Enzyme regulation

Cofactors and coenzymes. Reversible, irreversible, competitive, and noncompetitive inhibitors. Allosteric enzymes. Feedback inhibition.

Introduction

The cells of your body are capable of making many different enzymes, and at first you might think: *great, let's crank all of those enzymes up and metabolize as fast as possible!* As it turns out, though, you really don't want to produce and activate all of those enzymes at the same time, or in the same cell.

Needs and conditions vary from cell to cell and change in individual cells over time. For instance, stomach cells need different enzymes than fat storage cells, skin cells, blood cells, or nerve cells. Also, a digestive cell works much harder to process and break down nutrients during the time that follows a meal as compared with many hours after a meal. As these cellular demands and conditions changes, so do the amounts and functionality of different enzymes.

Because enzymes guide and regulate the metabolism of a cell, they tend to be carefully controlled. In this article, we'll take a look at factors that can affect or control enzyme activity. These include pH and temperature (discussed in the active site article), as well as:

- **Regulatory molecules.** Enzyme activity may be turned "up" or "down" by activator and inhibitor molecules that bind specifically to the enzyme.
- **Cofactors.** Many enzymes are only active when bound to non-protein helper molecules known as cofactors.
- **Compartmentalization.** Storing enzymes in specific compartments can keep them from doing damage or provide the right conditions for activity.
- **Feedback inhibition.** Key metabolic enzymes are often inhibited by the end product of the pathway they control (feedback inhibition).

In the rest of this article, we'll examine these factors one at a time, seeing how each can affect enzyme activity.

Regulatory molecules

Enzymes can be regulated by other molecules that either increase or reduce their activity. Molecules that increase the activity of an enzyme are called **activators**, while molecules that decrease the activity of an enzyme are called **inhibitors**.

There are many kinds of molecules that block or promote enzyme function, and that affect enzyme function by different routes.

Competitive vs. noncompetitive

In many well-studied cases, an activator or inhibitor's binding is reversible, meaning that the molecule doesn't permanently attach to the enzyme. Some important types of drugs act as reversible inhibitors. For example, the drug tipranivir, which is used to treat HIV, is a reversible inhibitor.^11start superscript, 1, end superscript It blocks activity of a viral enzyme that helps the virus make more copies of itself.

Reversible inhibitors are divided into groups based on their binding behavior. We won't discuss all of the types here, but we will look at two important groups: competitive and noncompetitive inhibitors.

- An inhibitor may bind to an enzyme and block binding of the substrate, for example, by attaching to the active site. This is called **competitive inhibition**, because the inhibitor "competes" with the substrate for the enzyme. That is, only the inhibitor or the substrate can be bound at a given moment.
- In **noncompetitive inhibition**, the inhibitor doesn't block the substrate from binding to the active site. Instead, it attaches at another site and blocks the enzyme from doing its job. This inhibition is said to be "noncompetitive" because the inhibitor and substrate can both be bound at the same time.

