MEDICAL CHEMISTRY
GENERAL CHEMISTRY

University Of Fallujah
College Of Medicine

Lecture : Medical Chemistry (Enzymology)

Stage : 1st Stage

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Date: 21 / 5 / 2026

Learning Objective :

- Define Enzymes and Their Functions .
- Classify Enzymes into the six major classes.
- Understand Enzyme Structure and Cofactors.
- Mechanism of Enzyme Action.
- Analyze Enzyme Kinetics.
- Evaluate Factors Affecting Enzyme Activity.
- Differentiate Types of Enzyme Inhibition.
- Apply Enzymology in Medical Diagnostics.

ENZYMES

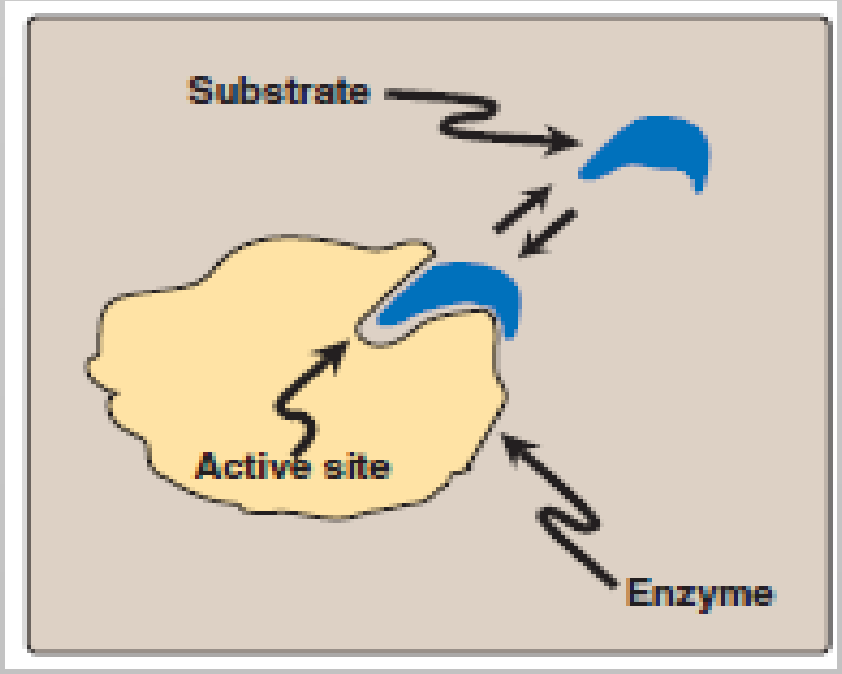
Enzymes are protein catalysts that increase the velocity of a chemical reaction, and are not consumed during the reaction. The presence and maintenance of enzymes is essential for the breakdown of nutrient to supply energy and chemical building blocks ; the assembly of those building blocks into proteins , 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.

ENZYMES

* 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.

A substrate is a molecule acted upon by an enzyme. A substrate is loaded into the active site of the enzyme, or the place that allows weak bonds to be formed between the two molecules (Substrate and enzyme).



❑ Effect of Enzyme on Chemical Reaction

- Enzymes are the most significant and highly specialized proteins,
- They have a high degree of specificity for their substrates, they accelerate chemical reactions greatly, and they function in aqueous solutions under very mild conditions of temperature and pH.

❑ Enzyme Nomenclature

- Enzymes are named by the type of reaction that they catalyse. Usually this means adding the suffix –**ase** to the name of their
- substrate or reaction that they catalyse e.g. Lactase hydrolyses lactose into glucose and galactose

Enzymes classification

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

1/ Oxidoreductases : catalyze oxidation and reduction, Example: oxidase, reductase, dehydrogenase….

2/ Transferases : catalyze transfer of moieties such as methyl, phosphoryl, amino groups, Ex: ALT (alanine transferase)

3/ Hydrolase: catalyze hydrolytic cleavage of c-c , c-n , c-o , and other bonds, Ex: Urease, lipase

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

5/ Isomerase : catalyze geometric or structural changes within a molecule, Ex: Isomerase, mutase…

6/ Ligase: catalyze the joining together of two molecules coupled to the hydrolysis of ATP, Ex: Carboxylase.

