Receptors Functions and Signal Transduction L2

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Hormone Activity

- Hormones affect only specific target tissues with specific receptors
- Receptors are dynamic and constantly synthesized and broken down
  - Down-regulation- decrease in receptor number or response may be due to internalization of receptors
  - Up-regulation- increase in receptor number or activity,

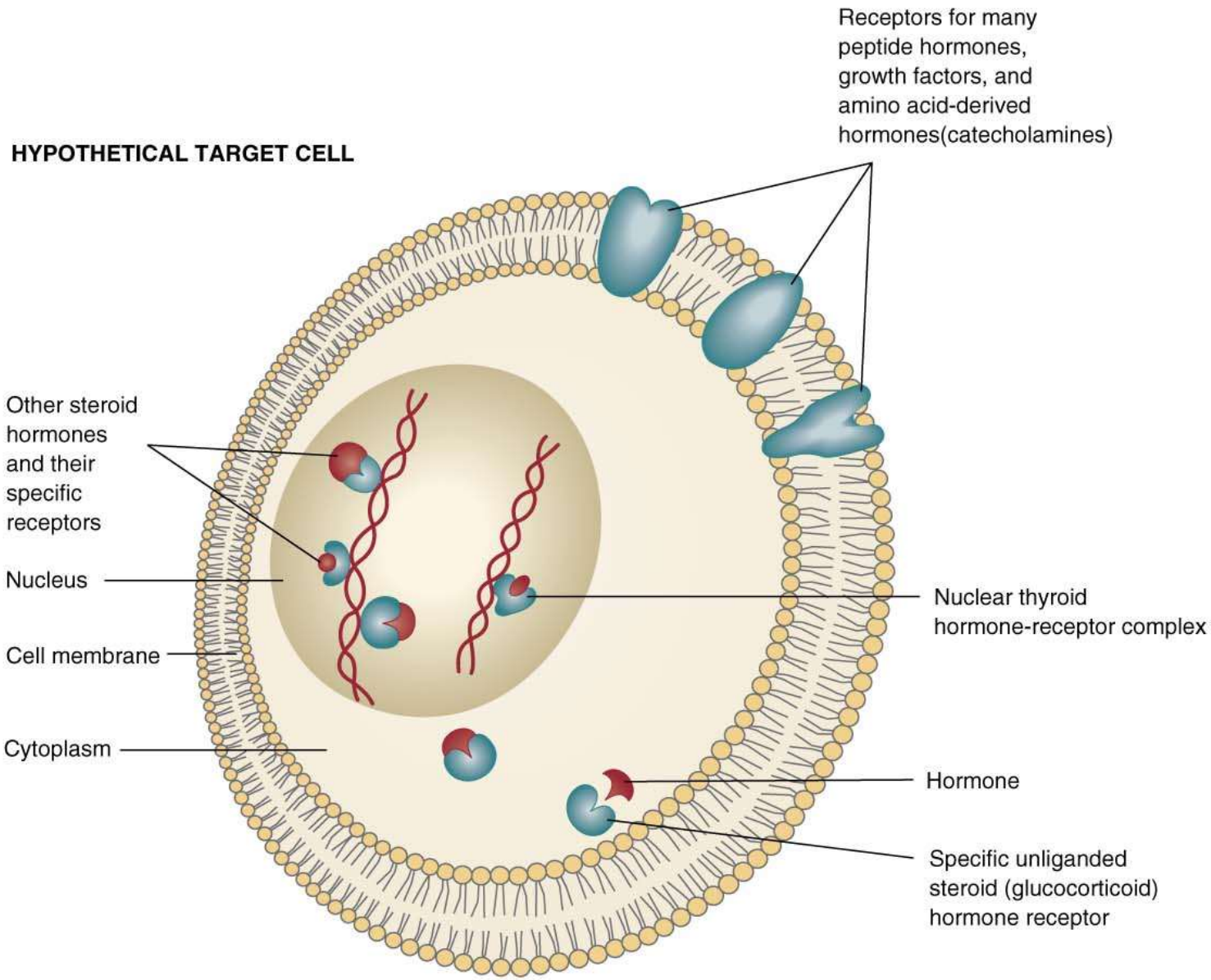
may be due to externalization of receptors or synthesis of new receptors.

Effects of [Hormone] on Tissue Response

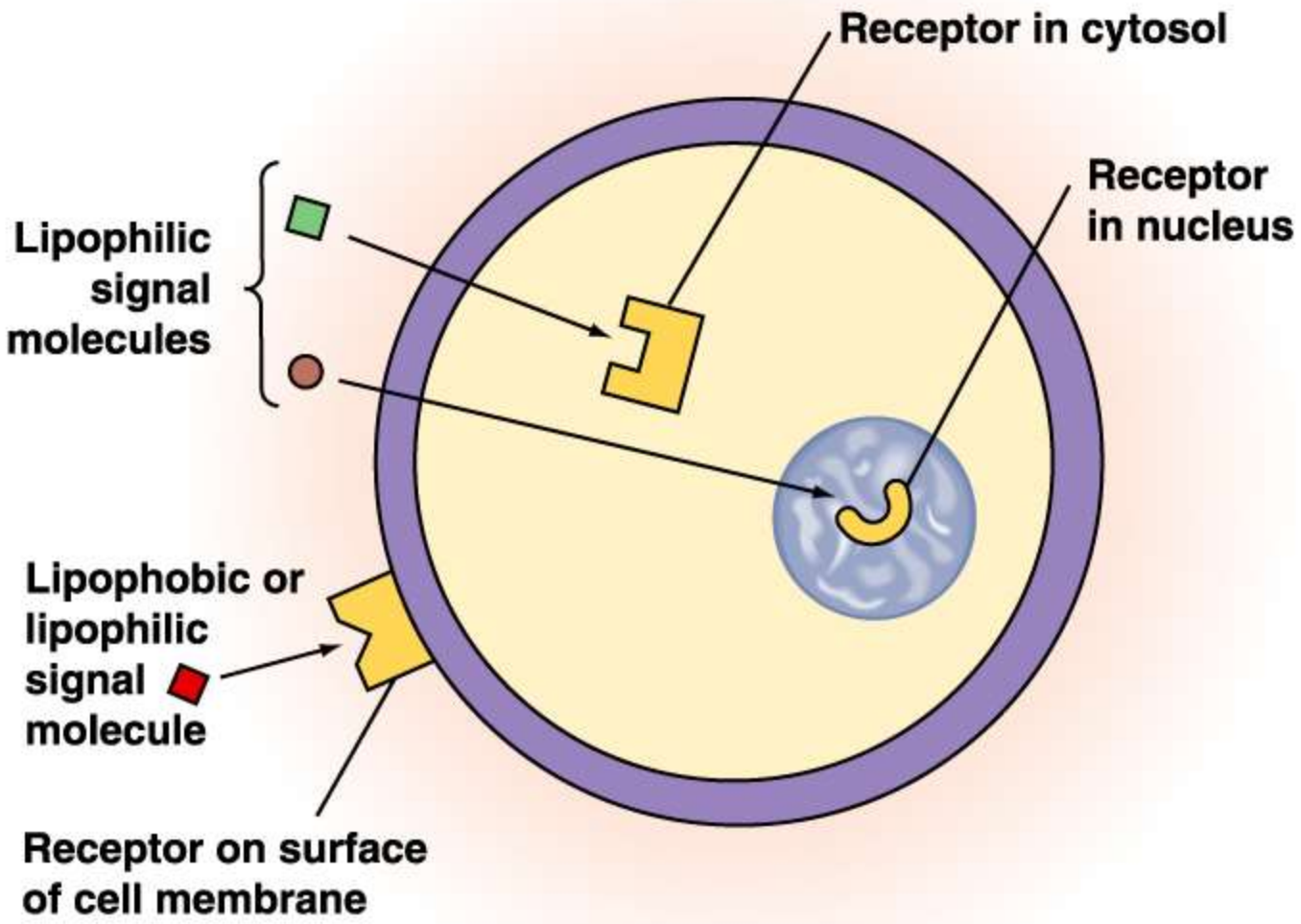
- Priming effect (upregulation):
  - Increase number of receptors formed on target cells in response to particular hormone.
  - Greater response by the target cell.
- Desensitization (downregulation):
  - Prolonged exposure to high [polypeptide hormone].
    - Subsequent exposure to the same [hormone]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

