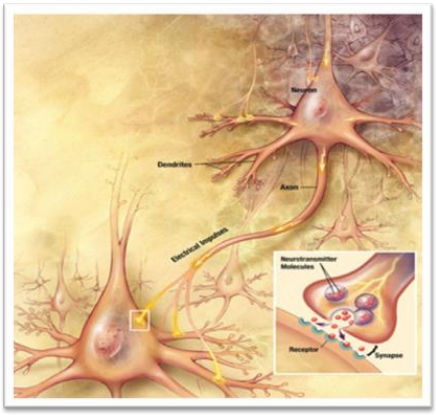
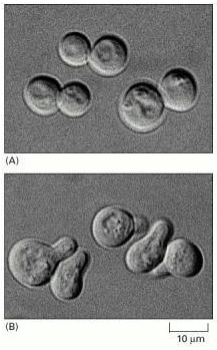
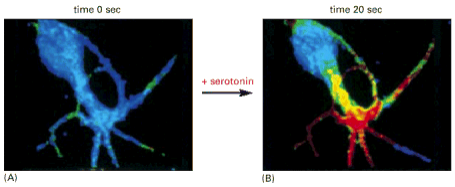
Cell Communication







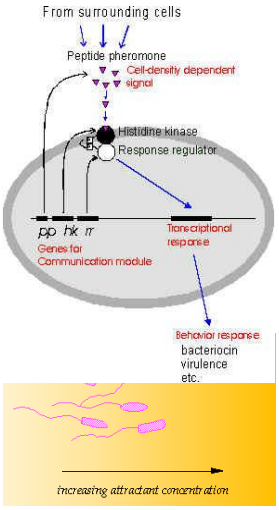
MIT/AB/RRE/EGR SITH/2014

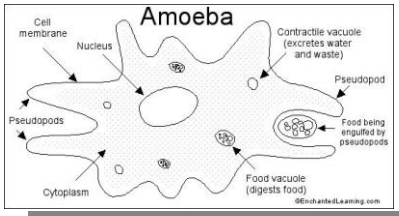
Cellular Signaling

- an organism does involves communication (signaling) among cells
  - e.g., Sensing the environment, moving, digesting food
- Cell-to-cell communication ~ cellular internet
  - Is essential for multicellular organisms
  - Cells must signal, receive, interpret and respond to chemical signals secreted by other cells
  - Ex: Embryonic development & hormone action rely on Cell-Cell communication.
- *Cell signaling* – communication between cells
  - Signaling cell: sends a signal (usually chemical)
  - Target cell: receives the signal

Cell Signaling

- Signaling in bacteria
  - •Bacteria can respond to their environment
  - •Chemotaxis, phototaxis etc.
- Other single cells - receptor

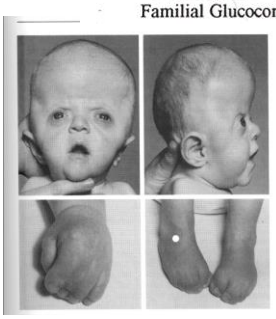




Without the cell surface receptors, the amoeba will not find where the food is

RECEPTOR DISEASES

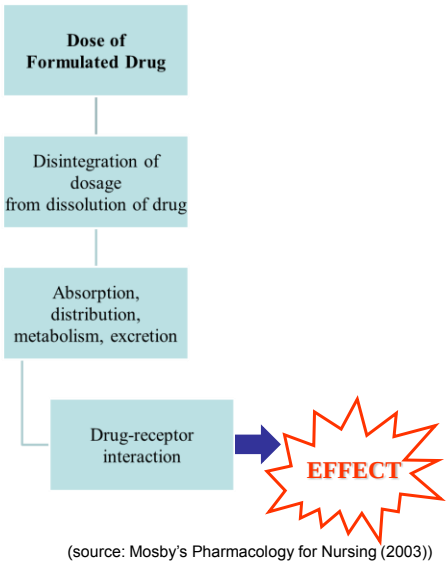
DISEASE	RECEPTOR DYSFUNCTION
Testicular feminization, pseudohermaphoditism	Testosterone Receptor
Graves Disease	Thyroid Receptor
Leprechaunism, Insulin-resistant Diabetes, Rabson-Mendenhall Syndrome	Insulin Receptor
Familial Hypercholesterolemia, Coronary Heart Disease	LDL-Receptor
Myasthenia Gravis	Acetylcholine Receptor
Cystic Fibrosis	GABA Receptor/Chloride Channel
Dysautonomia, Asthma?	Adrenergic Receptor
Schizophrenia, Parkinson's Disease	Dopamine Receptor
Color Blindness	Red/Green Cone Opsins
Retinitis Pigmentosa	Rhodopsin
Nephrogenic Diabetes Insipidus	V2 Vasopressin Receptor
Familial Glucocorticoid Deficiency	ACTH Receptor



Apert Syndrome

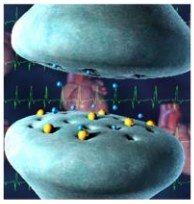
- D2-D3 FGFR2 linker mutations responsible for AS
- ~67% Ser252Trp
  32% Pro253Arg
- Severe limb phenotype

PHASES OF DRUG ACTIVITY



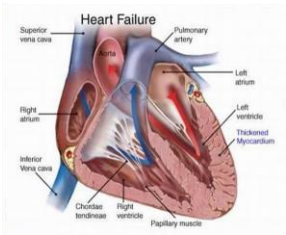
(source: Mosby's Pharmacology for Nursing (2003))

