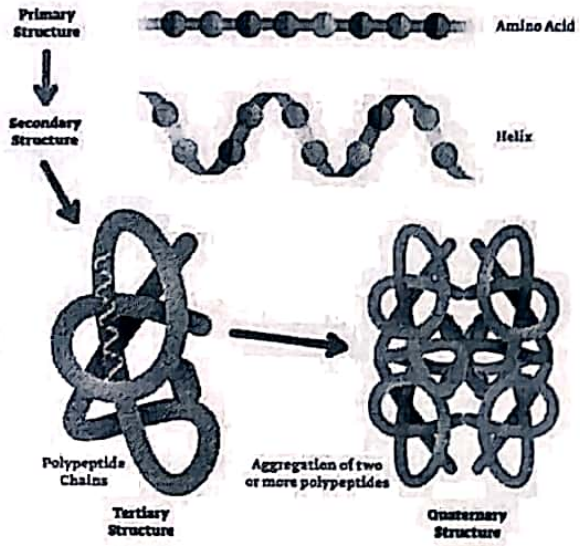
Protein Structure

Protein structure is the three-dimensional arrangement of atoms in an amino acid chain molecule.

Proteins are polymers – specifically polypeptides – formed from sequences of amino acids, the monomers of the polymer.

A single amino acid monomer may also be called a *residue* indicating a repeating unit of a polymer.



Importance of Proteins

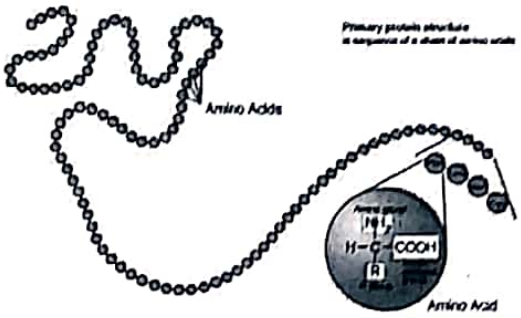
- Muscle structure depends on protein-protein interactions
- Transport across membranes involves protein-solute interactions
- Nerve activity requires transmitter substance-protein interactions
- Immune protection requires antibody-antigen interactions

Types of Protein structure

- **Primary Structure**
- **Secondary Structure**
- **Tertiary Structure**
- **Quaternary Structure**

Primary Structure

A protein usually undergoes reversible structural changes in performing its biological function. The alternative structures of the same protein are referred to as different conformations, and transitions between them are called conformational changes.



Primary Structure

The primary structure of a protein refers to the sequence of amino acids in the polypeptide chain.

The primary structure is held together by peptide bonds that are made during the process of protein biosynthesis.

The two ends of the polypeptide chain are referred to as the carboxyl terminus (C-terminus) and the amino terminus (N-terminus) based on the nature of the free group on each extremity.

Counting of residues always starts at the N-terminal end (NH_2-group), which is the end where the amino group is not involved in a peptide bond.

For example, insulin is composed of 51 amino acids in 2 chains. One chain has 31 amino acids, and the other has 20 amino acids.

20 Amino Acids

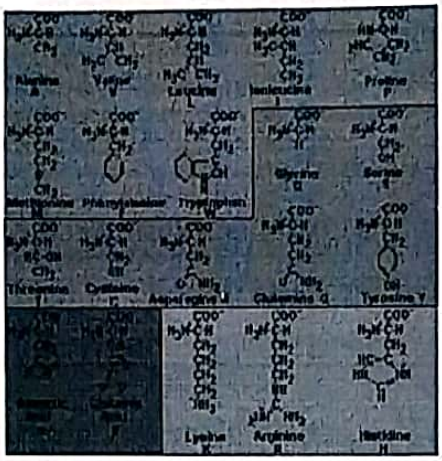
Protein structures range in size from tens to several thousand amino acids.

- **Polypeptide chains → Amino Acids**
- **Largest polypeptide chain approx has 5000AA but most have less than 2000AA**
- **Amino Acid Basic Structure H2N-CH-COOH**
- **Arrangement of the 20 amino acids in the polypeptide is the amino acid sequence which composes the primary structure of the protein.**

Nonpolar, hydrophobic

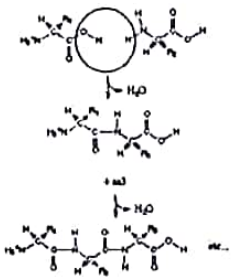
Pola ; uncharged

Polar, charged



Bond Formation

- Linking two amino acids together.
- Proteins form by amino acids undergoing condensation reactions, in which the amino acids lose one water molecule per reaction in order to attach to one another with a peptide bond.
- By convention, a chain under 30 amino acids is often identified as a peptide, rather than a protein.