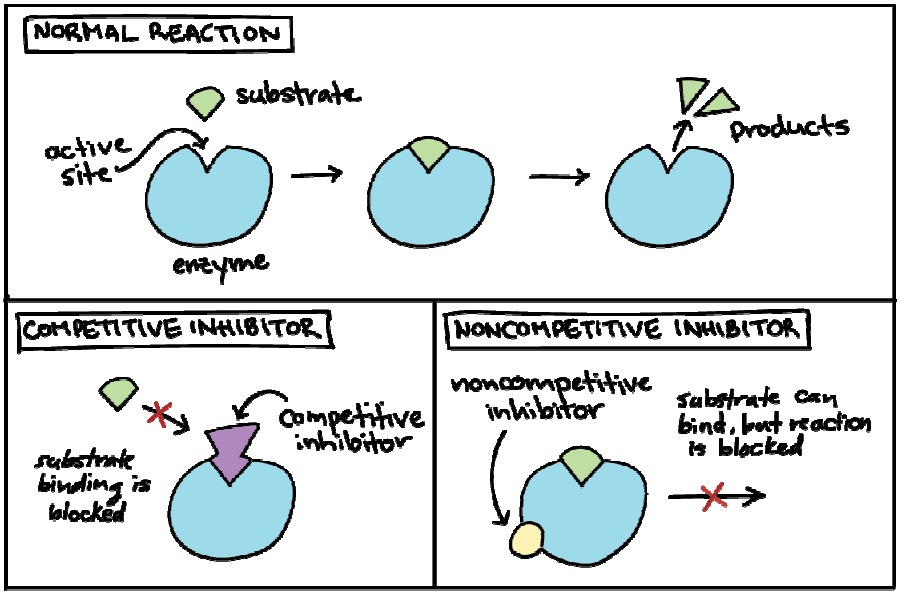


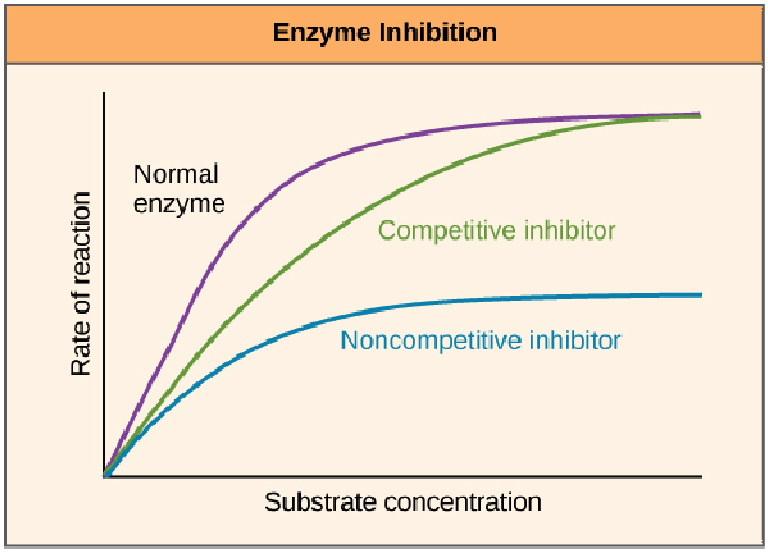
Diagram illustrating competitive and noncompetitive inhibition. The competitive inhibitor binds to the active site and prevents the substrate from binding there. The noncompetitive inhibitor binds to a different site on the enzyme; it doesn't block substrate binding, but it causes other changes in the enzyme so that it can no longer catalyze the reaction efficiently.

Competitive and non-competitive inhibitors can be told apart by how they affect an enzyme's activity at different substrate concentrations.

- If an inhibitor is competitive, it will decrease reaction rate when there's not much substrate, but can be "out-competed" by lots of substrate. That is, the enzyme can still reach its maximum reaction rate given enough substrate. In that case, almost all the active sites of almost all the enzyme molecules will be occupied by the substrate rather than the inhibitor.

- If an inhibitor is noncompetitive, the enzyme-catalyzed reaction will never reach its normal maximum rate even with a lot of substrate. This is because the enzyme molecules with the noncompetitive inhibitor bound are "poisoned" and can't do their job, regardless of how much substrate is available.

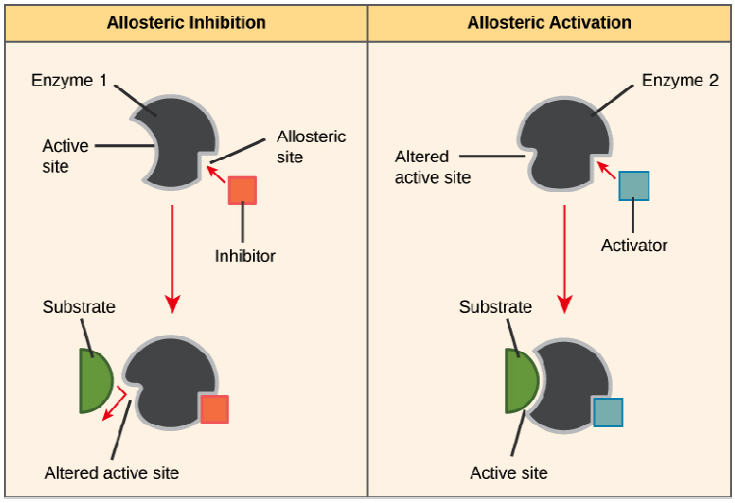
  On a graph of reaction velocity (y-axis) at different substrate concentrations (x-axis), you can tell these two types of inhibitors apart by the shape of the curves:



This plot shows rate of reaction versus substrate concentration for an enzyme in the absence of inhibitor, and for enzyme in the presence of competitive and noncompetitive inhibitors. Both competitive and noncompetitive inhibitors slow the rate of reaction, but competitive inhibitors can be overcome by high concentrations of substrate, whereas noncompetitive inhibitors cannot.

Allosteric regulation

Allosteric regulation, broadly speaking, is just any form of regulation where the regulatory molecule (an activator or inhibitor) binds to an enzyme someplace other than the active site. The place where the regulator binds is called the **allosteric site**.



The left part of this diagram shows allosteric inhibition. The allosteric inhibitor binds to an enzyme at a site other than the active site. The shape of the active site is altered so that the enzyme can no longer bind to its substrate.

The right part of this diagram shows allosteric activation. The allosteric activator binds to an enzyme at a site other than the active site. The shape of the active site is changed, allowing substrate to bind at a higher affinity.

Pretty much all cases of noncompetitive inhibition (along with some unique cases of competitive inhibition) are forms of allosteric regulation.

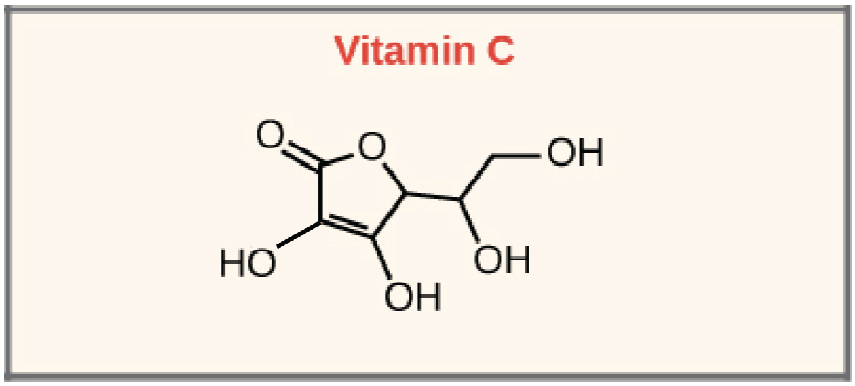
However, some enzymes that are allosterically regulated have a set of unique properties that set them apart. These enzymes, which include some of our key metabolic regulators, are often given the name of **allosteric enzymes**^22start superscript, 2, end superscript. Allosteric enzymes typically have multiple active sites located on different protein subunits. When an allosteric inhibitor binds to an enzyme, all active sites on the protein subunits are changed slightly so that they work less well.

There are also allosteric activators. Some allosteric activators bind to locations on an enzyme other than the active site, causing an increase in the function of the active site. Also, in a process called **cooperativity**, the substrate itself can serve as an allosteric activator: when it binds to one active site, the activity of the other active sites goes up.^{3}3start superscript, 3, end superscript This is considered allosteric regulation because the substrate affects active sites far from its binding site.

Cofactors and coenzymes

Many enzymes don’t work optimally, or even at all, unless bound to other non-protein helper molecules called **cofactors**. These may be attached temporarily to the enzyme through ionic or hydrogen bonds, or permanently through stronger covalent bonds.Common cofactors include inorganic ions such as iron \text {(Fe}^{2+})(Fe2+)left parenthesis, F, e, start superscript, 2, plus, end superscript, right parenthesis and magnesium (\text {Mg}^{2+})(Mg2+)left parenthesis, M, g, start superscript, 2, plus, end superscript, right parenthesis. For example, the enzyme that builds DNA molecules, DNA polymerase, requires magnesium ions to function.^44start superscript, 4, end superscript

Coenzymes are a subset of cofactors that are organic (carbon-based) molecules. The most common sources of coenzymes are dietary vitamins. Some vitamins are precursors to coenzymes and others act directly as coenzymes. For example, vitamin C is a coenzyme for several enzymes that take part in building the protein collagen, a key part of connective tissue.



