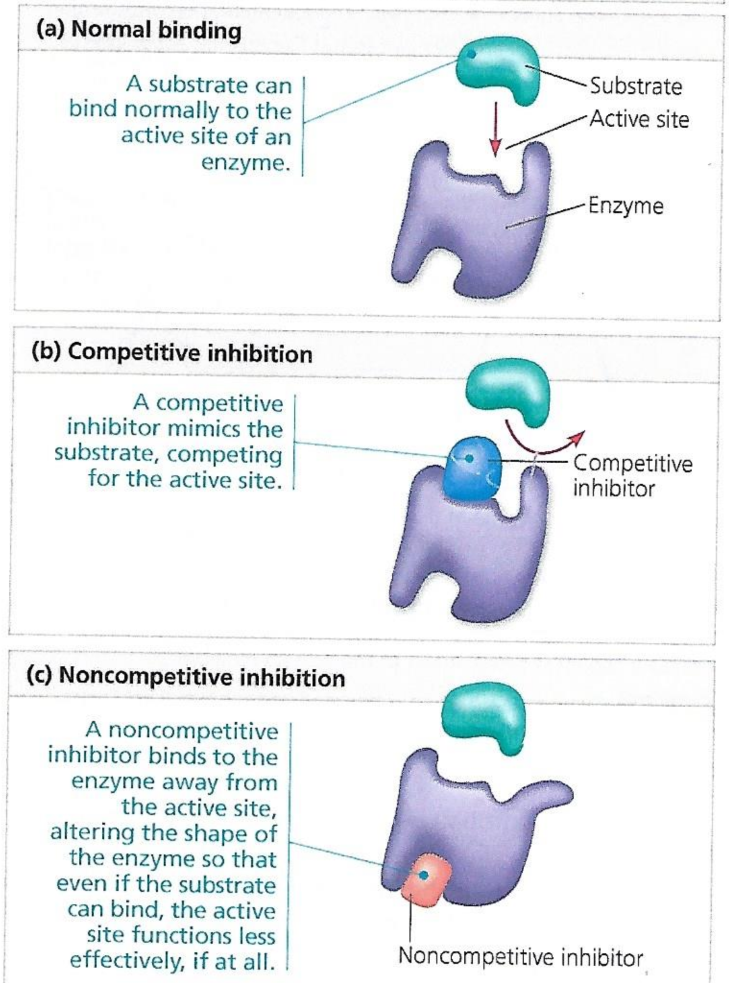
Enzyme Inhibitors

Certain chemicals selectively inhibit the action of specific enzymes. Sometimes the inhibitor attaches to the enzyme by covalent bonds, in which case the inhibition is usually irreversible. Many enzyme inhibitors, however, bind to the enzyme by weak interactions, and when this occurs, the inhibition is reversible. Some reversible inhibitors resemble the normal substrate molecule and compete for admission into the active site (**Figure 6.17a** and **b**). These mimics, called **competitive inhibitors**, reduce the productivity of enzymes by blocking substrates from entering active sites. This kind of inhibition can be overcome by increasing the concentration of substrate so that as active sites become available, more substrate molecules than inhibitor molecules are around to gain entry to the sites.

In contrast, **noncompetitive inhibitors** do not directly compete with the substrate to bind to the enzyme at the active site. Instead, they impede enzymatic reactions by binding to another part of the enzyme. This interaction causes the enzyme molecule to change its shape in such a way that the active site becomes much less effective at catalyzing the conversion of substrate to product (**Figure 6.17c**).

▼ Figure 6.17 Inhibition of enzyme activity.



