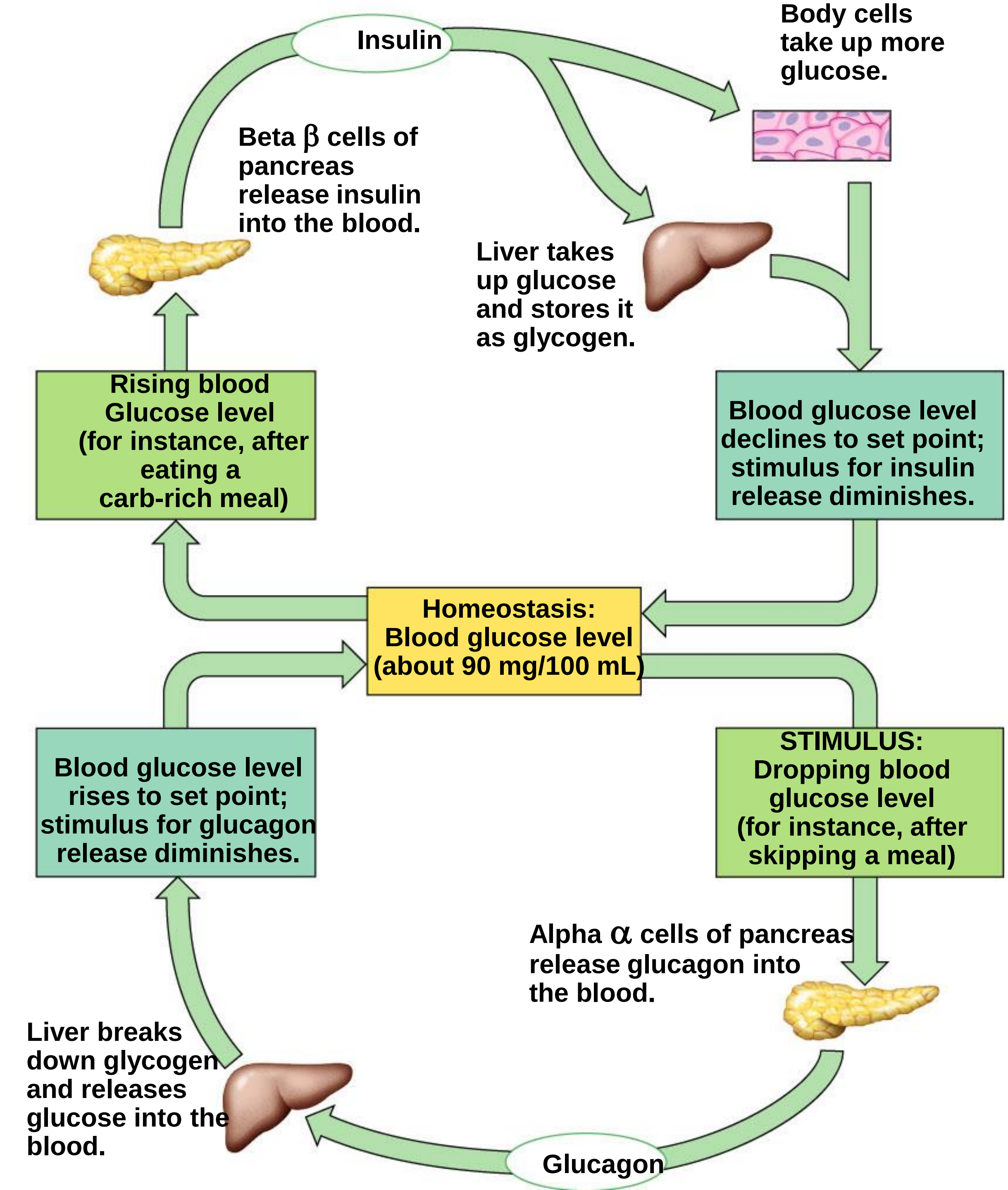
Cell Communication

Chapter 11



Blood leaving the intestine goes through the liver before reaching the heart and the rest of the body, so large amounts of sugar are pulled in quickly.

Muscle cells also store the glucose as glycogen.

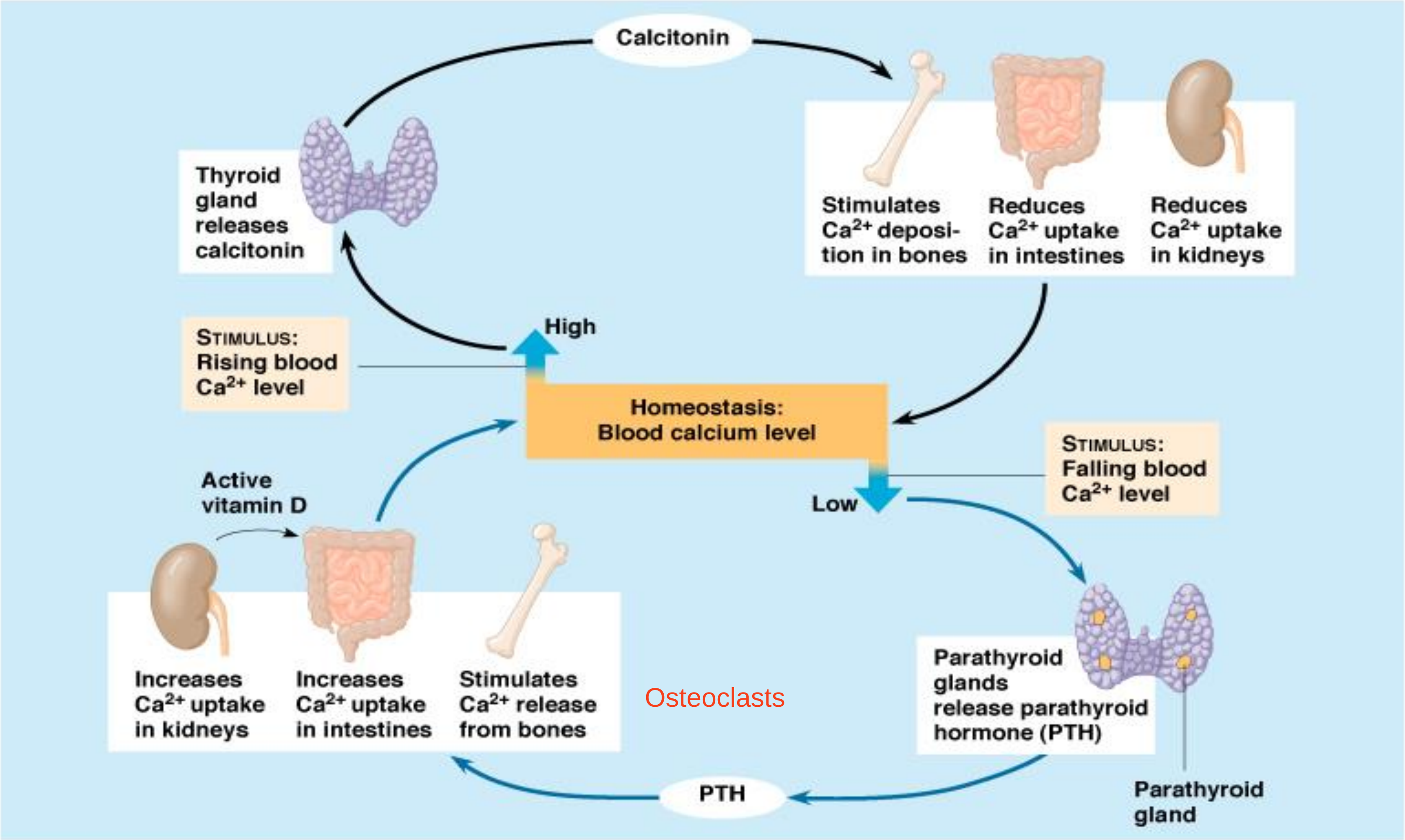
Adipose cells convert it into fat.

The only cells that do not respond are neurons. Cells in the brain take up glucose when they need it, they do not wait for a signal.

Islets of Langerhans in the pancreas has α & β cells

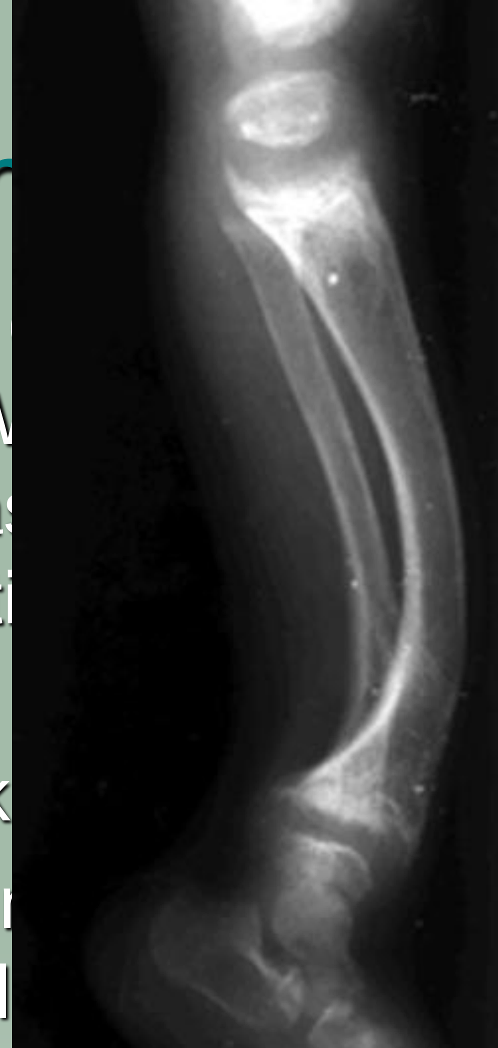
Diabetes mellitus

Calcium Homeostasis



Physical exam results

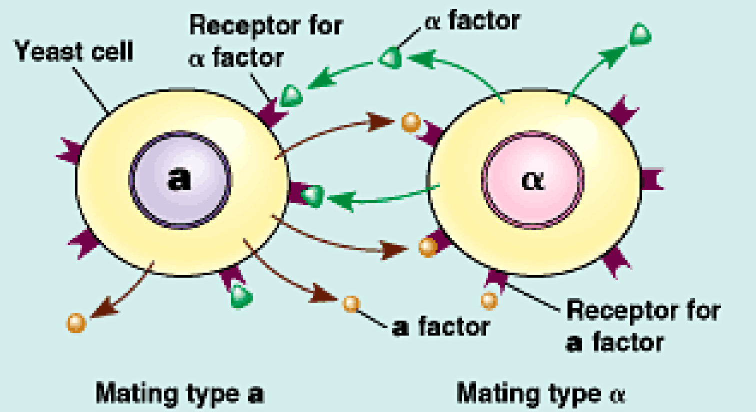
- A 50 year old patient has a routine blood screening and the results show abnormally high blood Ca^{2+} levels. (hypercalcaemia)
- What would you suspect the problem to be, and what would you look for next?
- If left untreated this person could wind up with a serious loss of bone density. Surgery can remove the problem.



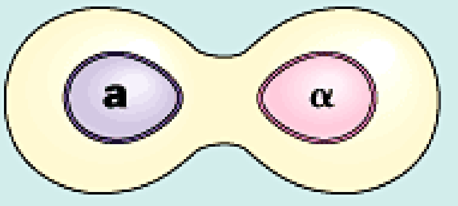
re not playing in the sunlight, they were working in factories from sunrise to sunset. Why don’t we have Rickets in the US today?

1. Cell signaling evolved early in the history of life

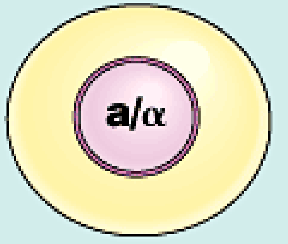
- One topic of cell "conversation" is sex.
- The yeast *Saccharomyces cerevisiae*, the yeast of bread, wine, and beer, identifies its mates by chemical signaling.
- What is the point of sex if both partners have the same genes?



Exchange of mating factors. Each cell secretes its mating factor, which binds to the other cell.



Mating. Binding of the factors to receptors induces changes in the cells that lead to their fusion.



New a/α cell. This cell combines in its nucleus all the genes from the a and α cells.

- Cell signaling has remained important in the microbial world.
  - *Myxobacteria*, soil-dwelling bacteria, use chemical signals to communicate nutrient availability.
  - When food is scarce, cells secrete a signal to other cells leading them to aggregate and form thick-walled spores.

Fig. 11.2

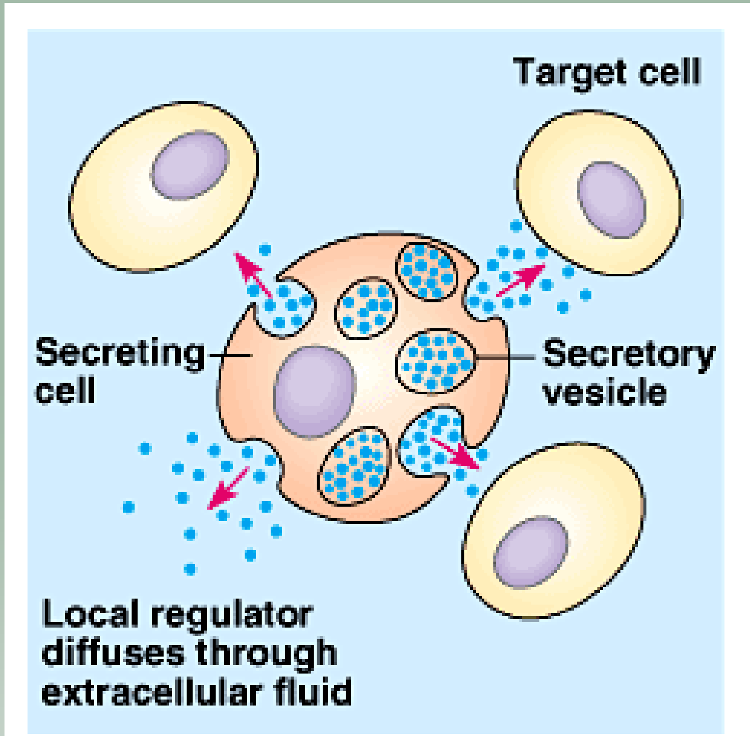
(Why would they want to do that?)

- This property might be essential for an organism that obtains its nutrients by scavenging extracellular macromolecules with the help of secreted hydrolases. A high cell density will result in increased concentrations of extracellular hydrolases.
- Protection: The spore enables cells in the middle to lay dormant until new food sources are available.

