CELL SIGNALING

- **Cell signaling** is part of a complex system of communication that governs basic cellular activities and coordinates cell actions.

- The ability of cells to perceive and correctly respond to their microenvironment is the basis of development, tissue repair, and immunity as well as normal tissue homeostasis

- Errors in cellular information processing are responsible for diseases such as cancer, autoimmunity, and diabetes.

- By understanding cell signaling, diseases may be treated effectively and, theoretically, artificial tissues may be created.

Definitions

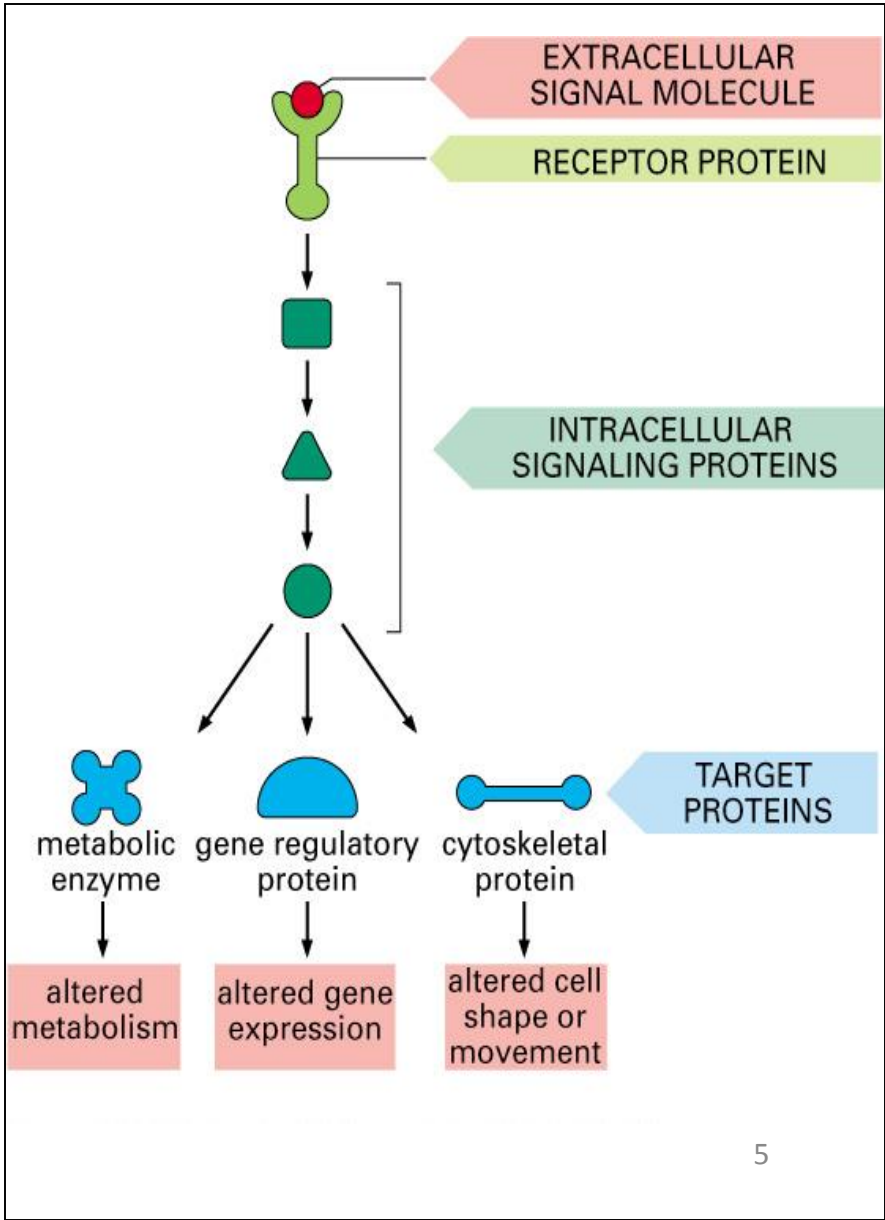
- *Signaling:* Cell-cell communication via signals.
- *Signal transduction:* Process of converting extracellular signals into intra-cellular responses.
- *Ligand:* The signaling molecule.
- *Receptors:* Bind specific ligands and in turn activate one or more intracellular pathways. These pathways depend on intracellular signaling proteins which process the signal and transmit the signal to appropriate intracellular targets. The targets at the end of signaling pathways are called effector proteins.

