Enzyme regulation

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

Introduction

The genome of a typical organism, such as yourself, will encode a variety of 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 or activate all of those enzymes at the same time, or in the same cell. This is partly just a cost-cutting measure: there's no point wasting energy and amino acids in building enzymes that aren't going to get used.

However, controlling which enzymes are produced and activated is also important for ensuring that the right reactions get carried out, and that the wrong ones don't. When an enzyme is active, it can channel substrate molecules down a particular pathway, so having the wrong enzymes "turned on" could cause precious molecules to be used up in the wrong pathway.

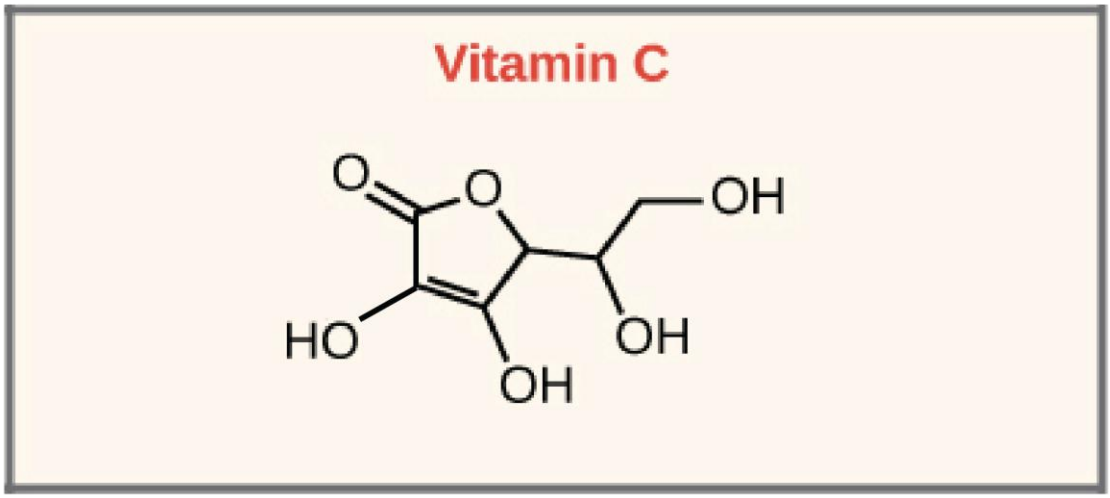
Because enzymes can have a strong impact on the metabolism of a cell, they are often regulated by multiple mechanisms. In this article, we'll take a look at a variety of factors that can affect or control enzyme activity. These include pH and temperature (discussed in the active site article), as well as:

- **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.
- **Regulatory molecules.** Enzyme activity may be turned "up" or "down" by activator and inhibitor molecules that bind specifically to the enzyme.
- **Feedback inhibition.** Key metabolic enzymes are often inhibited by the end product of the pathway they control (feedback inhibition).

Cells may also produce more or less of an enzyme by regulating expression of the gene for that enzyme. (We won't get into this here, but check out the gene regulation topic for more details). In the rest of this article, we'll examine the factors listed above one at a time, seeing how each can affect enzyme activity.

Cofactors and coenzymes

Many enzymes don't work optimally, or even at all, unless bound to other specific non-protein helper molecules. These helper molecules, called **cofactors**, may be loosely or tightly attached to the enzyme. Common cofactors include inorganic ions such as iron and magnesium. For example, the enzyme that builds DNA molecules, DNA polymerase, requires magnesium ions to function.



Chemical structure of vitamin C, which acts as a coenzyme for several enzymes.

Image modified from OpenStax Biology.

Coenzymes are cofactors that happen to be 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). This may be the cytosol, a specific organelle, or even a specific membrane inside of an organelle.

Compartmentalization means that enzymes needed for specific processes can be kept in the places where they act. This helps ensure they don't accidentally act on the wrong substrate or damage the cell. Compartmentalization can also give enzymes with the right microenvironment to function.

For instance, digestive enzymes of the lysosome work best at a pH around 5.0, which is found in the acidic interior of the lysosome (but not in the cytosol, which has a pH of about 7.2). 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.

Irreversible inhibitors

Drugs, toxins, and poisons often act by inhibiting enzymes. Some of the most hazardous poisons are **irreversible inhibitors** of enzymes, meaning that they attach permanently to the enzyme and make it unable to catalyze reactions.

For example, molecules of the nerve gas sarin covalently bind to the amino acid serine, which is found in the active site of various enzymes. One of these is acetylcholinesterase, an enzyme that plays a key role in terminating nerve signals to muscle. Its inactivation causes many of the symptoms of sarin poisoning, like muscle spasms and loss of control of bodily functions.

However, irreversible inhibitors aren't all bad. A number of important drugs used to treat human diseases are also irreversible inhibitors. For instance, aspirin irreversibly inhibits an enzyme that generates prostaglandins (chemical messengers that promote inflammation) by transferring a chemical group to a serine in the active site. Some cancer drugs are also irreversible inhibitors, acting on enzymes that promote cancer cell.

Competitive and noncompetitive inhibitors

In many cases, inhibition is reversible, meaning that the inhibitor can attach to and detach from the enzyme multiple times. Some important types of drugs act as reversible inhibitors. For example, the drug tipranivir, which is used to treat HIV, is a reversible inhibitor. It blocks activity of a viral enzyme that helps the virus make more copies of itself.

