CHAPTER 11

Cell Communication

Multicellular Organisms

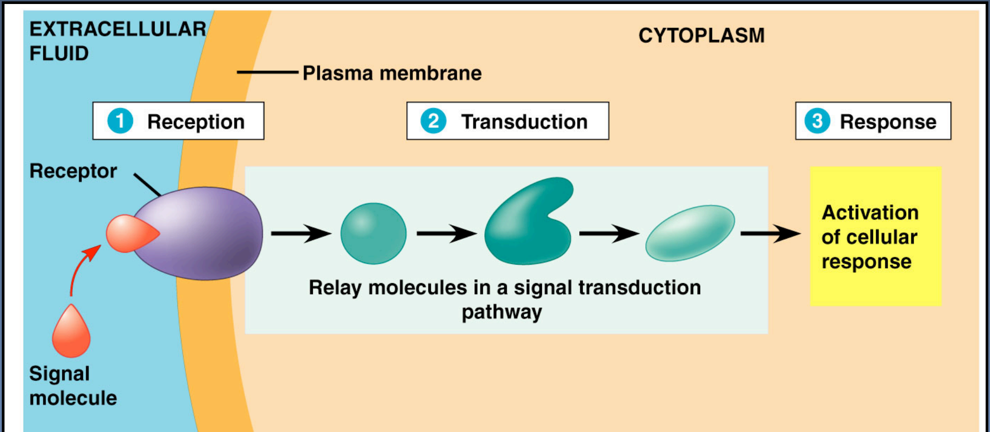
- Many multicellular organisms have trillions of cells which must communicate with one another.
- Such communication enables the creature to coordinate cellular activities ensuring the vitality of the organism.

Signal Transduction Pathways

- There are three main stages to a signal transduction pathway:
- 1. Reception—a surface protein in the cell membrane receives a signal on its surface.
- 2. Transduction—the change in the protein stimulates a series of events that leads to changes in the cell.
- 3. Response—nearly all cellular activity changes in one way or another.

Cell Signaling in Yeast

- So, how do cell signals elicit changes?
- This process is called a *signal transduction pathway*, and is a series of steps whereby the signal received by the surface of the cell is passed through a series of steps in the cell bringing about changes in *transcription* and *translation*.



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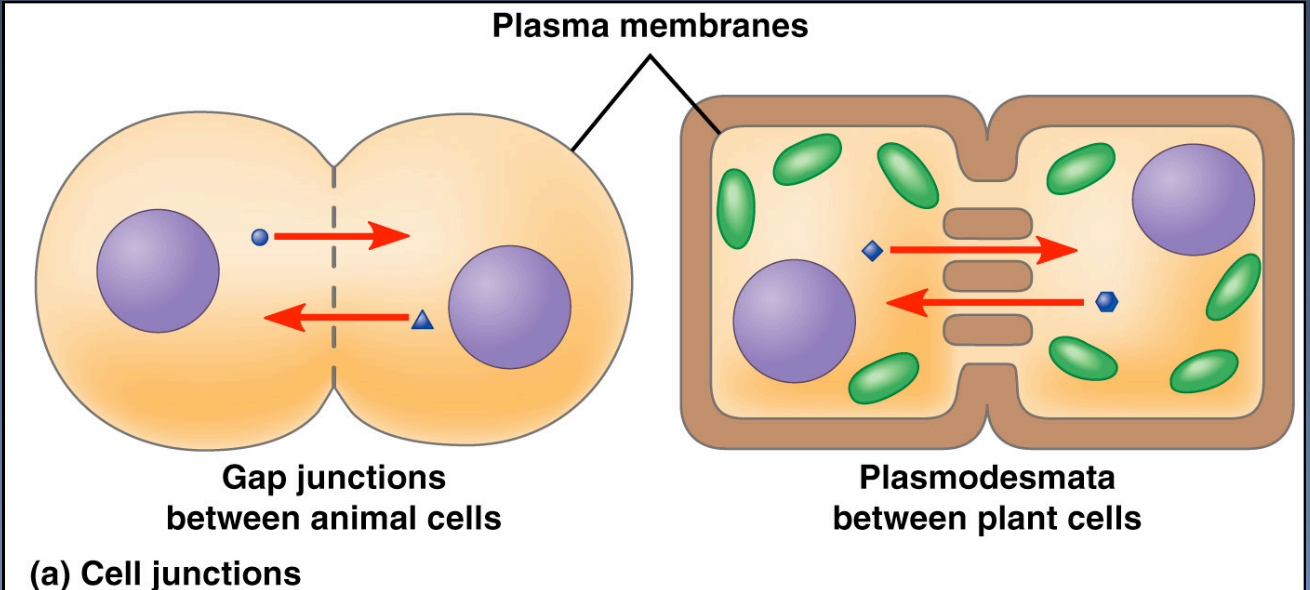
Local Signaling

- Plants and animals have cellular junctions that connect the cytoplasms of adjacent cells.
- Cytosolic substances can pass freely from cell to cell.



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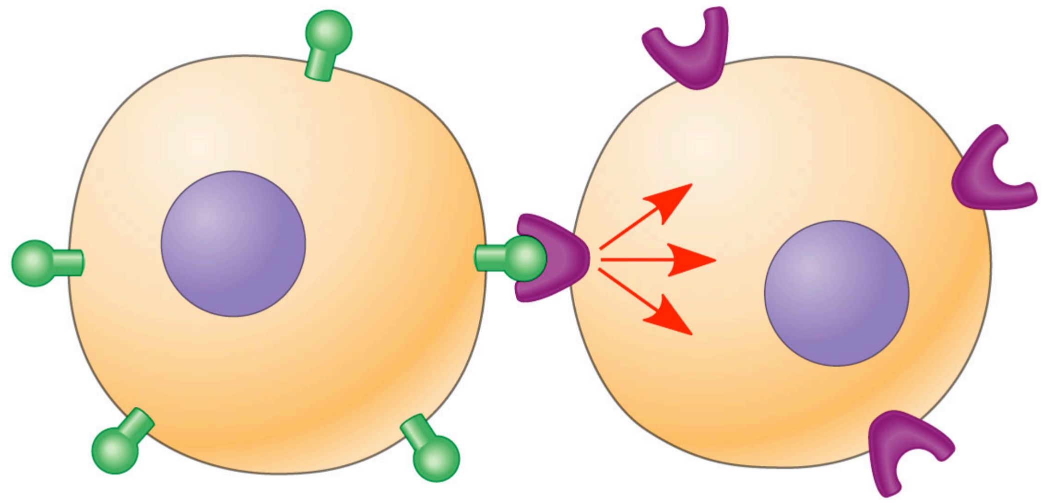
Local Signaling

- Additionally, animal cells can also communicate via direct contact of membrane-bound cell-surface molecules in a process called cell-cell recognition.



(b) Cell-cell recognition

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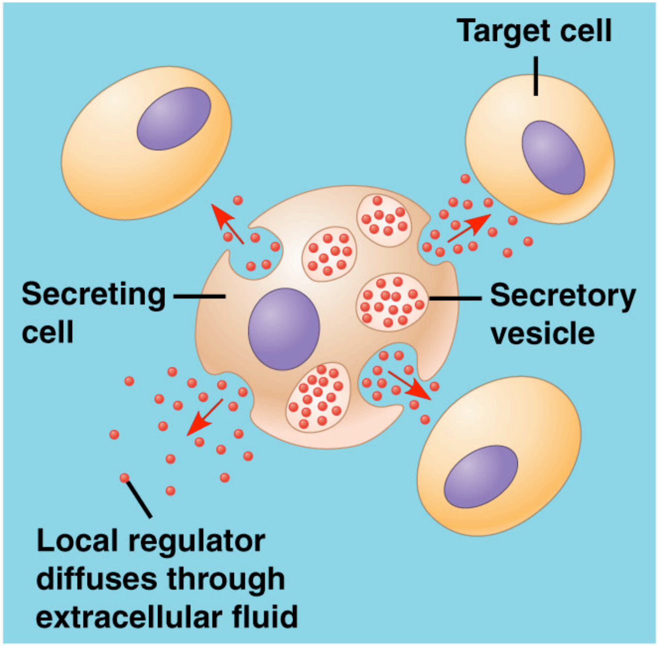
Local Signaling

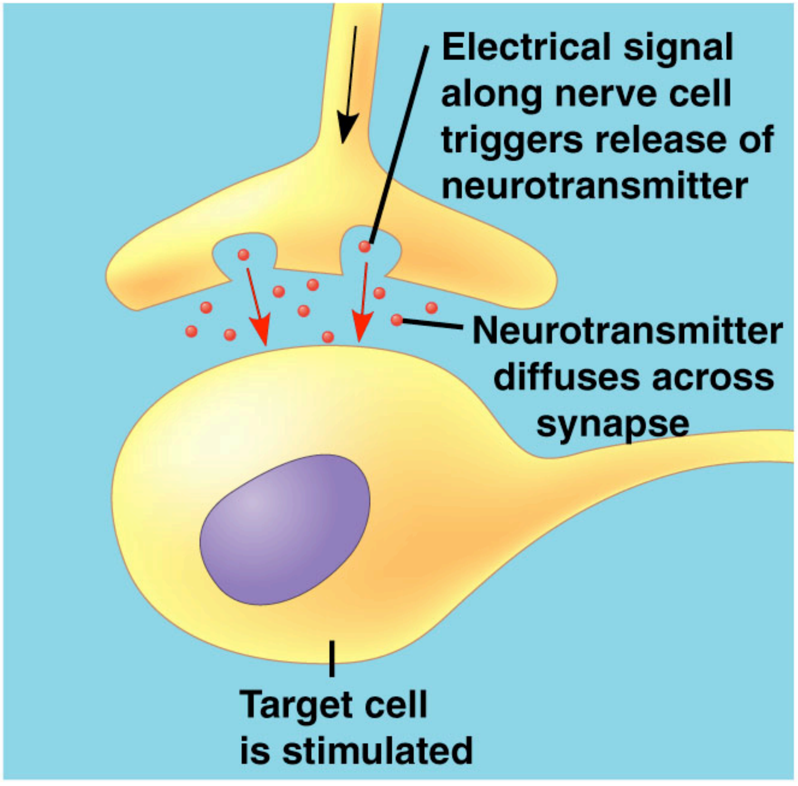
- Local regulators travel short distances and influence cells in the immediate vicinity.
- This type of local signaling is called paracrine signaling.



(a) Paracrine signaling

Local Signaling

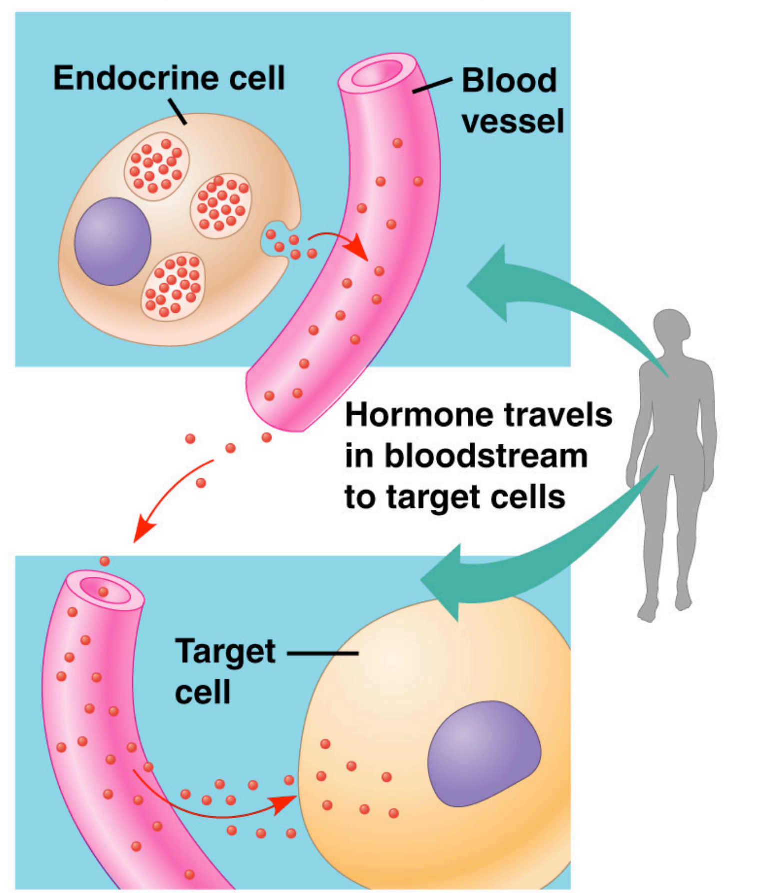
- Another type of local signaling is called <u>synaptic signaling</u>. This occurs in an animal's nervous system and involves the release of a chemical signal in response to an electrical signal from the nervous system.
- These neurotransmitters diffuse across the synapse and elicit a change in the target cell.



