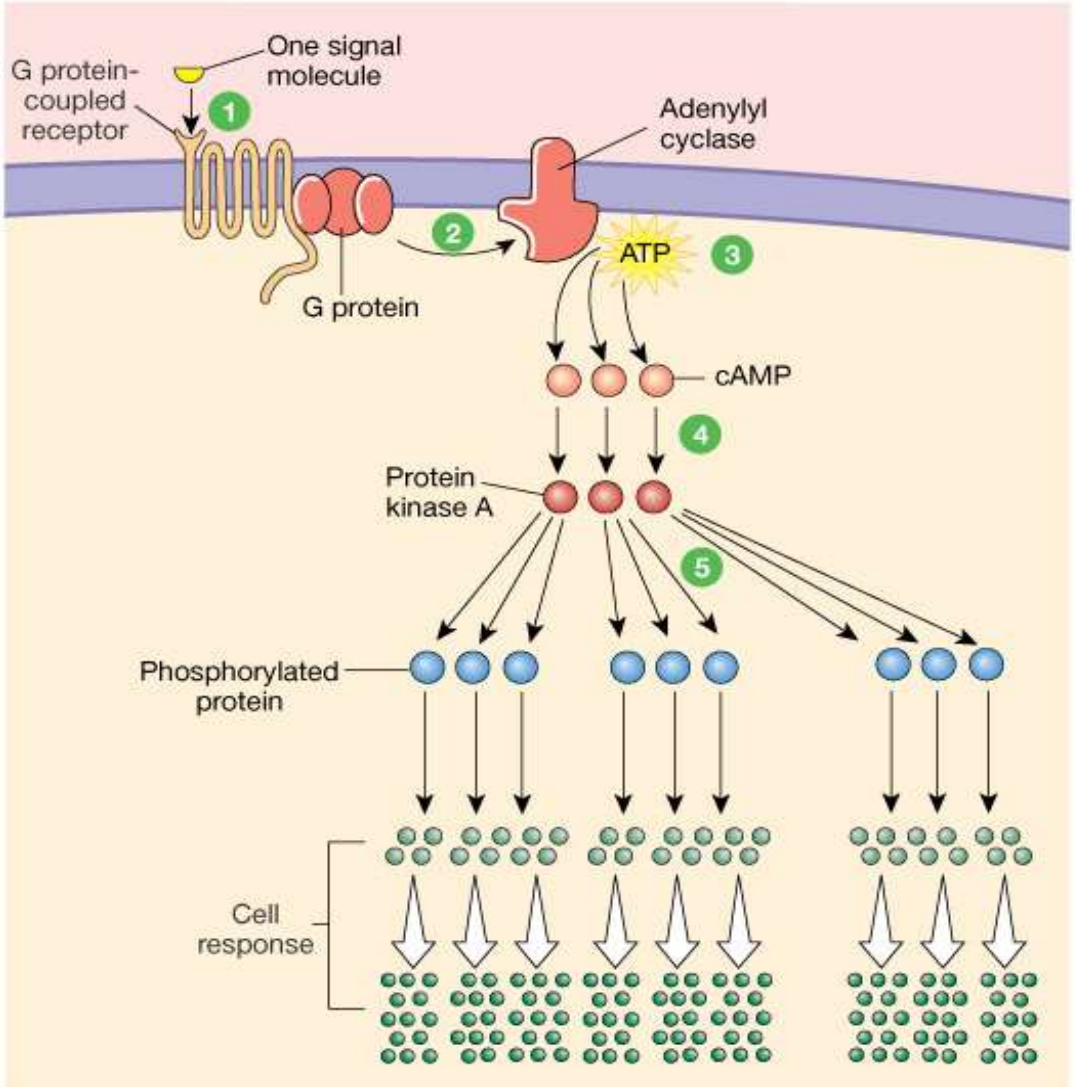
Figure 15–31. Molecular Biology of the Cell, 4th Edition.


Extracellular fluid
Receptor ligand complex
L
Membrane
R
Intracellular fluid
One ligand is amplified into many intracellular molecules

Signals are amplified



G-Protein-coupled Receptors



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.

Summary of how cAMP activates transcription:

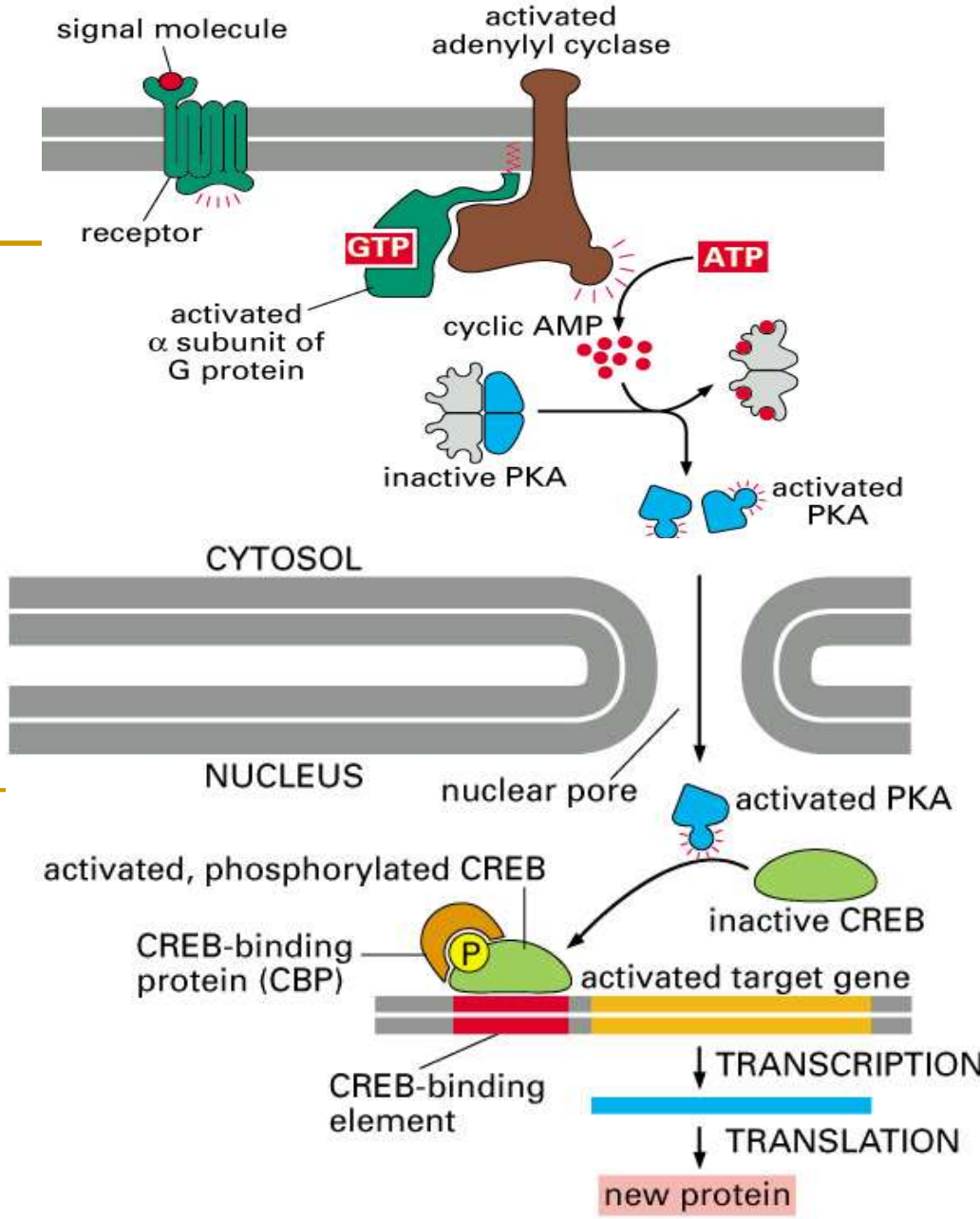
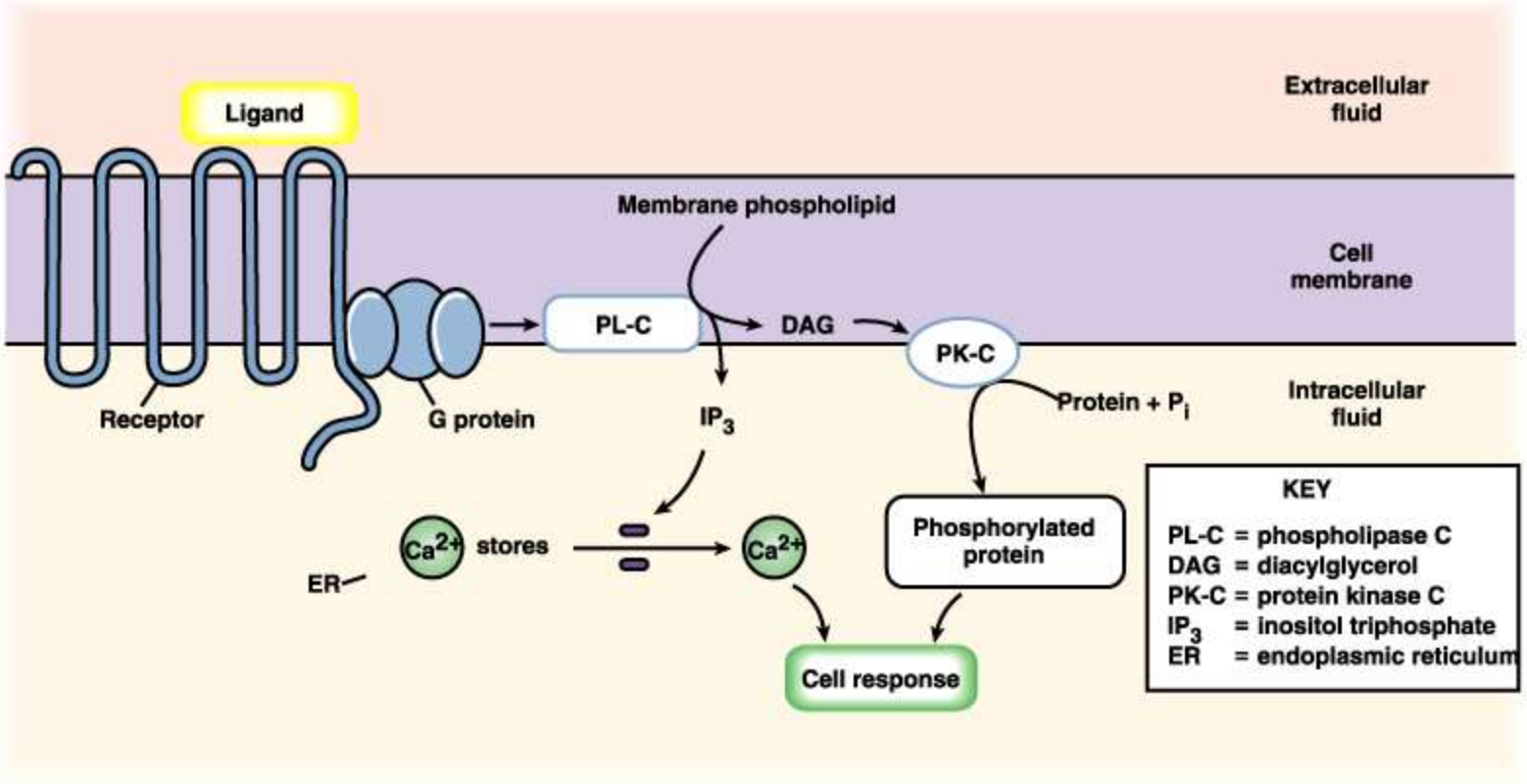


Figure 15–33 part 2 of 2. Molecular Biology of the Cell, 4th Edition.

(CREB= cAMP Response Element Binding protein)

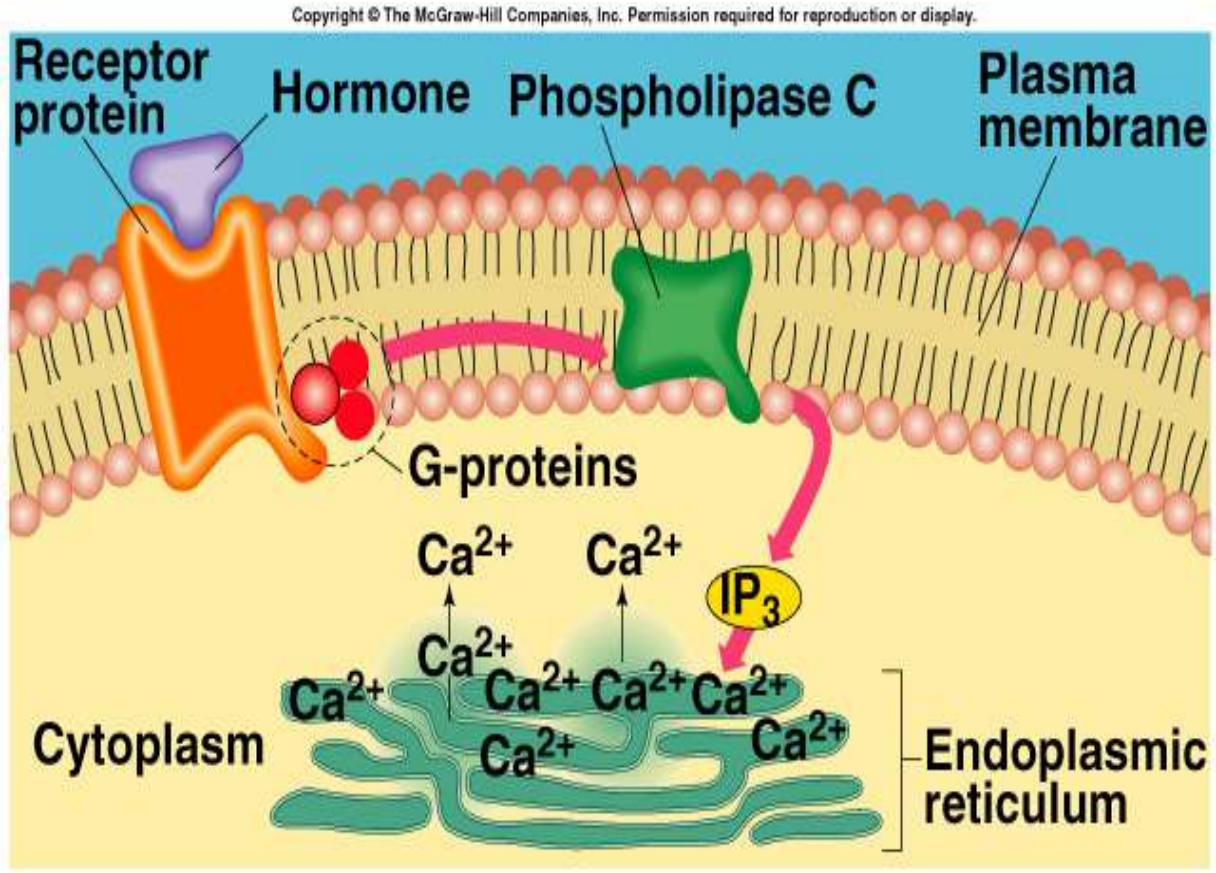
Phospholipase-C-Ca^{2+}

- Binding of Epinephrine to a-adrenergic receptor in plasma membrane activates a G-protein intermediate, phospholipase C.
  - Phospholipase C splits phospholipid into IP_3 and DAG.
    - Both derivatives serve as 2^{nd} messengers.
- IP_3 diffuses through cytoplasm to endoplasmic reticulum (ER).
  - Binding of IP_3 to receptor protein in ER causes Ca^{2+} channels to open and release of calcium to the cytoplasm


Ligand
Extracellular fluid
Membrane phospholipid
Cell membrane
PL-C
DAG
PK-C
Receptor
G protein
IP3
Protein + Pi
Intracellular fluid
Ca2+ stores
ER
Ca2+
Phosphorylated protein
Cell response
KEY
PL-C = phospholipase C
DAG = diacylglycerol
PK-C = protein kinase C
IP3 = inositol triphosphate
ER = endoplasmic reticulum

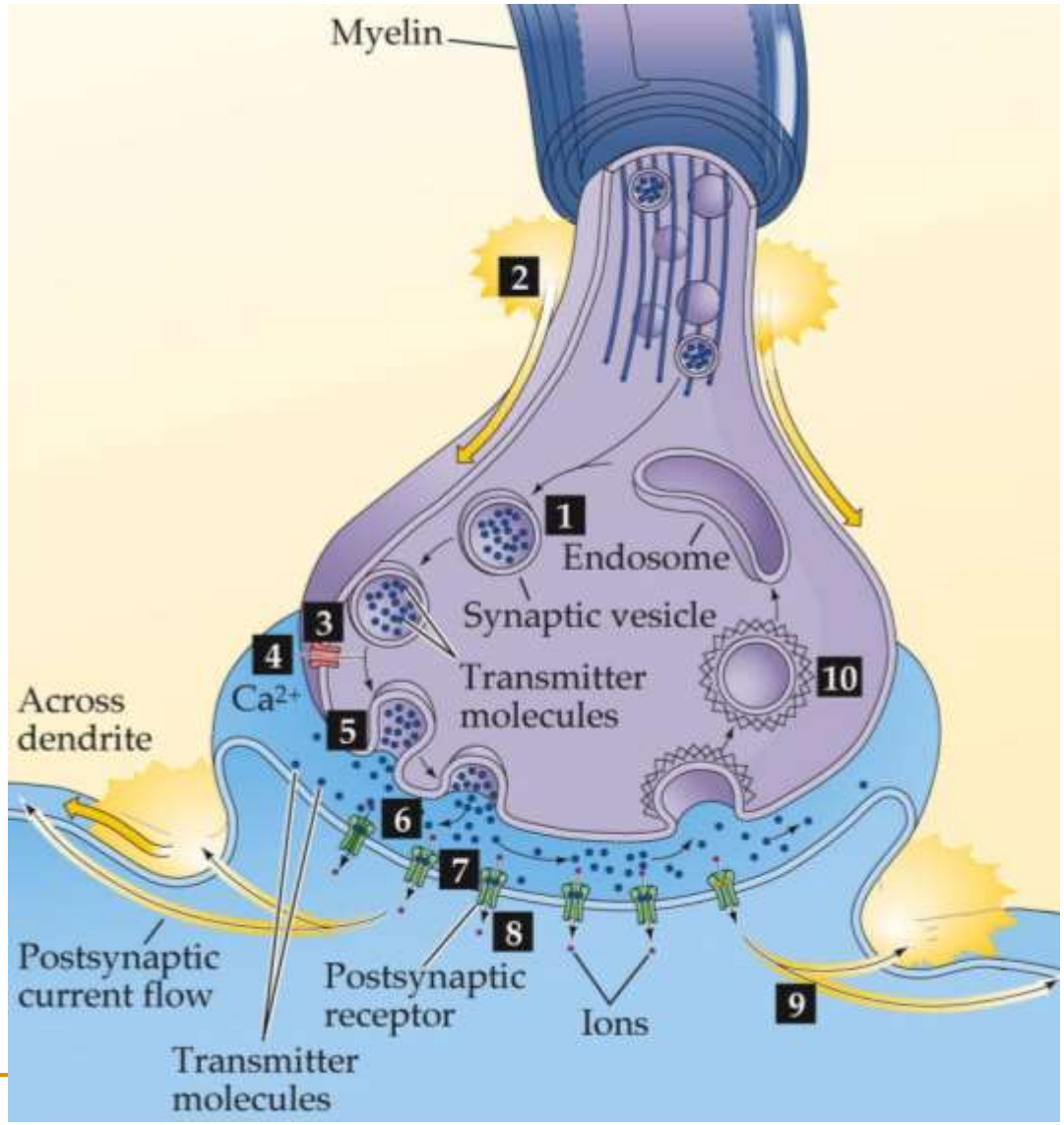
Ca^{2+}- Calmodulin Protein kinas B (continued)

- Ca^{2+} diffuses into the cytoplasm.
  - Ca^{2+} binds to calmodulin.
- Calmodulin activates specific protein kinase enzymes.
  - Alters the metabolism of the cell, producing the hormone's effects.

