Cell Communication

No cell lives in isolation

- survival depends on an elaborate intercellular communication network that coordinates growth, differentiation and metabolism
- cells adjacent to one another frequently communicate through cell-cell contact
- other forms of communication cover larger distances = extracellular signaling molecules

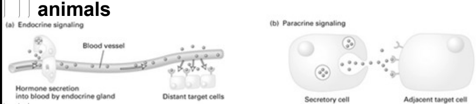
Extracellular Signalling

- signaling molecules are released by **signaling cells**
- the signal is called the **ligand**
- the ligand binds to its specific **receptor** on a **target cell**
- this ligand-receptor interaction induces a conformational or shape-change in the receptor
- produces a specific response - called the cellular response
- can include a vast array of compounds
  - e.g. small amino acid derivatives, small peptides, proteins

Cell-to-cell communication by extracellular signaling usually involves six steps

- (1) synthesis of the signaling molecule by the signaling cell
- (2) release of the signaling molecule by the signaling cell
- (3) transport of the signal to the target cell
- (4) detection of the signal by a specific receptor protein – receptor-ligand specificity
- (5) a change in cellular metabolism, function, or development = ***cellular response***
  - triggered by the receptor-ligand complex – specific to the ligand-receptor complex
- (6) removal of the signal, which usually terminates the cellular response – degredation of ligand

Signaling molecules operate over various distances in animals

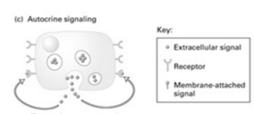


-extracellular signaling can occur over:

1. large distances or endocrine signaling – signaling molecules are called ***hormones***
- act on target cells distant from their site of synthesis
-usually carried through the bloodstream

2. short distances or paracrine signaling – affects target cells within proximity to the cell that synthesized the molecule
-usually mediated by neurotransmitters and some growth factors

Signaling molecules operate over various distances in animals

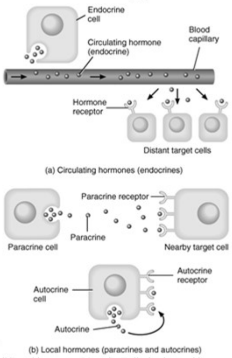


-extracellular signaling can occur over:

3. no distance or autocrine signaling – the signal feeds-back and affects itself
-action of many growth factors
-these compounds generally act on themselves to regulate proliferation
-seen frequently in tumor cells

-many compounds can act through two or even three types of cell signaling
e.g. growth factors (e.g. EGF) – paracrine and autocrine and endocrine
-epinephrine – endocrine and paracrine

Circulating & Local Hormones



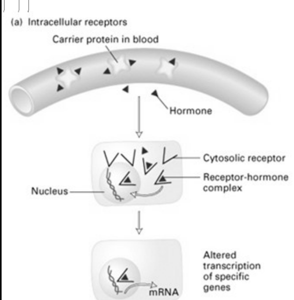
- ***Circulating hormones***
  - act on distant targets
  - travel in blood
  - endocrine hormones
- ***Local hormones***
  - paracrine hormones & autocrine hormones

Hormones

- **two types**
  - **lipid soluble**
  - **water soluble**

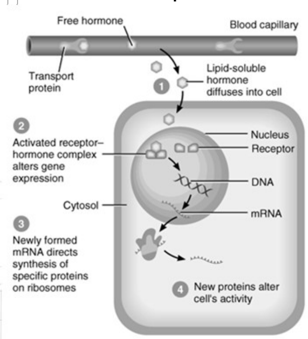
  - **Pages 978-979**

Lipid-Soluble Hormones



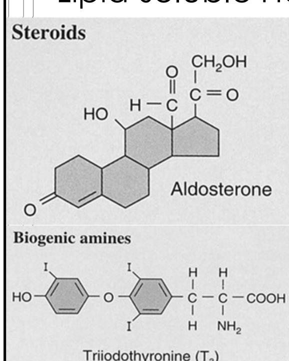
-lipid-soluble hormones can easily enter a cell by diffusing through the plasma membrane
-**PROBLEM**: how do they travel in the water-based blood??
-**SOLUTION**: they are carried by carrier-proteins
-these hormones then enter their target cell where they result in a specific cellular effect or response