(b) Synaptic signaling

Long-Distance Signaling

- Plants and animals use hormones for long-distance signaling.
- This type of signaling is also called endocrine signaling, and involves specialized cells releasing hormones into vessels of the circulatory system. When these hormones reach the target cells, they elicit a change.



(c) Hormonal signaling

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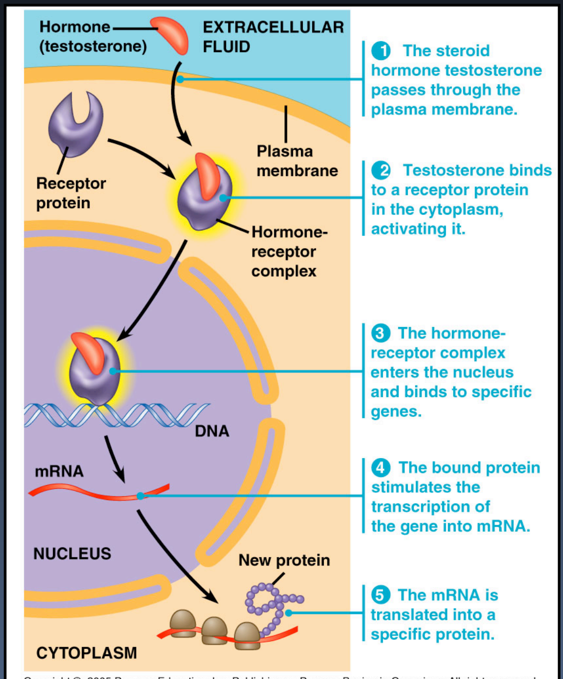
So, Now What Happens?

- 1. A receptor molecule on the surface of a cell must recognize the chemical signal and the information it carries.
- 2. The transduction of the signal must occur before the cell can respond.
- 3. The cell must then respond.

3 Stages of Cell Signaling

- 1. Reception. This is the process by which the target cell detects the outside signal.
  - Detection occurs when a signal molecule binds to a receptor protein on the surface or inside the cell.



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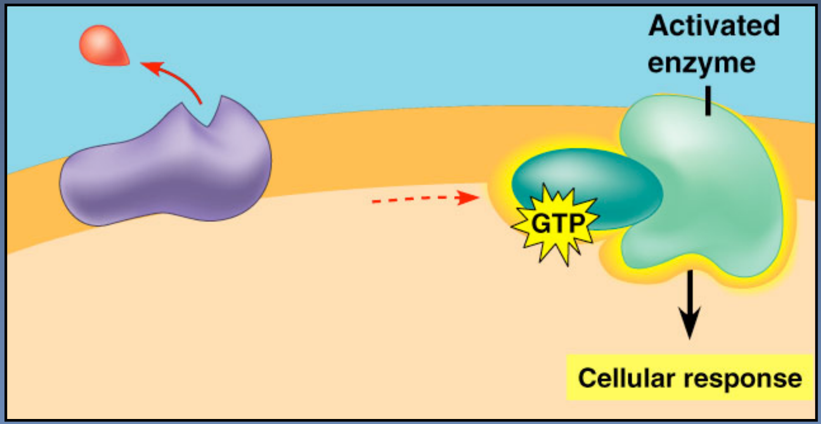
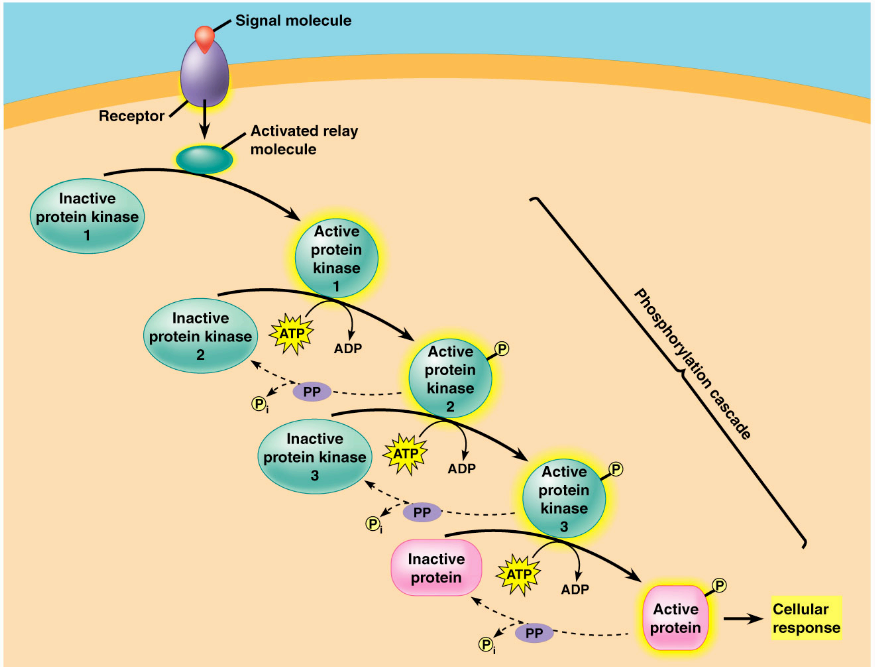


3 Stages of Cell Signaling

- 2. Transduction. When the signaling molecule changes the receptor protein in some way, transduction is initiated. This is the stage where the signal is converted into a form bringing about a specific cellular response.

3 Stages of Cell Signaling

- Transduction can occur in one step, but often involves many steps.



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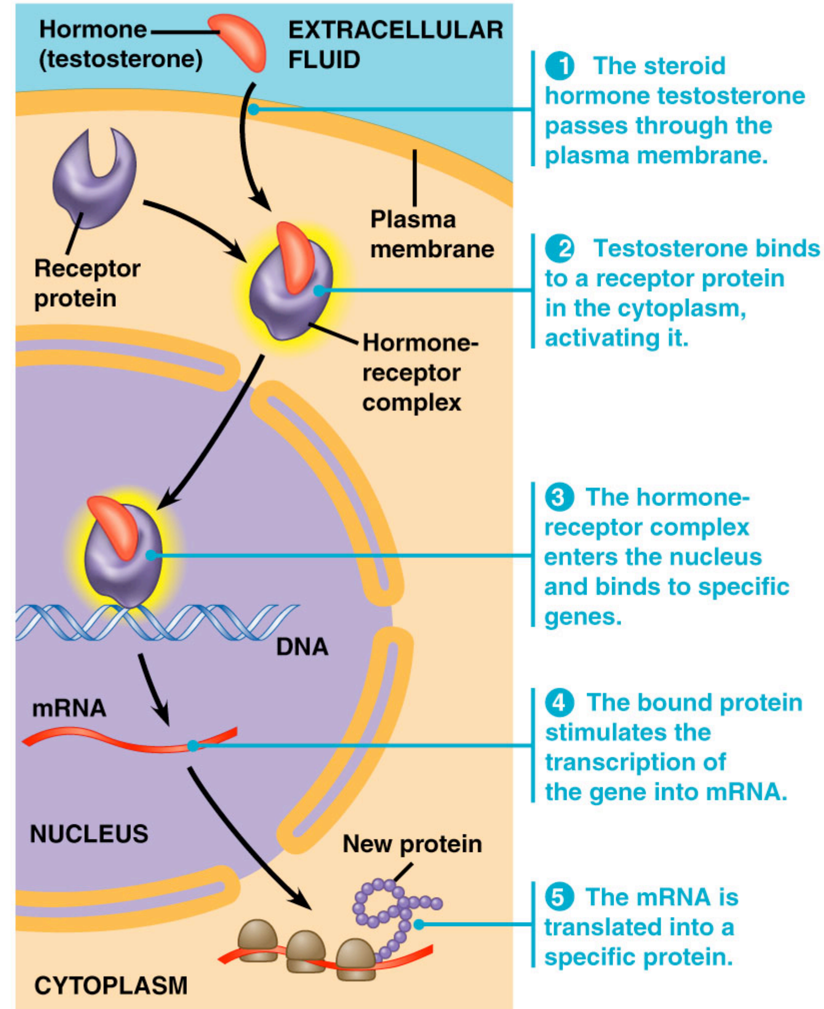

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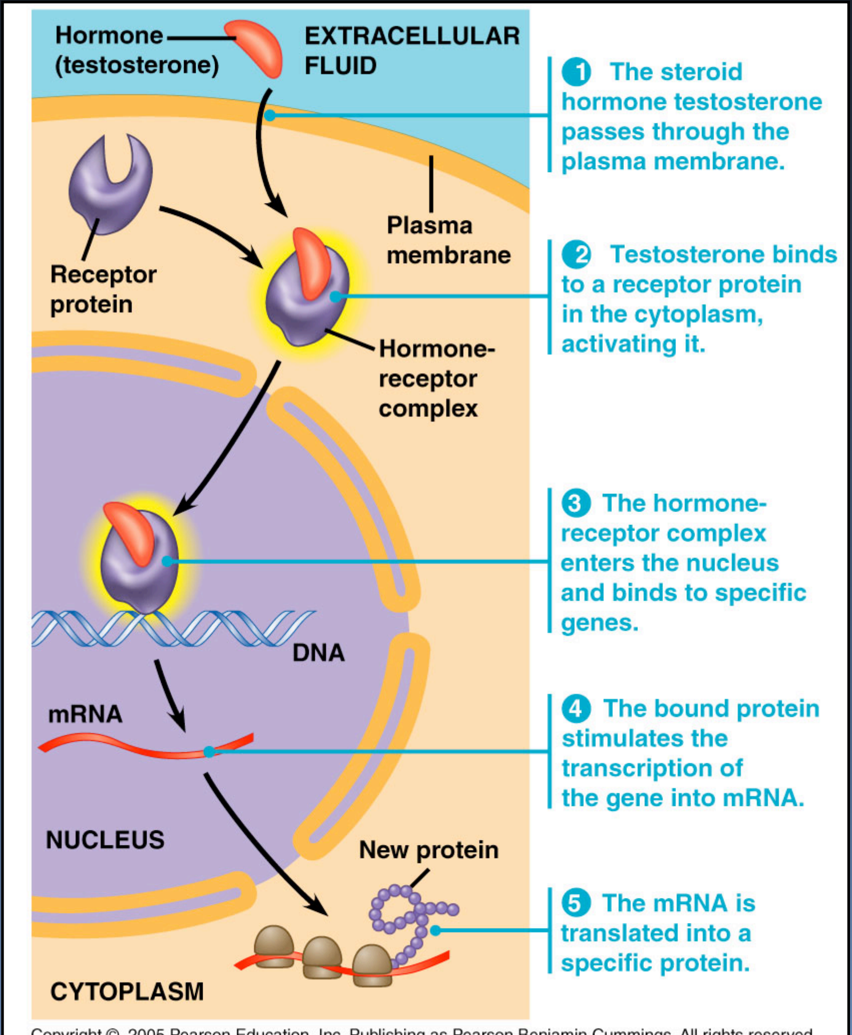
3 Stages of Cell Signaling

- 3. <u>Response</u>. The response occurs when the transduced signal triggers a specific cellular response.



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1. Reception

- The signal created is received by a receptor protein on <u>or</u> in the target cell.
- The signal-receptor interaction is similar to the enzyme-substrate reaction.
- The signal behaves as a ligand—a molecule that binds specifically to another molecule.
- This binding generally causes a shape change that allows for further events to occur inside the cell.

