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Molecular Biology of the Cell

Fifth Edition

Chapter 15

Mechanisms of Cell Communication

The Relationship Between Signal and Response Varies in Different Signaling Pathways

-The function of an intracellular signaling system is to **detect** and **measure** a specific stimulus in one location of a cell and then generate an appropriately timed and measured response at another location.

-The system accomplishes this task by sending information in the form of molecular "signals" from the sensor to the target, often through a series of intermediaries that do not simply pass the signal along but process it in various ways.

-All signaling systems do not work in precisely the _: each has evolved specialized behaviors that produce a response that is appropriate for the cell function that system controls.

In the following paragraphs, we list some of these behaviors and describe how they vary in different systems:

1. **Response timing** varies dramatically in different signaling systems, according to the **speed required for the response**. In some cases, such as synaptic signaling, the response can occur within milliseconds. In other cases, as in the control of cell fate by morphogens during development, a full response can require hours or days.

The Relationship Between Signal and Response Varies in Different Signaling Pathways

2. **Sensitivity to extracellular signals can vary greatly**.

Hormones tend to act at very low concentrations on their distant target cells, which are therefore **highly sensitive to low concentrations of signal**.

Neurotransmitters, on the other hand, operate at **much higher concentrations** at a synapse, reducing the need for high sensitivity in postsynaptic receptors.

Sensitivity is often controlled by changes in the number or affinity of the receptors on the target cell.

✓ A particularly important mechanism for increasing the sensitivity of a signaling system is **signal amplification**, whereby a small number of activated cell-surface receptors evoke a large intracellular response either by producing large amounts of a second messenger or by activating many copies of a downstream signaling protein.

3. **Dynamic range of a signaling system is related to its sensitivity.** Some systems, like those involved in simple developmental decisions, are responsive over a narrow range of extracellular signal concentrations. Other systems, like those controlling vision or the metabolic response to some hormones, are highly responsive over a much broader range of signal strengths.

4. **Persistence of a response can vary greatly.** A transient response of less than a second is appropriate in some synaptic responses, for example, while a prolonged or even permanent response is required in cell fate decisions during development.

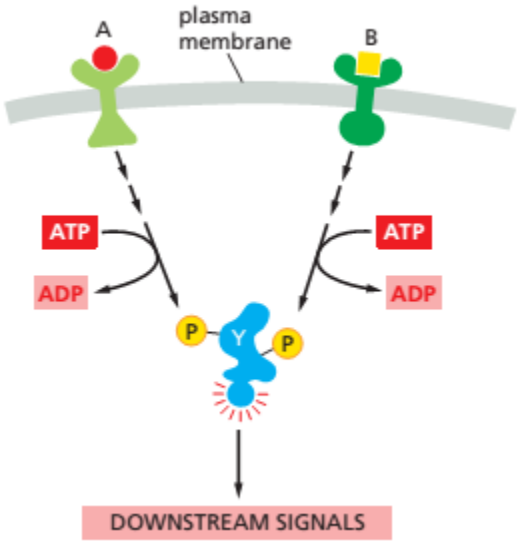
✓ Numerous mechanisms, including **positive feedback**, can be used to alter the duration and reversibility of a response.

The Relationship Between Signal and Response Varies in Different Signaling Pathways

5. **Signal processing can convert a simple signal into a complex response.** In many systems, for example, a **gradual increase** in an extracellular signal is converted into an **abrupt, switchlike response**. In other cases, a **simple input signal** is converted into an **oscillatory response**, produced by a repeating series of transient intracellular signals.

✓ **Feedback** usually lies at the heart of biochemical switches and oscillators.

6. **Integration allows a response to be governed by multiple inputs.** For example, **specific combinations of extracellular signals** are generally required to stimulate complex cell behaviors such as cell survival and proliferation. The cell therefore has to integrate information coming from multiple signals, which often depends on **intracellular coincidence detectors**; these proteins are equivalent to AND gates in the microprocessor of a computer, in that they are only activated if they receive multiple converging signals.



