Cell –cell communication

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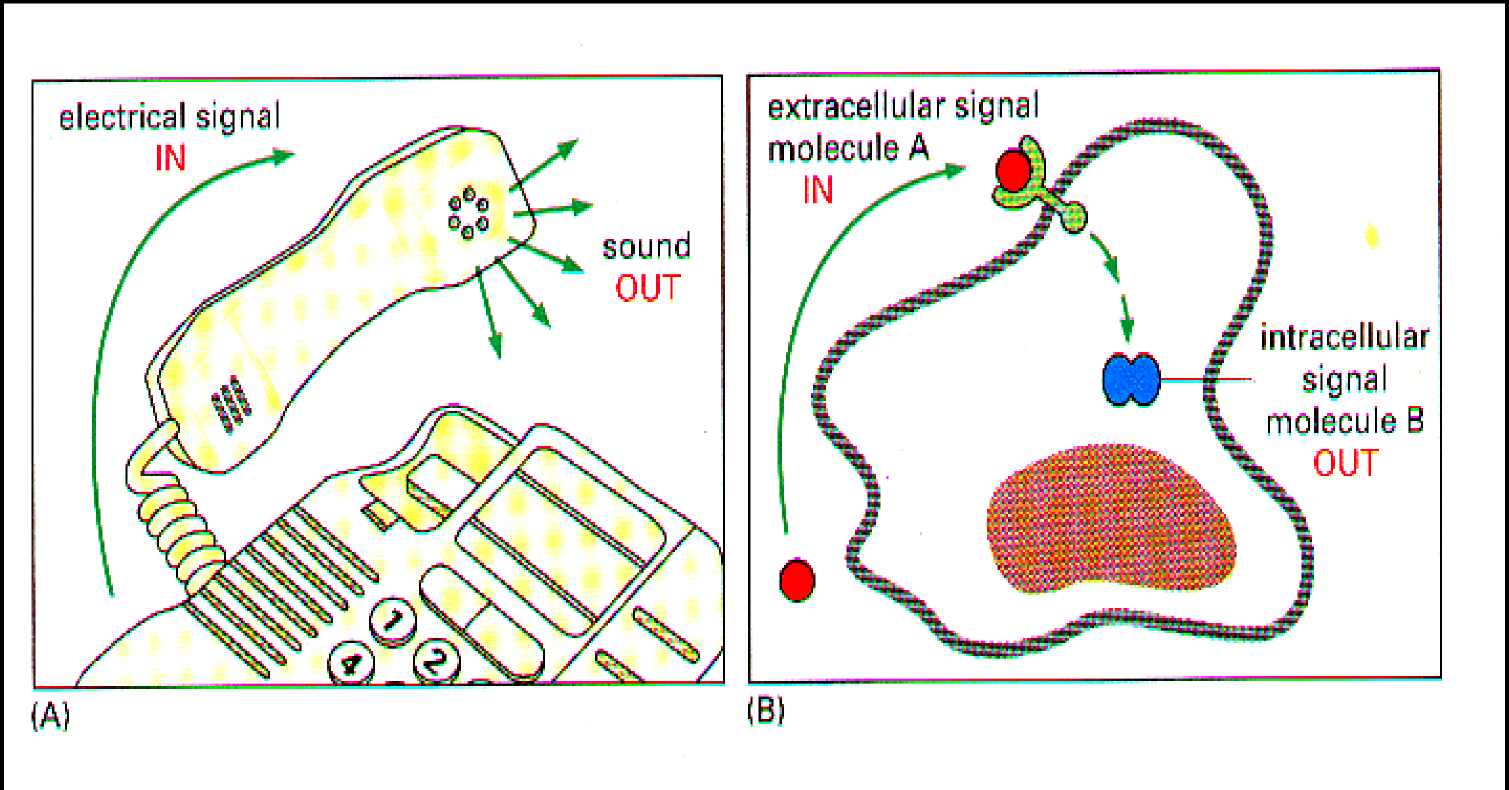
Lecture Outline

1. Types of intercellular communication
2. The primary receiver – Receptors
3. - the concept of AMPLIFICATION
4. Types of receptors
5. Ion Channels – Membrane depolarization
6. Trimeric G-Protein coupled receptors
   - the cAMP signal pathway
   - the phophatidyl inositol pathway, Ca^{++} release
7. Tyrosine Kinase – MAP Kinase Cascade
8. Internal cytosolic receptor systems

I. Cell Communication – Signal Transduction



External signal is <u>received</u> and <u>converted</u> to another form to elicit a <u>response</u>

External signals are converted to Internal Responses

- Cells sense and respond to the environment

  Prokaryotes: chemicals
  Humans:
  - light - rods & cones of the eye
  - sound – hair cells of inner ear
  - chemicals in food – nose & tongue

- Cells communicate with each other

  Direct contact
  Chemical signals

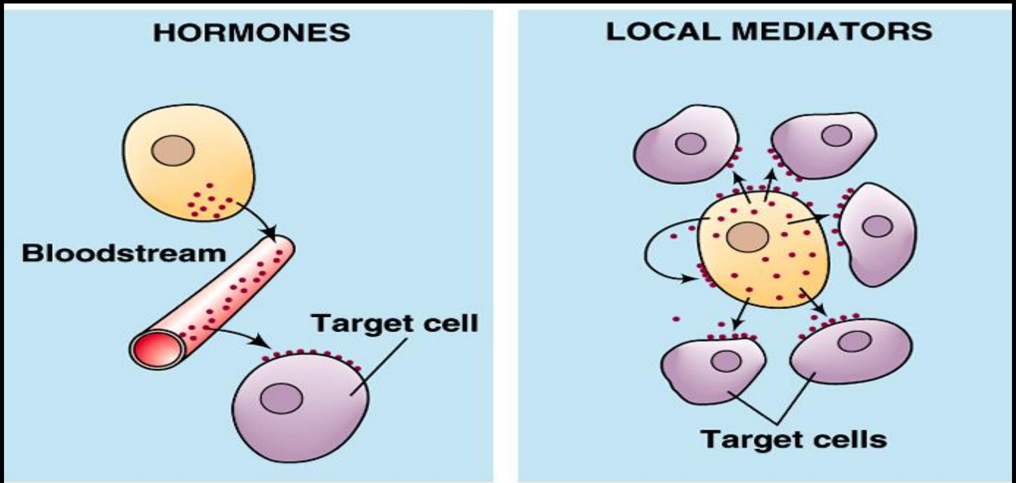
General principles:

1. Signals act over different ranges.
2. Signals have different chemical natures.
3. The <u>same</u> signal can induce a <u>different</u> response in <u>different</u> cells.
4. Cells respond to <u>sets</u> of signals.
5. Receptors relay signals via intracellular signaling ***cascades***.

Signals act over different ranges

Endocrine

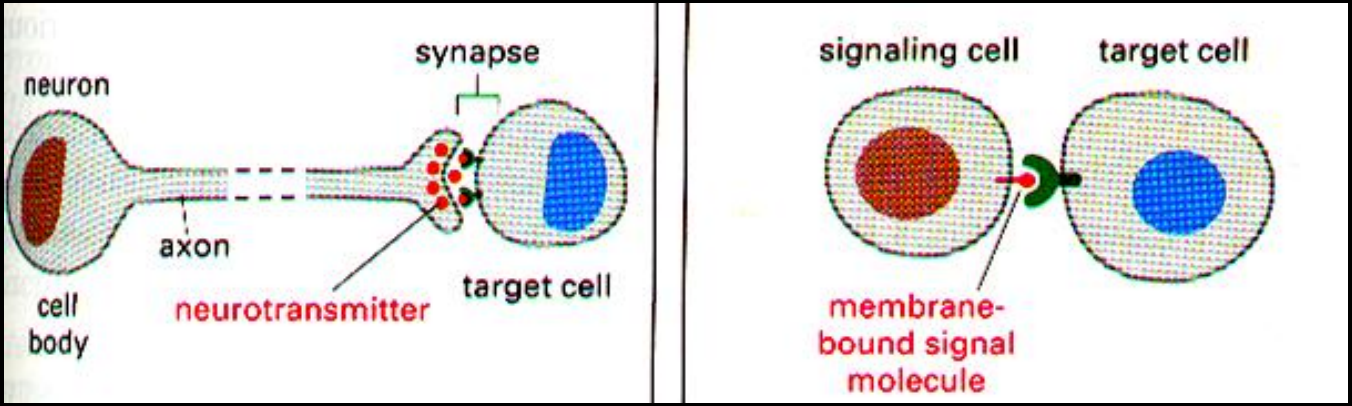
long distance
ex. estrogen, epinephrine



Like Fig 11.4

Paracrine

local
ex. nitric oxide, histamines, prostaglandins

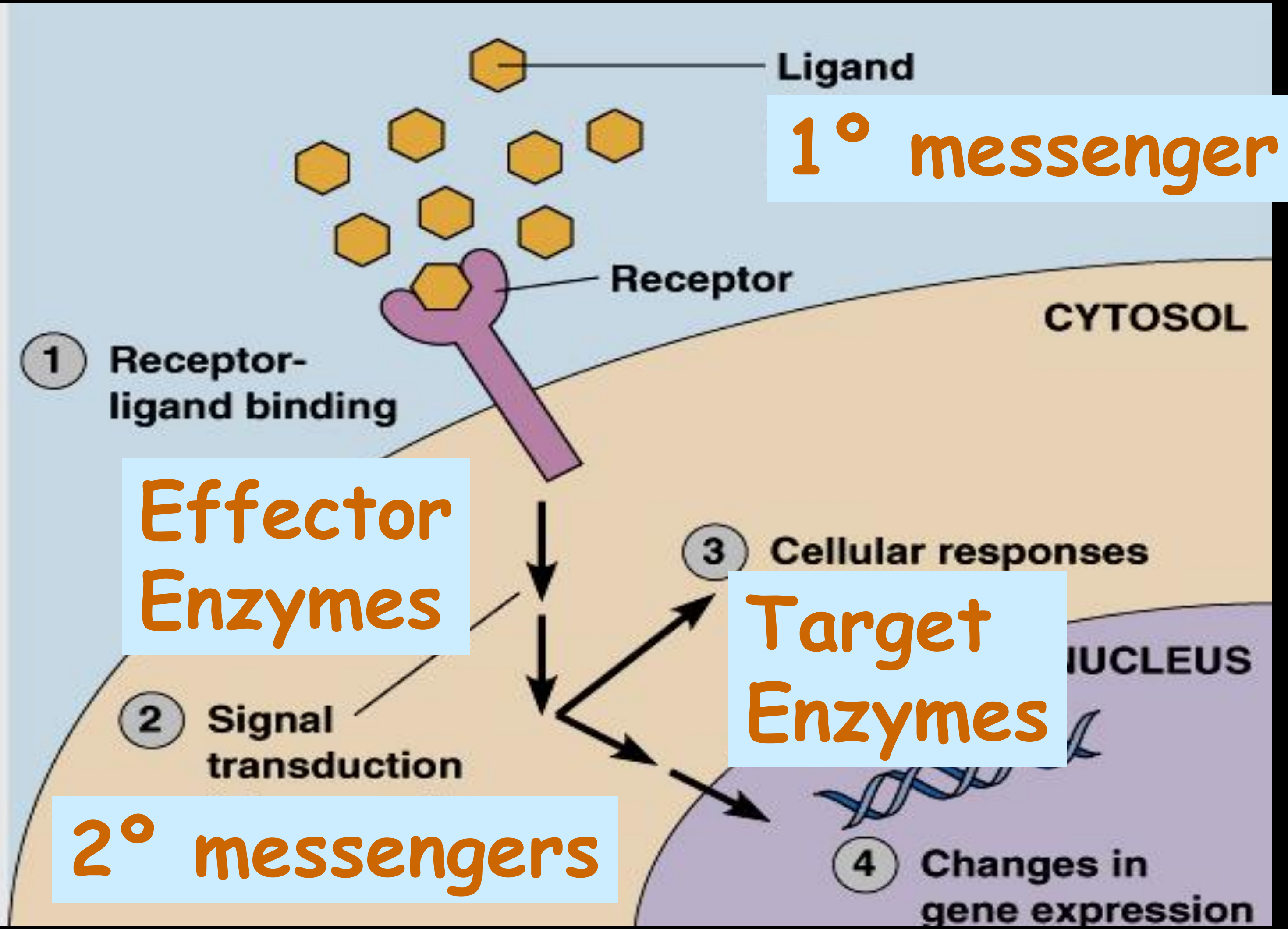


Neuronal/Synaptic

ex. neurotransmitters

direct contact
Cell-cell recognition

ex. delta/notch



Cells detect signal & respond

Signal transduction: ability of cell to translate receptor-ligand interaction into a change in behavior or gene expression

Primary Messenger

Secondary Messengers

Target Enzymes

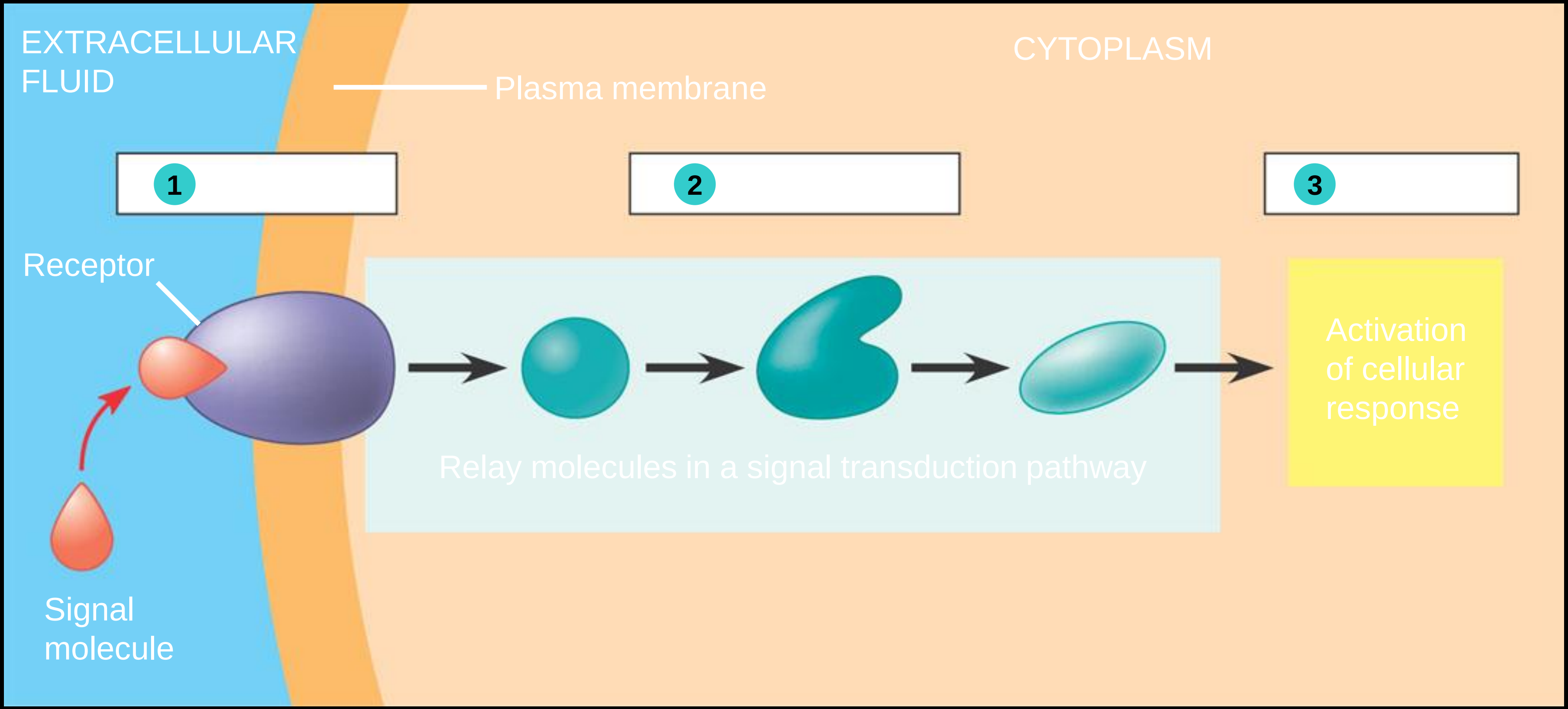


Figure 11.5

Cascade Effect

Each protein in a signaling pathway

- **Amplifies** the signal by activating multiple copies of the next component in the pathway