Toxins and poisons are often irreversible enzy
tors. An example is sarin, a nerve gas. Sarin was re
terrorists in the Tokyo subway in 1995, killing sev
and injuring many others. This small molecule bi
lently to the R group on the amino acid serine, wh
in the active site of acetylcholinesterase, an enzym
in the nervous system. Other examples include the
DDT and parathion, inhibitors of key enzymes in t
system. Finally, many antibiotics are inhibitors of s
enzymes in bacteria. For instance, penicillin blocks
site of an enzyme that many bacteria use to make c

Citing enzyme inhibitors that are metabolic po
give the impression that enzyme inhibition is gener
mal and harmful. In fact, molecules naturally prese
cell often regulate enzyme activity by acting as inh
regulation—selective inhibition—is essential to the
cellular metabolism, as we will discuss in Concept 6.5

The Evolution of Enzymes

EVOLUTION Thus far, biochemists have identified m
4,000 different enzymes in various species, most lik
small fraction of all enzymes. How did this grand pr
of enzymes arise? Recall that most enzymes are prot
proteins are encoded by genes. A permanent change
known as a *mutation*, can result in a protein with one
changed amino acids. In the case of an enzyme, if the
amino acids are in the active site or some other cruc
the altered enzyme might have a novel activity or mi
to a different substrate. Under environmental conditi
the new function benefits the organism, natural selec
tend to favor the mutated form of the gene, causing it
in the population. This simplified model is generally
as the main way in which the multitude of different e
arose over the past few billion years of life's history.

CONCEPT CHECK 6.4

1. Many spontaneous reactions occur very slowly. Why d
spontaneous reactions occur instantly?
2. Why do enzymes act only on very specific substrates?
3. **WHAT IF?** Malonate is an inhibitor of the enzyme su
dehydrogenase. How would you determine whether m
nate is a competitive or noncompetitive inhibitor?

For suggested answers, see Appendix A.

CONCEPT 6.5

Regulation of enzyme activity helps control metabolism

Chemical chaos would result if all of a cell's metabolic pathways were operating simultaneously. Intrinsic to li
processes is a cell's ability to tightly regulate its metabo
pathways by controlling when and where its various en
are active. It does this either by switching on and off the

that encode specific enzymes (as we will discuss in Unit Two) or, as we discuss here, by regulating the activity of enzymes once they are made.

Allosteric Regulation of Enzymes

In many cases, the molecules that naturally regulate enzyme activity in a cell behave something like reversible noncompetitive inhibitors (see Figure 6.17c): These regulatory molecules change an enzyme's shape and the functioning of its active site by binding to a site elsewhere on the molecule, via noncovalent interactions. **Allosteric regulation** is the term used to describe any case in which a protein's function at one site is affected by the binding of a regulatory molecule to a separate site. It may result in either inhibition or stimulation of an enzyme's activity.