Beta blockers

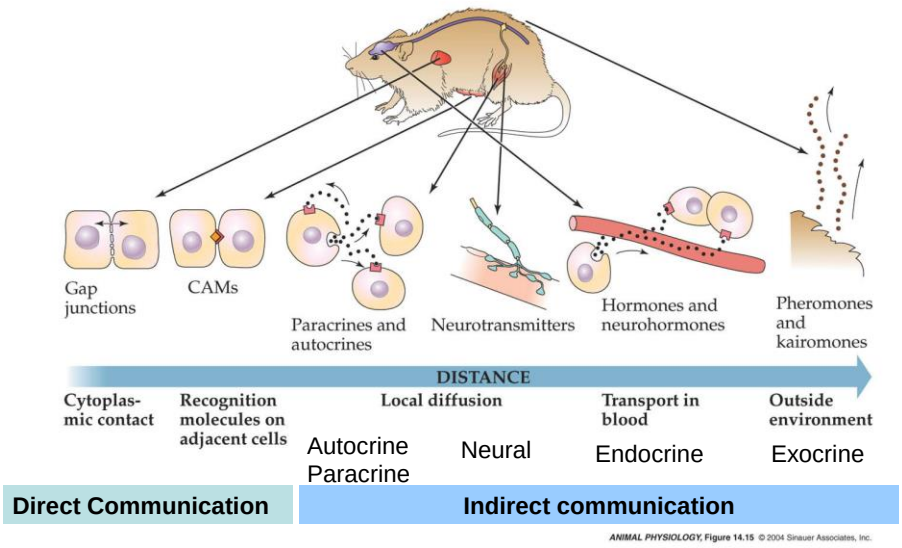


…it outcompetes the natural neurotransmitter

The drug has the same shape as the shape of neurotransmitter combining with the receptor molecule…



Signaling in multicellular organisms



Direct communication

- In local signaling, animal cells
  - May communicate via direct contact

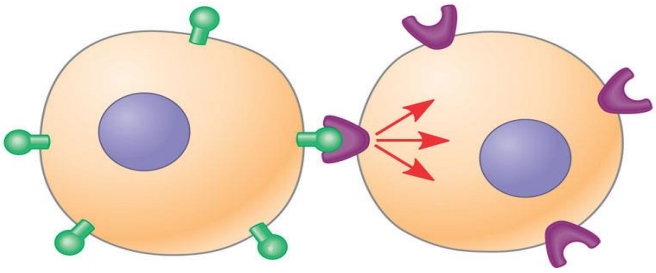
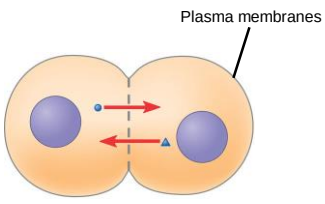


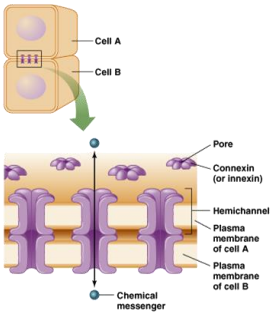
Figure 11.3(b) Cell-cell recognition. Two cells in an animal may communicate by interaction between molecules protruding from their surfaces.

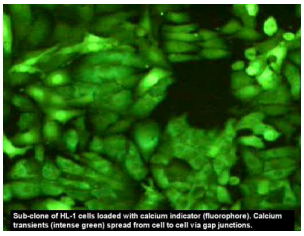
Direct Contact – Cell Junctions

- Animal cells
  - Have cell junctions that directly connect the cytoplasm of adjacent cells (Diffusion)
  - Gap junctions allow signaling information to be shared by neighboring cells : Ca2+, cAMP etc. but not for proteins or nucleic acids, Intracellular electrodes, small water-soluble dyes



(a) Cell junctions. animals cells have cell junctions that allow molecules to pass readily between adjacent cells without crossing plasma membranes.

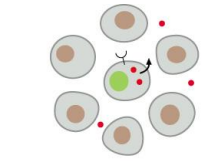




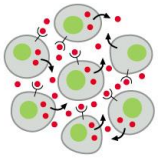
- Allows *Hydrophilic* chemical messengers to travel across the hydrophobic lipid membrane
- Signaling molecules are often ions

Indirect communication-Local regulation

- Autocrine
  - Cellular self-signaling
  - Autocrine signaling can coordinate decision by groups of identical cells



A SINGLE SIGNALING CELL RECEIVES A WEAK AUTOCRINE SIGNAL



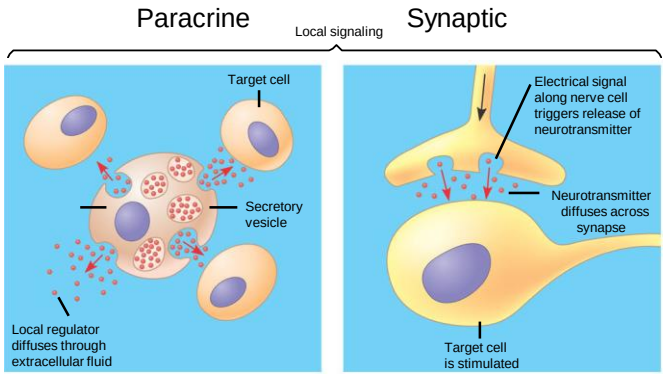
IN A GROUP OF IDENTICAL SIGNALING CELLS, EACH CELL RECEIVES A STRONG AUTOCRINE SIGNAL

Community effect" in early development
In tumor biology---cancer cells stimulate their own proliferation

- Paracrine
  - Features most similar to endocrine signaling
  - Major difference
    - Target cell found in the same tissue
    - Messenger molecules carried across extra-cellular matrix or through extra-cellular fluid
    - Many growth factors are associated with the matrix

Local Regulation

- In other cases, animal cells communicate using local regulators.

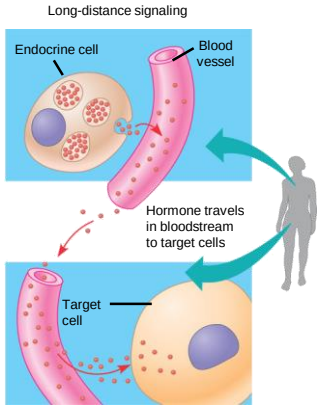


(a) Paracrine signaling. A secreting cell acts on nearby target cells by discharging molecules of a local regulator (a growth factor, for example) into the extracellular fluid.

(b) Synaptic signaling. A nerve cell releases neurotransmitter molecules into a synapse, stimulating the target cell.