2. Communicating cells may be close together or far apart

- Multicellular organisms also release signaling molecules that target other cells.
  - <u>Example of Close-signaling</u>*:*
  - ***Paracrine*** *signaling*
    - "local regulators"
      - Ex = growth factors
    - One cell can impact many neighbors

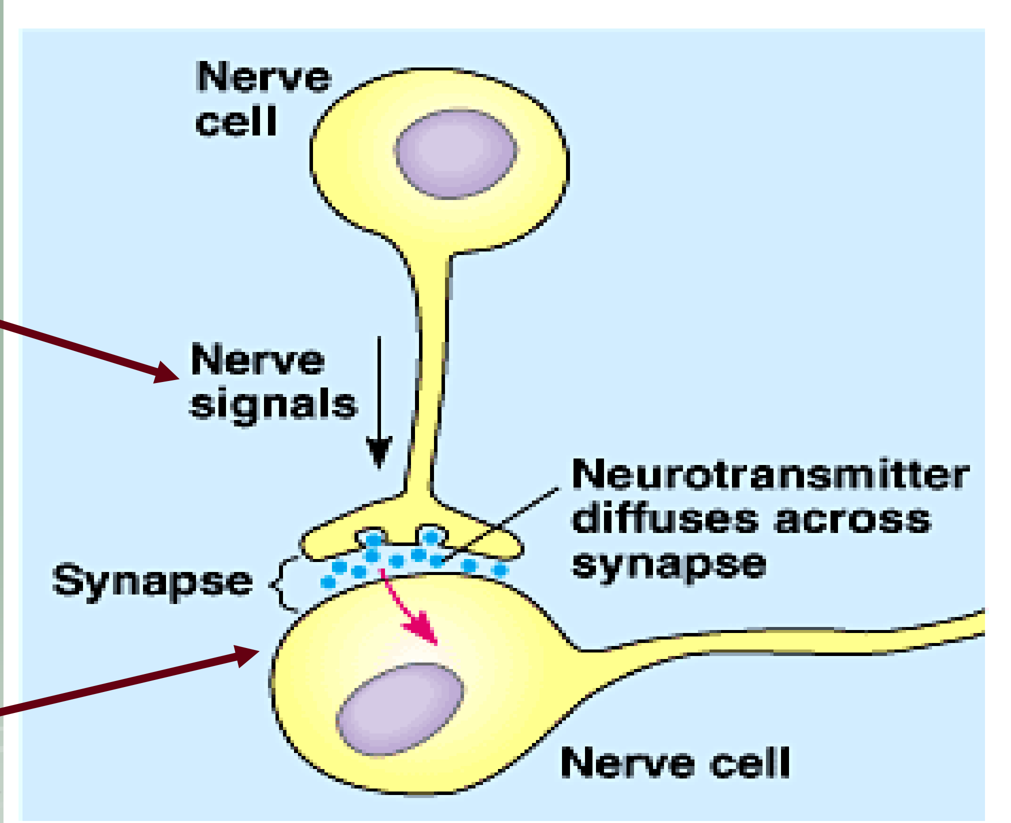
"Exocrine Glands" secrete Substances to exclusive targets



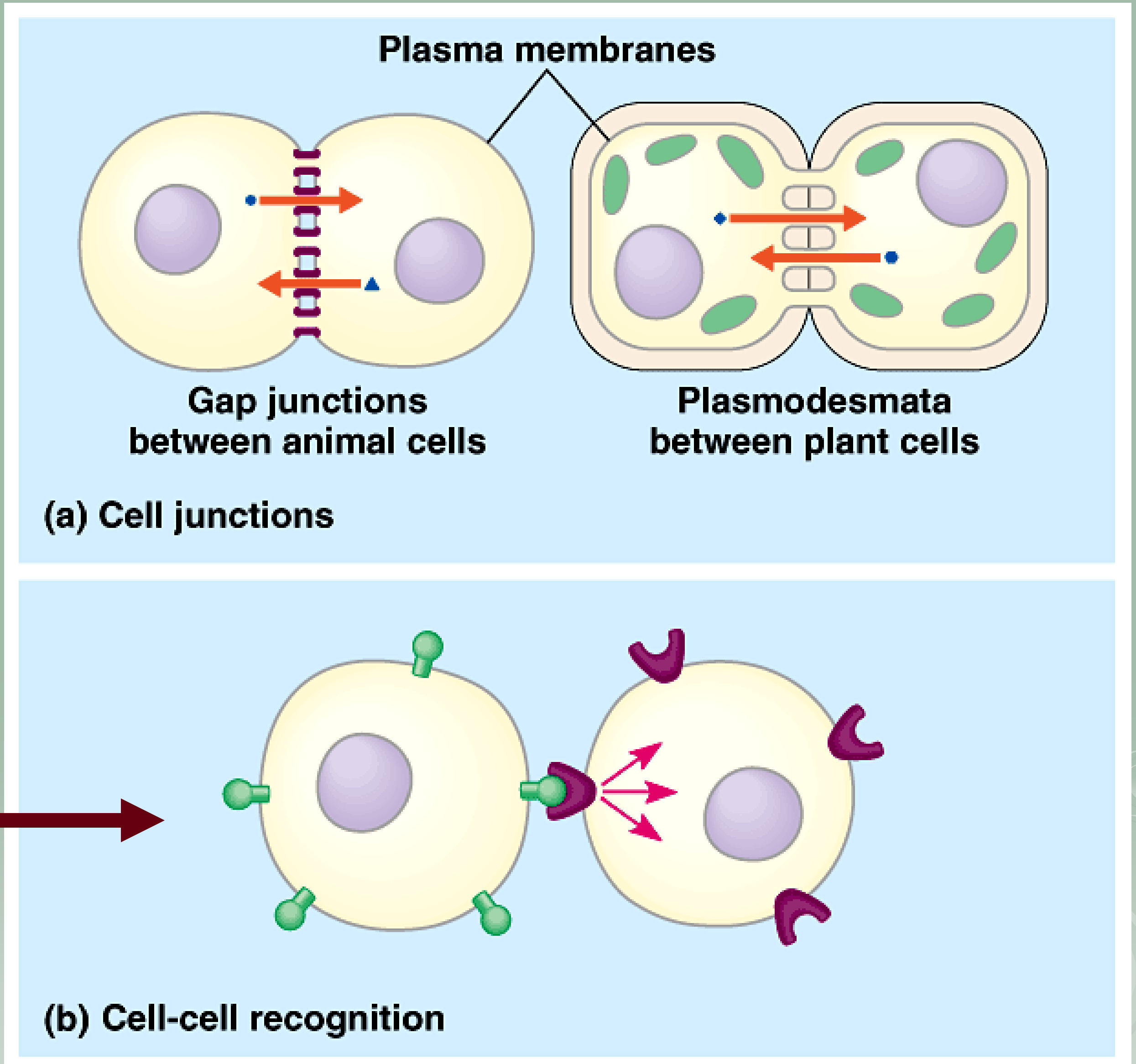
- <u>Another example of close signaling:</u> In **synaptic** signaling, a nerve cell produces a neurotransmitter that diffuses to a single cell that is almost touching the sender.

Electrical signal prompts release of neurotransmitter

Detection of neurotransmitter begins a new electrical signal



- Cells may communicate by direct contact.



Immune connection: Macrophage will use direct contact to alert T cells that invaders are present

- <u>Far-away signaling:</u> Plants and animals use **hormones** to signal at greater distances.
  - ANIMALS: “endocrine” cells (or glands) release hormones into the circulatory system (carries them far away)
  - PLANTS: hormones may travel in vessels, but more often travel from cell to cell or by diffusion in air.

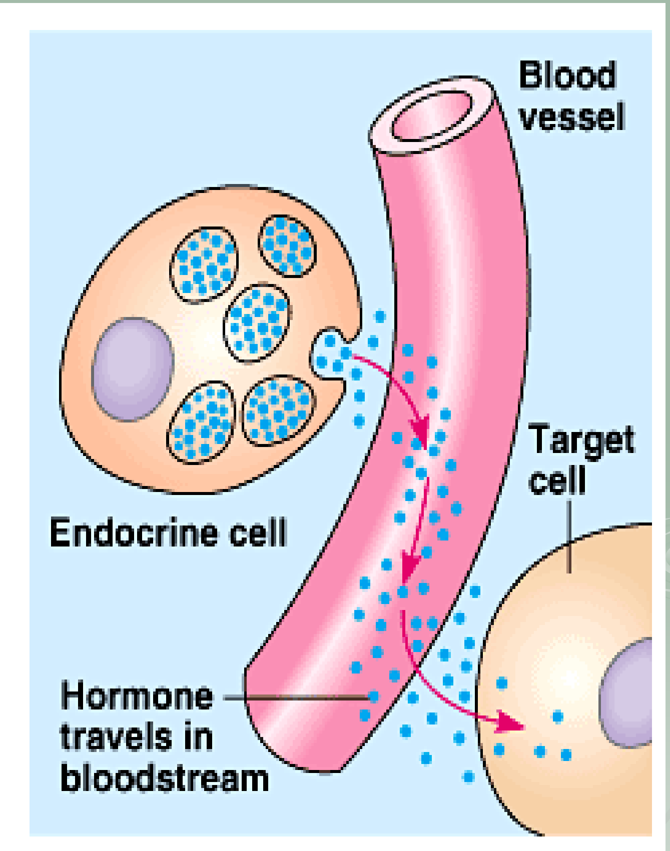


Fig. 11.3b

There are 3 stages to cellular signaling

- **Reception** - chemical signal binds to a cellular protein, changing its shape
- **Transduction** - binding leads to a change in the receptor that triggers a series of changes along a signal-transduction *pathway.*
- **Response**, transduced signal triggers a specific cellular activity.

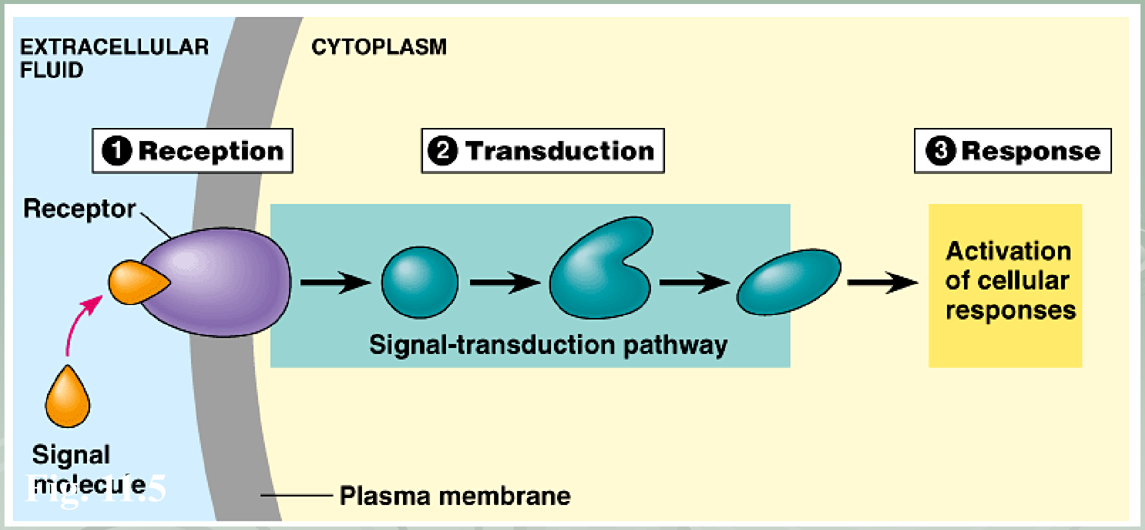
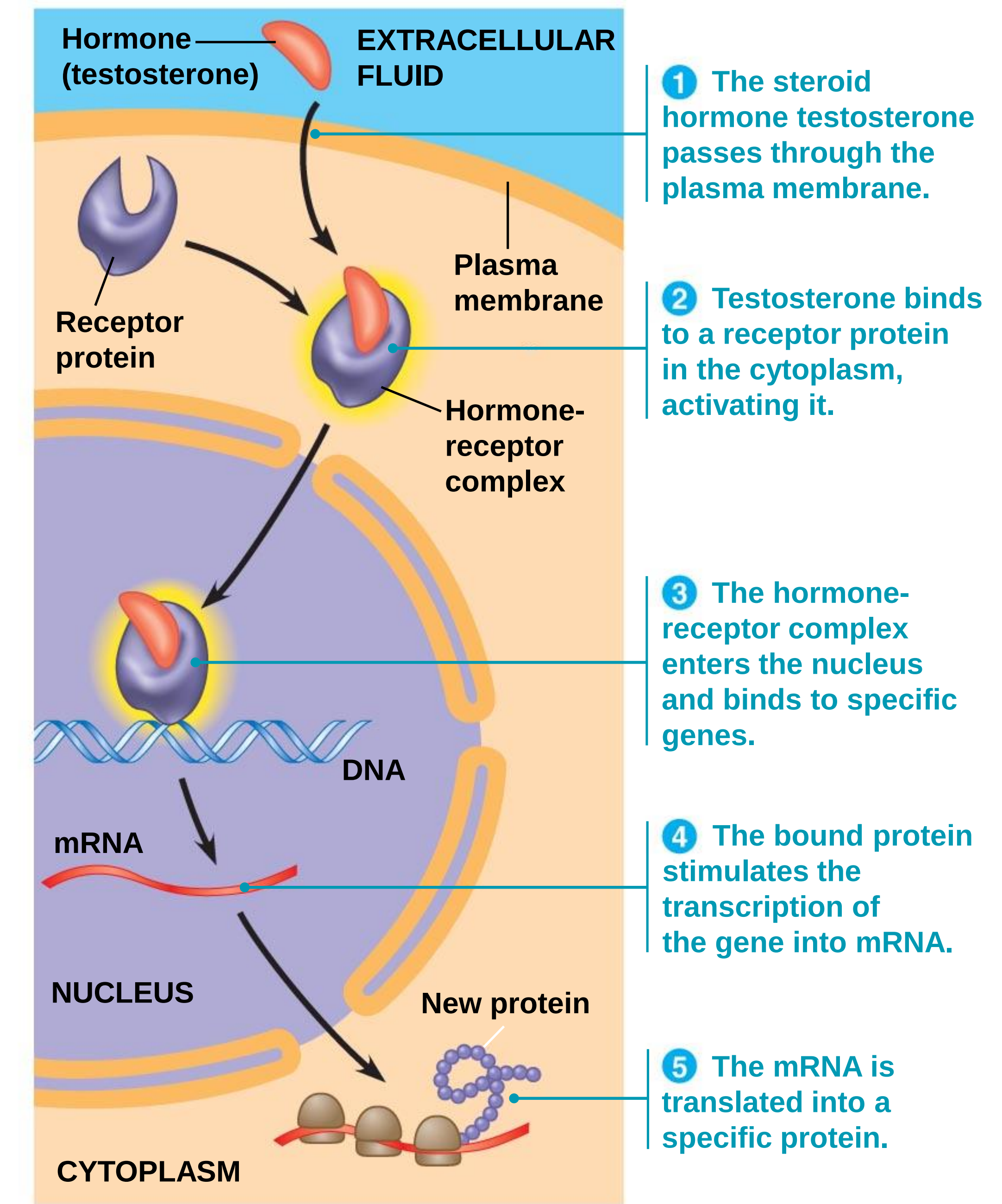


Fig. 11.5

Intracellular Receptors

- Lipid soluble signals can pass through the membrane, so their receptors are not on the cell membrane.
- Steroids and Nitric Oxide (NO) are examples.
  - NO triggers blood vessel dilation, and it can be a neurotransmitter



Hormone
(testosterone)
EXTRACELLULAR FLUID
Receptor protein
Plasma membrane
Hormone-receptor complex
DNA
mRNA
NUCLEUS
New protein
CYTOPLASM
1 The steroid hormone testosterone passes through the plasma membrane.
2 Testosterone binds to a receptor protein in the cytoplasm, activating it.
3 The hormone-receptor complex enters the nucleus and binds to specific genes.
4 The bound protein stimulates the transcription of the gene into mRNA.
5 The mRNA is translated into a specific protein.