Action of Lipid-Soluble Hormones



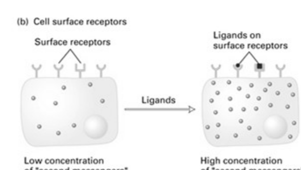
- Hormone diffuses through phospholipid bilayer & into cell
- Binds to receptor **turning on/off specific genes**
- New mRNA is formed & directs synthesis of new proteins
- **New protein alters cell's activity**

Lipid-soluble Hormones



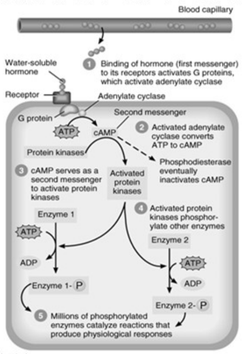
- ***Steroids***
  - lipids derived from cholesterol in SER
  - different functional groups attached to core of structure provide uniqueness
  - interact with specific intracellular receptors (within the cell) to turn specific genes on or off
  - effective for hours or days
- ***Thyroid hormones***
  - tyrosine ring plus attached iodines are lipid-soluble
  - activate enzymes involved in the catabolism of fats and glucose
  - help set our basal metabolic rate
- ***Retinoids***
  - vitamin A derivatives
  - have dramatic effects on cell proliferation and differentiation plus cellular death (i.e. apoptosis)

Water-soluble Hormones



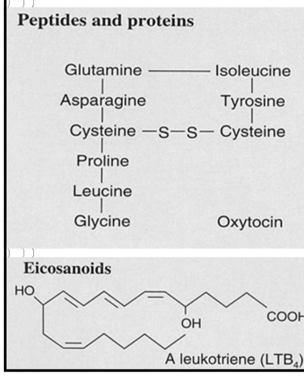
-water soluble hormones **can easily travel within the blood**
-PROBLEM: how do they enter a cell and result in a cellular response??
-SOLUTION: binding to specific cell-surface receptors;
this binding activates the receptor and results in a series of cellular events called the second messenger system

Action of Water-Soluble Hormones



- **Can not diffuse through plasma membrane**
- Hormone receptors are integral membrane proteins
  - act as first messenger
- Receptor protein activates G-protein in membrane
- G-protein activates adenylate cyclase to convert ATP to cAMP in the cytosol
- Cyclic AMP is the **2nd messenger**
- Activates kinases in the cytosol to speed up/slow down physiological responses
- Phosphodiesterase inactivates cAMP quickly
- Cell response is turned off unless new hormone molecules arrive

Water-soluble Hormones



- ***Amino acid derivatives, small peptides and protein hormones***
  - modified amino acids or amino acids put together
    - serotonin, melatonin, histamine, epinephrine
  - larger peptide hormones
    - insulin and glucagon
- ***Eicosanoids***
  - prostaglandins

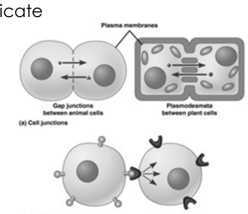
- http://learn.genetics.utah.edu/content/cells/cellcom/

The Cellular "Internet"

- Within multicellular organisms, cells must communicate with one another to coordinate their activities
- A ***signal transduction pathway*** is a series of steps by which a signal on a cell's surface is converted into a specific cellular response
- Signal transduction pathways are very **similar in all organisms**, even organisms as different as unicellular yeasts and multicellular mammals

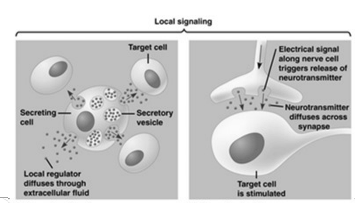
Local (Short-Distance) Signaling

- Cells may communicate by direct contact
  - **Plasmodesmata** in plant cells
  - **Gap junctions** in animal cells
- Animal cells can also use **cell-cell recognition**
  - Membrane-bound surface molecules can interact and communicate