1 primary signal - activates an enzyme activity, processes 100 substrates per second

Primary enzyme activates 100 target enzymes

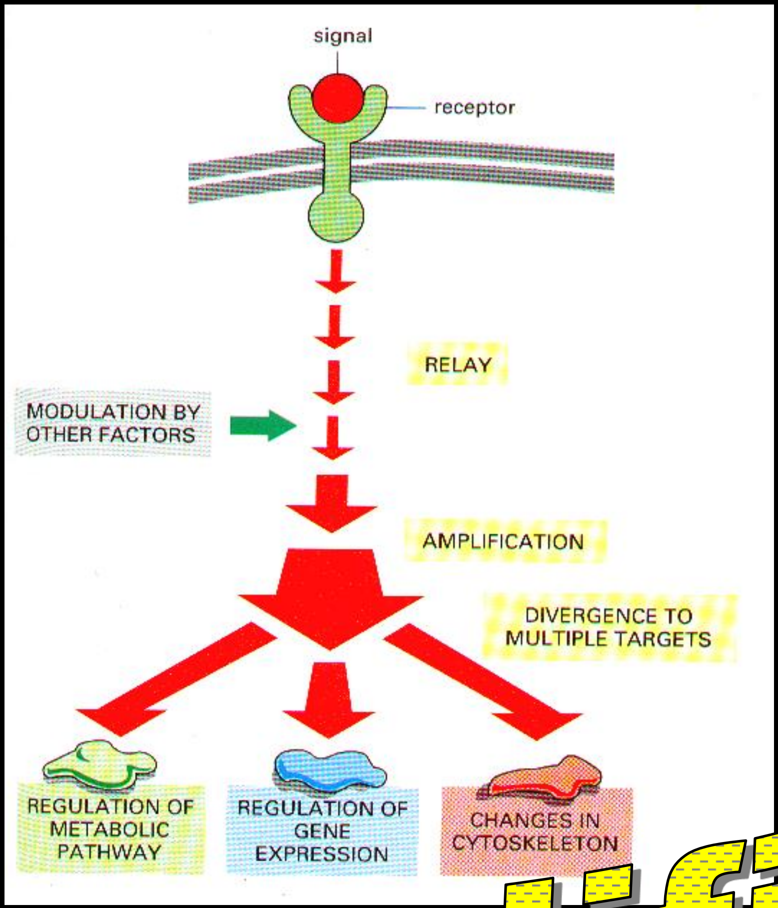
Each of the 100 enzymes activates an additional 100 dowstream target enzymes

Each of the 10,000 downstream targets activates 100 control factors

so rapidly have

1,000,000 active control fac

Receptors relay signals via intracellular SIGNALING CASCADES



Push doorbell

↓

Ring bell

↓

Enzymatic activation of more ENZYMES

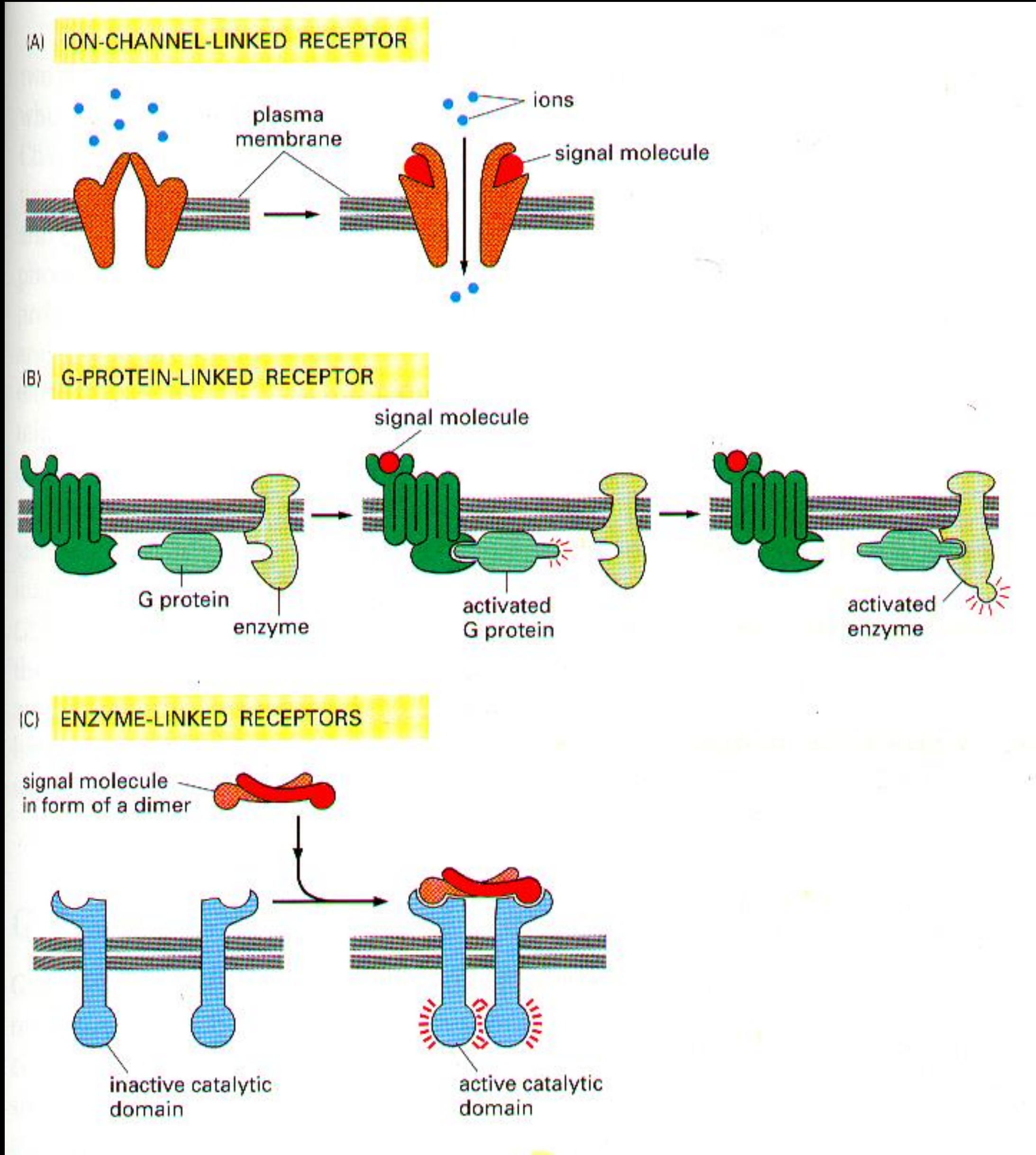
amplification

Cell-surface receptors -large &/or hydrophilic ligands

ion-channel-linked

Trimeric
G-protein-linked

enzyme-linked
(tyrosine kinase)



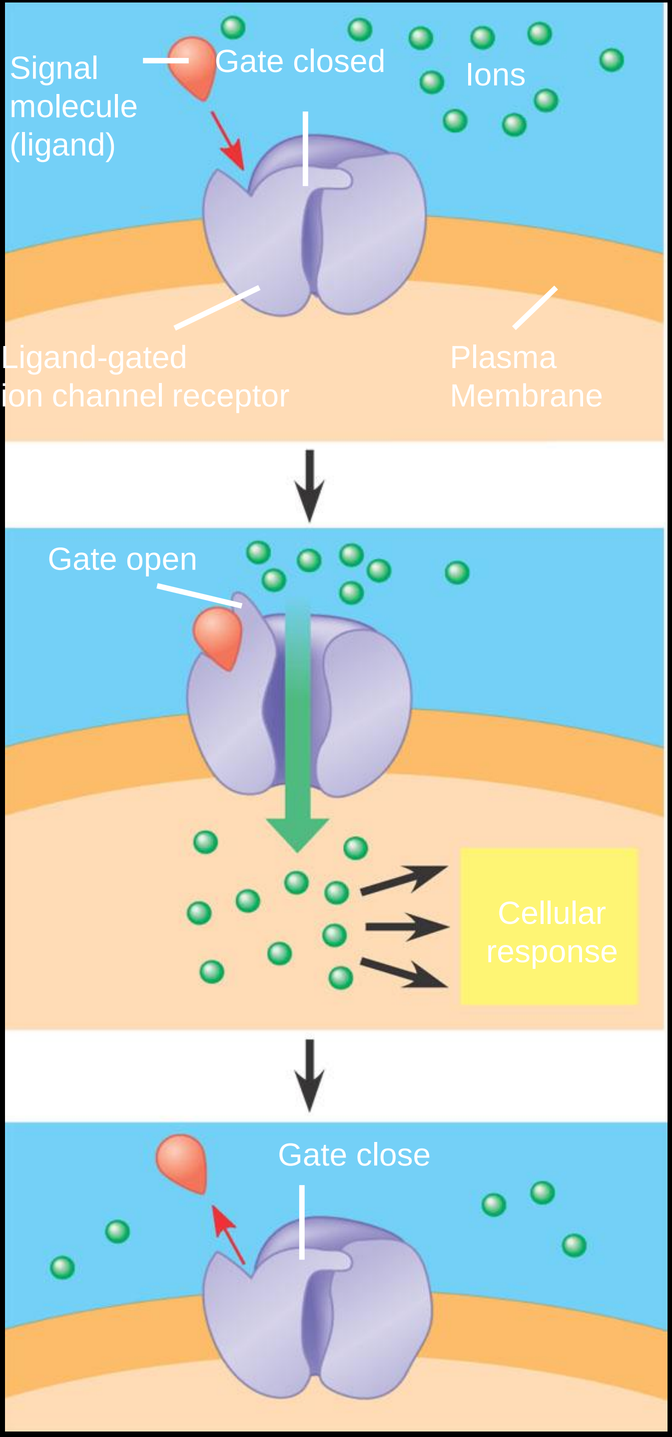
Ion channel receptors

Examples:

Muscle Contraction

Nerve Cell communication

Figure 11.7



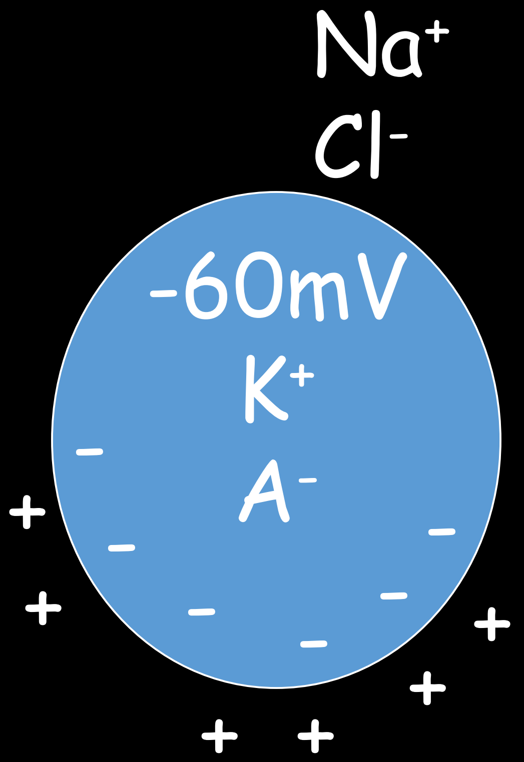
Review:

Remember the Na^+/K^+ ATPase (Na^+/K^+ pump)?

$[Na^+]$ inside ~10mM; outside ~150mM

$[K^+]$ inside ~100mM; outside ~5mM

cell has membrane potential ~ -60mV

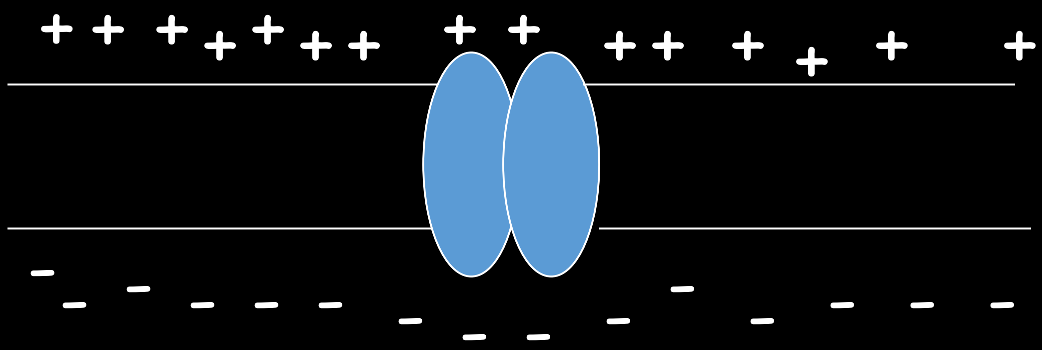


Gated ion channels

specifically let ions through membrane

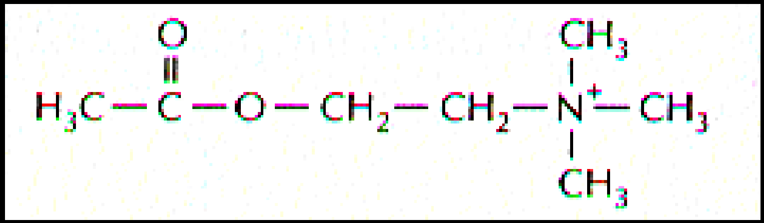
"keys": small molecules (ligand-gated)

or change in membrane potential (voltage-gated)