Six Major Classes of Enzymes

TABLE 6-3 International Classification of Enzymes

Class no.	Class name	Type of reaction catalyzed
1	Oxidoreductases	Transfer of electrons (hydride ions or H atoms)
2	Transferases	Group transfer reactions
3	Hydrolases	Hydrolysis reactions (transfer of functional groups to water)
4	Lyases	Cleavage of C—C, C—O, C—N, or other bonds by elimination, leaving double bonds or rings, or addition of groups to double bonds
5	Isomerases	Transfer of groups within molecules to yield isomeric forms
6	Ligases	Formation of C—C, C—S, C—O, and C—N bonds by condensation reactions coupled to cleavage of ATP or similar cofactor

Enzyme structure

Properties of enzymes

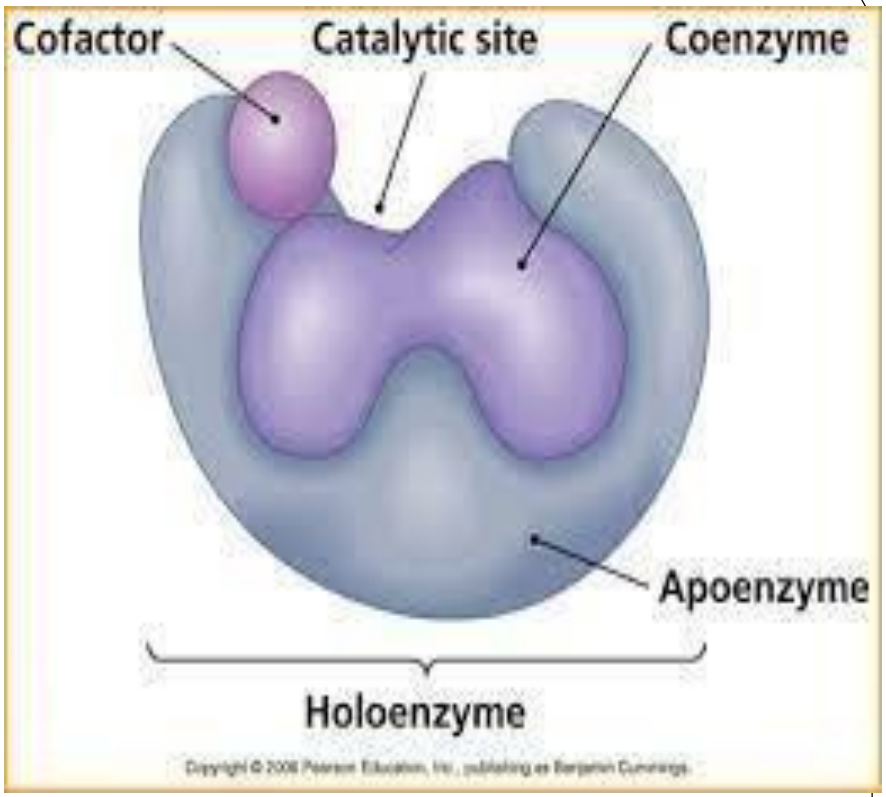
- **1.** Enzyme are protein and require the presence of additional chemical components to catalyse reactions.

- **Cofactors** are inorganic ions such as zinc , Mn2+etc.

- **Coenzymes : Coenzymes are organic compounds required by many enzymes for catalytic activity.**

- **They are often vitamins, or derivatives of** that act as temporary carriers of groups in the reaction e.g. nicotinamide adenine dinucletide (NAD), **Coenzyme A (CoA).**