1. Reception

- Thus, the ligand binding acts similarly to the binding of an allosteric regulator onto that of an enzyme.

Plasma Membrane Receptors

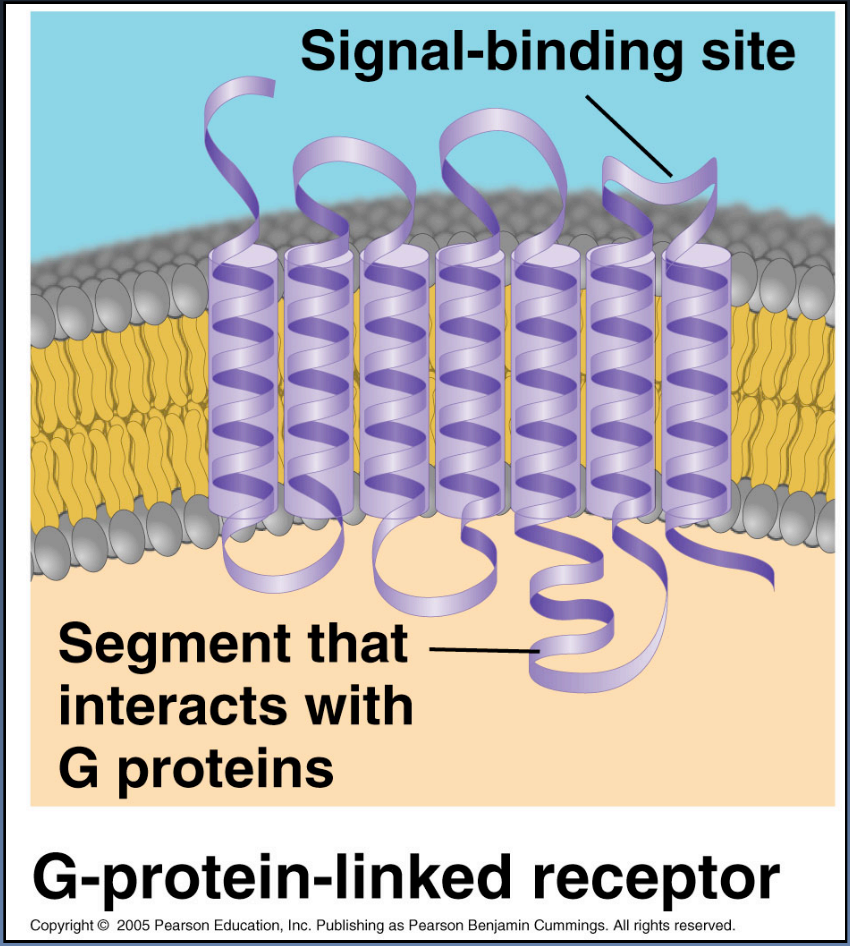
- Most water-soluble signaling molecules bind to sites on receptor proteins embedded in the cell’s plasma membrane.
- The signal is then transmitted to the inside of the cell.

Plasma Membrane Receptors

- There are three major types of membrane receptors:
  - A. G protein-coupled receptors
  - B. Receptor tyrosine kinases
  - C. Ion channel receptors

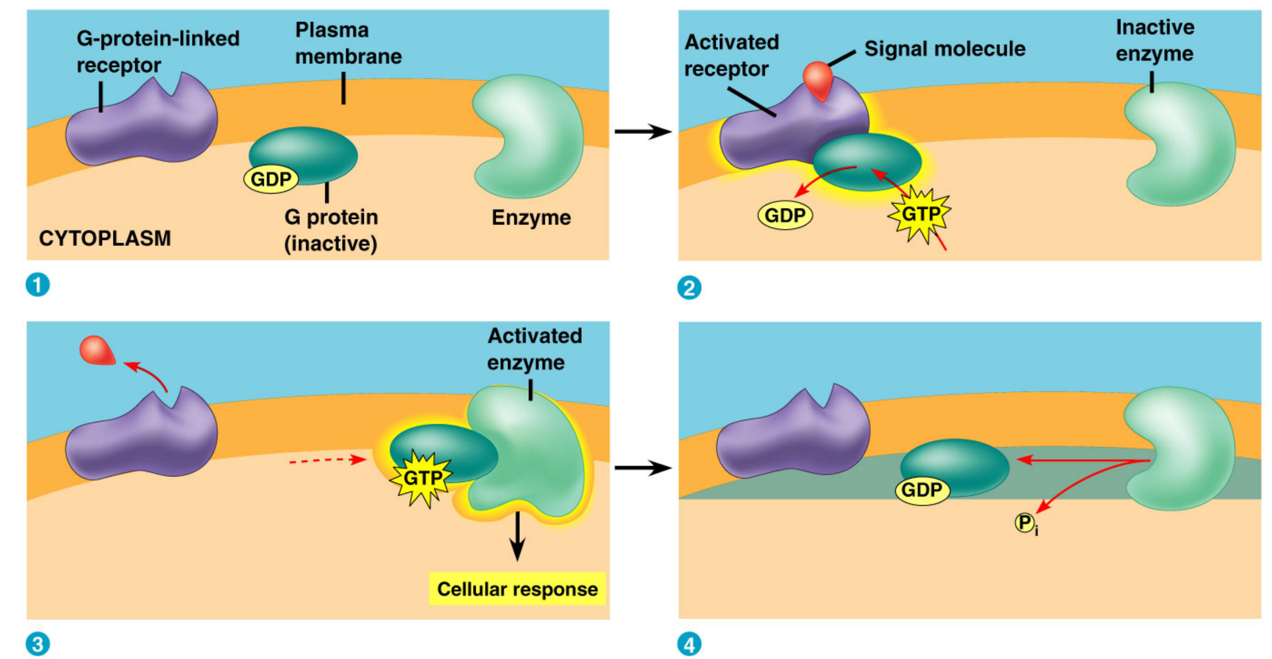
A. G Protein-Coupled Receptors

- These receptors are embedded in the plasma membrane and work with the help of a G-protein.
- G-proteins are proteins that bind energy rich GTP molecules.
- They are all similar in structure and have seven α helicies which span the membrane.



A. G Protein-Coupled Receptors

- G-protein receptors are embedded in the plasma membrane. When they receive the signal, they activate the associated G-protein which, in turn, activates an enzyme starting the signal cascade.



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A. G Protein-Coupled Receptors

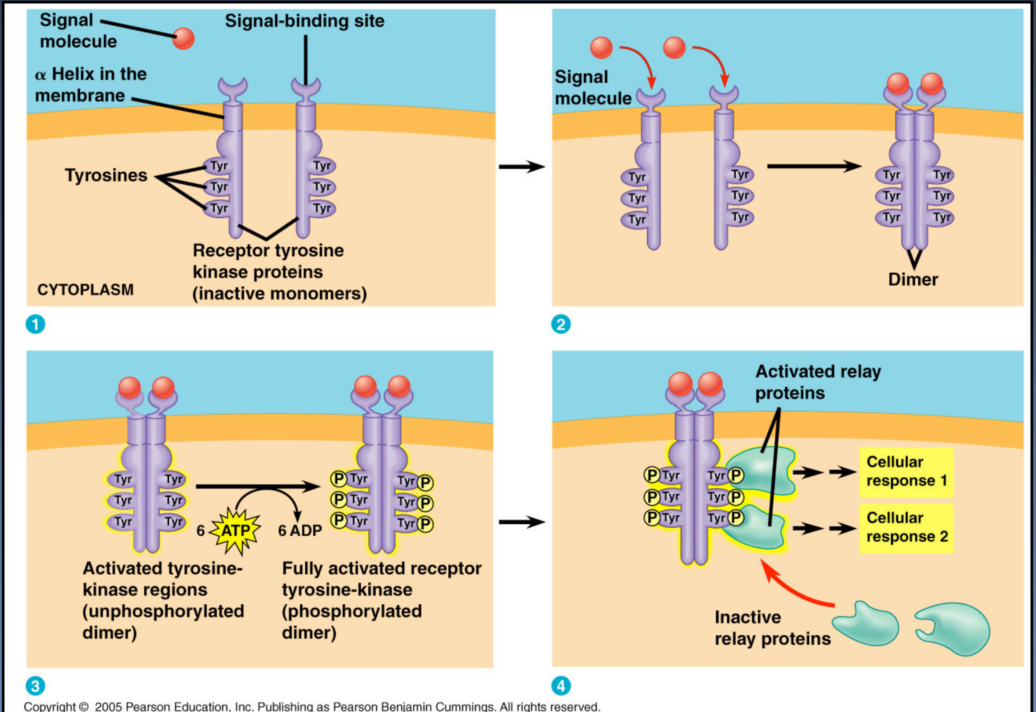
- These protein receptors are very widespread and diverse in their functions.
- They are involved in embryonic development and sensory reception such as vision and smell, as well as many other functions.
- They bind:
  - Odors
  - Pheromones
  - Hormones
  - Neurotransmitters

A. G Protein-Coupled Receptors

- G-protein systems are involved in numerous human diseases.
- Cholera, pertussis, and botulism are common bacteria-induced illnesses that produce toxins which interfere with G-protein function.
  - This interference causes the symptoms associated with the illnesses-massive diarrhea, muscle contraction, coughing attacks, etc.

B. Receptor Tyrosine Kinases

- Receptor tyrosine kinases belong to a major class of plasma membrane receptors which have enzymatic activity.



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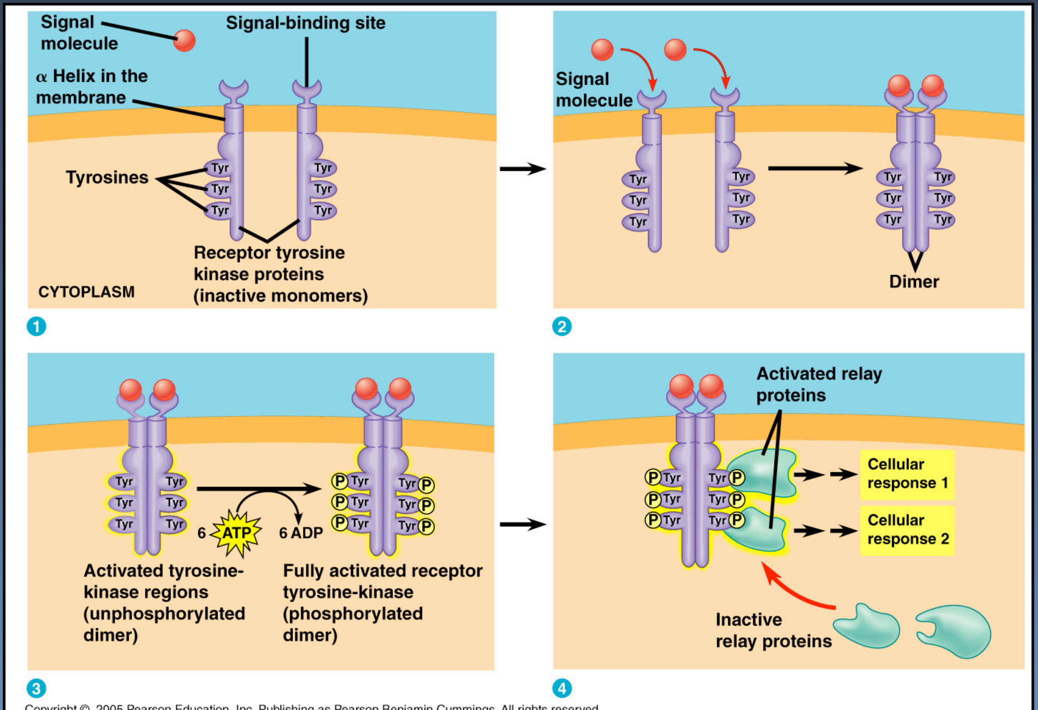
B. Receptor Tyrosine Kinases

- The part of the receptor protein which extends into the cytoplasm acts as the tyrosine kinase—the enzyme that catalyzes the transfer of the phosphate from ATP to the amino acid tyrosine on the substrate protein.



