Receptors and Signal Transduction

Dr. Simge Aykan

Department of Physiology

December 2019

Local Signalling

- Direct contact
  - Cell junctions
  - Cell-cell recognition
- Important during embryonic development and immune response

Local and Long Distance Signalling

- Messenger molecules are secreted by the signaling cell

- Local signalling
  - Paracrine signalling
  - Synaptic signalling

- Long distance signalling
  - Hormonal signalling

- Communication between cells
  - *Signal* : chemical messengers (ligands; hormones, neurotransmitters, paracrine substances…)
  - *Signal Detection (reception)*: receptors (specific target protein)
  - *Transduction* of signal into a physiologically meaningful response (cell division, growth…)
  - *Response*

Reception

- Reception: A signaling molecule binds to a receptor protein, causing it to change shape
  - Shape change can directly activate receptor and enable it to interact with other cellular molecules
  - Two or more receptors may aggregate and lead to further molecular events

- Receptors
  - Plasma membrane proteins
  - Intracellular proteins

Plasma Membrane Receptors

- Transmembrane proteins
- Water-soluble (polar) signaling molecules bind

- G protein-coupled receptors (GPCRs)
- Receptor tyrosine kinases
- Ion channel receptors

G protein-coupled receptors (GPCRs)

- Largest family of plasma membrane receptors
- Receptors that work with the help of GTP binding protein (G protein)
- Many different signalling molecules (ligands) use GPCRs
  - Variation in binding sites and G proteins inside the cell
  - Very similar in main structure: seven transmembrane α helices
- Roles in embryonic development and sensory reception (vision, smell, taste)
- Involved in human disease; e.g.; Bacteria (cholera, botulism..) produce toxins that interfere with G protein function

Receptor tyrosine kinases (RTKs)

- A major class of plasma membrane receptors characterized by having enzymatic activity
    - Kinase: any enzyme that catalyzes the transfer of phosphate groups
- The part of the receptor protein extending into the cytoplasm functions more specifically as a tyrosine kinase, an enzyme that catalyzes the transfer of a phosphate group from ATP to the amino acid tyrosine on a substrate protein
- One RTK may activate ten or more different transduction pathways and cellular responses (cell growth and cell reproduction)
- GPCR; activation of one pathway, RTK; activation of many pathways
- Abnormal RTKs are associated with many kinds of cancer.

Ion Channel Receptors

- Type of membrane receptor containing a region that can act as a “gate” when the receptor changes shape allowing or blocking the flow of specific ions (Na+, Ca2+…)

- Neurotransmitter receptor at the synapse
- Voltage gated ion channels
- Channels on the organelles (Endoplasmic reticulum)

Intracellular Receptors

- In cytoplasm or nucleus of target cells
- Ligands are hydrophobic or small molecules that can pass plasma membrane
  - Steroid and thyroid hormones, nitric oxide (NO)
- Hormon-receptor complex that is active and usually turns particular genes on or off (*acts as a transcription factor*)

Transduction

- Cascades of molecular interactions relay signals from receptors to target molecules in the cell
- A multistep pathway involving many molecules
  - activation of proteins by addition or removal of phosphate groups or release of other small molecules or ions that act as messengers
  - Multistep amplifies the signal
  - More opportunities for coordination and control than do simpler systems (regulation of the response)

Signal Transduction Pathways

- Phosphorylation and dephosphorylation of proteins is a widespread cellular mechanism for regulating protein activity
  - Protein kinase: An enzyme that transfers phosphate groups from ATP to a protein
    - Mostly act on proteins different from themselves (exception; Tyrosine kinase)
    - Mostly phosphorylate serine or threonine amino acids (Serine/threonine kinases)
  - Protein phosphatase: remove phosphate groups from proteins-dephosphorylation (usually inactivation)
    - Reuse of proteins (can be phosphorylated again)

Phosphorylation Cascade

- Different proteins in a pathway are phosphorylated in turn
  - each protein adds a phosphate group to the next one in line

Second Messengers

- Second messengers: small, non-protein, water-soluble molecules or ions
  - can spread throughout the cell by diffusion
- Participate in G-protein coupled receptor and receptor tyrosine kinase pathways
- Cyclic AMP (cAMP) and Ca^{2+}