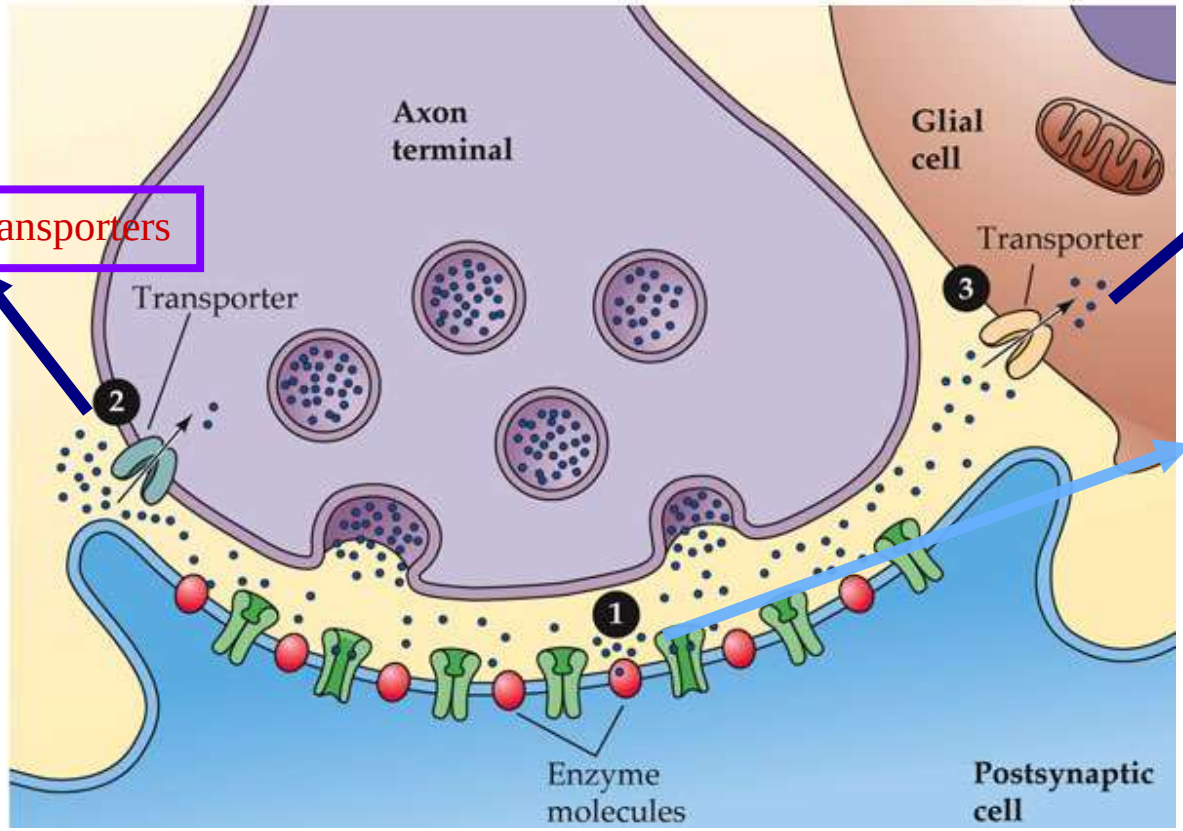


Neurotransmitter Release: exocytosis and endocytosis

1. Transmitter synthesized and stored
2. Action Potential
3. Depolarization: open voltage-gated Ca^{2+} channels
4. Ca^{2+} enter cell
5. Ca^{2+} causes vesicles to fuse with membrane
6. Neurotransmitter released (exocytosis)
7. Neurotransmitter binds to postsynaptic receptors
8. Opening or closing of postsynaptic channels
9. Postsynaptic current excites or inhibits postsynaptic potential to change excitability of cell
10. Retrieval of vesicles from plasma membrane (endocytosis)



Transmitter Inactivation: reuptake and enzymatic breakdown



Reuptake by transporters

Reuptake by transporters (glial cells)

Enzymatic breakdown

Neurotransmitter can be recycled in presynaptic terminal or can be broken down by enzymes within the cell

NT – Receptor Binding

Receptors are large, dynamic proteins that exist along and within the cell membrane.

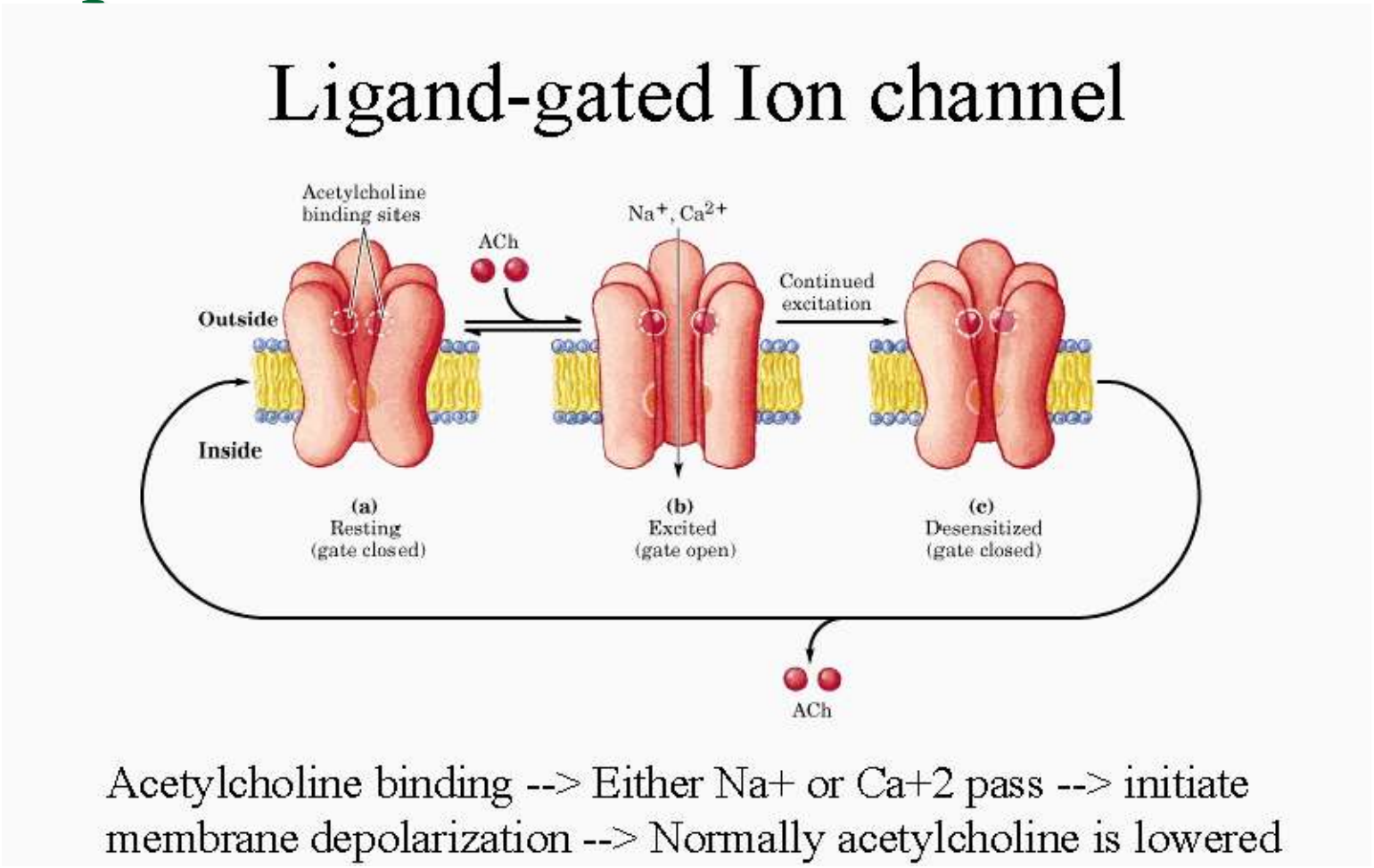
Dynamic – they can increase in number and avidity for their neurotransmitter according to circumstances.

Two Types of Post synaptic Receptors:

Ionotropic receptors: NT binding results in direct opening of specific ion channels

Metabotropic receptors: binding of NT initiates a sequence of internal molecular events which in turn open specific ion channels

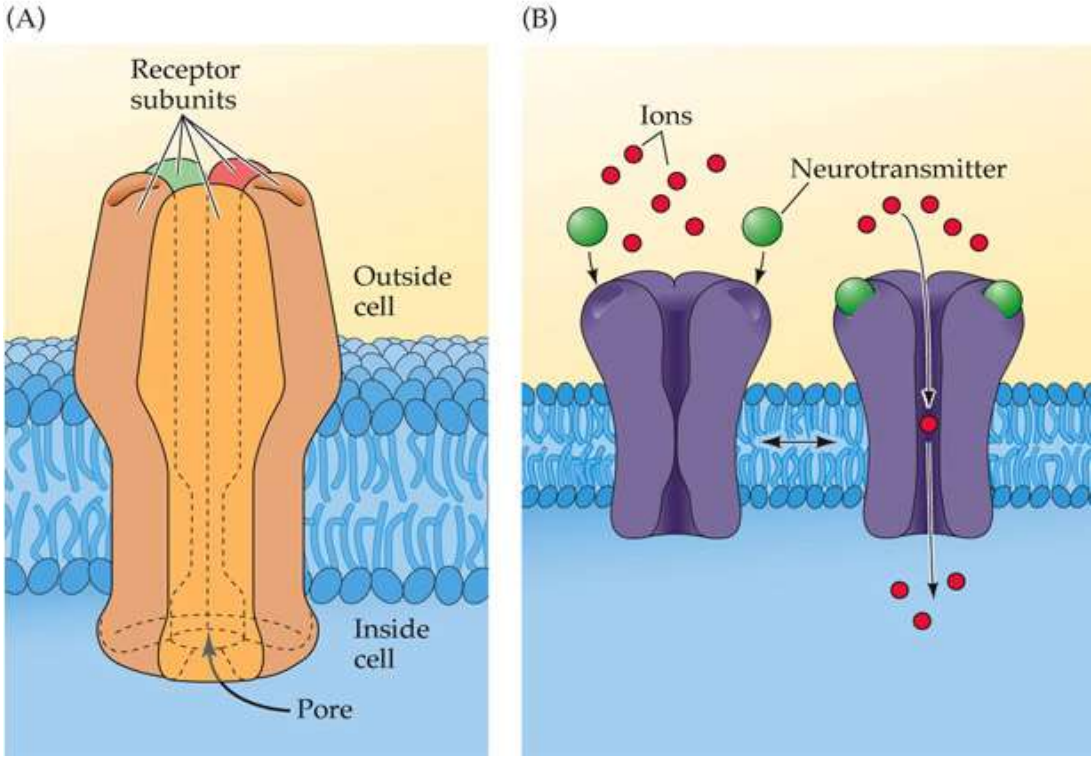
NT binding -> Membrane Potential Response



Ionotropic Receptors

Work very fast; important role in fast neurotransmission

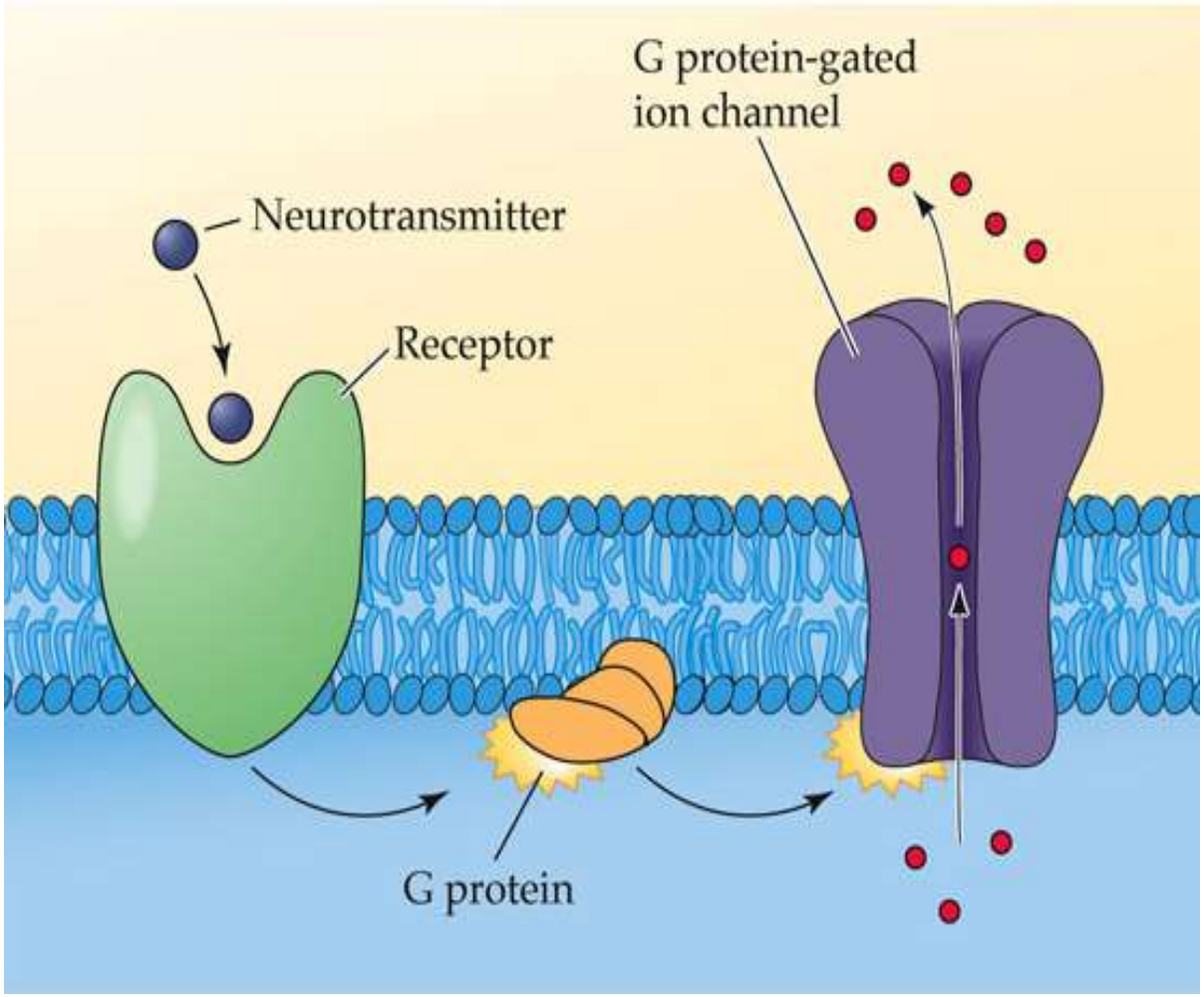
1. Each is made of several subunits (together form the complete receptor)
2. At center of receptors is channel or pore to allow flow of ions
3. At rest - receptor channels are closed
4. When neurotransmitter binds -- channel immediately opens
5. When ligand leaves binding site -- channel quickly closes



Metabotropic **Receptors…**

Work by activating other proteins called **G proteins**

1. Each is made of several transmembrane regions
2. Stimulate or inhibit the opening of ion channels in the cell membrane
3. Work more slowly than ionotrophic receptors



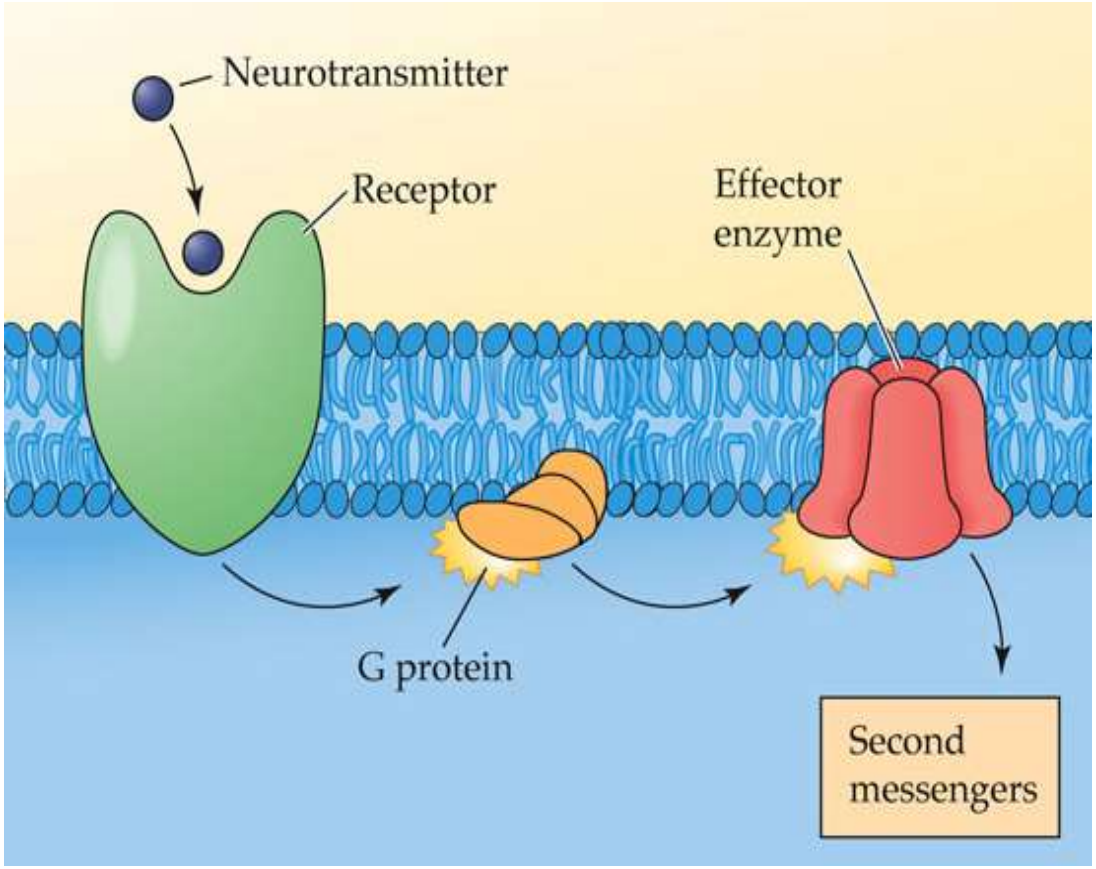
Metabotropic Receptors…

1. Stimulate or inhibit certain effector enzymes
2. Most effector enzymes controlled by G proteins are involved in synthesis of second messengers.

   *First messenger: ligand.

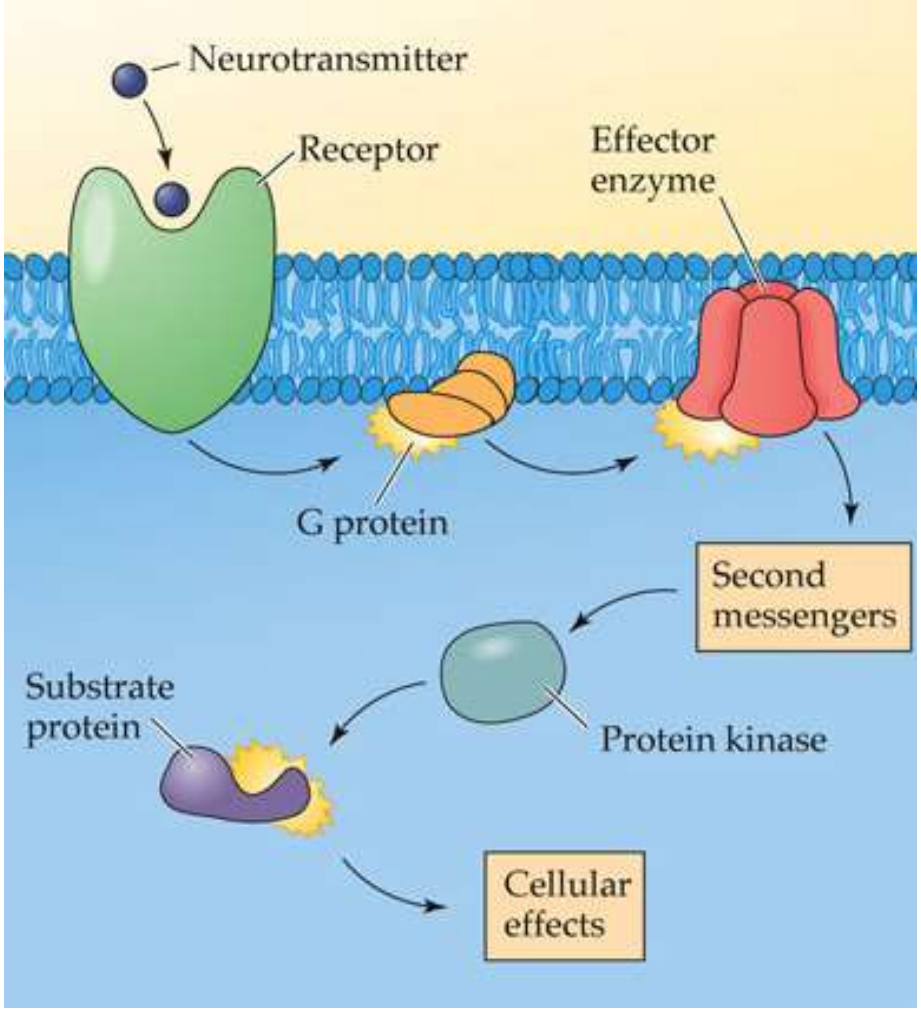
   *Second messenger:

   effector enzyme



Second messengers: Activate Protein Kinases

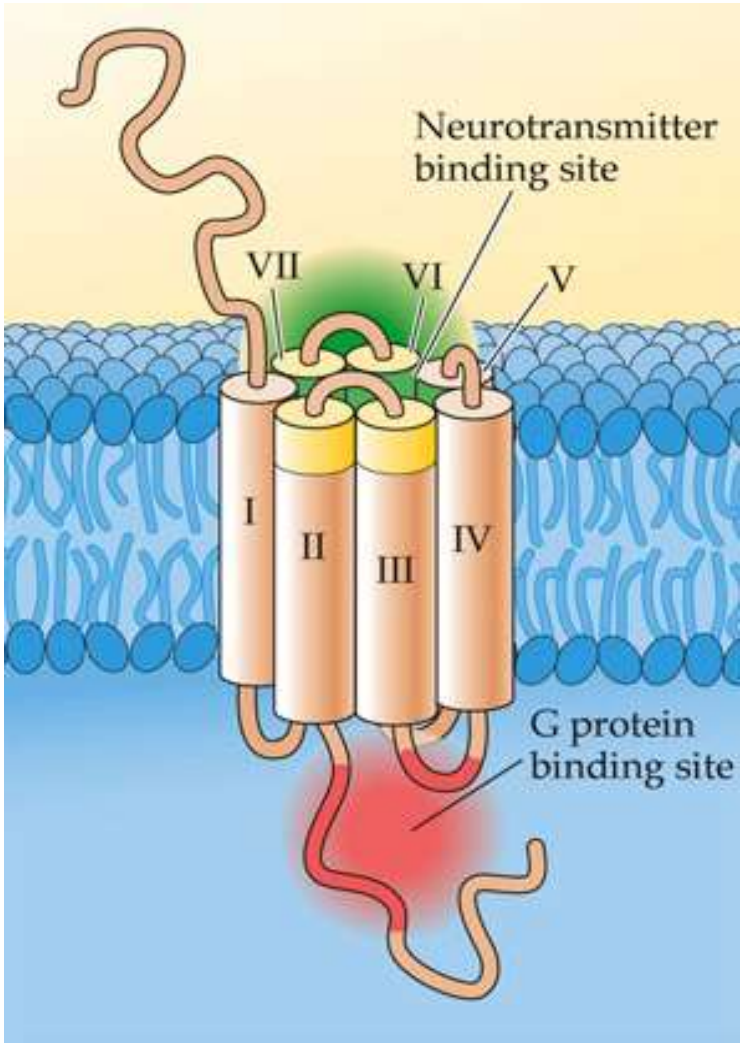
Can work by affecting:
NT production, no. synapses formed, sensitivity of receptors, or expression of genes (long term effects).
Can result in amplification - interconnections.

