Cell Communication

Peter Takizawa
Department of Cell Biology

1. Enormously complicated.
2. Focus on the concepts.
3. Don’t try to remember name of every protein.
4. Have taken out names in most figures, where names are listed, probably important.
• General principles of signaling
• Why is signaling so complicated?
• Signaling through steroids and ion channels
• Cellular signal processing
Cells communicate to elicit responses and coordinate activities.

GPSCY, Saturday night?

Language

Nah, gotta study the TCA cycle.

Response

Detection and interpretation

Cells communicate to change in behavior in one cell and coordinate activities. The language of cells consists of small molecules. Receptors in cells detect small molecules and connections between receptors and cellular machinery interpret the signals. Cells respond to small molecules by activating certain biochemical pathways.
The molecular language of cells consist of a variety of small molecules.

A large number of different molecules function as signaling molecules, and they differ in size and chemical composition. Some are hydrophilic and can’t cross the cell membrane. For example, some peptides and proteins function as signaling molecules and neither of these can diffuse across the cell membrane. Other signaling molecules are hydrophobic and can readily diffuse across the cell membrane. These include gases, oxygen and carbon dioxide, and steroids.
The same signaling molecule can evoke different responses.

Like our language where the same word can have many different meanings, the same small molecule can have different effects on different cells. For example, acetylcholine is a neurotransmitter that stimulates contraction in skeletal muscle, but in cardiac muscle cells acetylcholine decreases the rate of contraction. The difference between skeletal and cardiac muscle cells is in how they are wired biochemically to respond to acetylcholine.
One molecule can elicit multiple cellular changes to produce an integrated response.

- **Muscle:** dilate blood vessels
- **Heart:** increase contraction
- **Skin:** constrict blood vessels
- **Liver:** activate glycolysis

Epinephrine

One signaling molecule can elicit different responses depending on tissue or organ to produce an integrated response. For example, epinephrine affects cells in a variety of organs and tissues to produce a flight or fight response in an organism. Cells respond differently to epinephrine depending on which organ or tissue they reside. The biochemical wiring in these cells differs to produce responses to epinephrine.
Cells generate fast and transient or slow and long-term responses to signaling molecules. Cell responses to signaling events can take different lengths of times. A fast response is achieved by altering the activities of existing proteins that lead to changes in cell shape or metabolism. The response is fast because the signaling event acts directly on machinery that controls shape or metabolism. Fast responses are usually reversible as once the signaling molecule is removed the activities of the cell’s proteins returns to normal.

Cells also respond to signaling molecules by altering gene expression to produce more or less of certain proteins. This is slow response because it requires time to build up or remove protein to cause a change in cell behavior. The slow response often generates long-term changes in cells such as differentiation into a specific type of cell.

Some signaling molecules elicit both types of pathways in cells.
Local versus long distance signaling

Communication between cells can be classified based on the distance over which the communication takes place.
Paracrine signaling involves communication between neighboring cells.

In paracrine signaling, the signal released by one cell affects cells only in the surrounding area. Importantly, the signaling molecule does not enter blood stream. The connective tissue surrounding the cells restricts the diffusion of the signaling molecule. A special type of paracrine signaling is autocrine in which the cell that produces the signaling molecule also responds to that signaling molecule. Paracrine signaling is important during development as it allows organisms to produce cells that will develop different functions. A signaling molecule (morphogen) released from one point will diffuse away from that point creating a gradient of morphogen concentration. Cells will respond differently depending on the concentration of the morphogen.
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Endocrine signaling involves communication between distal cells.

Endocrine signaling involves cells located at different parts of an organism. Signaling molecules secreted by one cell enter blood stream and travel through blood stream to other parts of body. Cells throughout the body have an opportunity to detect and respond to the signaling molecule. Signaling molecules in endocrine signaling are called hormones.
A third type of signaling involves direct interaction between cells. Proteins in the cell membranes of different cells can bind each other and the interaction between these proteins can alter cell behavior. For example, a T-cell uses its receptor to recognize antigen on the surface of antigen presenting cell. Another form of this type of signaling is the communication between neurons and their target cells. Neurons make contact with their target cell and but don’t communicate via these contacts. Instead, they release neurotransmitter at these contact points to affect their target cell.
Endocrine and cell-contact signaling require ligand-receptor binding of different strengths.