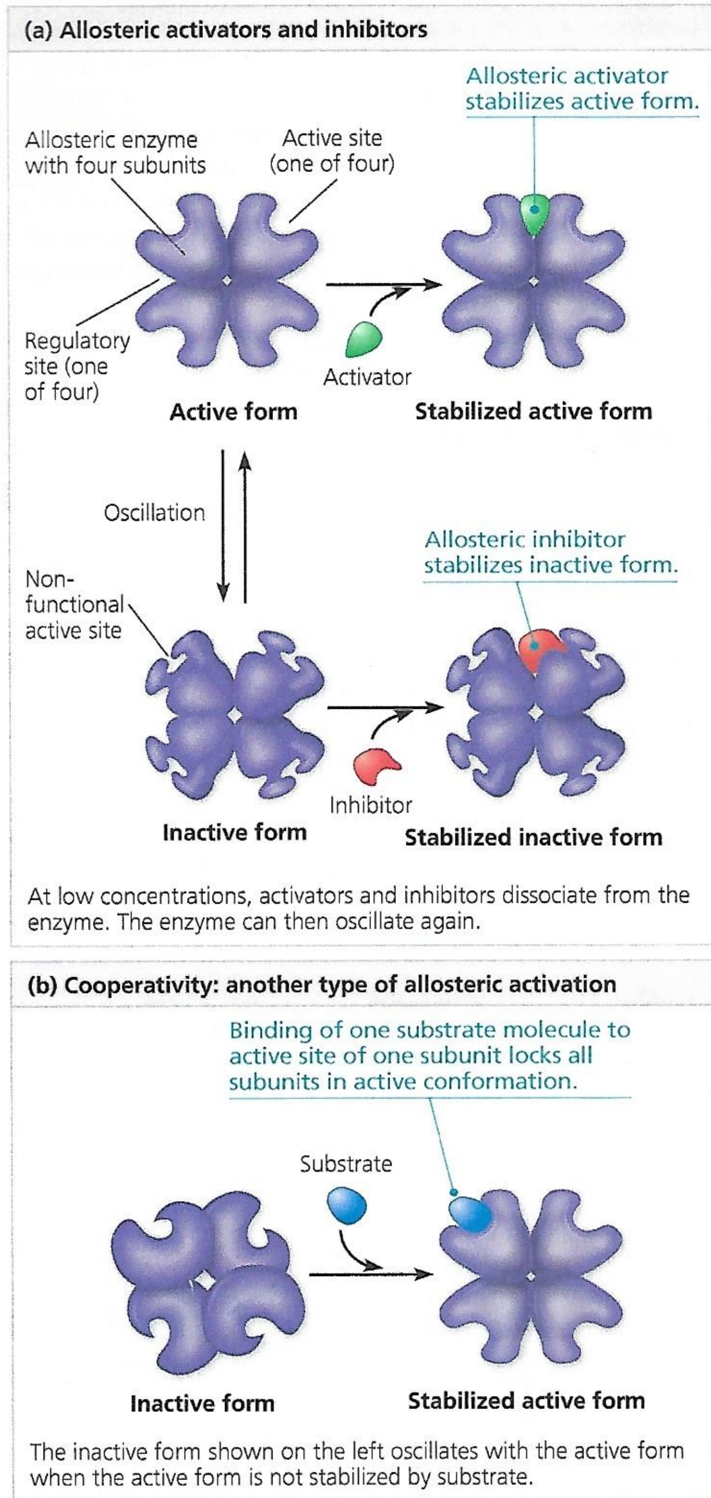
Allosteric Activation and Inhibition

Most enzymes known to be allosterically regulated are constructed from two or more subunits, each composed of a polypeptide chain with its own active site. The entire complex oscillates between two different shapes, one catalytically active and the other inactive **(Figure 6.18a)**. In the simplest kind of allosteric regulation, an activating or inhibiting regulatory molecule binds to a regulatory site (sometimes called an allosteric site), often located where subunits join. The binding of an *activator* to a regulatory site stabilizes the shape that has functional active sites, whereas the binding of an *inhibitor* stabilizes the inactive form of the enzyme. The subunits of an allosteric enzyme fit together in such a way that a shape change in one subunit is transmitted to all others. Through this interaction of subunits, a single activator or inhibitor molecule that binds to one regulatory site will affect the active sites of all subunits.

Fluctuating concentrations of regulators can cause a sophisticated pattern of response in the activity of cellular enzymes. The products of ATP hydrolysis (ADP and Ⓟi), for example, play a complex role in balancing the flow of traffic between anabolic and catabolic pathways by their effects on key enzymes. ATP binds to several catabolic enzymes allosterically, lowering their affinity for substrate and thus inhibiting their activity. ADP, however, functions as an activator of the same enzymes. This is logical because catabolism functions in regenerating ATP. If ATP production lags behind its use, ADP accumulates and activates the enzymes that speed up catabolism, producing more ATP. If the supply of ATP exceeds demand, then catabolism slows down as ATP molecules accumulate and bind to the same enzymes, inhibiting them. (You'll see examples of this type of regulation when you learn about cellular respiration in the next chapter.) ATP, ADP, and other related molecules also affect key enzymes in anabolic pathways. In this way, allosteric enzymes control the rates of important reactions in both sorts of metabolic pathways.