Cyclic AMP

- cyclic adenosine monophosphate
- adenylyl cyclase
  - Converts ATP to cAMP in response
  - Embedded in the plasma membrane
  - 20 fold increase in cAMP
- cAMP broadcasts the signal to the cytoplasm
- Activation of protein kinase A (serine/threonine kinase) phosphorylates various proteins
- Phosphodiesterase; converts cAMP to AMP
  - Termination of the signal

Chlorea

1. The cholera toxin binds to a membrane ganglioside on secretory cell in the small intestine
2. A toxin subunit enters the cell, causing sustained activation of a G protein
3. This G protein activates adenylate cyclase
4. Adenylate cyclase catalyzes the formation of cAMP
5. cAMP activates protein kinases
6. Phosphorylation of proteins enhances the secretion of chloride ions
7. The flow of negatively charged chloride ions out of the cell causes positively charged sodium ions to follow them
8. Water follows the electrolytes into the lümen of the small intestine by osmosis, resulting in severe diarrhea

Calcium Ions and Inositol Trisphosphate (IP3)

- Many of the signaling molecules that function in animals—including neurotransmitters, growth factors, and some hormones—induce responses in their target cells via signal transduction pathways that increase the cytosolic concentration of calcium ions

- Calcium is even more widely used than cAMP as a second messenger

- Increase in the cytosolic concentration of Ca2+
  - muscle cell contraction, secretion of certain substances, cell division …

- Second messenger in both GPCRs and RTKs

Calcium as a second messenger

- Level of Ca^{2+} in the blood and extracellular fluid is often more than 10,000 times higher than that in the cytosol
- Calcium ions are actively transported out of the cell and are actively imported from the cytosol into the endoplasmic reticulum by various protein pumps
- In response to a signal, the cytosolic calcium level usually rise by a mechanism that releases Ca^{2+} from the ER

- inositol trisphosphate (IP3) and diacylglycerol (DAG) are produced by cleavage of a certain kind of phospholipid in the plasma membrane

- IP3 opens a calcium channel in ER membrane

- Ca2+ diffuses to the cytosol

Response

- Cell signaling leads to regulation of transcription or cytoplasmic activities

- Many signaling pathways ultimately regulate protein synthesis, usually by turning specific genes on or off in the nucleus

- A signaling pathway may *regulate the activity* of proteins rather than causing their synthesis by activating gene expression
  - This directly affects proteins that function outside the nucleus.

Regulation of response

- The extent and specificity of the response are regulated
  - Degree of signal amplification
  - Control points
  - Efficiency of response (scaffolding proteins)
  - Termination of the signal

Signal Amplification

- The amplification effect stems from the fact that these proteins persist in the active form long enough to process multiple molecules of substrate before they become inactive again

- As a result binding of a single molecule can lead to release of hundreds of millions of molecules

The Specificity of Cell Signaling and Coordination of the Response

- Epinephrine stimulates the liver cell to break down glycogen, but the main response of the heart cell to epinephrine is contraction, leading to a more rapid heartbeat
  - How do we account for this difference?

- Different kinds of cells turn on different sets of genes, different kinds of cells have different collections of proteins

Different effects of one neurotransmitter

- ACh
  - Skeletal muscle → contraction
  - Heart muscle → inhibition of contraction

Signaling Efficiency: Scaffolding Proteins and Signaling Complexes

- Most relay molecules are proteins, and proteins are too large to diffuse quickly through the viscous cytosol
  - How does a particular protein kinase, for instance, find its substrate?

- Scaffolding proteins, large relay proteins to which several other relay proteins are simultaneously attached

- This enhances the speed and accuracy of signal transfer between cells, because the rate of protein-protein interaction is not limited by diffusion.

Termination of the Signal

- For a cell of a multicellular organism to remain capable of responding to incoming signals, each molecular change in its signaling pathways must last only a short time
  - cholera example

- The binding of signaling molecules to receptors is reversible. As the external concentration of signaling molecules falls, fewer receptors are bound at any given moment. When the number of active receptors falls below that threshold, the cellular response ceases