Long Distance Signaling

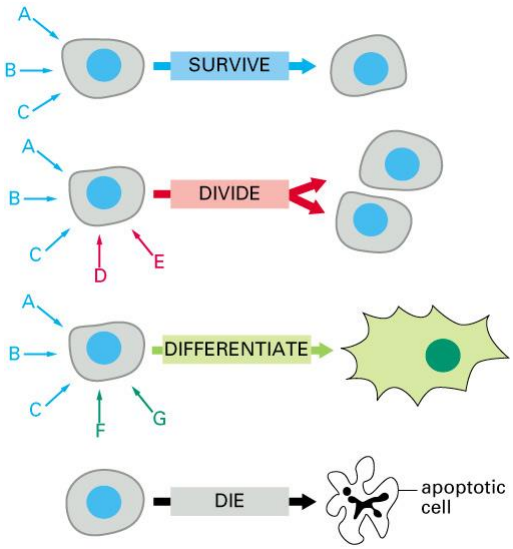
- Endocrine
  - Cells producing signaling factors are physically separated
  - Messenger molecules are secreted
  - Carried in blood or extra-cellular fluid
  - Target Cells
    - Membrane receptors
      - Intracellular actions via signal cascade
    - Cytoplasmic receptors
      - Usually a specific transport system to move signal molecule-receptor complex to nucleus – *response element*
- Ex: Insulin



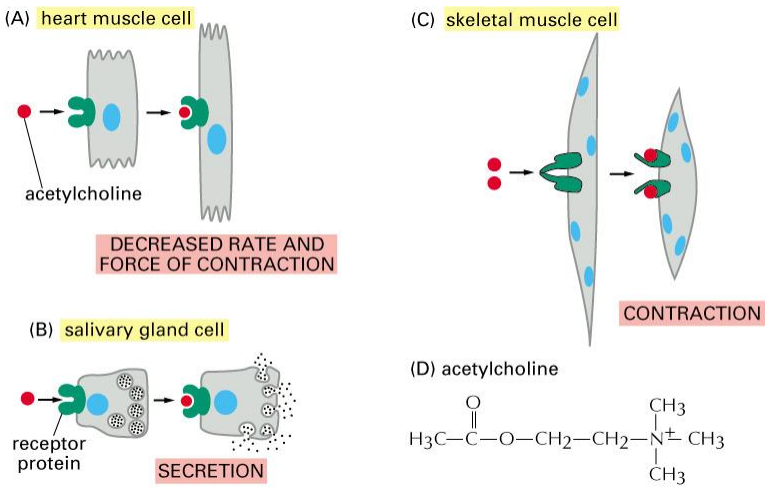
(c) Hormonal signaling. Specialized endocrine cells secrete hormones into body fluids, often the blood. Hormones may reach virtually all body cells.

Figure 11.4 C

Each cell is programmed to respond to specific combinations of extracellular signal molecules

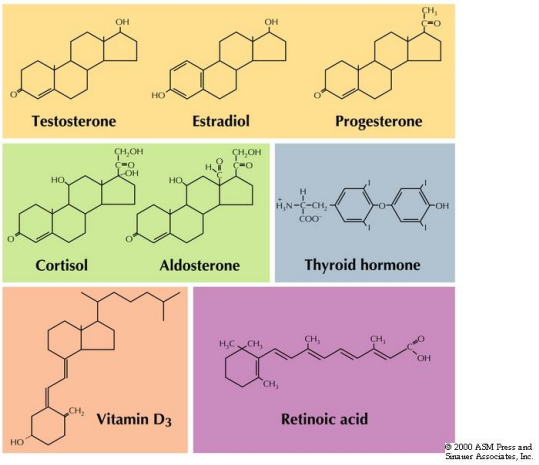


Different cells can respond differently to the same extracellular signal molecules

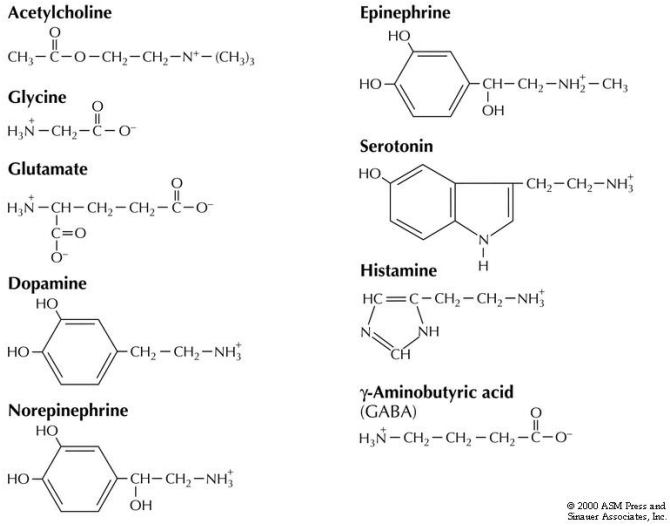


Cell Signaling

- Forms of signaling molecules
  - Gasses
    - NO
    - CO
  - Steroid Hormones
    - Testosterone
    - Estradiol
    - Progesterone
    - Glucocorticoids
      - Cortisol
    - Mineralocorticoids
      - Aldosterone