A simple intracellular signaling pathway activated by an extracellular signal molecule

The signal molecule usually binds to a receptor protein in the PM of the target cell.

The receptor activates one or more intracellular signaling pathways, involving a series of signaling proteins.

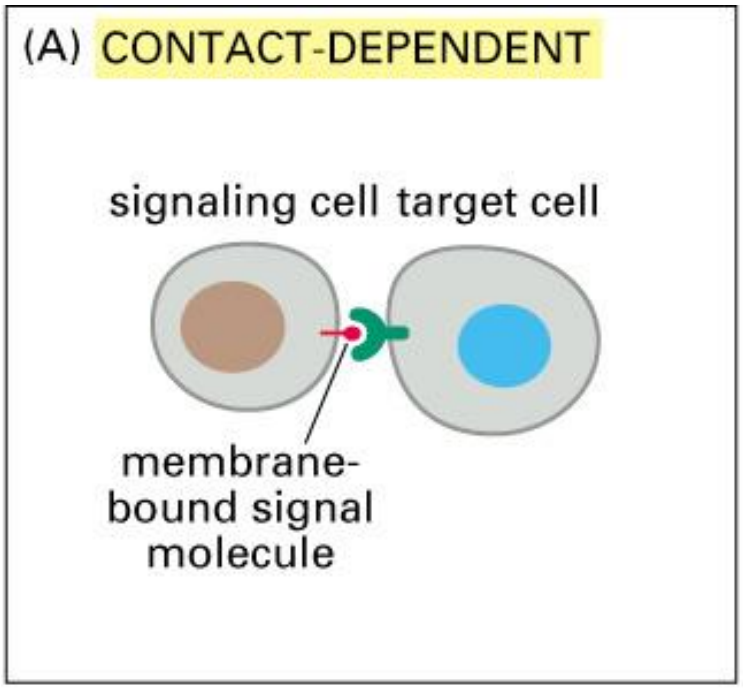
Finally, one or more of the intracellular signaling proteins alter the activity of effector proteins and thereby the behaviour of the cell.



Four forms of intercellular signaling

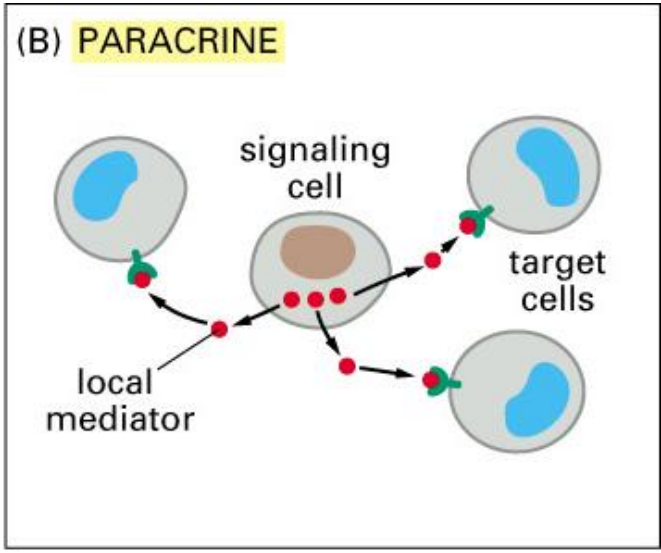
- Cells usually communicate with each other through **extracellular messenger molecules.**