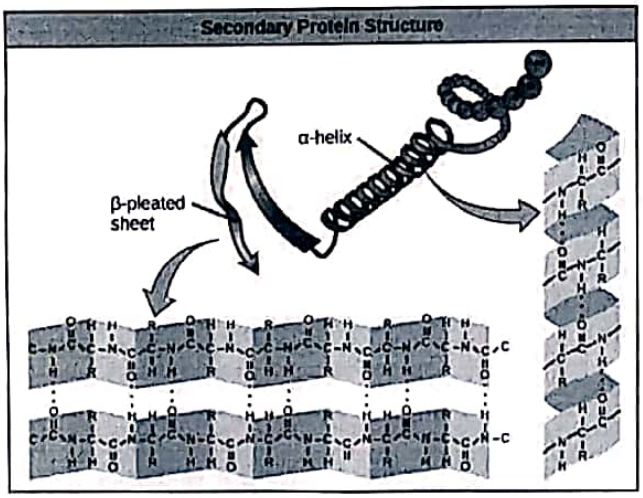


Protein Secondary Structure

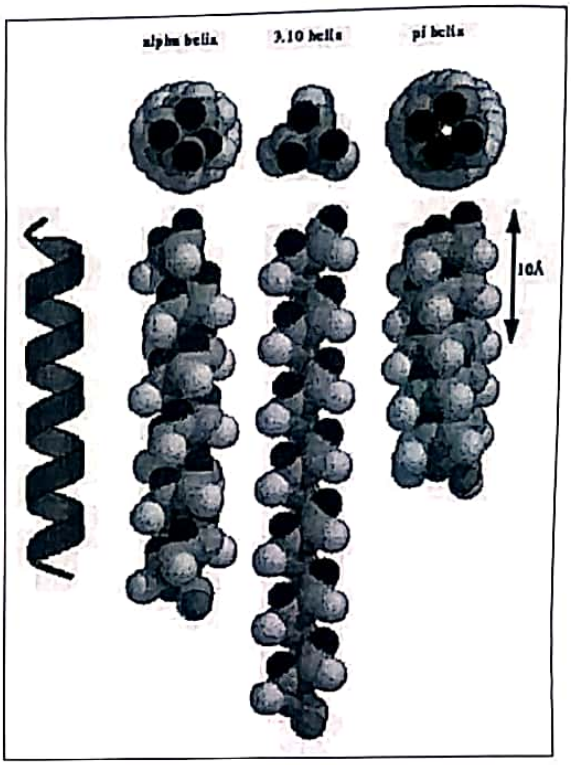
The peptide chain tends to assume an asymmetric helical shape; some of the fibrous proteins consist of elongated helices around a straight screw axis. Such structural features result from properties common to all peptide chains. The product of their effects is the secondary structure of the protein.

Hydrogen bonding between amino groups and carboxyl groups in neighboring regions of the protein chain sometimes causes certain patterns of folding to occur.
Known as alpha helices and beta sheets, these stable folding patterns make up the secondary structure of a protein.

The most common types of secondary structures are the α helix and the β pleated sheet. Both structures are held in shape by hydrogen bonds, which form between the carbonyl O of one amino acid and the amino H of another.



Helix Structures



Alpha Helix

Structure Features

In a helix, the carbonyl (C=O) of one amino acid is hydrogen bonded to the amine H (N-H) of an amino acid. The pattern of bonding pulls the polypeptide chain into a helical structure that resembles a curled spring, with each turn of the helix containing 3.6 amino acids.

In a β pleated sheet, two or more segments of a polypeptide chain line up next to each other, forming a sheet-like structure held together by hydrogen bonds. The hydrogen bonds form between carbonyl and amine groups of backbones. The strands of a β pleated sheet may be parallel, pointing in the same direction as their N- and C-terminal ends, or antiparallel.

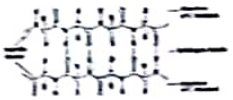
Certain amino acids are to be found in α helices or β pleated sheets. Many proteins contain both α helices and β pleated sheets, though some contain just one type of secondary structure or do not form either type.