The different types of signaling differ in the strength of interaction between the signaling molecule and the receptor for that molecule. In endocrine signaling, the hormones are present at low concentration because there are distributed throughout the body. In addition, cells are often bathed in a variety of different hormones and other signaling molecules. Thus, the receptors on cells have to distinguish between several different molecules at low concentration. This requires a high affinity interaction between the receptor and its hormone.

In paracrine signaling or signaling via neurons, the signaling molecule is usually present at higher concentration and is sometimes the only signaling molecule present (neurotransmission). Consequently, the strength of the interaction between the receptor and its signaling molecule is usually lower than in endocrine signaling.

The importance of the strength of interaction between receptor and its signaling molecule comes when the cell wants to turn off its response to the signaling molecule. A low affinity interaction can more easily be broken to terminate a response whereas a high affinity interaction is more difficult to disrupt and cell’s need a different approach to terminate responses to hormones.
Why is signaling so complicated?
Combinations of signaling molecules generate different responses.

A cell’s response usually depends upon presence of different combination of signaling molecules. Most of the cells in our bodies are surrounded by many different types of signaling molecules and cell’s often detect several of these signaling molecules. Altering cell behavior often requires changing the amounts of more than one type of signaling molecule.
Signaling pathways involve multiple steps and proteins.

A cell’s response to a signaling molecules often involves a biochemical pathway with multiple components. Each component can modulate the strength or breadth of the cell’s responses to a particular signaling molecule.
Crosstalk between signaling proteins generates nuanced responses.

Cells employ many different biochemical pathways to respond to different signaling molecules. Often, these pathways will interact with each other by sharing components or through a component in one pathway affecting the activity of a component in another pathway.
Feedback loops regulate the strength and frequency of signals.

Signaling pathways can also regulate their own strength through positive and negative feedback. Positive feedback occurs when a downstream component in a pathway increases the strength of the pathway by increasing the activity of an upstream component. For example, a signaling molecule can activate through a biochemical pathway a specific enzyme. In positive feedback, that enzyme would alter the pathway so that the pathway increases the rate of producing the active enzyme. In pathways that use positive feedback, the response to a signaling molecule can become independent of the presence of the signaling molecule because once the pathway is activated, it becomes self-sustaining through positive feedback.

In negative feedback, the downstream component decreases the activity of an upstream component to decrease the strength of the pathway. For example, an active enzyme could alter the pathway to slow the rate at which the pathway produces active enzyme. Negative feedback is more often used in signaling pathways because it can produce a variety of responses depending on the parameters of the pathway.
A signaling molecule directly changes cell behavior when the receptor to which it binds initiated a change in the cell. Here, there a few intermediary events between receptor binding its signaling molecule and a cell’s response. In contrast, cellular signal processing requires many steps between receptor binding a signaling molecule and the cell’s response.
Steroids and small hydrophobic molecules diffuse across plasma membrane.

Steroids are hydrophobic molecules that can diffuse across the cell membrane. The receptors for steroids are transcription factors. Some of these receptors are kept in the cytosol by a chaperone that hides the nuclear localization sequence (NLS) in the receptor. When the receptor binds steroid, it releases the chaperone, exposing the NLS. Once imported into the nucleus, the receptor can activate transcription.
Nuclear receptors share common domain structure. 

Steroid receptors share common motifs; DNA-binding domain, steroid-binding domain and a variable domain that functions as activator of transcription.
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Binding ligand causes conformational change in nuclear receptors.