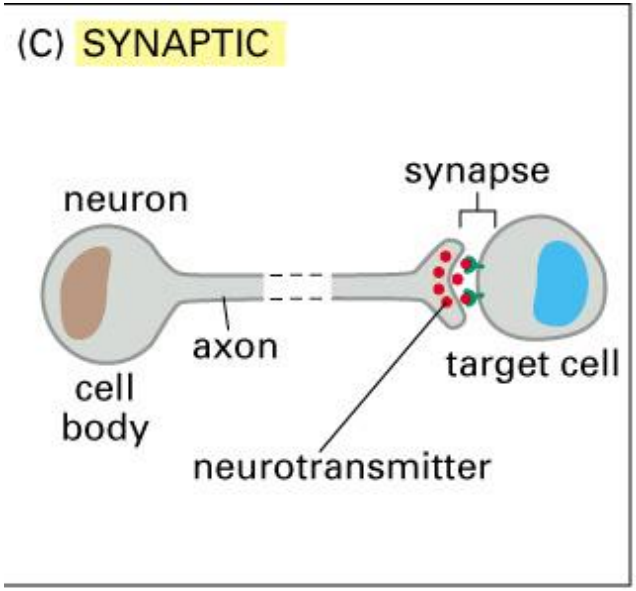
1. Contact dependent signaling requires cells to be in direct membrane-membrane contact. This is important during development and in immune responses.



Four forms of intercellular signaling

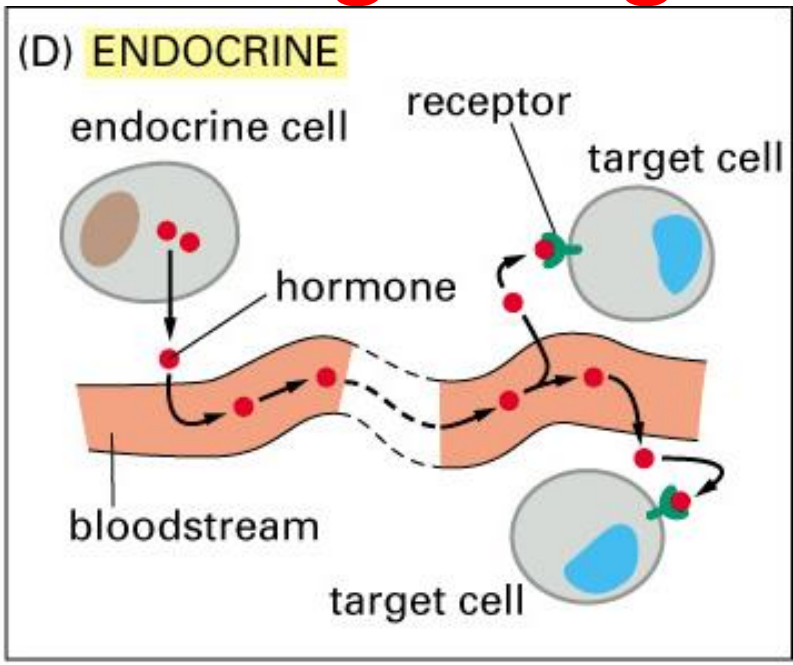
- 2. paracrine signaling depends on local mediators that are released into the extracellular space and act on neighbouring cells. E.g. nerve-muscle
- 3. synaptic signaling is performed by neurons that transmit signals electrically along their axons and release neurotransmitters at synapses.

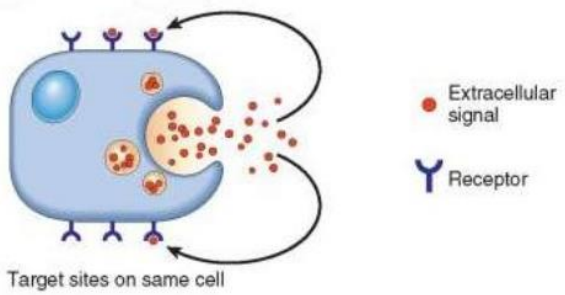




Four forms of intercellular signaling

- 4. endocrine signaling depends on endocrine cells, which secrete hormones into the bloodstream for distribution throughout the body
- Autocrine signaling- cell that releases the signal is also the target.