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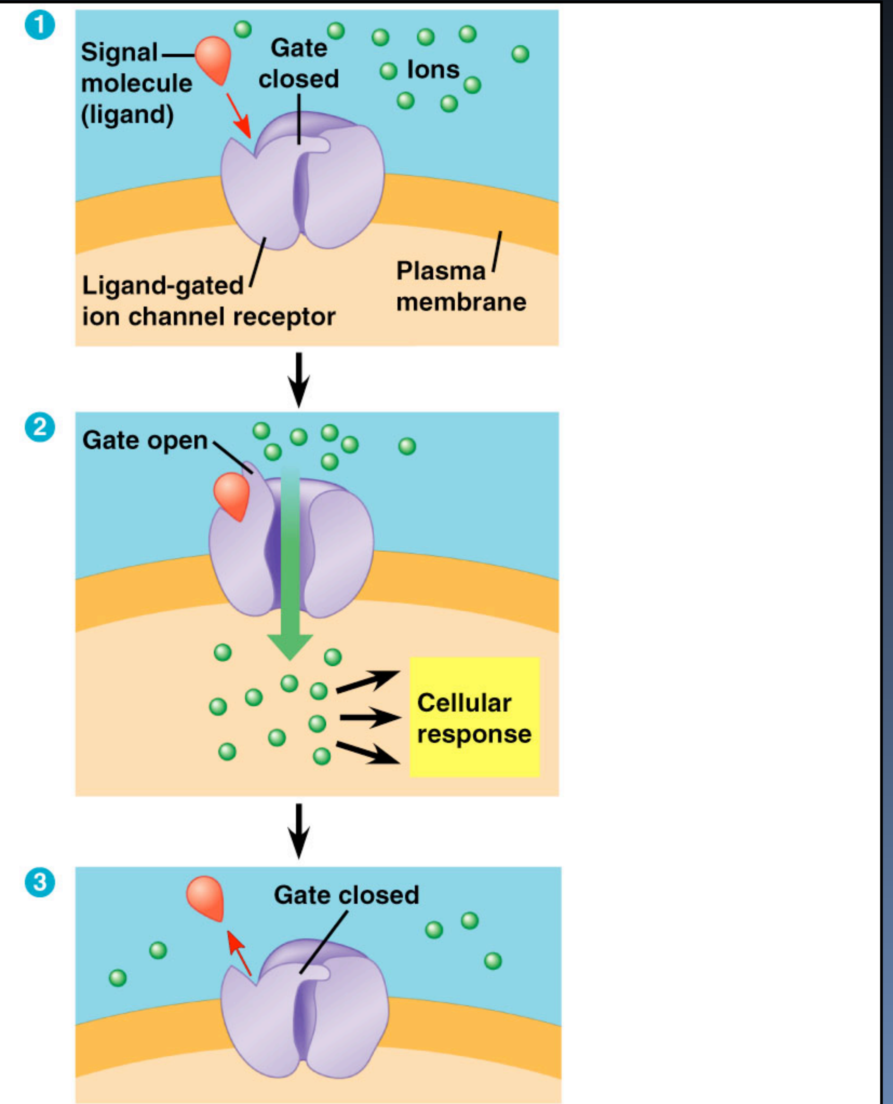
B. Receptor Tyrosine Kinases

- One receptor tyrosine kinase can activate a number of different transduction pathways.
- The ability of these receptors to trigger so many pathways is a key difference between receptor tyrosine kinases and G-protein coupled receptors.

C. Ion Channel Receptors

- Ligand-gated ion channels are a type of membrane receptor with a region that acts as a gate.



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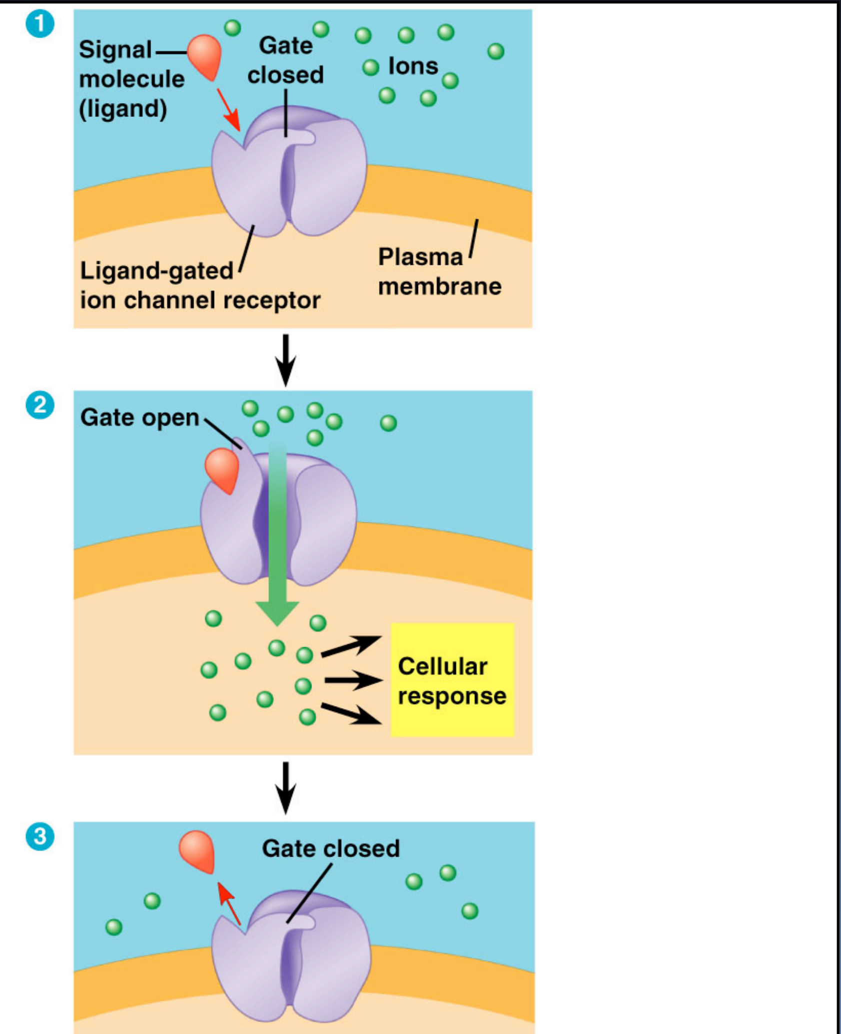
C. Ion Channel Receptors

- When a signaling molecule binds to the receptor, a conformational change occurs and a gate opens or closes.
- This opening or closing allows for the flow or blockage of specific ions—eg. Ca^{2+}, Na^{+}, etc.



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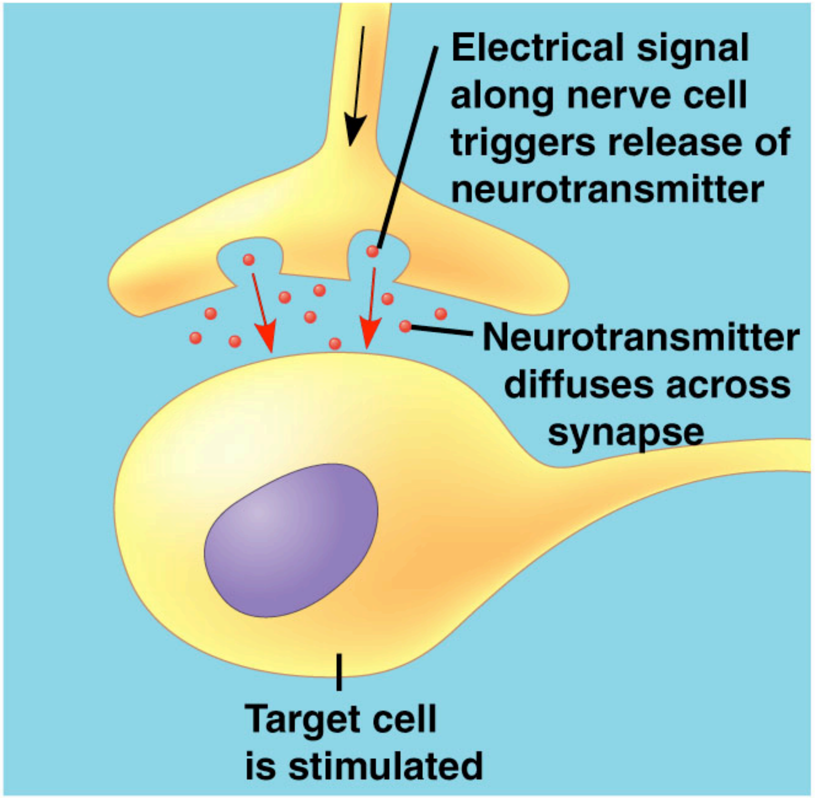
C. Ion Channel Receptors

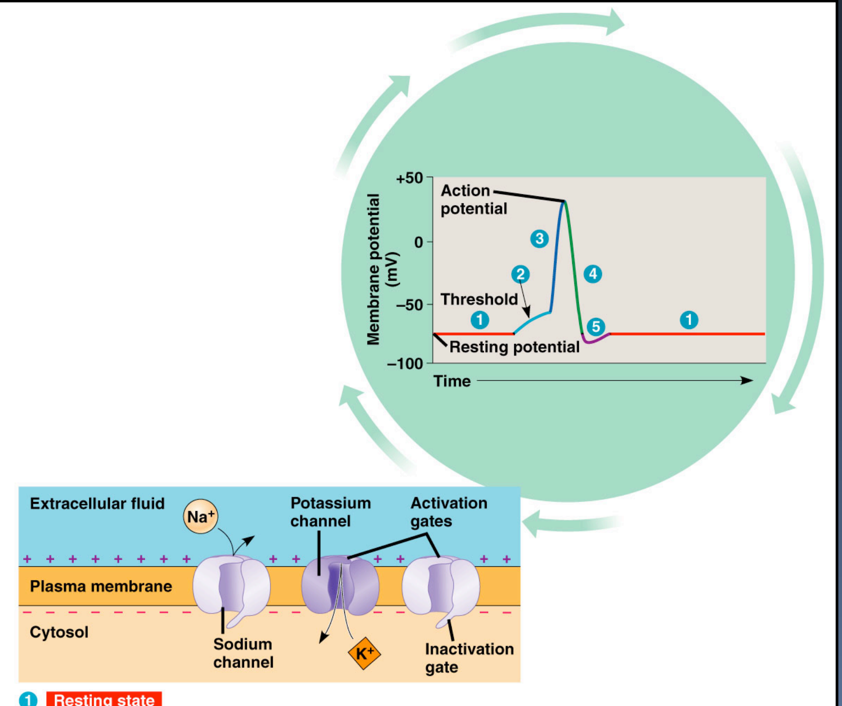
- These channels are very important to the nervous system.
- When a neurotransmitter molecule is released at the synapse, it acts as a ligand and binds to the ion channel on the receiving cell.



(b) Synaptic signaling

C. Ion Channel Receptors

- Binding, in turn, causes the channel to open and ions flow through the gate triggering an electrical signal that rapidly moves along the length of the receiving cell.



