CELL SIGNALLING

RECEPTORS

Sashidhar Mulugu
Associate Professor
Department of Biomedical Science
Bharathidasan University

RECEPTORS

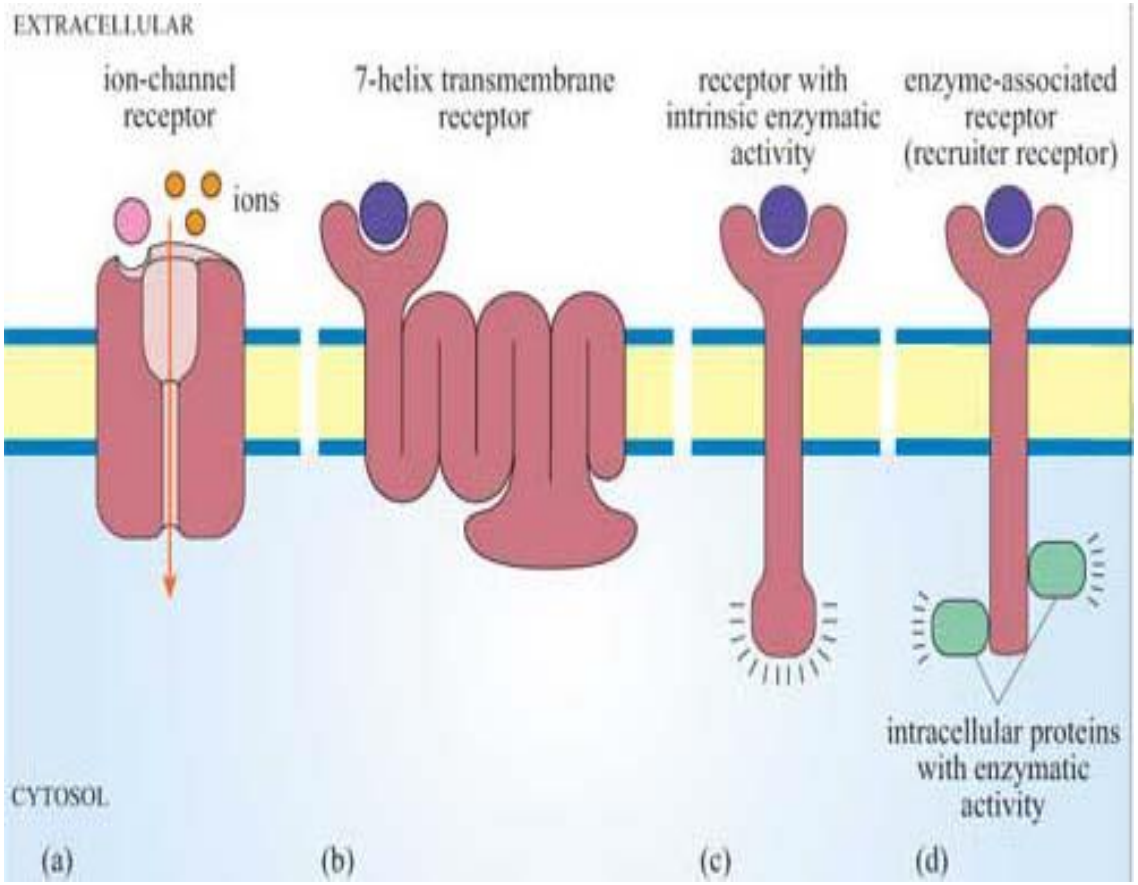
- Most receptors are on cell surface --- Water soluble signalling molecules cannot cross membrane lipid bilayer but are capable of binding to specific receptors embedded in the plasma membrane.
- Receptors have an a) **Extracellular** domain that binds signalling molecule b) a **hydrophobic** transmembrane domain and c) intracellular domain.
- On binding a ligand, there induces a conformational change in the receptor, in particular of the intracellular region which in turn activates a relay of intracellular signalling molecules… thus bringing about appropriate cellular responses such as altered metabolism, altered cytoskeleton or altered gene expression or cell division.
- **Properties of Receptors** – a) **Specificity** – Signalling molecule or ligand recognizes and binds to its specific receptor just as an enzyme binds to its substrate and this binding is independent from competition from other signalling molecules
- b) **High Affinity** – Receptors usually bind to their signalling molecules with high affinity as determined by their affinity constants Ki and also the interaction shows low dissociation constants Kd indicating high affinity binding.