Tertiary Protein Structure

- Defines the three dimensional conformation of an entire peptide chain in space.
- Determined by the primary structure.

Most proteins contain multiple helices and sheets, in addition to other less common patterns. The ensemble of formations and folds in a single linear chain of amino acids — sometimes called a polypeptide — constitutes the tertiary structure of a protein

The tertiary structure is the product of the interactions between the side chains (R) of the amino acids composing the protein. Some of these contain positively or negatively charged groups, others are polar, and still others are nonpolar. The number of carbon atoms in the side chain varies from zero in glycine to nine in tryptophan. Positively and negatively charged side chains have the tendency to attract each other

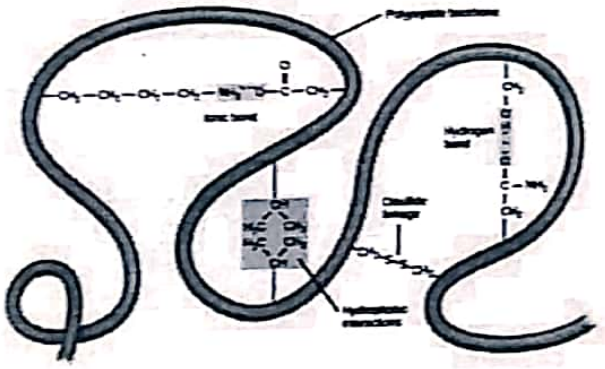


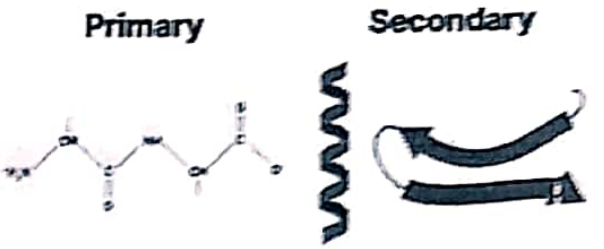
The overall three-dimensional structure of a polypeptide is called its tertiary structure. The tertiary structure is primarily due to interactions between the R groups of the amino acids that make up the protein.

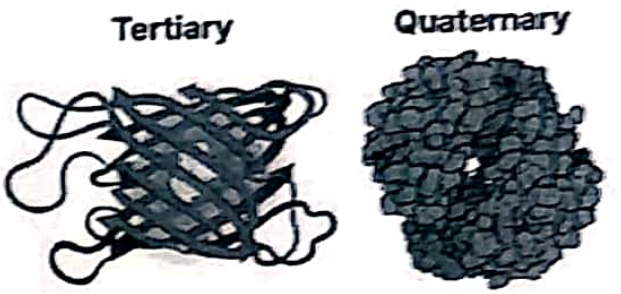
R group interactions that contribute to tertiary structure include hydrogen bonding, ionic bonding, dipole-dipole interactions.

For example, R groups with like charges repel one another, while those with opposite charges can form an ionic bond. Similarly, polar R groups can form hydrogen bonds and other dipole-dipole interactions. Also important to tertiary structure are hydrophobic interactions, in which nonpolar, hydrophobic R groups cluster together on the inside of the protein, leaving hydrophilic amino acids on the outside to interact with surrounding water molecules.

Most proteins contain multiple helices and sheets, in addition to other less common patterns. The ensemble of formations and folds in a single linear chain of amino acids — sometimes called a polypeptide — constitutes the tertiary structure of a protein