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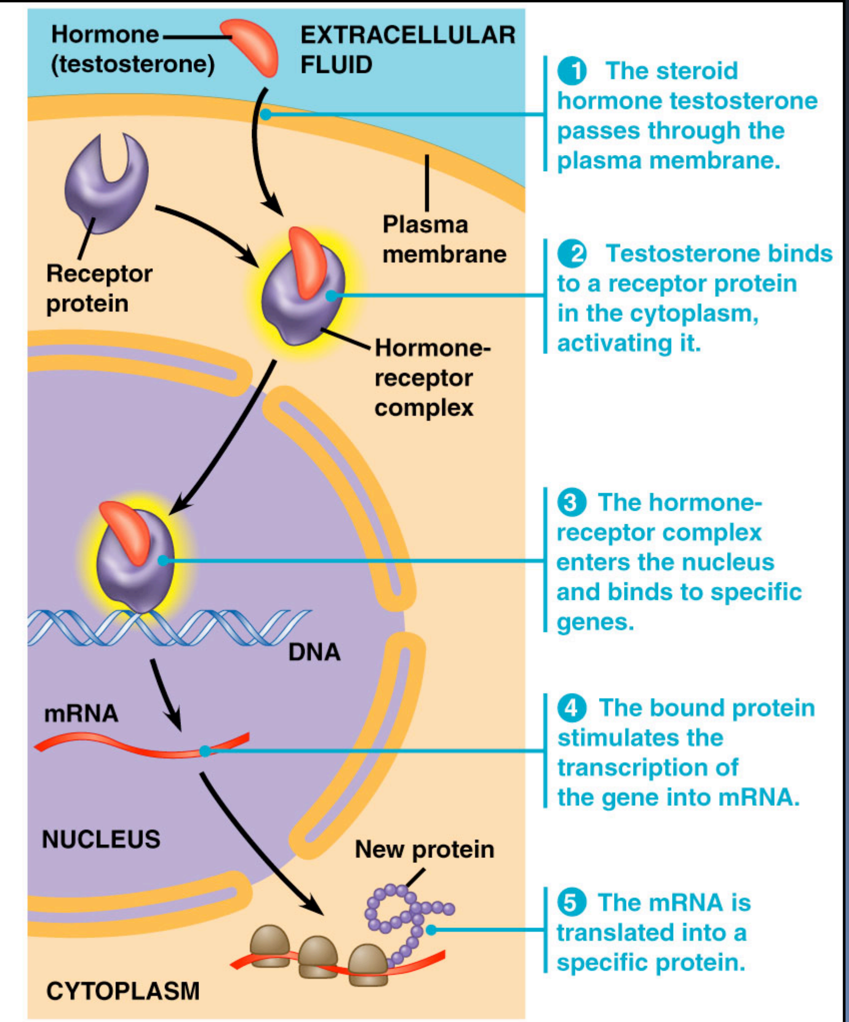
Intracellular Receptors

- Intracellular receptor proteins can also be found in the nucleus or the cytoplasm of target cells.
- In order to reach these receptors, the chemical messenger must pass through the plasma membrane.
- Steroid hormones, thyroid hormones, and nitric oxide are common messengers that pass through the plasma membrane.

Intracellular Receptors

- Once they pass through the membrane, the signals activate a receptor protein which then enters the nucleus and turns on transcription and translation.



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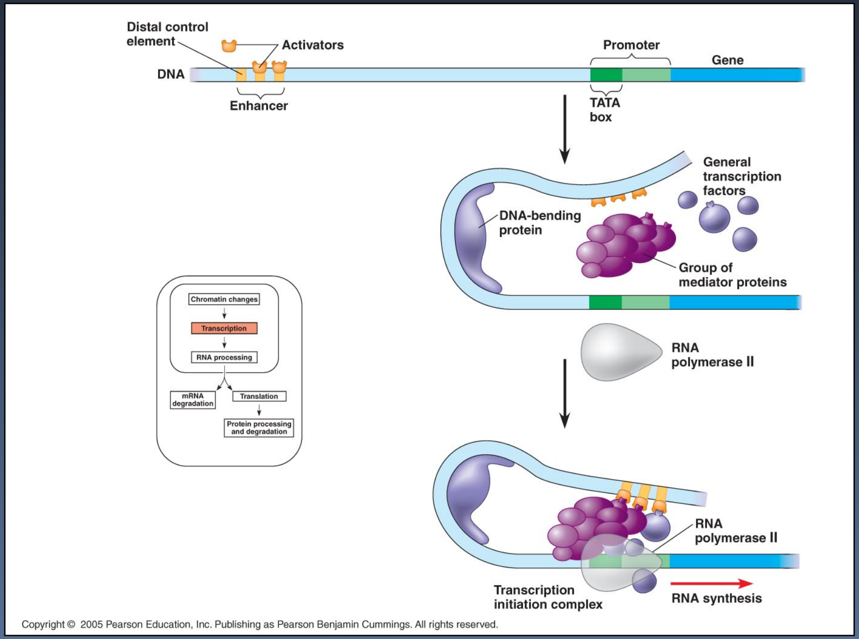
Intracellular Receptors

- How does this happen?
- These activated receptor proteins act as transcription factors which control the transcription of genes into mRNA, and ultimately the production of protein.

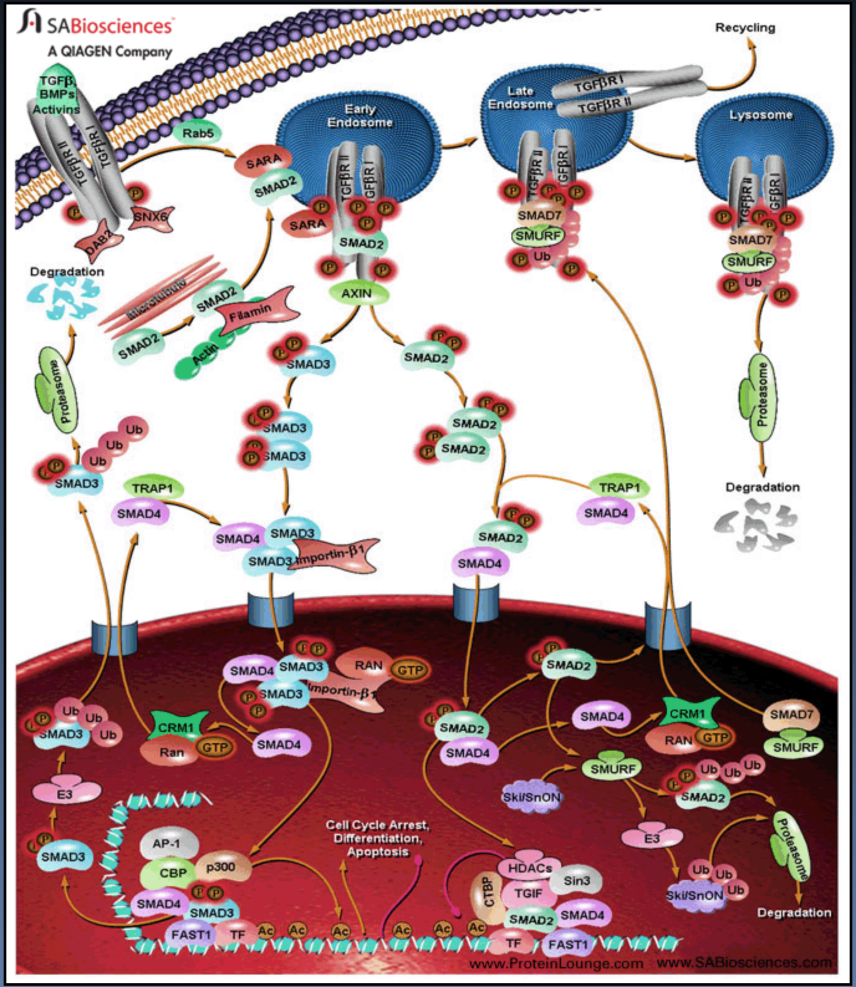


2. Signal Transduction

- Cell signaling is usually a multistep pathway.
- These steps can include:
  - The addition of phosphate groups.
  - The removal of phosphate groups.
  - Release of small molecules or ions which act as messengers.

2. Signal Transduction

- By this method, the signal is often amplified as a small number of initial molecules interact with a larger number of molecules in the next step of the pathway.



http://sabiosciences.com/pathway.php?sn=SMAD_Signaling_Network

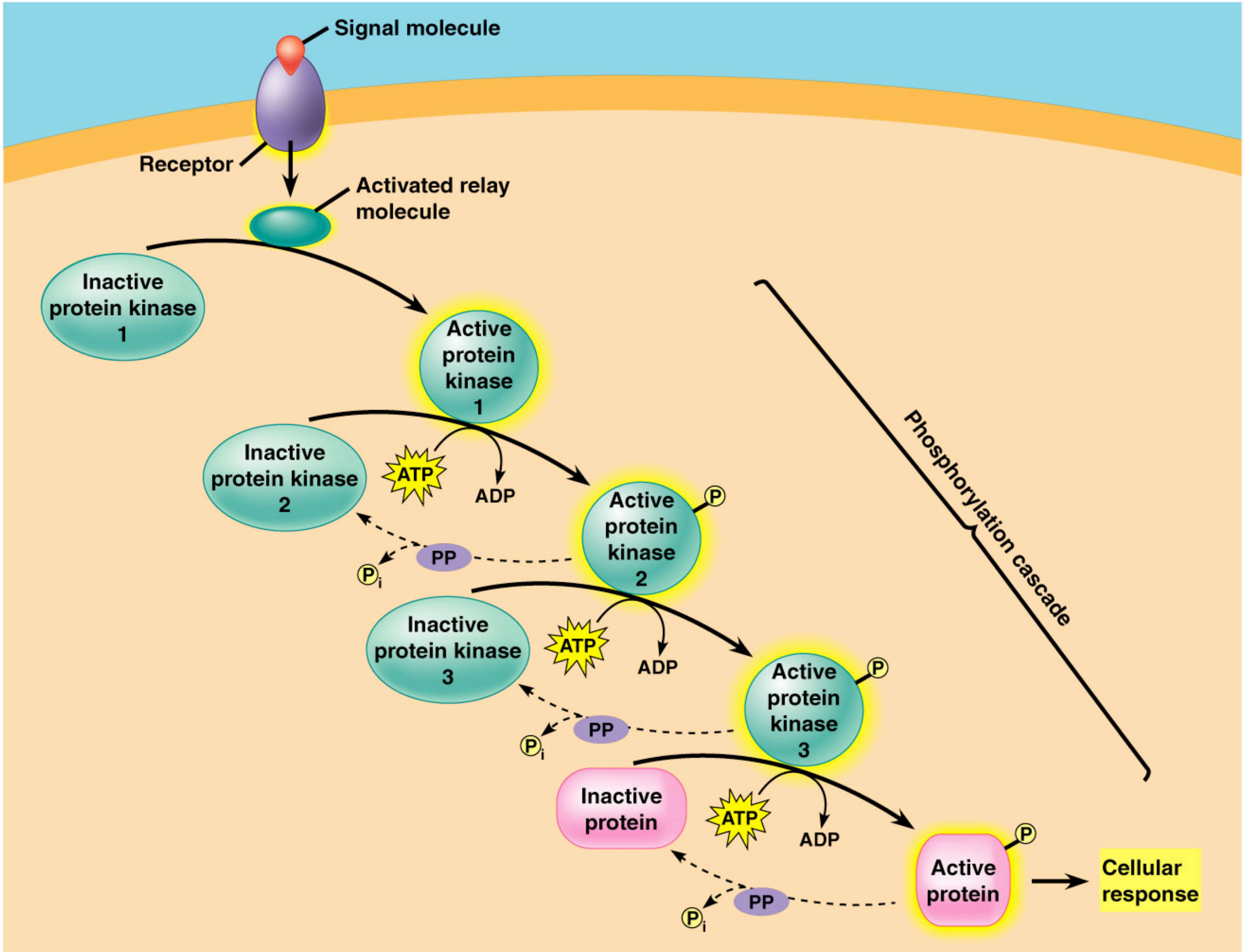
Signal Transduction Pathway

- The first step in the pathway is the attachment of the signaling molecule to the receptor protein.
- From here, the relay molecules (mostly proteins) transmit the signal to the next step—usually resulting in a change in protein conformation.
- These pathways can regulate both the activity of the proteins, or the synthesis of them.

Protein Kinases

- The phosphorylation and dephosphorylation of proteins is a common cellular mechanism for regulating protein activity.
  - Protein kinases are enzymes that transfer a phosphate group from ATP to a protein.
    - These are very important—at least 2% of our genes code for protein kinases.
- Each cell may have more than 100 different kinds of protein kinases.

