Molecular Cell Biology

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Module 7

Cell Signaling Mechanisms

Lecture 1

Introduction to Signals and Signal Transduction

Signal transduction

- Responding to a signal from the environment (intracellular or extra cellular) is a fundamental character of all living cells or organisms.
- Bacteria – respond to changes in oxygen, nutrients, pH, toxins or even other organisms attacking them.
- Plants – respond to light, touch, hormones etc.
- Animals – Developmental signals and others.
- Cells do not do anything without a cue or signal. Hence all the normal functions of a cell require signals/cues.
- From this view point all the pathological conditions/diseases are due to deregulation of one or more signaling pathways.
- Understanding of signaling pathways is essential so that we can target them for therapeutic interventions.

Signals, ligands and receptors

- Signals in biology refer to the molecules, ions, gases, sound, mechanical touch, stress, temperature, heat and physical factors that elicit a response when they communicate/contact with a cell or when they bind or diffuse into a cell.
- If the signal comes from outside the cell – extracellular signal.
- If the signal is generated inside the cell - intracellular signal.
- If the signaling molecule binds with a receptor - call it a Ligand/agonist/first messenger (with a message).
- Receptors bind with ligands and can be located on the cell surface, cytosol or nucleus.

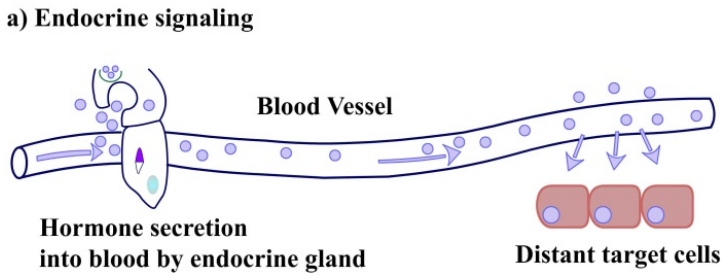
Ligands/ First messengers

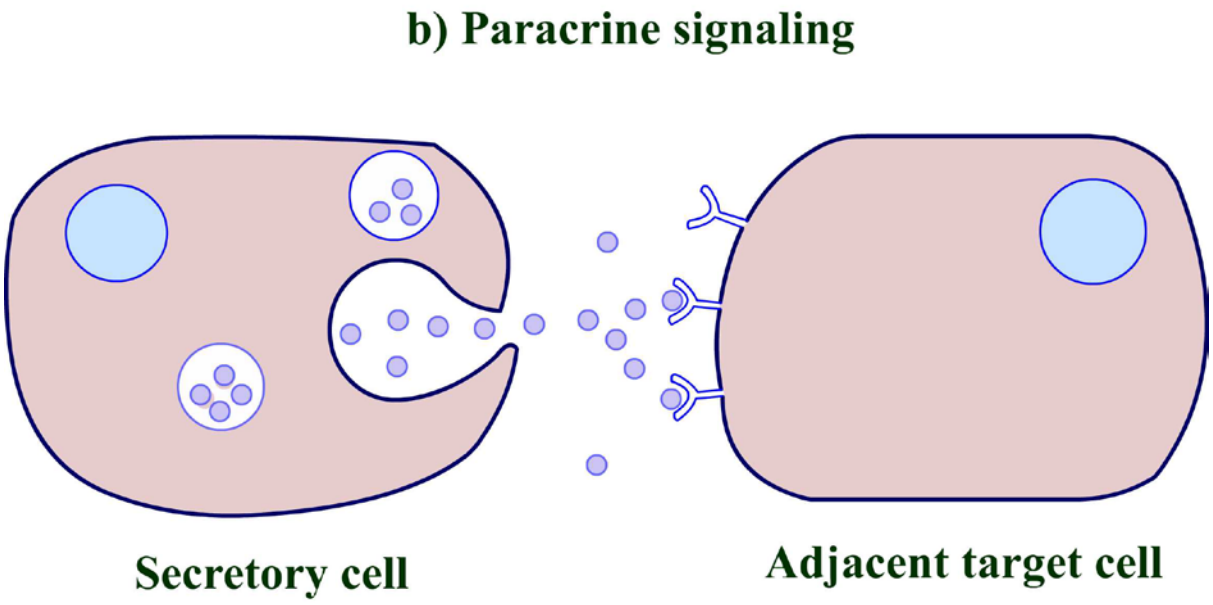
- Lipophilic molecules can enter the membrane and bind to intracellular receptors: steroids, thyroxine, and retinoic acids.
- Lipophilic molecules binding to cell surface receptors: prostaglandins.
- Hydrophilic molecules that are not able to cross the membrane bind to cell surface receptors:

- peptides: growth hormones, cytokines, gastrin, glucagon, insulin, TSH, LH, FSH, Parathyroid hormone, secretin
- b) amino acid derivatives : epinephrine, norepinephrine, serotonin, dopamine, histamine.