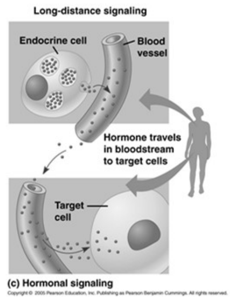
Local (Short-Distance) Signaling

- Messenger molecules can also be secreted by the signaling cell
- **Paracrine signaling**:
  - One cell secretes (releases) molecules that act on nearby "target" cells
  - Example: growth factors
- **Synaptic Signaling**:
  - Nerve cells release chemical messengers (**neurotransmitters**) that stimulate the target cell



Long-Distance Signaling

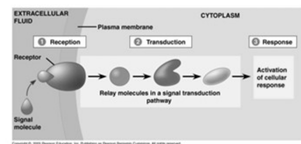
- **Endocrine (hormone) signaling**
  - Specialized cells release hormone molecules, which travel (usually by diffusion through cells or through the circulatory system) to target cells elsewhere in the organism



(c) Hormonal signaling

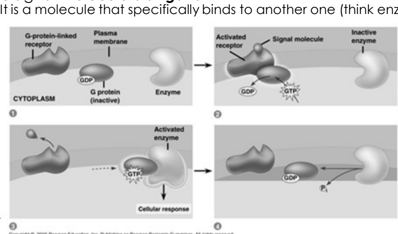
The Three Stages of Cell Signaling

- There are 3 stages at the "receiving end" of a cellular conversation:
  1. **R**eception
  2. **T**ransduction
  3. **R**esponse



Stage 1: Reception

- The target cell "detects" that there is a signal molecule coming from outside the cell
  - The signal is detected when it binds to a protein on the cell's surface or inside the cell
  - The signal molecule "searches out" **specific** receptor proteins
    - The signal molecule is a ***ligand***
      - It is a molecule that specifically binds to another one (think enzymes!)

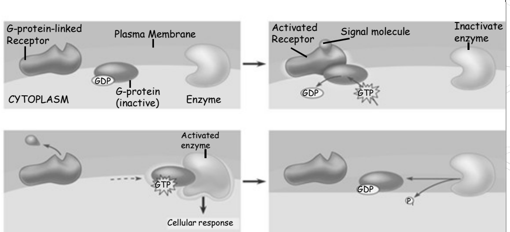


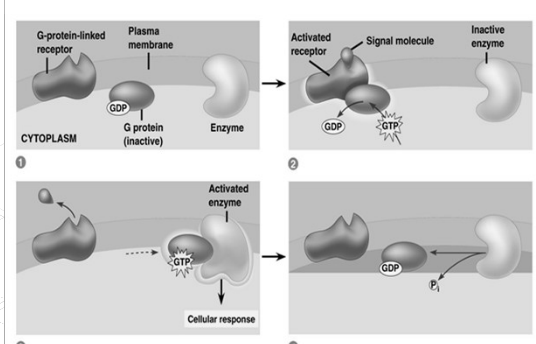
Three major classes of cell-surface receptors

- **G-protein coupled receptors**
  - **Coupled with G-protein**
  - **Ligand binding activates the receptor, which activates the G protein, which activates an *effector enzyme* to generate an *intracellular second messenger***
    - e.g. ***adenylyl cyclase*** – converts ATP to ***cAMP***
  - **Depending on regulation at the effector enzyme – this pathway can be either activated or inhibited**

G-protein-linked receptors

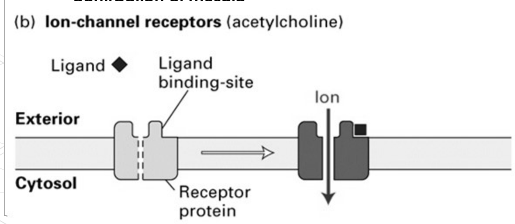
- Very common





3 classes of receptors

- Ion-channel receptors
  - Numerous in neuron membranes (Na/K pumps)
  - Also in muscle cell membranes—binding of ACh to muscle receptors allows ion movement & ultimately contraction of muscle



Ion channel receptors

When ligand binds, channel can open or close.