Protein Kinases



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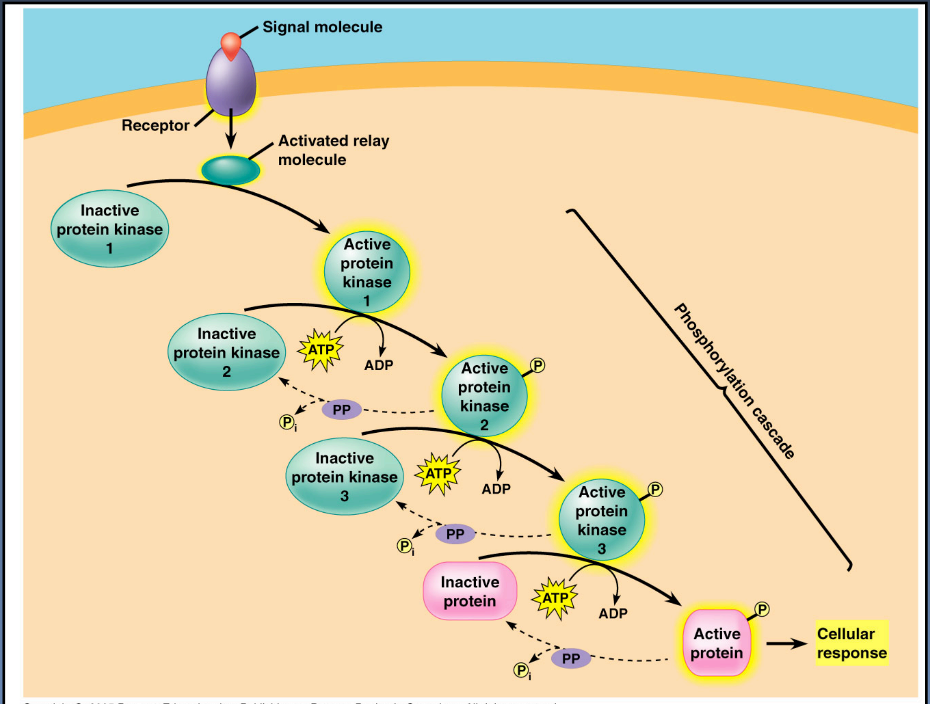
Protein Kinases

- Many relay molecules in a signal transduction pathway are protein kinases; these often act on other protein kinases in the pathway.



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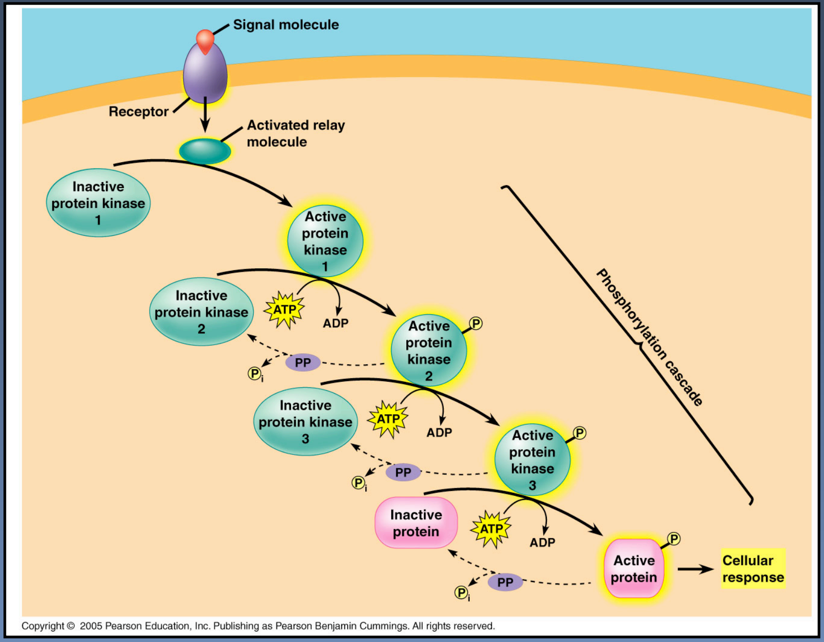
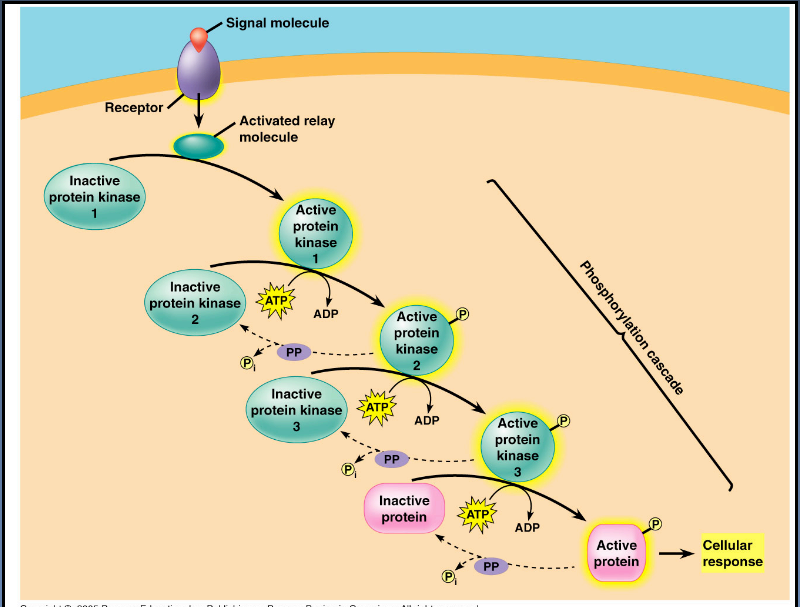
Phosphorylation Cascade

- In such a cascade, a series of different molecules in the pathway are phosphorylated, and in turn, each molecule adds a phosphate group to the next one in the series.



Phosphorylation Cascade

- Generally speaking, phosphorylation activates each molecule, and dephosphorylation returns it to its inactive form; each often results in a change in molecular shape.



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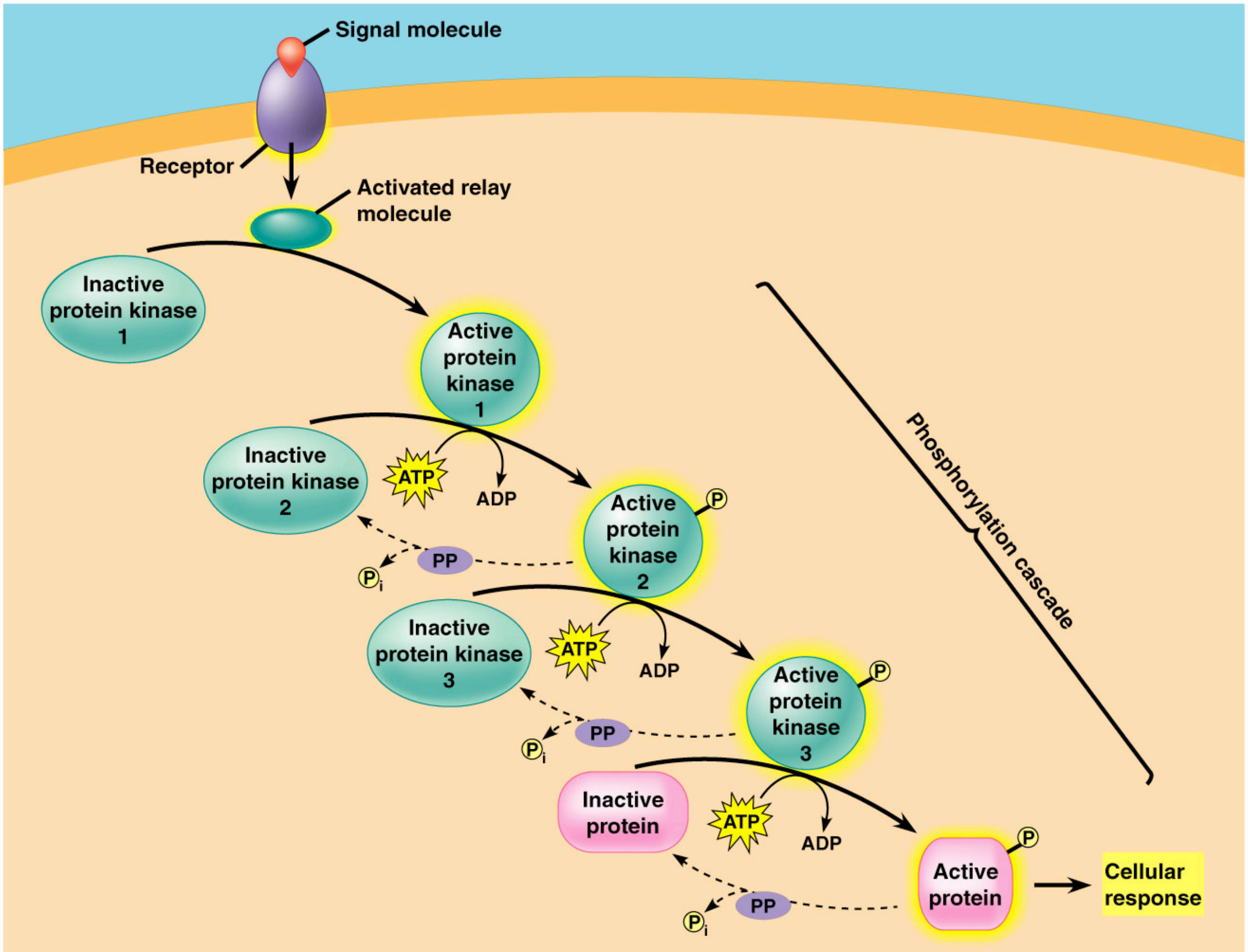
Protein Phosphatases

- As we said, phosphorylation and dephosphorylation of proteins are common cellular mechanisms for regulating protein activity.
  - Phosphatases rapidly remove phosphate groups from proteins in a process called dephosphorylation.
  - They act as off switches in the signal pathway, and they make the protein kinases available for reuse.

Protein Phosphatases



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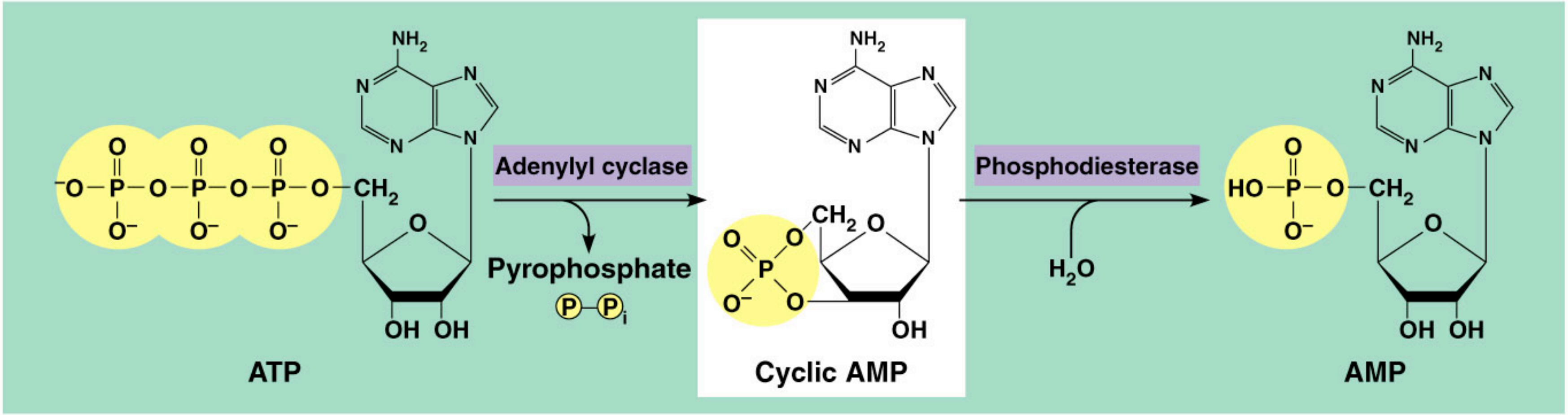
Second Messengers

- Some components of the signal transduction pathways are NOT proteins.
- Many of these pathways involve second messengers, which are often small, water soluble molecules or ions. Additionally, they can easily diffuse through the cytoplasm.
- Second messengers participate in signal transduction pathways initiated by both G protein-coupled receptors and receptor tyrosine kinases.
  - cAMP and Ca^{2+} are the two most commonly used second messengers.

Cyclic AMP

- Embedded within the membrane is an enzyme called adenylyl cyclase which converts ATP to cAMP in response to the extracellular signal.