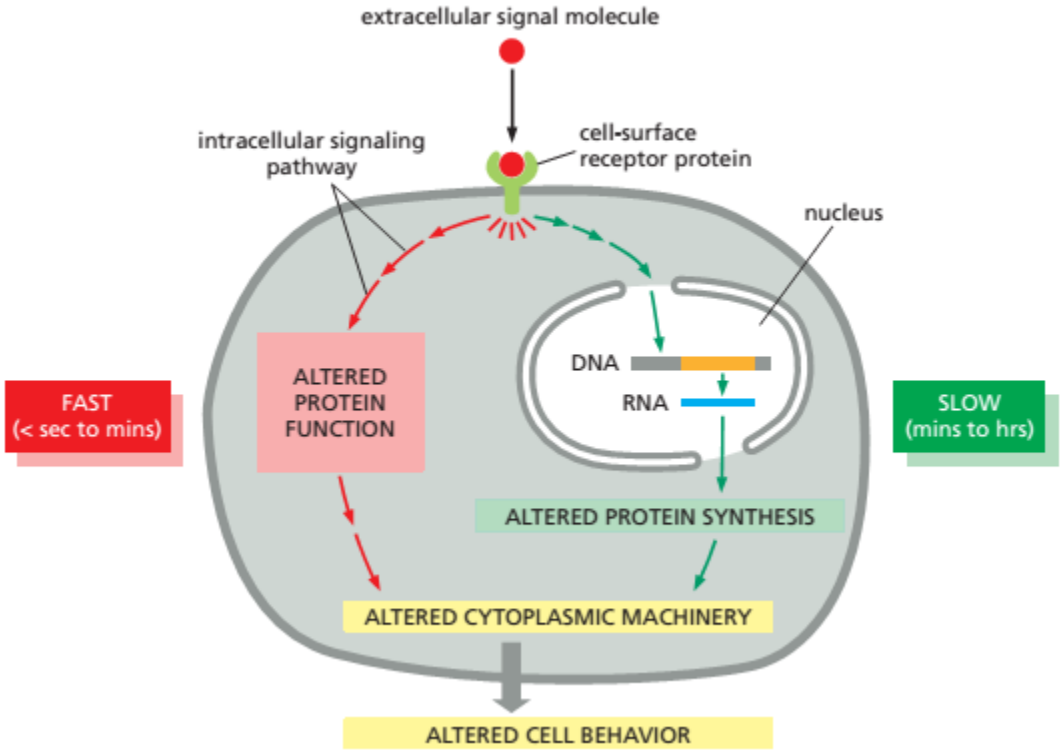
7. **Coordination of multiple responses in one cell can be achieved by a single extracellular signal.** Some extracellular signal molecules, for example, stimulate a cell to both grow and divide. This **coordination generally depends on mechanisms for distributing a signal to multiple effectors, by creating branches in the signaling pathway**.

✓ In some cases, the branching of signaling pathways can allow one signal to **modulate** the strength of a response to other signals.

The Speed of a Response Depends on the Turnover of Signaling Molecules

The speed of any signaling response depends on the nature of the intracellular signaling molecules that carry out the target cell's response.

- When the response requires only changes in proteins already present in the cell, it can occur very rapidly: an allosteric change in a neurotransmitter-gated ion channel, for example, can alter the plasma membrane electrical potential in milliseconds, and responses that depend solely on protein phosphorylation can occur within seconds.
- When the response involves changes in gene expression and the synthesis of new proteins, it usually requires many minutes or hours, regardless of the mode of signal delivery.



The Speed of a Response Depends on the Turnover of Signaling Molecules

It is important to consider what happens when the signal is withdrawn:

- ✓ During development, transient extracellular signals often produce **lasting effects**: they can trigger a change in the cell's development that persists indefinitely through cell memory mechanisms.

- ✓ In most cases in adult tissues, however, the response fades when a signal ceases.

Often the effect is transient because the signal exerts its effects by altering the concentrations of intracellular molecules that are short-lived (unstable), undergoing continual turnover. Thus, once the extracellular signal is gone, the degradation of the old molecules quickly wipes out all traces of the signal's action.

It follows that the speed with which a cell responds to signal removal depends on the rate of destruction, or turnover, of the intracellular molecules that the signal affects.

This turnover rate can determine the **promptness** of the response when an extracellular signal arrives.

The Speed of a Response Depends on the Turnover of Signaling Molecules

Consider, for example, two intracellular signaling molecules, X and Y, both of which are normally maintained at a steady-state concentration of 1000 molecules per cell.

- The cell synthesizes and degrades molecule **Y** at a rate of **100 molecules per second**, with each molecule having an average lifetime of 10 seconds.
- Molecule **X** has a turnover rate that is 10 times slower than that of Y: it is both synthesized and degraded at a rate of **10 molecules per second**, so that each molecule has an average lifetime in the cell of 100 seconds.

If a signal acting on the cell causes a tenfold increase in the synthesis rates of both X and Y with no change in the molecular lifetimes, at the end of 1 second the concentration of Y will have increased by nearly 900 molecules per cell (10 × 100 – 100), while the concentration of X will have increased by only 90 molecules per cell.

In fact, after a molecule's synthesis rate has been either increased or decreased abruptly, the time required for the molecule to shift halfway from its old to its new equilibrium concentration is equal to its half-life—that is, equal to the time that would be required for its concentration to fall by half if all synthesis were stopped.

