

Signal Transduction I

Signal transduction is just that. The manner by which cells transmit chemical signals that initiate a plethora of biochemical and cellular events. How much of this is known? Surprisingly little. A number of intracellular messengers have been defined but unlike the metabolisms we've studied thus far there is great variation and much more to be defined.

So why do cells need to communicate?

- Coordination of movement
 - bacterial movement towards a chemical gradient
 - green algae - colonies swimming through the water
- Coordination of metabolism - insulin glucagon effects on metabolism
- Coordination of growth - wound healing, skin, blood and gut cells

Three basic types of intercellular signaling

- I - intracellular signal via gap junctions
 - tight junctions that form a cytoplasmic bridge between cells
 - allows the signaling molecules to be transferred directly between cells
- II - Secreted extracellular messenger
 - one cell "talking" to another
 - ex. insulin glucagon, growth factors
- III - Anchored extracellular messenger
 - signaling occurs between cells in physical contact
 - transforming growth factor

Hormones are chemical signals that reach their target via the blood stream.

1. Every different hormone binds to a specific receptor and in binding a significant alteration in receptor conformation results in a biochemical response inside the cell
2. This can be thought of as an allosteric modification with two distinct conformations; bound and free.
3. The binding of the hormone leads to a transduction of the hormone signal into a biochemical response.
4. Hormone receptors are proteins and are typically classified as a cell surface receptor or an intracellular receptor. Each have different roles and very different means of regulating biochemical / cellular function.

Intracellular Hormone Receptors

The steroid/thyroid hormone receptor superfamily (e.g. glucocorticoid, vitamin D, retinoic acid and thyroid hormone receptors) is a class of proteins that reside in the cytoplasm and bind the lipophilic steroid/thyroid hormones. These hormones are capable of freely penetrating the hydrophobic plasma membrane. Upon binding ligand the hormone-receptor complex translocates to the nucleus and bind to specific DNA sequences termed hormone response elements. The binding of the complex to an these DNA elements results in altered transcription rates of the associated gene.

Cell surface receptors

The cell surface receptors are a general classification of the proteins which specifically bind water soluble hormones. These receptors are very complex and varied. A key

component of this class of receptors is that they possess at least one transmembrane spanning domain. From there all bets are off. The mechanism of the cell surface receptors varies depending on the type of hormone bound and the second messenger system involved.

- Each receptor binds specifically to ONE hormone at the appropriate hormone concentration.
- The association of hormone with its receptor is defined by the equilibria process $K_d = \frac{[R][L]}{[RL]}$ - the dissociation constant. Similar to K_m - measures affinity.
- The effective concentrations are very low 10^{-6} to 10^{-15} M
- Each receptor will have various but distinct second messenger systems associated with it.
- The specificity of action of an organism to a hormone (tissue and cell type) depends on which receptors are expressed in each cell and to which signaling pathway is linked to the receptor.

There are three phases to a water soluble hormone action

1. hormone or first messenger
2. receptor binding and initiation of the second messenger system
3. amplification and cascade of the second messenger system

1) Messengers

First messengers - secreted signaling molecules

- Hormones - secreted from endocrine glands (usually into the blood stream) effects are long distance
- Neurotransmitters - signaling molecules released in special regions of the cell and move across a synaptic cleft in neurons
- Local Mediators (paracrine - Greek for besides) similar effect to hormones but effect is very short. Signaling between neighboring cells

Structure of 1st messengers vary greatly - we already know most of them

1) amino acid derivatives

- tyrosine -> thyroid hormones T3/T4, epinephrine, dopamine
- glutamate -> histamine
- tryptophan -> serotonin

2) Peptides - usually made in pre/pro format, large families

- insulin, glucagon, oxytocin, growth factors

3) Fatty acids and eicosanoids - can act as local mediators

- TXA, LTE, phosphatidic acid, lysophosphatidic acid

4) Steroids - cholesterol derivatives

- progesterone, estrogen, testosterone
- site of action usually in nucleus w/ DNA binding protein

5) NO Nitric Oxide - small short lived gas molecule - responsible for dilation and Viagra

2) 1st messengers elicit cellular response by binding to receptors - signal transduction

three general methods of signaling
I Ion channel system

-> binding of ligand (1st messenger) to receptor opens a specific ion channel. The receptor itself may be the ion channel. Often called ligand gated channel. Ion flux leads to a significant biochemical change. Typically Ca^{+2} or K^{+}/Na^{+}

II Receptors without enzymatic activity (Second messenger systems)
1st messenger binds to receptor and activates production of a new molecule - heterotrimeric G proteins

III Receptors with integral enzymatic activity
1st messenger binding activates an enzyme activity in the receptor itself - leads to new proteins interacting with intracellular portion and a new second messenger molecule.