In another kind of allosteric activation, a *substrate* molecule binding to one active site in a multisubunit enzyme triggers a shape change in all the subunits, thereby increasing catalytic activity at the other active sites **(Figure 6.18b)**. Called **cooperativity**, this mechanism amplifies the response of enzymes to substrates: One substrate molecule primes an enzyme to act on additional substrate molecules more readily. Cooperativity is considered allosteric regulation because binding of the substrate to one active site affects catalysis in another active site.

▼ **Figure 6.18 Allosteric regulation of enzyme activity.**



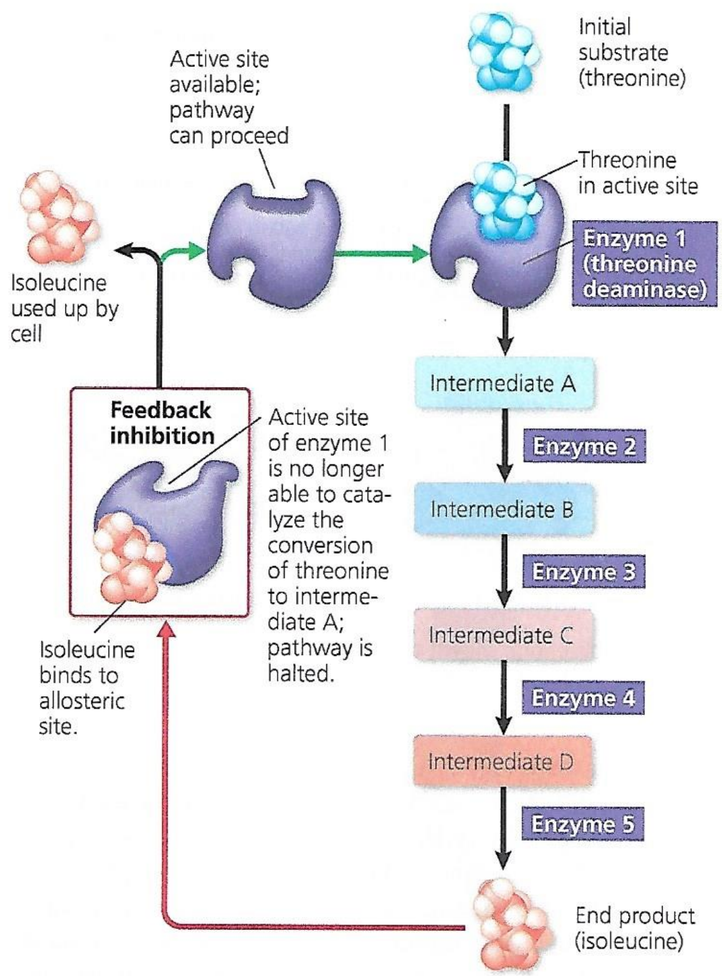
At low concentrations, activators and inhibitors dissociate from the enzyme. The enzyme can then oscillate again.

The inactive form shown on the left oscillates with the active form when the active form is not stabilized by substrate.

Although hemoglobin is not an enzyme (it carries O_2 rather than catalyzing a reaction), classic studies of hemoglobin have elucidated the principle of cooperativity. Hemoglobin is made up of four subunits, each with an oxygen-binding site (see Figure 3.22). The binding of an oxygen molecule to one binding site increases the affinity for oxygen of the remaining binding sites. Thus, where oxygen is at high levels, such as in the lungs or gills, hemoglobin's affinity for oxygen increases as more binding sites are filled. In oxygen-deprived tissues, however, *the release of each oxygen molecule decreases the oxygen* affinity of the other binding sites, resulting in the release of oxygen where it is most needed. Cooperativity works similarly in multisubunit enzymes that have been studied.