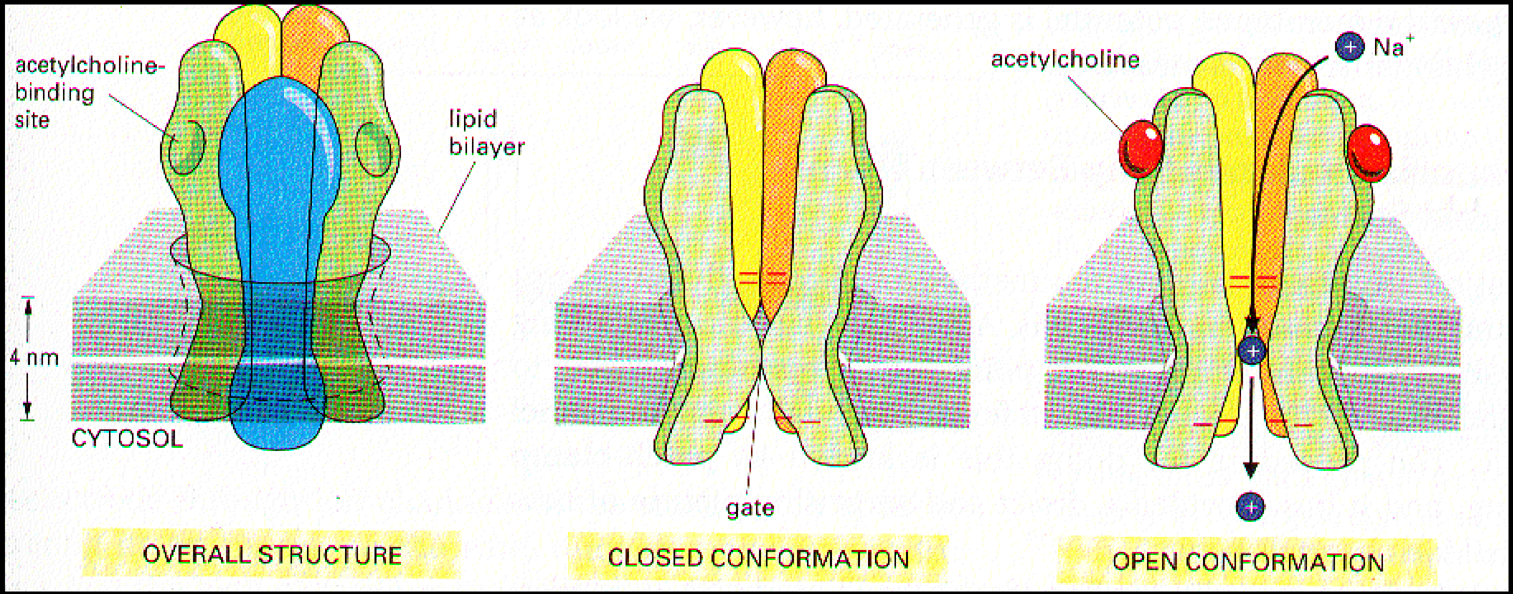


-60 mV inside

Acetylcholine:



common neurotransmitter



opens ligand-gated Na^+ channels on muscle cell and some nerve cells

Gated ion channels

specifically let ions through membrane

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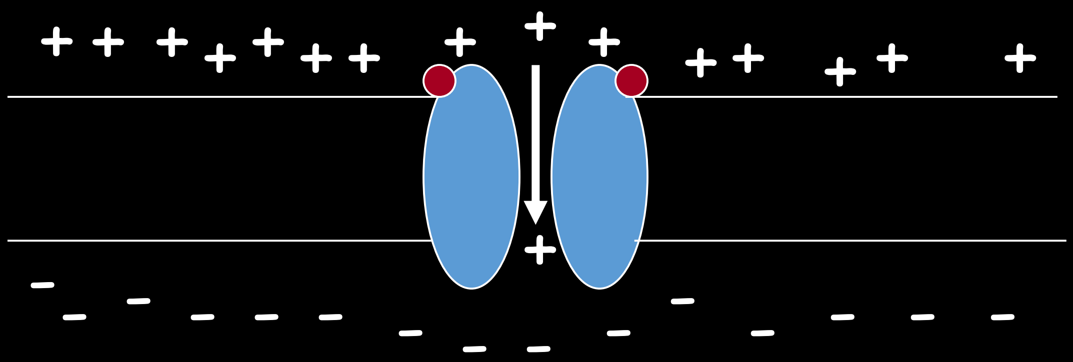

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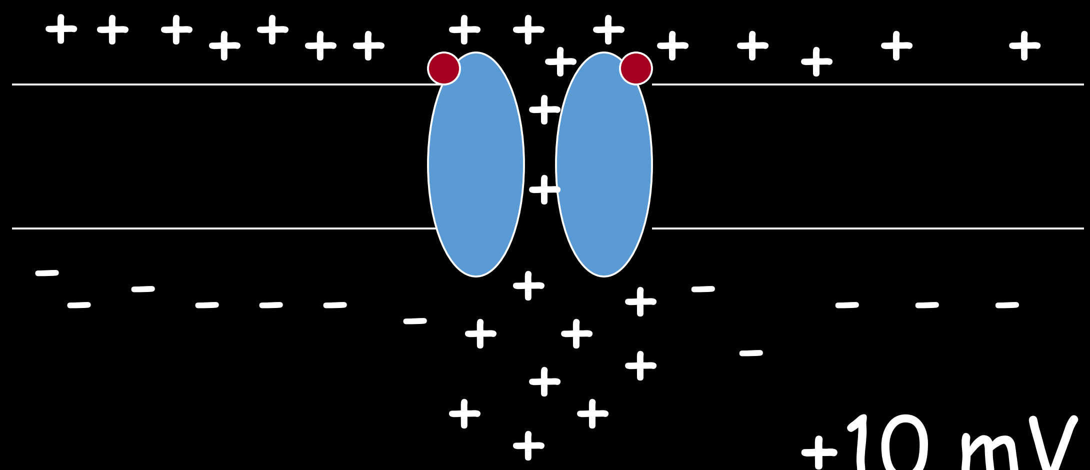


+10 mV inside

Influx of Na^+ ions causes local, transient depolarization of membrane potential

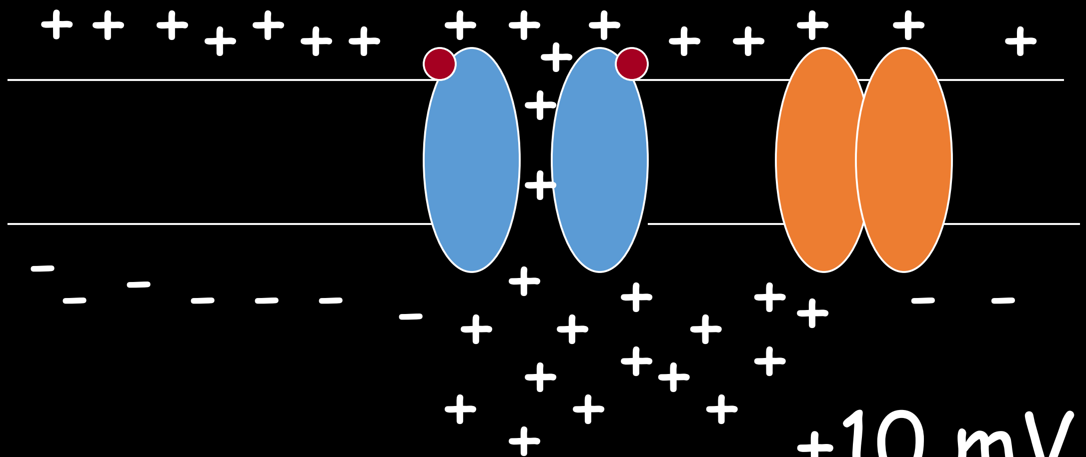
nerve impulse (action potential)

Gated ion channels

specifically let ions through membrane

"keys": small molecules (ligand-gated)

or change in membrane potential (voltage-gated)



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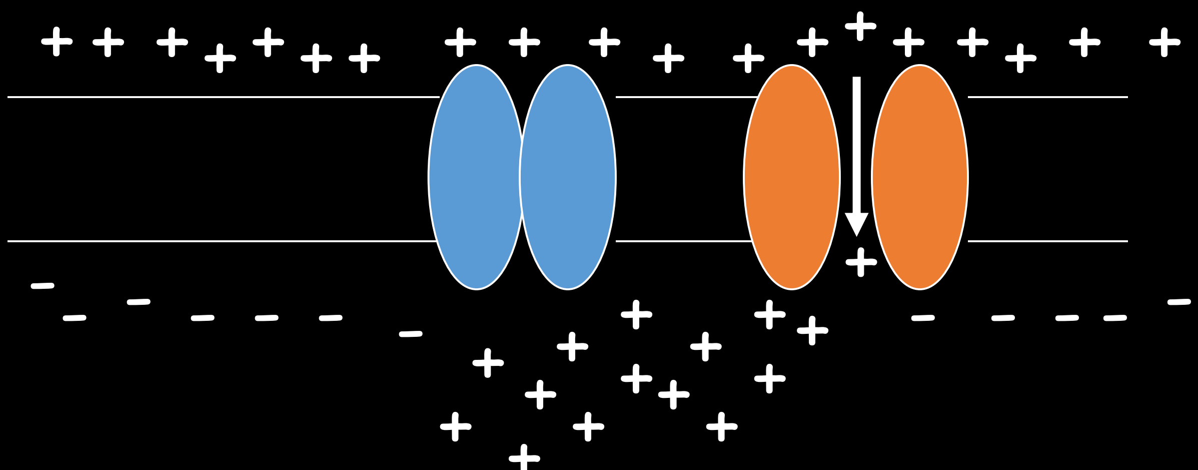

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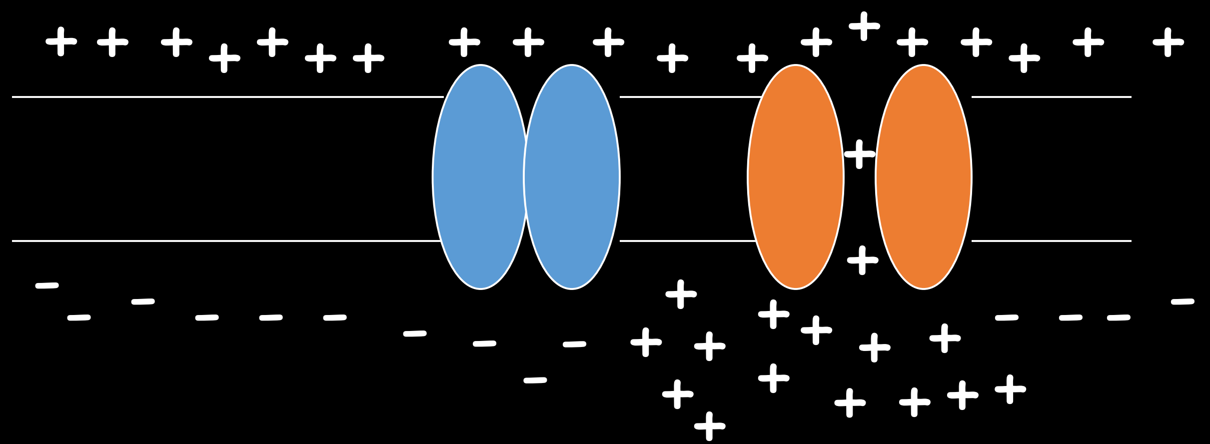


+10 mV inside

Influx of Na^+ ions causes local, transient depolarization of membrane potential

nerve impulse (action potential)

Transmission of action potential

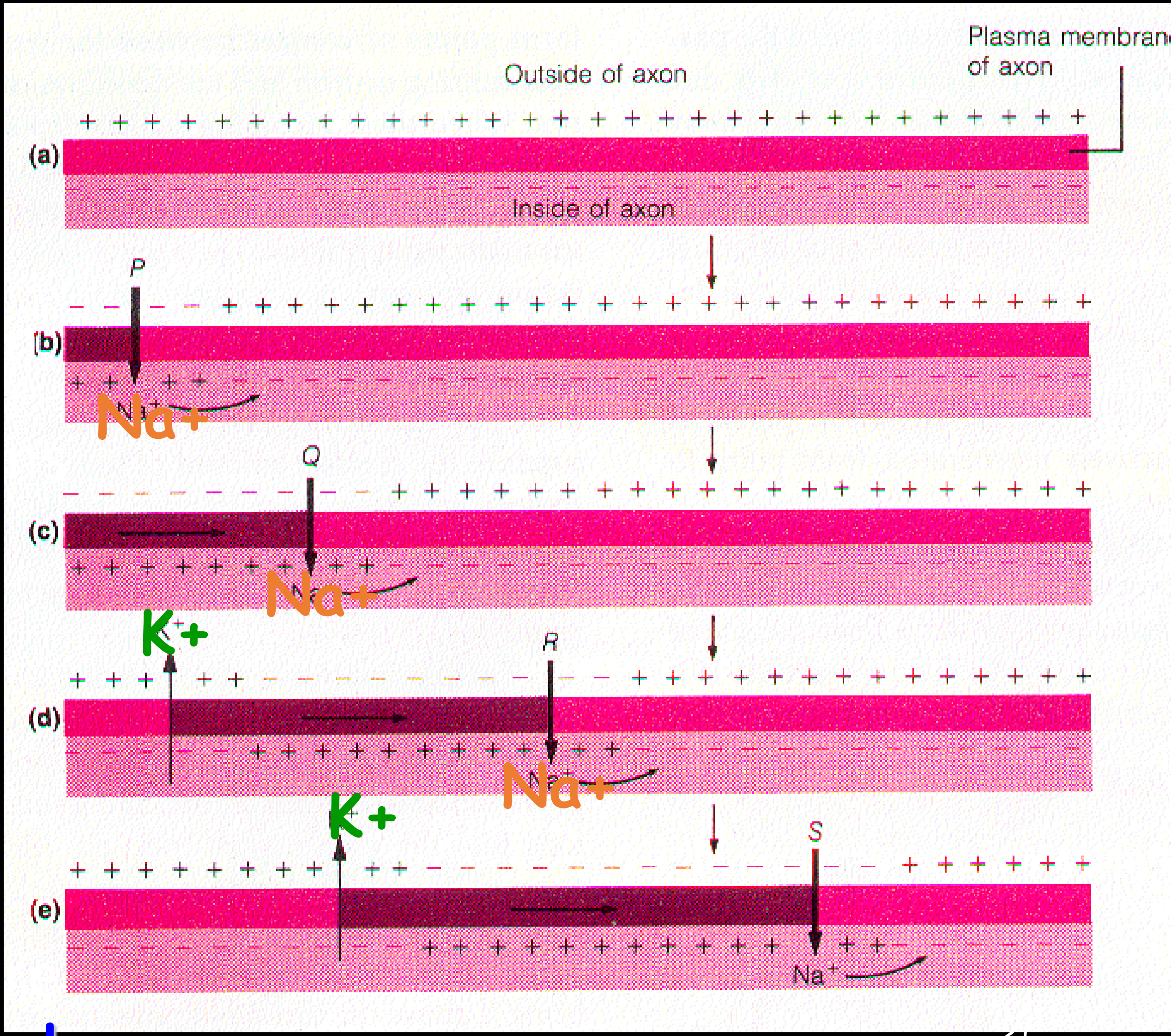
a. polarized

b. Action potential Initiated by
Ligand-gated Na^+ channels opening
Local depolarizatio

Depolarization ope
Voltage-gated Na^+ channels

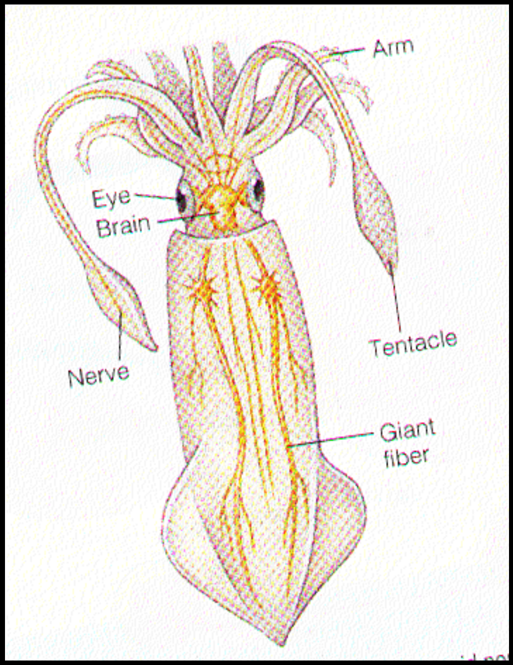
re-polarization
Na^+channels close K^+ channels open