Effects of hormone concentration 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.



. 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

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

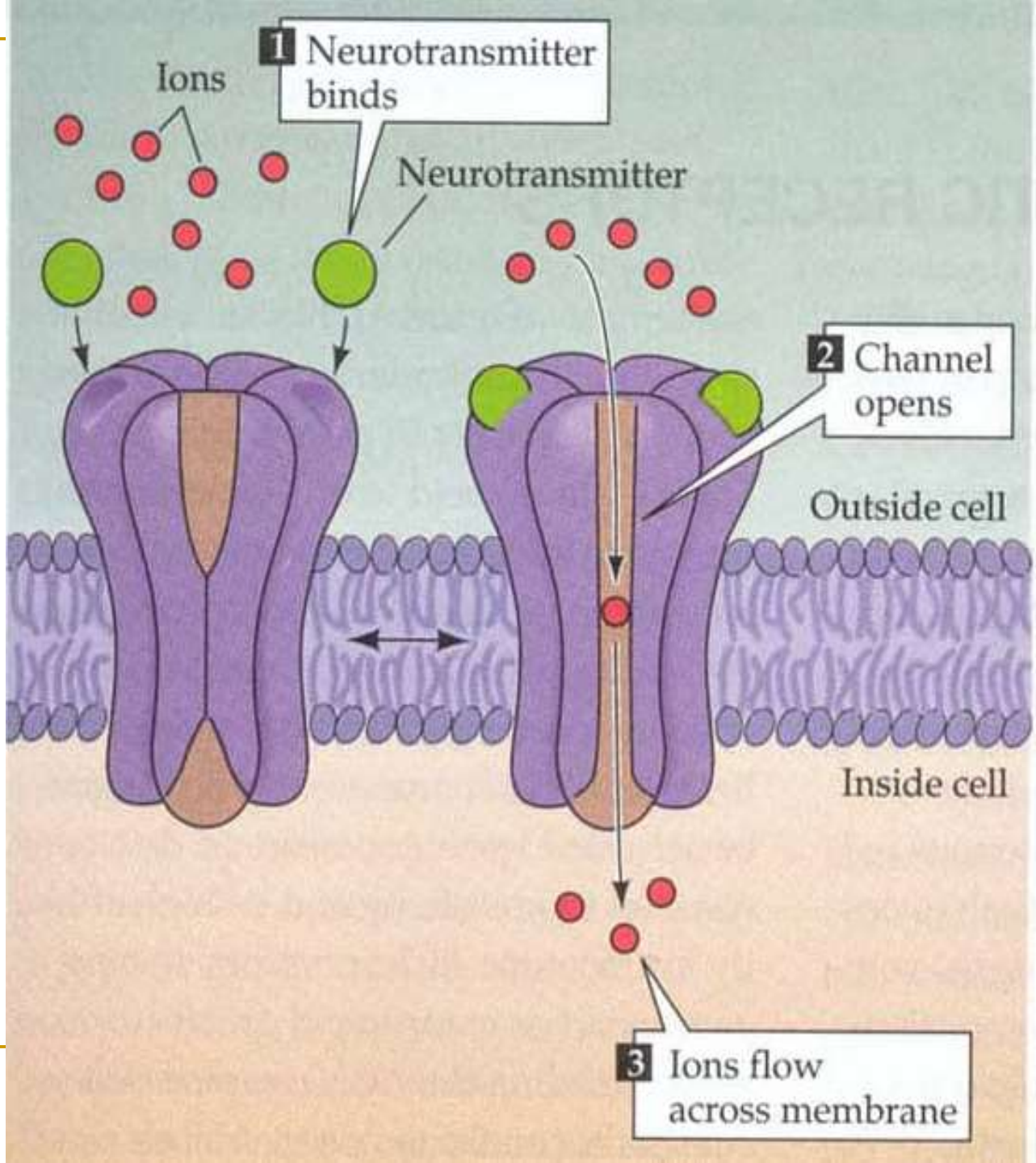
  DNA binding protein

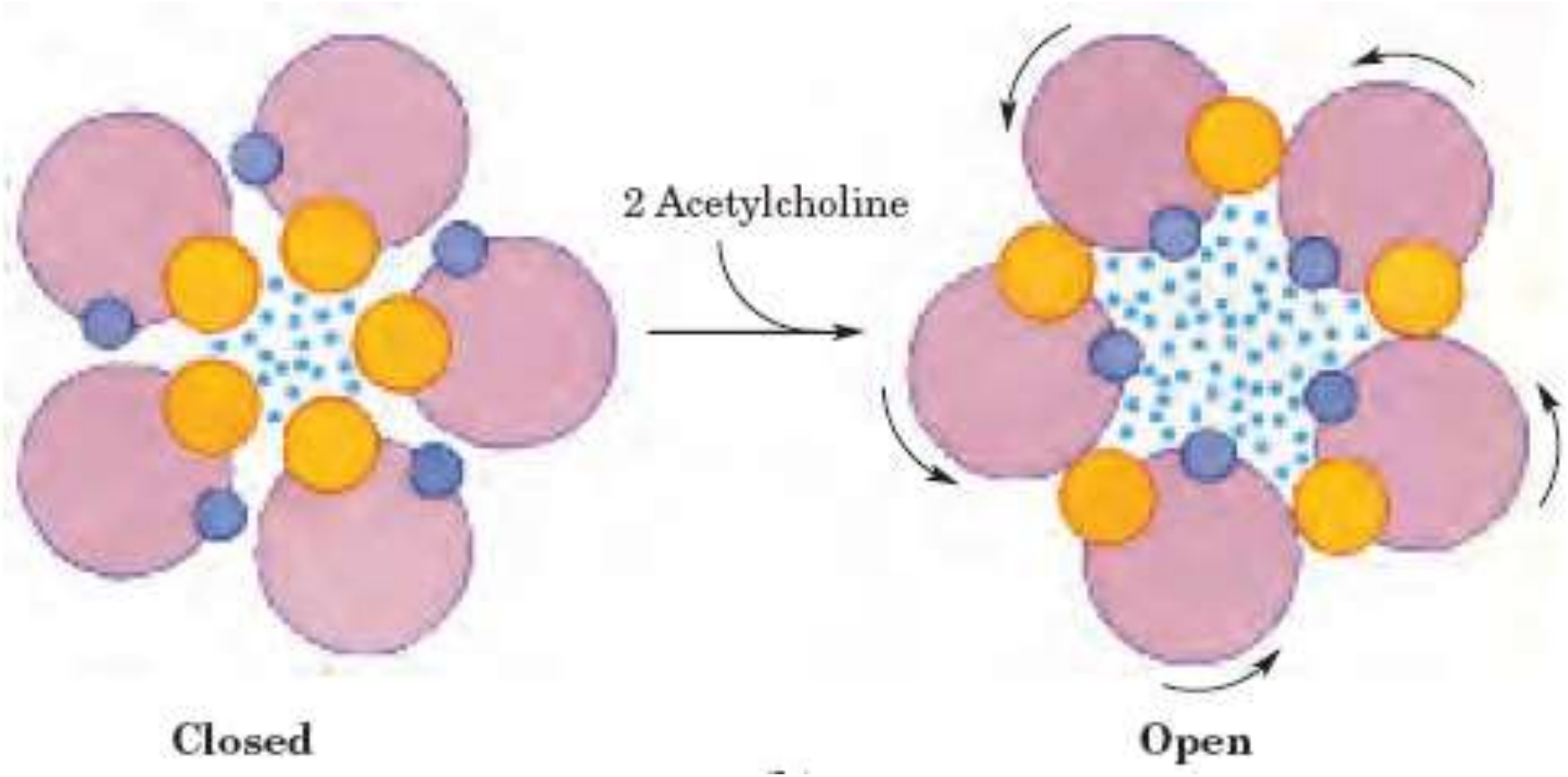
1. membrane receptors

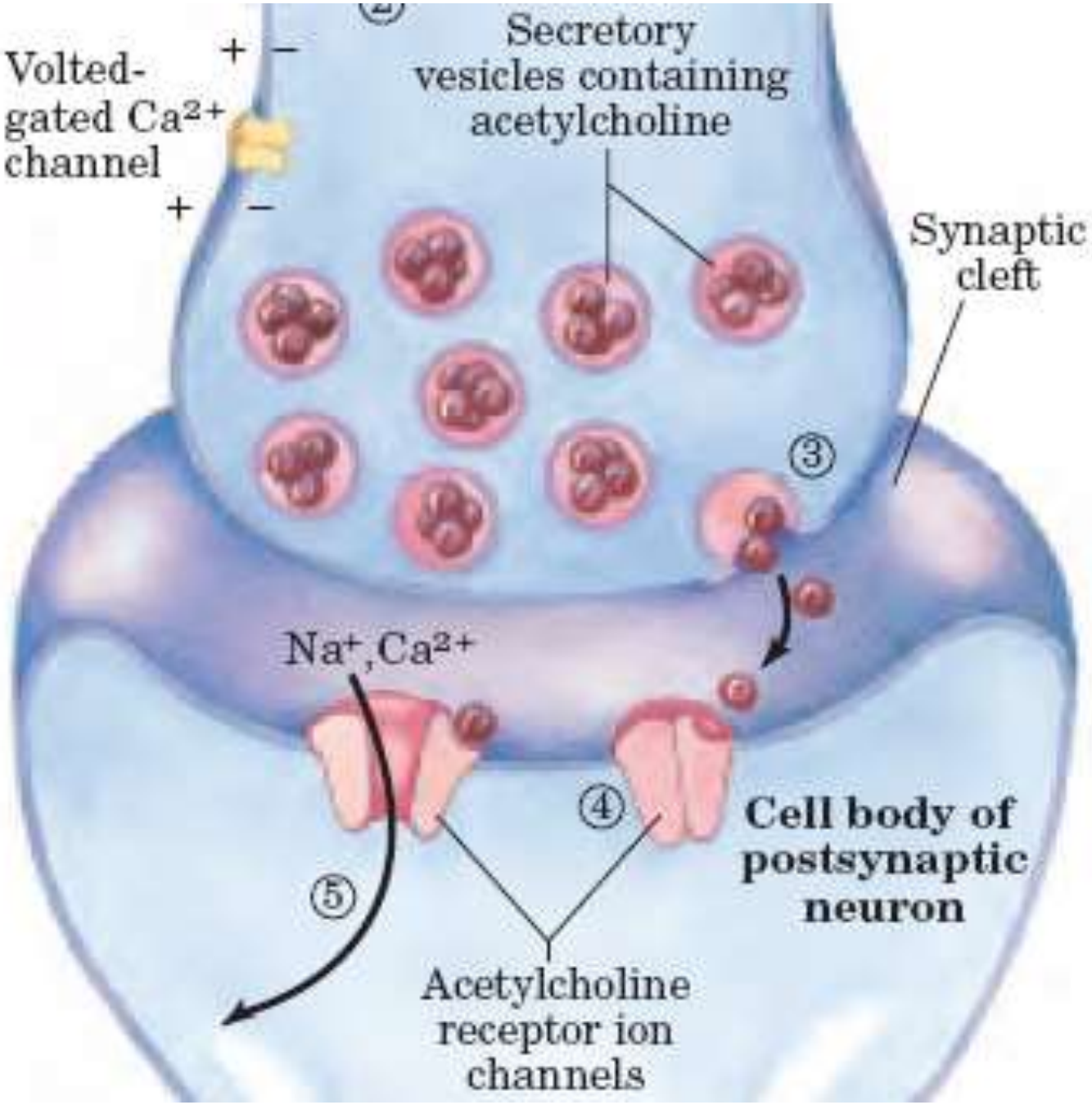
1- Ligand-gate ion channels type

(cyclic receptor)