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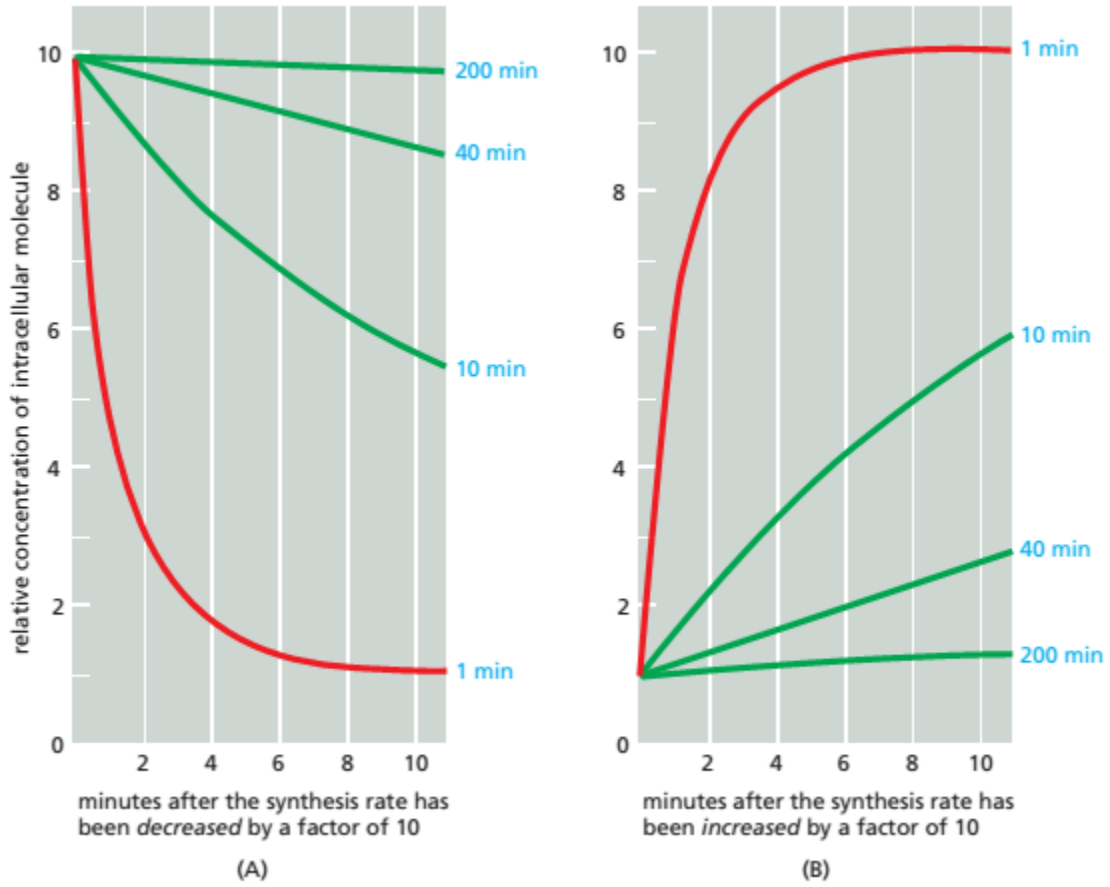


Figure 15–14 The importance of rapid turnover. The graphs show the predicted relative rates of change in the intracellular concentrations of molecules with differing turnover times when their synthesis rates are either (A) decreased or (B) increased suddenly by a factor of 10. In both cases, the concentrations of those molecules that are normally degraded rapidly in the cell *(red lines)* change quickly, whereas the concentrations of those that are normally degraded slowly *(green lines)* change proportionally more slowly. The numbers (in *blue)* on the right are the half-lives assumed for each of the different molecules.

The Speed of a Response Depends on the Turnover of Signaling Molecules

-The same principles apply to proteins and small molecules, whether the molecules are in the extracellular space or inside cells.

-Many intracellular proteins have short half-lives, some surviving for less than 10 minutes.
-In most cases, these are **key regulatory proteins** whose concentrations are rapidly controlled in the cell by changes in their rates of synthesis.

-Many cell responses to extracellular signals depend on the conversion of intracellular signaling proteins from an inactive to an active form, rather than on their synthesis or degradation.

-Phosphorylation or the **binding of GTP**, for example, commonly activates signaling proteins. Even in these cases, however, the activation must be rapidly and continuously reversed (by dephosphorylation or GTP hydrolysis to GDP, respectively, in these examples) to make rapid signaling possible.

❖ **These inactivation processes play a crucial part in determining the magnitude, rapidity, and duration of the response.**

Cells Can Respond Abruptly to a Gradually Increasing Signal

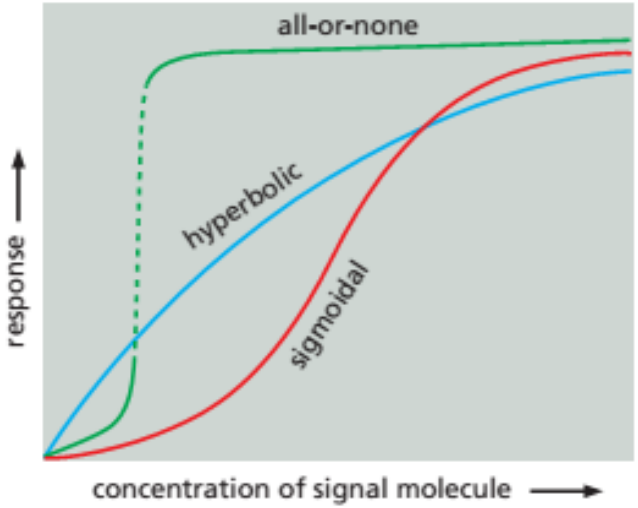
Some signaling systems are capable of generating a **smoothly graded response over a wide range of extracellular signal concentrations** (Figure 15–15, blue line); such systems are useful, for example, in the fine tuning of metabolic processes by some hormones.