– Neurotransmitters



– Peptide Hormones
– and Growth Factors

TABLE 13.1 Representative Peptide Hormones, Neuropeptides, and Growth Factors

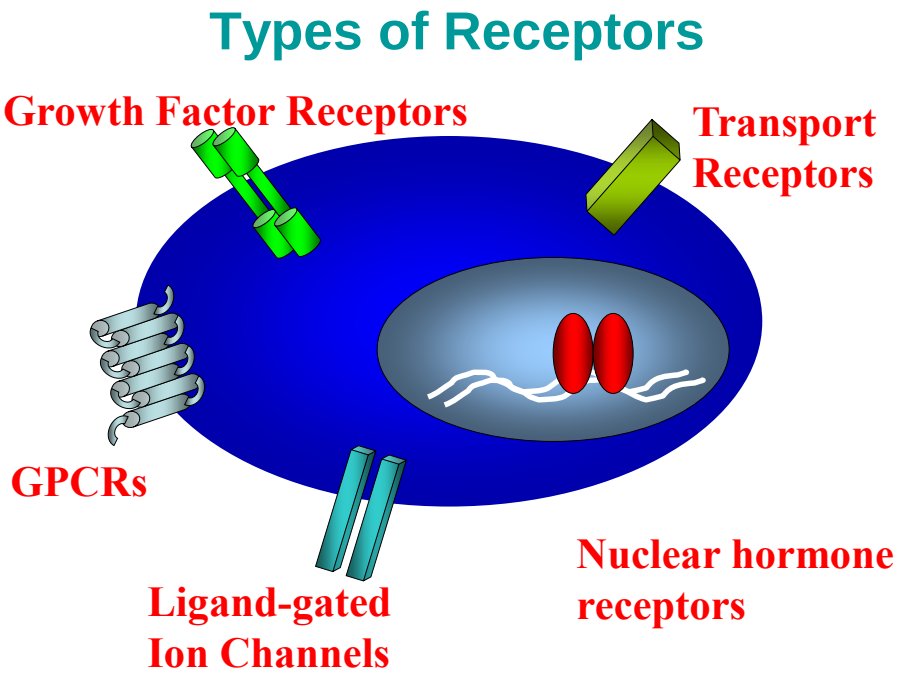
Signaling molecule	Size[a]	Activities[b]
Peptide hormones		
Insulin	A = 21, B = 30	Regulation of glucose uptake; stimulation of cell proliferation
Glucagon	29	Stimulation of glucose synthesis
Growth hormone	191	General stimulation of growth
Follicle-stimulating hormone (FSH)	α = 92, β = 118	Stimulation of the growth of oocytes and ovarian follicles
Prolactin	198	Stimulation of milk production
Neuropeptides and neurohormones		
Substance P	11	Sensory synaptic transmission
Oxytocin	9	Stimulation of smooth muscle contraction
Vasopressin	9	Stimulation of water reabsorption in the kidney
Enkephalins	5	Analgesics
β-Endorphin	31	Analgesic
Growth factors		
Nerve growth factor (NGF)	118	Differentiation and survival of neurons
Epidermal growth factor (EGF)	53	Proliferation of many types of cells
Platelet-derived growth factor (PDGF)	A = 125, B = 109	Proliferation of fibroblasts and other cell types
Interleukin-2	133	Proliferation of T lymphocytes
Erythropoietin	166	Development of red blood cells

[a] Size is indicated in number of amino acids. Some hormones and growth factors consist of two different polypeptide chains, which are designated either A and B or α and β.

[b] Most of these hormones and growth factors possess other activities in addition to those indicated.

Reception

- A signal molecule binds to a receptor protein, causing it to change shape.
- The binding between signal molecules (ligand) and the receptor protein is highly specific.
- A conformational change in a receptor is often the initial transduction of the signal.



Cellular Response to a signal

- Cell signaling leads to regulation of cytoplasmic activities or transcription.
  - Cytoplasmic Responses.
    - In the cytoplasm signaling pathways regulate a variety of cellular activities
  - Nuclear Responses.
    - Regulate genes by activating transcription

Nuclear Response
Other pathways regulate genes by activating transcription factors that turn genes on or off

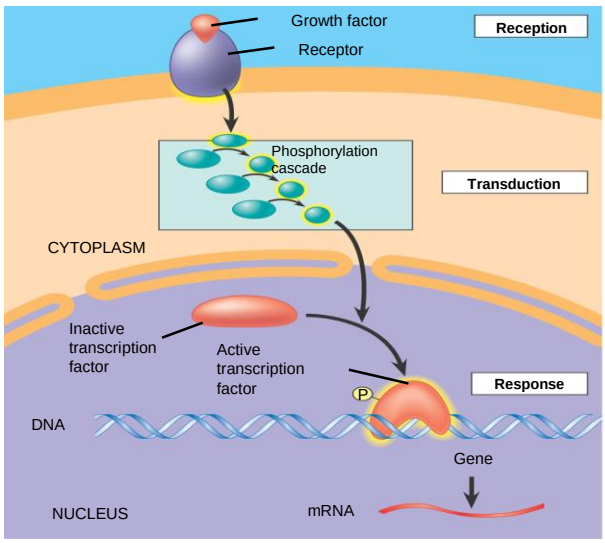


Figure 11.14

Signal Transduction

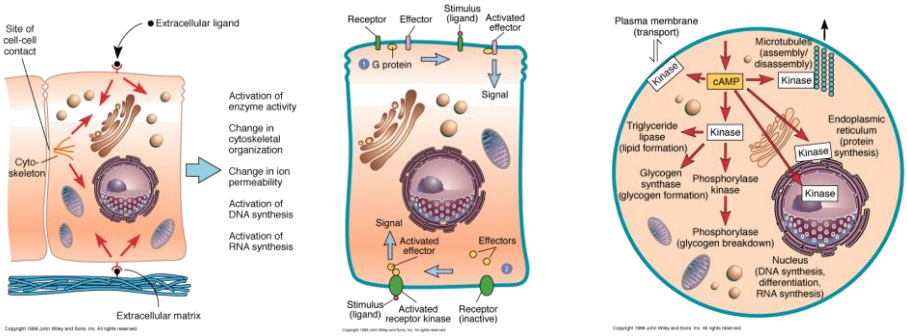
("Transduced" means changed).

Signal Transduction is the process by which a cell converts an extracellular signal into a series of response.

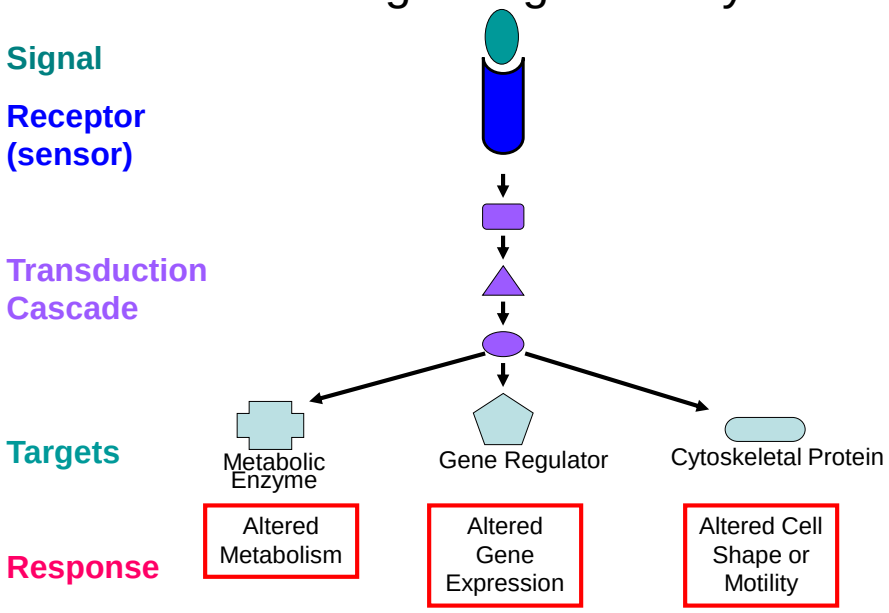
Involved in:
Cell-cell communication

Cell's response to environment

Intracellular homeostasis- internal communication



Generic Signalling Pathway



Adapted from Molecular Biology of the Cell,(2002), 4th edition, Alberts et al.