ligand→receptor→ion channel open or close

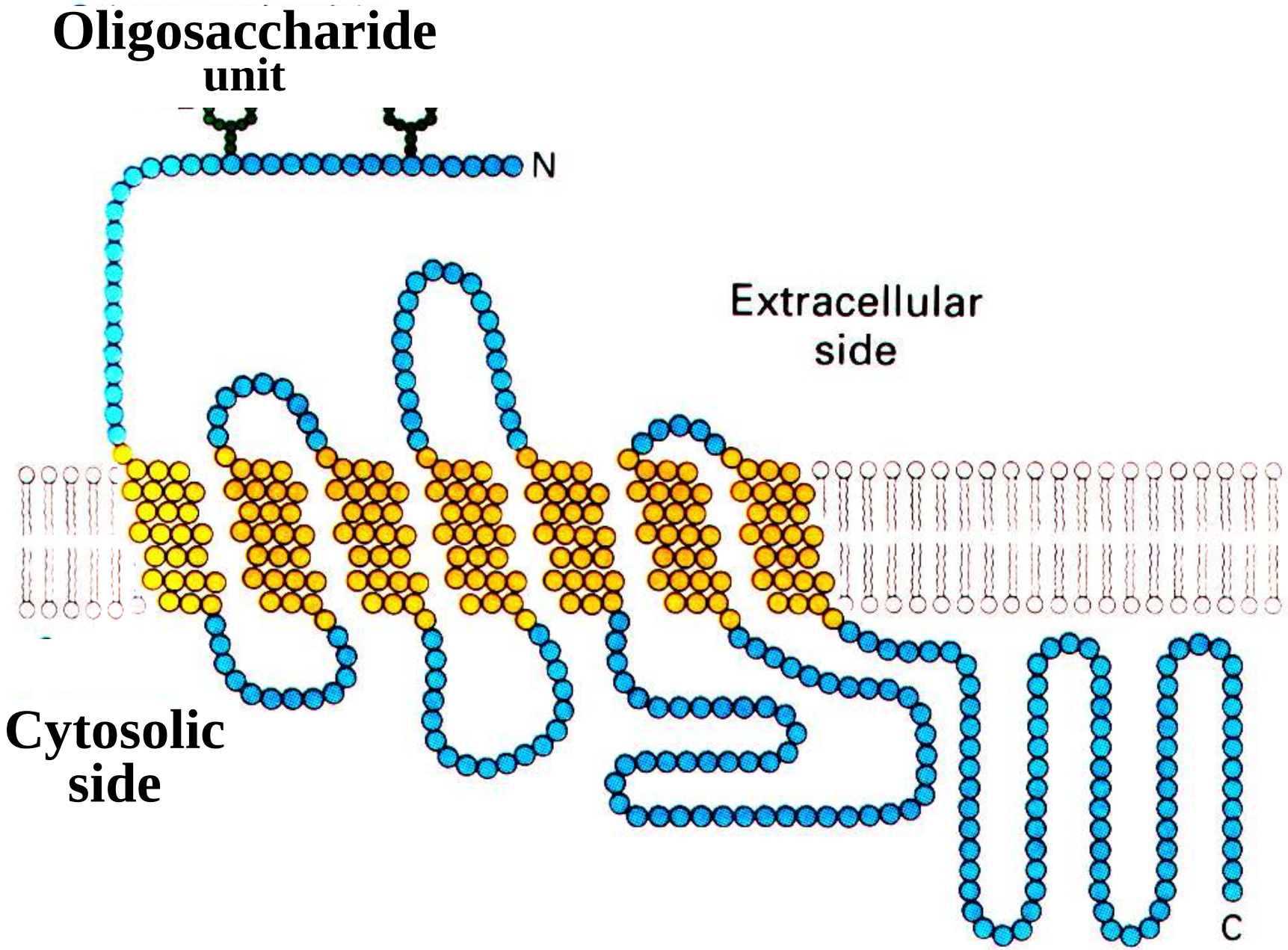

Ions
1 Neurotransmitter binds
Neurotransmitter
2 Channel opens
Outside cell
Inside cell
3 Ions flow across membrane


