Enzymes

Enzymes are organic catalysts that catalyze the chemical reactions , created by living cells and they are specific biologic protein catalysts . The presence and maintenance of enzymes is essential for the breakdown of nutrient to supply energy and chemical building blocks ; the assembly of those building blocks into proteins , DNA , membranes , cells , and tissues ;and the harnessing of energy to power cell motility , neural function , and muscle contraction . Deficiencies in the quantity or catalytic activity of enzyme can result from genetic defects, nutritional deficits, or toxins. Defective enzymes can result from the genetic mutation or infection by viral or bacterial pathogens e.g. vibero cholera.

The enzymes increase the rate of chemical reactions and are neither consumes nor permanently altered as a consequence of their participation in a reaction.

Unlike most catalysts used in synthetic chemistry enzymes are specific both for the type of reaction catalyzed and for a single substrate.

The enzymes are also stereospecific catalysts catalyze only one stereoisomer , since they bind substrate through at least three points of attachment.

Enzymes classification

According to the type of reaction catalyzed , the enzymes are grouped into six classes :

1/ oxidoreductase : catalyze oxidation and reduction

2/ transferase : catalyze transfer of moieties such as methyl or phosphoryl groups .

3/ hydrolase: catalyze hydrolytic cleavage of c-c , c-n , c-o , and other bonds .

4/ lyases : catalyze cleavage of c-c , c-o , c-n , and other bonds by atom elimination , leaving double bonds .

5/ isomerase : catalyze geometric or structural changes within a molecule .

6/ ligase : catalyze the joining together of two molecules coupled to the hydrolysis of ATP .

Enzyme structure

The enzymes consist from amino acids connected to each other by peptide bonds forming long chain . Enzyme needs for activators to achieve its performance , these activators are classified into :

1/ Cofactor : the most common cofactors are metal ions , bind in a transient , dissociable manner either to enzyme or to a substrate therefore cofactors must be present in the medium surrounding the enzyme for catalysis to occur .

Enzymes that require a metal ion cofactor termed metal activated enzymes to distinguish them from the metaloenzymes for which metal ion serves as prostheticgroups.

2/ Coenzymes : serve as group transfer agents that transport many substrates from their point of generation to their point of utilization . chemical groups that are transported by coenzymes include methyl groups , acyl groups .

3/ Prosthetic groups : prosthetic groups are distinguished by their tight , stable , incorporation into proteins structure by covalent or non covalent forces , like flavin mononucleotides (FMN) and metal ions .

The enzymes that contain tightly bound metal ions are termed metalloenzymes . Many coenzymes and cofactors and prosthetic groups are derivatives of B vitamin.

The peptide chain of enzyme has three dimensional structure which make the enzyme more rigid and stable , and hold the active site in the suitable places . The active sites are functional groups connected to each other by special system and there are certain distances between them as a result of the three dimensional structure in the protein , these functional groups form certain site on the surface of enzyme called active site , at which the catalysis occurs .

Substrates bind to the active site at a region complementary to a portion of the substrate .

The active site also binds and orients cofactor and prosthetic group .

Enzymes that required cofactor are called Apoenzyme.

Apoenzyme together with its cofactor is called Holoenzyme .

Hypothesis of enzyme action (Models of enzyme action)

1/ Lock and key model :

The model is suggested by Emil Fisher in 1894. According to this model , both the enzyme and the substrate possess specific complementary geometric shapes that fit exactly . (active site and substrate have complementary structures and they fit together like a key in a lock) .

Inspite of this model explains enzyme specificity , it fails to explain the stabilization of the transition state .

2/ Induced fit model :

It is the most currently accepted model , suggested by Daniel Koshland in 1958, since enzyme are rather flexible structure , the active site is continually reshaped by interactions with the substrate as the substrate interacts with the enzyme . the active site continues to change until the substrate is completely bound .

Another expression : the substrate induces a conformational changes in the enzyme. This align amino acid side chain or other groups on the enzyme in the correct spatial orientation for substrate binding , catalysis or both .

Mechanism of enzyme action

1/ Lowering the activation energy by creating an environment in which the transition state is stabilized .

2/ Lowering the energy of the transition state.

3/ Providing an alternative pathway . For example , temporarily reacting with substrate to form an intermediate ES complex , which would be impossible in the absence of enzyme .

4/ Increases in temperatures speed up reactions . Thus , temperature increases help the enzyme function .

$$E+S \leftrightarrow ES \rightarrow E+P$$

Inhibition of enzymes

Enzyme reaction rates can be decreased by various types of enzymes inhibitors.

There are two types of inhibitions :

1/ Reversible inhibition : which includes :

A/ Competitive inhibition : in competitive inhibition , the inhibitor and the substrate compete for the enzyme (they cannot bind at the same time) . often competitive inhibitors strongly resemble the real substrate of the enzyme . For example methotrexate is a competitive inhibitor of the enzyme dihydrofolate reductase which catalyzes the reduction of dihydrofolate to tetrahydrofolate . this is a competitive inhibition because of the similarity between the structures of methotrexate and dihydrofolate .