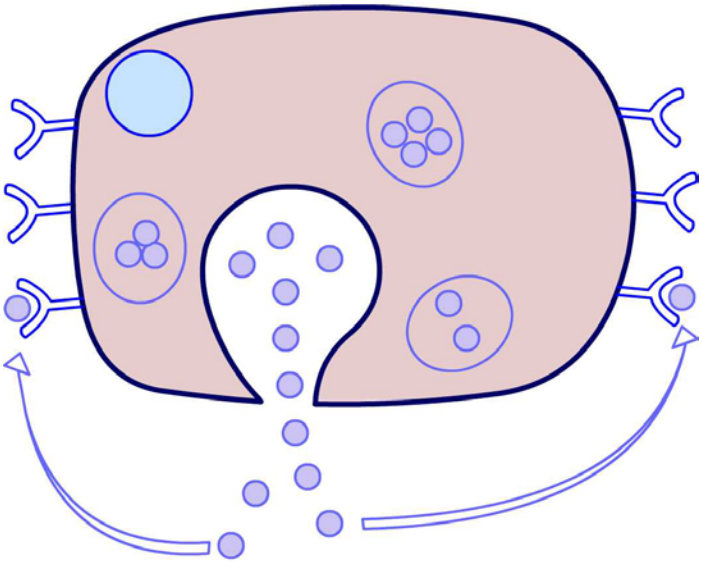
- Some ligands are initially synthesized as trans membrane inactive proteins and then cleaved by enzymes and secreted out into the extracellular compartment Growth factors
- The word “signal transduction” started to appear in the biological literature in the 1970s.
  - GTP and GTP-binding proteins in metabolic regulation were described by Alfred G. Gilman and Martin Rodbell
  - They were awarded the Nobel Prize in 1994 for their discovery of G-proteins and their role in signal transduction in cells