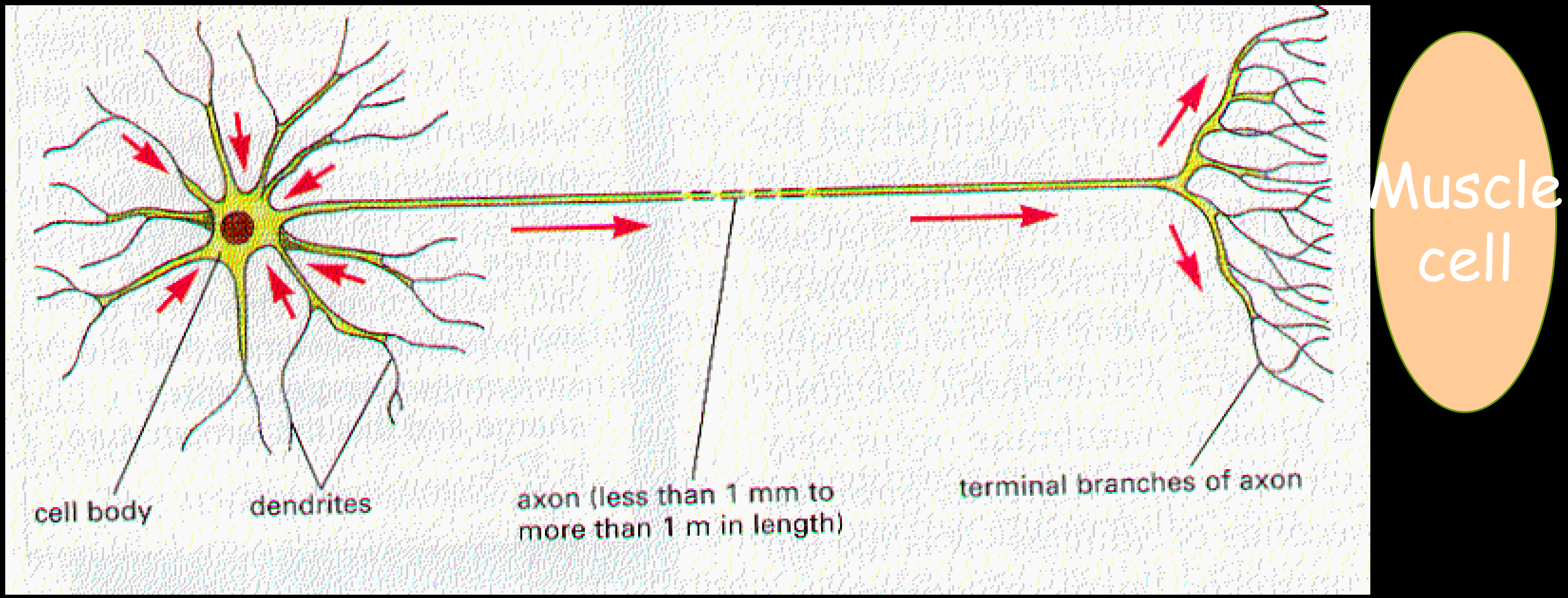
Action potential
Propagates to as mo
Voltage-gated channels open



Action potential:

nerve impulse; rapid,
self-propagating electrical signal





Signal transmitted to muscle cell across a synapse

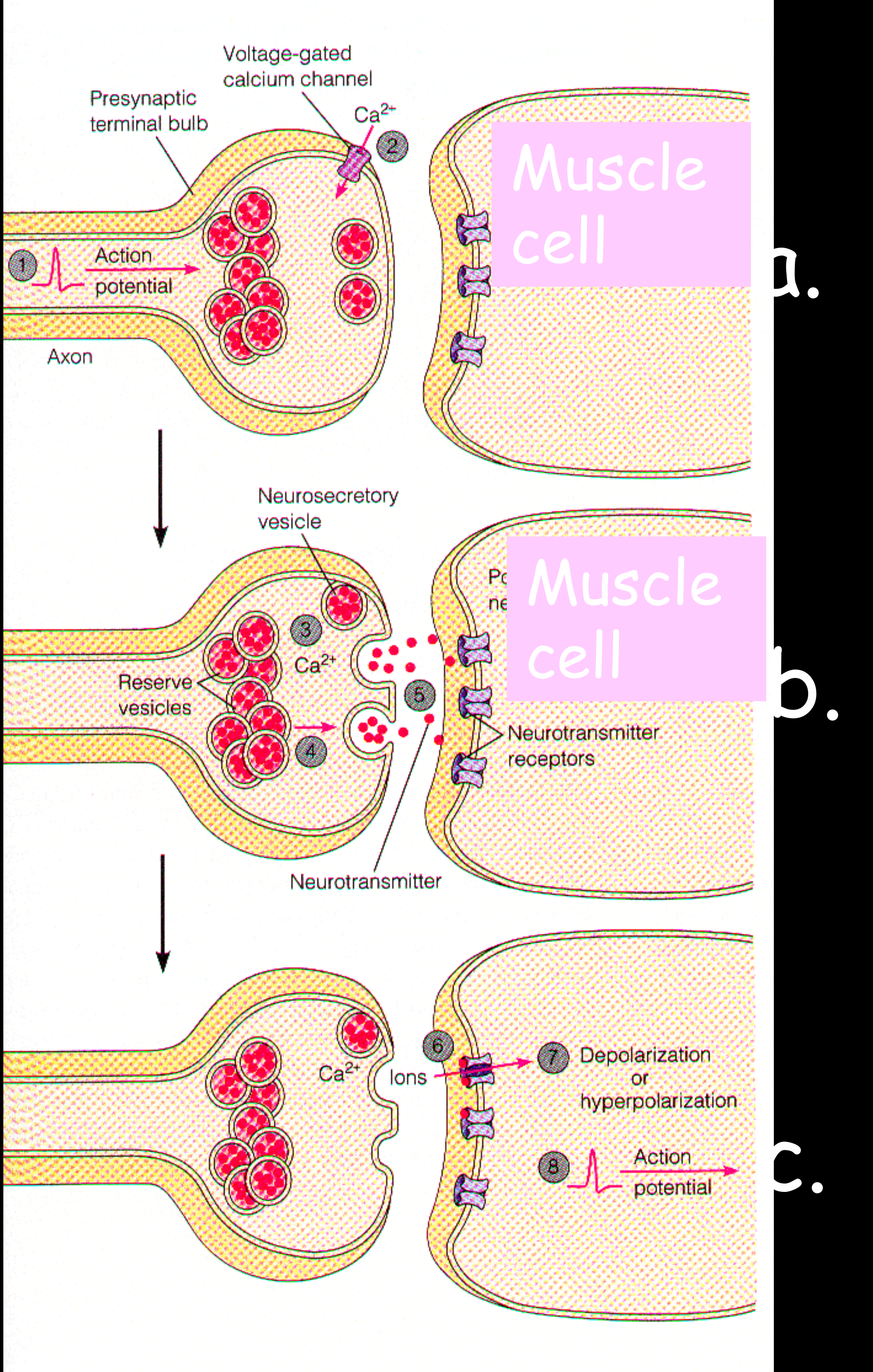
a. Depolarization opens voltage-gated Ca^{+2} channels

b. Ca^{+2} rushes in; Vesicles fuse with membrane

c. Neurotransmitter released; opens ligand-gated Na^{+} channels on muscle cell

Depolarizes muscle cell

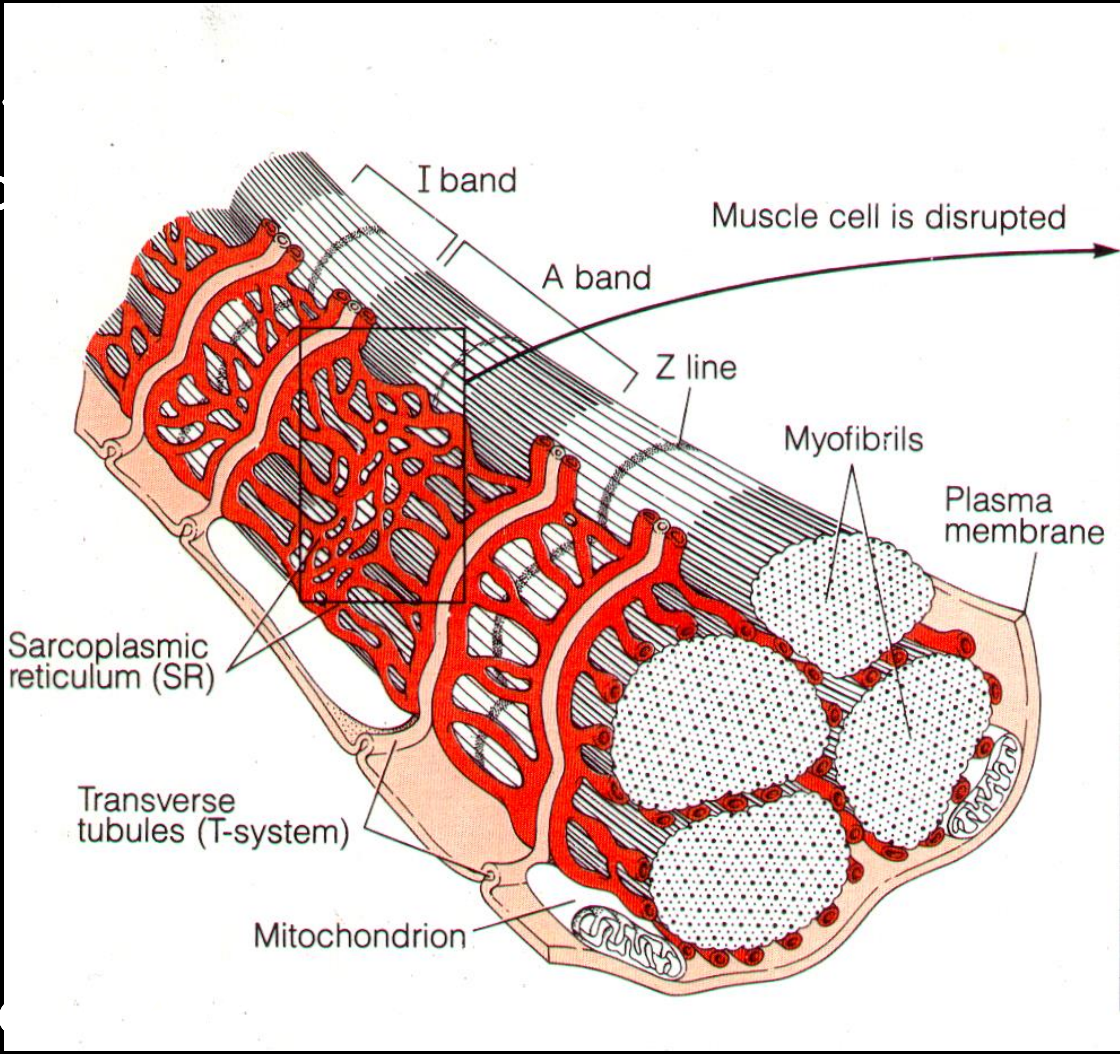
Signal: electrical to chemical to electrical



Depolarization of Muscle Cell Results in release of [Ca^{++}]:

Typically in cytosol Ca^{++} is
maintained ultra-low by ac
"pumps" Ca^{++}/ATPases "vac

Ca^{++} Stored in
<u>Smooth</u>
<u>Endoplasmic</u>
<u>reticulum</u>



Ca^{++} from SER
In Cytosol
Triggers Activation of My
To "walk along" actin filaments – causing contraction

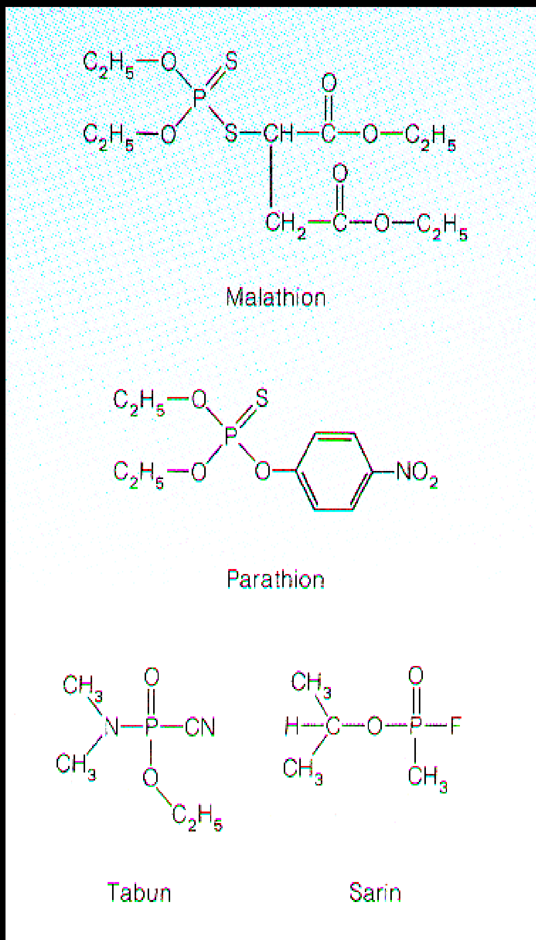
Turning off the synapse…….