Autocrine Signalling

Each cell is programmed to respond to specific combinations of extracellular signals

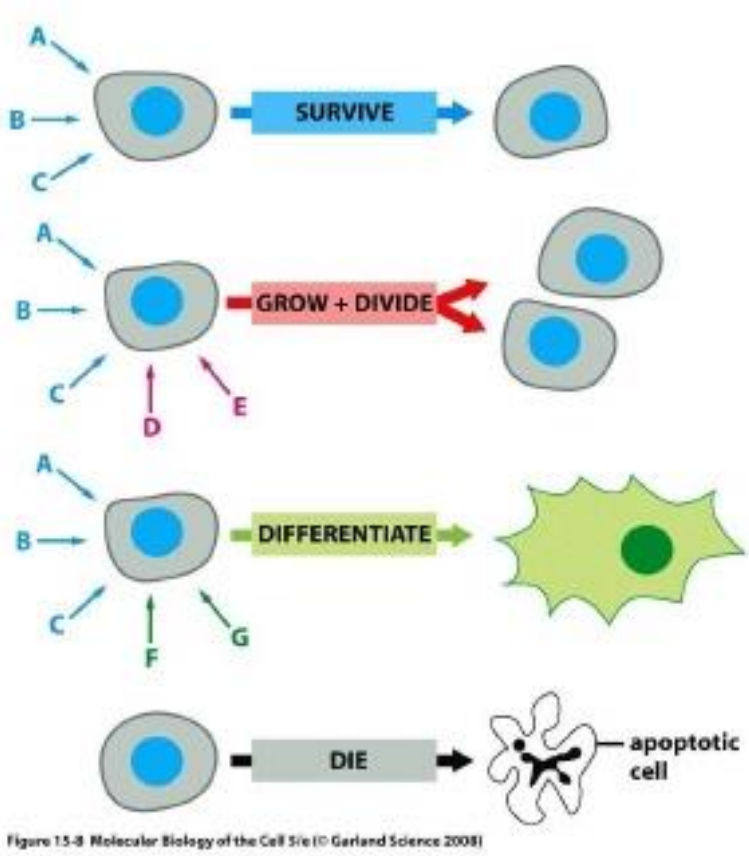


Figure 15-8 Molecular Biology of the Cell 5/e (© Garland Science 2008)

A cell may require multiple signals (A,B,C) to survive. Additional signals to grow and divide (D,E) or differentiate (F,G). If appropriate survival signals are deprived off, the cell undergoes apoptosis.