Signaling Molecules Operate Over Various Distances





c) Autocrine signaling

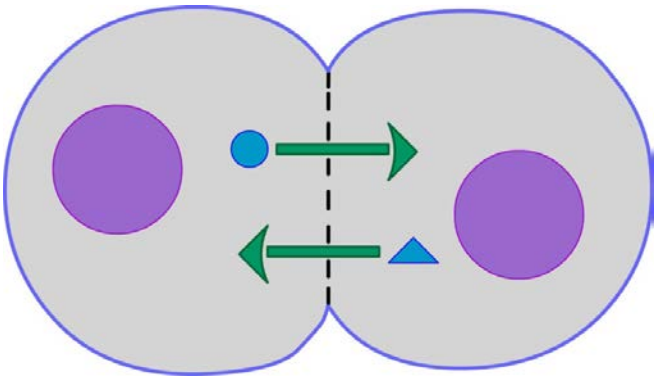


Target sites on same cell

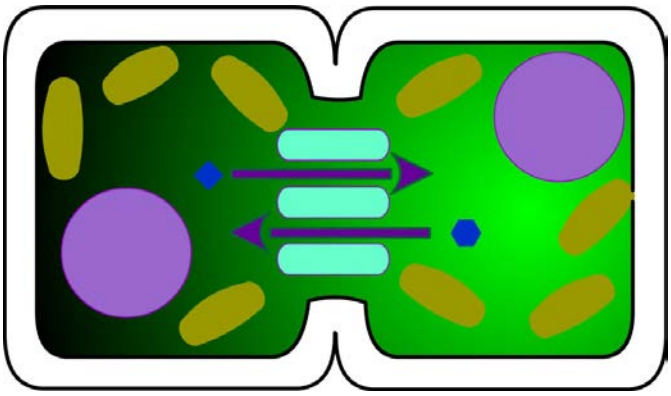
Animal and plant cells

- Have cell junctions that directly connect the cytoplasm of adjacent cells

Plasma membranes



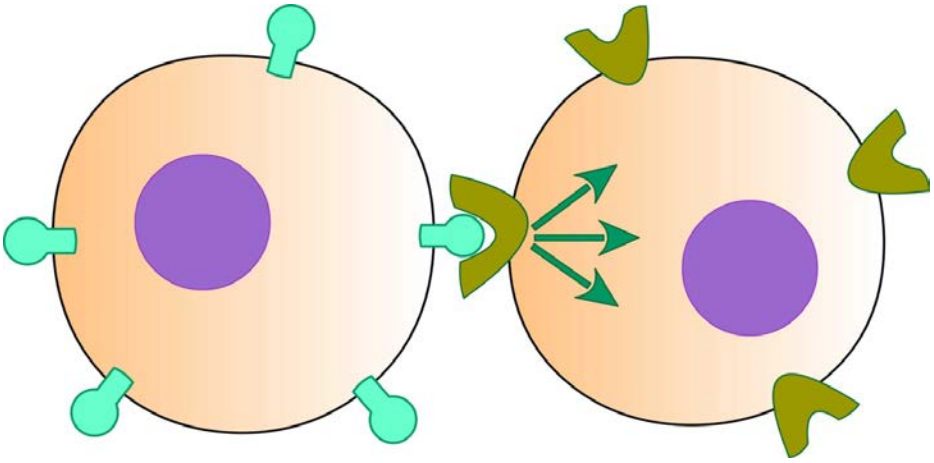
Gap junctions
between animal cells



Plasmodesmata
between plant cells

Cell junctions: Both animals and plants have cell junctions that allow molecules to pass readily between adjacent cells without crossing plasma membranes

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



Specificity

- Specificity is an important criterion in ligand-receptor interactions. High specificity means the ligand binds with a specific receptor that is expressed only in certain cell types.
- Receptor and ligand generally have complementary structural features.
- Non-covalent interactions similar to antigen-antibody reactions and enzyme-substrate reactions with high affinity (low Kd values) co-operativity.

Amplification

- The actual cell concentrations of ligands may be very low and are often transient and short-lived but the effects they ellicit are not small and may be some major changes.
- Ligand-receptor binding may result in the activation of a cascade of enzymes.
- Amplification is achieved through multiple enzymes and scaffolding proteins.

Signal integration

- Cells often receive multiple signals and they can be conflicting signals from reciprocal pathways
- Parallel signaling pathways may be activated
- Several signaling pathways may also work for a common goal
- Therefore the signals, pathways and systems have to be coordinated to provide an integrated cellular response

Termination of signal/Desensitization

- A transient signal emanating from a ligand must produce a rapid and major cellular response.
- Sometimes the signal persists and the sensitivity to the ligand decreases.
- Desensitization can be ahieved by a feedback loop, dephosphorylation, endocytosis.
- The receptor may now have less affinity, less activity or less expression.

Cell-surface and nuclear receptors

- G Protein Coupled receptors
- Ion-channel receptors
- Receptor tyrosine kinases
- Receptor serine/threonine kinases
- Receptors with phosphatase activity
- Receptors lacking enzyme activity but associate with intracellular enzymes
- Cell adhesion receptors
- Nuclear receptors