Acetylcholine degraded by acetylcholinesterase or removed by re-uptake & endocytosis

a.

b.

c.



if not removed……

a,b Pesticides
c Nerve gases

Potent enzyme inhibitors

Post-synaptic membrane can't repolarize

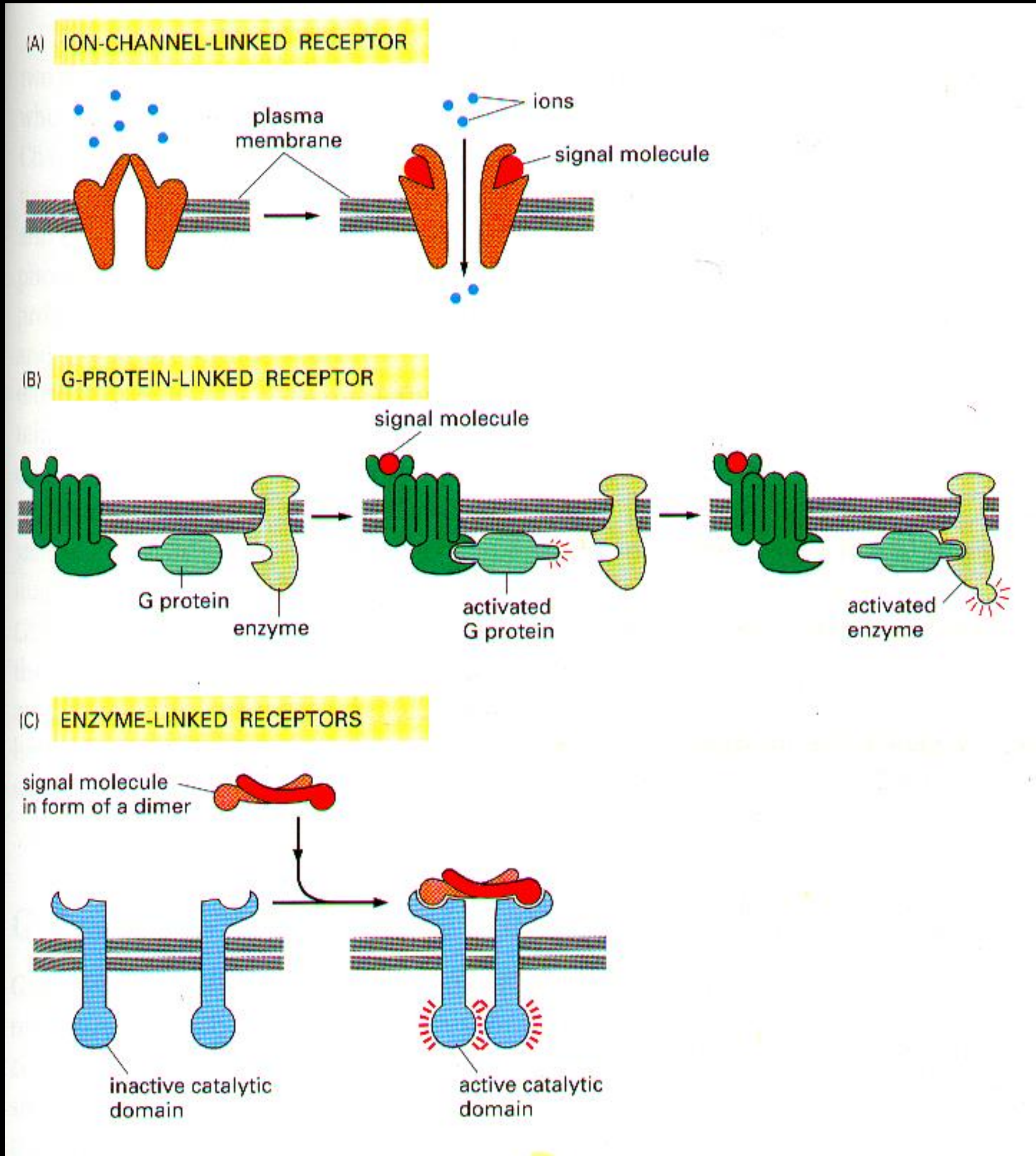
Paralysis, Tetany

Cell-surface receptors -large &/or hydrophilic ligands

ion-channel-linked

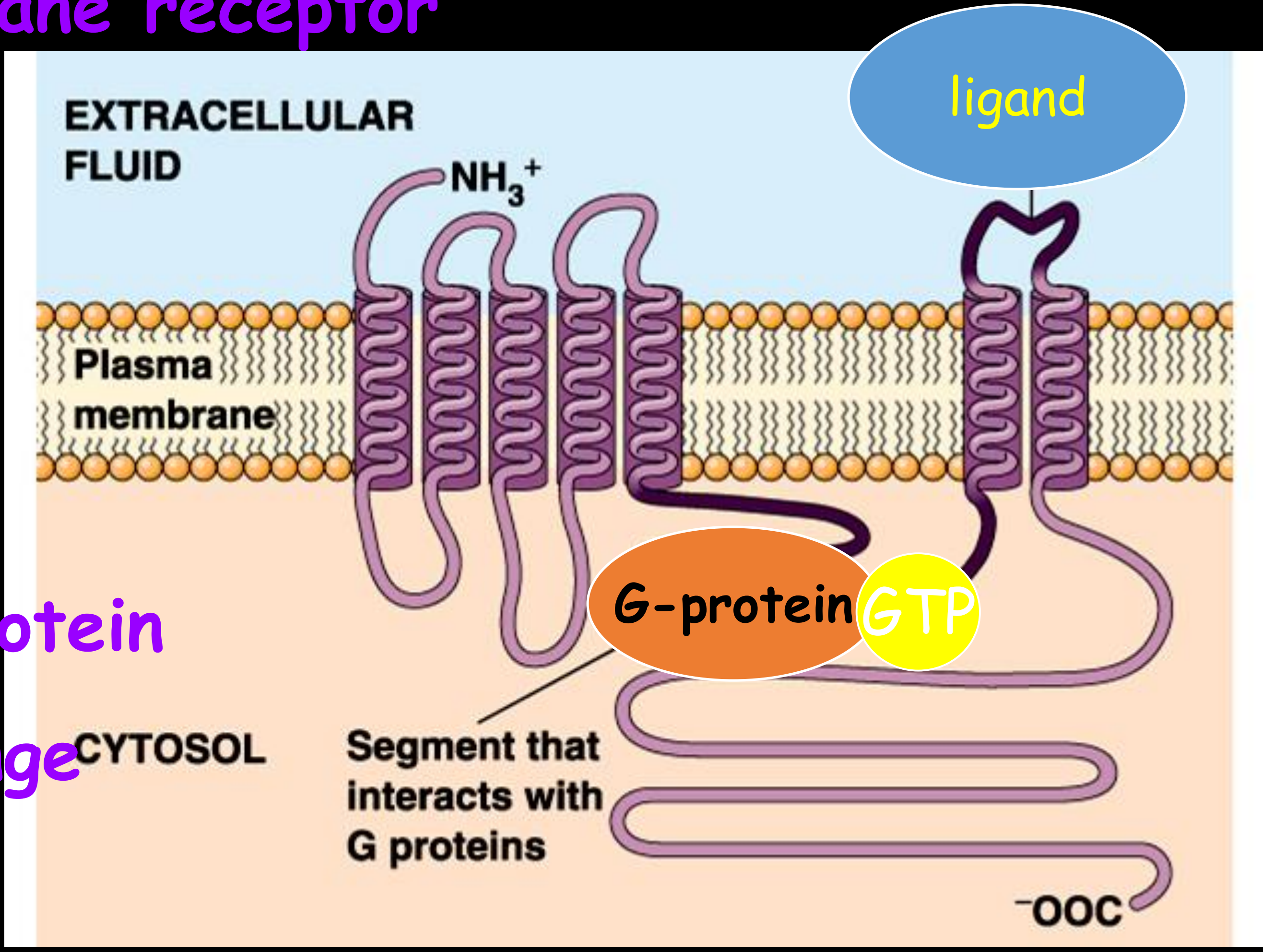
Trimeric
G-protein-linked

enzyme-linked
(tyrosine kinase)



Trimeric G protein-linked receptors:
largest family of cell-surface receptors

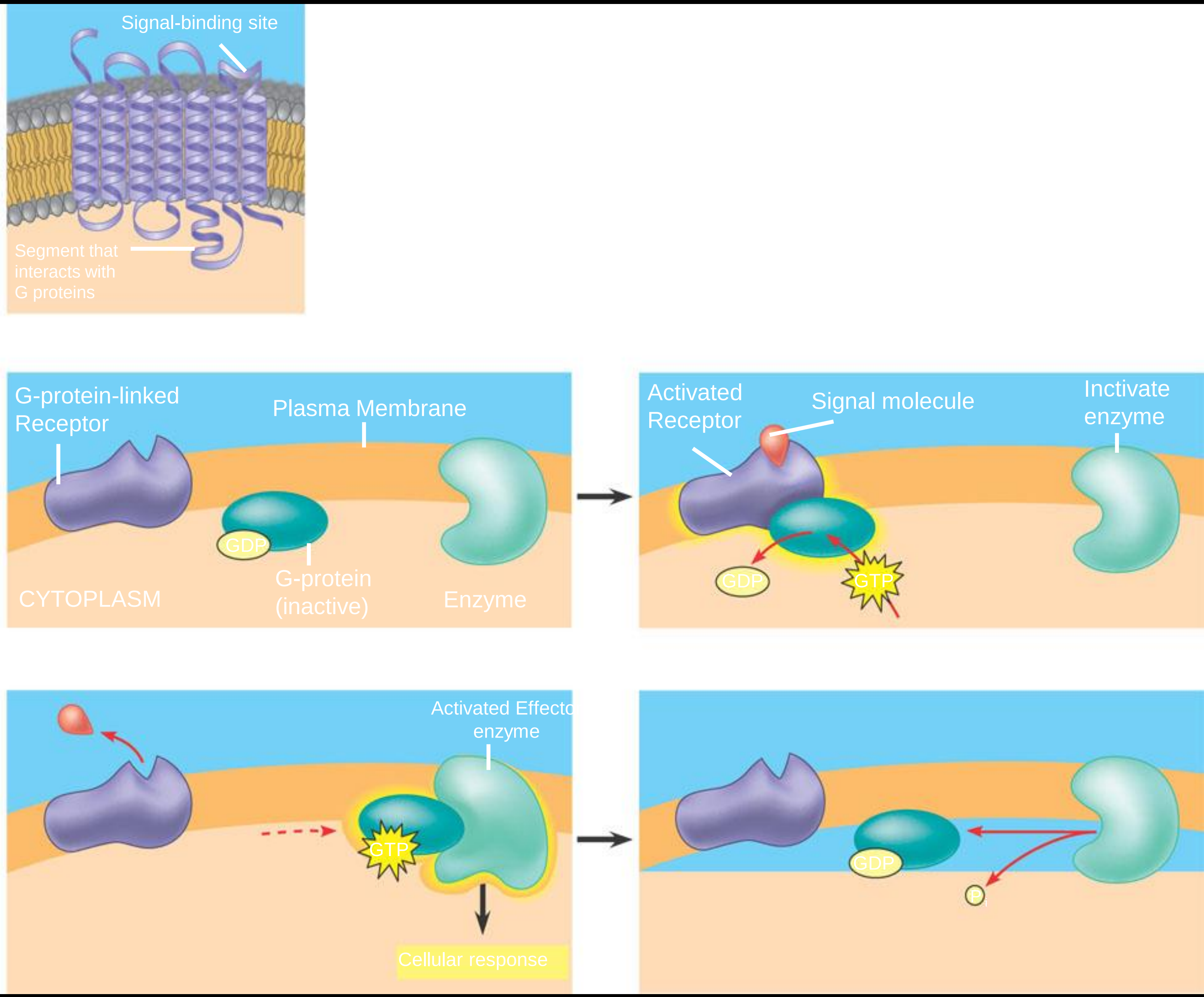
7-pass membrane receptor



Ligand binding

activates G-protein

by GTP exchange



Signal-binding site
Segment that interacts with G proteins
G-protein-linked Receptor
Plasma Membrane
GDP
G-protein (inactive)
CYTOPLASM
Enzyme
Activated Receptor
Signal molecule
Inctivate enzyme
GDP
GTP
Activated Effecto enzyme
GTP
Cellular response
GDP

Figure 11.7

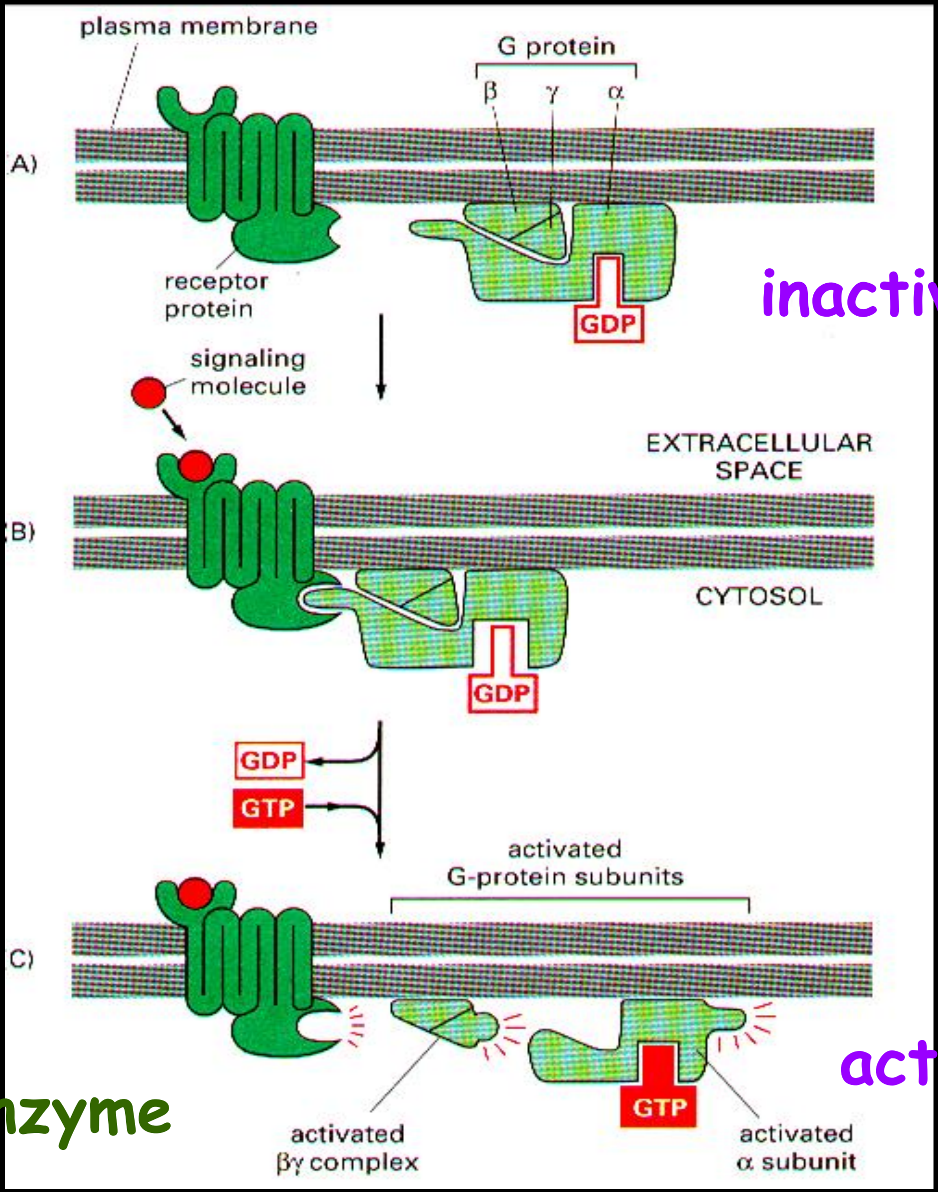
G-protein activation

"*molecular switch*"

(b) Ligand binds
G-protein associates

(c) GDP-GTP exchange
•α-Subunit dissociates

Active G-Protein-GTP
-> allosteric modulator
of target effector enzyme



inactive

active

- All G-proteins – similar structure/activation

- There are TWO broad subclasses of trimeric G-protein-activated signal transduction pathways:

depends on their target effector enzymes

A. **adenylyl cyclase**

B. **phospholipase C**

An activated G_{α}-protein-GTP

- Can trigger the formation of cAMP, which then acts as a second messenger in cellular pathways