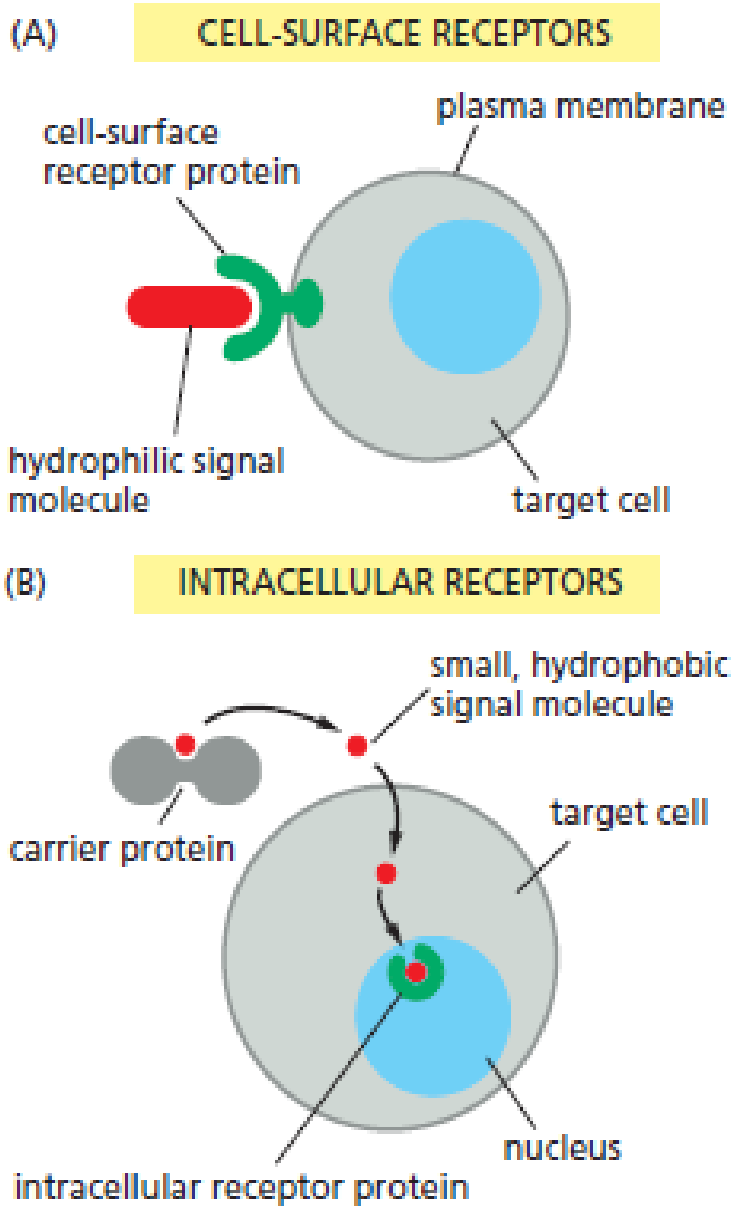
Extracellular signal molecules bind to specific receptors

- Extracellular signal molecules include proteins, small peptides, amino acids, nucleotides, steroids, retinoids, fatty acid derivatives, NO, CO.
- Target cells respond by means of receptors.
- Receptors are of two types:

Receptors

1. mostly, receptors are transmembrane proteins on the target-cell surface. When they bind to Extra cellular molecule (a ligand), and act as signal transducer, they become activated and generate various intracellular signals that alter the behaviour of cell.

2. Intracellular receptors-the signal molecule has to be small to diffuse across the PM and bind to receptor proteins inside the target cell-either in the cytosol or nucleus.



Types of Signaling ligands

Produced by signaling cells, bind to receptors in target cells, act as chemical signals

1. Small Hydrophobic Ligands
2. Other Ligands
3. Water-Soluble Ligands

Small hydrophobic ligands

- Small hydrophobic ligands can directly diffuse through the plasma membrane and interact with internal receptors. Important members of this class of ligands are the steroid hormones.

Other Ligands

- Nitric oxide (NO) is a gas that also acts as a ligand. It is able to diffuse directly across the plasma membrane; one of its roles is to interact with receptors in smooth muscle and induce relaxation of the tissue. NO has a very short half-life; therefore, it only functions over short distances.

Water-soluble ligands

- Water-soluble ligands are polar and, therefore, cannot pass through the plasma membrane unaided. Instead, most water-soluble ligands bind to the extracellular receptors.
- Cell-surface receptors include: ion-channel, G-protein, and enzyme-linked protein receptors. The binding of these ligands to these receptors results in a series of cellular changes. These water soluble ligands are quite diverse and include small molecules, peptides, and proteins.