Transduction

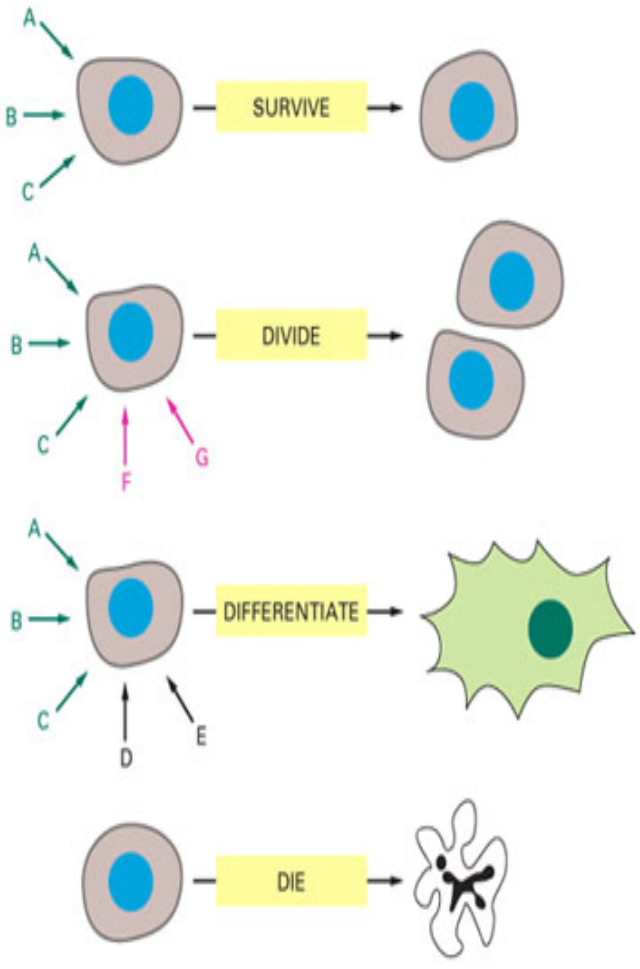
- **Transduction** means the action of leading across or bringing across
- The action of transferring the signal from one compartment of the cell to another or to transmit the signal from outside to inside
- Conveying the message from the signal/ligand into a response that is essentially a chemical change
- This is mediated by **receptors** and **signaling intermediates**
- Intracellular signaling is often initiated with second messengers such as cAMP
- Earl W. Sutherland was awarded the Nobel Prize in 1971 for his discoveries concerning the mechanisms of action of hormones.
- Identification of cyclic AMP (cAMP) as the second messenger to adrenaline or glucagon was a great discovery as it became possible to link activation of specific classes of receptors with specific biochemical responses.

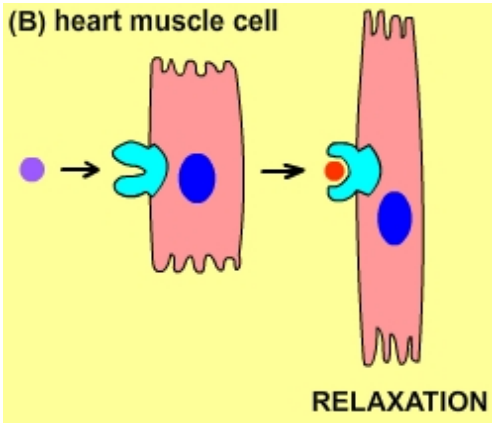
Signaling intermediates

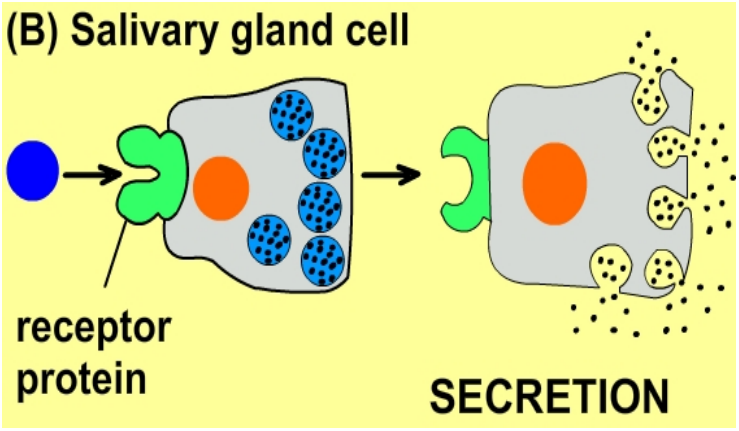
- Cellular signaling intermediates include kinases, phosphatases, GTPases and adapter proteins with interaction domains forming a scaffold.
- They help in transmitting the signal and its amplification