B/ Uncompetitive inhibition : In this inhibition the inhibitor cannot bind to the free enzyme , but only to ES complex . The EIS complex thus formed is enzymatically inactive . This type of inhibition is rare .

C/ noncompetitive inhibition : noncompetitive inhibitors can bind to the enzyme at the same time as the substrate . Both EI and EIS complexes are enzymatically inactive .

2/ Irreversible inhibition :

Irreversible inhibitors react with enzyme and form a covalent adduct with the protein . the inactivation is irreversible . these compounds include eflornithine a drug used to treat parasitic disease . Penicillin and aspirin also act in this manner .

*In many organisms inhibitors may act as part of a feed-back mechanism . If an enzyme produces too much of one substance in the organism , that substance may act as an inhibitor for the enzyme at the beginning of the pathway that produces it causing production of the substance to slow down or stop the enzyme activity when there is a sufficient amount .

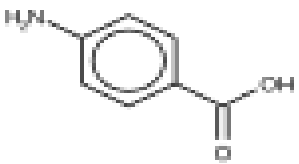
This inhibition called negative feedback .

Uses of inhibitors

Since the inhibitors modulate the function of enzymes they are often used as drug . The common example of an inhibitor that is used as a drug is " Aspirin " which inhibit the COX-1 and COX-2 enzymes that produce the inflammation messenger prostaglandin thus suppressing pain and inflammation . Other enzyme inhibitor are poisons .

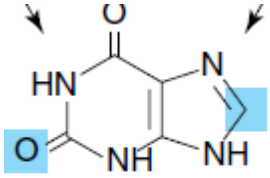
Other example is the sulfonamide which is a competitive inhibitor to some enzymes found in the pathogenic microorganisms . the microorganisms need for p-amino benzoic acid to create the coenzymes which are responsible for the formation of amino and nucleic acids , since sulfonamide resembles the structure of p-amino benzoic acid therefore it will compete this acid .

Sulfanilamide

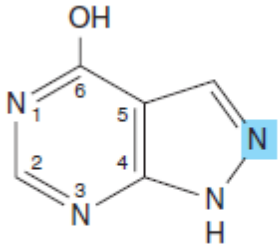


PABA

The drug allopurinol is a competitive inhibitor to the enzyme xanthine oxidase which oxidizes the xanthine to uric acid this inhibition prevents the formation of uric acid which its accumulation causes gout .



Xanthine



Alloburinol

Lovastatin is antihyperlipidemic agent competitively inhibits the first committed step in cholesterol synthesis because lovastatin is a structural analog of the substrate of the enzyme HMG-CoA reductase which is responsible for the reduction HMG to mevalonic acid then to cholesterol.

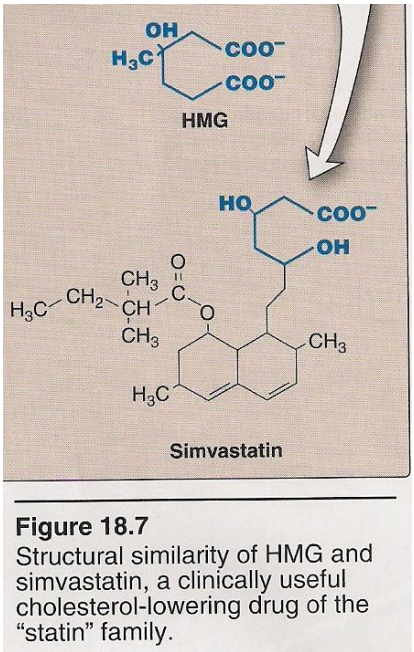


Figure 18.7
Structural similarity of HMG and simvastatin, a clinically useful cholesterol-lowering drug of the "statin" family.

Factors affecting catalytic activity of enzymes

1/ temperature : as temperature rises , reacting molecules have more kinetic energy . This increases the chance of successful collision and so the rate increase . There is a certain temperature at which the enzymes catalytic activity is at its greatest , this optimal temperature is usually around human body temperature (37.5 c) for the enzymes in the human cells . Above this temperature the enzyme structure begins to break down (denaturate)

2/ PH : Each enzyme works within quite a small pH range . There is a pH at which the enzyme activity is greatest (the optimal pH) this is because changes in pH can make , break the molecular bonds , changing the shape of enzyme and its activity .

3/ concentration of enzymes and substrates : the rate of reaction increases with increasing substrate concentration up to a point above which any further increase in substrate concentration produces no significant change in reaction rate ,this is because the active sites of the enzymes will be saturated with substrate .

When substrate concentration is high and temperature and pH is kept constant , the rate of reaction is proportional to the enzyme concentration .