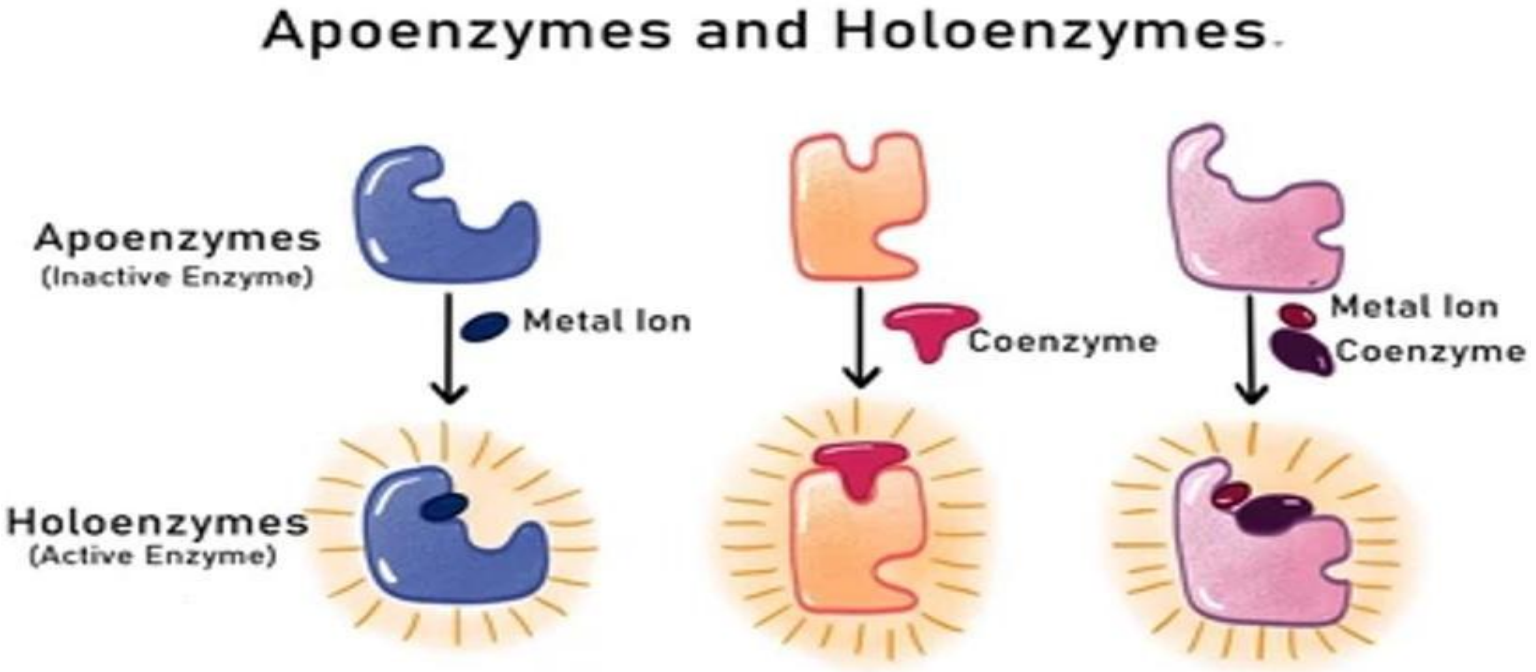
- **Coenzymes or cofactors** that are tightly covalently linked to the enzyme protein are known as **prosthetic groups**.



2. Enzymes are highly specific
Interact with one or only a few substrates and catalyse one type of reaction.

Properties of enzymes

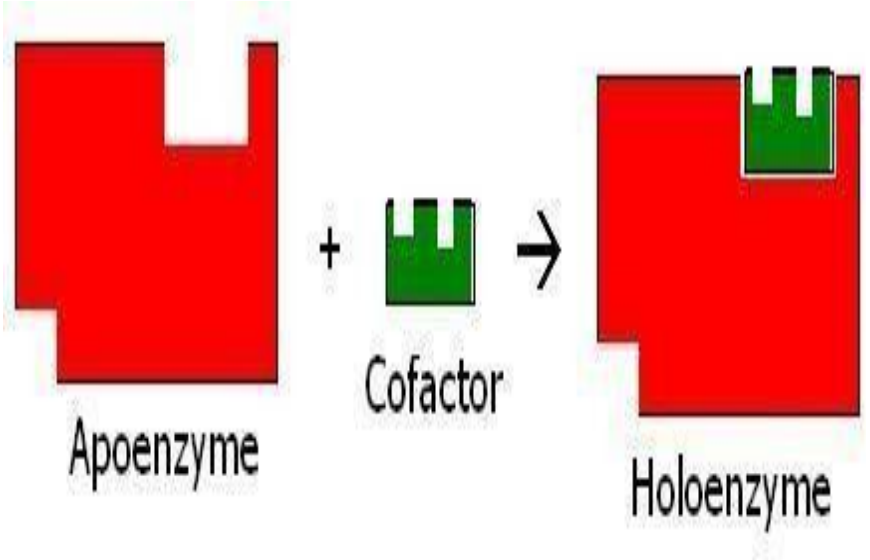
- The protein part of such an enzyme is called the **apoenzyme or apoprotein**
- A complete, catalytically active enzyme together with its bound coenzyme and/or metal ion is called a **holoenzyme**