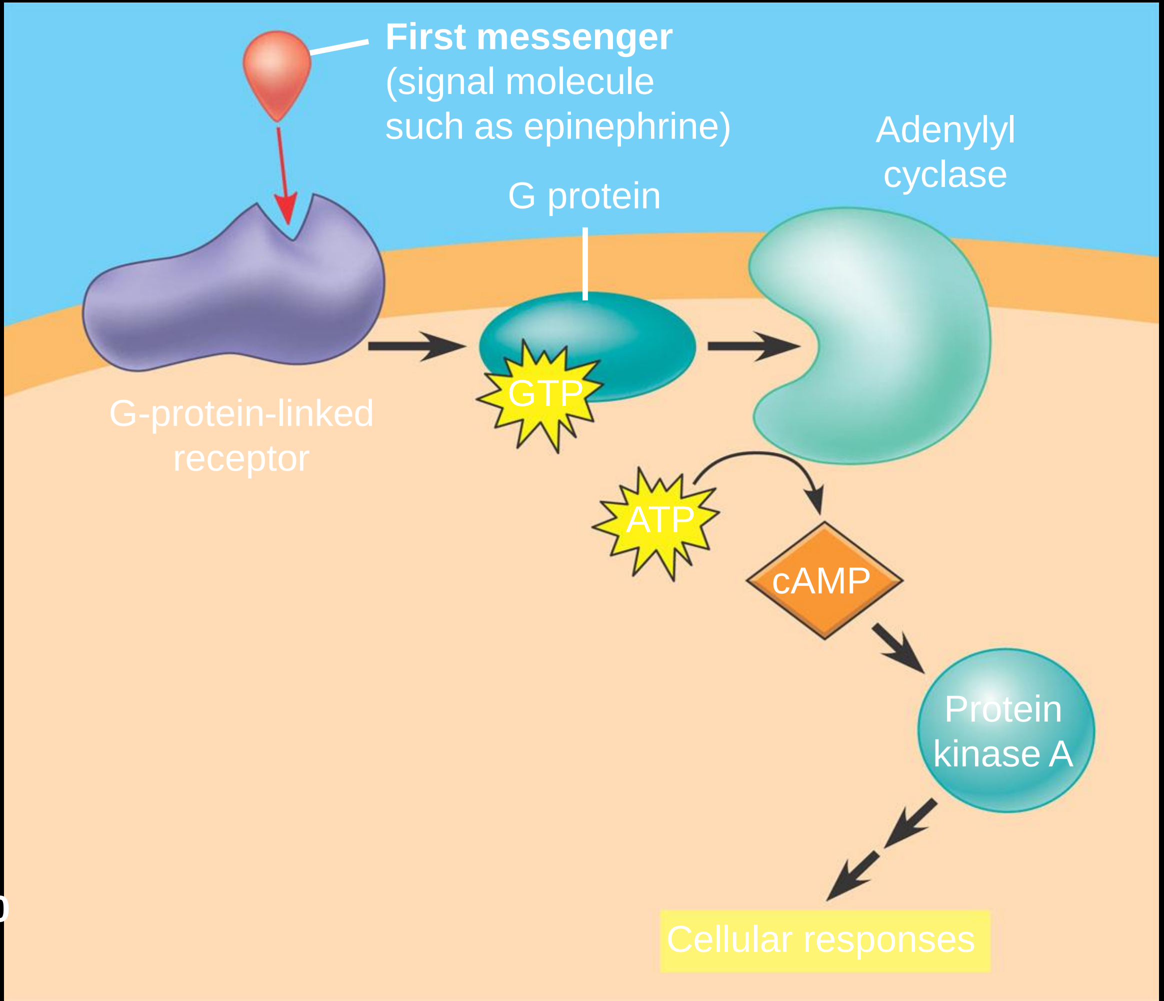
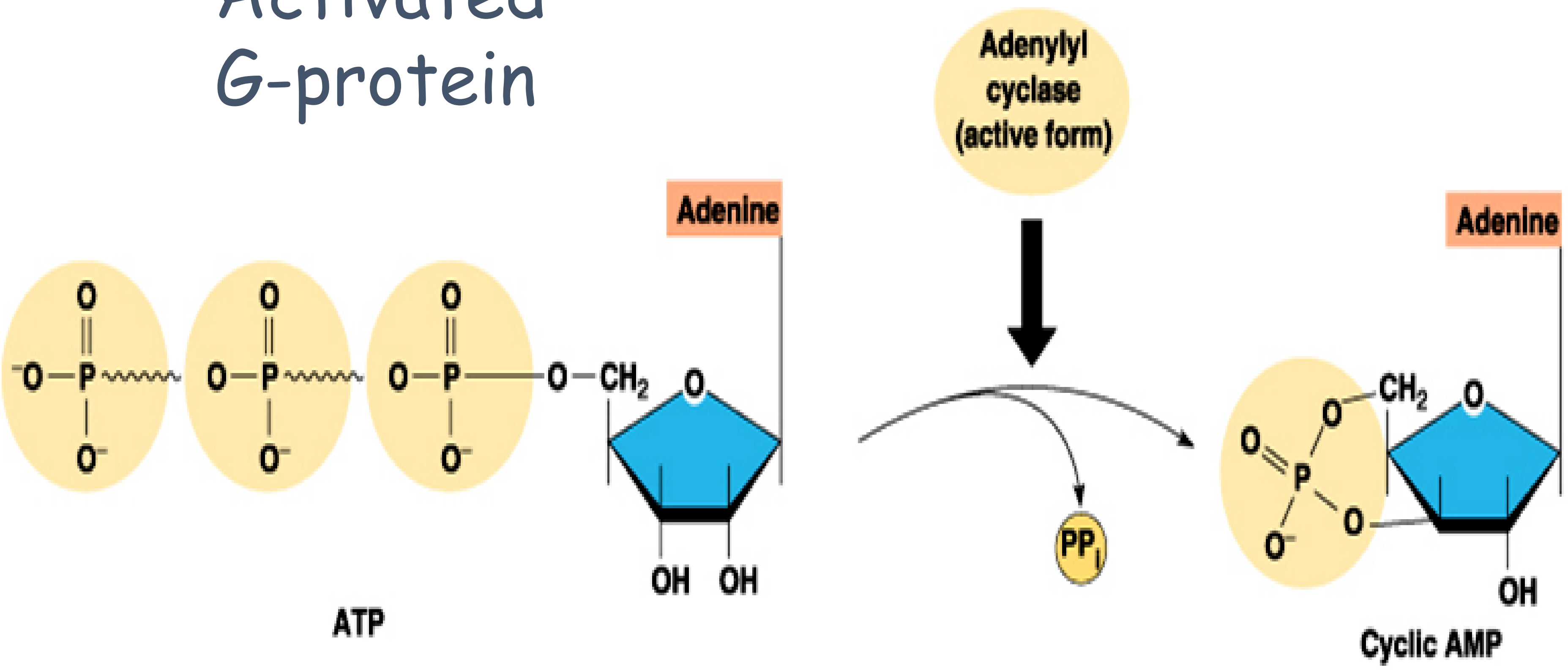


Figure 11.10

G-protein-GTP activation of

Effector Enzyme **adenylyl cyclase** produces the 2nd messenger **cAMP**

Activated G-protein



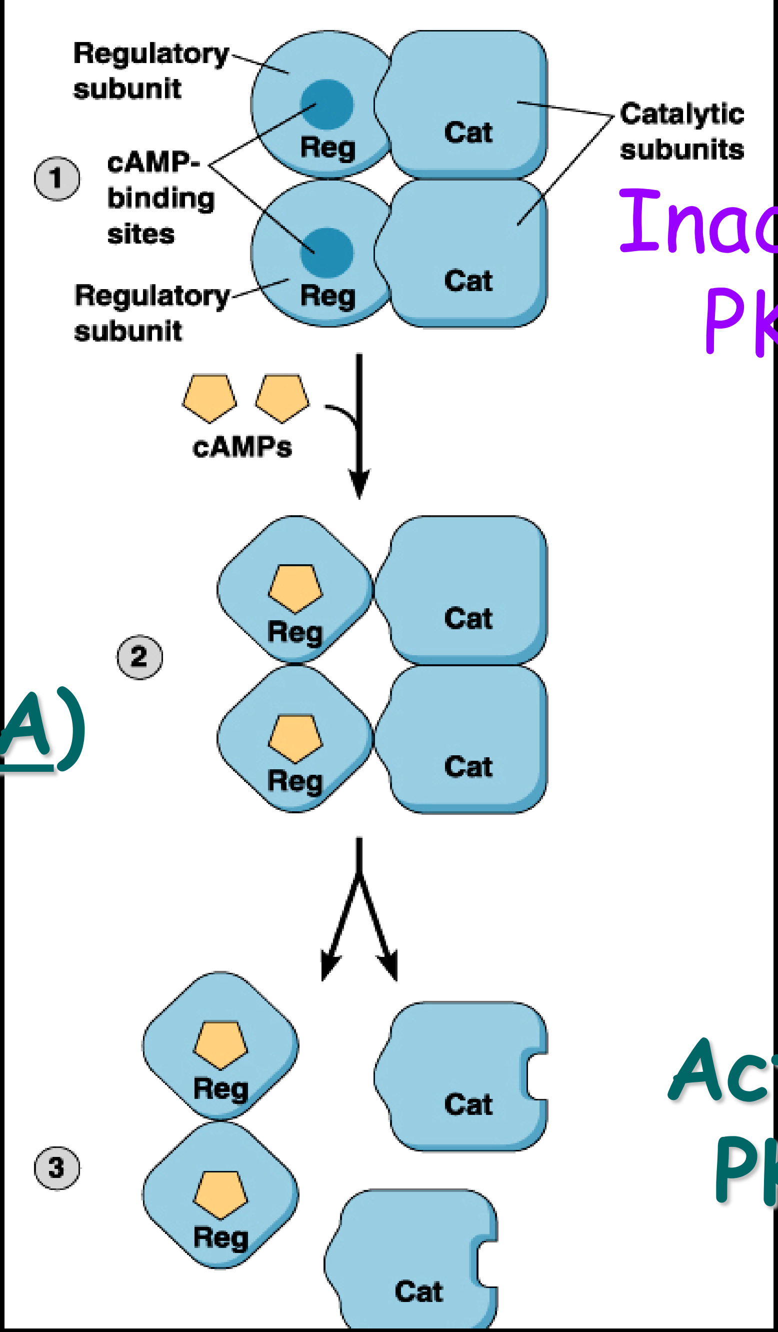
Like Fig 11-9

cAMP

activates target enzyme

Protein Kinase A (PKA)