Intracellular Receptors (inside the cell)

- Intracellular receptors are proteins found in the cytoplasm or in the nucleus.
- Many signal molecules are small or hydrophobic and can readily cross the plasma membrane, use these intracellular receptors.
  - Ex: Steroid hormones, Thyroid hormones.
  - Ex: Testosterone
    - Binds to intracellular receptors and enter nucleus to turn on genes that control male sex characteristics.

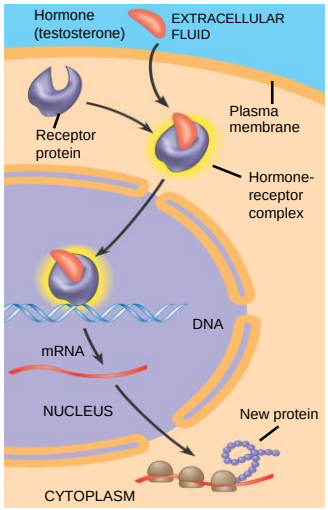
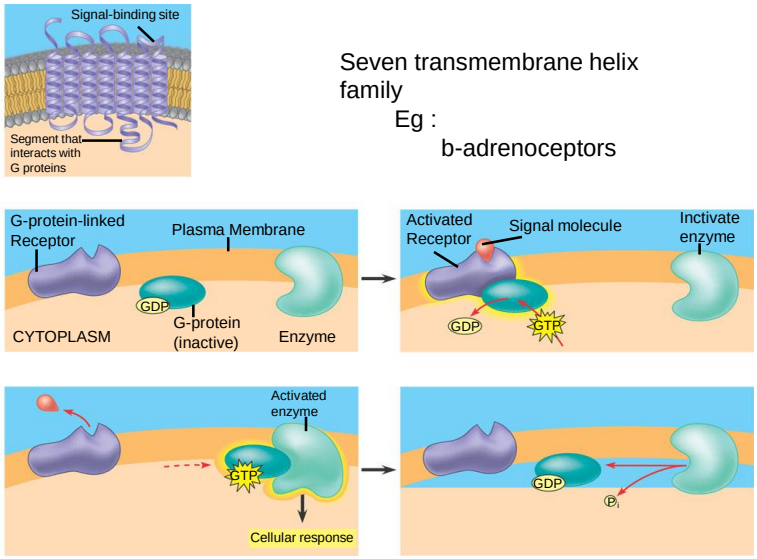


Figure 11.6

Receptors in the Plasma Membrane

- There are three main types of membrane receptors
  - G-protein-linked receptors (uses G proteins)
  - Tyrosine kinase receptors (can trigger more than one pathway, includes kinase enzyme, forms dimers)
  - Ion channels (acts as “gates”)
    - Ex: Ca^{2+} or Na^{+} channels

Work with the help of G-proteins



Seven transmembrane helix family

Eg :

b-adrenoceptors

Figure 11.7

Enzyme linked : Phosphorylate Tyrosine!

Six classes:

1. **Receptor tyrosine kinases**
2. **Tyrosine kinase-associated receptors**
3. **Receptor-like tyrosine phosphatases**
4. **Receptor serine/threonine kinases**
5. **Receptor guanylyl cyclases**
6. **Histidine-kinase-associated receptors**