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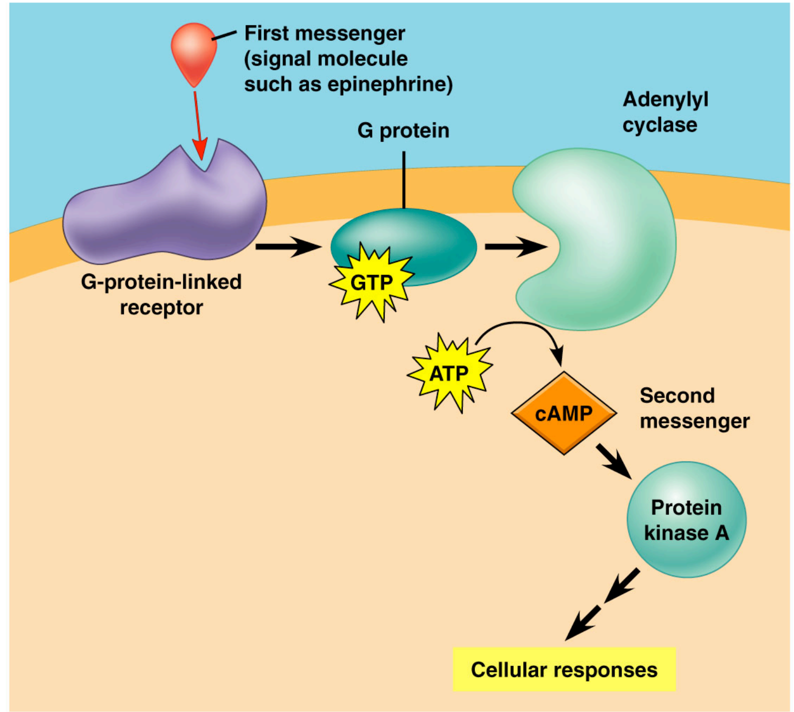
Cyclic AMP

- In response to the external signal, a receptor protein activates adenylyl cyclase, catalyzing the synthesis of many molecules of cAMP.
- Thus, in a matter of seconds, the amount of cAMP can be dramatically increased.



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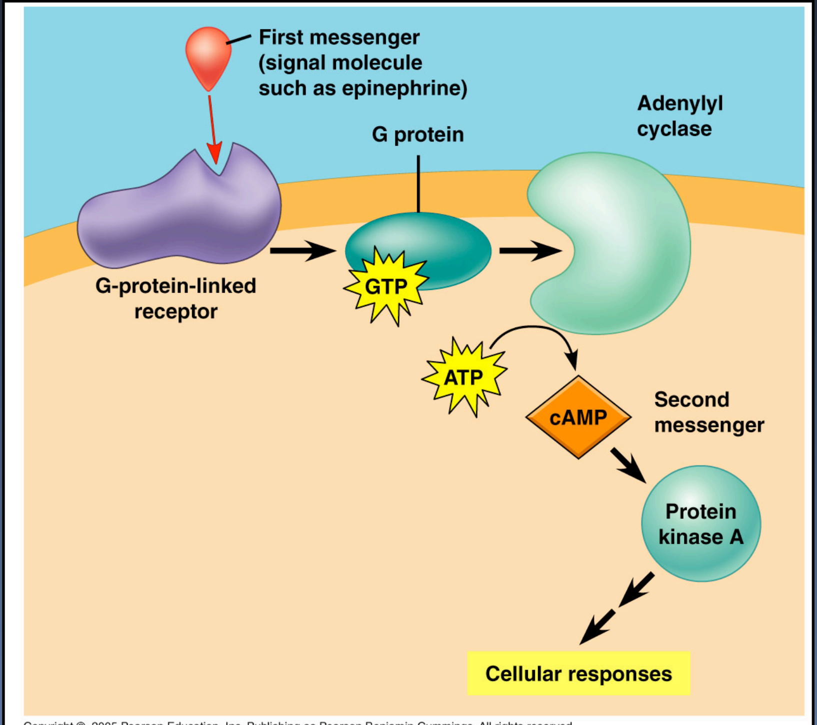
Cyclic AMP

- Not long after cAMP is created, phosphodiesterase converts it to AMP and the pathway shuts down.
  - The immediate effect of cAMP is usually the activation of a serine/threonine kinase called protein kinase A.
  - This leads to further transmission of the signal.



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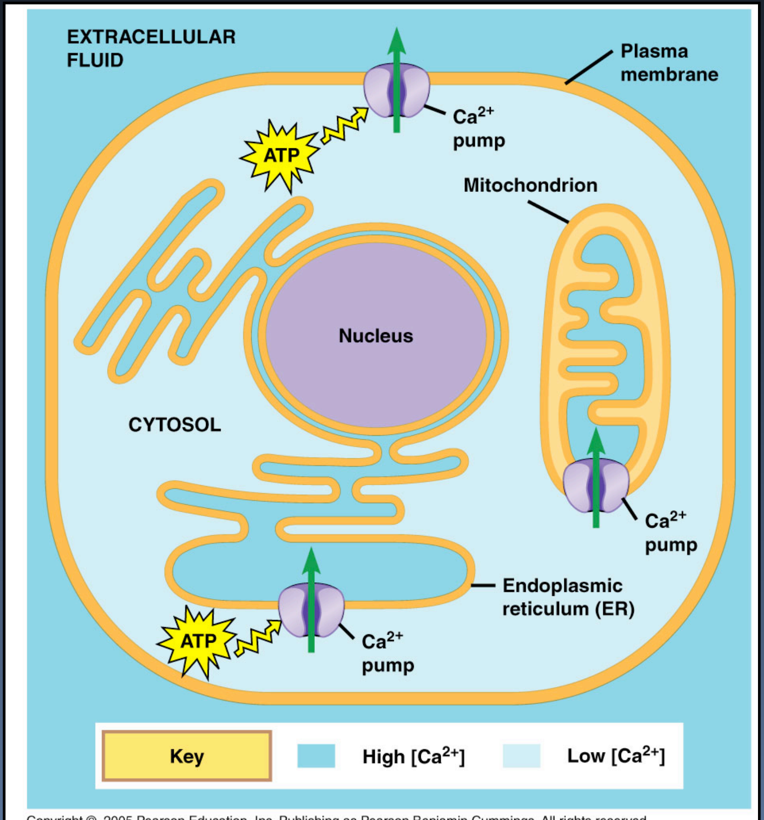
Cyclic AMP

- Cell metabolism can be further regulated by other G-protein systems that inhibit adenylyl cyclase.
- In such cases, a different signaling molecule activates different receptors which, in turn, activate inhibitory G-proteins.

Ca^{2+} and IP_3

- Many signaling molecules induce responses in their target cells by signal transduction pathways.
- These pathways increase the cytosolic concentration of Ca^{2+} ions.



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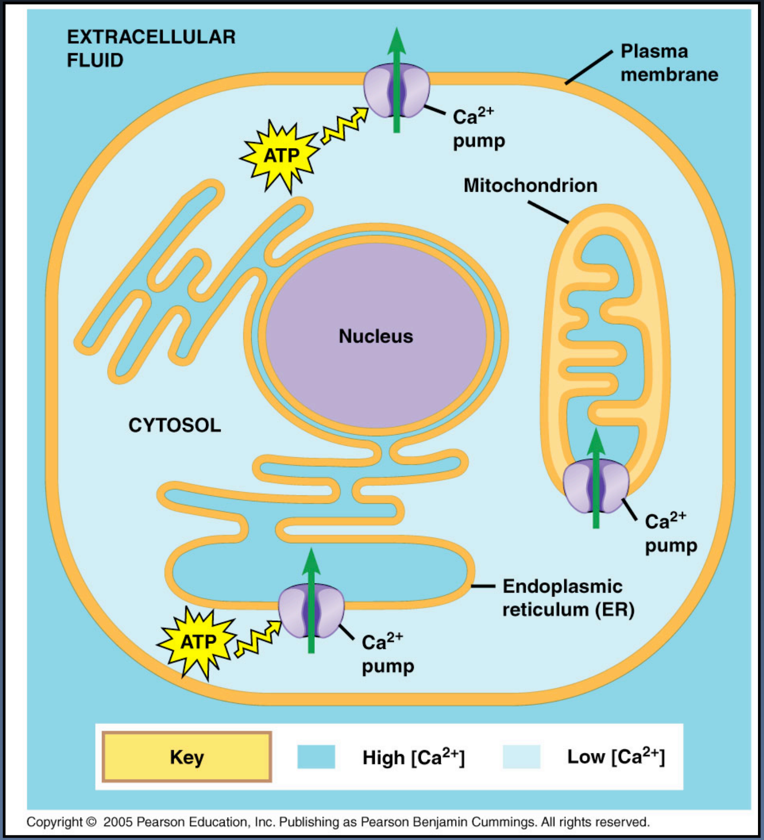
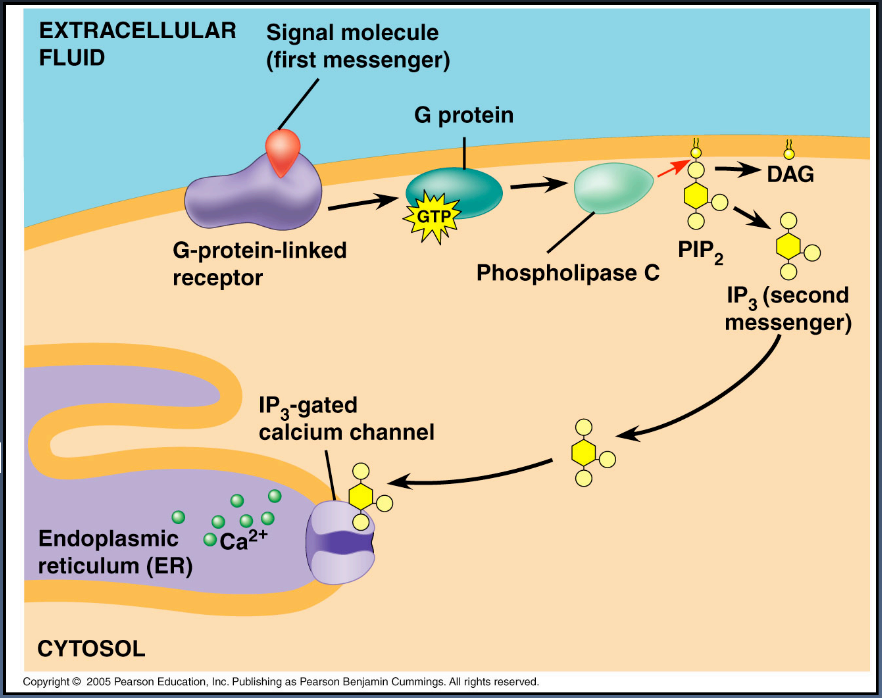
Ca^{2+} and IP_3

- Calcium is actively pumped out of the cell and thus the concentration of Ca^{2+} is about 10,000x *lower* in the cytoplasm of the cell.



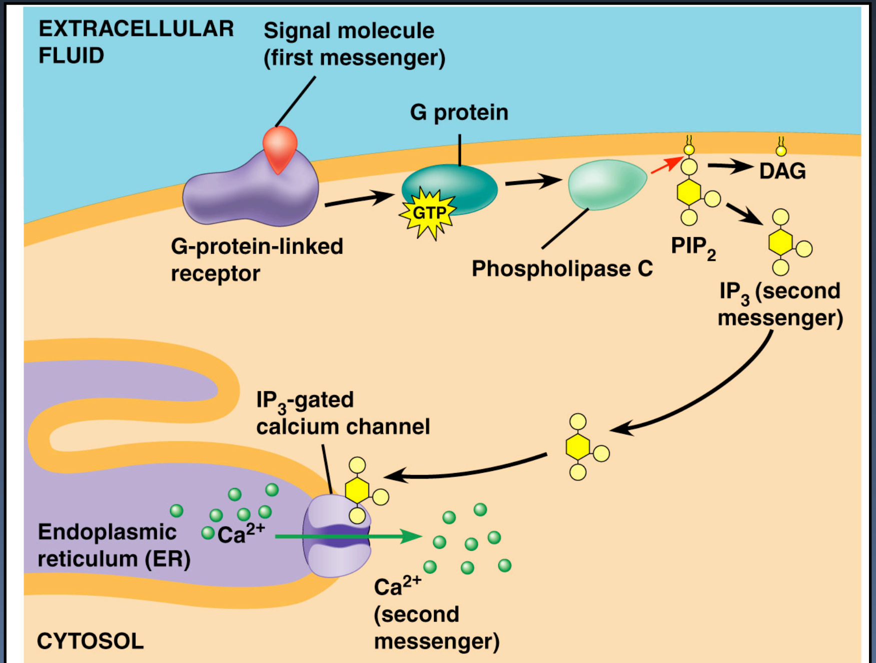
Ca^{2+} and IP_3

- When an appropriate signal is received, a variety of second messengers get involved resulting in an increase in cytoplasmic calcium concentration.