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

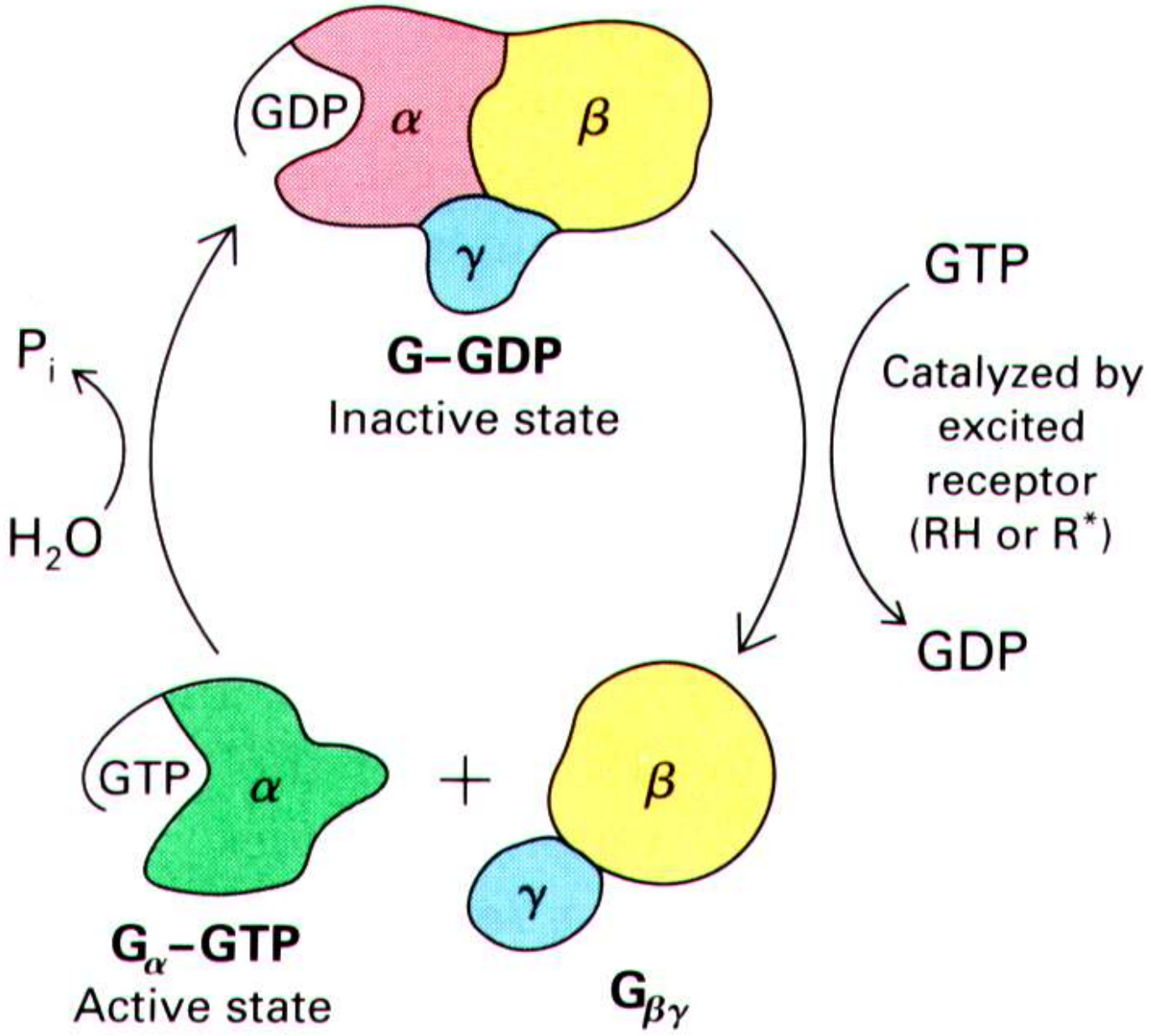
2- G Protein-Coupled Receptors

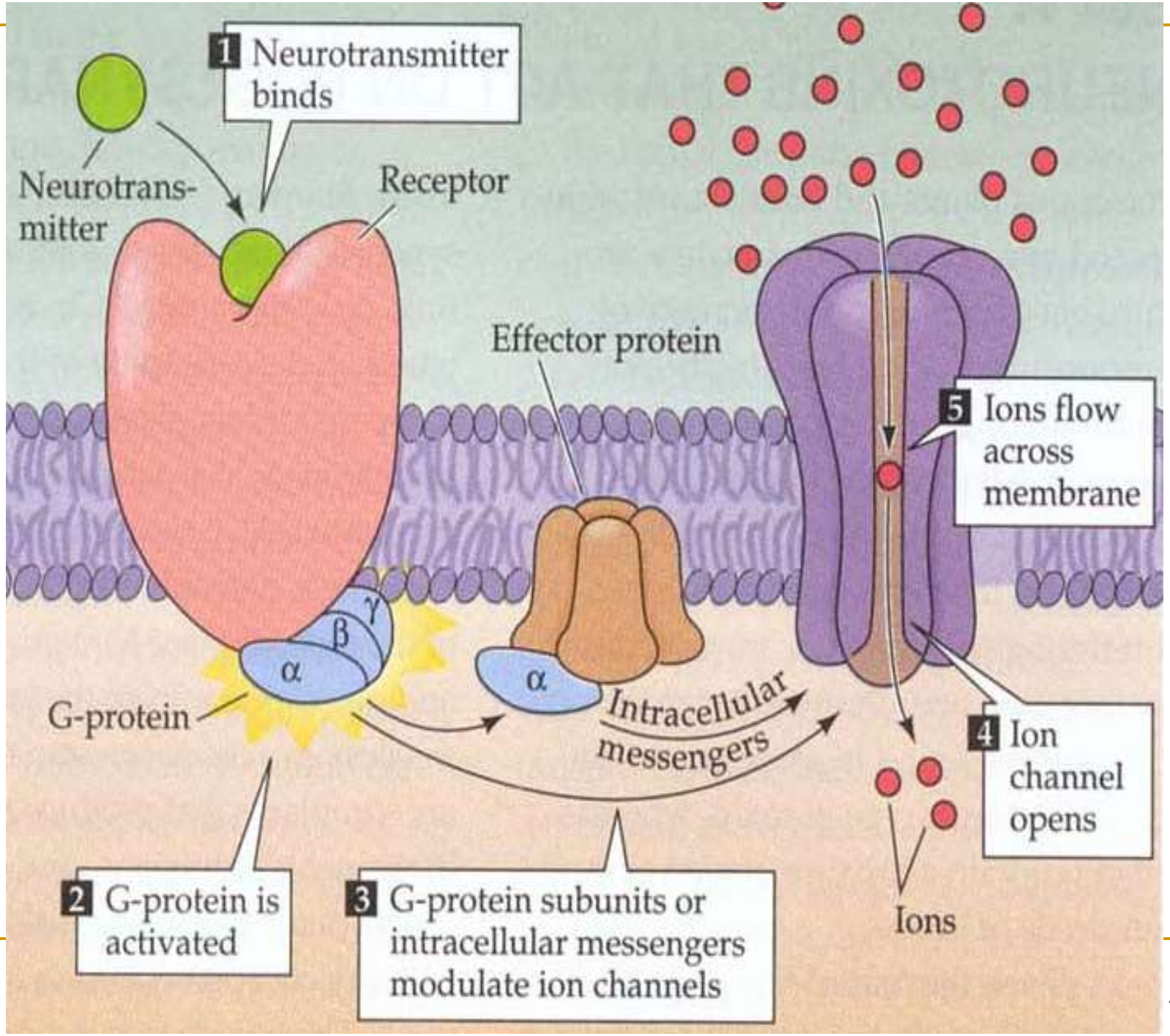
I- 7-helices transmembrane receptor

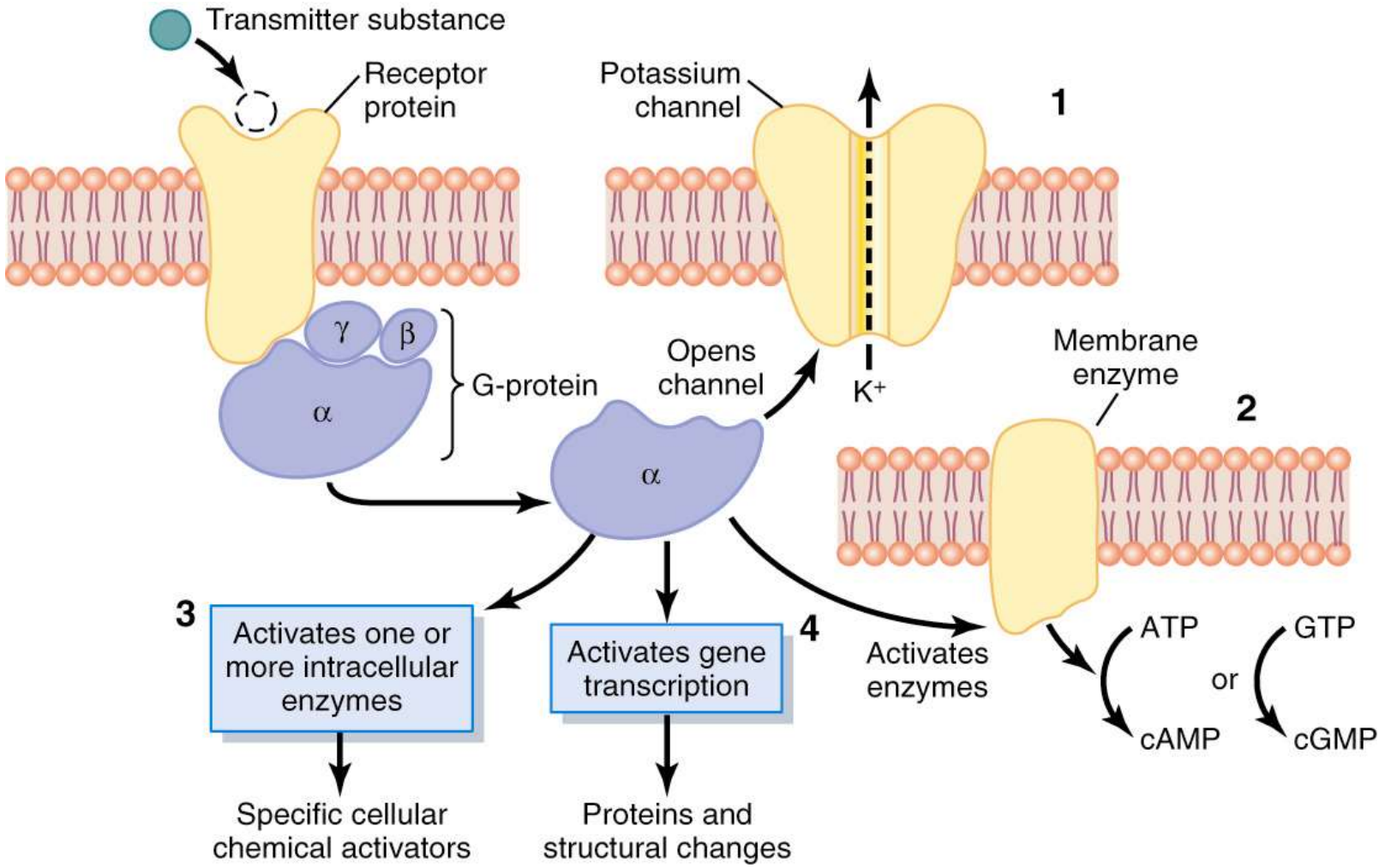