- C) **Saturation Kinetics** – Number of receptors on the surface of a cell is limited and the number varies from less than a dozen to several thousand depending on the receptor type. Increasing the signal ligand concentration would eventually result in **receptor saturation** meaning all sites being occupied by ligands.
- d) **Reversibility** – Normally the binding of a signalling ligand to a receptor is reversible and this is necessary property to prevent permanent activation of the receptor
- e) **Physiological Response** – Ligand receptor binding triggers a physiological response characteristic for its interaction such as binding of insulin to insulin receptor (INSR) stimulates glucose transport into target cells. The magnitude of the response is directly related to the number of receptors to which the ligands bind.

STRUCTURAL CLASSES OF SIGNALLING RECEPTORS

- They can be structurally classified into Single –pass transmembrane receptors (with one extracellular , one transmembrane and one intracellular region) and Multi – pass transmembrane receptors.
- Based on signal transduction functions they can be classified into 4 types of receptors : 1. Ion – channel Receptors
- 2. 7 – Helix Transmembrane receptors
- 3. Receptors with Intrinsic enzymatic activity (RIEA)
- 4. Enzyme associated receptors (Recruitor receptors)

FOUR MAJOR CLASSES OF RECEPTORS



- Broadly two super families or classes of receptors are there based on structural organization .
- Single – pass receptors : Enzyme linked receptors are heterogenous in structure in that they consist of a polypeptide chain which has only one transmembrane helix (single pass) . Enzymes linked receptors on activation either function directly as **enzymes** of indirectly being **associated with the enzymes that they activate.** Majority of them are **protein kinases** or **are associated with protein kinases.** Binding of ligand to enzyme – linked receptors results in **phosphorylation** of specific sets of proteins in target cells.
- Examples are dimeric receptor tyrosine kinases (RTKs), monomeric receptors guanylyl cyclase (RGCs) , protein tyrosine phosphatases and protein – serine / threonine kinases.

- RTKs and RGCs are catalytic receptors that catalyze phosphorylation.
- Protein – tyrosine phosphatases catalyze the removal of phosphate groups from tyrosine residues of proteins.
- Protein – serine / threonine kinases catalyze phosphorylation of serine / threonine residues in proteins.
- Ion – Channel Receptors : These are those that can directly act as **effector** molecules such as **acetylcholine receptor.**
- Thus while responding to **acetylcholine,** these receptors allow passage of the specific ions, thereby affecting changes in the membrane potential of the cell. Acetylcholine receptors are extremely important in the transmission of electrical signals between excitable cells.

- Seven – pass Receptors : These contain seven transmembrane **alpha helices** and have a common mode of action with a N-terminal extracellular region and C- terminal intracellular tail. The seven hydrophobic regions of 20 to 28 residues each pass in and out of the membrane giving the polypeptide a snake – like form. Hence the receptors are called **serpentine receptors**.
- All the receptors in this class are **G protein coupled receptors** (GPCRs), which are linked to trimeric G proteins that consist of 3 subunits alpha, beta and gamma. GPCRs interact through G proteins with a membrane bound enzyme (target protein). Examples are adrenergic receptors (bind adrenaline), light activated rhodospin (mediates phototransduction-light energy is converted to neurochemical reaction) and the alpha factor receptor which is product of STE2 gene in S.cerevisiae.

- In some situations the intracellular tail contains an enzymatic domain – hence are known as Receptors with intrinsic enzymatic activity (RIEA) as seen in receptor tyrosine kinases involved in response to many growth factors.
- Receptors that require cytosolic or membrane bound protein with enzymatic activity for signalling. Since they do not have intrinsic activity they as enzyme associated receptors or recruitor receptors. (although GPCRs also function by recruiting cytosolic signalling molecule).
- Besides the 4 groups of cell surface receptors, another group of receptors function as DNA – binding molecules, and thus regulate gene transcription. They are called Receptors with Intrinsic Transcriptional Activity and are different from RIEA. Most of them are intracellular and require ready access of the ligand to the intracellular component.