3) Second messengers Third phase of the signal transduction concept

- A second messenger is a molecule produced in response to a 1st messenger binding to a receptor.
- Leads to an amplification of original signal
- second messenger may directly effect target protein / DNA or mostly leads to a chain of second messengers with a wide variety of effects
- specific control and response – cAMP
- Many different signaling proteins are involved (thousands). The design of the proteins organization comprise the signaling pathways

One of the first signaling systems identified was a visual pigment - retinal rod cell - rhodopsin

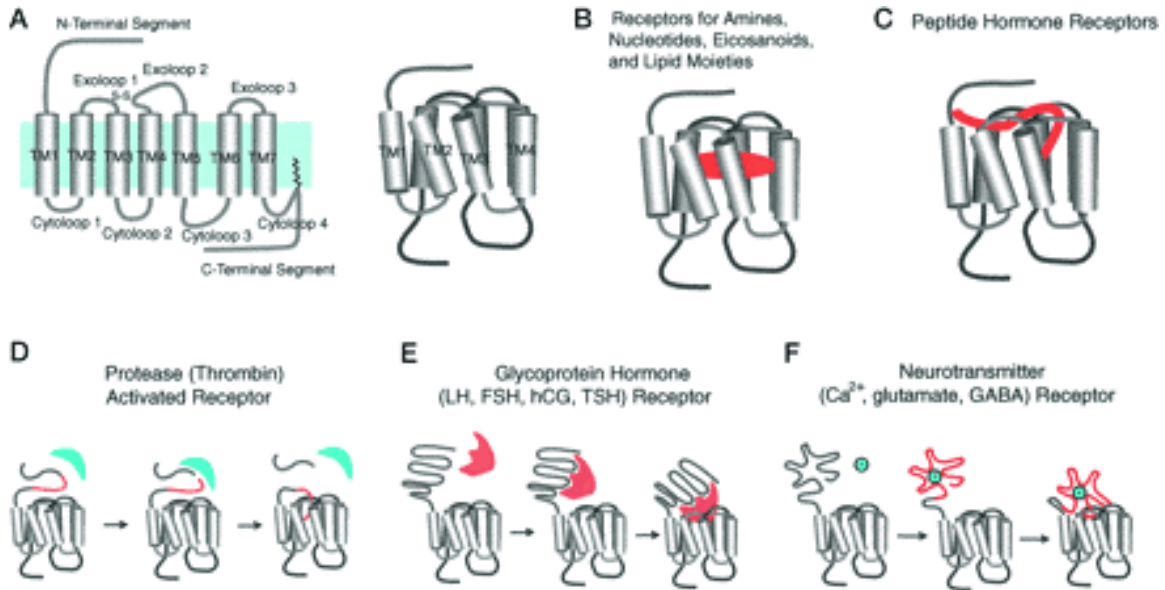
- first messenger is light
- receptor is retinal/rhodopsin – a kind of a G protein
- second messenger is cGMP
- Physiologic effect is the flux of ions -> membrane potential which triggers neurotransmitter release

G-Protein Coupled Receptors - Seven pass receptors / Heterotrimeric G proteins -

- many seven pass receptors with unknown number of ligands / hormones
- all receptors act through G proteins

There are several different classifications of receptors that couple signal transduction to G-proteins. These classes of receptor are termed G-protein coupled receptors, GPCRs. Well over 1000 different GPCRs have been cloned, most being orphan receptors having no as yet identified ligand.

- These proteins possess seven transmembrane spanning domains
- The cytosolic side has the N-terminal and is glycosylated
- Binding of hormone to the receptor initiate a twisting of two or more of the TM helixes.
- Ligand (epinephrine) binding takes place within the hydrophobic core, not the loops. Other agonists (ligands which bind and activate receptors i.e. hormones) act in other ways.



- Long term activation / hormone levels leads to the deactivation of a receptor in two ways
 1. The receptor is phosphorylated by protein kinases at the C – terminal domain. The result is a decrease in the interaction with the G proteins
 2. The receptors are removed (endocytosis) from the cell surface and either the hormone is degraded and the receptor returned or the receptor is degraded never to be seen again!