Other signaling systems generate significant responses only when the signal concentration rises beyond some threshold value. These abrupt responses are of two types.

One is a **sigmoidal response**, in which low concentrations of stimulus do not have much effect, but then the response rises steeply and continuously at intermediate stimulus levels (Figure 15–15, red line).
Such systems provide a filter to reduce inappropriate responses to low-level background signals but respond with high sensitivity when the stimulus falls within a small range of physiological signal concentrations.

A second type of abrupt response is the **discontinuous** or **all-or-none response**, in which the response switches on completely (and often irreversibly) when the signal reaches some threshold concentration (Figure 15–15, green line).

Figure 15–15 Signal processing can produce smoothly graded or switchlike responses. Some cell responses increase gradually as the concentration of extracellular signal molecule increases, eventually reaching a plateau as the signaling pathway is saturated, resulting in a *hyperbolic* response curve *(blue line)*. In other cases, the signaling system reduces the response at low signal concentrations and then produces a steeper response at some intermediate signal concentration—resulting in a *sigmoidal* response curve *(red line)*. In still other cases, the response is more abrupt and switchlike; the cell switches completely between a low and high response, without any stable intermediate response *(green line)*.



Cells Can Respond Abruptly to a Gradually Increasing Signal

Such responses are particularly useful for controlling the choice between two alternative cell states, and they generally involve positive feedback.

Cells use a variety of molecular mechanisms to produce a sigmoidal response to increasing signal concentrations:

- In one mechanism, more than one intracellular signaling molecule must bind to its downstream target protein to induce a response. For example, four molecules of the second messenger cyclic AMP must bind simultaneously to each molecule of cyclic-AMP-dependent protein kinase (PKA) to activate the kinase.
- A similar sharpening of response is seen when the activation of an intracellular signaling protein requires phosphorylation at more than one site. Such responses become sharper as the number of required molecules or phosphate groups increases, and if the number is large enough, responses become almost all-or-none.

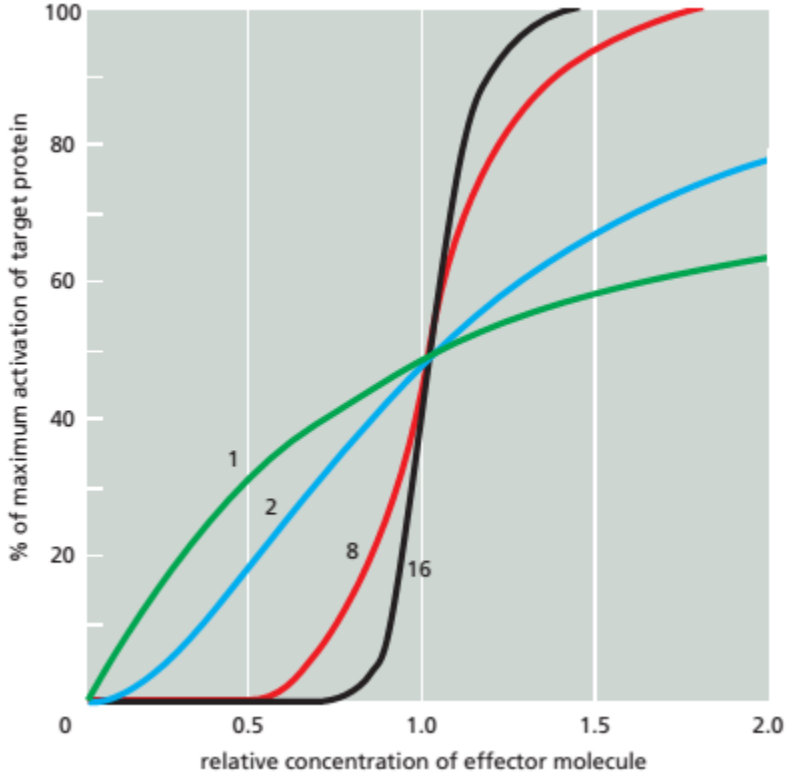


Figure 15–16 Activation curves for an allosteric protein as a function of effector molecule concentration. The curves show how the sharpness of the activation response increases with an increase in the number of allosteric effector molecules that must be bound simultaneously to activate the target protein. The curves shown are those expected, under certain conditions, if the activation requires the simultaneous binding of 1, 2, 8, or 16 effector molecules.

Cells Can Respond Abruptly to a Gradually Increasing Signal

Responses are also sharpened when an intracellular signaling molecule activates one enzyme and also inhibits another enzyme that catalyzes the opposite reaction.

A well-studied example of this common type of regulation is the stimulation of glycogen breakdown in skeletal muscle cells induced by the hormone adrenaline (epinephrine).