phosphorylates target proteins



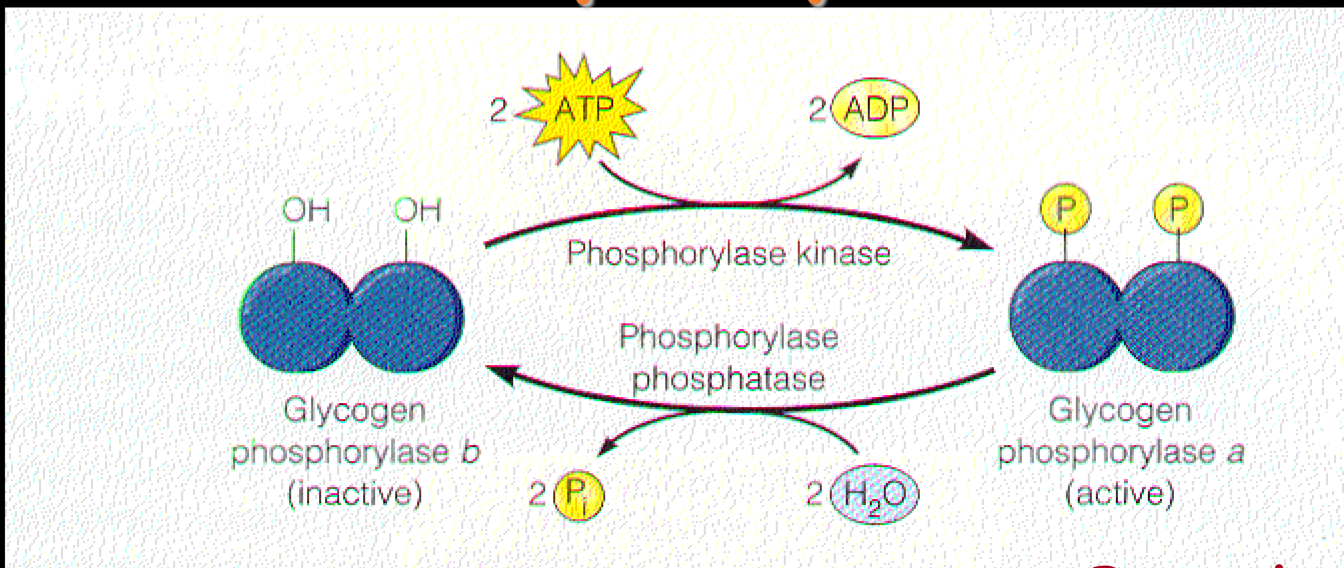
Inactive PKA

Active PKA

Protein Kinase A

Phosphorylates downstream target enzymes

Phosphorylase kinase



P

ctive

Breaks down
Starch
Into Glucose

A Signal *Cascade*

amplification

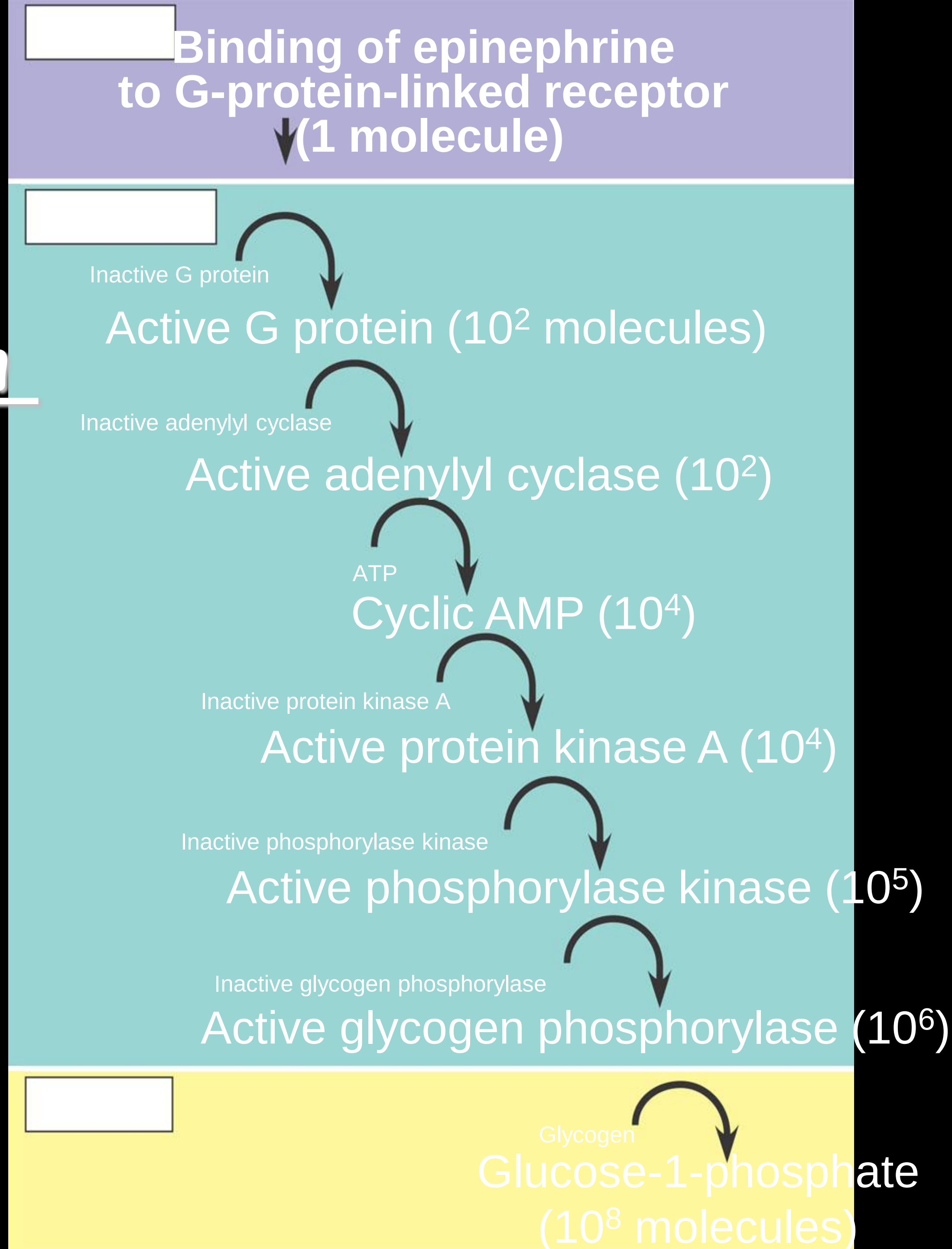


Figure 11.13

1

10^2

10^4

10^5

10^6

10^8

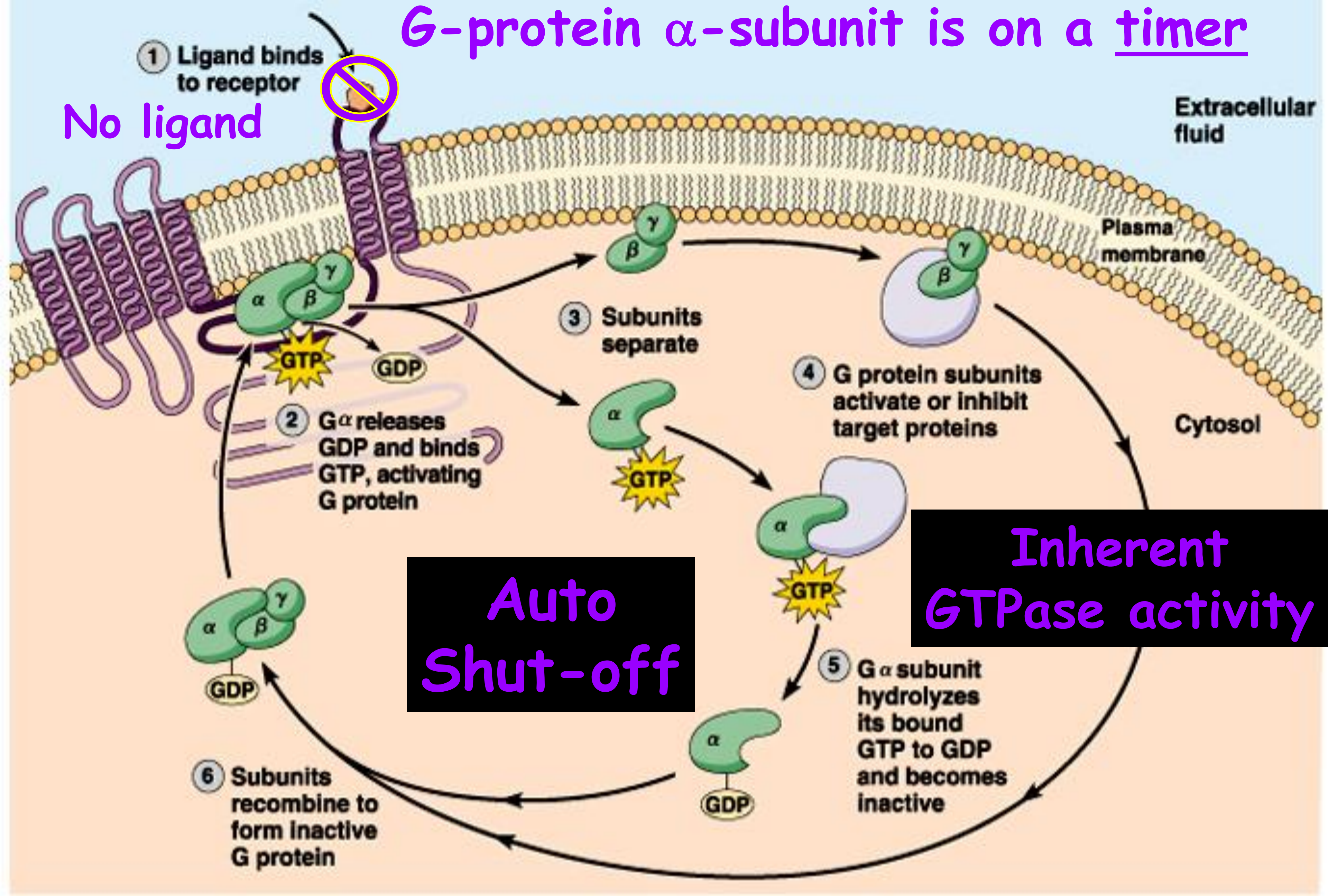
What are targets for Protein Kinase A??

cAMP regulated pathways

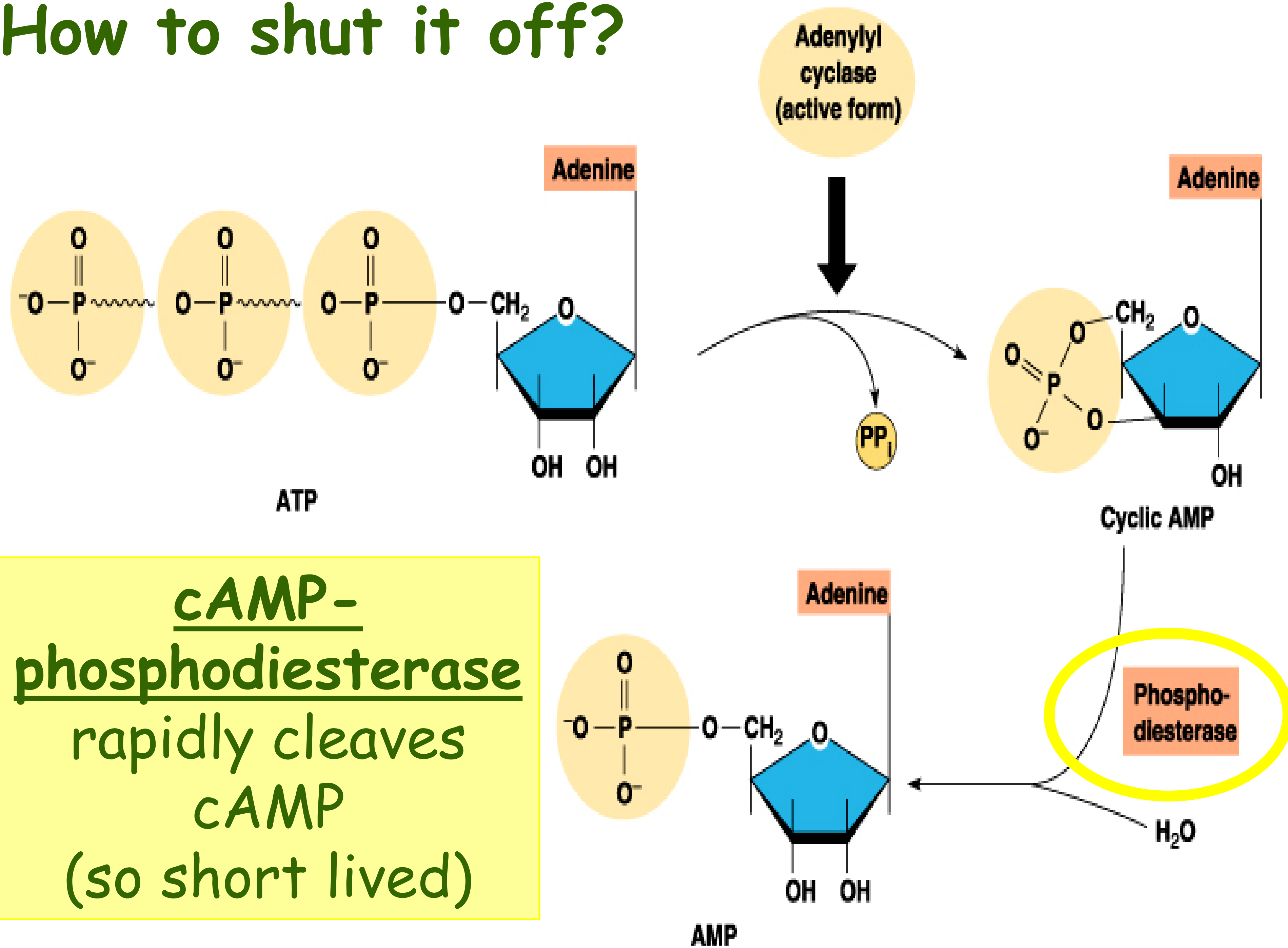
Function	target tissue	signal
Glycogen breakdown	muscle,liver	epinephrine
Heart rate	cardiovascular	epinephrine
Water reabsorption	kidney	antidiuretic hormone

How to shut it off?

G-protein α-subunit is on a timer

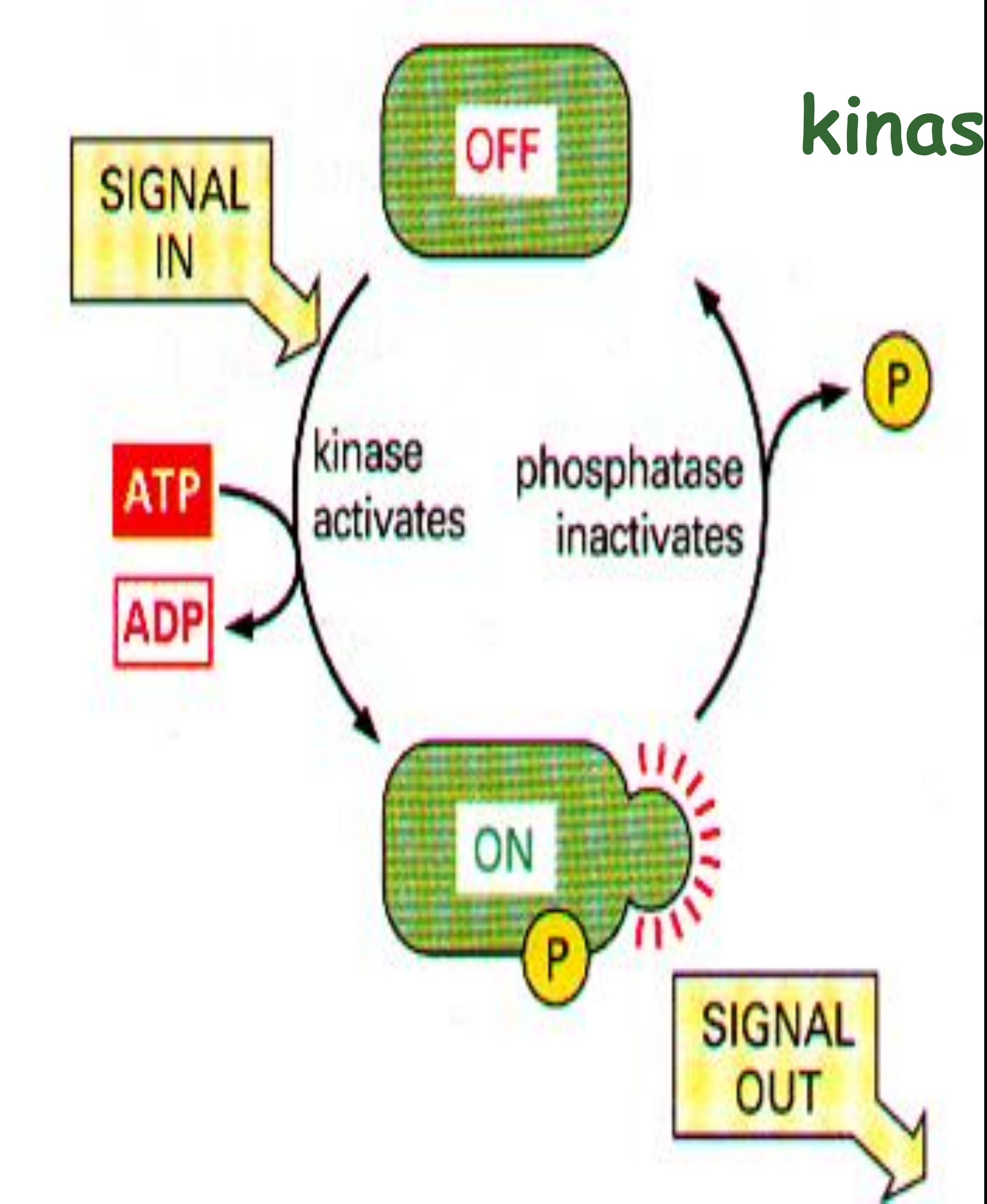


How to shut it off?



<u>cAMP-phosphodiesterase</u> rapidly cleaves cAMP (so short lived)

How do you turn it off?



kinases – phosphatases

Diametrically Opposed…

Remember: whether you <u>active</u> or <u>inactivate</u> by adding P depends on the specific protein

What if you can't turn off cascade?