Ex: neurotransmitters bind as ligands for Na+ ion channels

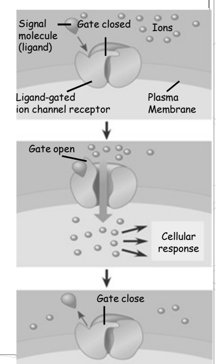
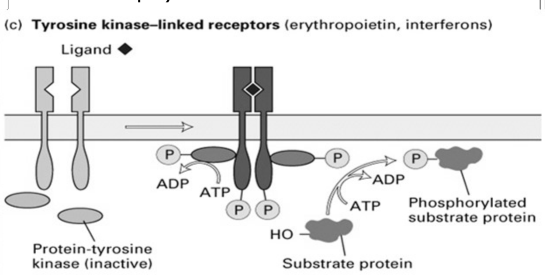


Figure 11.7

3 classes of receptors

- Receptor Tyrosine-kinases
  - Produce MANY cellular responses (unlike G-receptor)



Receptor tyrosine kinases

- Multiple pathway response

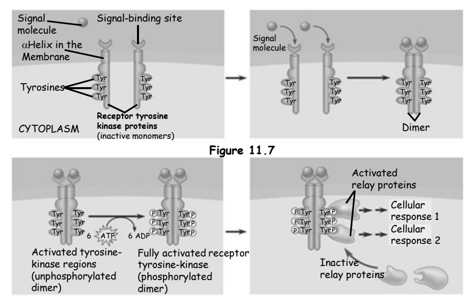


Figure 11.7

*Intracellular Receptors

- Target protein is INSIDE the cell
- Must be hydrophobic molecule

Why can the signal molecule meet its target INSIDE the cell?

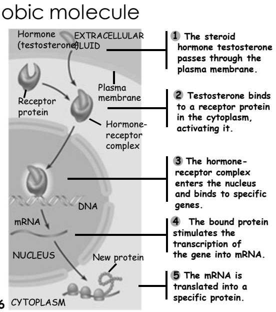


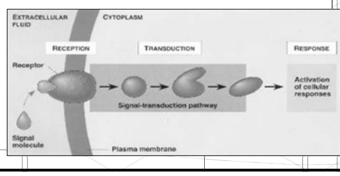
Figure 11.6

Stage 2: Transduction

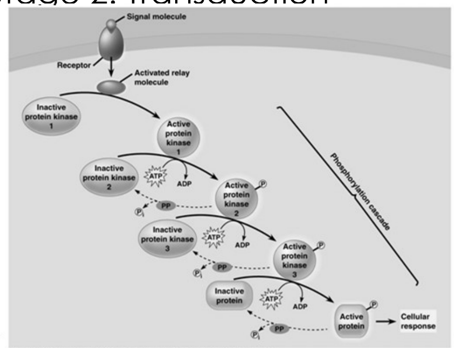
- This stage converts the signal into a form that can bring about a specific cellular response
  - One signal-activated receptor activates another protein, which activates another molecule, etc., etc.
  - These act as ***relay molecules***
  - Often the message is transferred using ***protein kinases***, which transfer phosphate groups from ATP molecules to proteins

Step Two - Transduction

- Signal initiated by *conformational change* of receptor protein
- Signal is turned into a *cellular response*.
- Signaling cascades relay signals to target
- Multistep pathways can **amplify a signal**
  - **Second messengers** involved



Stage 2: Transduction



A phosphorylation cascade

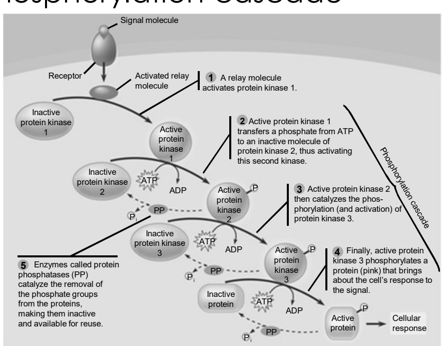
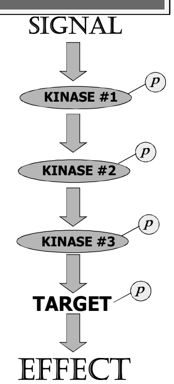