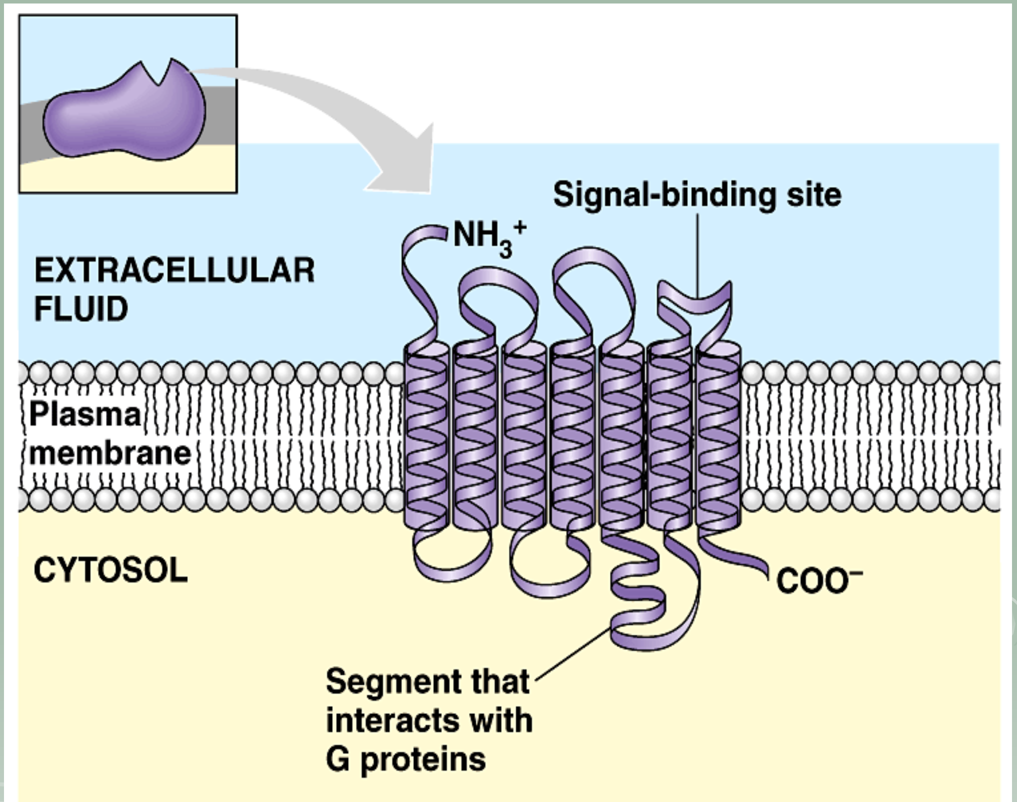
Types of signal receptor proteins

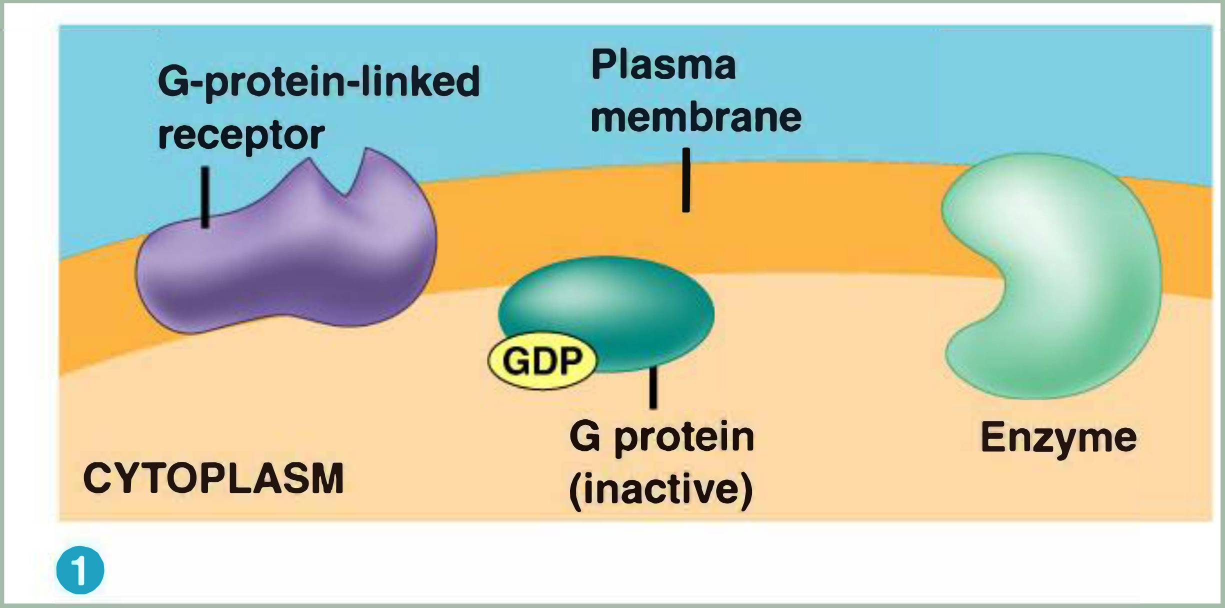
- Most are embedded in plasma membrane
  - Detect signals from extracellular environment
- Three major types of receptors are
  1. **G-protein-linked receptors**,
  2. **Tyrosine-kinase receptors**, and
  3. **Ligand gated ion-channel receptors.**

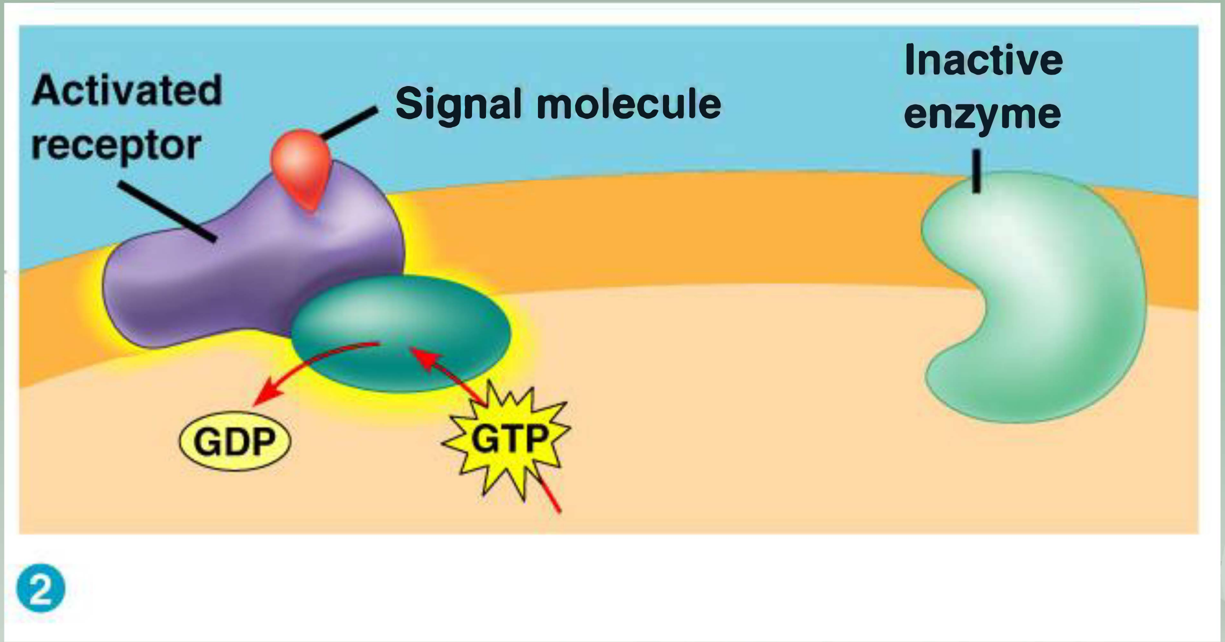
Video

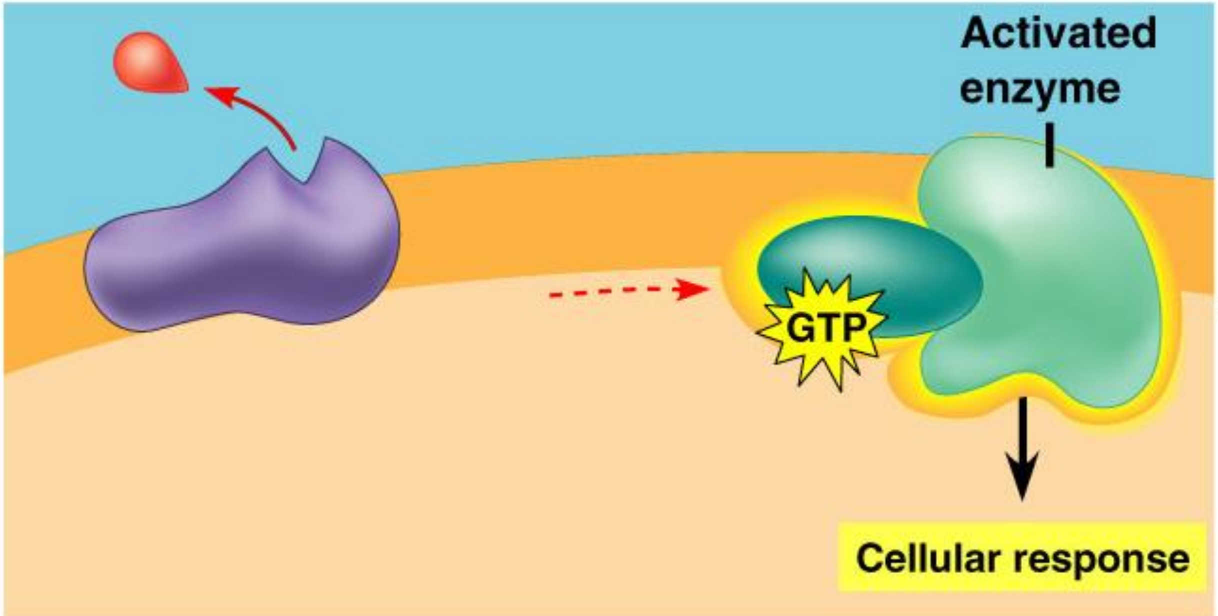
G Protein Linked Receptors

- **Binding to a signal allows them to activate specific G proteins**
- Used in detecting:
  - Yeast mating signals
  - Neurotransmitters
  - Epinepherine
  - Sensory signals (vision, smell)
  - Much more

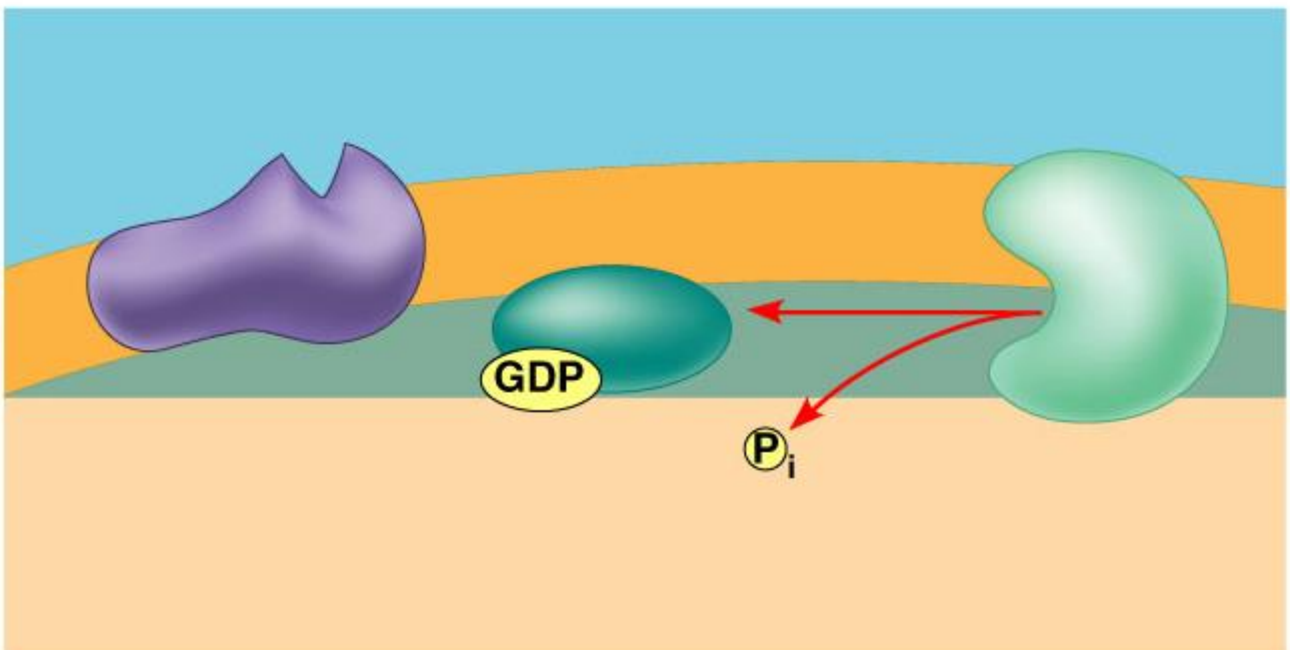



G-protein-linked receptor
Plasma membrane
GDP
G protein (inactive)
Enzyme
CYTOPLASM
1