In absence of steroid, receptor in conformation that allows inhibitory protein (chaperone) to bind and hide the NLS. Binding to steroid causes a conformational change in the receptor that releases inhibitory protein, exposing the NLS.
Steroids alter cell behavior through two rounds of transcription. As mentioned, steroids bind their receptors which are transcription factors. These transcription factors, when bound to steroid, increase the expression of a set of genes called primary response genes. The primary response genes encode proteins that function as transcription factors. Some of these transcription factors increase the expression of a set of genes called secondary response genes. These genes encode proteins that alter cell behavior. Some of the transcription factors encoded by the primary response genes inhibit the expression of the primary response genes. This is an example of negative feedback. Thus, steroids not only lead to the activation of genes that change cell behavior but also genes that turn off the cells response to the steroid.
Signaling via ion channels
Ligand-gated ion channels open upon binding ligand.

Some receptors are ion channels. In the absence of ligand (signaling molecule), the channel is closed. When bound to the ligand, the channel opens allowing ion to diffuse across the cell membrane. The ion channels are usually specific for one ion (often sodium) and when open cause depolarization of the cell membrane.
Acetylcholine binds and opens sodium channel leading to muscle contraction.

An example of a ligand-gated ion channel is the acetylcholine receptor in skeletal muscle cells. When the acetylcholine receptor binds acetylcholine, it opens allowing Na$^+$ to enter the cell. This causes the membrane to depolarize and opens voltage-gated sodium channels. The rapid depolarization of the cell membrane generates an action potential that ultimately triggers the opening of calcium channels inside the cell. The rise in cytosolic calcium induces muscle contraction. The benefit of ligand-gated ion channels is that the cell’s response to acetylcholine is fast (milliseconds).
Signal transduction: cellular signal processing
Receptors bind specific signaling molecules and activate cellular events.

Signaling molecules act via protein receptors in plasma membrane. Receptors contain binding site for ligand and another domain that interacts with downstream machinery. Ligand binding induces conformational change in the receptor that activates or inactivates downstream machinery.
Several proteins relay binding state of receptor to cell machinery.

Several components relay the binding state of the receptor to the cell machinery (metabolism, gene expression, morphology). These components are often used in different cells but each type of cell will connect the components to different parts of its machinery. As a result, different cells will produce different responses to the same signaling molecule.
Signaling cascades amplify concentration of signaling molecules.

One benefit of having many components between signaling molecule and cell machinery is it allows for amplification of signal. Many signaling molecules are present at low concentration (e.g. $10^{-10}$ M). Cells contain only ~1000 receptors for a given ligand but they need to activate hundreds of thousands or millions of proteins to alter cell behavior. To amplify the signal signaling pathways activate enzymes each of which is capable of producing many copies of an active molecule or protein. For example, adenylyl cyclase is an enzyme that produces cAMP and can increase the cytosolic concentration of cAMP to $10^{-6}$ M. Also, each activated kinase can phosphorylate and activate many copies of enzymes leading to further amplification.
Cells attenuate signaling reactions to limit amount and time of cellular response.

In addition to responding to ligands, cells also regulate the strength and duration of their response to a ligand. If a cell’s response to a ligand is too strong or remains active for too long, the cell can become damaged structurally or its other biochemical pathways can be negatively affected. In some instances, this can lead to cell death. Therefore, signaling pathways will usually trigger reactions that reduce the strength of a cell’s response to a ligand (negative feedback). These reactions will often reduce the number of receptors in the plasma membrane or prevent the receptor from activating a cellular response.
GTP-binding proteins function as switches to indicate receptor activation.

There are several themes in signal processing that are common to most pathways. One is the idea of biochemical switches that relay on and off states depending on whether a receptor is bound to ligand. GTP-binding proteins are example of biochemical switch. The protein is inactive when bound to GDP and active when bound to GTP. To convert between these states, GTP-binding proteins rely on two proteins. Guanine nucleotide exchange factors (GEFs) catalyze the release of GDP allowing the protein to bind GTP. GEFs turn on GTP-binding proteins. In contrast, GTPase activating proteins (GAPs) increases the rate of GTP hydrolysis in GTP-binding proteins converting them to the GDP-bound or off state.
Kinases modulate activity of proteins during signaling reactions.