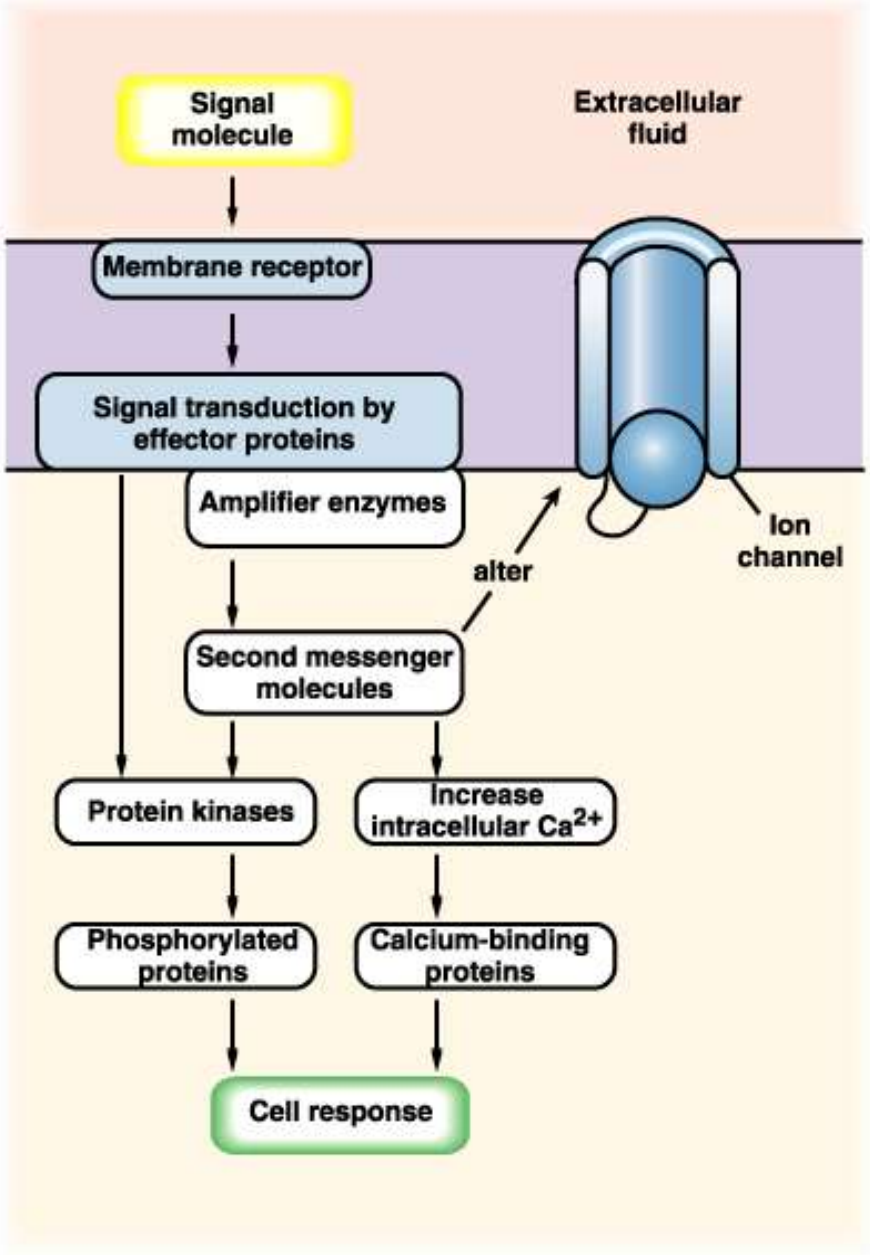


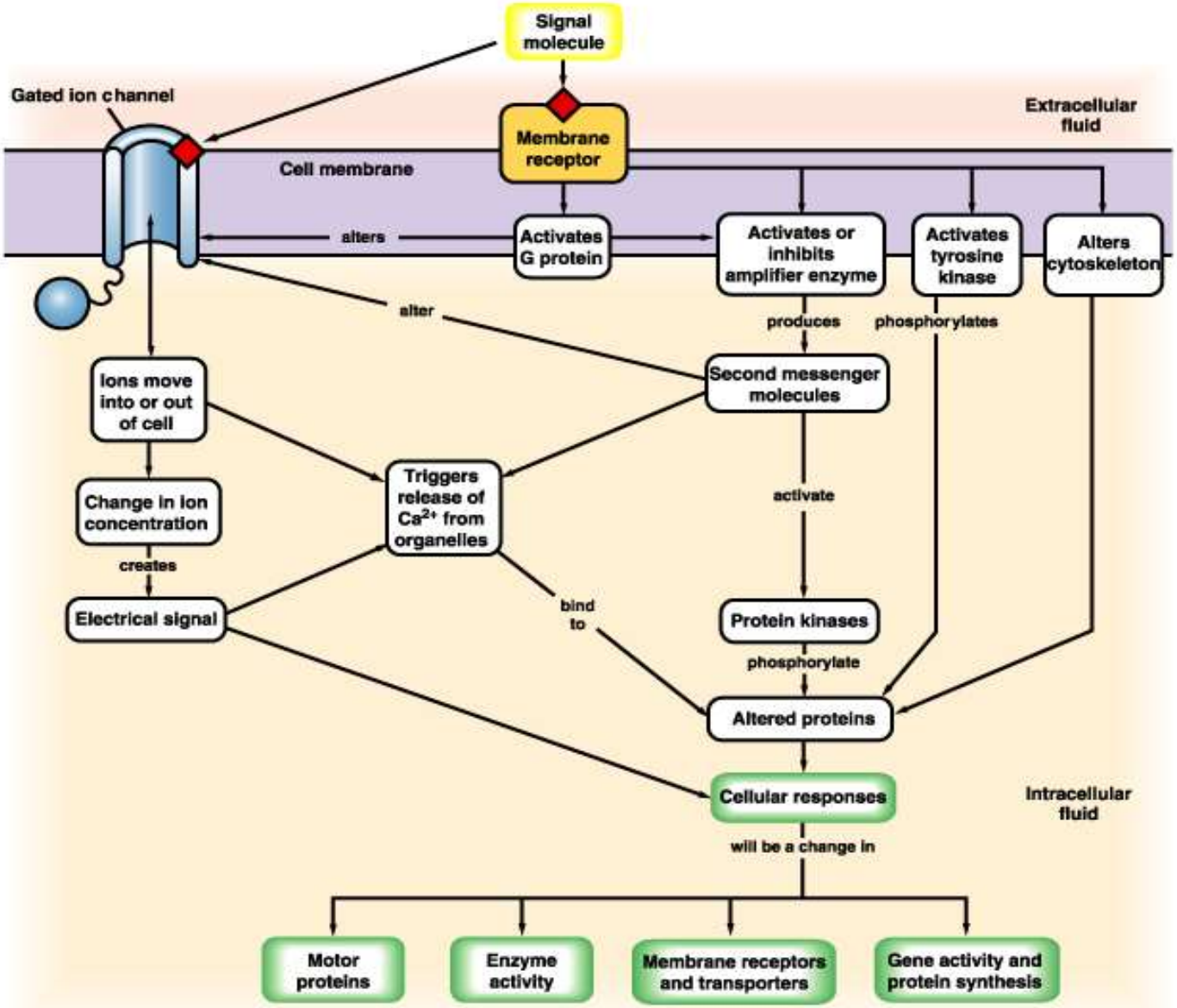
Other Metabotropic Receptors

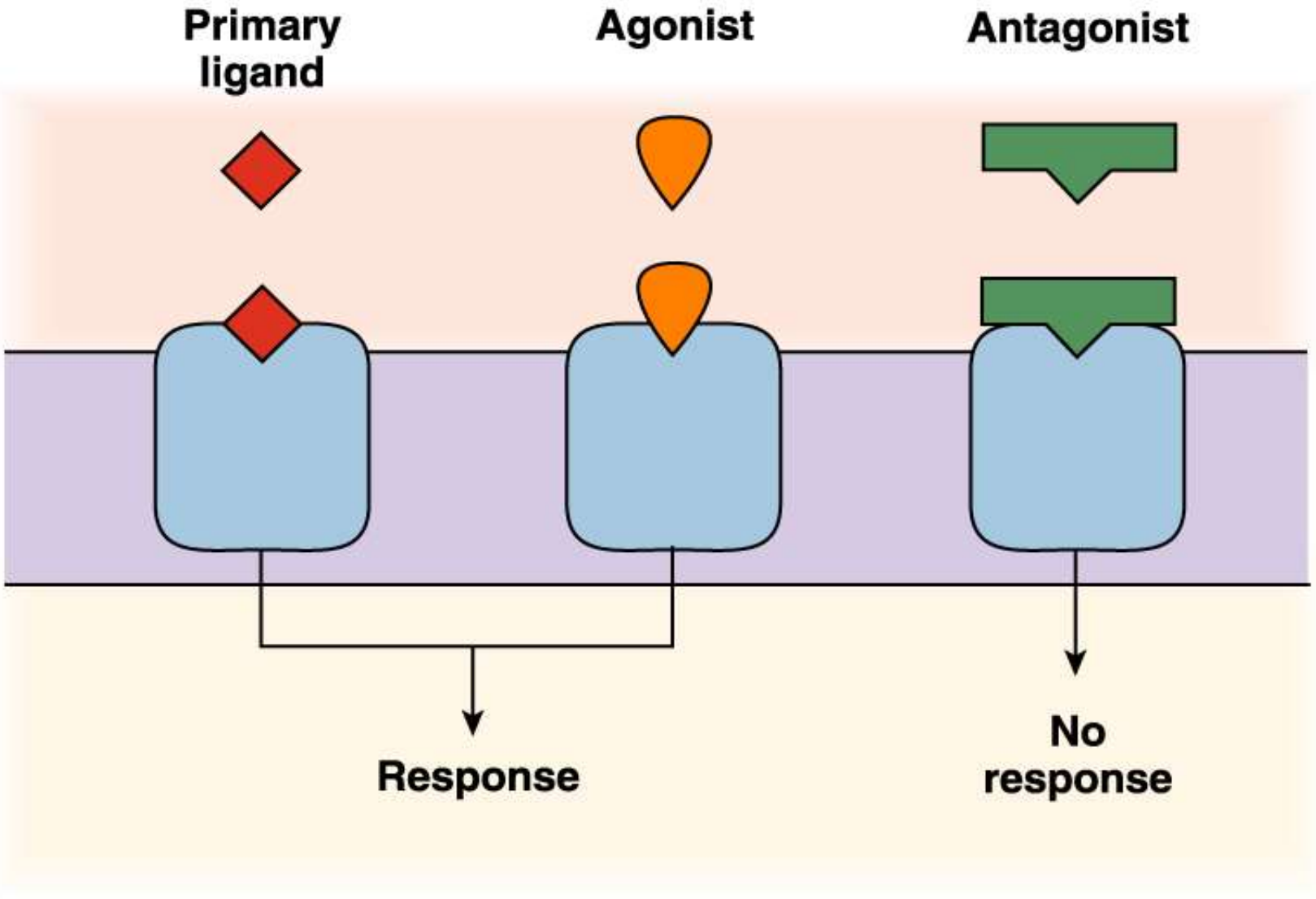
Work more slowly than ionotropic receptors

1. Though it takes longer for postsynapic cell to respond, response is somewhat longer-lasting
2. Comprise a single protein subunit, winding back-and-forth through cell membrane seven times (**transmembrane domains**)
3. They do not possess a channel or pore

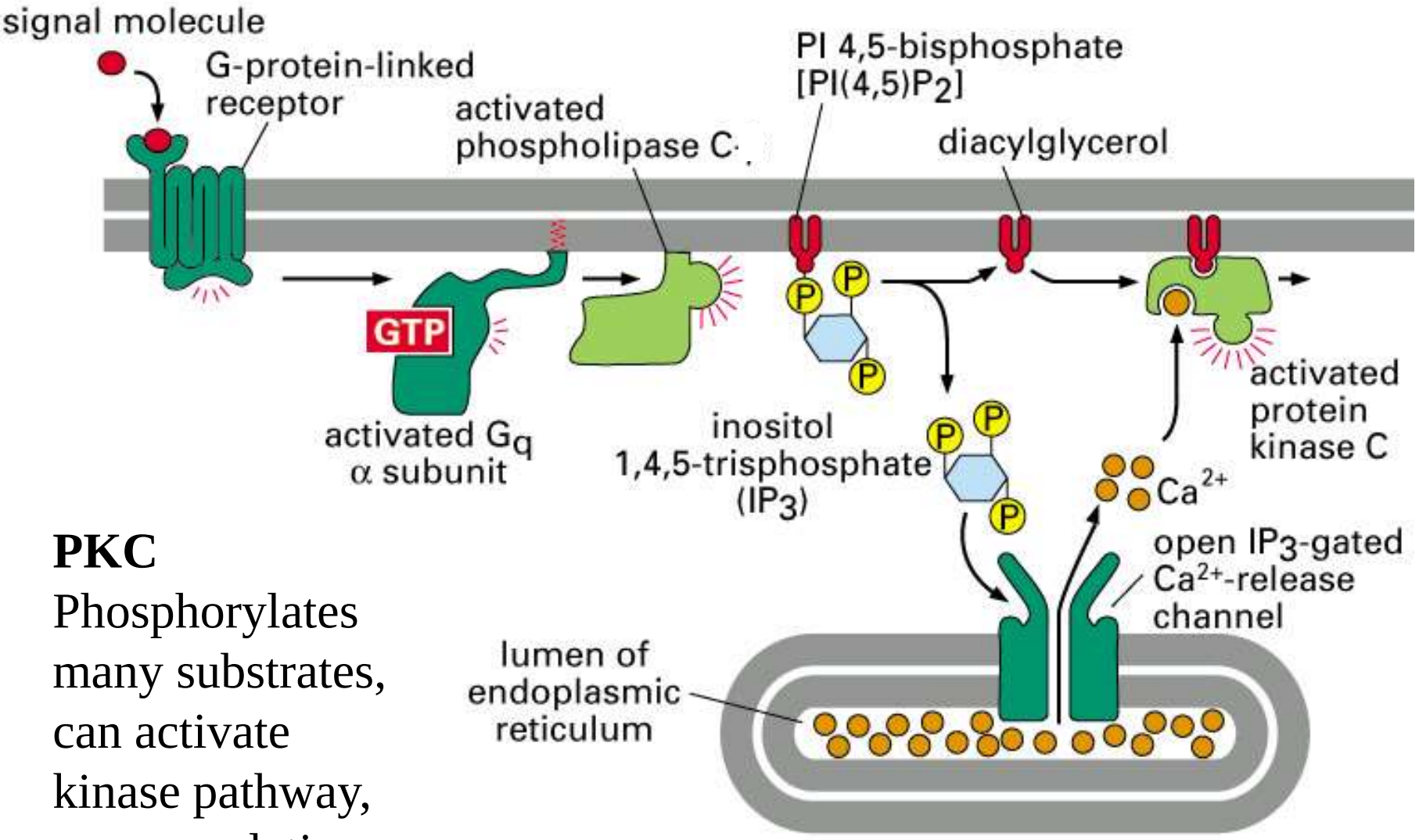



Signal molecule
Extracellular fluid
Membrane receptor
Signal transduction by effector proteins
Amplifier enzymes
Ion channel
alter
Second messenger molecules
Protein kinases
Increase intracellular Ca^{2+}
Phosphorylated proteins
Calcium-binding proteins
Cell response


Signal molecule
Gated ion channel
Extracellular fluid
Membrane receptor
Cell membrane
alters
Activates G protein
Activates or inhibits amplifier enzyme
Activates tyrosine kinase
Alters cytoskeleton
alter
produces
phosphorylates
Ions move into or out of cell
Second messenger molecules
Triggers release of Ca^{2+} from organelles
Change in ion concentration
activate
creates
Electrical signal
bind to
Protein kinases
phosphorylate
Altered proteins
Cellular responses
Intracellular fluid
will be a change in
Motor proteins
Enzyme activity
Membrane receptors and transporters
Gene activity and protein synthesis


Primary ligand
Agonist
Antagonist
Response
No response

PLC- signaling pathway



PKC

Phosphorylates many substrates, can activate kinase pathway, gene regulation


THANK YOU

Receptors Functions and Signal Transduction- L4- L5

Faisal I. Mohammed, MD, PhD

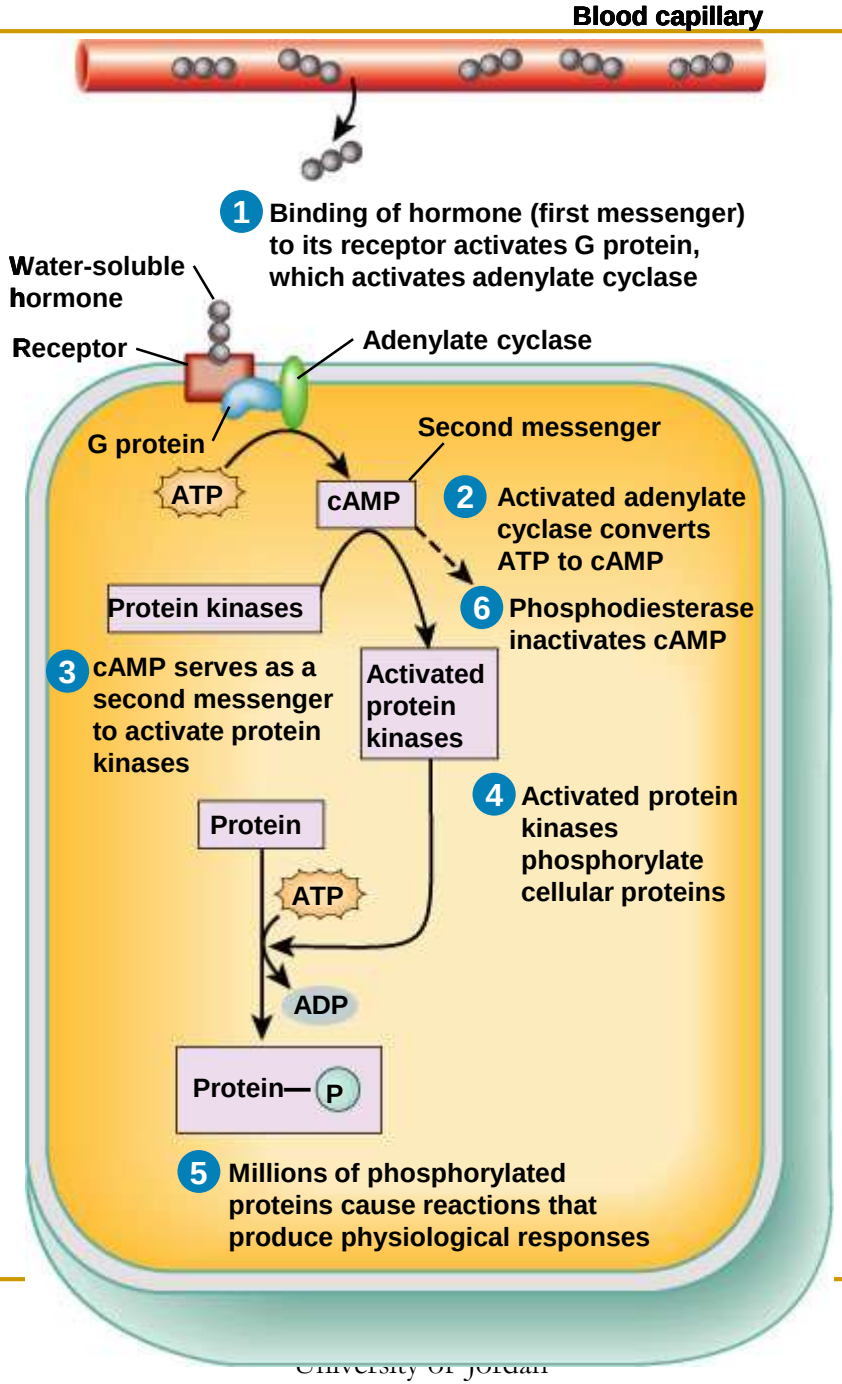
- **Receptors superfamilies:**
- Ionotropic receptors (ligand-gated channels)
- Metabotropic receptors (G protein-coupled receptors)
- Tyrosine Kinase