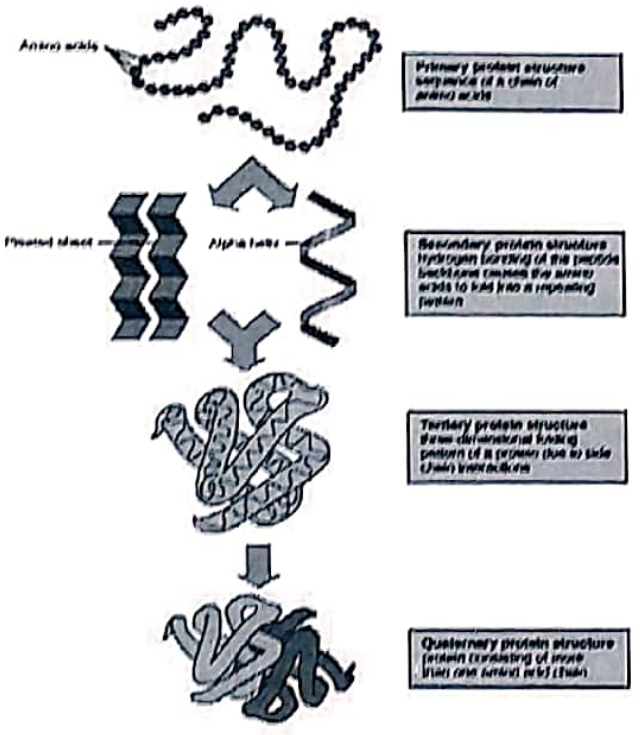


Quaternary Structure

- **Not all proteins have a quaternary structure**
- **A composite of multiple poly-peptide chains is called an oligomer or multimeric.**
- **Hemoglobin is an example of a tetramer**

Quaternary structure is the three-dimensional structure consisting of the aggregation of two or more individual polypeptide chains called subunits that operate as a single functional unit known as multimer. The resulting multimer is stabilized as in tertiary structure.

There are many possible quaternary structure organizations. Complexes of two or more polypeptides i.e. multiple subunits are called multimers. It would be called a dimer if it contains two subunits, a trimer if it contains three subunits, a tetramer if it contains four subunits, and a pentamer if it contains five subunits.
The subunits are frequently related to one another by symmetry operations, such as a 2-fold axis in a dimer.



Conclusion

The final shape adopted by a newly synthesized protein is typically the most energetically favourable one. As proteins fold, they lose a variety of conformations before reaching their final form, which is unique and compact.

Folded proteins are stabilized by thousands of noncovalent bonds between amino acids. Also chemical forces between a protein and its immediate environment contribute to protein shape and stability.

Even though proteins are considered macromolecules, they are too small to visualize, even with a microscope. So, scientists found new indirect methods to figure out what they look like and how they are folded. The most commonly method used to study protein structures is X-ray crystallography. With this method, solid crystals of purified proteins are placed in an X-ray beam, and the pattern of deflected X-rays is used to predict the positions of the thousands of atoms within the protein crystal.

Cell Signaling

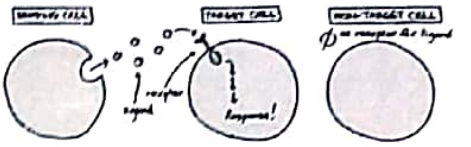
- Cell signaling is part of a complex system of communication that governs basic activities of cells and coordinates cell actions.
- The ability of cells to perceive and correctly respond to their microenvironment is the basis of development, tissue repair, and immunity as well as normal tissue homeostasis.
- Errors in cellular information processing are responsible for diseases such as cancer, autoimmunity, and diabetes.
- Each cell is programmed to respond to specific extracellular signal molecules, and is the basis of development, tissue repair, immunity etc.
- Errors in signaling interactions may cause diseases such as cancer, autoimmunity, and diabetes. By understanding cell signaling, diseases may be treated more effectively and, theoretically, artificial tissues may be created.

Cell signaling or cell communication is the ability of a cell to receive, process, and transmit signals with its environment and with itself. It is a fundamental property of all cells in every living organism such as bacteria, plants, and animals.

Signals that originate from outside a cell i.e extracellular signals can be physical agents like mechanical pressure, tension, temperature, light, or chemical signals e.g., small molecules, peptides, or gas.

Chemical signals can be hydrophobic or hydrophilic.

Cell signaling can occur over short or long distances.



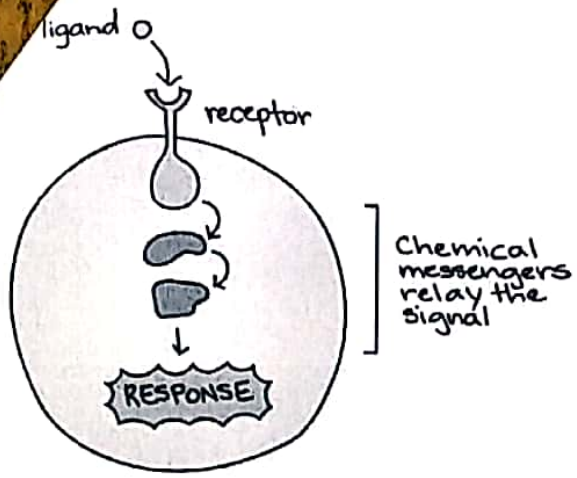
All cells can't respond to a particular chemical message. For communication between cells, the neighboring cell must have the a receptor for that signal. When a signaling molecule binds to its receptor, it alters the shape or activity of the receptor, triggering a change inside of the cell.