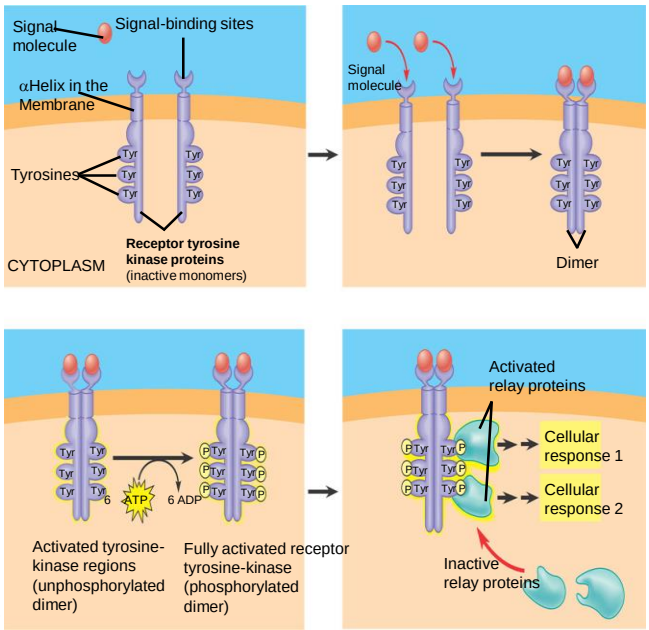


Figure 11.7

Ion channel receptors

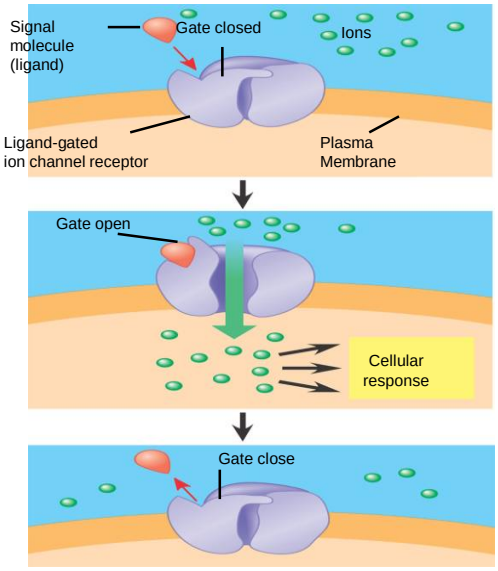
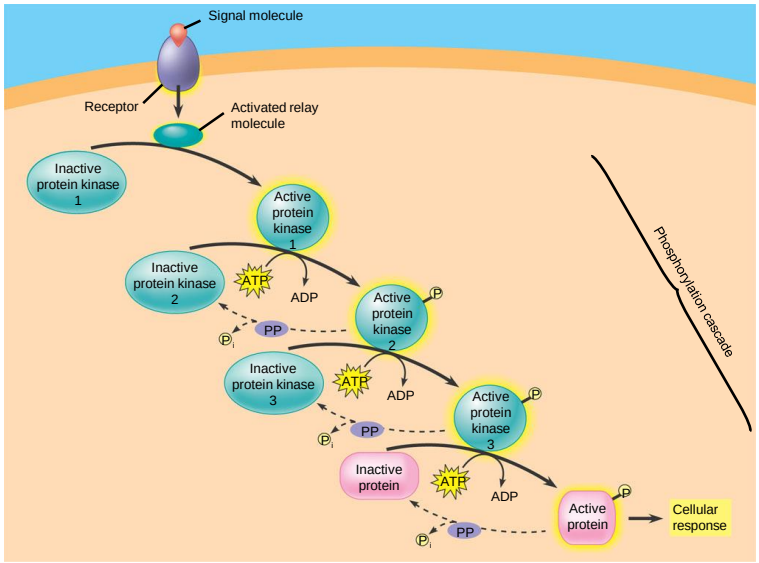


Figure 11.7

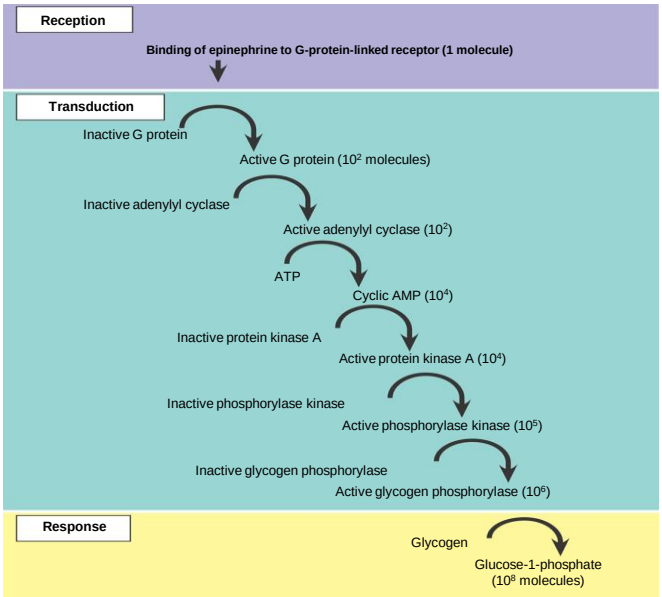
Transduction: Multi-step pathway

- Cascades of molecular interactions relay signals from receptors to target molecules in the cell
- Advantages of multistep pathways
  - Can amplify a signal at each step
  - Each step provides more opportunities for coordination and regulation
- At each step in a pathway
  - The signal is transduced into a different form, commonly a conformational (shape) change in a protein.
  - Signal usually **never** enters the cell.
  - Information is passed along because of the conformational change of the protein.

Cascade : A series of different molecules in a pathway are phosphorylated

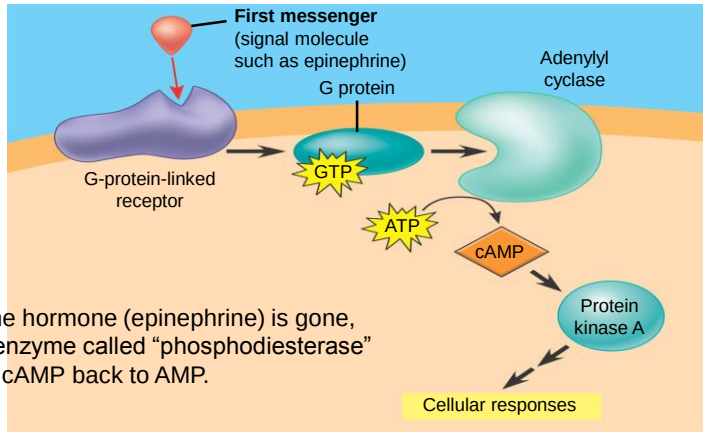


Cytoplasmic response to a signal



Epinephrine (Adrenaline) stimulates G-Proteins

- Many G-proteins stimulate Adenylyl cyclase, which triggers the formation of cAMP, which then acts as a second messenger in cellular pathways



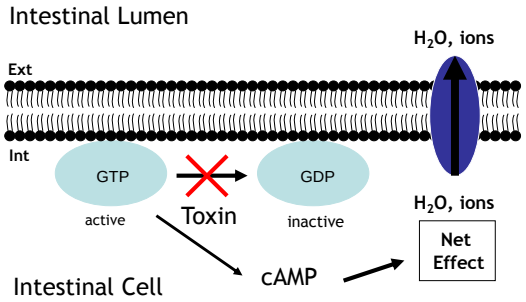
•When the hormone (epinephrine) is gone, another enzyme called "phosphodiesterase" converts cAMP back to AMP.

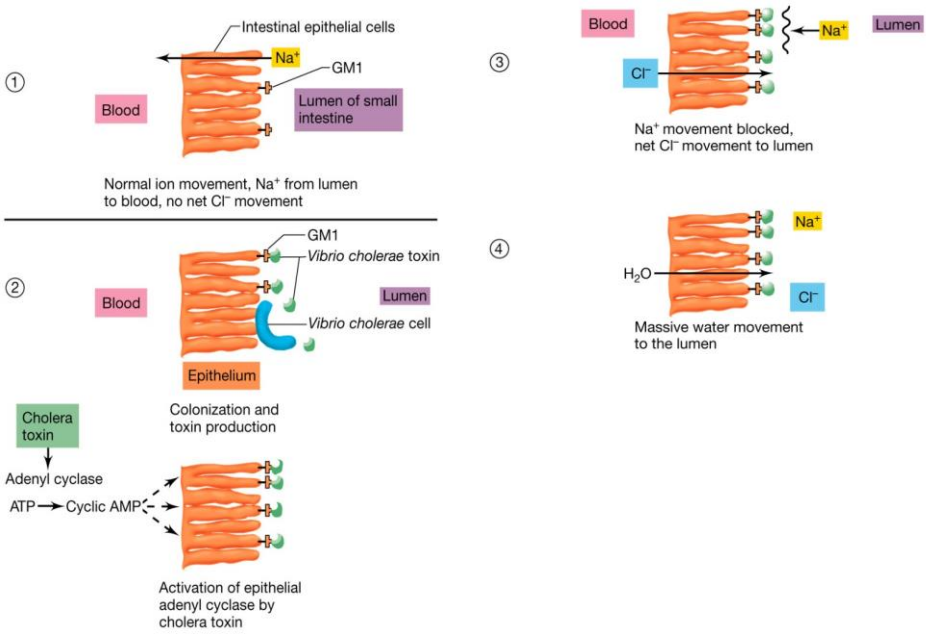
Small Molecules and Ions as Second Messengers