Vibrio cholera - causes cholera
7 great pandemics, Ganges Valley, Bangladesh

Normal gut: H_2O, NaCl, $NaHCO_3$ secretion controlled by hormones via Gs/cAMP signal pathways

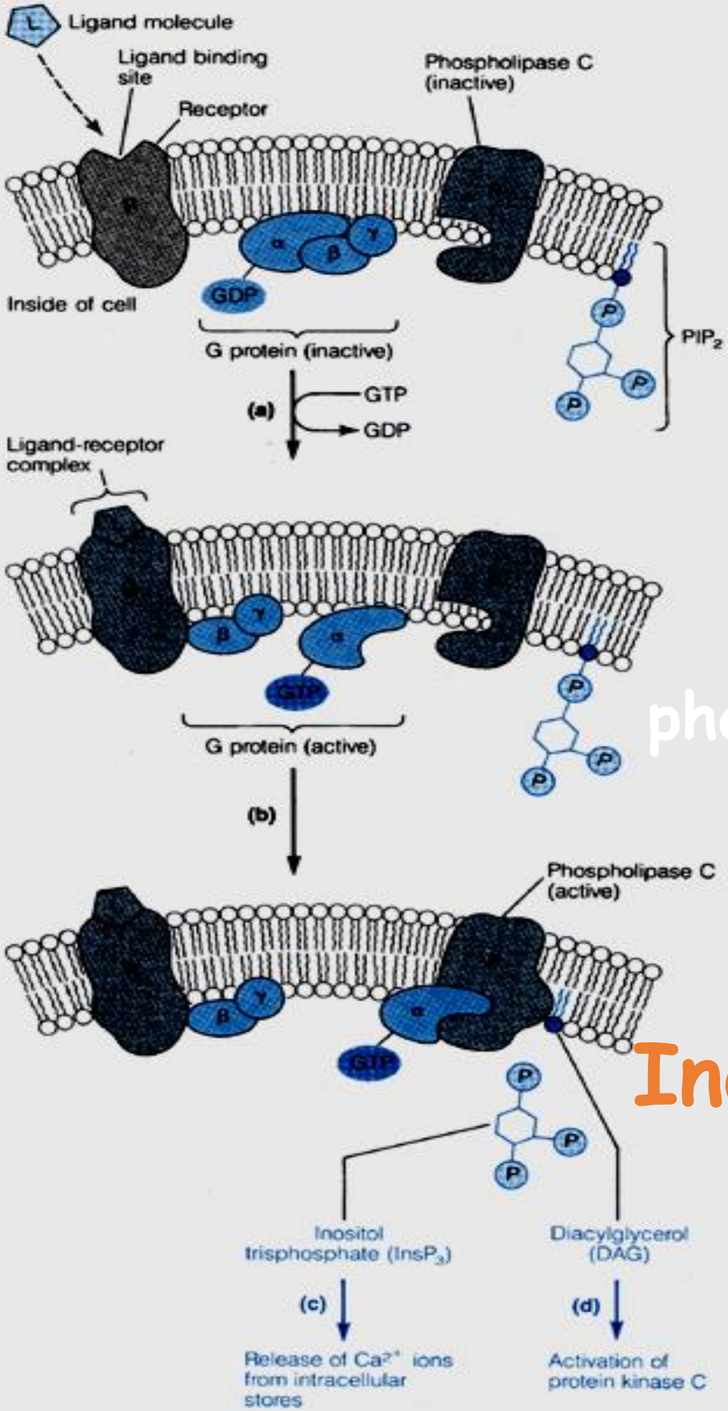
V. cholera – secretes enterotoxin, chemically modifies αGs – no GTPase activity - stays ON

Severe watery diarrhea - dehydration, death

TWO subclasses of trimeric G-protein-activated signal transduction pathways:

A. target protein adenylate cyclase
    cAMP-> PKA

B. target protein <u>phospholipase C</u>



target effector enzyme is **Phospholipase C**

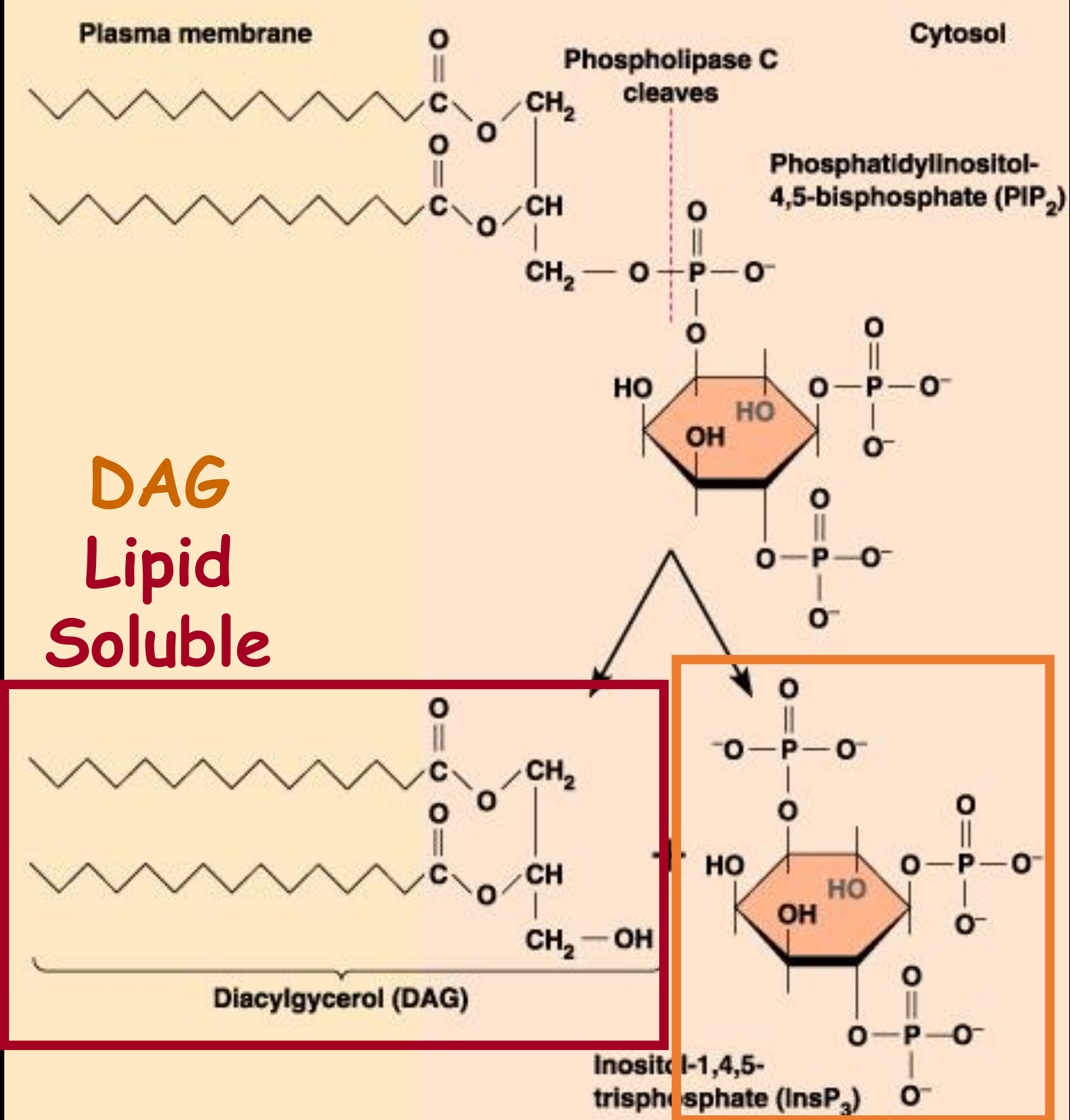
↓

PLC cleaves a membrane phospholipid (Phoshatidyl inositol) to

<u>two</u> 2nd Messengers:

Inositol-1,4,5-Trisphosphate (InsP3) &

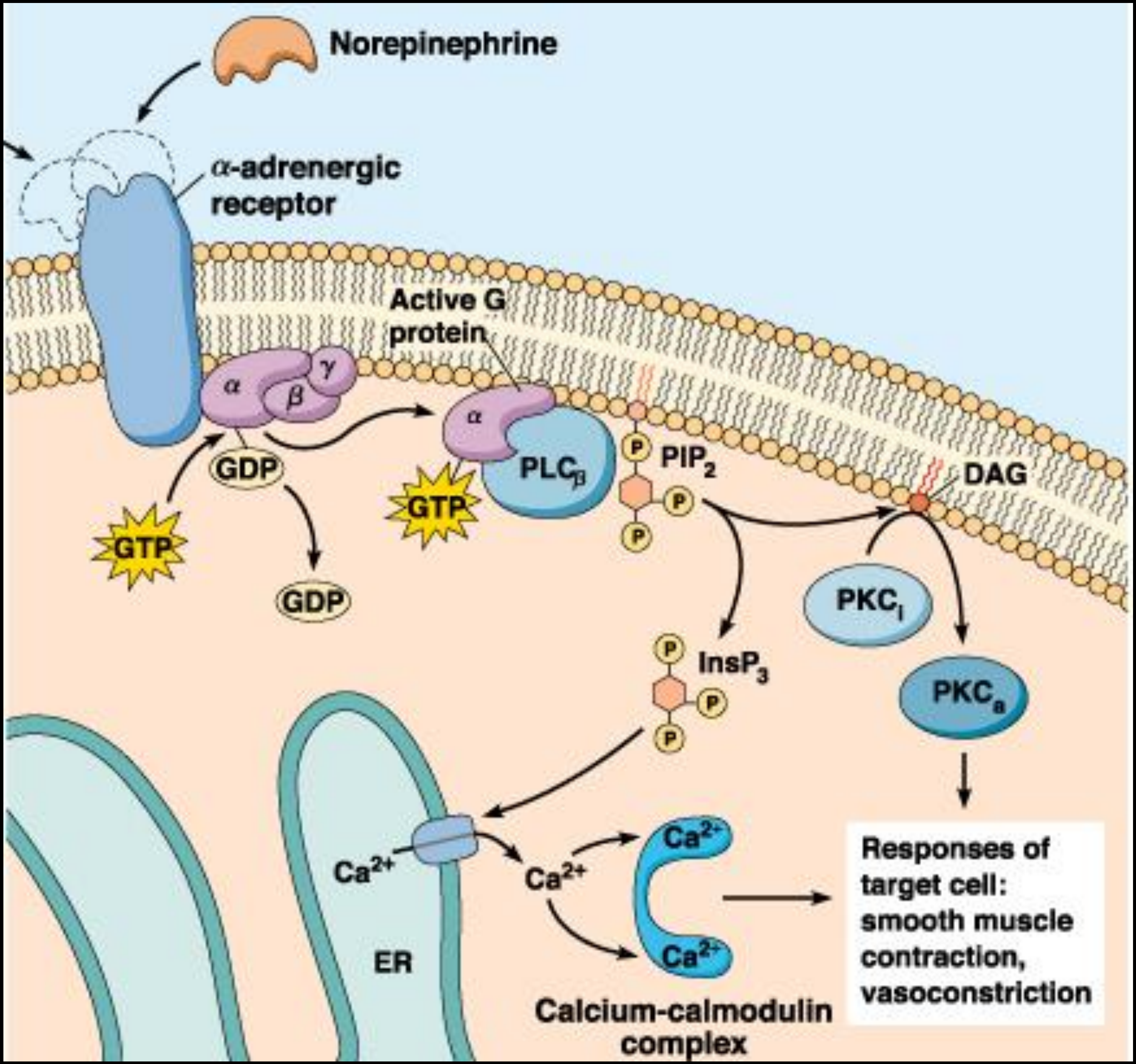
Diacylglycerol (DAG)



PIP$_2$

DAG
Lipid
Soluble

InsP$_3$
Water
Soluble



DAG
Activates
Protein Kinase C
(Starts Cascade)

$InsP_3$
Ligand for ER
ligand-gated Ca^{++} channels

↑ Ca^{++} levels

Response:

Protein Kinase C phosphorylates target proteins (ser & thr)

- cell growth
- regulation of ion channels
- cytoskeleton
- increases cell pH
- Protein secretion

Ca++

Binds & activates calmodulin

Calmodulin-binding proteins activated (kinases & phosphatases)

1 A signal molecule binds to a receptor, leading to activation of phospholipase C.

2 Phospholipase C cleaves a plasma membrane phospholipid called PIP_2 into DAG and IP_3.

3 DAG functions as a second messenger in other pathways.

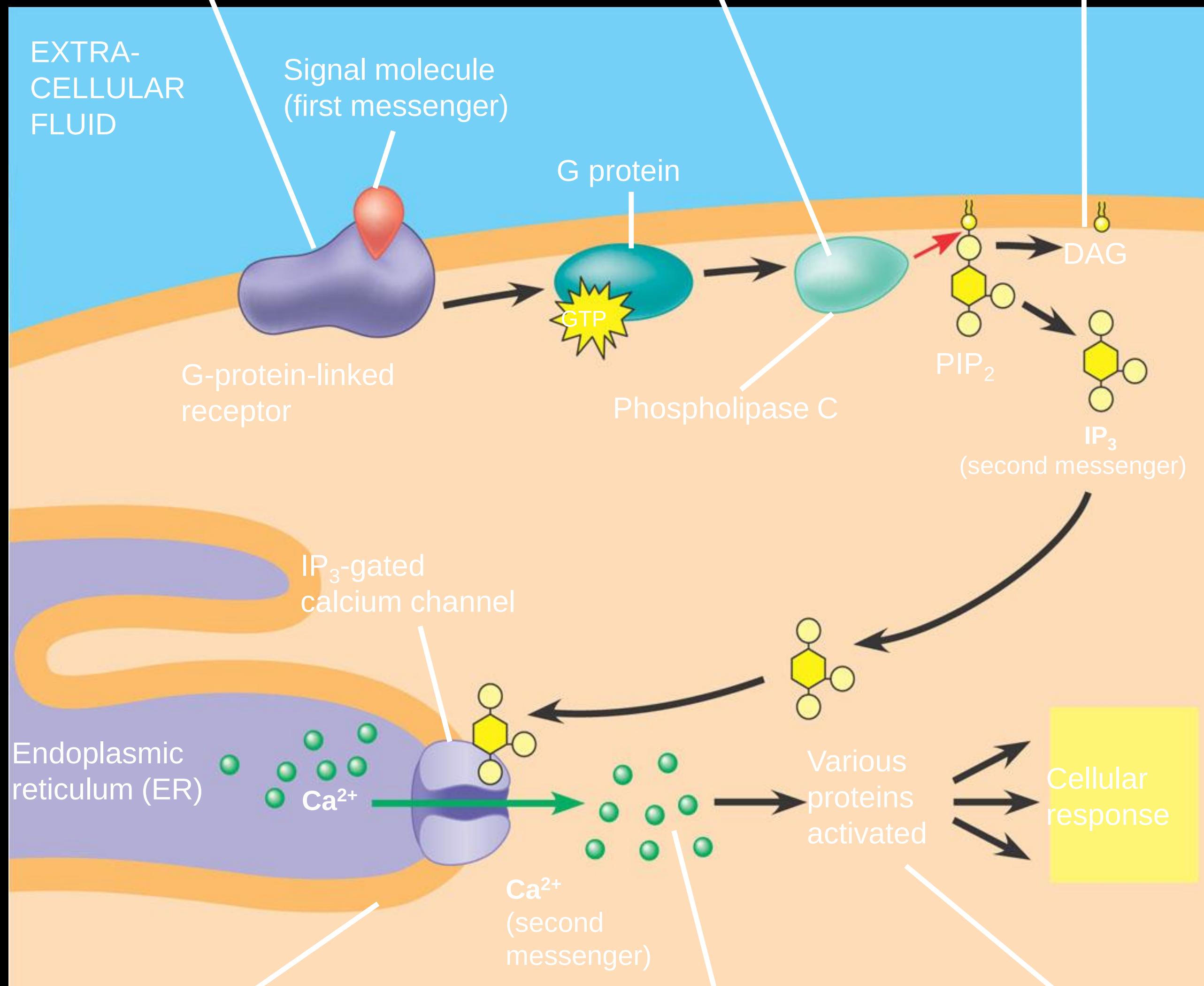


Figure 11.12

4 IP_3 quickly diffuses through the cytosol and binds to an IP_3–gated calcium channel in the ER membrane, causing it to open.

5 Calcium ions flow out of the ER (down their concentration gradient), raising the Ca^{2+} level in the cytosol.

6 The calcium ions activate the next protein in one or more signaling pathways.

Summary

- signaling is endocrine, paracrine, synaptic, or direct cell contact
- signal transduction is mediated by *receptor proteins*
- Receptors bind primary signal (ligand)
- Some amplification event occurs
- Example: ligand gated ion channel opens
  influx of ions triggers change in activity
  (vesicle fusion in nerve end, contraction in muscle)
- Example: ligand binds to 7-pass membrane receptor
  catalyzes GTP exchange
  to G_a-subunit of trimeric G-protein
  active G_a-subunit-GTP is allosteric activator of
  effector enzymes:
    - ADENYLATE CYCLASE: makes cyclic AMP
    - PHOSPHOLIPASE C: makes DAG and IP_3
  these second messengers activate target enzymes
  Trigger *cascades*
- Must shut off cascade: removal of ligand, hydrolysis of GTP, phosphodiesterase, protein phosphatases, Ca^{++} ion pumps