Receptors can be synthesized from various biosynthetic pathways and released through passive or active transports, or even from cell damage.

Receptors play a key role in cell signaling as they are able to detect chemical signals or physical stimuli. Receptor are generally proteins located on the cell surface or within the interior of the cell e.g. cytoplasm, organelles, and nucleus.

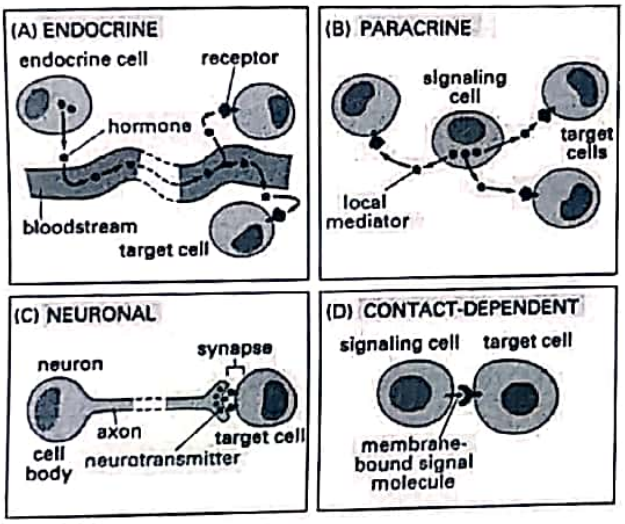
Signaling molecules are often called ligands. The message carried by a ligand is often relayed through a chain of chemical messengers inside the cell which leads to a change in the cell, e.g. alteration in the activity of a gene, cell division etc.

Some receptors do not contain enzymatic or channel like domains but are instead linked to enzymes or transporters. Other receptors like nuclear receptors have a different mechanism such as changing their DNA binding properties and cellular localization to the nucleus.



Types of Cell Signaling

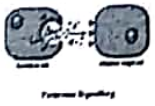
- Paracrine
- Autocrine
- Endocrine
- Contact Dependent



1. Paracrine signaling

Cells that are near one another communicate through the release of chemical messengers i.e. ligands that can diffuse through the space between the cells. This type of signaling, in which cells communicate over relatively short distances, is known as paracrine signaling.

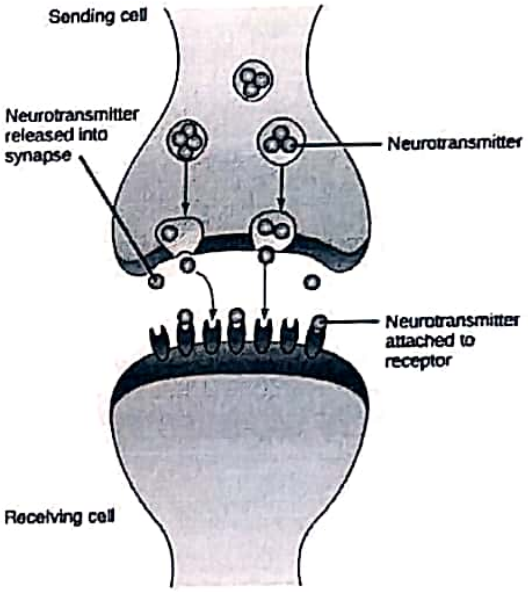
Paracrine signaling allows cells to locally coordinate activities with their neighbors. Although they're used in many different tissues and contexts, paracrine signals are especially important during development. In paracrine signaling, a cell produces a signal to induce changes in nearby cells, altering the behavior of those cells. Signaling molecules known as paracrine factors diffuse over a short distance called local action. e.g. retinoic acid target only cells in the nearby of the emitting cell. Neurotransmitters represent another example of a paracrine signal.



Synaptic signaling:-

One unique example of paracrine signaling is synaptic signaling, in which nerve cells transmit signals. This process is named for the synapse, the junction between two nerve cells where signal transmission occurs.