- Second messengers transmit signals from plasma membranes to metabolic mechanisms in the cytoplasm.
  - 2nd messengers are small, nonprotein, water-soluble molecules or ions (so they can diffuse throughout the cell)
  - Extracellular signal molecules are the "first messengers".
  - Ex: Cyclic AMP (cAMP) & Ca^{2+} (second messengers)

Microbial Diseases and Cell Signaling

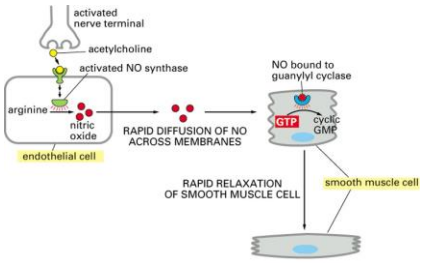
- Cholera bacterium (from contaminated water) gets into intestinal lining.
- Produces a toxin which is an enzyme that modifies a G-protein involved in salt and water secretion.
- The G-protein stays stuck inactivated from & cAMP concentration stays high, causing the cell to secrete large amounts of water & salts into the intestines (diarrhea)





Another example of drugs affecting cell signaling

- cGMP is a compound that relaxes smooth muscles in arterial walls.
- A drug that inhibits the hydrolysis of cGMP to GMP (doesn't let cGMP get back to GMP) was found to prolongs the signal of relaxation of arteries, which increases blood flow to the heart.
- This drug was prescribed for chest pain.
- Now…used for E.D. (Viagra) *Think about it.
  - Ex: Viagra is an external signal from a chemical (drug) which leads to dilation of blood vessels (a response). Originally intended for heart patients.



Other 2nd messengers: Ca^{2+} and (IP_3)

- Calcium is an important second messenger. Because cells are able to regulate its Ca^{2+} concentration in the cytosol.
  - *Normally, [Ca^{2+}]* in cytosol is lower than outside the cell.
  - Acts as a second messenger in many different pathways
  - Ex: Neurotransmitters, Growth factors, hormones
  - *Calcium is needed for muscle contraction, secretion of substances & cell division*
- Other second messengers such as inositol triphosphate (IP_3) and diacylglycerol
  - Can trigger an increase in calcium in the cytosol

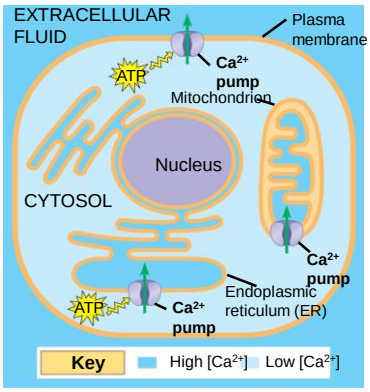
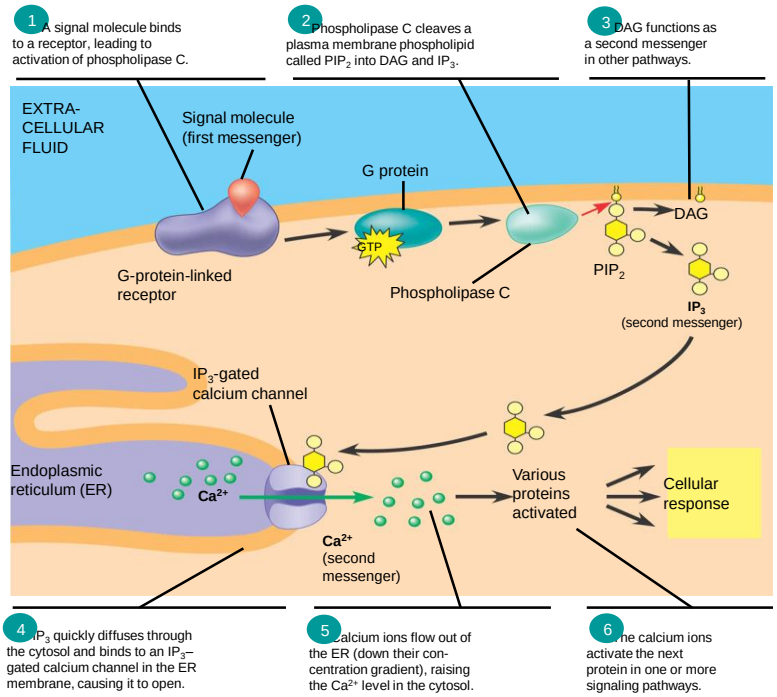
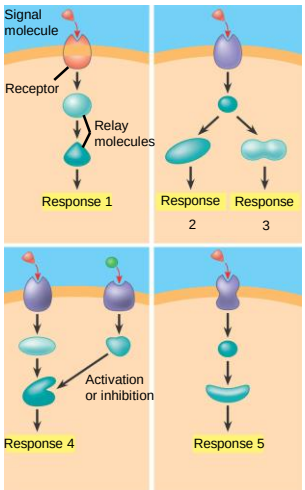


Figure 11.11



Pathway branching and "cross-talk"