SIGNAL TRANSDUCTION MECHANISMS

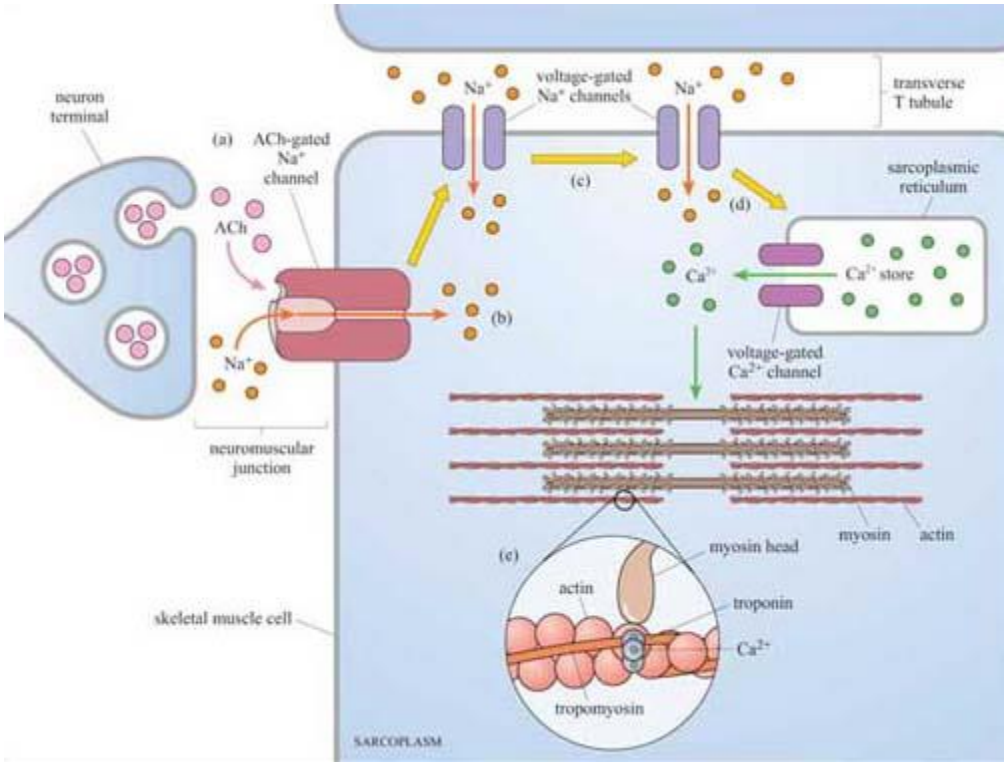
- 1. Signalling information has to be transmitted from the receptor in the plasma membrane across the cytoplasam to the nucleus (If gene transcription is the response required), the cytoskeleton (If cell movement or another change to cell morphology is the response) or various other subcellular compartments.
- 2. These responses are expected to occur within a suitable time frame so as to have some synchronicity with regarding transmission or signal and cellular response.
- 3. In a typical model of signalling a chain of intracellular mediators successively activates the next target in the chain, as in a branching network of activation, diversification and modulation of response.
- 4. Thus the branched molecular network of activation (or deactivation) of signalling molecules linking receptor activation to the intracellular targets is referred to as a **signal transduction pathway (or cascade).**

SECOND MESSENGERS

- Intracellular signalling molecules have properties that allow control of the speed, duration and target of the signal and be categorized accordingly. Broadly they can be divided into 2 groups on the basis of their molecular characteristics, **Second Messengers and Signalling Proteins.**
- 1. Second Messengers are small readily diffusible intracellular mediators regulating the activity of other target signalling molecules. The calcium ions Ca2+ is a classic example of a second messenger being released in large quantities in response to a signal (amplifying the signal) and diffusing rapidly through the cytosol and help in broadcasting the signal quickly to several distant parts of the cell. Eg. Ca2+ ions mediate and coordinate contraction of skeletal muscle cells. Thus if rapid response is needed second messengers will definitely be present in the signalling pathway.

Contraction of Skeletal Muscle Cells - Mechanism

- A. Acetylcholine (ACH) is released from the neuronal terminal and binds to ACH – gated Na+ channels on the surface of the muscle cell.
- B. The receptors are ion channels and hence promote local depolarization (increase in membrane potential caused by entry of sodium ions)
- C. Depolarization is propagated in the muscle cell by voltage gated Na+ ion channels which allow further Na+ ion entry.
- D. Increased general deploarization triggers rapid release of Ca2+ ions into sarcoplasam (muscle cytoplasam) through voltage-gated Ca2+ from stores in sarcoplasmic reticulum; the Ca2+ ions spread throughout the muscle cell.
- E. Rapid increase of Ca2+ ions in sarcoplasam enables rapid and synchronous contraction of muscles filaments and Ca2+ ions achieves this by binding to inhibitory protein complex of tropomyosin and troponin which under resting conditions prevent **actin** and **myosin filaments** from interacting.



- Calcium ions help to synchronize rapid contraction of skeletal muscle cells.

- 2. Second messengers are water soluble such as cyclic nucleotides cAMP and cGMP and act similarly to Ca2+ ions by diffusing through the cytosol, whereas second messengers such as diacylglycerol (DAG) are lipid soluble and diffuse along the inside of the plasma membrane where other key signalling proteins are anchored.
- 3. In the G protien coupled receptor (GPCR) system the effector enzyme adenylyl cyclase synthesizes the second messenger cAMP from ATP and guanylyl cyclase synthesizes cGMP from GTP.
- 4. Resultant rise in cAMP and cGMP affects various cell types in different ways. Diverse effects of cAMP are mediated by enzymes called protein kinases A (PKAs) and does not function in signalling pathways mediated by receptor tyrosine kinases (RTKs).