Kinases are another common component of signaling pathways. Kinases add phosphate groups to proteins. The presence of phosphate will alter the activity, stability and/or location of the protein. Phosphatases remove phosphate groups.
Take home points...

• Cells respond with rapid and transient change and/or slow and long-term change

• Paracrine signaling -> ligand remain local; Endocrine -> ligand enters blood stream

• Steroids diffuse across cell membrane to change gene expression

• Receptors bind external ligand and trigger cellular response

• GTP-binding proteins and kinases act as switches in signaling pathways
Types of cellular signaling pathways

We will explore 3 signaling pathways that are very common: those that use G-protein coupled receptors, those that use receptor tyrosine kinases and those that use MAP kinases.
Cellular signal processing through trimeric G-proteins

G-protein coupled receptors use heterotrimeric GTP-binding proteins which contain 3 subunits. The alpha subunit binds and hydrolyzes GTP. The beta and gamma subunits keep the alpha subunit in an inactive state. Heterotrimeric GTP–binding proteins usually associate with membranes via hydrophobic tails attached to C-termini of the alpha and gamma subunits. When the alpha subunit binds GTP, it dissociates from beta-gamma subunits. The freed alpha is the main effector of downstream events, but the beta-gamma may also activate some signaling events. Two of the most common downstream targets of the alpha subunit are adenylyl cyclase and phospholipases, but there are many more. There are several families of trimer G–proteins. The founding member is Gs whose alpha subunit activates adenylyl cyclase. The Gi type inhibits adenylyl cyclase.
G-protein coupled receptors transmit signals through heterotrimeric GTP-binding proteins.

Signaling through trimeric G proteins usually occurs via 7 transmembrane receptors which comprise a large family of receptor proteins including those that mediate olfaction. The receptors span the cell membrane 7 times. Upon binding ligand, the receptor undergoes a conformational change that activates its GEF domain. The GEF domain catalyzes nucleotide exchange on an associated G alpha subunit, leading to an alpha subunit bound to GTP. In GTP-binding state alpha factor and beta-gamma dissociate and activate downstream proteins.
Adenylyl cyclase is a common downstream effector of $G_\alpha$ subunits.

One of the major downstream effectors of G alphas is adenylyl cyclase. Adenylyl cyclase is plasma–membrane bound protein that catalyzes the conversion of ATP in cyclic AMP. It increases the cytoplasmic concentration of cAMP 20 fold in a few seconds. cAMP is secondary message that will trigger further downstream signaling events. G alpha i inhibits adenylyl cyclase to turn down production of cAMP.
Cholera toxin and pertussis toxin hyper-activate adenylyl cyclase through modification of $G_\alpha$

Two toxins that affect human function by modifying the activity of the alpha subunit of heterotrimeric G-proteins. Cholera toxin affects intestinal epithelial cells by adding ADP-ribose to $G_\text{as}$ which prevents $G_\text{as}$ from hydrolyzing GTP. Consequently, $G_\text{as}$ is always active and continuously activates adenylyl cyclase. This results in constant high levels of cAMP in cells and prolonged activation of protein kinase A. Protein kinase A opens chloride channels in the plasma membrane, leading to an efflux of chloride ions and secretion of sodium and water into the lumen of the intestine and prolonged diarrhea.

Pertussis toxin affects cells of the respiratory tract. In contrast to cholera toxin, pertussis toxin adds ADP-Ribose to $G_\text{ai}$ subunit of heterotrimeric G-proteins. This modification prevents $G_\text{ai}$ from interacting with receptors and $G_\text{ai}$ remains in a GDP-bound state. Consequently, $G_\text{ai}$ is not active and cannot reduce the activity of adenylyl cyclase. cAMP builds up in cells and triggers a strong cellular response. How this response leads to whooping cough is unclear.
Rapid and localized increase in cAMP levels during signaling events.

\[ [\text{cAMP}] = 5 \times 10^{-8} \text{ M} \quad \text{and} \quad [\text{cAMP}] = 1 \times 10^{-6} \text{ M} \]

These images show the experimental evidence of cAMP increase during signaling event. The cell expresses a fluorescent protein that fluoresces when it binds cAMP. Serotonin was added to activate a G-protein coupled receptor. In few seconds protein fluorescence increases dramatically in localized fashion.
cAMP activates protein kinase A that has several downstream targets.