Adrenaline's binding to a G-protein-coupled cell-surface receptor increases the intracellular concentration of cyclic AMP, which both

1. activates an enzyme that promotes glycogen breakdown and
2. inhibits an enzyme that promotes glycogen synthesis.

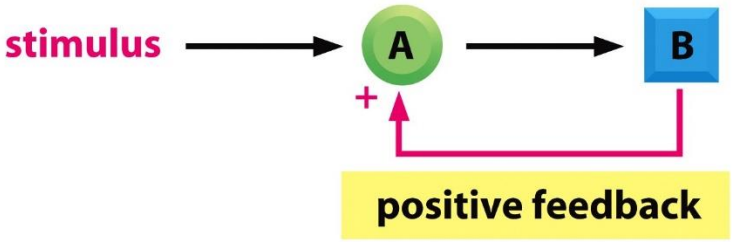
Positive Feedback Can Generate an All-or-None Response

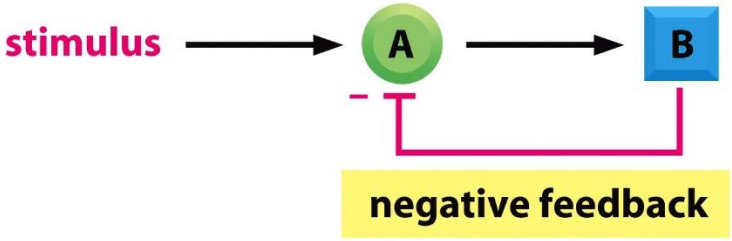
- Like intracellular metabolic pathways and the systems controlling gene activity, **most intracellular signaling systems incorporate feedback loops,** in which **the output of a process acts back to regulate that same process.**

- In positive feedback, the output stimulates its own production; in negative feedback, the output inhibits its own production.

- Feedback loops are of great general importance in biology, and they regulate many chemical and physical processes in cells.

- Those that regulate cell signaling can either operate exclusively within the target cell or involve the secretion of extracellular signals.





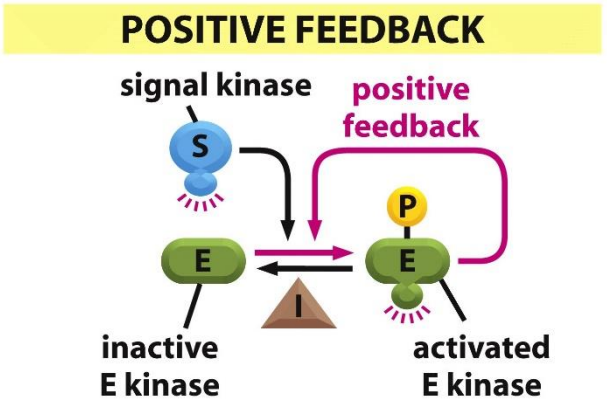
Positive Feedback Can Generate an All-or-None Response

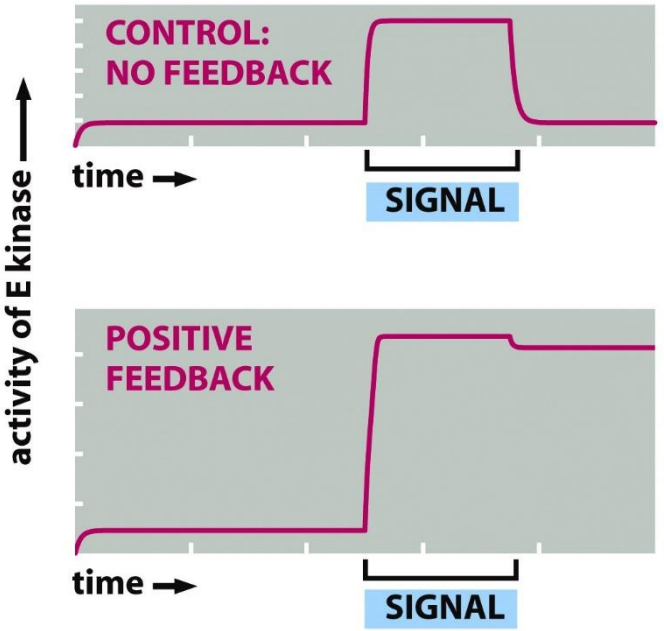
Positive feedback in a signaling pathway can transform the behavior of the responding cell.

If the positive feedback is of only **moderate strength**, its effect will be simply to steepen the response to the signal, generating a **sigmoidal response**;
but if the feedback is **strong enough**, it can produce an **all-or-none response**.

This response goes hand in hand with a further property: once the responding system has switched to the high level of activation, this condition is often **self-sustaining** and can persist even after the signal strength drops back below its critical value.

In such a case, the system is said to be bistable: it can exist in either a "**switched-off**" or a "**switched-on**" state, and a transient stimulus can flip it from the one state to the other.