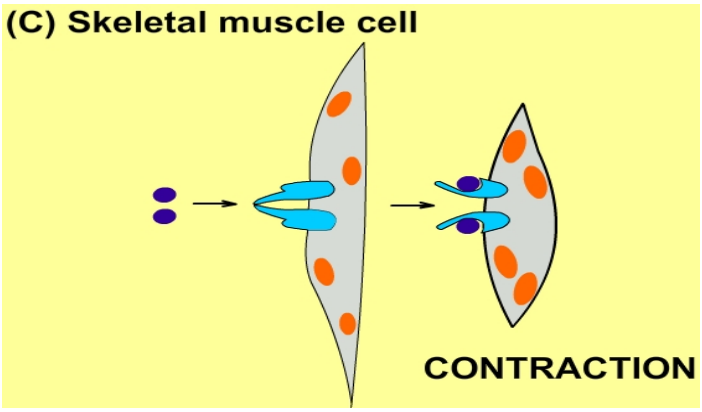
Responses

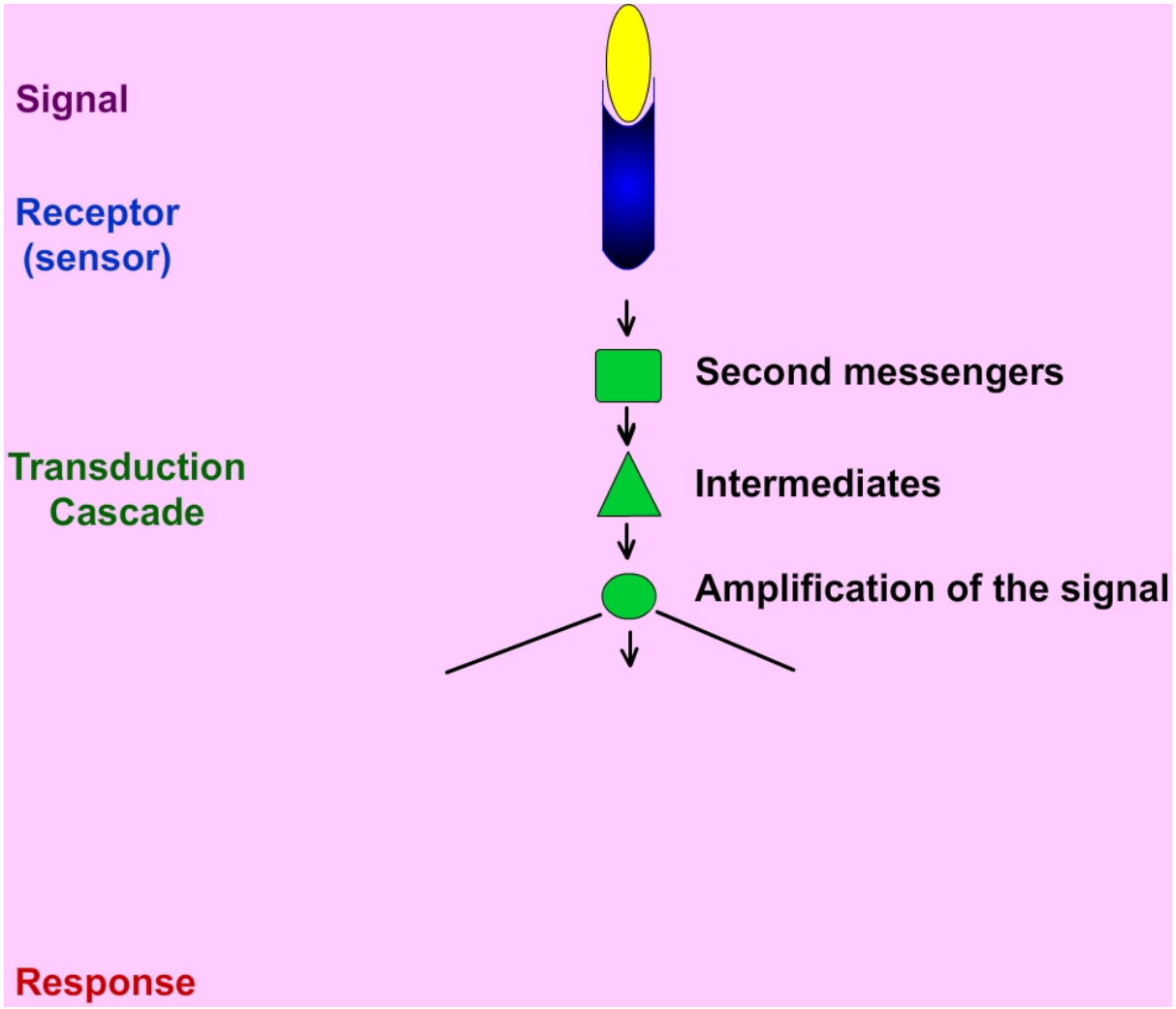
- Cells need **cues or signals** to carry out their functions or physiological processes.
- What are the physiological processes?
- Development, proliferation, differentiation, migration, cell death, survival etc need signals.