TABLE 3.2 Comparison of Ionotropic and Metabotropic Receptors

Characteristics	Ionotropic receptors	Metabotropic receptors
Structure	4 or 5 subunits that assemble in the cell membrane	1 subunit
Mechanism of action	Contain an intrinsic ion channel that opens in response to neuro-transmitter or drug binding	Activate G proteins in response to neurotrans-mitter or drug binding
Coupled to second messengers?	No	Yes
Speed of action	Fast	Slower

Almost all neurotransmitters discovered so far have more than one kind of receptor -- called **receptor subtypes.**

Water-soluble Hormones



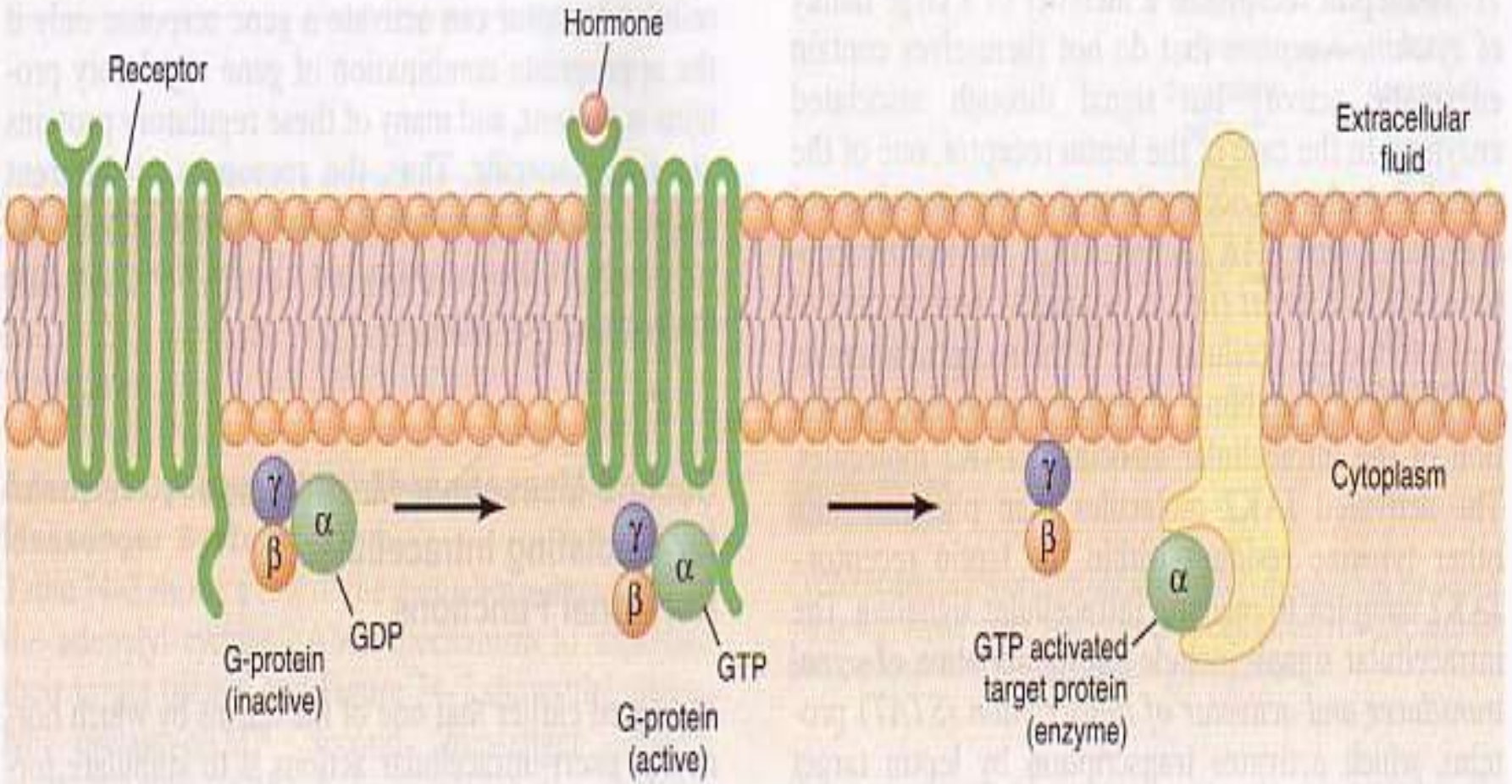
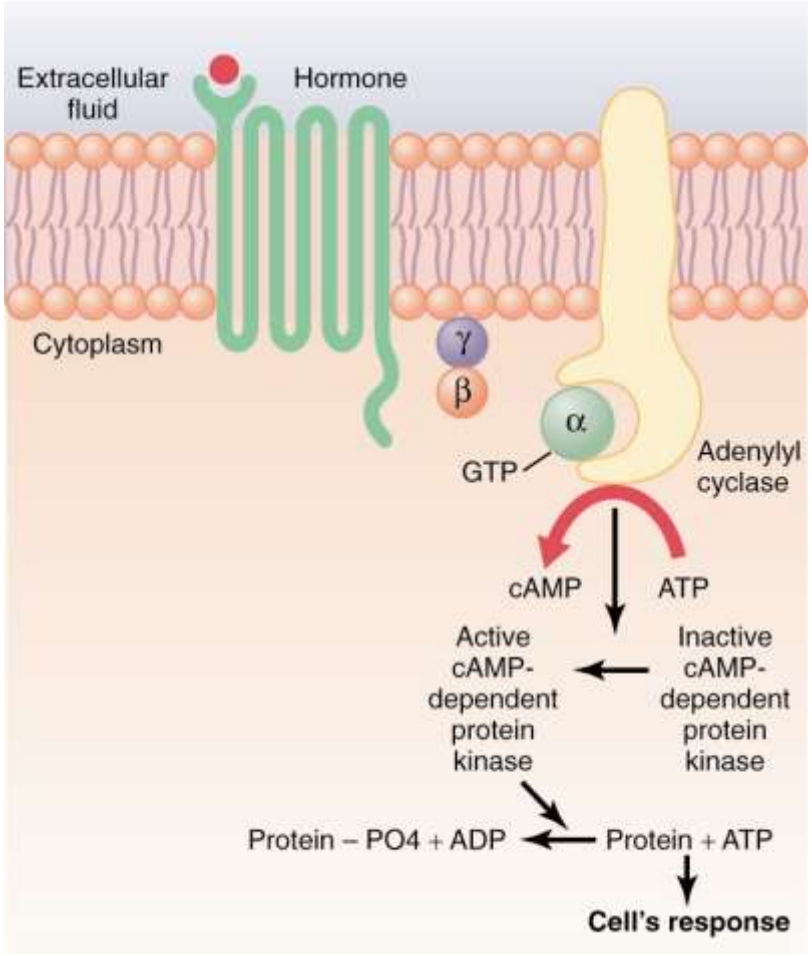


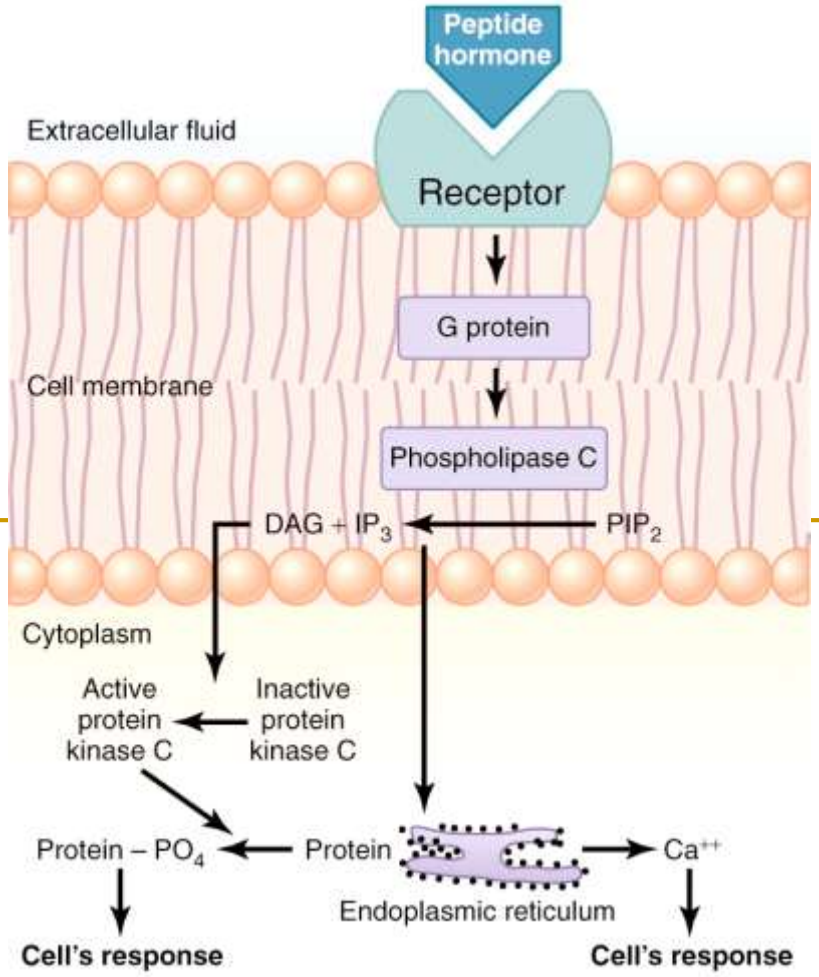
Figure 74–4

Mechanism of activation of a G protein–coupled receptor. When the hormone activates the receptor, the inactive α, β, and γ G protein complex associates with the receptor and is activated, with an exchange of guanosine triphosphate (GTP) for guanosine diphosphate (GDP). This causes the α subunit (to which the GTP is bound) to dissociate from the β and γ subunits of the G protein and to interact with membrane-bound target proteins (enzymes) that initiate intracellular signals.

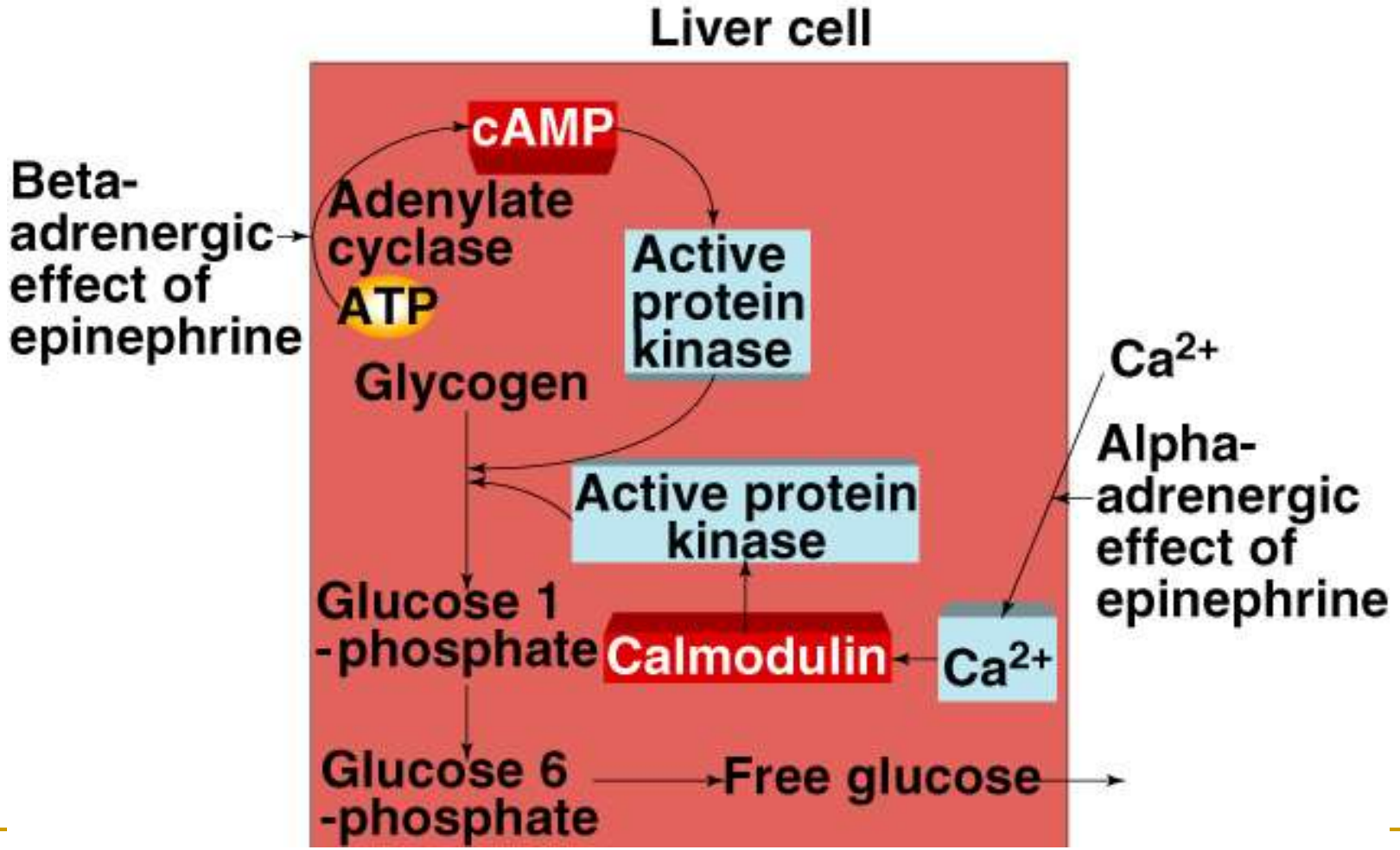
Cyclic Monophasphate (cAMP) Second Messenger Mechanism

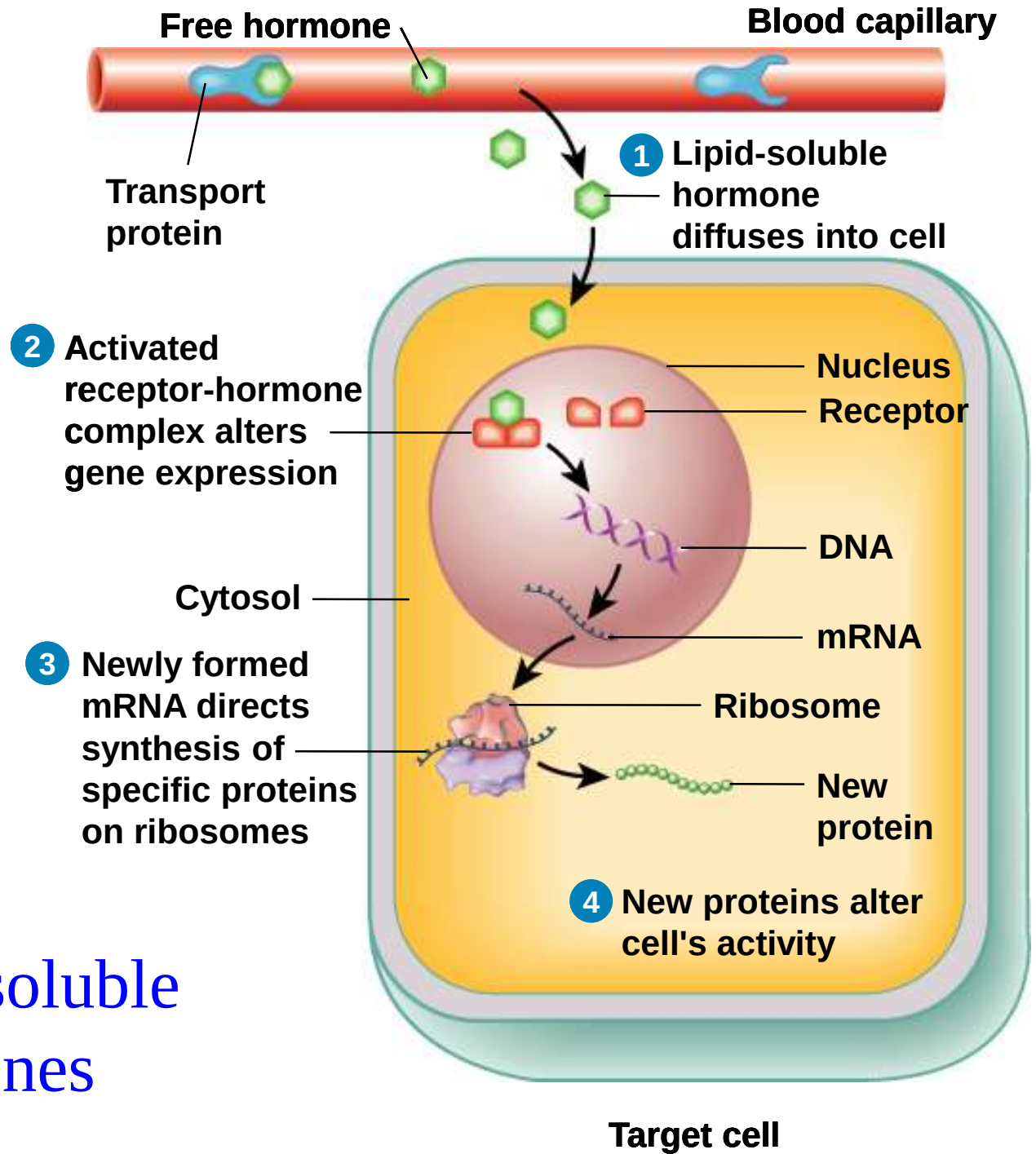


Cell Membrane Phospholipid Second Messenger System



Epinephrine Can Act Through Two 2nd Messenger Systems

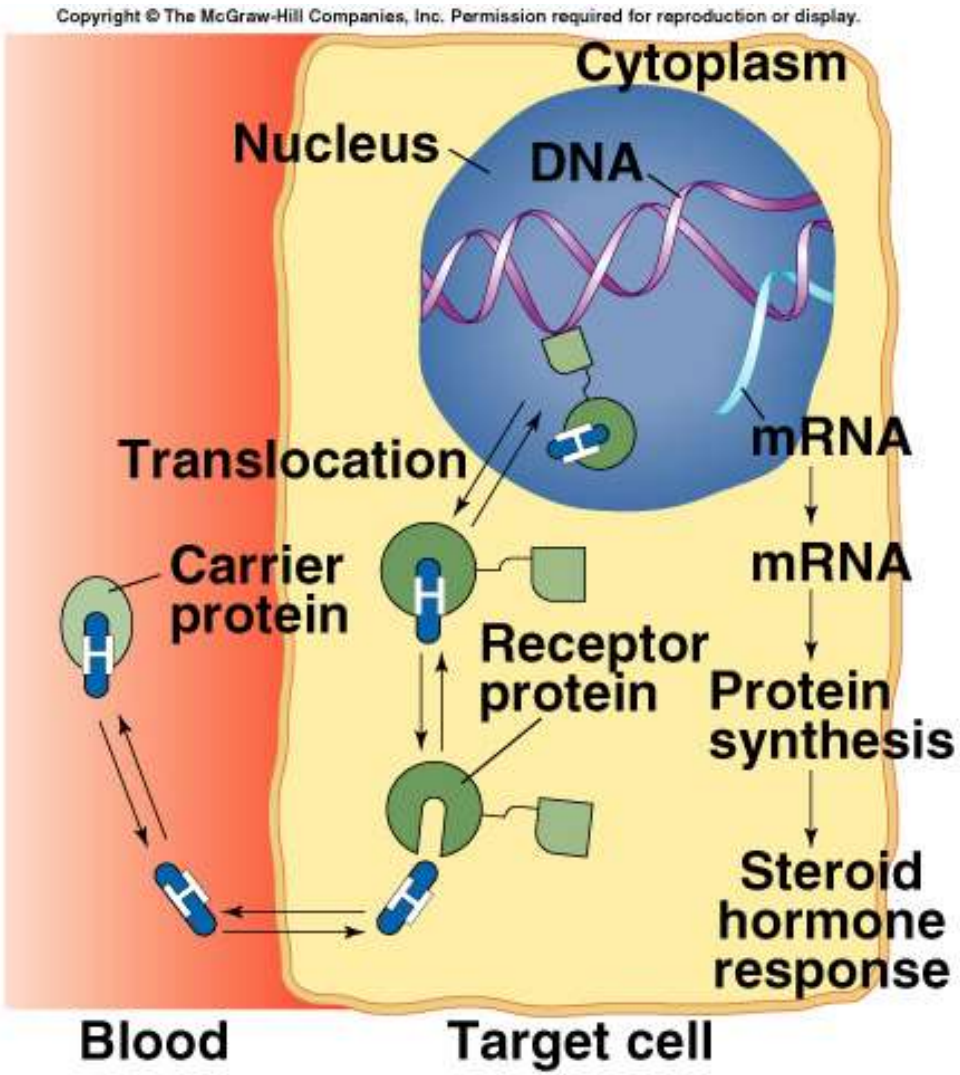




Lipid-soluble Hormones

Hormones That Bind to Nuclear Receptor Proteins

- Lipophilic steroid and thyroid hormones are attached to plasma carrier proteins.
  - Hormones dissociate from carrier proteins to pass through lipid component of the target plasma membrane.
- Receptors for the lipophilic hormones are known as nuclear hormone receptors.