Activated receptor
Signal molecule
Inactive enzyme
GDP
GTP
2

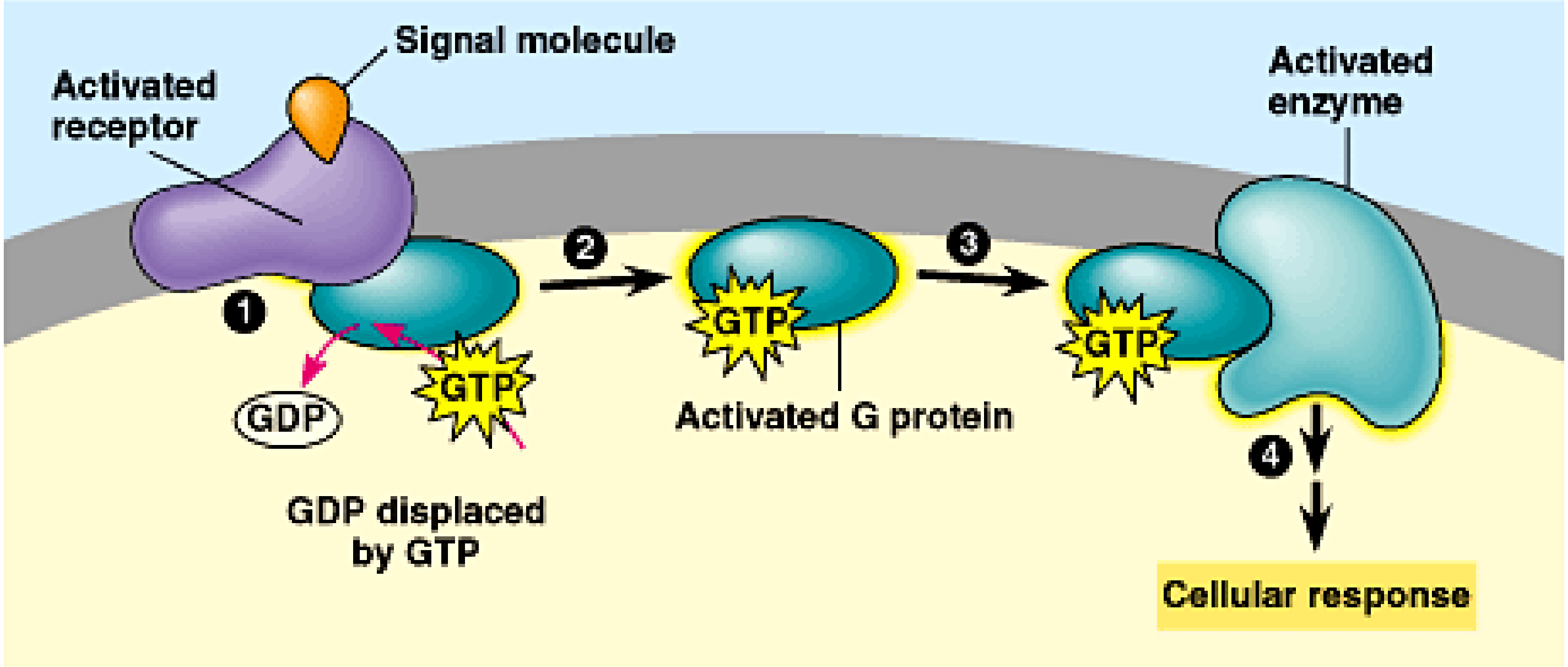


3



4

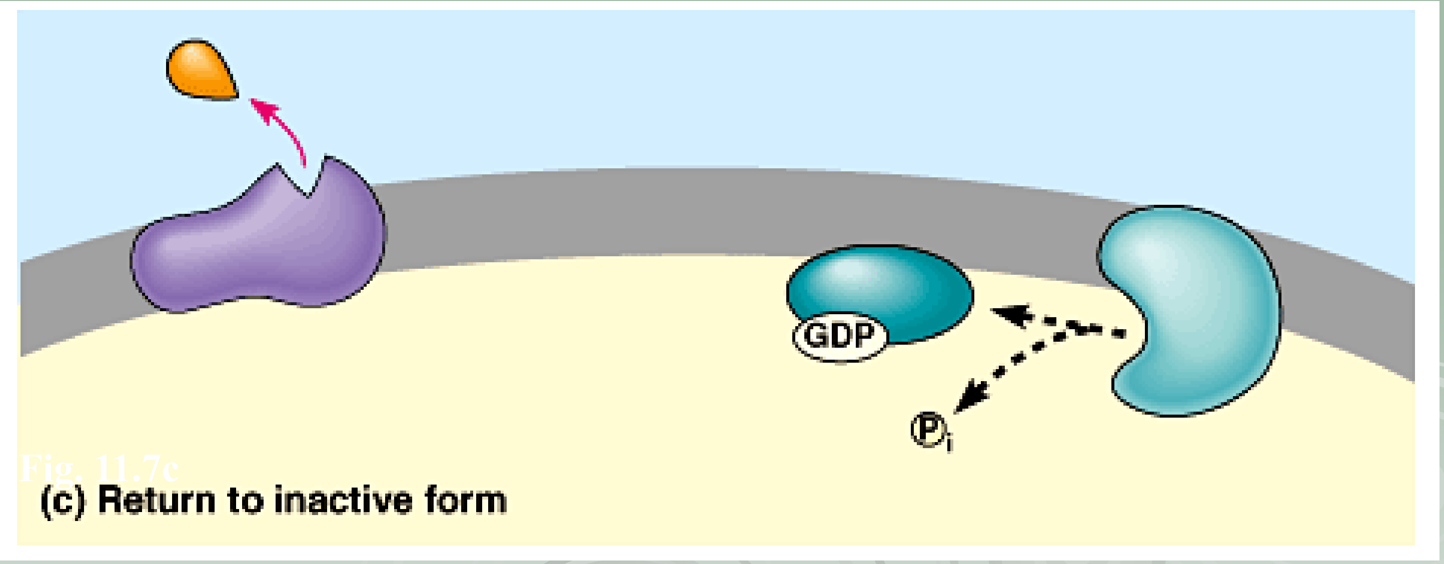
- The **G protein** acts as an on-off switch.
  - If GDP is bound, the G protein is inactive.
  - If GTP is bound, the G protein is active.
    - G protein receptors put G proteins in the active state



(b) G-protein system in action

All signals need an off switch.

- The G protein acts as a GTPase enzyme and hydrolyzes the GTP, which activated it, to GDP.
- This change turns the G protein off.
- The whole system can be shut down quickly when the extracellular signal molecule is no

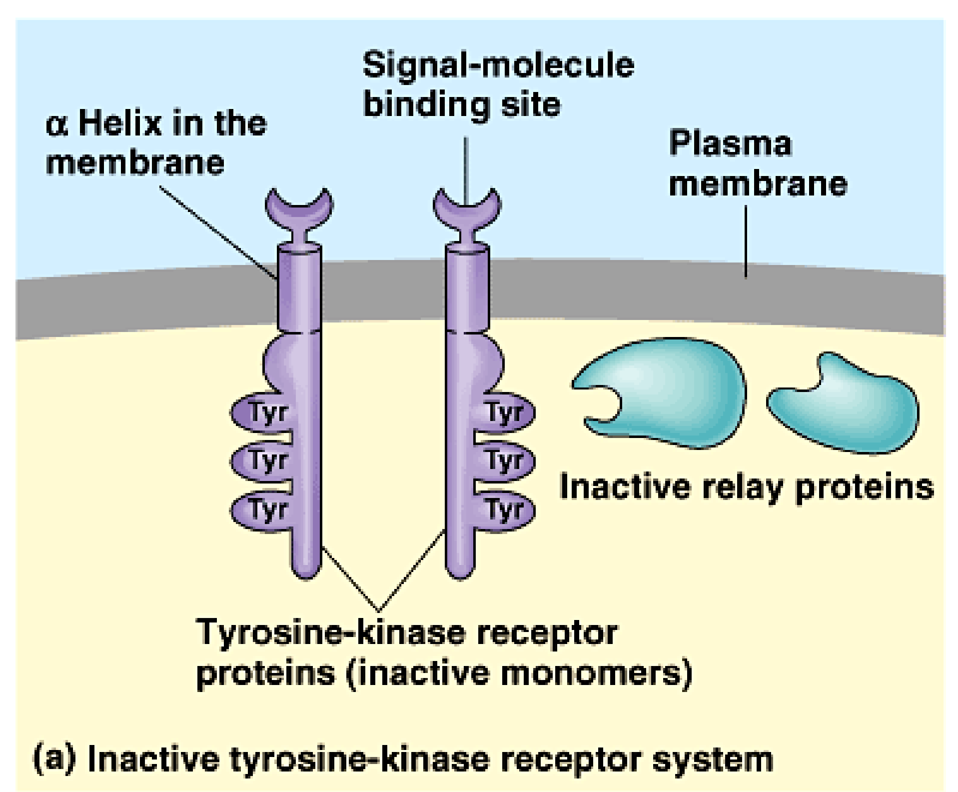


Downstream targets of activated G proteins

- Ion channels on organelle membranes – could be told to open or close
- Enzymes that make second messengers
  - Ex. The enzyme adenylyl cyclase is “told” to make cAMP by an activated G protein
  - Ex. Phospholipase C is “told” to make DAG & IP3 by another activated G protein
  - These second messengers (cAMP, DAG, IP3) each do different things

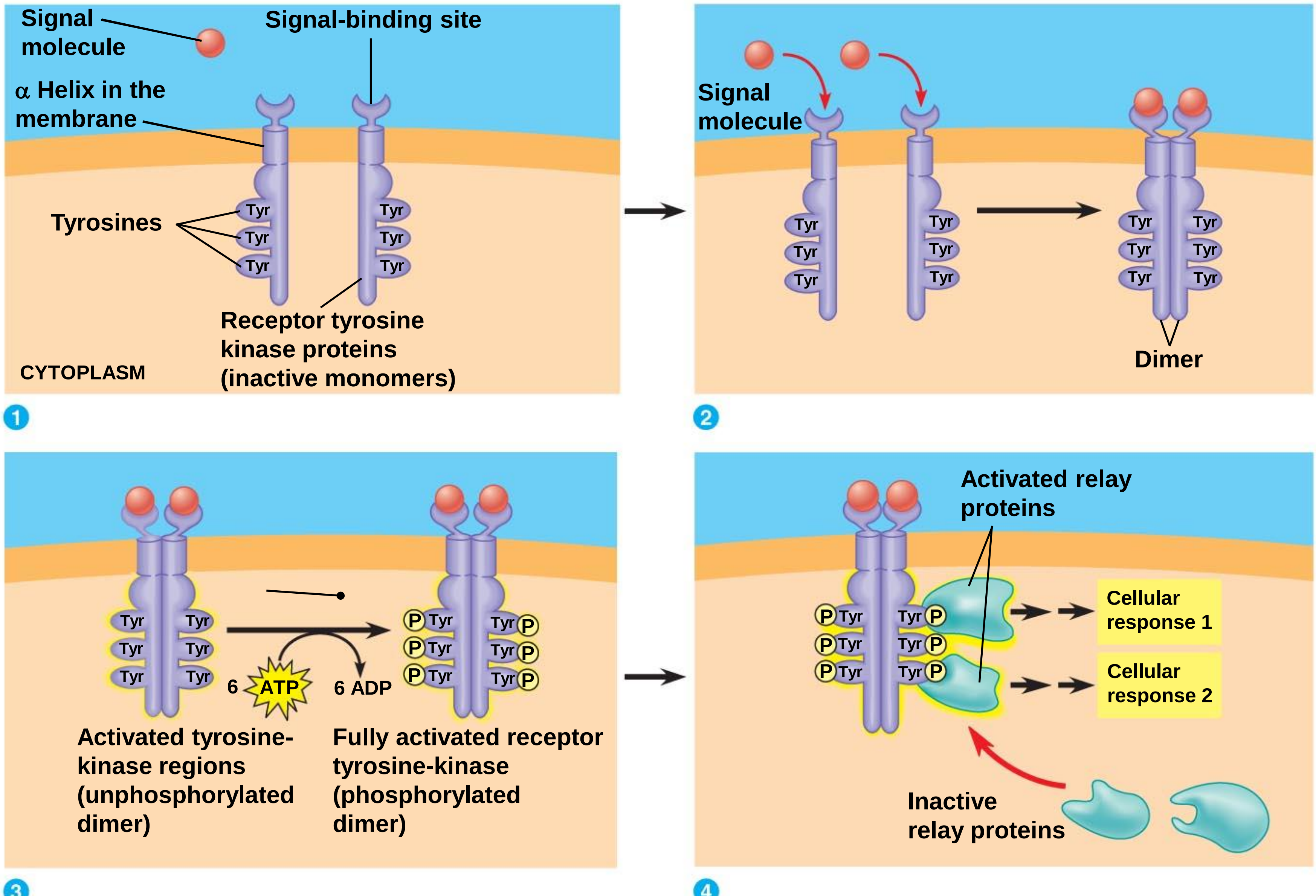
Tyrosine Kinase Receptors

- Several parts:
  - an extracellular signal-binding sites,
  - a single alpha helix spanning the membrane, and
  - an intracellular tail with several tyrosines.

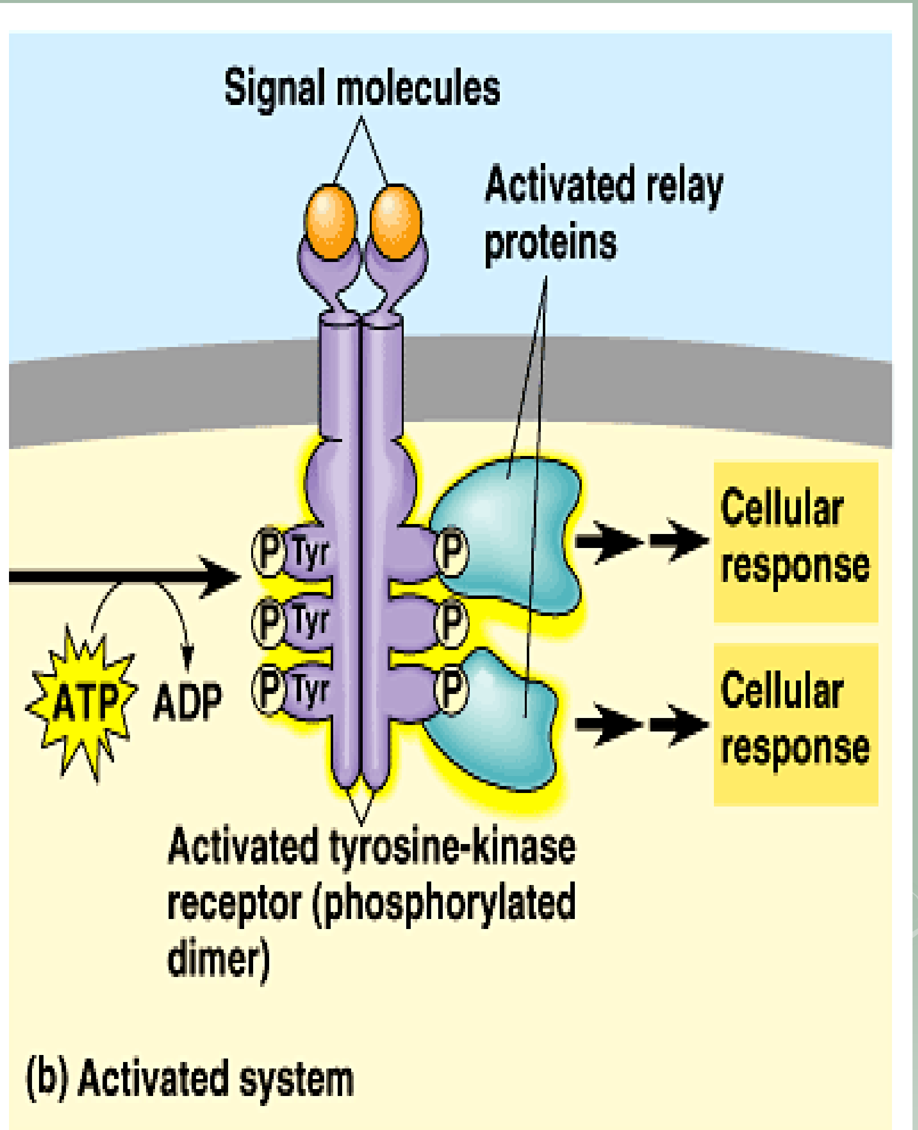


(a) Inactive tyrosine-kinase receptor system

Fig. 11.8a


Signal molecule
Signal-binding site
α Helix in the membrane
Tyrosines
Tyr
Receptor tyrosine kinase proteins (inactive monomers)
CYTOPLASM
1
Signal molecule
Dimer
2
Activated tyrosine-kinase regions (unphosphorylated dimer)
6 ATP
6 ADP
P
Fully activated receptor tyrosine-kinase (phosphorylated dimer)
3
Activated relay proteins
Cellular response 1
Cellular response 2
Inactive relay proteins
4