Most of the effects of increased cAMP are mediated by protein kinase A. Protein kinase A is tetramer of two catalytic subunits and two regulatory subunits. The regulatory subunits inhibit activity of catalytic. cAMP binds regulatory subunits and causes them to dissociate from the catalytic subunits. Once freed, the catalytic subunits are active and can phosphorylate target proteins. Protein kinase A has many downstream targets. For example in some cells, it actsives glycogen phosphorylase that breaks down glycogen while inactivating the enzyme glycogen synthase. In other cells protein kinase A phosphorylates the transcription factor CREB that binds to DNA and activates transcription of specific genes.
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Phosphodiesterase reduces cAMP levels to limit signaling reactions.

Cells must turn off signals to prevent over activation. Cells express a consistent level of phosphodiesterase that converts cAMP into 5′-AMP and keeps cytosolic concentrations of cAMP at a low level in resting cells. Activation of receptor increases activity of adenyl cyclase and the production of cAMP overwhelms phosphodiesterase to increase cAMP. When adenyl cyclase is turned off, phosphodiesterase returns cAMP levels to normal.
Heterotrimeric G-protein signaling via phospholipids

Certain phospholipids on inner leaflet of the cell membrane are critical for signaling reactions. Breakdown of these phospholipids generates second messages similar to cAMP. In addition, some proteins recognize specific phospholipids and the presence of these phospholipids in the cell membrane recruits proteins to cell membrane to regulate their activity.
Plasma membrane contains a variety of phosphatidylinositol lipids.

Phosphatidylinositol lipids are phospholipids and one of the most important in signaling. Phosphatidylinositols contain an inositol head group that can contain phosphates at different positions. The different combinations of phosphates are recognized by different proteins and lead to unique cell responses.
Another downstream effector of trimeric G proteins is phospholipase C. Phospholipase C is an enzyme that cleaves the head groups from phospholipids. Phospholipase C cleaves the head group phosphatidylinositol 4,5-phosphate to produce diacylglycerol and inositol-1,4,5 triphosphate (IP3). IP3 binds Ca-channels in ER and opens them releasing Ca into the cytoplasm. DAG stays in the membrane and activates protein kinase c.
IP$_3$ opens calcium channels in ER and DAG activates protein kinase C.

IP$_3$ diffuses to ER where it binds IP$_3$ receptors. (IP$_3$ secondary message). Binding of IP$_3$ opens IP$_3$ channels releasing Ca into cytoplasm. Protein kinase C binds Ca and traffics to plasma membrane where it binds DAG, leading to its activation. Protein kinase C has many cellular targets, and there are different classes of protein kinase C with different targets.
Receptor Tyrosine Kinases
Receptor tyrosine kinases contain ligand-binding domain and kinase domain.

Receptor tyrosine kinase contain a cytoplasmic kinase domain in addition to an extracellular domain that binds ligand.
Binding ligand activates kinase domain, causing cross-phosphorylation.

Receptor tyrosine kinases are inactive in the absence of signaling molecule because they are monomers that don’t interact with targets efficiently. When bound to ligand the receptors dimerize. Dimerization allows the kinase domain in one receptor to phosphorylate its partner receptor and vice versa.
Phosphorylated cytoplasmic domains recruit downstream signaling proteins.

The phosphorylated C-tails of receptor tyrosine kinases are recognized by different downstream signaling proteins. These proteins have domains that recognize portion of the receptor and a phosphate. The phosphorylated receptor brings together proteins in common signaling pathway. As a result enzymes are closer to their substrates. In the absence of phosphorylated receptor, enzymes and substrates are at low concentration in cytosol and the reactions are very inefficient. Clustering them on the receptor increases local concentration accelerating the reaction.
Receptors bring signaling enzymes closer to substrates at plasma membrane.