Ca^{2+} and IP_3

- IP_3 and diacylglycerol are two messengers produced by the alteration of a phospholipid in the plasma membrane.
- This leads to the increase in the Ca^{2+} concentration within the cytoplasm.



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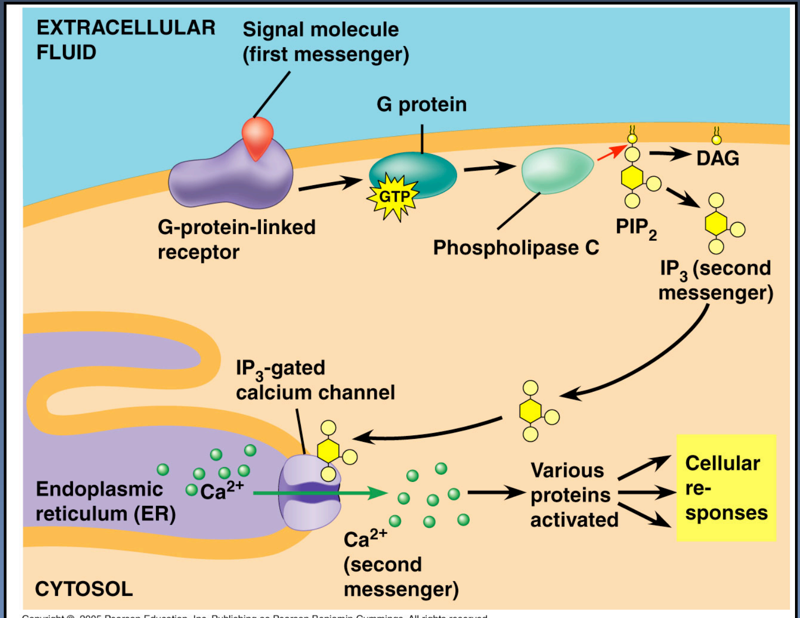
3. Cellular Responses

- Many signaling pathways ultimately regulate protein synthesis, usually by turning specific genes on and off.



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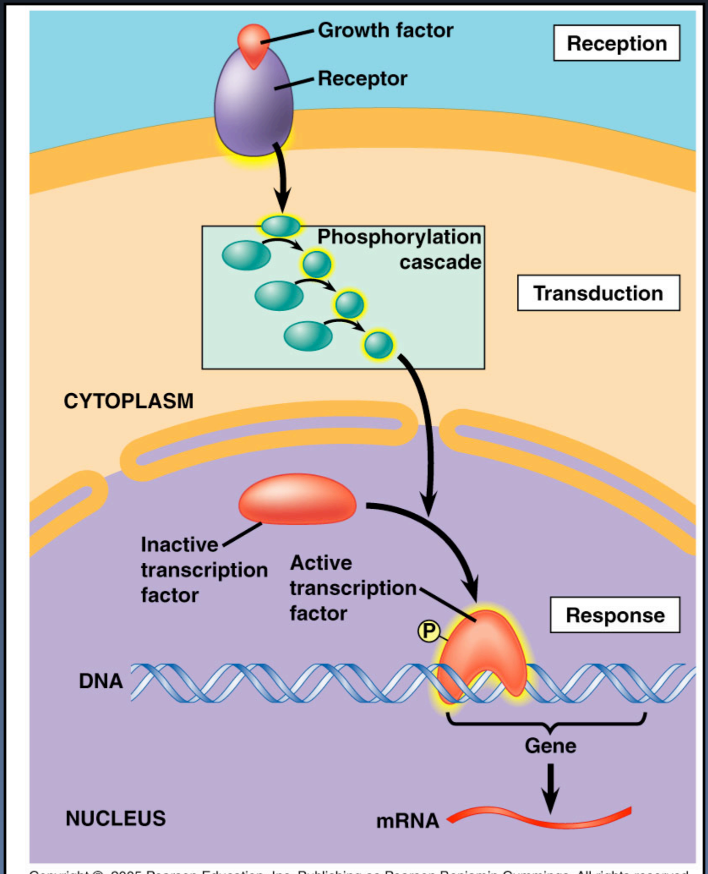

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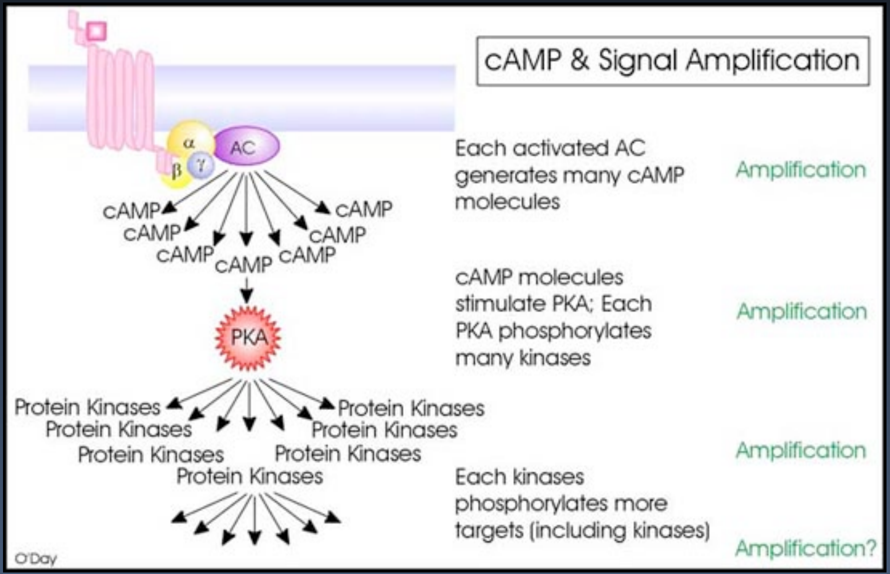
Fine Tuning Cellular Response

- There are many benefits to having multiple events in a signal transduction pathway.
- Two important benefits:
  - 1. They easily amplify the signal.
  - 2. They provide different points where the response can be regulated.

1. Signal Amplification

- Elaborate enzyme cascades amplify a cell's response to an external signal.
  - Such cascades serve to activate many more products in the following stage—in much the same way as occurs during a nuclear chain reaction.



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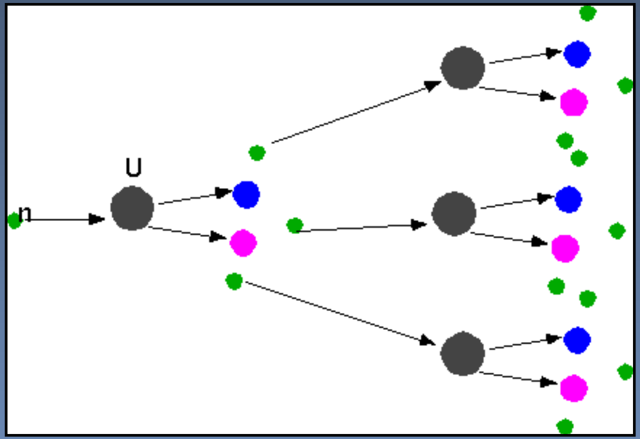

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1. Signal Amplification

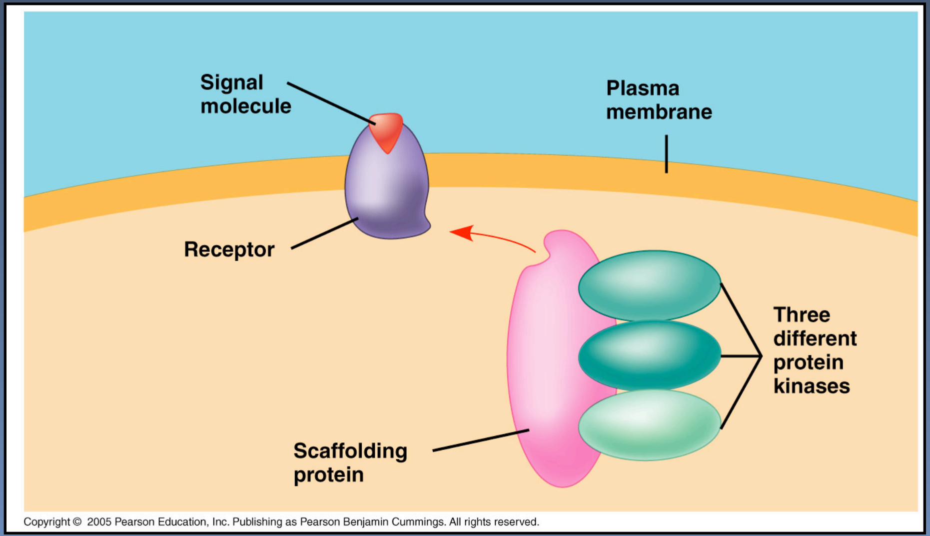
- The reason this occurs is because the activated proteins remain in the cytoplasm long enough to process numerous molecules of substrate before they become deactivated.

2. Different Regulation Points

- When there are many steps involved, different substances can bind to different proteins, inactivating them, and ultimately controlling the pathway and hence the response.

Signal Efficiency

- There are many large relay proteins that assist in increasing the efficiency of the signal transduction.
- They are necessary because the signal alone cannot simply diffuse through the cytosol.



Signal Termination

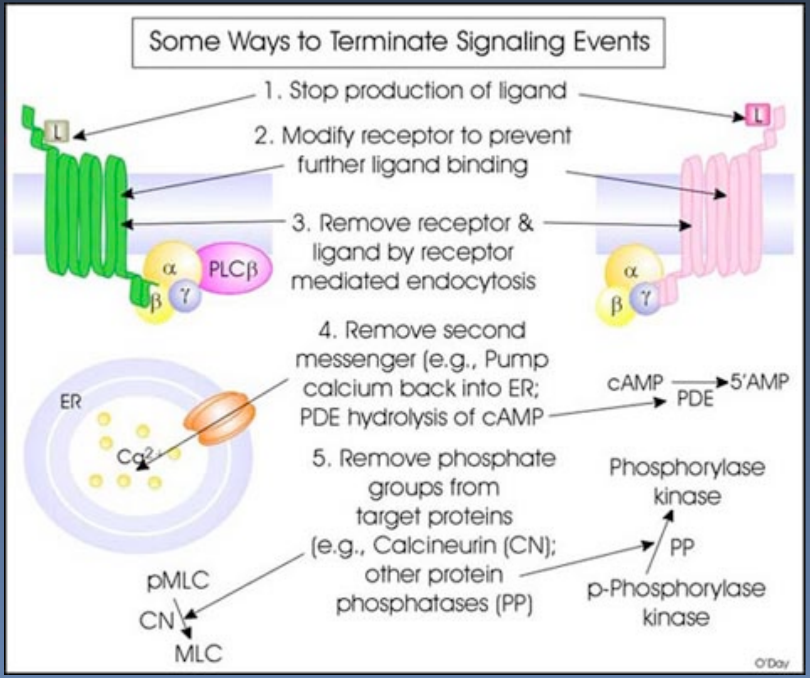
- Cells must remain continually receptive to signaling so the organism can sense the surrounding stimuli.

Signal Termination

- This occurs because of the reversibility of the changes the signals produce.
- The receptor reverts to its inactive form as do the relay molecules and the cell is now ready to respond to fresh stimuli.

Signal Termination

- Eventually, the signal needs to be terminated so that the cell doesn't unnecessarily make too much product or waste energy.
- Below are some ways in which signal termination occurs:



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