- How do these work?
  - Ligands bind to 2 receptors
  - Receptors join to form a dimer – activates the tyrosine kinase section of both
  - Each dimer acts as an enzyme – phosphorylates the other's tyrosines
  - Phosphorylated receptors can now activate a <u>wide variety of responses</u>



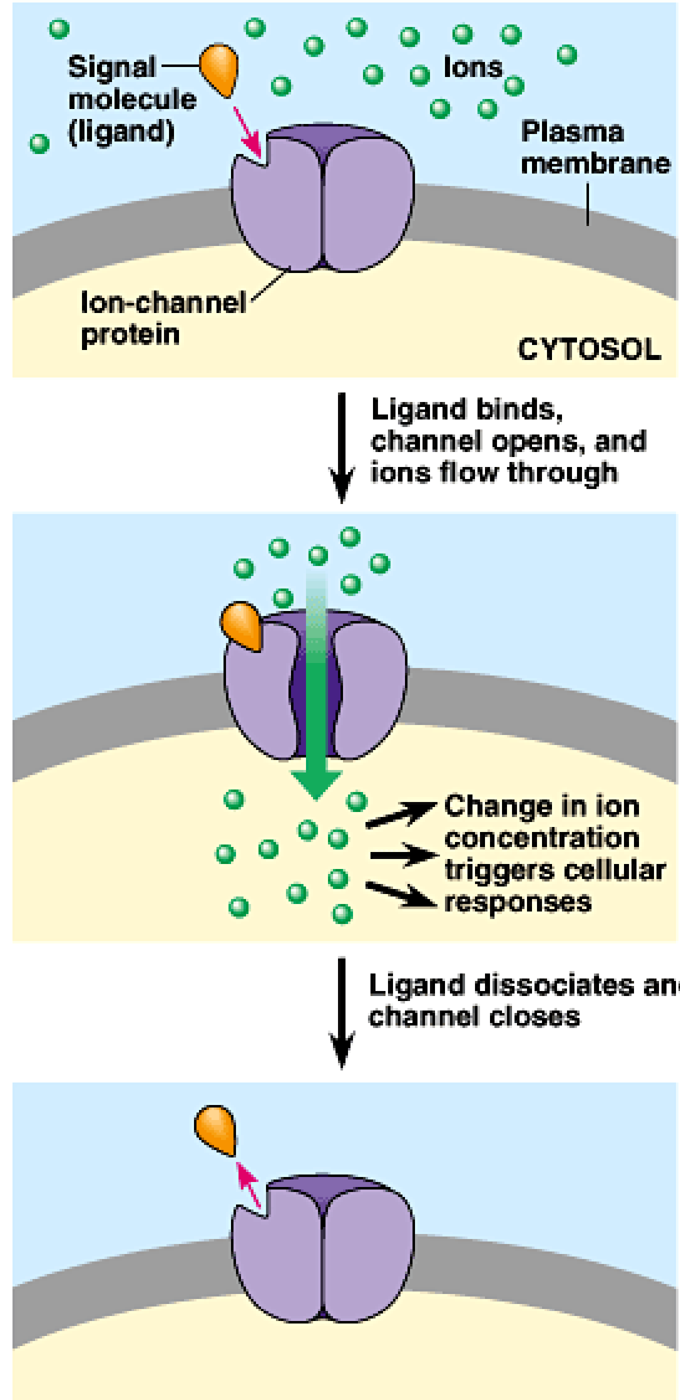
- Why are Tyrosine Kinase Receptors a good choice to detect growth factors (stimulate cells to grow & divide)?
- ns

Cell division requires a cell to build new proteins, organelles, duplicate its DNA, and undergo major cytoskeletal changes

  - A single G protein linked receptor will not be able to do all this

Ligand-gated ion channels

- protein pores that open or close in response to a chemical signal.
  - Binding changes protein's shape to allow or blocks ion flow, such as Na^+ or Ca^{2+}.
  - Ion flow changes the concentration inside the cell.
  - When the ligand dissociates, the channel reverts to original form
  - Very important in nerve & muscle cells



How does Transduction work?

- Usually a multistep pathway.
- Many steps can allow signal <u>amplification</u>
  - A <u>small</u> number of signal molecules can produce a <u>large</u> cellular response.
- Also, multistep pathways provide more opportunities for coordination and regulation than do simpler systems.

Transduction pathways frequently use PROTEIN PHOSPHORYLATION

- **Protein Kinases** – phosphorylate other proteins using ATP (activation)
  - http://www.celanphy.science.ru.nl/Bruce%20web/Flash%20Movies.htm
  - Most protein kinases act on other substrate proteins, unlike the tyrosine kinases that act on themselves.
  - Most phosphorylation occurs at either serine or threonine amino acids of the substrate protein – Why?
  - Phsophorylation leads to change in shape – Why?
- **Phosphytases** – Will dephosphorylate proteins when it is time for "deactivation" of the proteins

Here, Signal transduction involves many protein kinases (each phosphorylates the next)

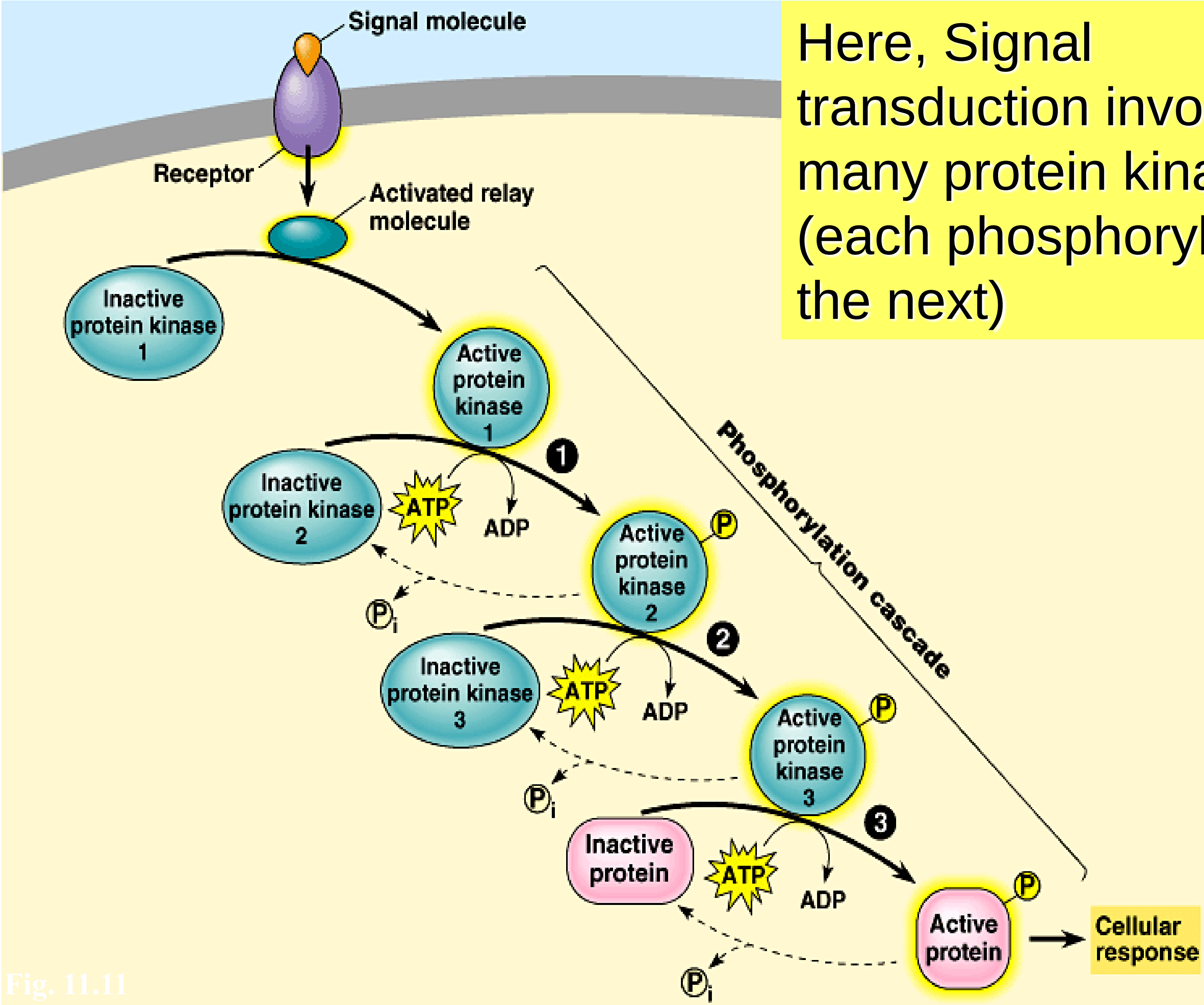


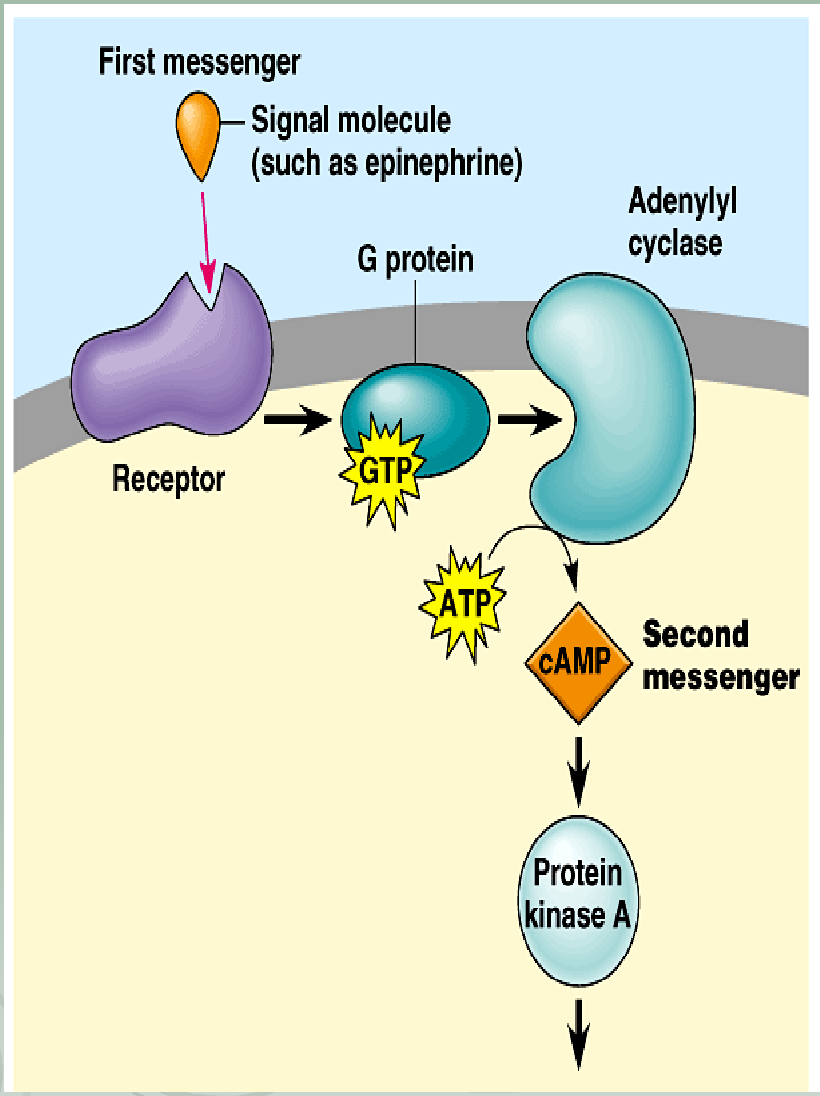
Fig. 11.11

Second Messengers

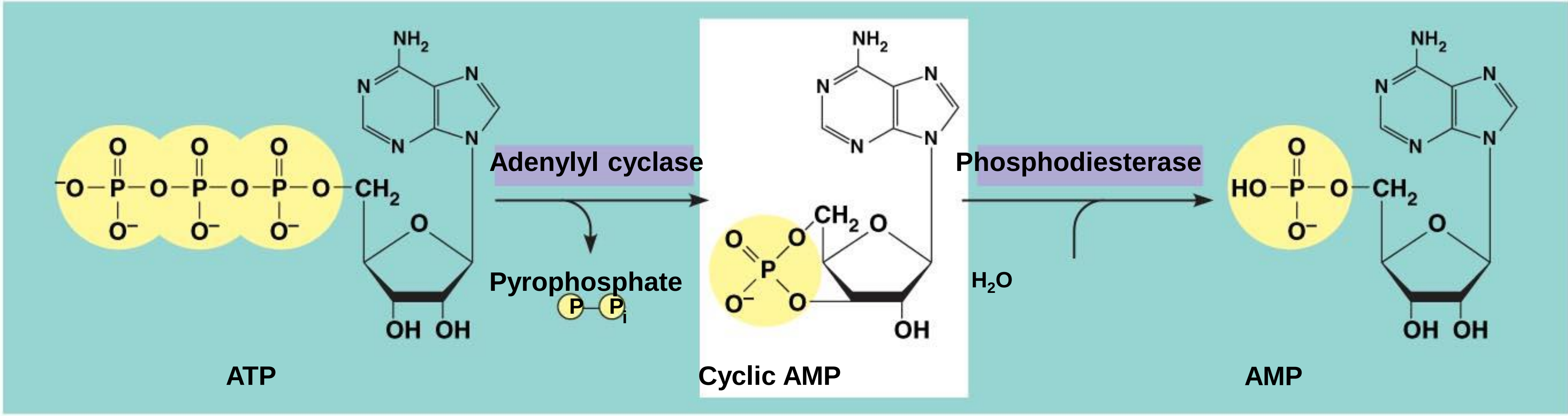
- Many signaling pathways involve small, nonprotein, water-soluble molecules or ions, called **second messengers**.
  - These molecules **rapidly diffuse** throughout the cell.
- Used by both G protein linked receptors and Tyrosine kinase receptors.
  - Two of the most important are **cyclic AMP and Ca^{2+}.**
- Animation on second messengers & transduction

Cyclic AMP (cAMP)

- 1^{st} messenger binds to G protein
- G protein linked receptor activates a G protein
- Activated G protein activates **Adenylyl Cyclase**
- Adenylyl cyclase makes cAMP (second messenger)
- cAMP diffuses through cell and activates **Protein Kinase A**
- Protein kinase A phosphorylates other proteins