Oligosaccharide unit
N
Extracellular side
Cytosolic side
C

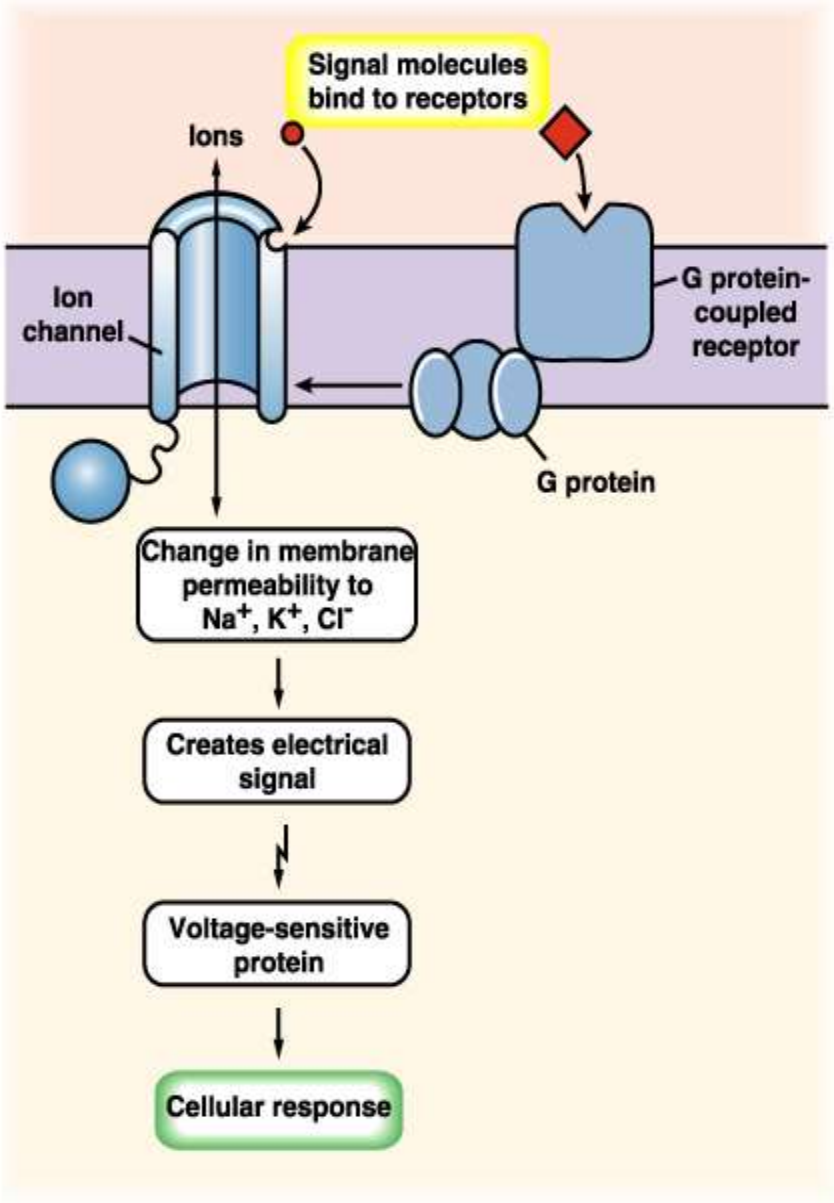
2) G protein (Guanylate binding protein)

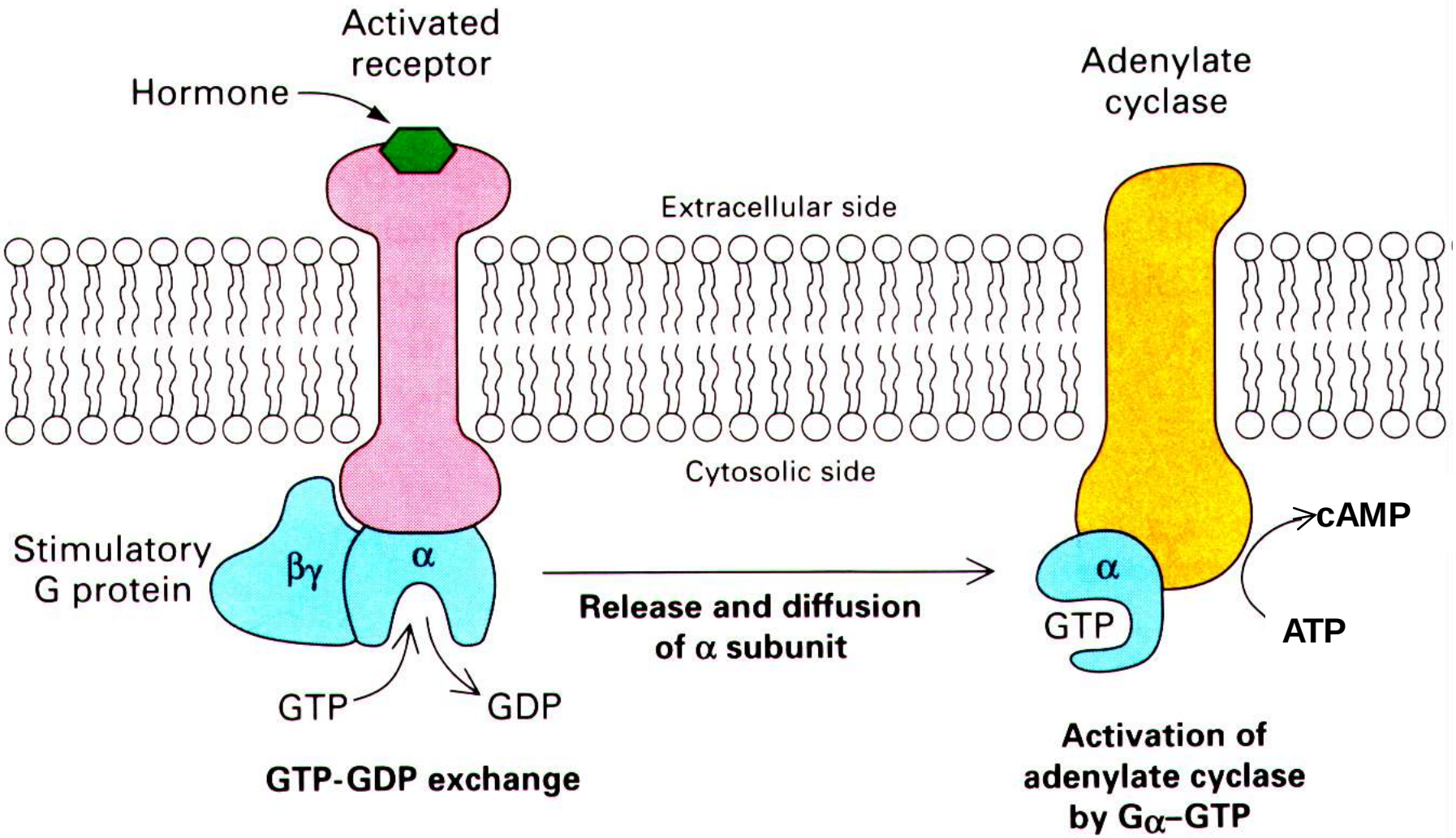
- G protein refers to any protein which binds to GDP or GTP and act as signal transduction.
- G proteins consist of three different subunits (α, β, γ-subunit) bound to GDP when exchanged to GTP activate α-subunit
- α-subunit carries GTPase activity, binding and hydrolysis of GTP.