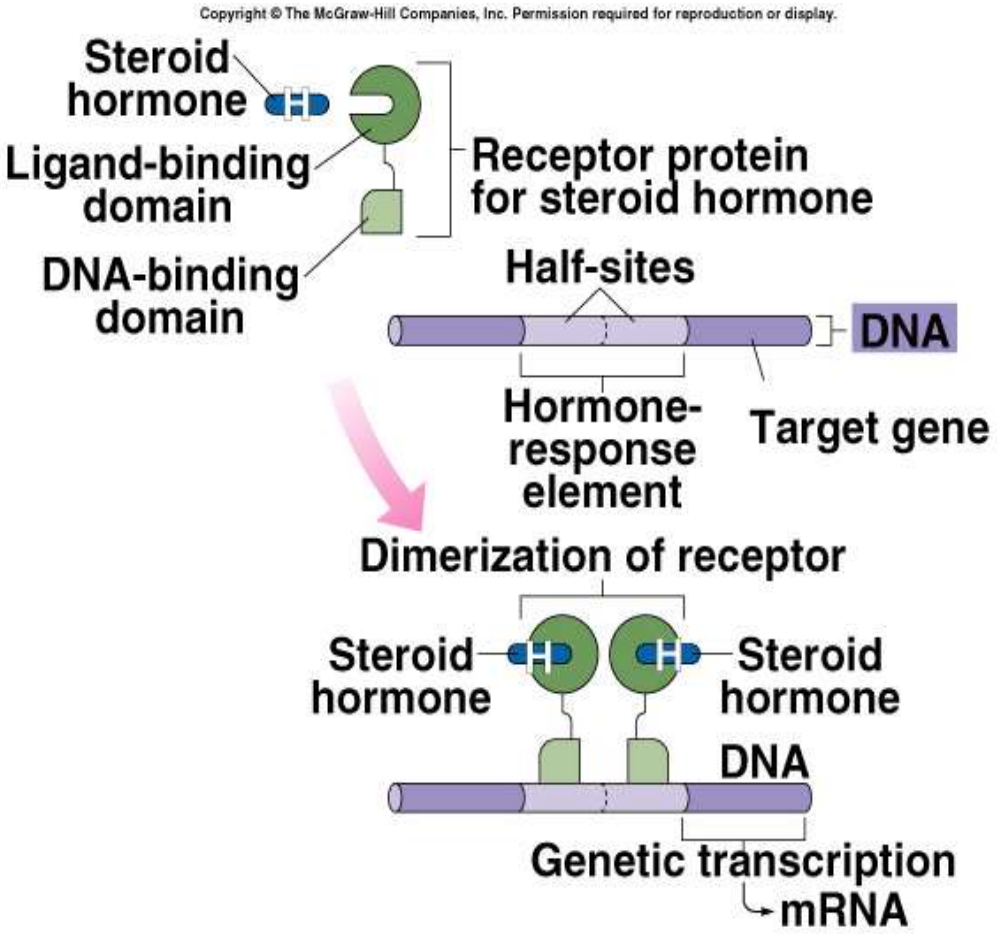


Nuclear Hormone Receptors

- Steroid receptors are located in cytoplasm and in the nucleus.
- Function within cell to activate genetic transcription.
  - Messenger RNA directs synthesis of specific enzyme proteins that change metabolism.
- Each nuclear hormone receptor has 2 regions:
  - A ligand (hormone)-binding domain.
  - DNA-binding domain.
- Receptor must be activated by binding to hormone before binding to specific region of DNA called HRE (hormone responsive element).
  - Located adjacent to gene that will be transcribed.

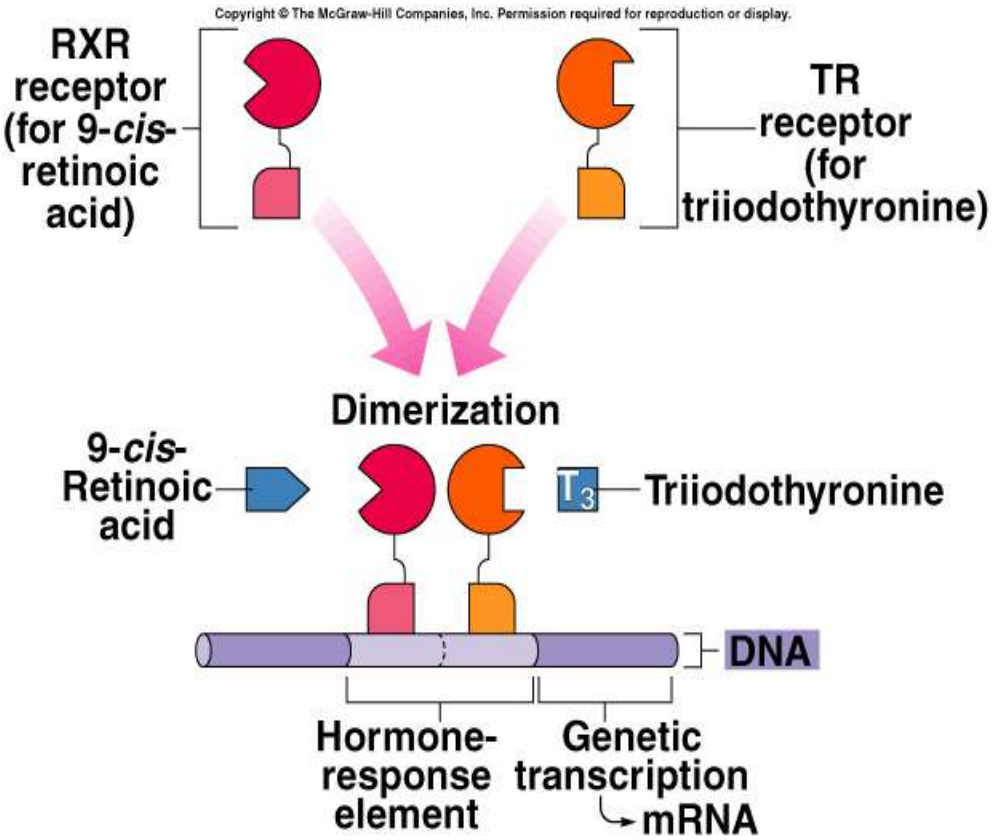
Mechanisms of Steroid Hormone Action

- Cytoplasmic receptor binds to steroid hormone.
- Translocates to nucleus.
- DNA-binding domain binds to specific HRE of the DNA.
- Dimerization occurs.
  - Process of 2 receptor units coming together at the 2 half-sites.
- Stimulates transcription of particular genes.

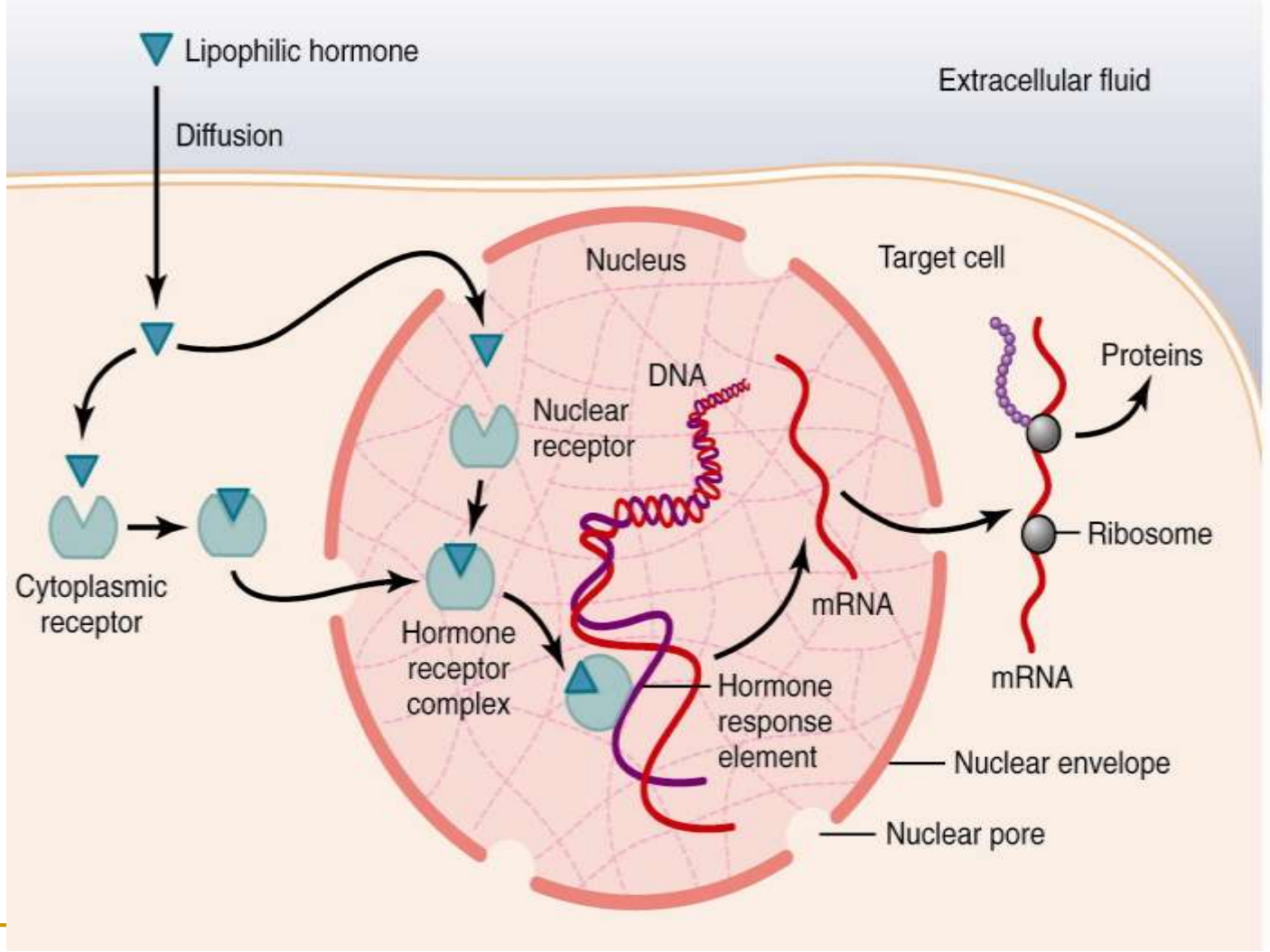


Mechanism of Thyroid Hormone Action

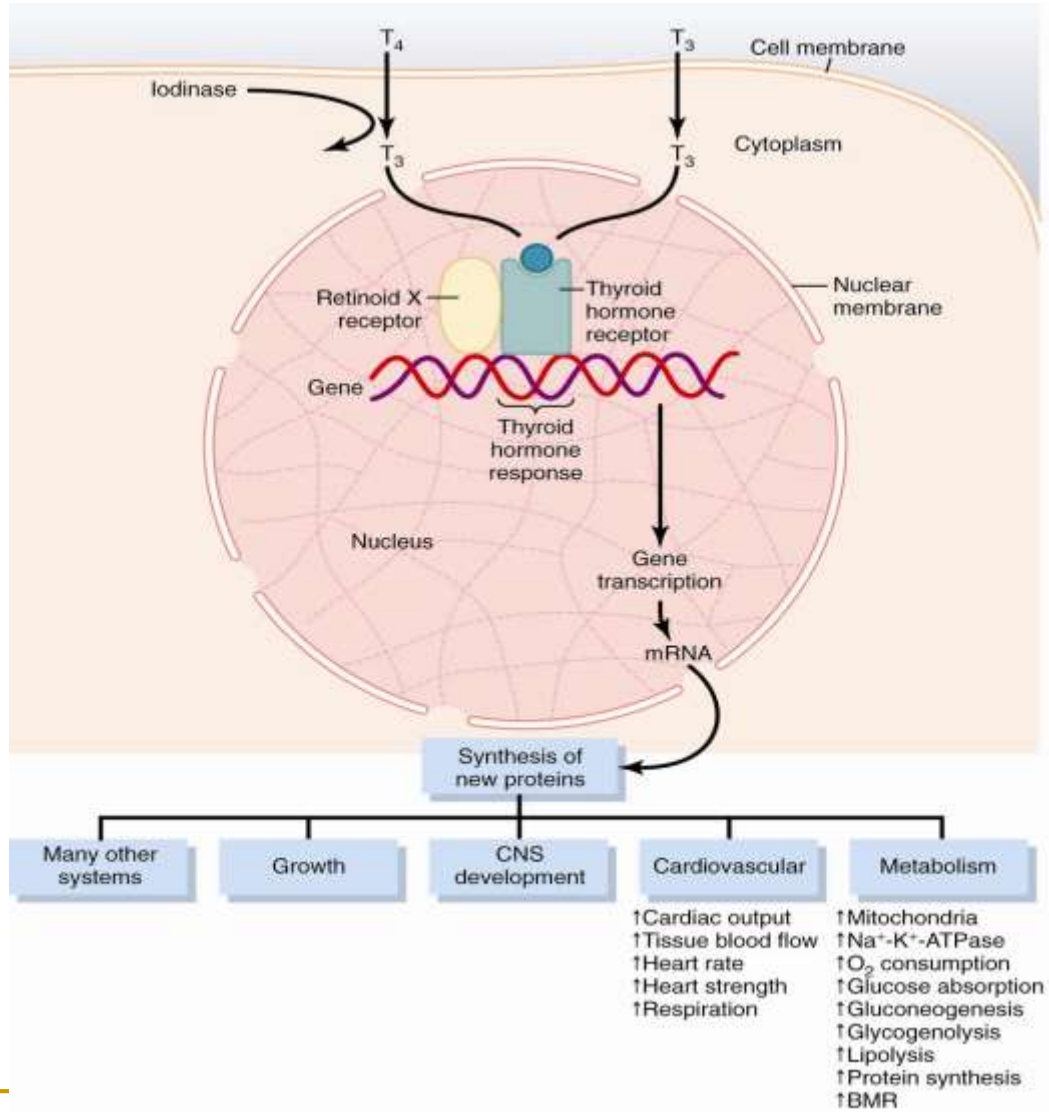
- T_4 passes into cytoplasm and is converted to T_3.
- Receptor proteins located in nucleus.
  - T_3 binds to ligand-binding domain.
  - Other half-site is vitamin A derivative (9-cis-retinoic) acid.
    - DNA-binding domain can then bind to the half-site of the HRE.
  - Two partners can bind to the DNA to activate HRE.
    - Stimulate transcription of genes.



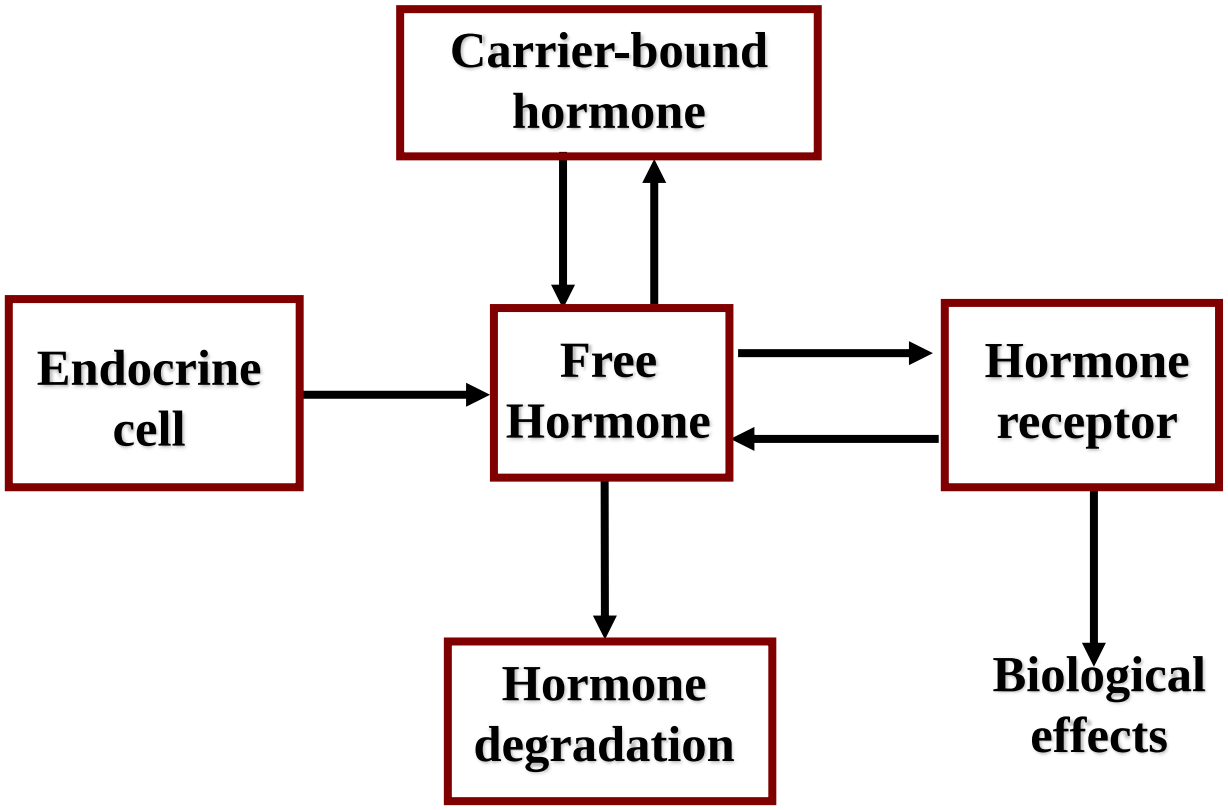
Steroid & Thyroid Hormones - Mechanism of Action



Actions of Thyroid Hormones



Determinants of Free Hormone Receptor Binding



Correlation of Plasma Half-Life & Metabolic Clearance of Hormones with Degree of Protein Binding