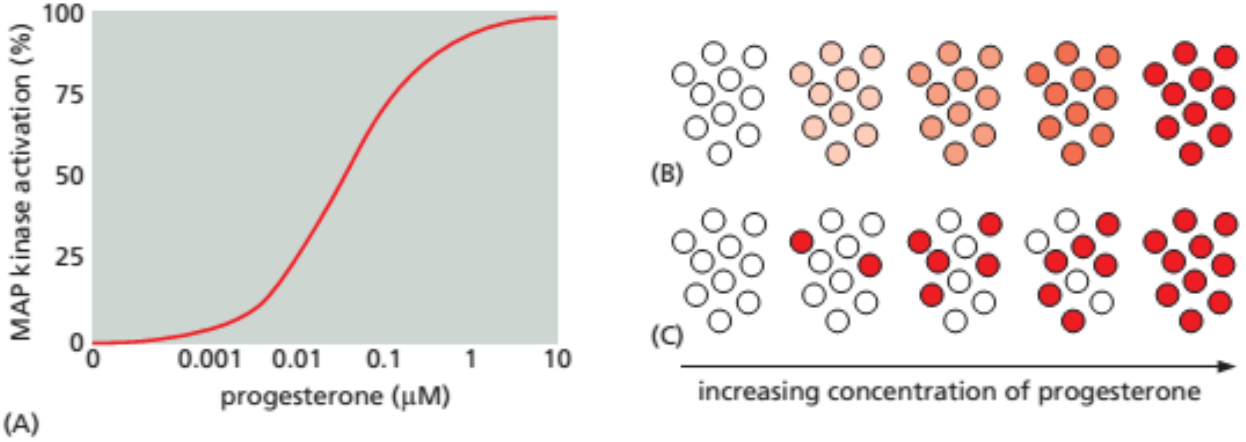
Positive Feedback Can Generate an All-or-None Response

- Through positive feedback, a transient extracellular signal can **induce long term changes in cells and their progeny that can persist for the lifetime of the organism**:
The signals that trigger **muscle-cell specification**, for example, turn on the transcription of a series of genes that encode muscle-specific transcription regulatory proteins, which stimulate the transcription of their own genes, as well as genes encoding various other muscle-cell proteins; in this way, the decision to become a muscle cell is made permanent.

- This type of **cell memory**, which depends on **positive feedback**, is one of the basic ways in which a cell can undergo a **lasting change of character without any alteration in its DNA sequence**.

- Studies of signaling responses in **large populations of cells** can give the false impression that a response is smoothly graded, even when strong positive feedback is causing an abrupt, discontinuous switch in the response in individual cells. Only by studying the response in **single cells** is it possible to see its all-or-none character (Figure 15–19).

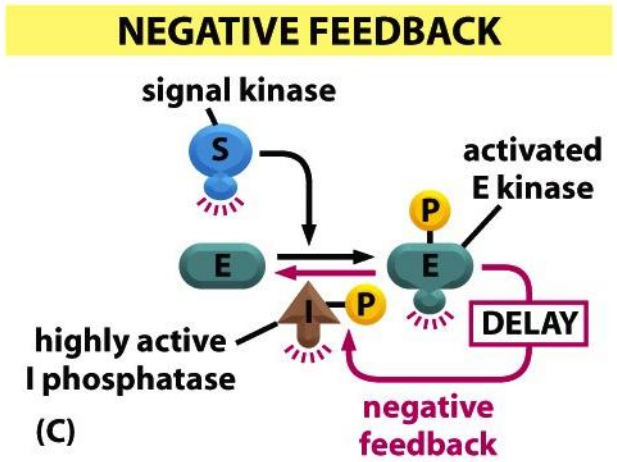
- The misleading smooth response in a cell population is due to the **random, intrinsic variability in signaling systems**: **all cells in a population do not respond identically to the same concentration of extracellular signal, especially at intermediate signal concentrations where the receptor is only partially occupied.**

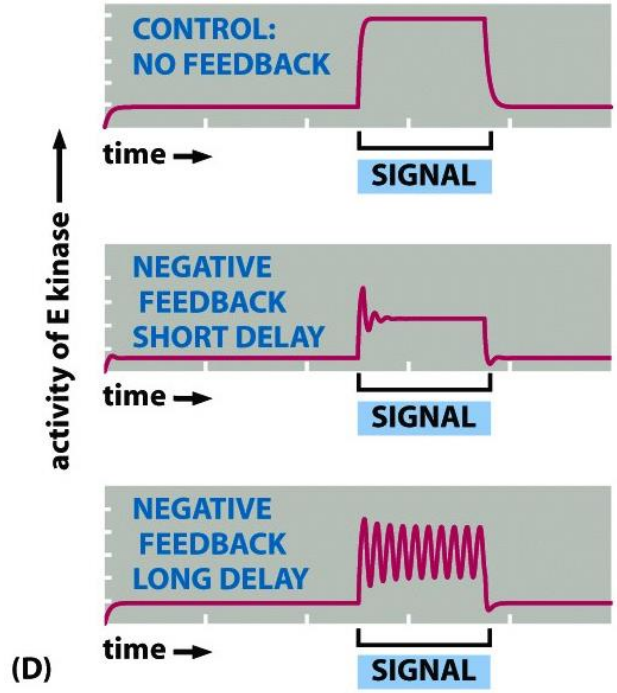


Negative Feedback is a Common Motif in Signaling Systems

- By contrast with positive feedback, **negative feedback counteracts the effect of a stimulus and thereby abbreviates and limits the level of the response, making the system less sensitive to perturbations.**