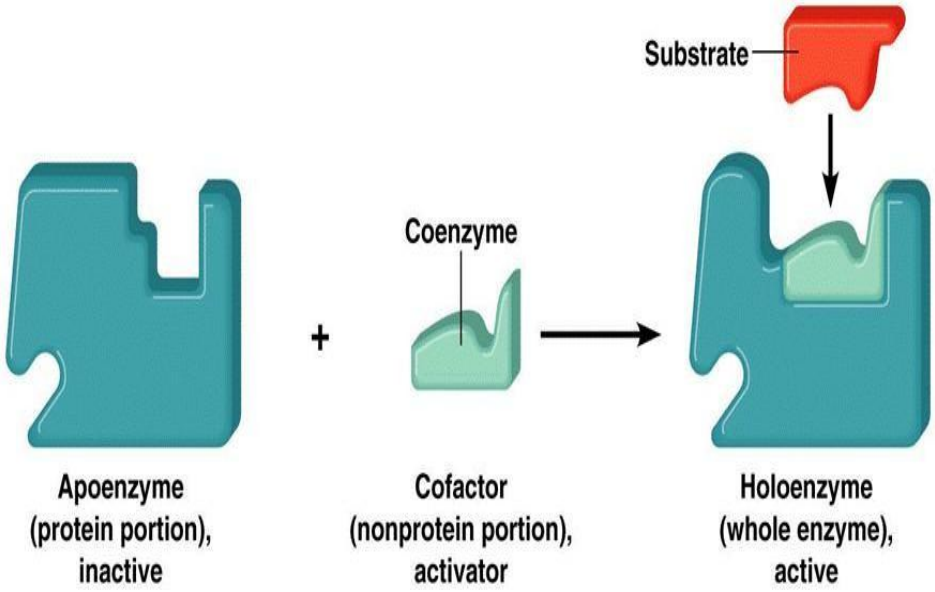


Holoenzymes:

Some enzymes require molecules other than proteins for enzymatic activity.

- The term holoenzyme refers to the active enzyme with its non-protein component.
- The term apoenzyme is inactive enzyme without its non-protein part.
- If the non-protein part is a metal ion such as Zn 2+ or Fe2+, it is called **a cofactor**.
- If it is a small organic molecule, it is termed a **coenzyme.**

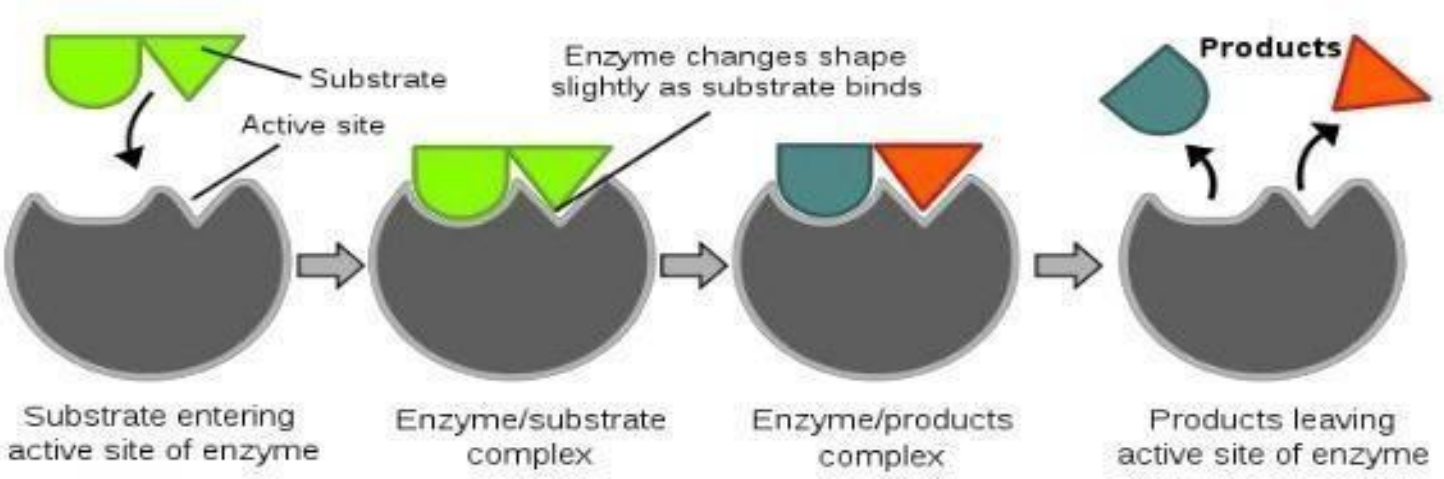




How do Enzymes Work?