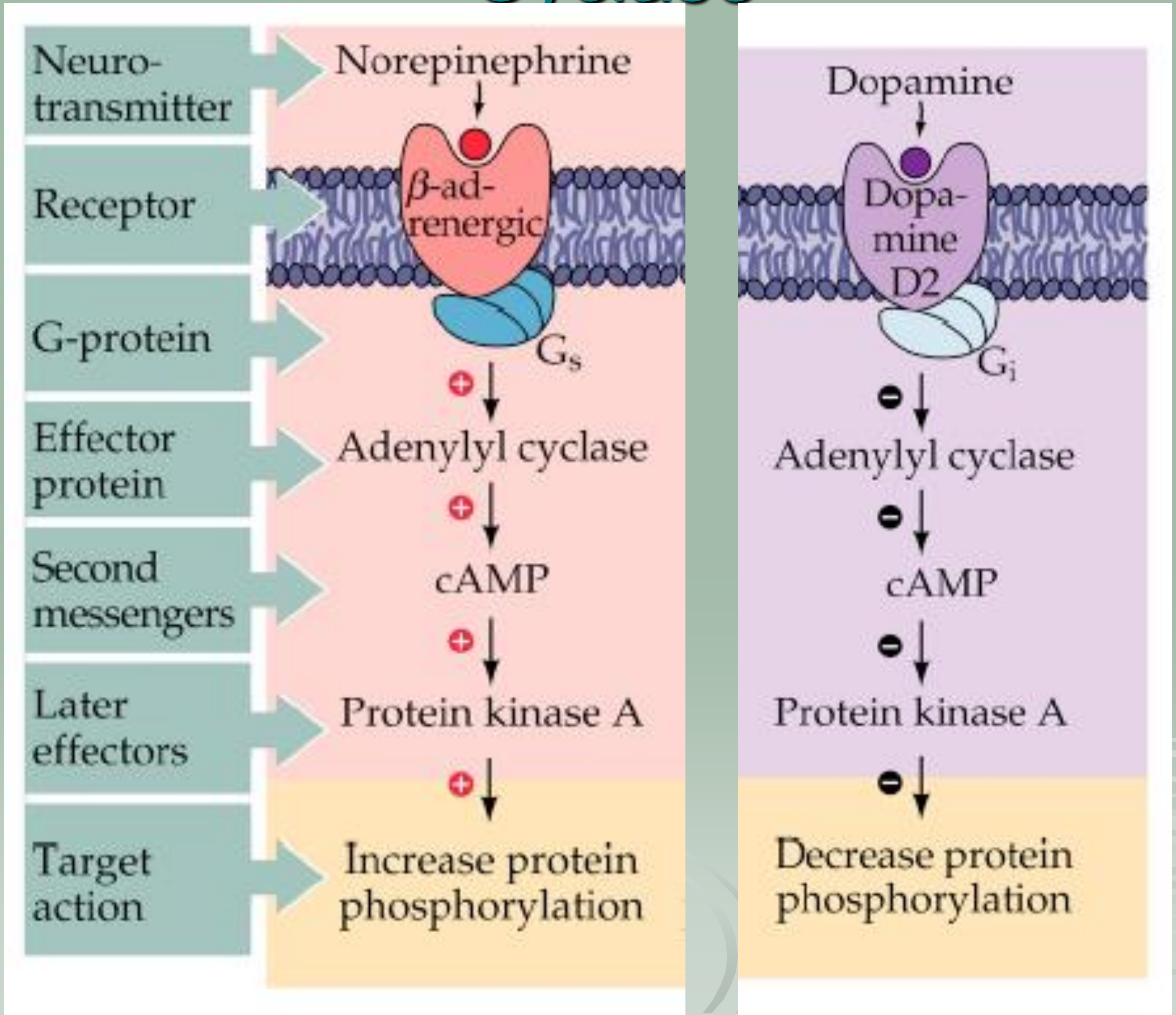


Adenylyl cyclase is the enzyme that converts ATP to cAMP



Phosphodiesterase is the enzyme that breaks the bond between C#3 of the Ribose and the Phosphate on cAMP converting it to AMP.

Some G proteins Inhibit Adenylyl Cyclase

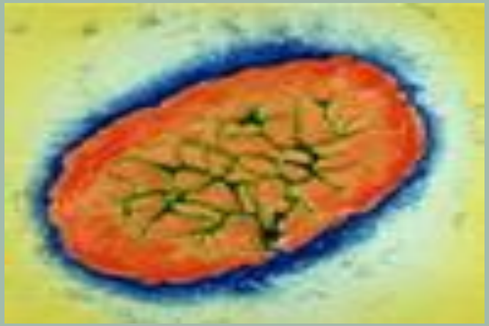


Certain microbes cause disease by disrupting the G-protein signaling pathways.

- *Vibrio cholerae*

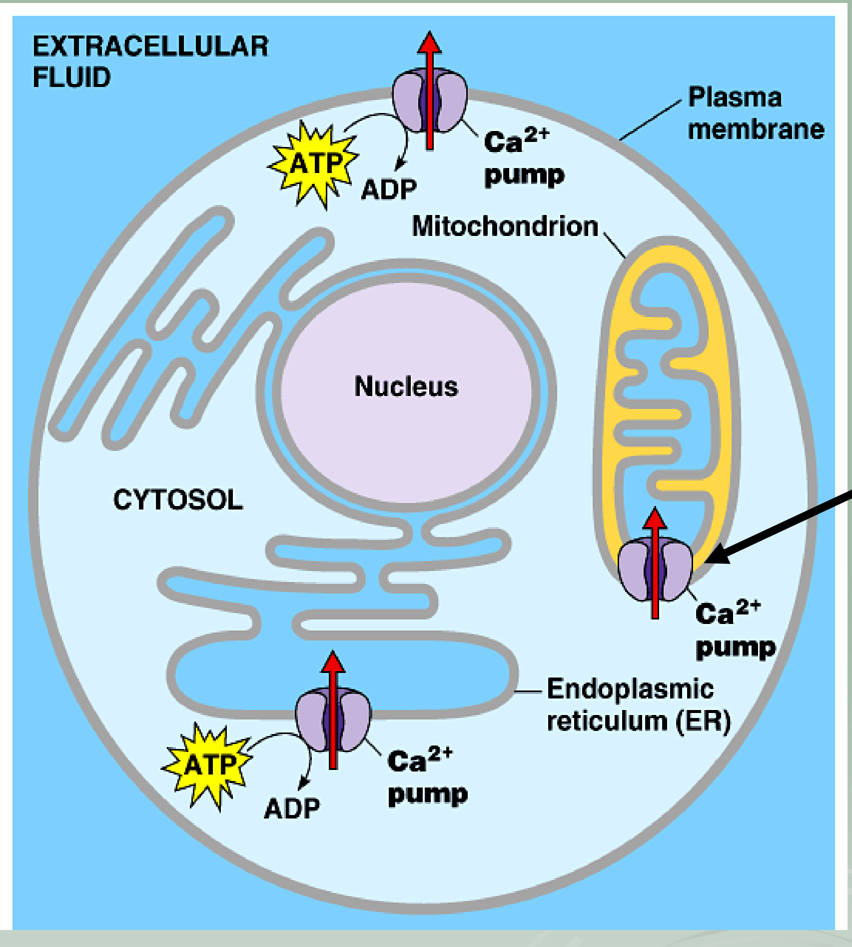
  - Toxin locks G protein in an active form
  - G protein activates adenylyl cyclase - high cAMP levels result
  - cAMP levels trigger intestinal cells to secrete many salts
  - Water follows (osmosis) and diarrhea results

- *Bordetella pertussis*



  - Also leads to high cAMP concentration
  - Affected G protein normally inhibits adenylyl cyclase
  - Toxin locks this G protein in inactive form, so adenylyl cyclase is not shut off

Ca^{2+} as a Second Messenger

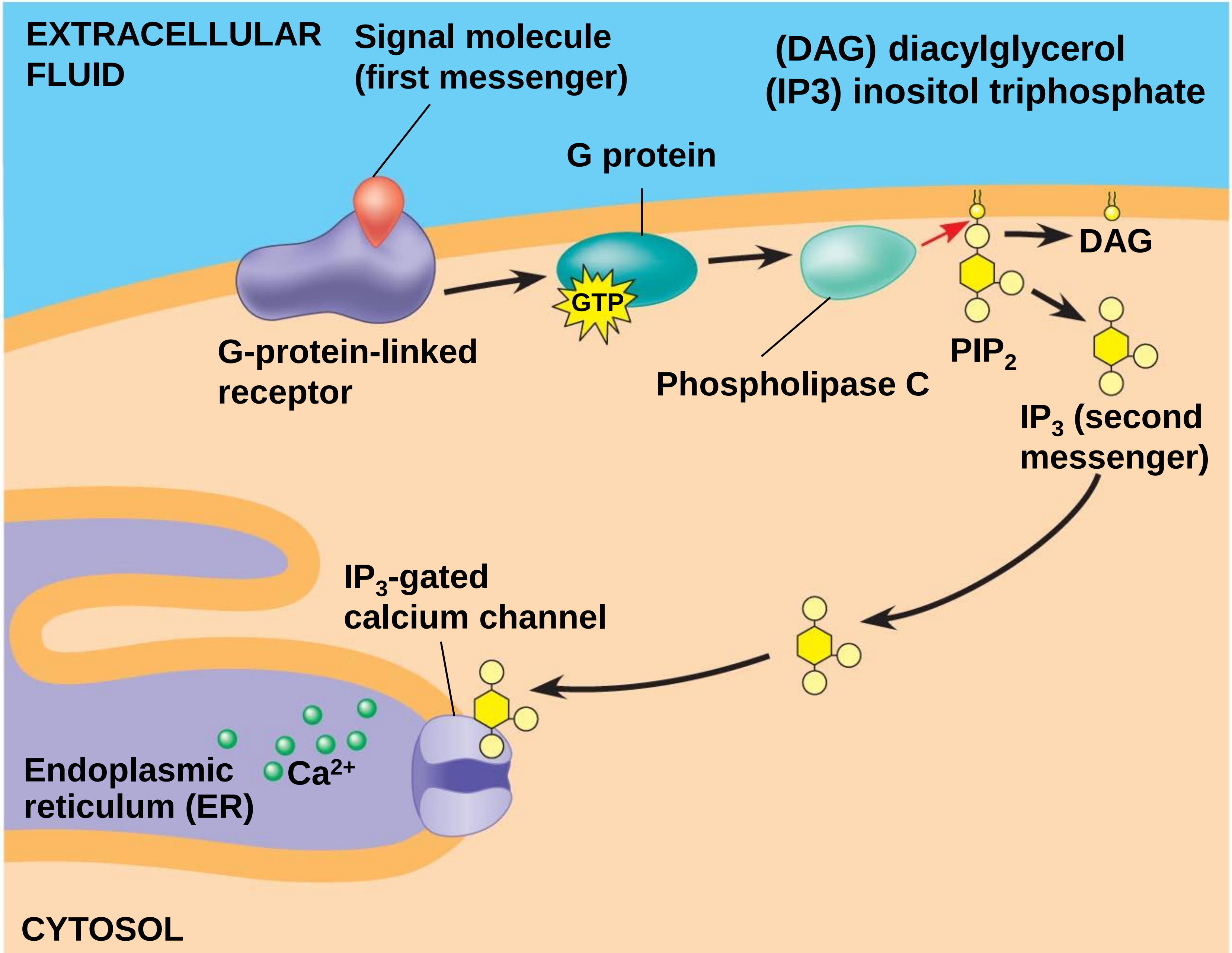


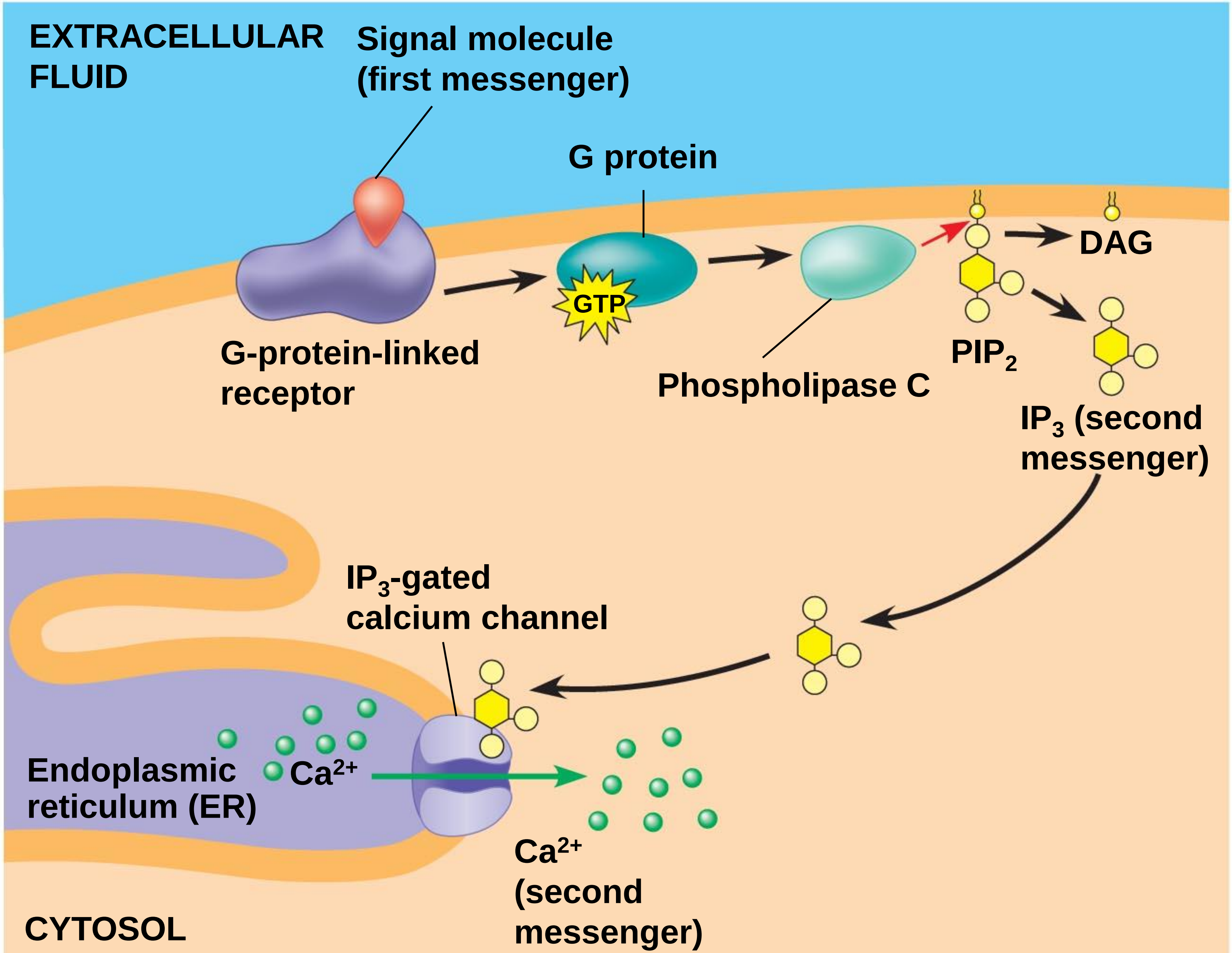
- Cells keep cytosolic Ca^{2+} low by default