- As with positive feedback, however, qualitatively different responses can be obtained when the feedback operates more powerfully.
- A **delayed negative feedback with a long enough delay** can produce responses that **oscillate**.
- The oscillations may persist for as long as the stimulus is present (Figure 15–18C and D) or they may even be generated spontaneously, without need of an external signal to drive them.
- Many such oscillators also contain positive feedback loops that generate sharper oscillations.
- If negative feedback operates with a short delay, the system behaves like a **change detector**. It gives a strong response to a stimulus, but the response rapidly decays even while the stimulus persists; if the stimulus is suddenly increased, however, the system responds strongly again, but, again, the response rapidly decays.
This is the phenomenon of adaptation.



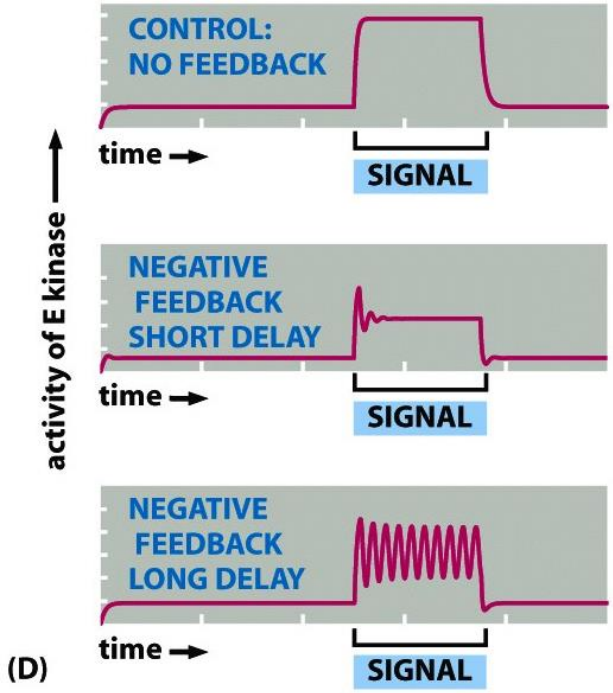


Cells Can Adjust Their Sensitivity to a Signal

- In responding to many types of stimuli, cells and organisms are able to detect the **same percentage of change in a signal over a wide range of stimulus strengths**.

- The target cells accomplish this through a reversible process of **adaptation**, or **desensitization**, whereby a prolonged exposure to a stimulus decreases the cells'response to that level of stimulus.

- In chemical signaling, adaptation enables cells to respond to changes in the concentration of an extracellular signal molecule (rather than to the absolute concentration of the signal) over a very wide range of signal concentrations.
- The underlying mechanism is negative feedback that operates with a short delay: a strong response modifies the signaling machinery involved, such that the machinery resets itself to become less responsive to the same level of signal (see Figure 15–18D, middle graph).
- Owing to the delay, however, a sudden increase in the signal is able to stimulate the cell again for a short period before the negative feedback has time to kick in.



Cells Can Adjust Their Sensitivity to a Signal

Adaptation to a signal molecule can occur in various ways:
It can result from inactivation of the receptors themselves. The binding of signal molecules to cell-surface receptors, for example, may induce the endocytosis and temporary sequestration of the receptors in endosomes.

In some cases, such signal-induced receptor endocytosis leads to the destruction of the receptors in lysosomes, a process referred to as receptor down-regulation (in other cases, however, activated receptors continue to signal after they have been endocytosed).

Receptors can also become inactivated on the cell surface—for example, by becoming phosphorylated—with a short delay following their activation.

Adaptation can also occur at sites downstream of the receptors, either by a change in intracellular signaling proteins involved in transducing the extracellular signal or by the production of an inhibitor protein that blocks the signal transduction process.