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
α
β
γ
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

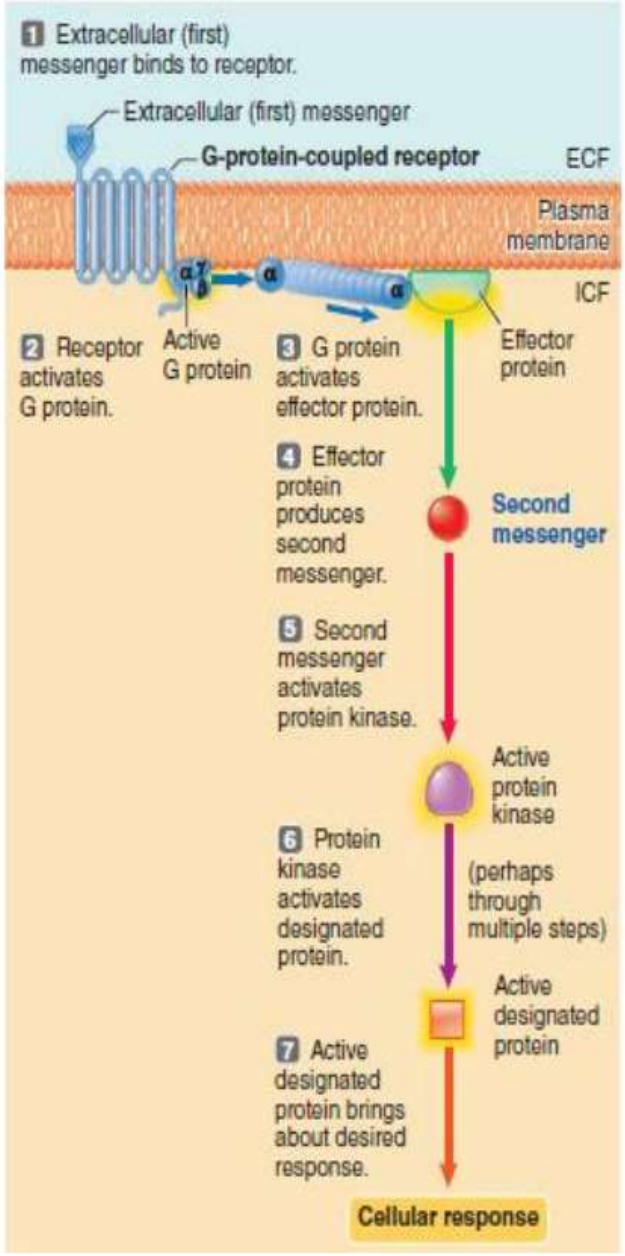

Transmitter substance
Receptor protein
Potassium channel
1
γ
β
α
G-protein
Opens channel
K+
Membrane enzyme
2
α
3
Activates one or more intracellular enzymes
Specific cellular chemical activators
4
Activates gene transcription
Proteins and structural changes
Activates enzymes
ATP
GTP
or
cAMP
cGMP


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

G Protein–Linked Hormone Receptors

- Binding of the first messenger to the receptor activates the **G protein**,
- On activation, a portion of the G protein shuttles along the membrane to alter the activity of a nearby membrane protein called the **effector protein**.
- Once altered, the effector protein leads to an increased concentration of an intracellular messenger, known as the **second messenger**.
- The second messenger relays the orders through a cascade of chemical reactions inside the cell that cause a change in the shape and function of designated proteins.