An example of a receptor tyrosine kinase is the PDGF receptor. Binding of growth factor leads to dimerization and cross phosphorylation. Different signaling proteins bind the phosphorylated domains on receptor. Many of these proteins have substrates that are localized to plasma membrane.
Phosphatidylinositols recruit signaling proteins to plasma membrane.

Receptor tyrosine kinases can also change the phospholipid composition of the cell membrane to recruit specific proteins. For example a phosphorylated receptor binds PI3 kinase. Binding of PI3 kinase leads to its activation and brings it closer to its substrates phosphoinositol 4,5-phosphate in the cell membrane PI3 kinase phosphorylates PI45 to convert it to PI345. PI345 is recognized by class of proteins with PH domains. Two kinases with PH domains are recruited to the cell membrane by PI345. One kinase phosphorylated the other leading to the activation of the second kinase. The second kinase can now activate its downstream targets.
Phosphatidylinositol 3-kinase (PI3 kinase) is a lipid kinase that plays a crucial role in cellular signaling. It is activated by the binding of a phosphorylated tyrosine kinase receptor to PI4P, which is present in the plasma membrane. Upon activation, PI3 kinase converts PI4P to PI(3,4,5)P3 (PIP3), a molecule that is recognized by the Pleckstrin Homology (PH) domain of various downstream effectors. This conversion brings PI3 kinase closer to its substrates and activates its downstream targets.

For example, a phosphorylated receptor tyrosine kinase binds PI3 kinase. Binding of PI3 kinase leads to its activation and brings it closer to its substrates phosphoinositol 4,5-phosphate (PI(4,5)P2) in the cell membrane. PI3 kinase phosphorylates PI(4,5)P2 to convert it to PI(3,4,5)P3. PI(3,4,5)P3 is recognized by a class of proteins with PH domains. Two kinases with PH domains are recruited to the cell membrane by PI(3,4,5)P3. One kinase phosphorylates the other, leading to the activation of the second kinase. The second kinase can now activate its downstream targets.
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MAP kinase pathways

MAP kinase pathways are activated by a variety of receptors. Many of these receptors are activated by growth factors or mitogens which gave rise to the name mitogen-activated pathway (MAP).
MAP kinase pathway is a cascade of three kinases.

Map kinase pathways contain a set of three kinases. At the top is MAPkkk that phosphorylates and activates MAPkk. MAPkk phosphorylates and activates MAPk which then phosphorylates variety of target proteins and regulates their activities.
MAP kinase pathways amplify signal.

The chain of three kinases allows cell to amplify a signal as the MAPkkk can phosphorylate several copies of MAPkk each of which can phosphorylate several MAPk.
Receptor tyrosine kinases recruit proteins that activate Ras which activates MAPKKK.

Some MAPKKK can be activated by a small GTP binding protein called Ras. Ras is activate when bound to GTP and is often activated by receptor tyrosine kinases in the following steps:
1. Activated receptor cross-phosphorylates.
2. Phosphorylated receptor recognized by adapter protein.
3. The adaptor protein recruits GEF for Ras.
4. Ras localized to plasma membrane via hydrophobic tail.
5. GEF catalyzes exchange on Ras leading to its activation and downstream effects.
Cells contain several different MAP kinase pathways. How is the fidelity of these pathways maintained so that kinases in one pathway only phosphorylate kinases in the same pathway?
Scaffolding proteins separate components of different MAP kinase pathways.

Scaffolding proteins tether MAP kinase proteins in common pathway to ensure that those kinases in phosphorylate only each other and not MAP kinases in other pathways.
Summary of pathways and crosstalk.
Internal wiring of cells triggers different responses to the same ligand.