(B) heart muscle cell
RELAXATION


(B) Salivary gland cell
receptor protein
SECRETION


(C) Skeletal muscle cell
CONTRACTION


Signal
Receptor (sensor)
Transduction Cascade
Second messengers
Intermediates
Amplification of the signal
Response

Major events of Signal transduction

Generation of signals

Ligands

Recognition of signals

Receptors

Transduction and amplification

Change of external signal into intracellular message

Effects or responses

Modification of cell behavior, gene expression, function etc

Termination/Desensitization of signals

Receptor endocytosis, Dephosphorylation

Dimerization

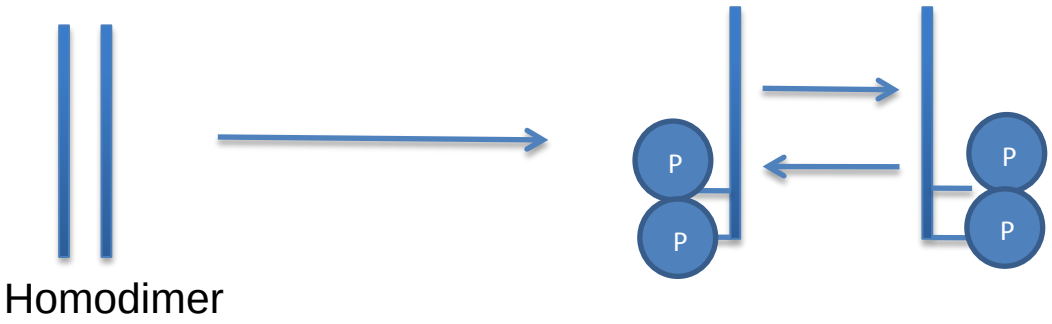
- Homodimers – formed between two identical receptors
- EGFR-EGFR
- Heterodimers – formed between two different receptors
- EGFR-ErbB2
- What are the advantages of dimerization?

Dimerization is an important mechanism for signal transduction

- Dimers have certain advantages in signaling than a monomer
- Relative distance and orientation of dimers (apart from ligands some antibodies
- can also activate some RTKs by their ability to cross bridge the dimers)
- Specificity can be generated for the ligand in a heterodimer
- Only one receptor may have the binding site for the ligand
- Even if one partner is inactive in its enzyme activity the other one can bind
- Increased affinity may be achieved through multiple contact points
- Two receptors may bring in several ligands for the given signaling pathway
- Multiple intracellular interaction partners
- Cross phosphorylation or transphosphorylation is achieved by dimers

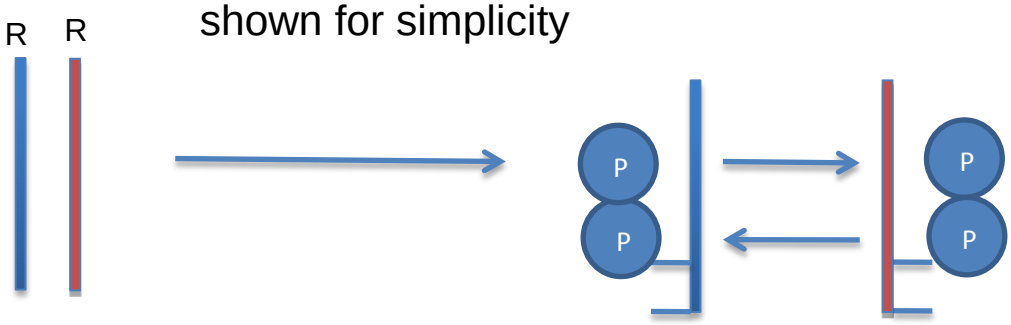
Phosphorylation

- Phosphorylation is an important mechanism of receptor activation.
- More than 99% of the phosphoamino acids in normal cells are phosphothronine and phosphoserine.
- Phosphotyrosine constitutes only 0.05 – 0.1 % of total
- phosphoamino acids → but very important!



Homodimer

Ligand binding not shown for simplicity



Heterodimer

Study Questions

1. What do we mean by signals?
2. Distinguish the differences between homo and heterodimers
3. Lipophilic molecules binding to cell surface receptors a) Tyrosine b) Androgen c) Prostaglandins d) Estrogen
4. Match the following

RTK	Estrogen
Peptide hormone	G-proteins
Steroid hormone	Insulin
Martin Rodbell	EGFR

5. ----------is a well-known second messenger