Reversible inhibitors can be divided into groups based on their binding behavior (whether they can bind only to the enzyme, to the enzyme in a complex with its substrate, etc.). 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, usually 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 changes the enzyme's activity, making it unable to efficiently

catalyze its reaction. This inhibition is said to be "noncompetitive" because the inhibitor and substrate don't compete for binding to the enzyme.

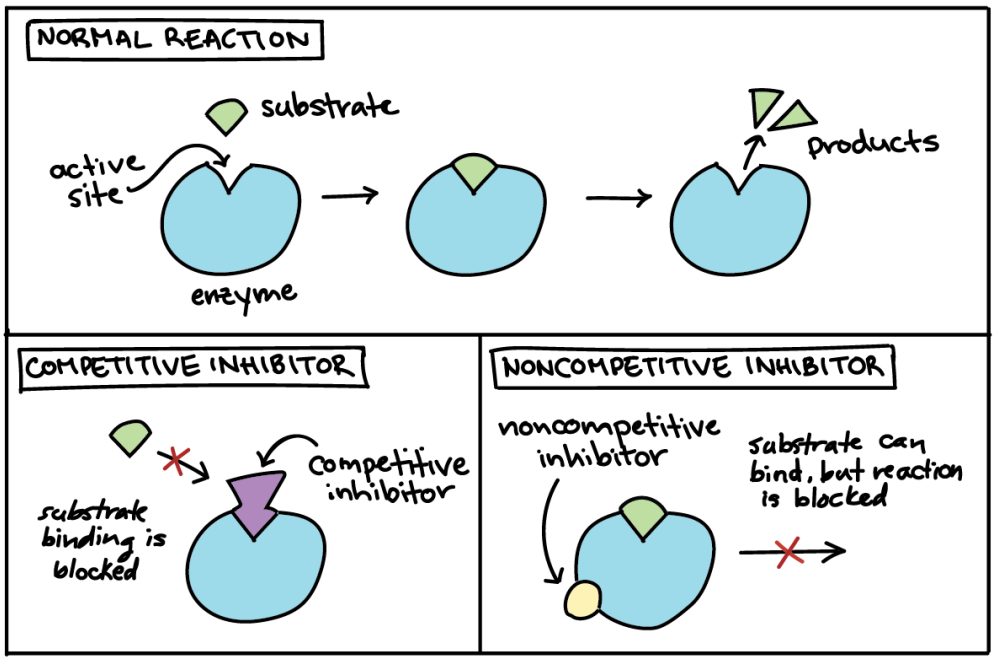


Diagram illustrating competitive and noncompetitive inhibition. The competitive inhibitor binds to the active site and prevents the substrate from binding there. The noncompetitive inhibitor binds to a different site on the enzyme; it doesn't block substrate binding, but it causes other changes in the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

Competitive and non-competitive inhibitors have different effects on enzymes' ability to catalyze reactions across different substrate concentrations.

- If an inhibitor is competitive, it will decrease reaction rate when substrate concentrations are low, but can be out-competed by addition of large amounts of substrate. That is, the enzyme can still reach its normal maximum reaction rate given enough substrate, because 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 can't carry out efficient catalysis, regardless of how much substrate is available.

If you want to see what this looks like on a graph, or if you are looking for information on Michaelis-Menten enzymes, check out a simple article on the basics of enzyme kinetics graphs.

Allosteric enzymes

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**. Pretty much all cases of noncompetitive inhibition (along with some cases of competitive inhibition, the ones where the inhibitor binds elsewhere than the active site) 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 most crucial metabolic regulators and serve as "gatekeepers" for metabolic pathways, are sometimes given the name of **allosteric enzymes**.

Allosteric enzymes typically have multiple active sites, exist in an equilibrium between active and inactive forms (all active sites "on" vs. all active sites "off"), and are very sensitive to changes in substrate concentration. They often also show **cooperativity**, in which binding of the substrate to one active site increases the tendency of the other active sites to bind the substrate.

Thanks to these properties, allosteric enzymes act as sensitive "switches" to turn their target pathways on or off.

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.

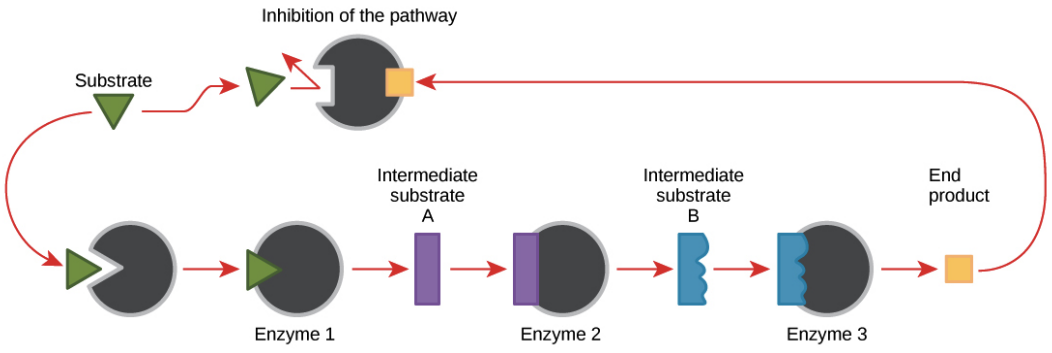


Diagram illustrating feedback inhibition. The end product of a multi-step metabolic pathway binds to an allosteric site on the enzyme that catalyzes the committed step of the pathway, reducing the enzyme's activity. This regulation helps slow the pathway down when levels of the end product are already 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.

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 present in a cell, much of it might go to waste, spontaneously breaking back down into its components (ADP and Pi).

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, ATP may act by binding to an enzyme and changing its shape so that it becomes more active.

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.