**Skeletal muscle**

acethycholine = contraction

**Cardiac muscle**

acethycholine = reduced contraction

Skeletal and cardiac muscle respond differently to acetycholine: skeletal muscle increase contraction whereas cardiac muscle reduces contraction. In skeletal muscle, acetylcholine directly opens Na\(^+\) channels leading to membrane depolarization and cell contraction. In cardiac muscle, acetylcholine acts through G-protein coupled receptor to hyper polarize membranes, making it more difficult to trigger contraction in these cells. Thus, the internal wiring of skeletal and cardiac muscle determines each cell’s response to acetylcholine.
Turning off the signal

Prolonged signaling reactions are damaging to cells and can lead to apoptosis.
Multivesicular bodies process receptors for degradation in lysosomes.

For receptors that bind tightly to their ligand, cells often have to degrade the receptor to turn off the signaling reactions. Receptors are endocytosed into clathrin-coated pits. After clathrin is removed, the membrane surrounding the vesicle undergoes invagination to form internal vesicles that contain receptors. The multivesicular body will fuse with the lysosome.
Receptors limit their ability to activate downstream components.

Negative feedback reduces receptor activity. An activated receptor turns on a kinase that phosphorylates the receptor. The phosphate groups recruit proteins that prevent receptor from activating G proteins or other enzymes.
Low affinity ligands can be digested or endocytosed to limit signaling reactions.

For receptors that bind ligand with low affinity, cells can often rely on degrading or removing the ligand. For example, in skeletal muscle, extracellular acetylcholine is either digested (by acetylcholineesterase) or endocytosed by cells. Because of the low affinity between acetylcholine and its receptor, the acetylcholine will often disassociate from the receptor and be destroyed.
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Cells reduce cytosolic calcium by pumping calcium out and sequestration in organelles.

In addition to turning off receptors, cells must also eliminate secondary messengers such as cAMP and calcium. Cells have a variety of means to reduce cytosolic calcium after a signaling event. Calcium pumps and exchangers in the cell membrane push calcium out of the cell, and some organelles, ER and mitochondria, contain pumps that take up calcium from the cytosol.
Signaling reactions produce rapid increase in cytosolic calcium that slowly decreases.

The image shows that change in cytosolic calcium during and after a signaling event. Upon stimulation of a cell, there is a rapid increase in cytosolic calcium that decays over time.
Cells sense different concentrations of signaling molecules
Concentration of signaling molecule determines frequency of calcium spikes.

In this graph, each spike represents a cell’s response, rise and fall in cytosolic calcium, to the presence of a signaling molecule (vasopressin). The spikes repeat as long as vasopressin is present. Note that the time between spikes decreases as the concentration of vasopressin increases. Proteins in the cells will be more or less active depending on the frequency of the spikes.
CaM-Kinase II is activated by high frequency calcium spikes.

For example, CAM–kinase is activated in presence of calcium. At low frequency spikes, CAM–kinase activated but as calcium levels fall, it becomes inactivated and return to baseline. At high frequency spikes, CAM–kinase is activated but its activity does not return to baseline after calcium levels decrease. Instead, some activity remains so that in the next rise of calcium even more CAM–kinase is activated leading to a tremendous increase in CAM–kinase activity over time.
CaM-Kinase II activated by calcium and autophosphorylation.

CaM kinase activated in two step process. Ca bind calmodulin that binds and partially activates Cam kinase. Cam kinase autophosphorylates itself to become fully active. If Ca levels fall, calmodulin dissociates, but CAM kinase retains some activity due to autophosphorylation. If a phosphatase removes phosphate, then Cam kinase is returned to its completely, inactive base state. In high frequency calcium spikes, calmodulin rebinds calcium and CAM kinase before the phosphatase has a chance to remove the phosphate group. This returns CAM kinase to its fully active state. In low frequency spikes, the phosphatase removes the phosphate before calmodulin rebinds calcium, returning CAM kinase to is base state.
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Take home points...

• Signal transduction starts with receptors binding ligand at the cell membrane.

• Heterotrimeric G-proteins activate adenylate cyclase and phospholipase C to trigger increase in cytosolic calcium

• Receptor tyrosine kinases recruit proteins to cell membrane and often trigger MAP-kinase pathways

• Cells utilize several mechanisms to turn off signals

• Cells can detect between difference in ligand concentrations