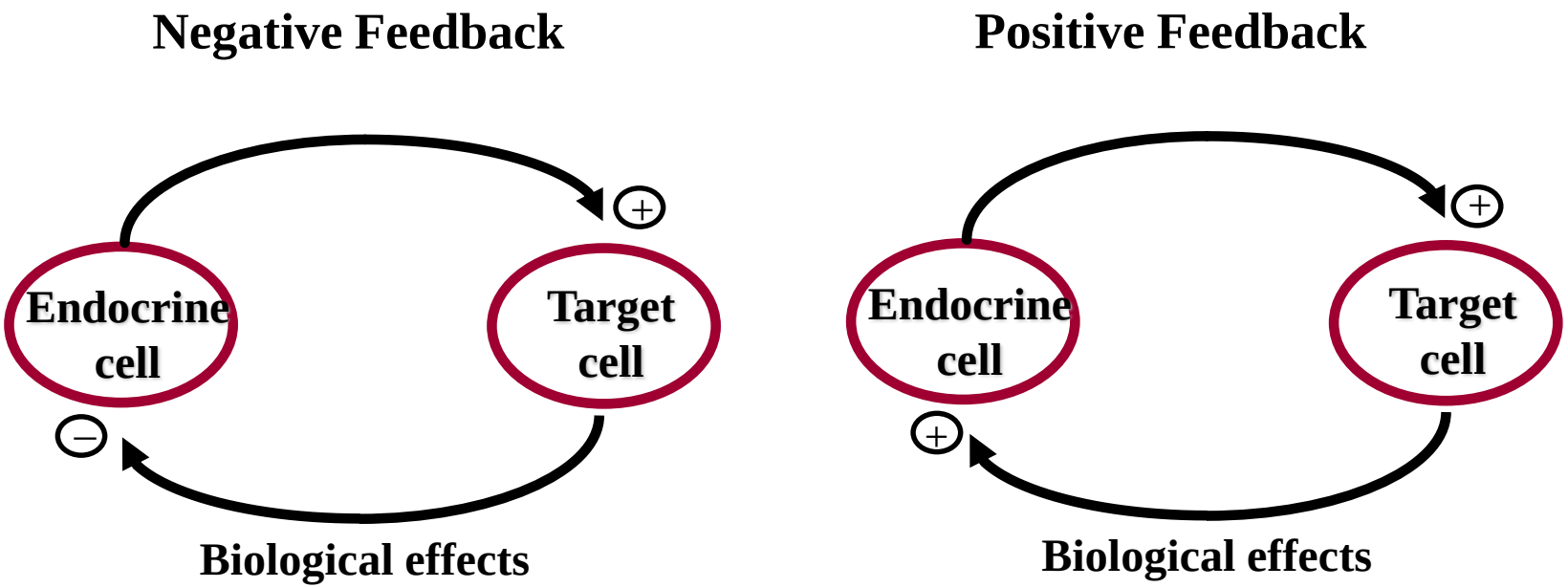
Hormone	Protein binding (%)	Plasma half-life	Metabolic clearance (ml/minute)
Thyroid			
Thyroxine	99.97	6 days	0.7
Triiodothyronine	99.7	1 day	18
Steroids			
Cortisol	94	100 min	140
Testosterone	89	85 min	860
Aldosterone	15	25 min	1100
Proteins			
Thyrotropin	little	50 min	50
Insulin	little	8 min	800
Antidiuretic hormone	little	8 min	600

MCR = (mg/minute removed) / (mg/ml of plasma) = ml cleared/minute

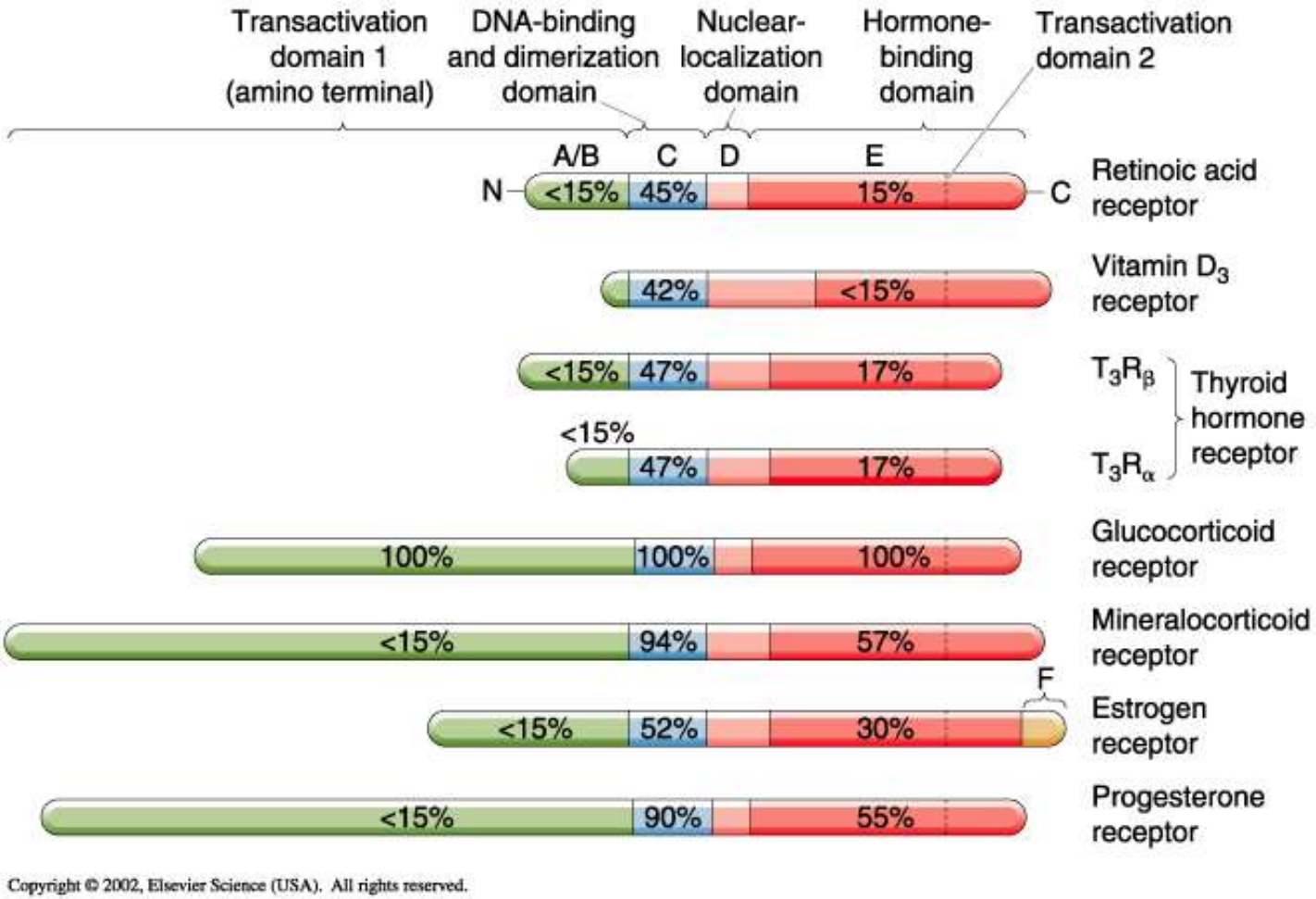
Circulating Transport Proteins

Transport Protein	Principle Hormone Transported
Specific	
Corticosteroid binding globulin (CBG, transcortin)	Cortisol, aldosterone
Thyroxine binding globulin (TBG)	Thyroxine, triiodothyronine
Sex hormone-binding globulin (SHBG)	Testosterone, estrogen
Nonspecific	
Albumin	Most steroids, thyroxine, triiodothyronine
Transthyretin (prealbumin)	Thyroxine, some steroids

Feedback Mechanisms



Steroid & Thyroid Hormones - Receptors



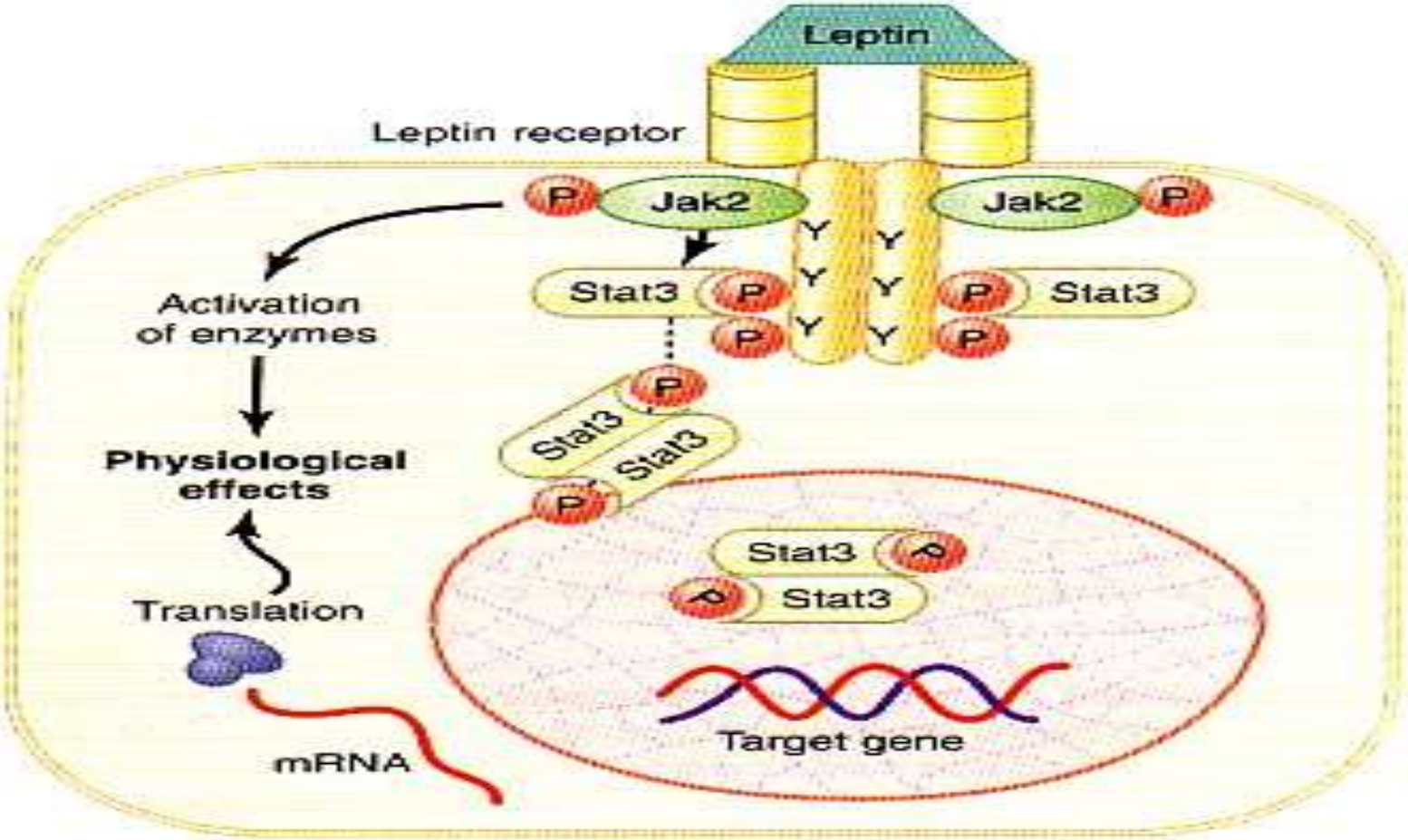
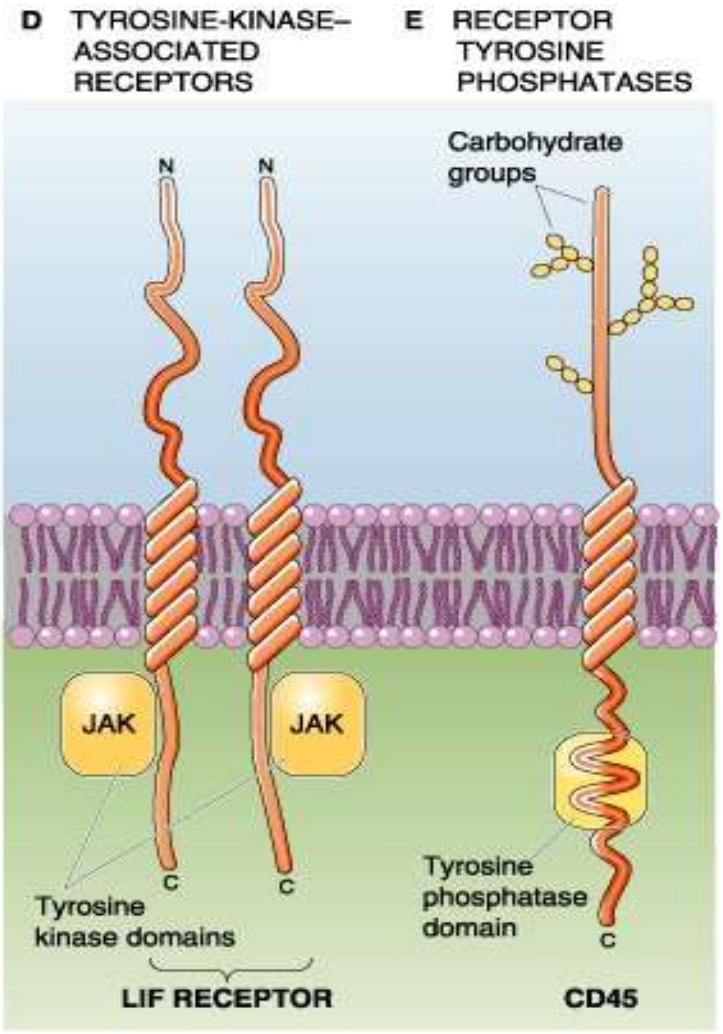


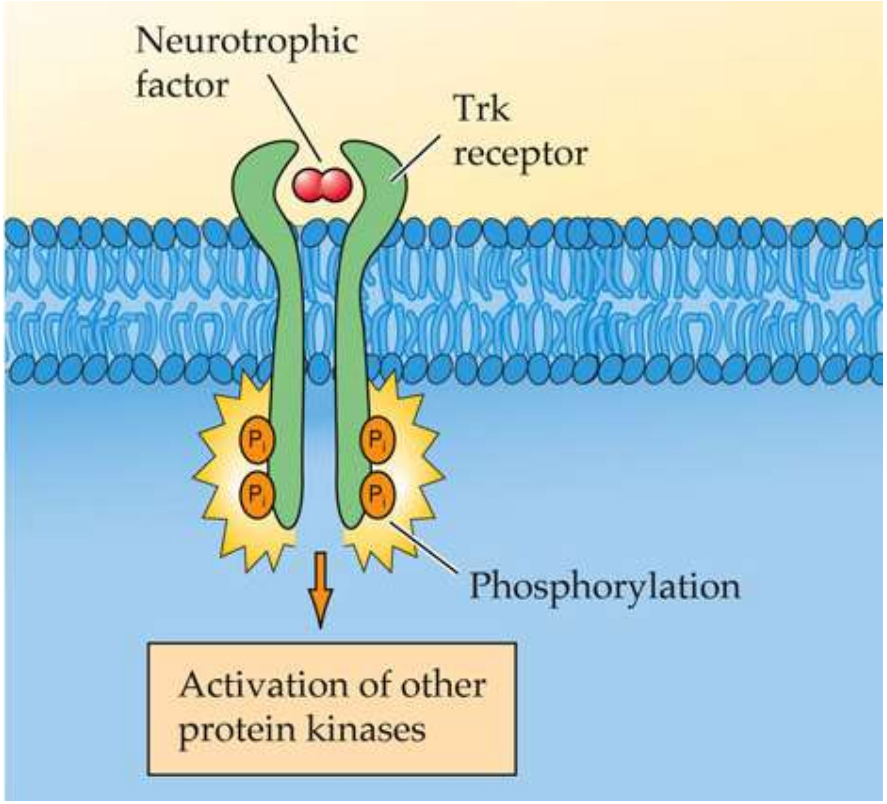
Figure 74–5

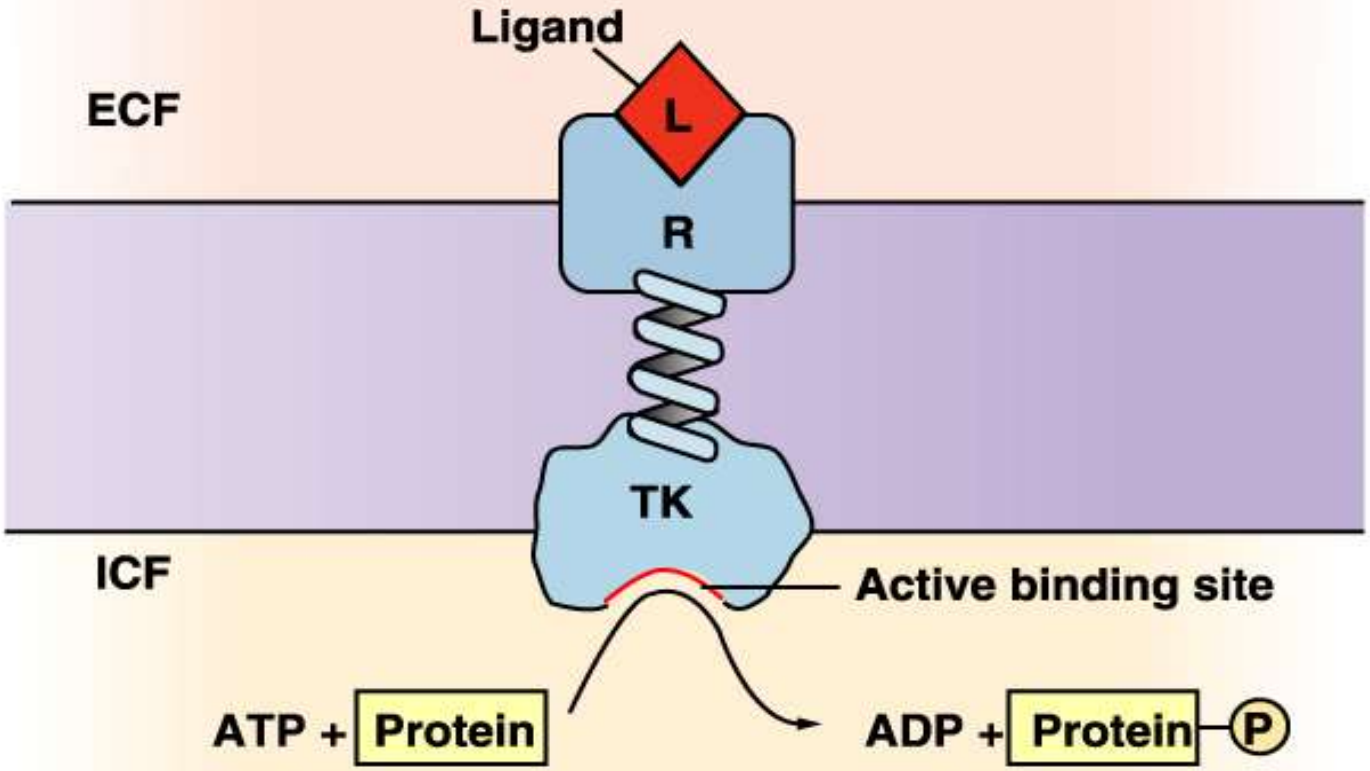
An enzyme-linked receptor—the leptin receptor. The receptor exists as a homodimer (two identical parts), and leptin binds to the extracellular part of the receptor, causing phosphorylation and activation of the intracellular associated janus kinase 2 (JAK2). This causes phosphorylation of signal transducer and activator of transcription (STAT) proteins, which then activates the transcription of target genes and the synthesis of proteins. JAK2 phosphorylation also activates several other enzyme systems that mediate some of the more rapid effects of leptin.