Signaling molecules

Types of Signaling Ligands:

A. Ligands that bind to cell-surface receptors:

1. Neurotransmitters (NT), i.e. norepinephrine, histamine - hydrophilic (charged, polar)

2. Peptide hormones (P), i.e. insulin - can't cross membrane

3. Growth factors (GF),

4. Lipophilic signaling molecules, i.e. prostaglandins

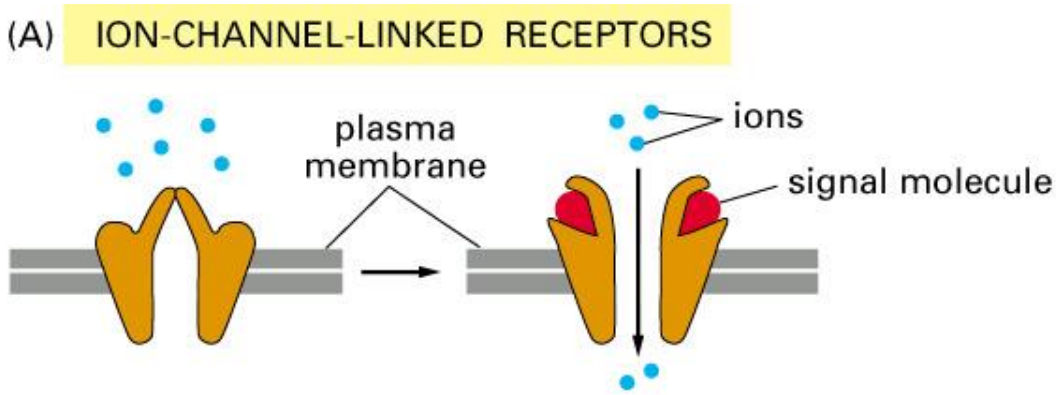
B. Ligands that bind to intracellular receptors:

lipid soluble hormones that diffuse across the plasma membrane and interact with receptors in the cytosol or nucleus. i.e. steroids, thyroxine, retinoic acid, nitric oxide.

Cell surface receptors

- Ion -channel-linked receptors bind a ligand and open a channel through the membrane that allows specific ions to pass through.
- G-protein-linked receptors bind a ligand and activate a membrane protein called a G-protein, which then interacts with either an ion channel or an enzyme in the membrane.
- Enzyme-linked receptors are cell-surface receptors with intracellular domains that are associated with an enzyme.