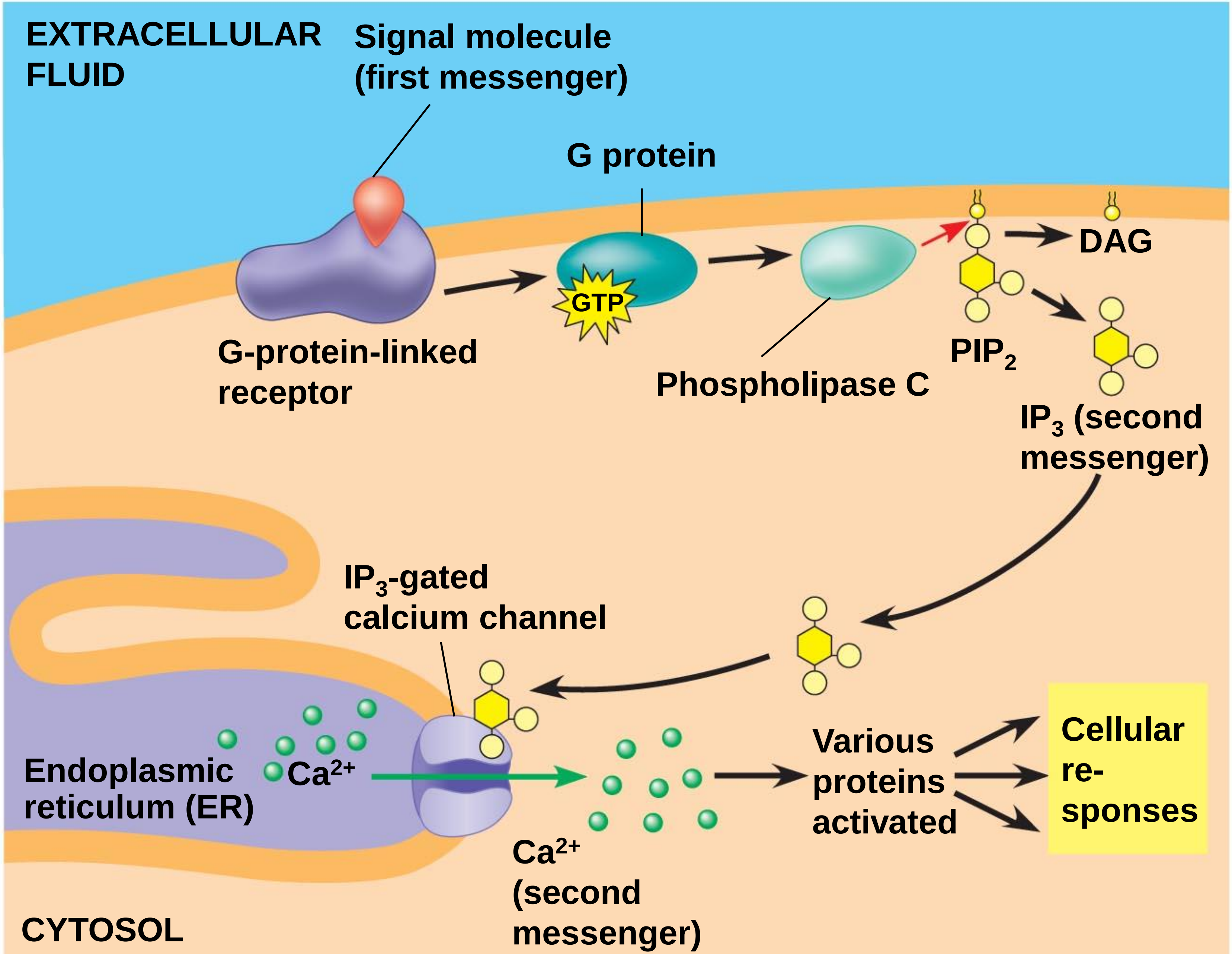
Why no ATP needed here???

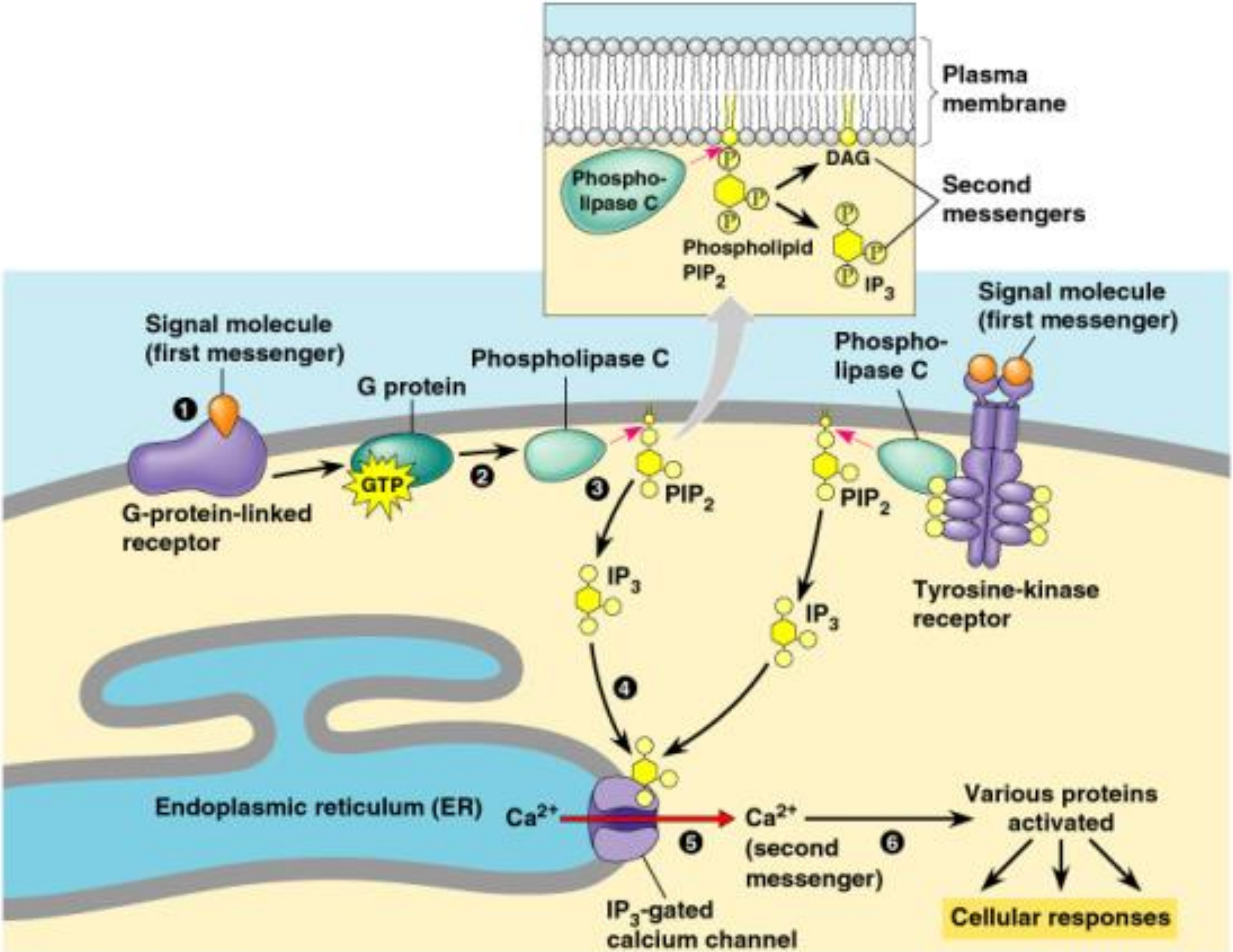
Ca^{2+} as a Second Messenger

- Signal pathways often work by increasing $[Ca^{2+}]$ in cytosol
  - In animal cells, increases in Ca^{2+} may cause contraction of muscle cells, secretion of some substances, and cell division.
  - In plant cells, increases in Ca^{2+} trigger responses for coping with environmental stress, including drought.
- Cells use Ca^{2+} as a second messenger in both G-protein pathways and tyrosine-kinase pathways.

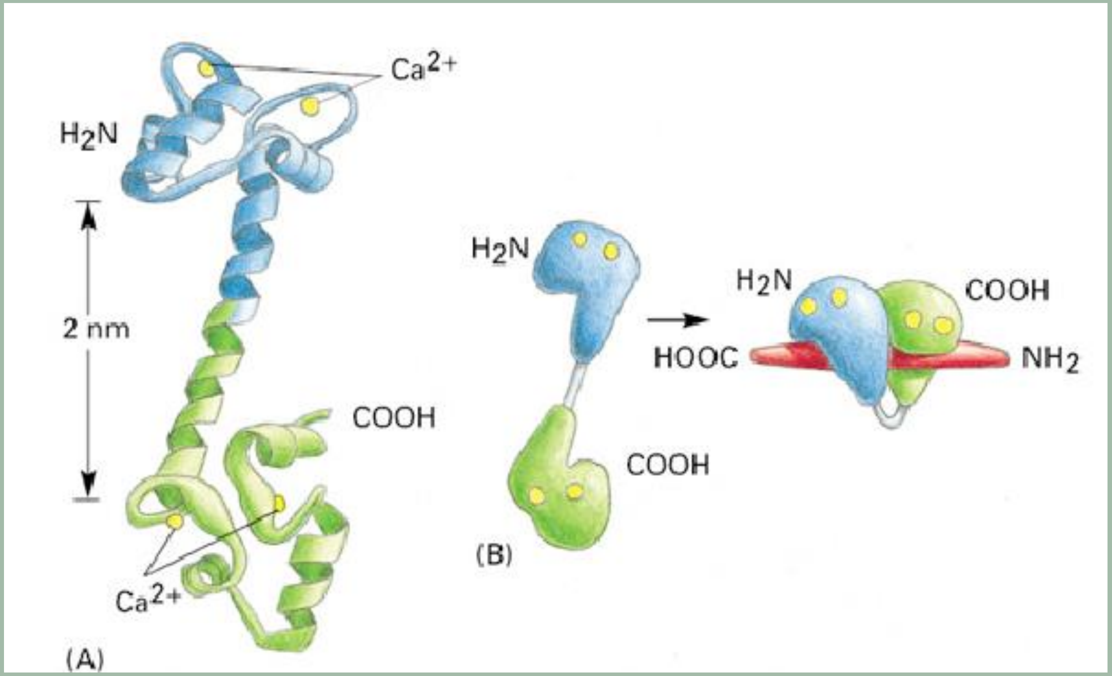

EXTRACELLULAR FLUID
Signal molecule (first messenger)
(DAG) diacylglycerol
(IP3) inositol triphosphate
G protein
GTP
DAG
G-protein-linked receptor
Phospholipase C
PIP2
IP3 (second messenger)
IP3-gated calcium channel
Endoplasmic reticulum (ER)
Ca2+
CYTOSOL


EXTRACELLULAR FLUID
Signal molecule (first messenger)
G protein
GTP
DAG
G-protein-linked receptor
Phospholipase C
PIP$_2$
IP$_3$ (second messenger)
IP$_3$-gated calcium channel
Endoplasmic reticulum (ER)
Ca^{2+}
Ca^{2+} (second messenger)
CYTOSOL

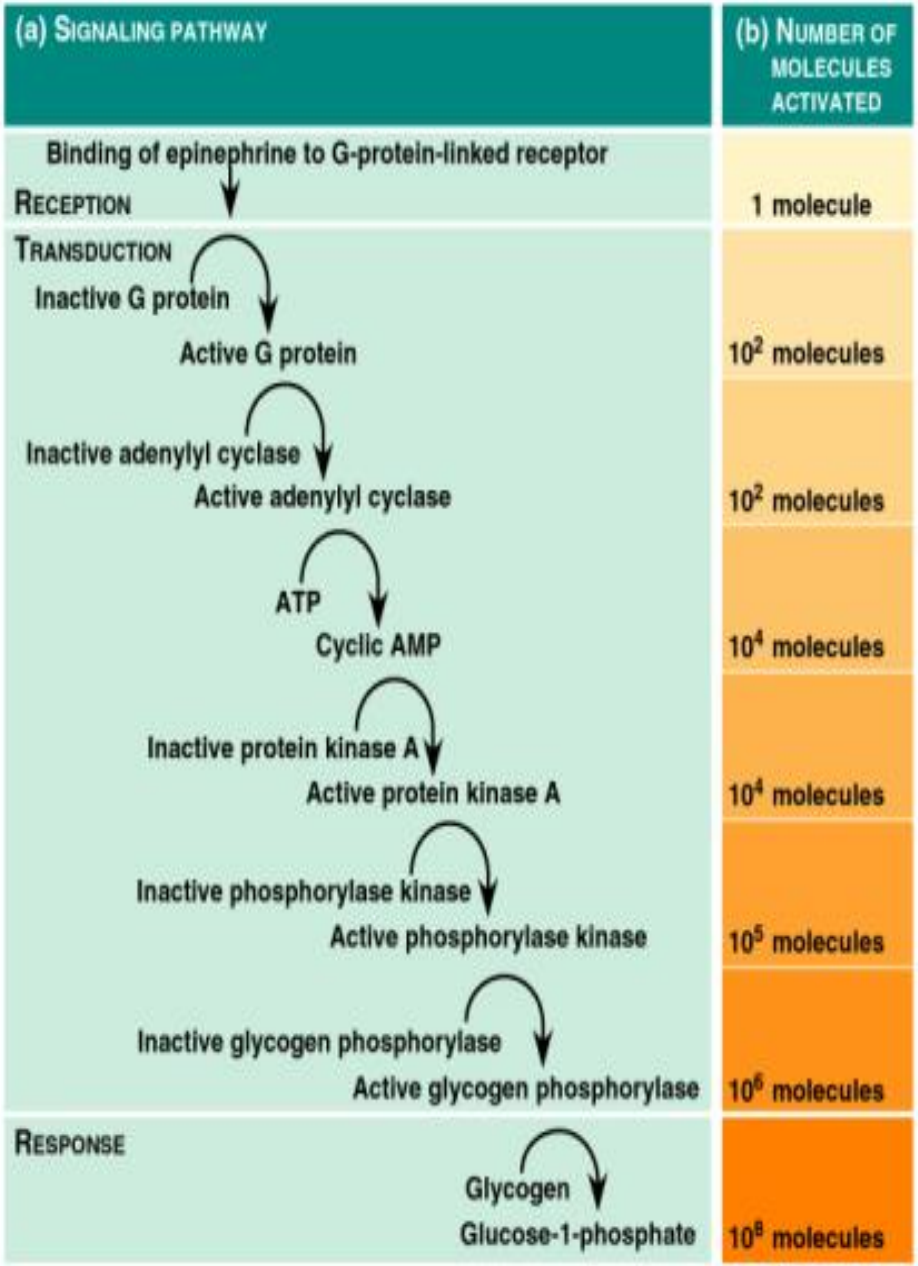

EXTRACELLULAR FLUID
Signal molecule (first messenger)
G protein
GTP
G-protein-linked receptor
Phospholipase C
PIP_2
DAG
IP_3 (second messenger)
IP_3-gated calcium channel
Endoplasmic reticulum (ER)
Ca^{2+}
Ca^{2+} (second messenger)
Various proteins activated
Cellular re- sponses
CYTOSOL