Tyrosine Kinase



Tyrosine Kinase Receptors:

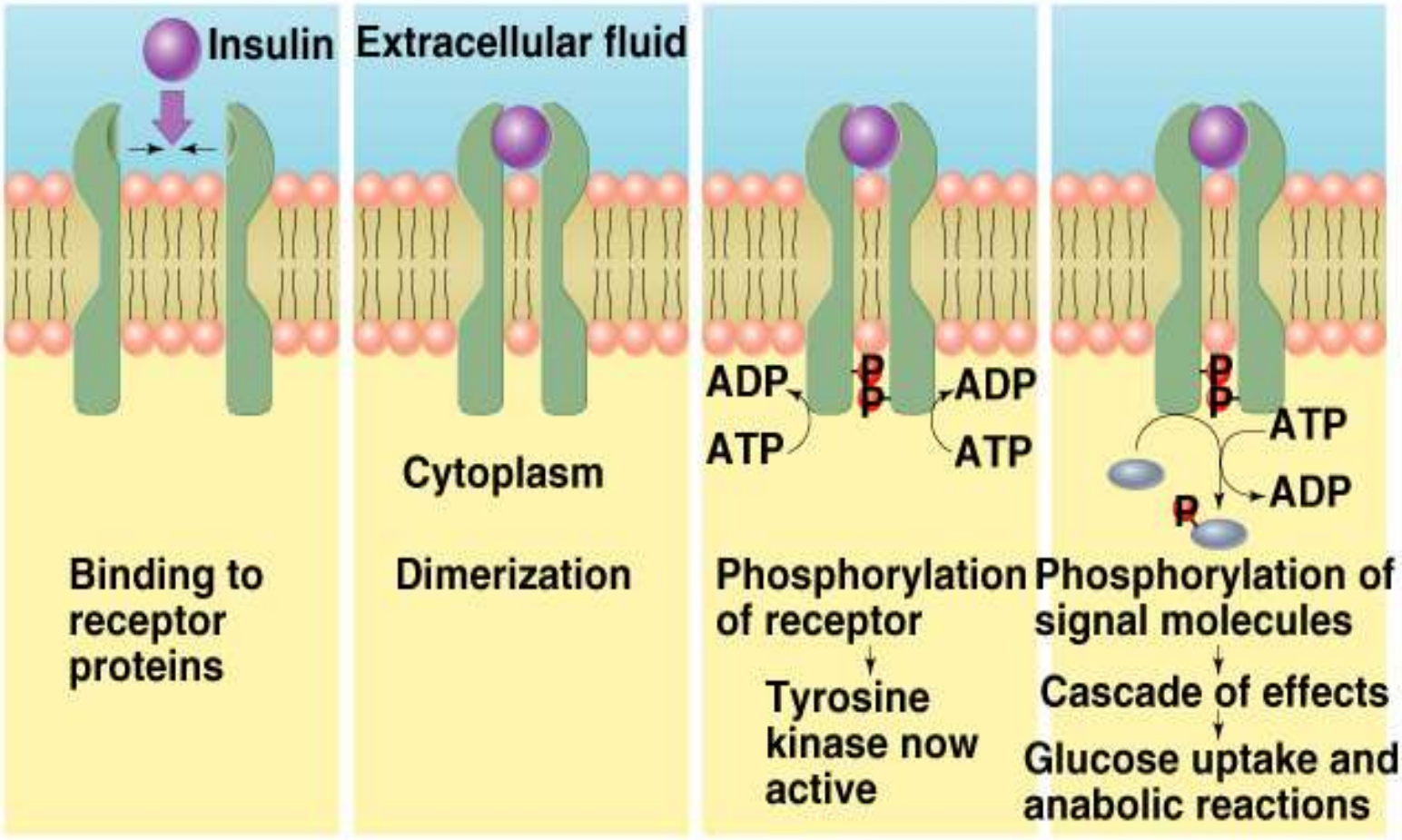


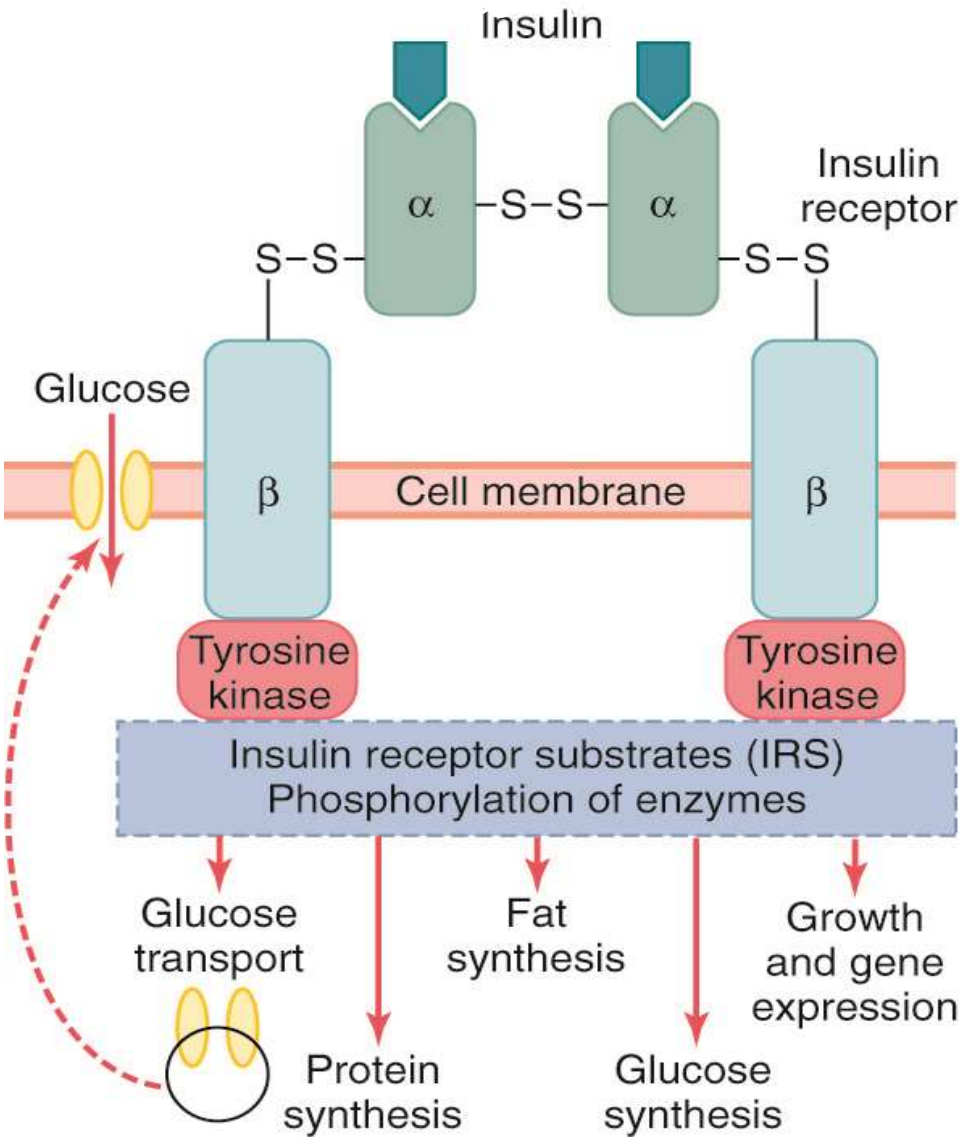

Ligand
L
ECF
R
TK
ICF
Active binding site
ATP + Protein
ADP + Protein
P

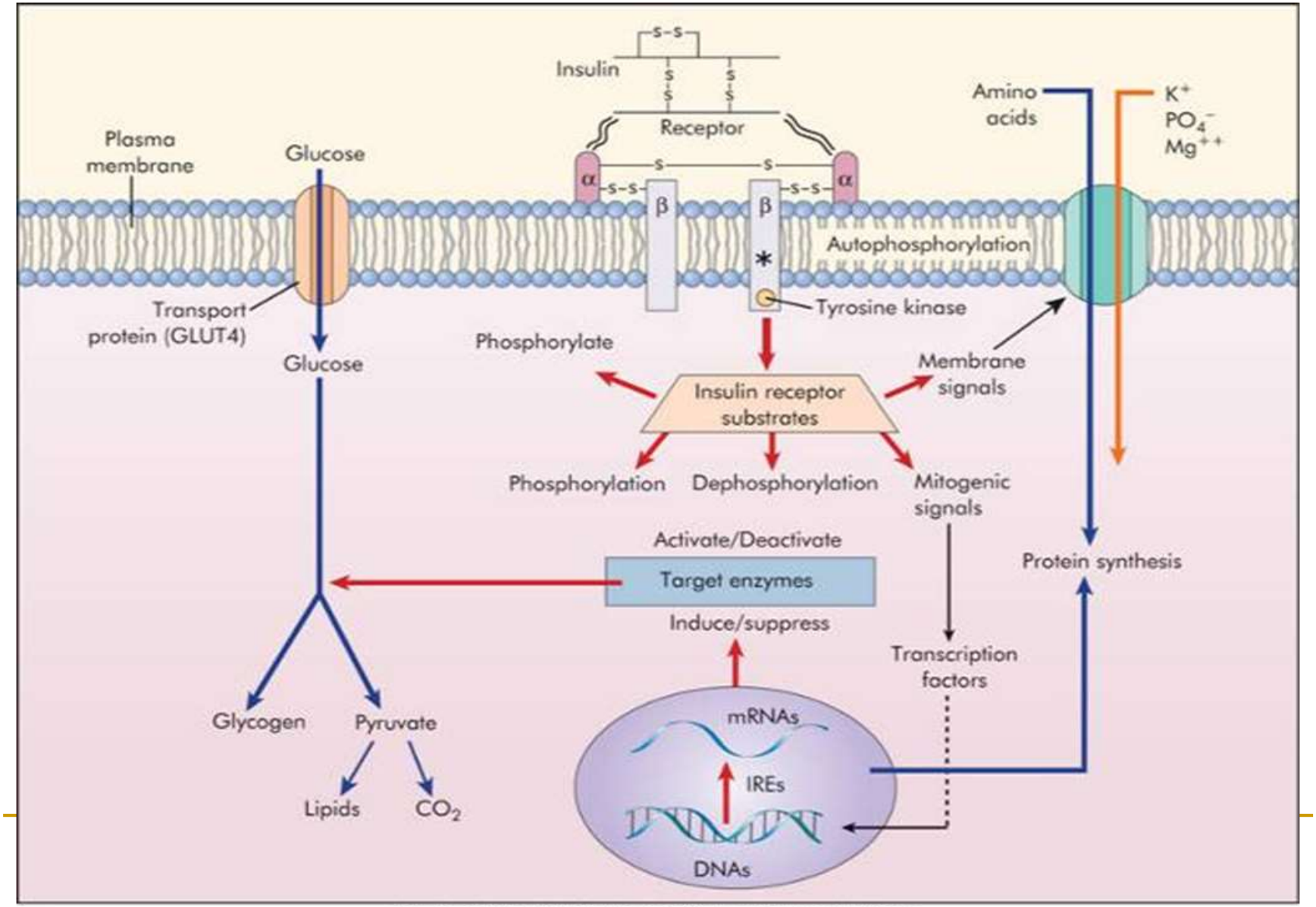
Tyrosine Kinase

- Insulin receptor consists of 2 units that dimerize when they bind with insulin.
  - Insulin binds to ligand–binding site on plasma membrane, activating enzymatic site in the cytoplasm.
- Autophosphorylation occurs, increasing tyrosine kinase activity.
- Activates signaling molecules.
  - Stimulate glycogen, fat and protein synthesis.
  - Stimulate insertion of GLUT-4 carrier proteins.

Tyrosine Kinase (continued)

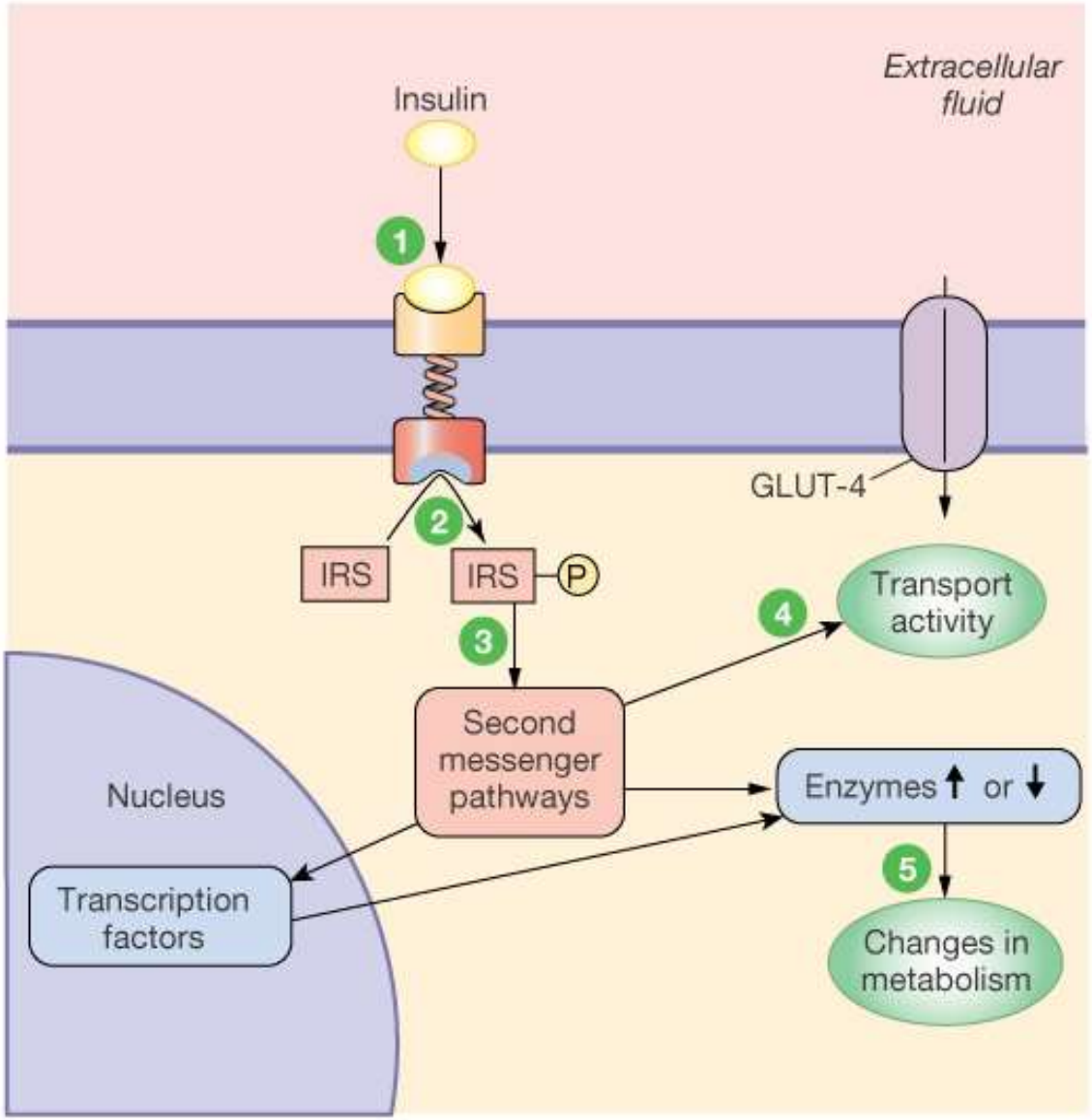



Insulin
α
S–S
α
Insulin receptor
S–S
S–S
Glucose
β
Cell membrane
β
Tyrosine kinase
Tyrosine kinase
Insulin receptor substrates (IRS)
Phosphorylation of enzymes
Glucose transport
Protein synthesis
Fat synthesis
Glucose synthesis
Growth and gene expression



From Berne RM, Levy MN: *Principles of physiology*, ed 3, St Louis, 2000, Mosby.

Insulin Action on Cells:



1. Insulin binds to tyrosine kinase receptor.
2. Receptor phosphorylates insulin-receptor substrates (IRS).
3. Second messenger pathways alter protein synthesis and existing proteins.
4. Membrane transport is modified.
5. Cell metabolism is changed.

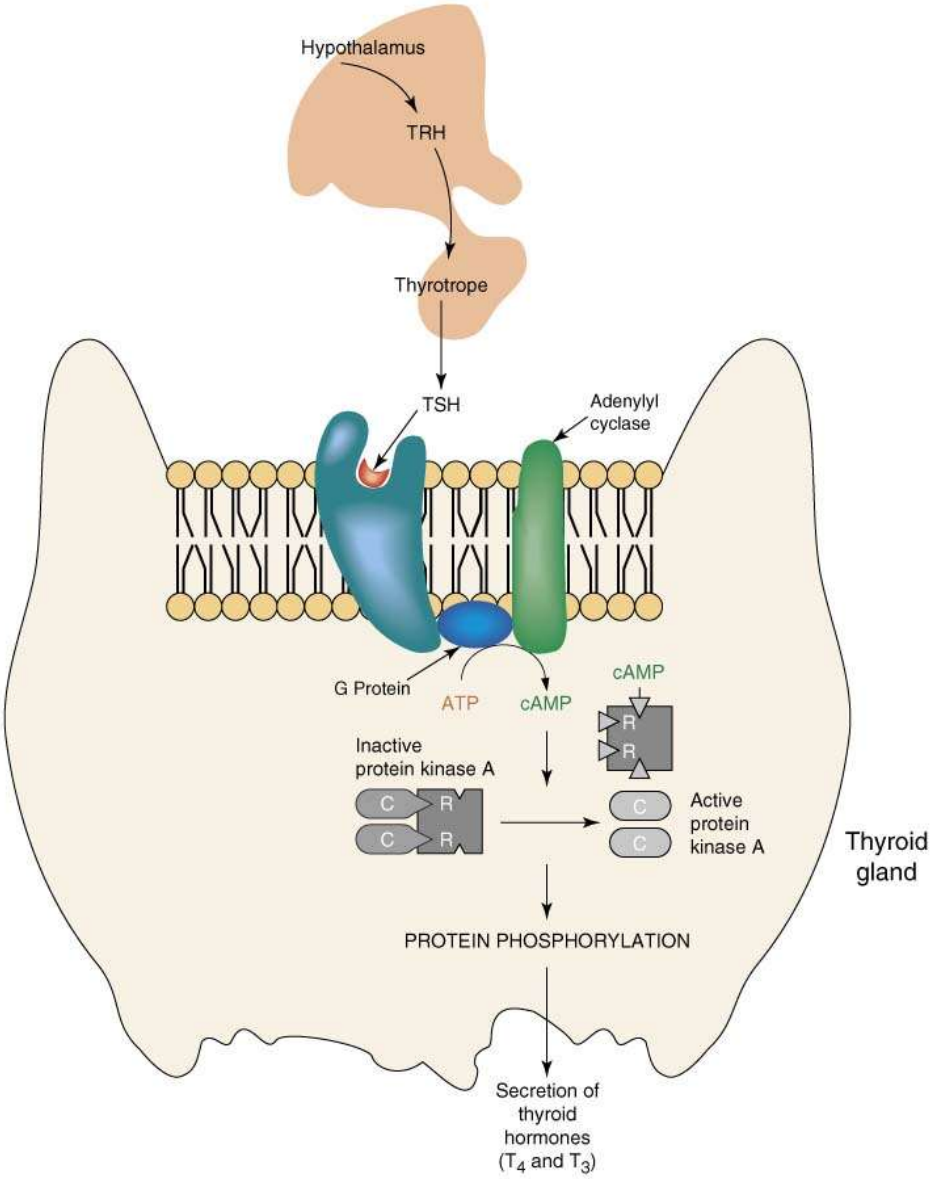


Figure 23.16. Effect of TSH on secretion of thyroid hormone.

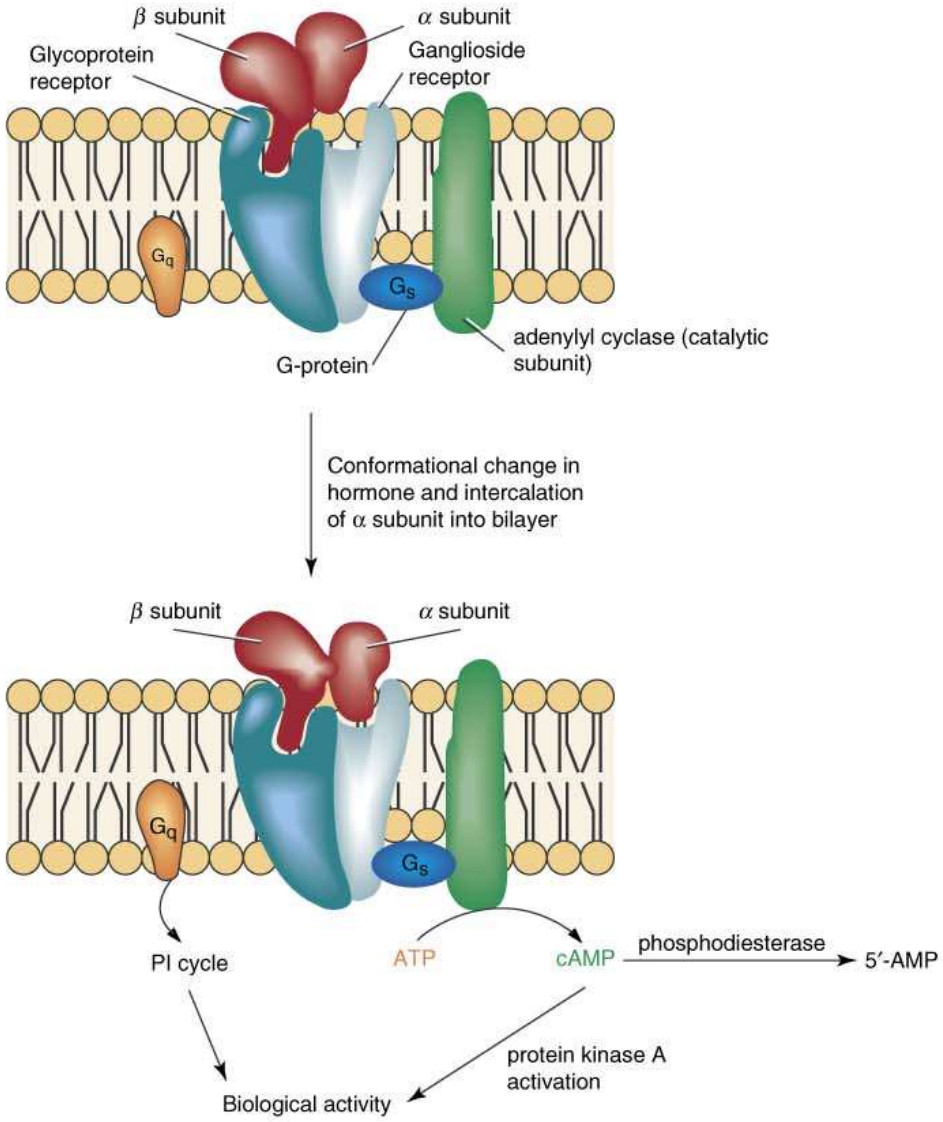


Figure 23.22. Model of TSH receptor. Adapted with modifications from Kohn, L. D., et al. In: G. Litwack (Ed.), *Biochemical Actions of Hormones*, Vol. 12. New York: Academic Press, 1985, p. 466.