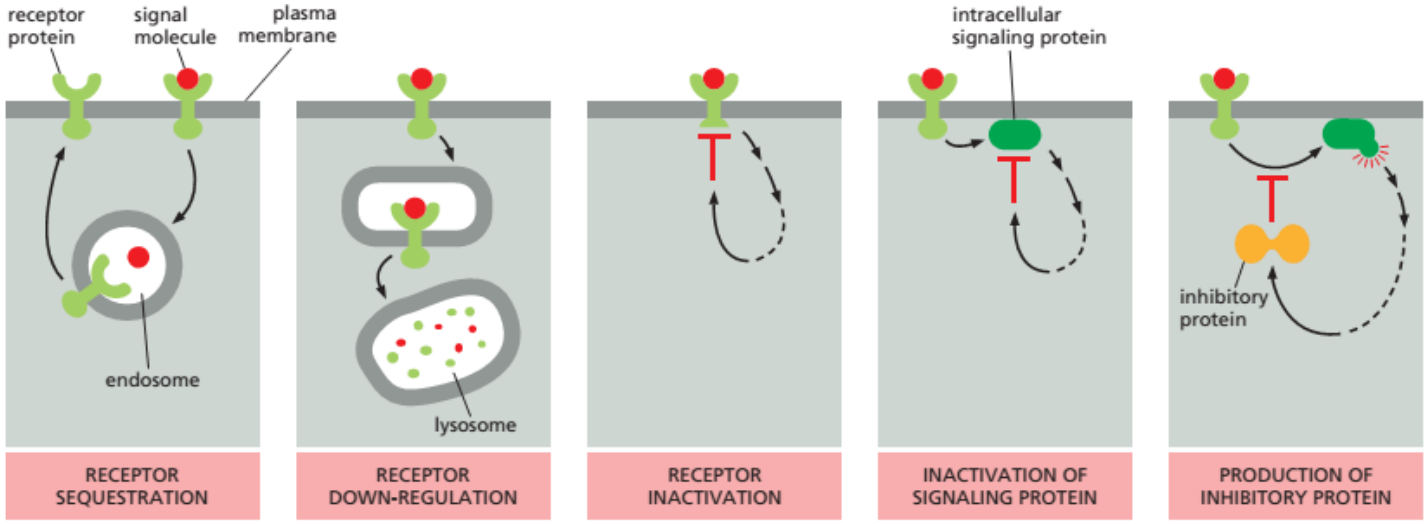


Figure 15–20 Some ways in which target cells can become adapted (desensitized) to an extracellular signal molecule. The mechanisms shown here that operate at the level of the receptor often involve phosphorylation or ubiquitylation of the receptor proteins.

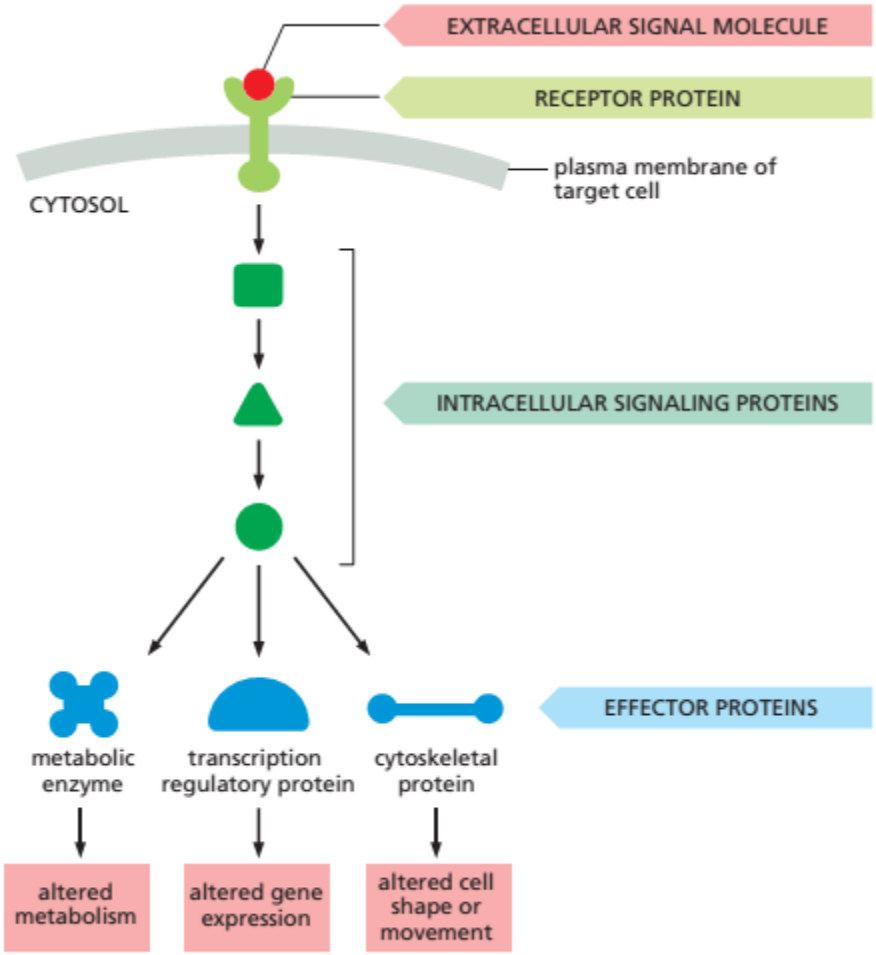


Figure 15–1 A simple intracellular signaling pathway activated by an extracellular signal molecule. The signal molecule usually binds to a receptor protein that is embedded in the plasma membrane of the target cell. The receptor activates one or more intracellular signaling pathways, involving a series of signaling proteins. Finally, one or more of the intracellular signaling proteins alters the activity of effector proteins and thereby the behavior of the cell.