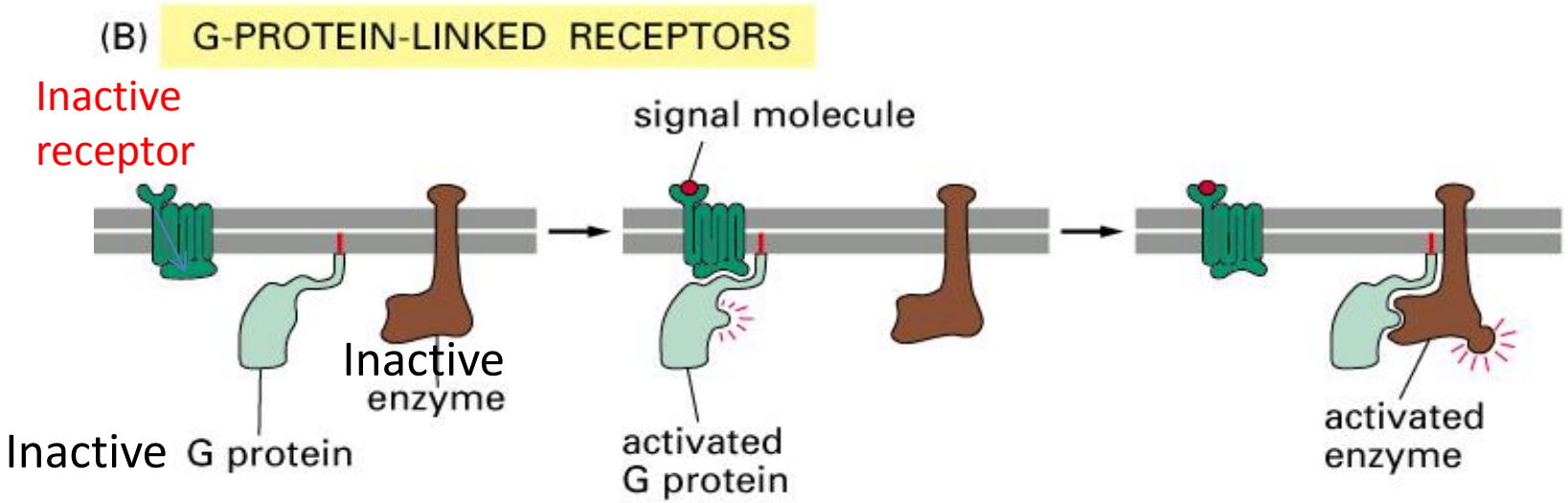
Ion channel-linked receptors



Also called transmitter-gated ion channels or ionotropic receptors. Found in nerve and muscle cells (electrically excitable). This type of signaling is mediated through neurotransmitters.

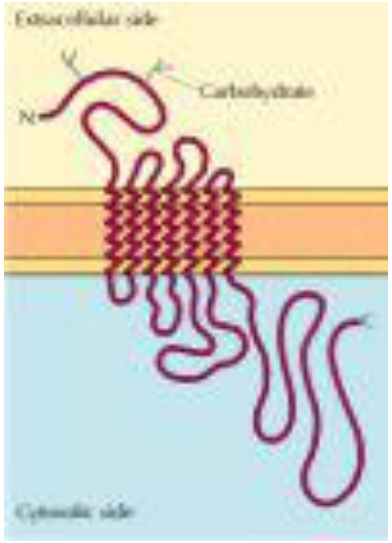
When a ligand binds to the extracellular region of the ion-channel-linked receptors, there is a conformational change in the receptor protein's structure that allows ions such as sodium, calcium, magnesium, and hydrogen to pass through .

G-protein-linked receptors



- The G protein-coupled receptors are characterized by seven membrane-spanning α helices

- ~45% of all pharmaceutical drugs are known to target GPCRs



Signal molecules

Biogenic amines: Adrenaline, noradrenaline, dopamine,, histamine, acetylcholine

Amino acids and ions: Glutamate, Ca^{2+}, GABA

Lipids : prostaglandins, leukotrienes (produced in leukocytes by the oxidation of arachidonic acid)

Peptides / proteins :

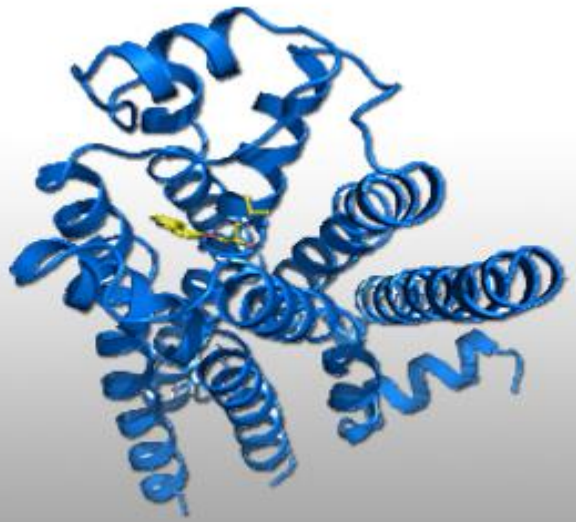
GnRH, angiotensin, bradykinin, thrombin, bombesin, glucagon, calcitonin, vasoactive intestinal peptides, PTH, FSH, LH, TSH