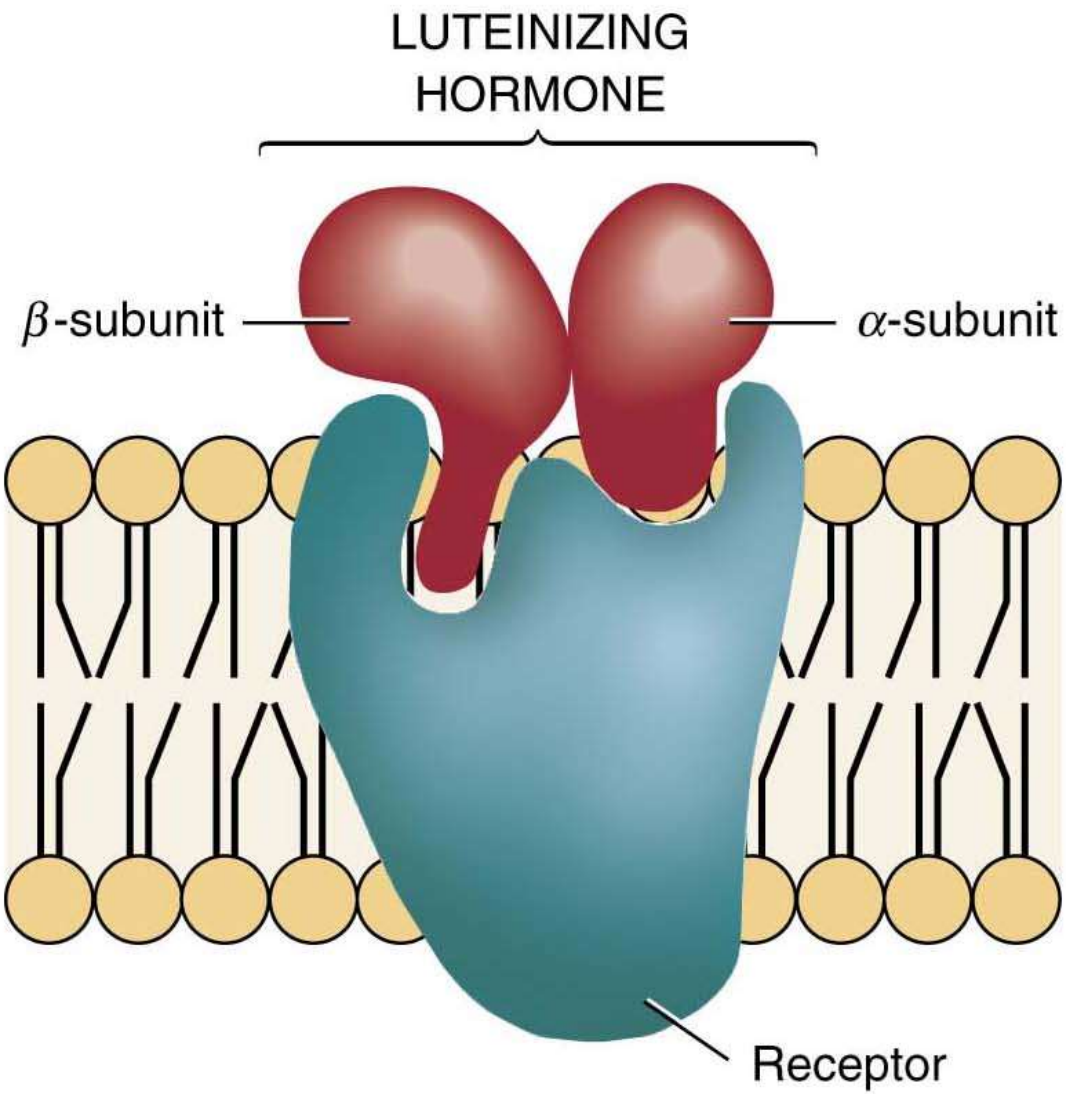


Figure 23.21. The interaction of α and β subunits of LH with LH receptor of rat Leydig cells. Adapted from Alonoso-Whipple, C., Couet, M. L., Doss, R. Koziarz, J., Ogunro, E. A., and Crowley, W. E. Jr. *Endocrinology* 123:1854, 1988.

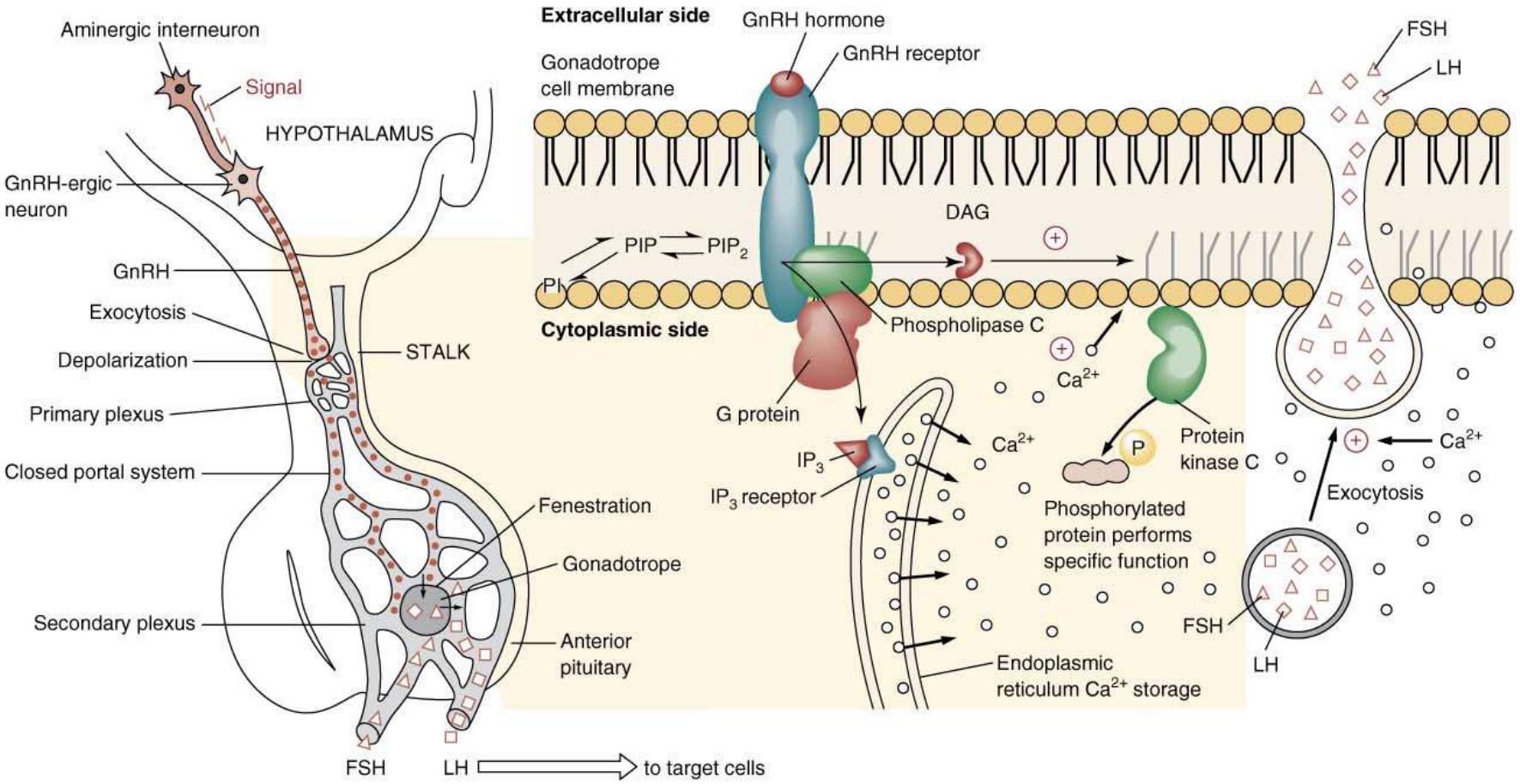
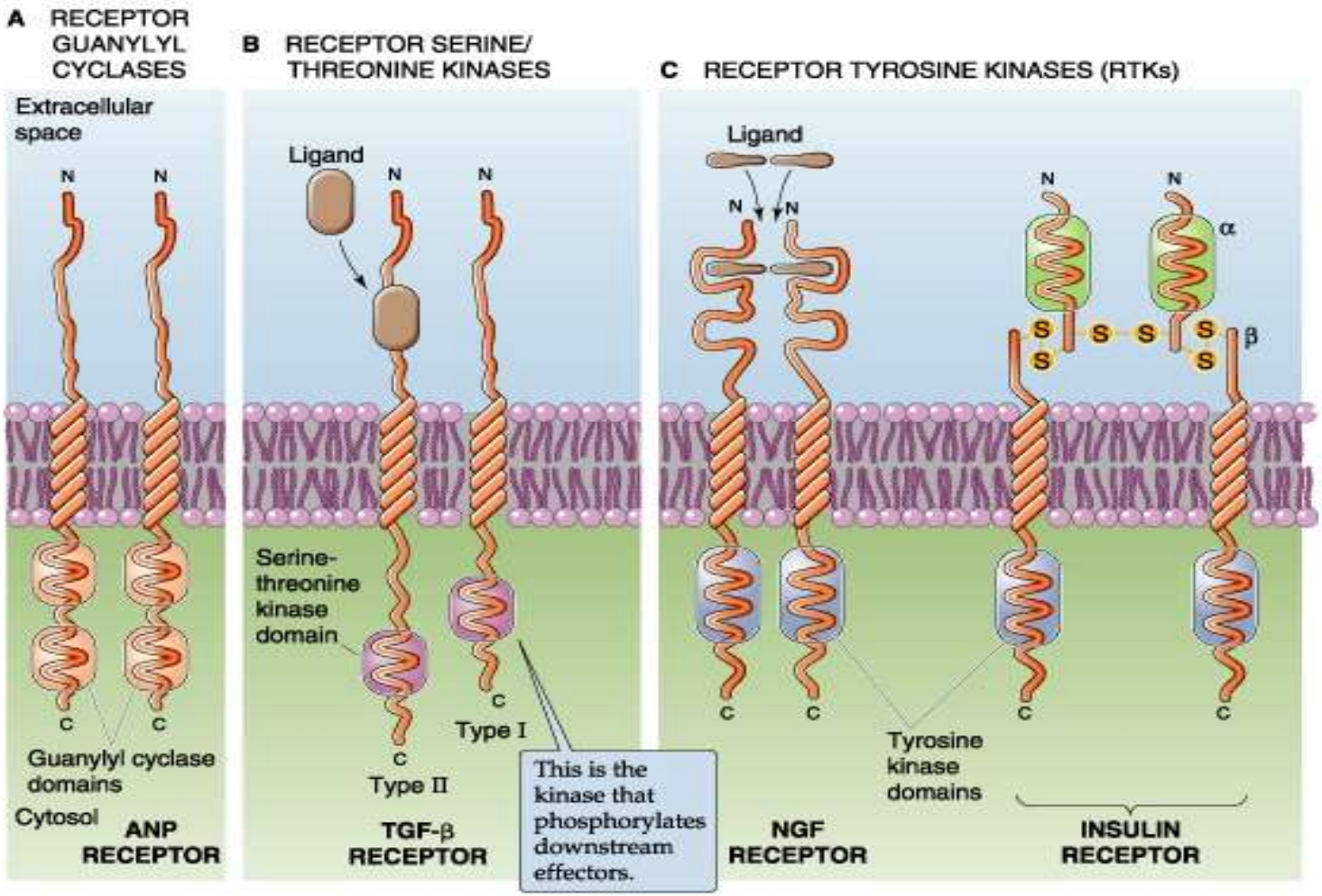
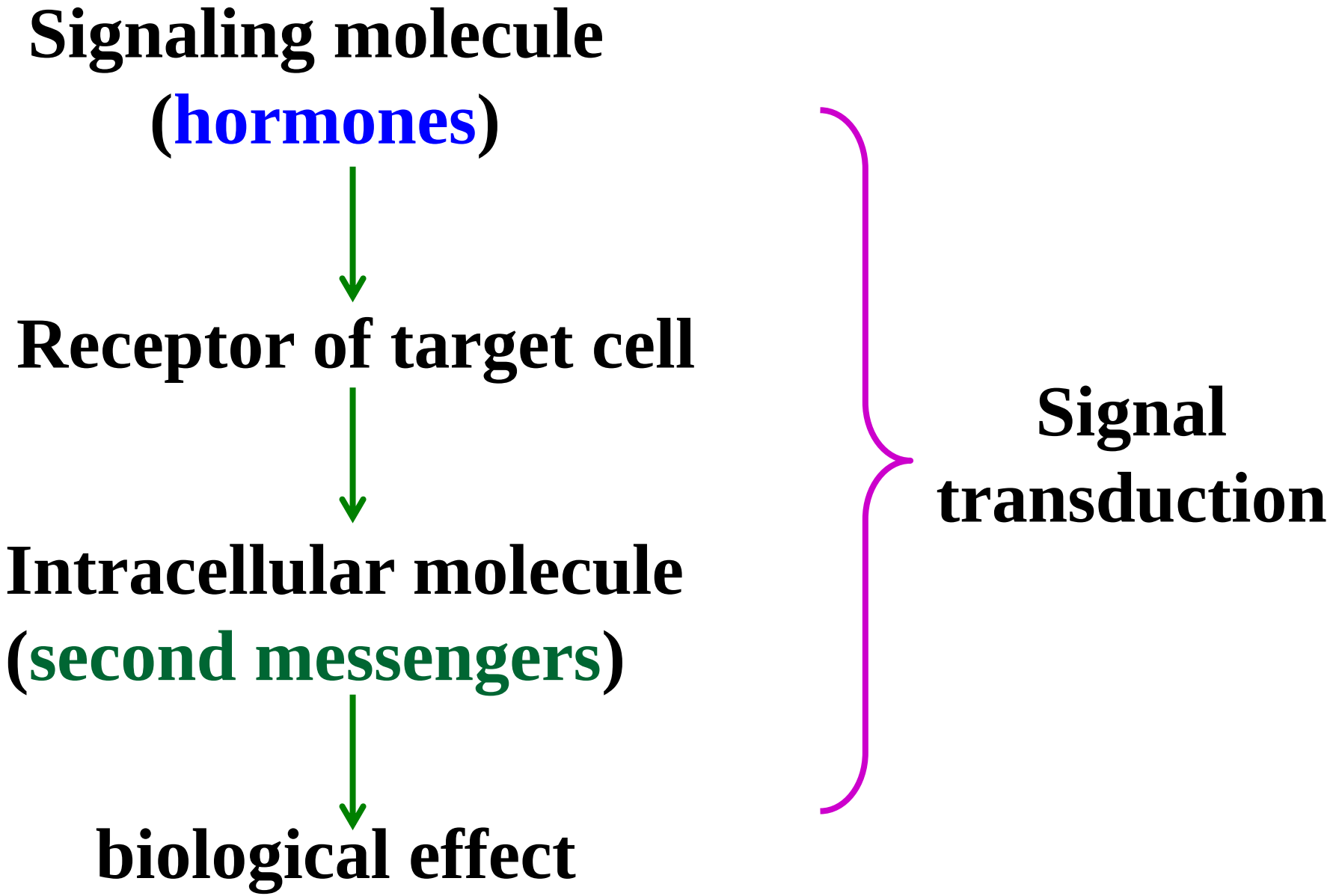


Figure 23.31. Regulation of secretion of LH and FSH by protein kinase C.

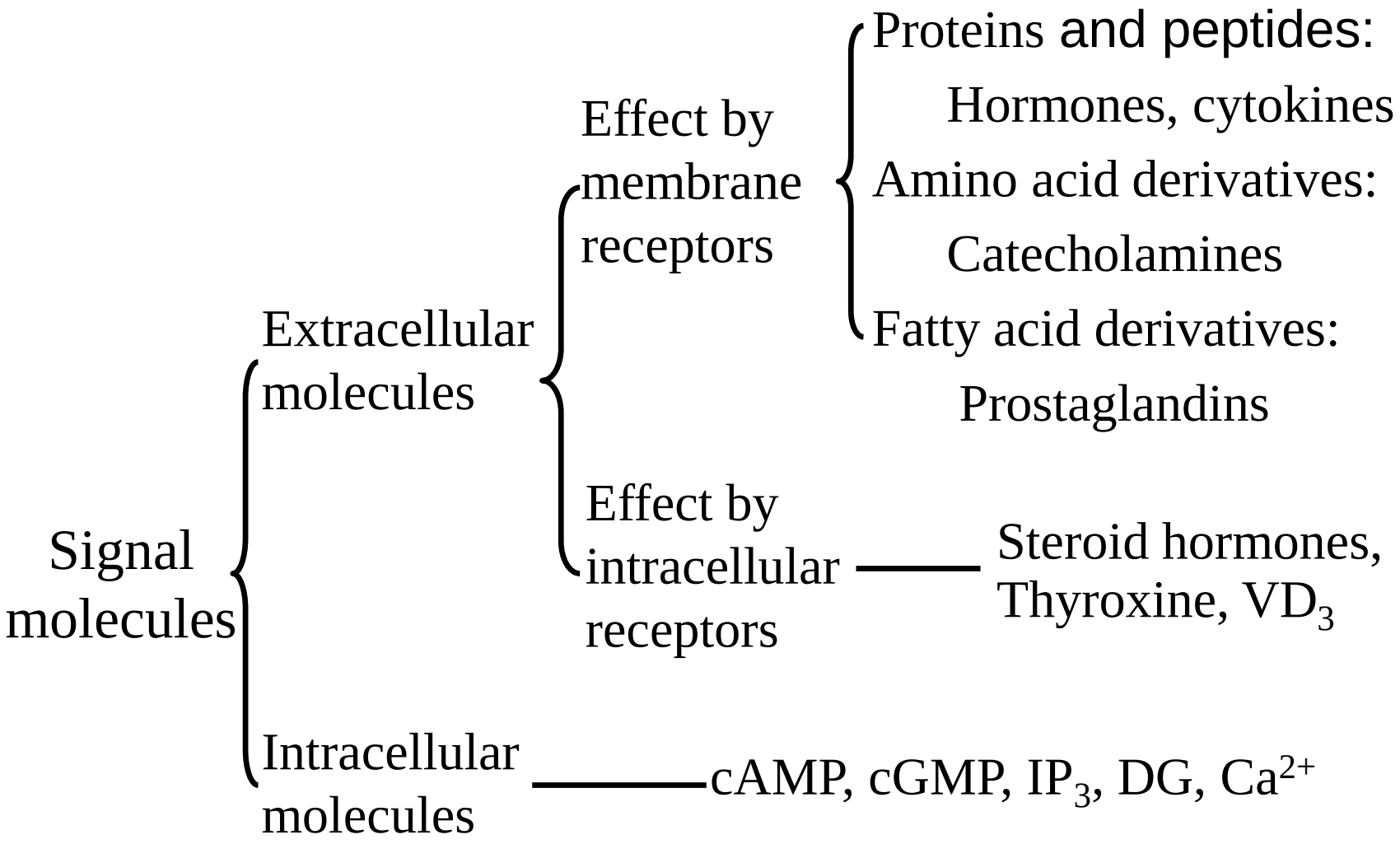
Textbook of Biochemistry With Clinical Correlations, *Sixth Edition*, Edited by Thomas M. Devlin. Copyright © 2006 John Wiley & Sons, Inc.




Signaling molecule
(hormones)
Receptor of target cell
Intracellular molecule
(second messengers)
biological effect
Signal
transduction

Third messengers:

Third messengers are the molecules which transmit message from outside to inside of nucleous or from inside to outside of nucleous, also called DNA binding protein.


Signal molecules
Extracellular molecules
Effect by membrane receptors
Proteins and peptides:
Hormones, cytokines
Amino acid derivatives:
Catecholamines
Fatty acid derivatives:
Prostaglandins
Effect by intracellular receptors
Steroid hormones, Thyroxine, VD3
Intracellular molecules
cAMP, cGMP, IP3, DG, Ca2+


THANKYOU