– Further help the cell coordinate incoming signals



Cell A. Pathway leads to a single response

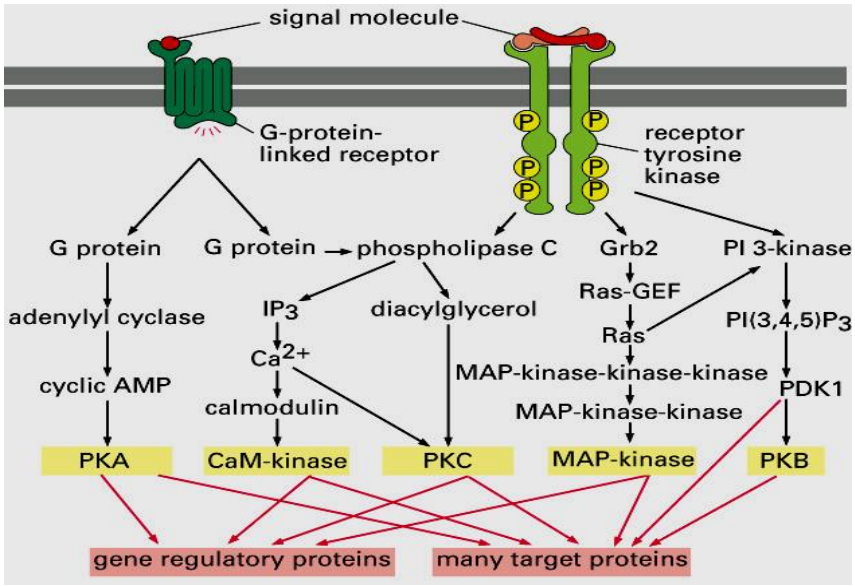
Cell B. Pathway branches, leading to two responses

Cell C. Cross-talk occurs between two pathways

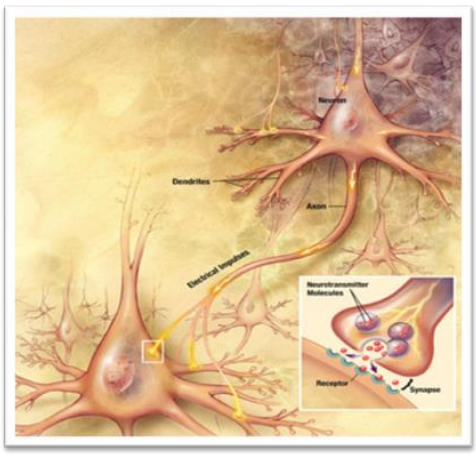
Cell D. Different receptor leads to a different response

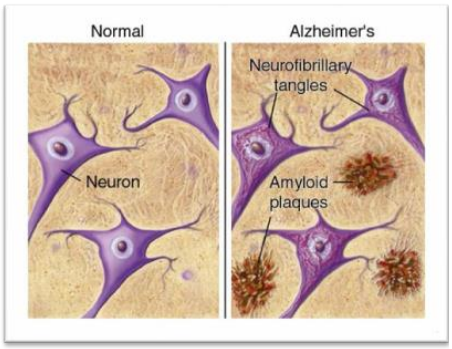
Figure 11.15

Brief summarization

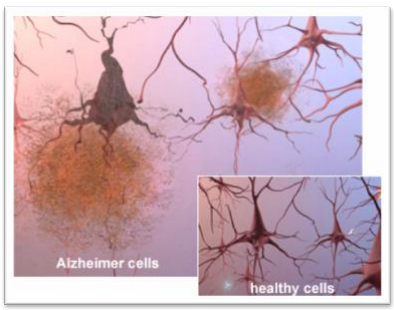


Normal Vs Alzheimer's

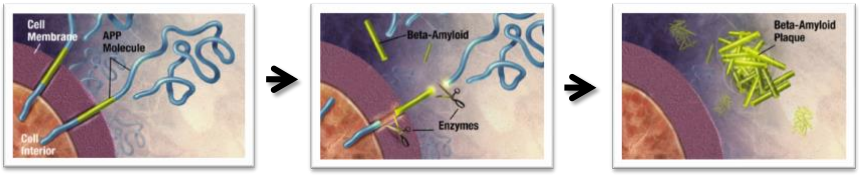


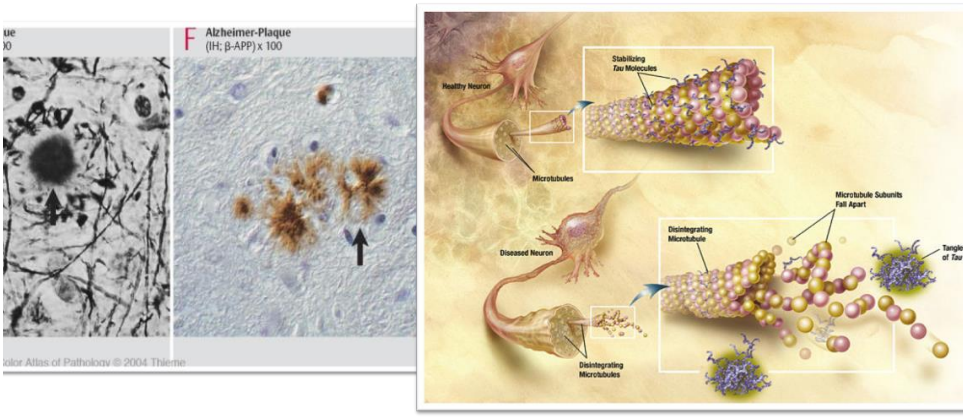


- To stay healthy, neurons (brain cells) must communicate with each other, carry out metabolism, and repair themselves.
- AD disrupts all three of these essential jobs.



Beta Amyloid (Aβ) a protein fragment snipped from an amyloid precursor protein (APP).





TREATMENT OF ALZHEIMER'S DISEASE?

Cholinergic drugs (also known as cholinesterase inhibitors or acetyl cholinesterase (AChe) inhibitors)

- Donepezil (Aricept)
  - Reversible mixed inhibitors of AChe binding mainly outside the active site (inhibition of hydrolysis of Acetylcholine by AChe)
- Galantamine (Razadyne)
  - acetyl cholinesterase inhibitors
  - Nicotinic receptor modulation
- Rivastigmine (Exelon)
  - Pseudoreversible competitive inhibitor of AChe and BuChe binding at active site

N-methyl-D-aspartate (NMDA) receptor antagonist

- Memantine (Namenda)
  - Regulating the activity of glutamate, by partially blocking NMDA receptors

Cells can adjust their sensitivity to a signal