Nucleotides : Adenosine nucleotides, adenine nucleotides, uridine nucleotides

Others : Light, odorants, pheromones, opiates

Historical background

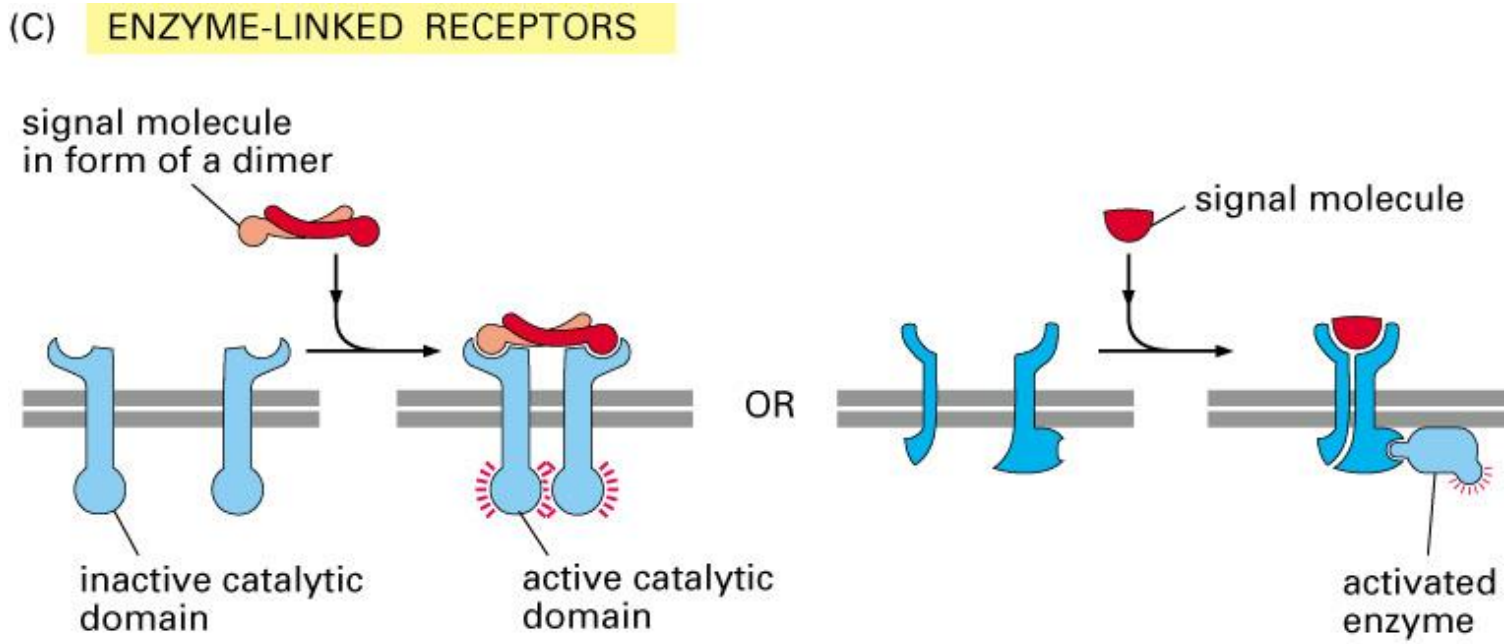
- **Robert Lefkowitz** and **Brian Kobilka:** the 2012 Nobel Prize in Chemistry for groundbreaking discoveries that revealed the inner workings of **G-protein–coupled receptors**.



G-protein-linked receptors

- The binding of ligands to the extracellular domain of these receptors induces a conformational change in the receptor and exposes a binding site for a G protein (bound to the inner face of the plasma membrane). G protein consists of α,β,γ subunits.

Enzyme-linked receptors



An example of enzyme-linked receptor is the tyrosine kinase receptor. Signaling molecules bind to the extracellular domain of two nearby tyrosine kinase receptors, which then dimerize. The tyrosine kinase receptor transfers phosphate groups to tyrosine molecules on the intracellular domain of the receptors and can then transmit the signal to the next messenger within the cytoplasm.

- This family includes the receptors for most polypeptide growth factors, so protein-tyrosine phosphorylation has been particularly well studied as a signaling mechanism involved in the control of animal cell growth and differentiation.