Feedback Inhibition

Earlier, we discussed the allosteric inhibition of an enzyme in an ATP-generating pathway by ATP itself. This is a common mode of metabolic control, called **feedback inhibition**, in which a metabolic pathway is halted by the inhibitory binding of its end product to an enzyme that acts early in the pathway. **Figure 6.19** shows an example of feedback inhibition operating on an anabolic pathway. Some cells use this five-step pathway to synthesize the amino acid isoleucine from threonine,

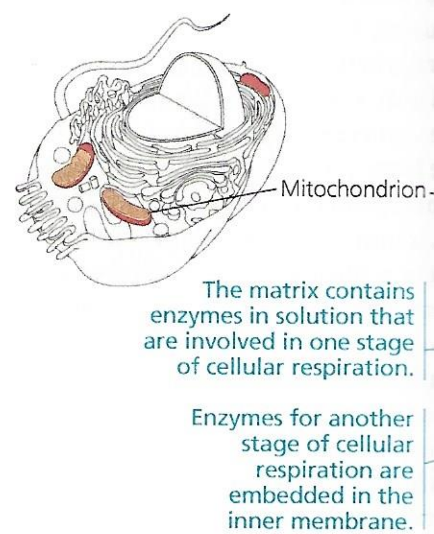


▲ **Figure 6.19 Feedback inhibition in isoleucine synthesis.**

another amino acid. As isoleucine accum its own synthesis by allosterically inhibi first step of the pathway. Feedback inh the cell from making more isoleucine thus wasting chemical resources.

Organization of Enzymes W

The cell is not just a bag of chemicals ent kinds of enzymes and substrates in *is compartmentalized*, and cellular stru to metabolic pathways. In some cases, several steps of a metabolic pathway is tienzyme complex. The arrangement fa of reactions, with the product from the the substrate for an adjacent enzyme in on, until the end product is released. S zyme complexes have fixed locations structural components of particular m solution within particular membrane- ganelles, each with its own internal ch example, in eukaryotic cells, the enzym reside in specific locations within mito



▲ **Figure 6.20 Organelles and structu** Organelles such as the mitochondrion (TEM) out specific functions, in this case cellular res

In this chapter, you have learned th tersecting set of chemical pathways ch choreographed interplay of thousands lular molecules. In the next chapter, w ration, the major catabolic pathway th molecules, releasing energy that can b processes of life.

CONCEPT CHECK 6.5

1. How do an activator and an inhibitor an allosterically regulated enzyme?

For suggested answers, see Appendix A

Although hemoglobin is not an enzyme (it carries O_2 rather than catalyzing a reaction), classic studies of hemoglobin have elucidated the principle of cooperativity. Hemoglobin is made up of four subunits, each with an oxygen-binding site (see Figure 3.22). The binding of an oxygen molecule to one binding site increases the affinity for oxygen of the remaining binding sites. Thus, where oxygen is at high levels, such as in the lungs or gills, hemoglobin's affinity for oxygen increases as more binding sites are filled. In oxygen-deprived tissues, however, the release of each oxygen molecule decreases the oxygen affinity of the other binding sites, resulting in the release of oxygen where it is most needed. Cooperativity works similarly in multisubunit enzymes that have been studied.