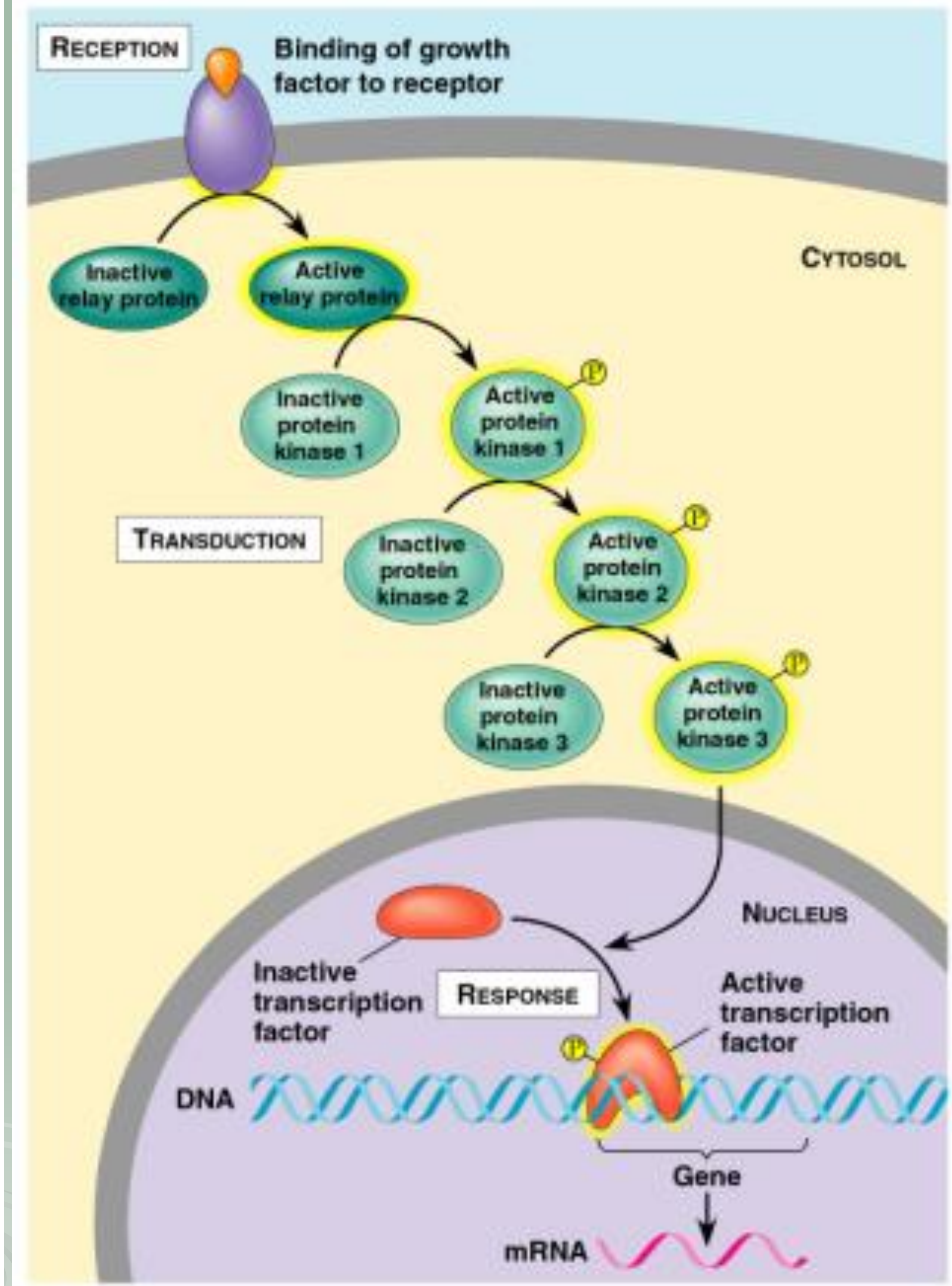

Plasma membrane
Phospho-lipase C
DAG
Second messengers
Phospholipid PIP2
IP3
Signal molecule (first messenger)
G protein
Phospholipase C
GTP
G-protein-linked receptor
PIP2
IP3
Phospho-lipase C
Signal molecule (first messenger)
Tyrosine-kinase receptor
Endoplasmic reticulum (ER)
Ca2+
Ca2+ (second messenger)
IP3-gated calcium channel
Various proteins activated
Cellular responses

- Ca^{2+} can activate pathways directly or bind to **calmodulin**



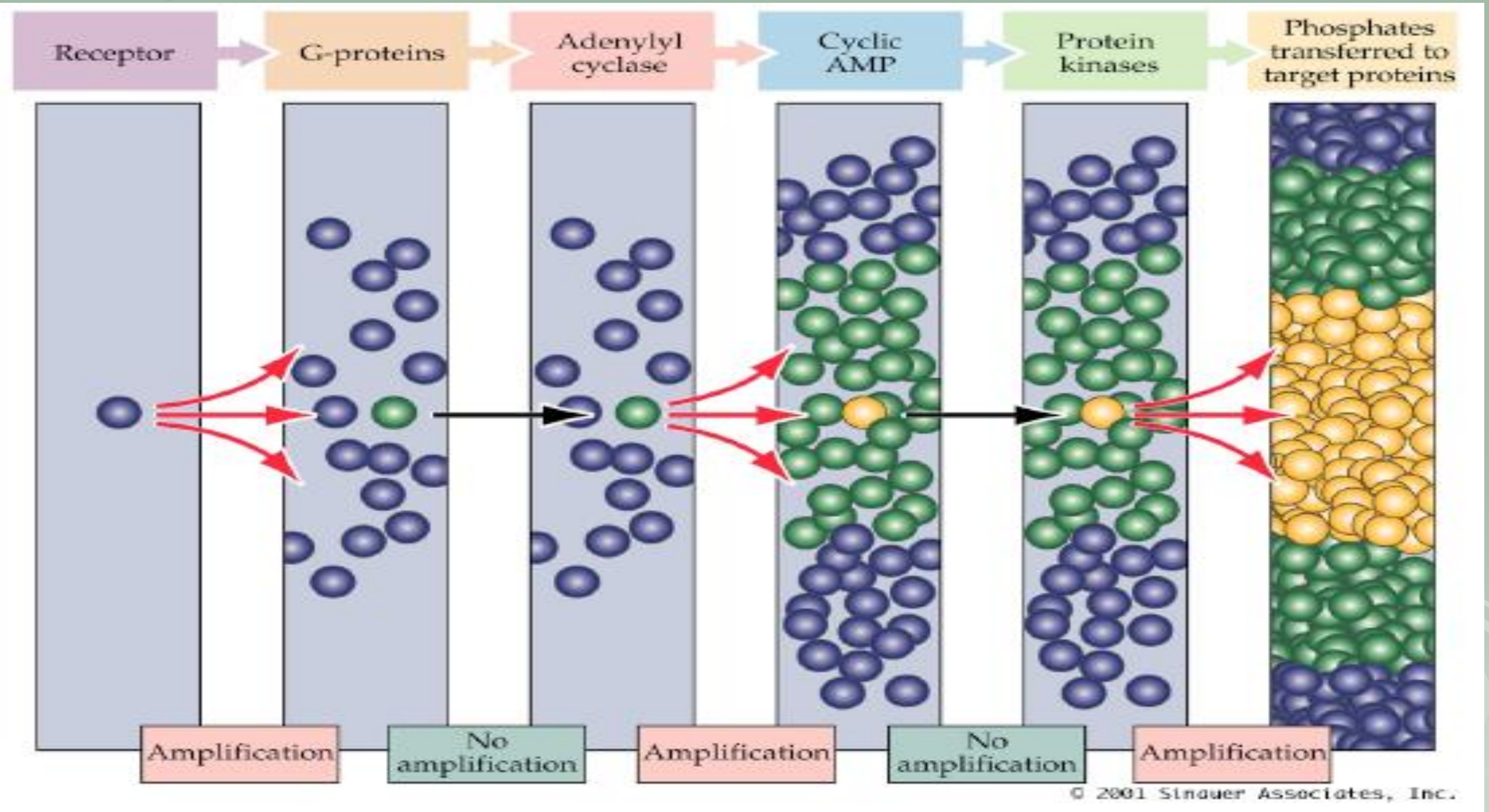
- Activated calmodulin can bind to other proteins – usually causes activation of kinases and phosphatases
- Calmodulin Animation


(a) Signaling pathway
(b) Number of molecules activated
Binding of epinephrine to G-protein-linked receptor
Reception
1 molecule
Transduction
Inactive G protein
Active G protein
10^2 molecules
Inactive adenylyl cyclase
Active adenylyl cyclase
10^2 molecules
ATP
Cyclic AMP
10^4 molecules
Inactive protein kinase A
Active protein kinase A
10^4 molecules
Inactive phosphorylase kinase
Active phosphorylase kinase
10^5 molecules
Inactive glycogen phosphorylase
Active glycogen phosphorylase
10^6 molecules
Response
Glycogen
Glucose-1-phosphate
10^8 molecules


Reception
Binding of growth factor to receptor
Inactive relay protein
Active relay protein
Cytosol
Inactive protein kinase 1
Active protein kinase 1
Transduction
Inactive protein kinase 2
Active protein kinase 2
Inactive protein kinase 3
Active protein kinase 3
Nucleus
Inactive transcription factor
Response
Active transcription factor
DNA
Gene
mRNA

Signal Amplification

- Results in tremendous increase in potency of initial signal
- Permits precise control of cell behavior



Why don’t all cells respond the same way to a single signal?

- Example: Epinephrine (adrenalin)
  - Signals liver & skeletal muscle to liberate glucose from glycogen
  - Signals cardiac muscle to contract rapidly
- These differences result from a basic observation:
  - *Different kinds of cells have different collections of proteins.*

- The response of a particular cell to a signal depends on its particular collection of receptor proteins, relay proteins, and proteins needed to carry out the response.

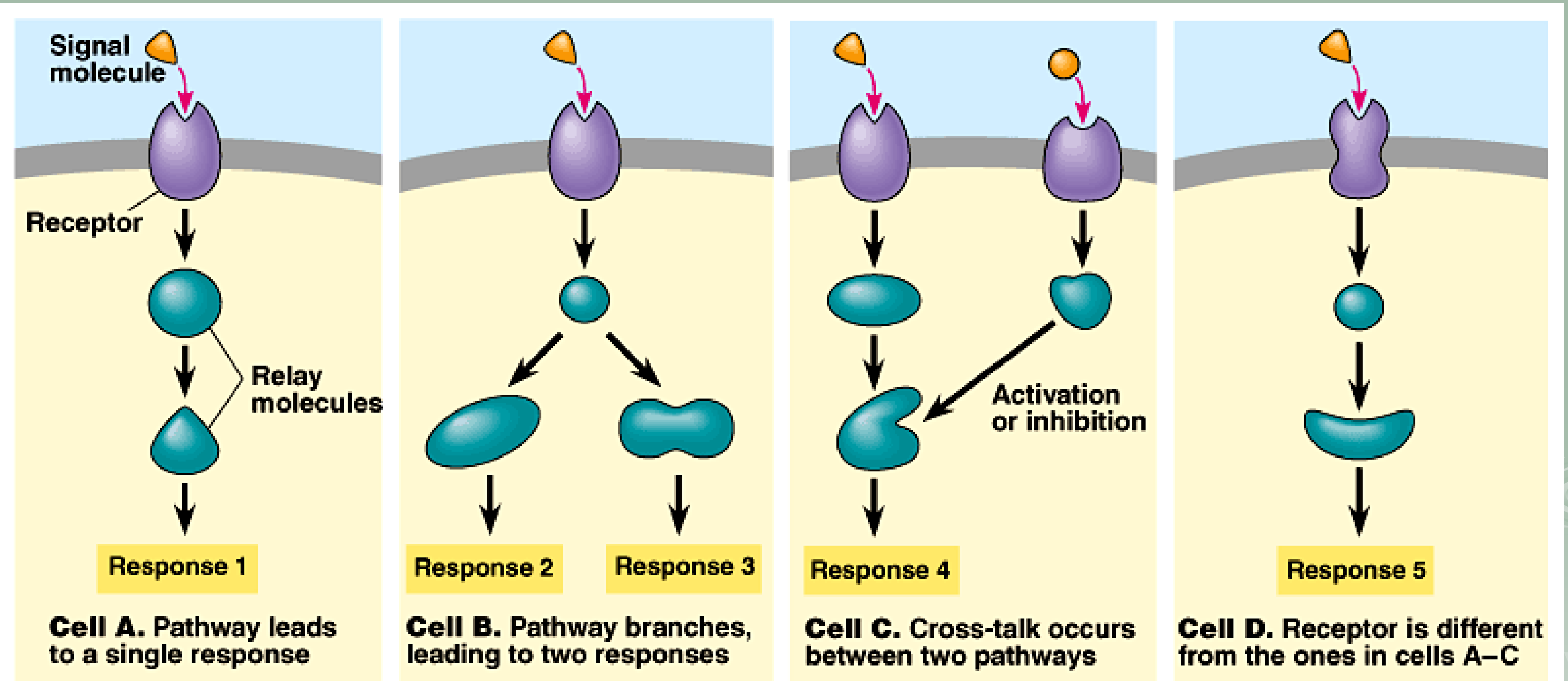


Fig. 11.18

Cellular Response

- Cellular responses can be
  - Change in the cytoplasm:
    - Change in cell metabolism, cytoskeletal arrangement, etc.
    - For example, epinephrine helps regulate cellular energy metabolism by activating enzymes that catalyze the breakdown of glycogen.
  - Change in transcription (gene expression)
  - Animation comparing different types of cellular response

- Rather than relying on diffusion of large relay molecules like proteins, many signal pathways are linked together physically by **scaffolding proteins**.
  - Scaffolding proteins may themselves be relay proteins to which several other relay proteins attach.
  - This hardwiring enhances the speed and accuracy of signal transfer between cells.

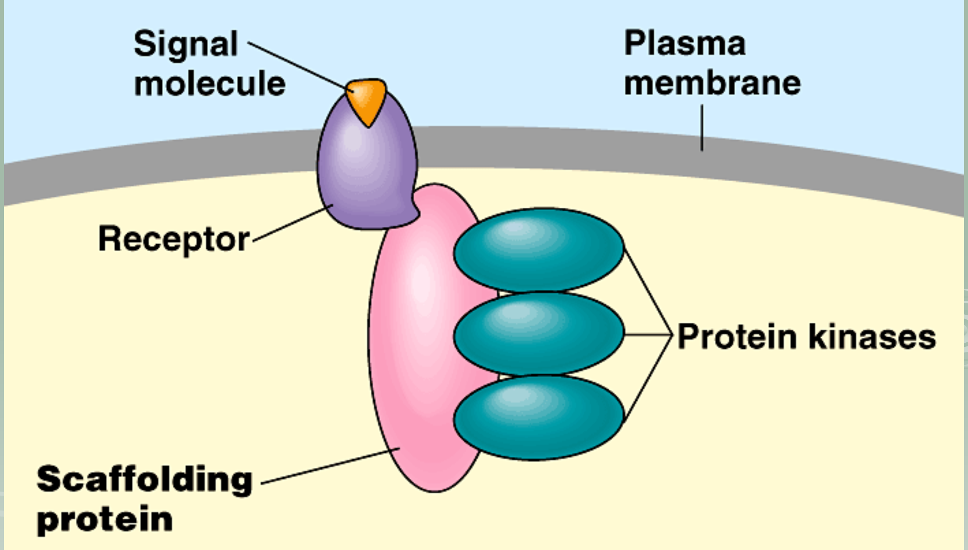


Fig. 11.19

Epinephrine Tutorial

- This is the animated tutorial from The Lifewire.com. It shows more detail on all of the steps involved in releasing glucose when epinephrine is received by liver cells.
- I recommend that you view the Narrated version first, and then do the step by step after seeing the entire process.
- Link

Blood Glucose Homeostasis