When the sending neuron fires, an electrical impulse moves rapidly through the cell, traveling down a long, fiber-like extension called an axon. When the impulse reaches the synapse, it triggers the release of ligands called neurotransmitters, which quickly cross the small gap between the nerve cells. When the neurotransmitters arrive at the receiving cell, they bind to receptors and cause a chemical change inside of the cell i.e. opening ion channels and changing the electrical potential across the membrane.



2. Autocrine signaling

In this case a cell signals, to itself releasing a ligand that binds to receptors on its own surface.

Autocrine signaling plays an important role in many processes i.e. autocrine signaling during development, helping cells take on and reinforce their correct identities.

Autocrine signaling in cancer play a key role in metastasis i.e. the spread of cancer from its original site to other parts of the body.

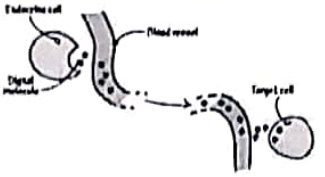
A signal may have both autocrine and paracrine effects, binding to the sending cell as well as other similar cells in the area.

Autocrine signaling involves a cell secreting a hormone or chemical messenger called the autocrine agent that binds to autocrine receptors on that same cell, leading to changes in the cell itself.

3 Endocrine Signalling

Endocrine signals are called hormones. Hormones are produced by endocrine cells and they travel through the blood to reach all parts of the body.

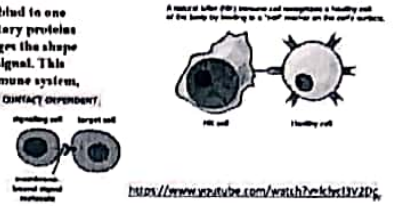
When cells transmit signals over long distances, they use the circulatory system as a distribution network for the messages they send. In endocrine signaling, signals are produced in form of hormone and released into the bloodstream, which carries them to target cells in distant parts of the body.
In humans, endocrine glands that release hormones are thyroid, hypothalamus, pituitary, pancreas etc.
Each endocrine gland releases one or more types of hormones, many of which are regulators of development and physiology.



4. Signaling through cell-cell contact

Gap junctions are tiny channels that directly connect neighboring cells. These water-filled channels allow small signaling molecules, called intercellular mediators, to diffuse between the two cells. Small molecules and ions are able to move between cells, but large molecules like proteins and DNA cannot fit through the channels without special assistance.
The transfer of signaling molecules transmits the current state of one cell to its neighbor. This allows a group of cells to coordinate their response to a signal that only one of them may have received.

In this type of signalling, two cells may bind to one another because they carry complementary proteins on their surfaces. This interaction changes the shape of one or both proteins, transmitting a signal. This kind of signaling is important in the immune system, where cells are infected by pathogens.



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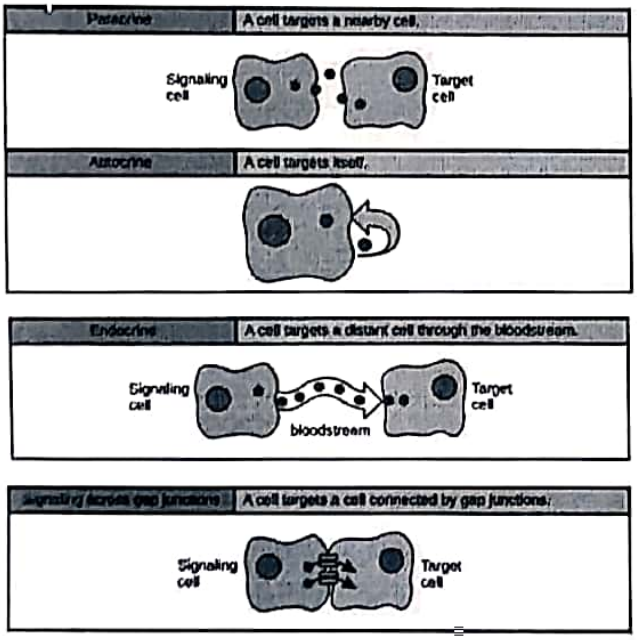


Receptors

Cells receive information from their neighbors through a class of proteins known as receptors.

Receptors bind with some molecules called ligands or may interact with light, mechanical temperature, pressure, etc.

Reception occurs when the target cell detects a signal.