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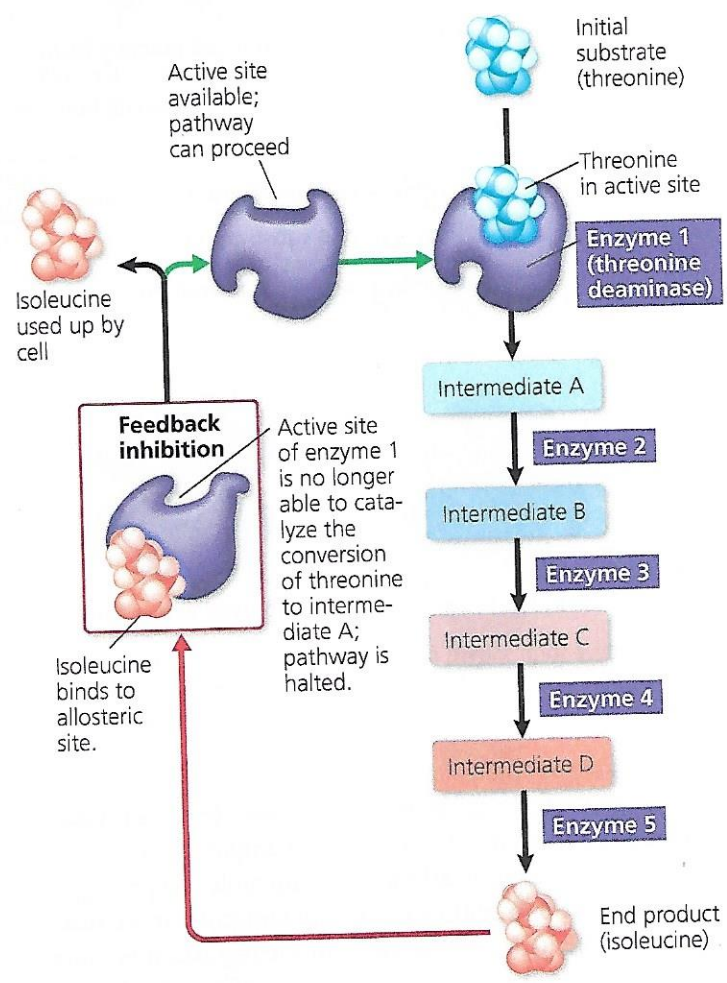
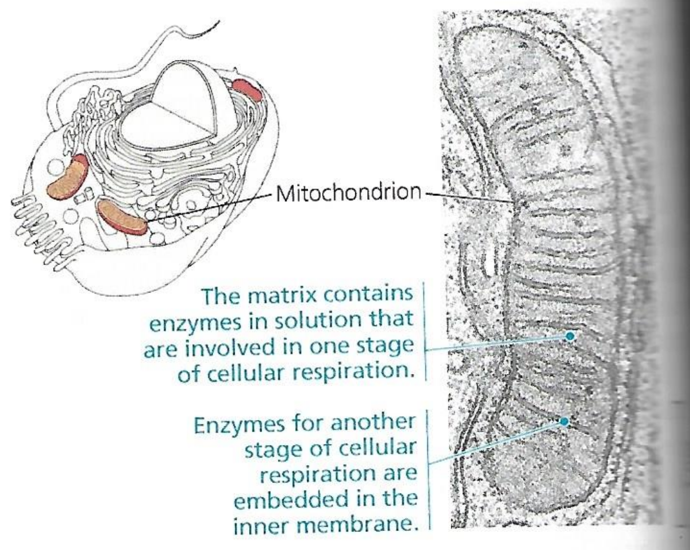


▲ Figure 6.19 Feedback inhibition in isoleucine synthesis.

Organization of Enzymes Within the Cell

The cell is not just a bag of chemicals with thousands of di ent kinds of enzymes and substrates in a random mix. The is compartmentalized, and cellular structures help bring to metabolic pathways. In some cases, a team of enzymes several steps of a metabolic pathway is assembled into a m tienzyme complex. The arrangement facilitates the seque of reactions, with the product from the first enzyme beco the substrate for an adjacent enzyme in the complex, and s on, until the end product is released. Some enzymes and e zyme complexes have fixed locations within the cell and a structural components of particular membranes. Others a solution within particular membrane-enclosed eukaryotic o ganelles, each with its own internal chemical environment. example, in eukaryotic cells, the enzymes for cellular resp reside in specific locations within mitochondria (**Figure 6.2**



▲ **Figure 6.20 Organelles and structural order in metabo**
Organelles such as the mitochondrion (TEM) contain enzymes that ca out specific functions, in this case cellular respiration.

In this chapter, you have learned that metabolism, the i tersecting set of chemical pathways characteristic of life, is choreographed interplay of thousands of different kinds of lular molecules. In the next chapter, we'll explore cellular re ration, the major catabolic pathway that breaks down orga molecules, releasing energy that can be used for the crucial processes of life.

CONCEPT CHECK 6.5

1. How do an activator and an inhibitor have different effects an allosterically regulated enzyme?

For suggested answers, see Appendix A.