G Protein–Linked Hormone Receptors

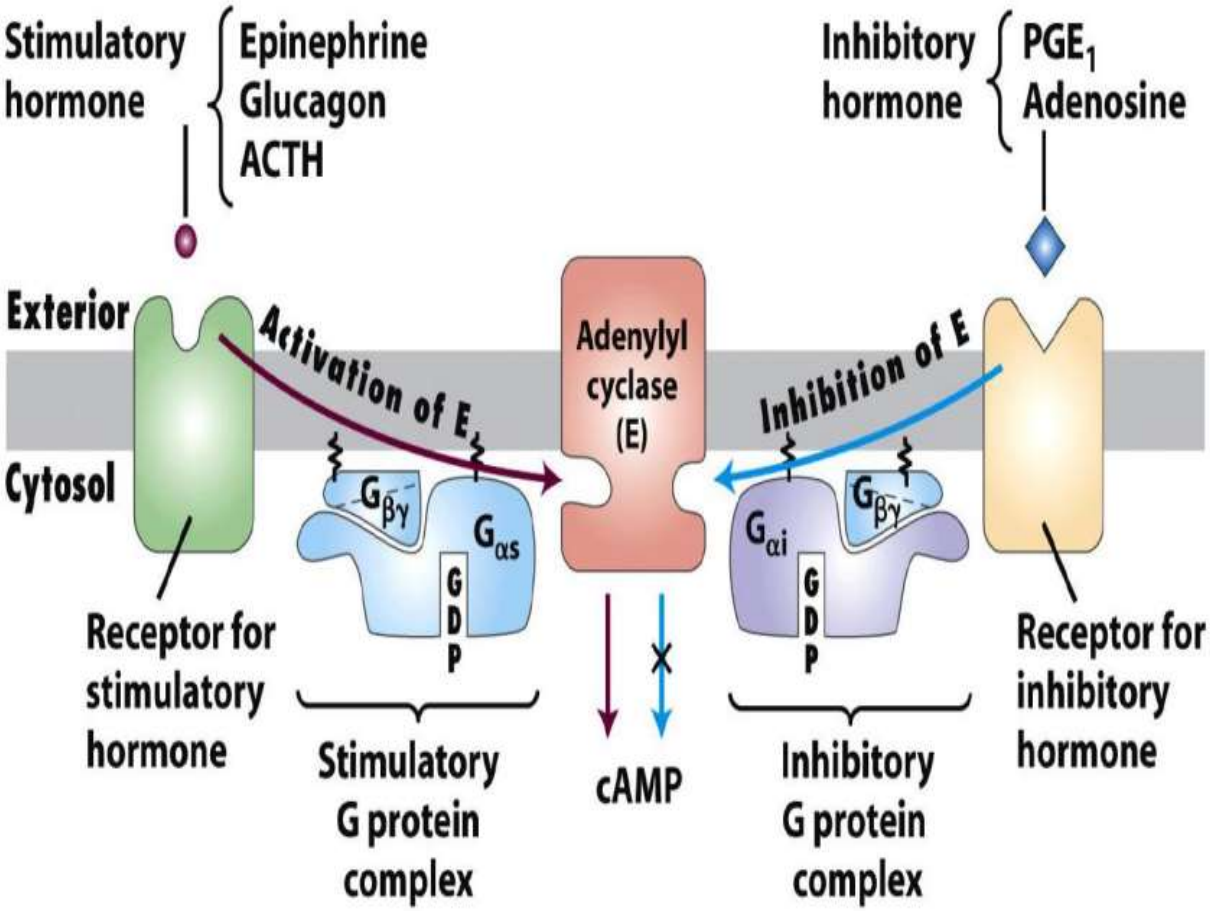


Figure 15-21

G Protein–Linked Hormone Receptors

- **Different** isoforms of G_α have different signal roles. E.g.:
  - The **stimulatory** $G_{s\alpha}$, when it binds GTP, **activates** Adenylate cyclase.
  - An **inhibitory** $G_{i\alpha}$, when it binds GTP, **inhibits** Adenylate cyclase.

Thus, depending on the coupling of a hormone receptor to an inhibitory or stimulatory G protein, a hormone can either increase or decrease the activity of intracellular enzymes.

- The complex of $G_{\gamma\beta}$ that is released when G_α binds GTP is itself an effector that binds to and **activates or inhibits** several other proteins.

  E.g., $G_{\gamma\beta}$ **inhibits** one of several isoforms of **Adenylate Cyclase**, contributing to rapid signal turnoff in cells that express that enzyme.

G Protein–Linked Hormone Receptors

Turn off of the signal:

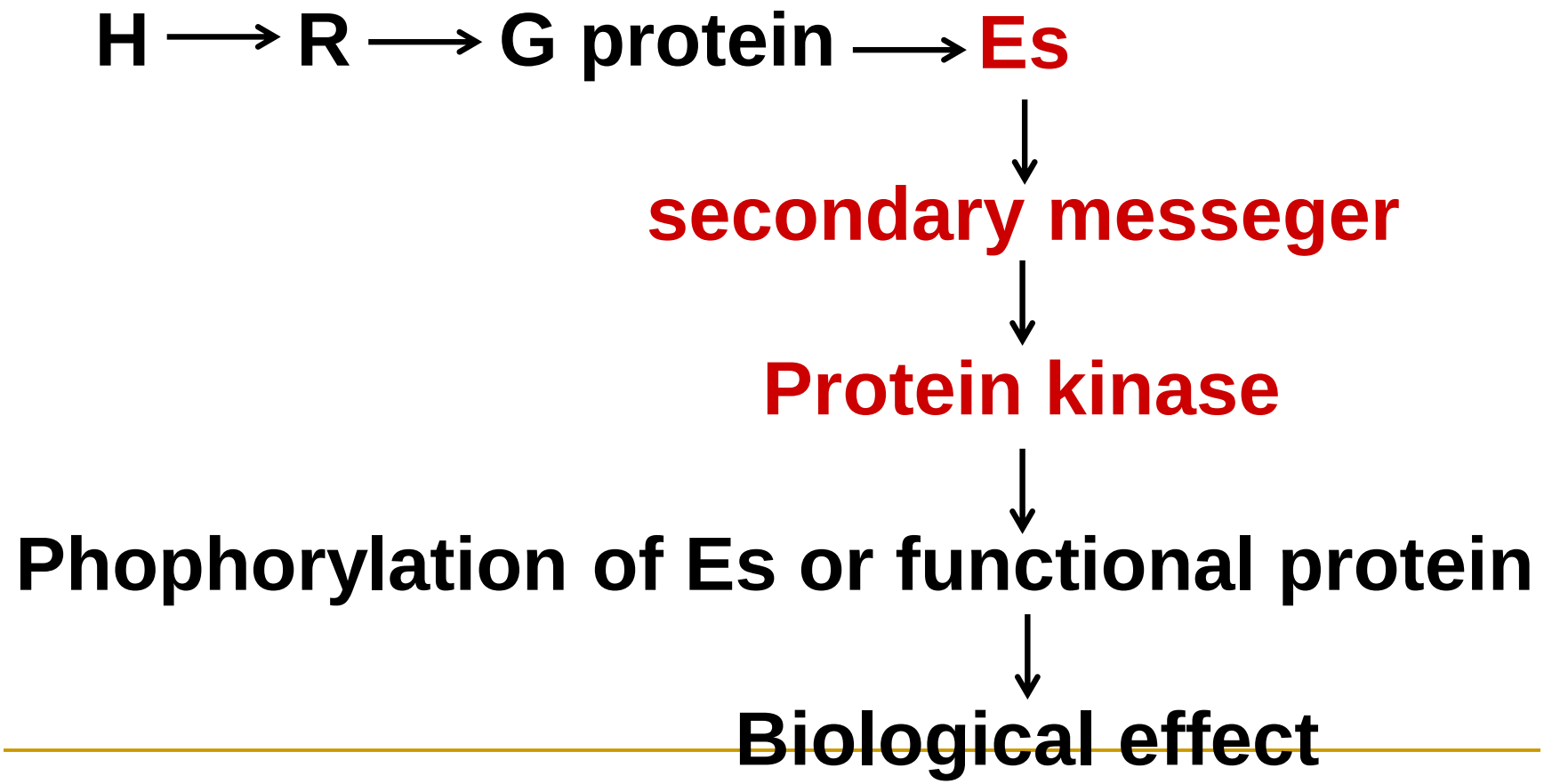
1. **Gα** hydrolyzes GTP to GDP + P_i. (**GTPase**).

   The presence of **GDP** on G_α causes it to rebind to the inhibitory **ßγ** complex.

   Adenylate Cyclase is no longer activated.

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

- Pathway of G protein linked receptor



Properties of binding of H and R

- high specificity
- high 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 ~


THANKYOU

Receptors Functions and Signal Transduction- L3

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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 B (calcium calmodulin dependent protein kinase)
- Cyclic nucleotides
  - cAMP & cGMP
  - Target: protein kinases ~

Second Messengers

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