Figure 11.8

Signal transduction cascades

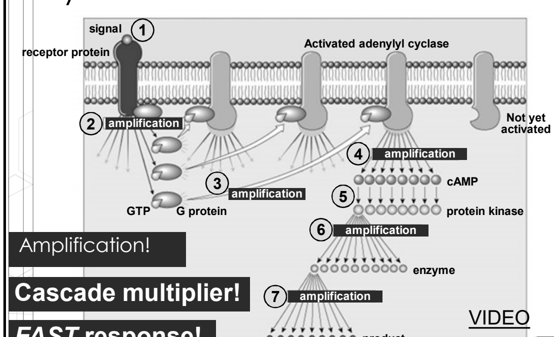
- the successive phosphorylation/activation of multiple kinases results in a cascade of phosphorylation/activation
- this cascade is frequently called a ***signal-transduction cascade***
- this cascade eventually leads to a specific cellular response
- e.g. changes in cell physiology and/or patterns of gene expression
- **RTK** pathways are involved in regulation of cell proliferation and differentiation, promotion of cell survival, and modulation of cellular metabolism



Second messengers

- produced by the activation of GPCRs and RTKs
- Hormone stimulation of G protein-coupled receptors leads to activation of ***adenylyl cyclase*** and synthesis of the second messenger ***cAMP***
  - most commonly studied second messenger
  - cAMP does not function in signal pathways initiated by RTKs
  - cAMP and other second messengers, such as Ca^{++} activate specific protein kinases (cAMP-dependent protein kinases or ***PKAs***)
- second messenger systems allow for ***amplification*** of an extracellular signal
  - one epinephrine molecule can bind one GPCR – this can result in the synthesis of multiple cAMP molecules which can go on to activate an amplified number of PKAs

Benefits of a 2° messenger system



Amplification!

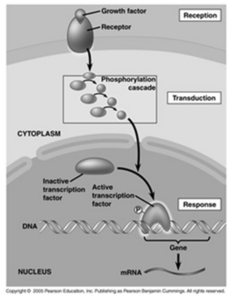
Cascade multiplier!

***FAST* response!**

VIDEO

Stage 3: Response

- The signal that was passed through the *signal transduction pathway* triggers a specific cellular response
  - Examples: enzyme action, cytoskeleton rearrangement, activation of genes, etc., etc.
  - Diagram example: transcription of mRNA

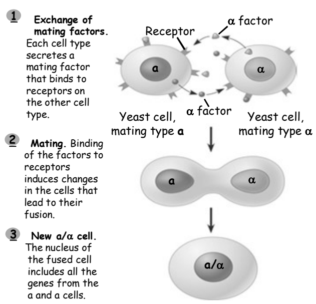


2 Types of Cellular Responses

- **Nuclear**
  - **Regulation/alteration of protein synthesis (turning genes on/off)**
- **Cytoplasmic**
  - **Activity of proteins (not their synthesis)**
  - **Ex. Epinephrine breaking down glycogen into glucose**
  - **Ex. Yeast mating (see book)**

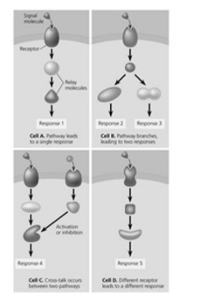
Yeast Sexual Reproduction

Yeast cells identify their mates by cell signaling.



The Specificity of Cell Signaling

- The particular proteins that a cell possesses determine which signal molecules it will respond to and how it will respond to them
- Liver cells and heart cells, for example, do not respond in the same way to epinephrine because they have different collections of proteins



Evolutionary Significance

- Unicellular and multicellular cell communication have similarities
- Yeast cells signal for sexual reproduction through signal transduction process.
- Bacteria secrete molecules to sense density of own population.
  - Quorum Sensing *(survival purpose)*

TEDED on Quorum Sensing