Signaling molecules interact with a target cell as a ligand to cell surface receptors, and/or by entering into the cell through its membrane or endocytosis for signaling e.g. in mammals, embryo cells exchange signals with cells of the uterus. In the human gastrointestinal tract, bacteria exchange signals with each other.

Types of Receptors

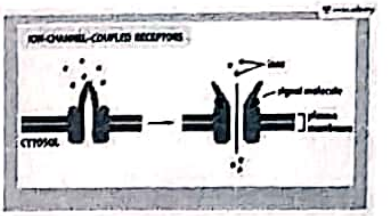
A. Cell surface receptors

Cell surface receptors play an essential role in the biological systems of single- and multi-cellular organisms. Malfunction or damage to these proteins is associated with cancer, heart disease, and asthma. These trans-membrane receptors are able to transmit information from outside the cell to i inside because they change conformation when a specific ligand binds to it.

These are of three types:-

1. Ion channel linked receptors

Ion channel linked receptors are a group of transmembrane ion-channel proteins which open to allow ions such as Na^+, K^+, Ca^{2+}, and Cl^- to pass through the membrane in response to the binding of a ligand e.g. neurotransmitter.



2. G protein–coupled receptors

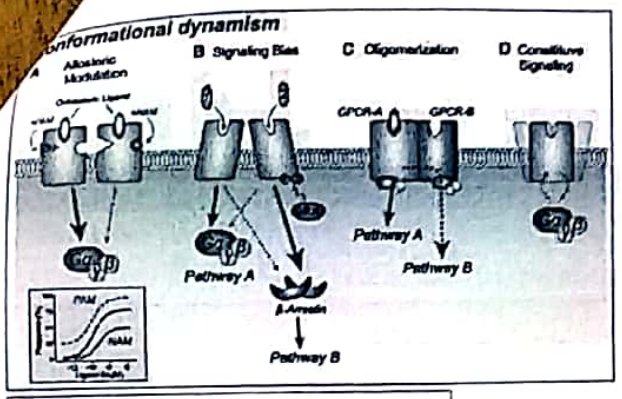
G protein-coupled receptors are a large group of evolutionarily-related proteins that are cell surface receptors that detect molecules outside the cell and activate cellular responses.

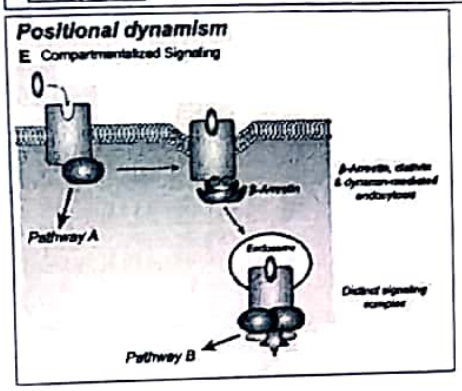
Coupling with G proteins, they are called seven-transmembrane receptors because they pass through the cell membrane seven times.

G protein-coupled receptors are found only in eukaryotes, yeast, and animals.

The ligands that bind and activate these receptors include light-sensitive compounds, hormones, and neurotransmitters, and vary in size from small molecules like peptides to large one like proteins.

G protein-coupled receptors are involved in many diseases. ht





3. Enzyme-linked receptors

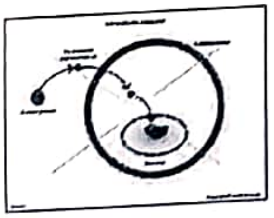
Enzyme-linked receptors are transmembrane receptor that, upon activation by an extracellular ligand, causes enzymatic activity on the intracellular side. Hence a catalytic receptor is an integral membrane protein possessing both enzymatic, catalytic, and receptor functions.

They have two important domains, an extra-cellular ligand binding domain and an intracellular domain, which has a catalytic function; and a single transmembrane helix.

The signaling molecule binds to the receptor on the outside of the cell and causes a conformational change on the catalytic function located on the receptor inside the cell.

B. Intracellular receptors

Intracellular receptors are receptors located inside the cell rather than on its cell membrane. Classic hormones that use intracellular receptors include thyroid and steroid hormones.



C. Steroid hormone receptor

Steroid hormone receptors are found in the nucleus, cytosol, and plasma membrane of target cells. They are generally intracellular receptors and initiate signal transduction for steroid hormones which can result in changes in gene expression over a time period of hours to days.

In addition to nuclear receptors, several G protein coupled receptors and ion channels also act as cell surface receptors for certain steroid hormones.