Enzyme compartmentalization

Enzymes are often compartmentalized (stored in a specific part of the cell where they do their job) -- for instance, in a particular organelle. Compartmentalization means that enzymes needed for specific processes can be kept in the places where they act, ensuring they can find their substrates readily, don't damage the cell, and have the right microenvironment to work well.

For instance, digestive enzymes of the lysosome work best at a pH around 5.05.05, point, 0, which is found in the acidic interior of the lysosome (but not in the cytosol, which has a pH of about 7.27.27, point, 2). Lysosomal enzymes have low activity at the pH of the cytosol, which may serve as "insurance" for the cell: even if a lysosome bursts and spills its enzymes, the enzymes will not begin digesting the cell, because they will no longer have the right pH to function.^55start superscript, 5, end superscript

Feedback inhibition of metabolic pathways

In the process of **feedback inhibition**, the end product of a metabolic pathway acts on the key enzyme regulating entry to that pathway, keeping more of the end product from being produced.

This may seem odd – why would a molecule want to turn off its own pathway? But it’s actually a clever way for the cell to make just the right amount of the product. When there’s little of the product, the enzyme will not be inhibited, and the pathway will go full steam ahead to replenish the supply. When there’s lots of the product sitting around, it will block the enzyme, preventing the production of new product until the existing supply has been used up.

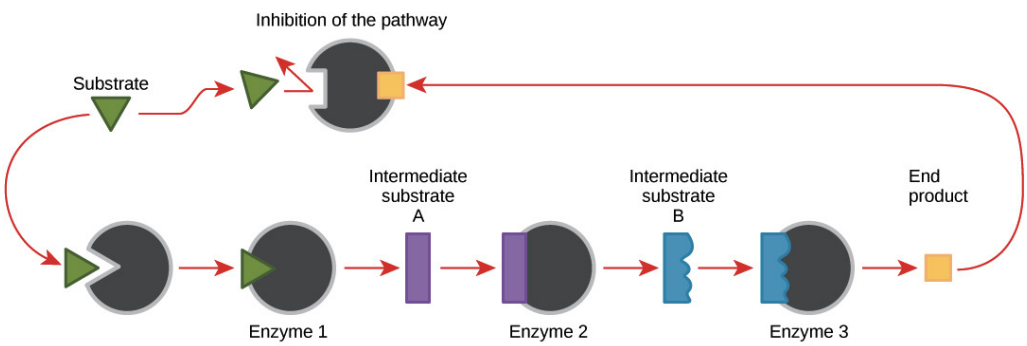


Diagram illustrating feedback inhibition. The end product of a multi-step metabolic pathway binds to an allosteric site on the enzyme that catalyzes the committed step of the pathway, reducing the enzyme's activity. This regulation helps slow the pathway down when levels of the end product are already high (when more is not needed).

Image credit: OpenStax Biology.

Typically, feedback inhibition acts at the **first committed step** of the pathway, meaning the first step that's effectively irreversible. However, feedback inhibition can sometimes hit multiple points along a pathway as well, particularly if the pathway has lots of branch points. The pathway steps regulated by feedback inhibition are often catalyzed by allosteric enzymes.^{6}6start superscript, 6, end superscript

For example, the energy carrier molecule ATP is an allosteric inhibitor of some of the enzymes involved in cellular respiration, a process that makes ATP to power cellular reactions. When there is lots of ATP, this feedback inhibition keeps more ATP from being made. This is useful because ATP is an unstable molecule. If too much ATP were made, much of it might go to waste, spontaneously breaking back down into its components (ADP and P_*i*start subscript, i, end subscript).

ADP, on the other hand, serves as a positive allosteric regulator (an allosteric **activator**) for some of the same enzymes that are inhibited by ATP. For instance, ADP may act by binding to an enzyme and changing its shape so that it becomes more active.^{7}7start superscript, 7, end superscript

Thanks to this pattern of regulation, when ADP levels are high compared to ATP levels, cellular respiration enzymes become very active and will make more ATP through cellular respiration.