- Enzyme-catalyzed reactions are characterized by the formation of a complex between substrate and enzyme (an ES complex).
- Substrate binding occurs in a pocket on the enzyme called the active site.

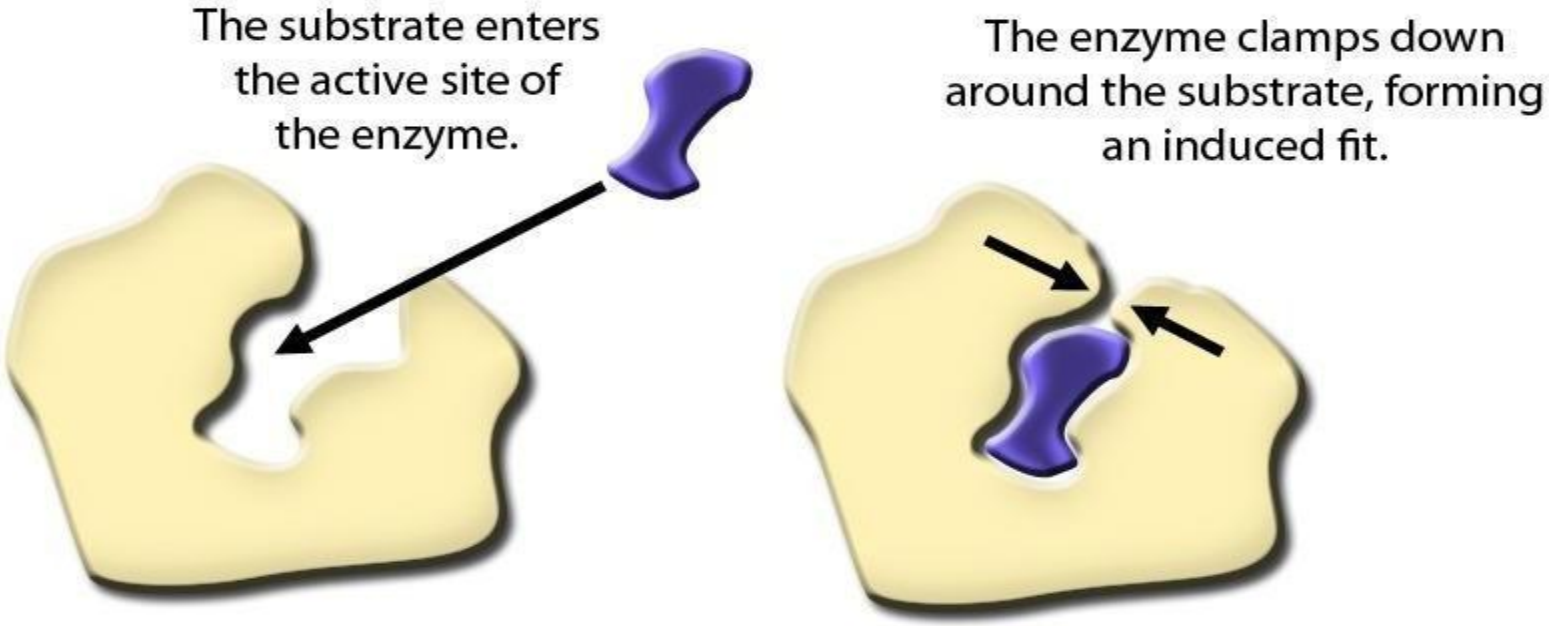
$$E + S \rightleftharpoons ES \rightleftharpoons EP \rightleftharpoons E + P$$



❑Enzyme Active Sites

- **Enzyme-catalyzed reactions take place within the confines of a pocket on the enzyme called the active site. The reactant molecule is referred to as the substrate.**
- The enzyme's active site is the site at which the enzyme binds to the substrates and increases their chances of reacting.

The surface of the active site is lined with amino acid residues



Reaction Rates as a Function of Enzyme and Substrate Conc.

The relationship between [S] and Vo has general shape for most enzymes (hyperbolic), which can be expressed algebraically by the Michaelis-Menten equation:

WhereV0= initial reaction velocity

[S] = substrate concentration

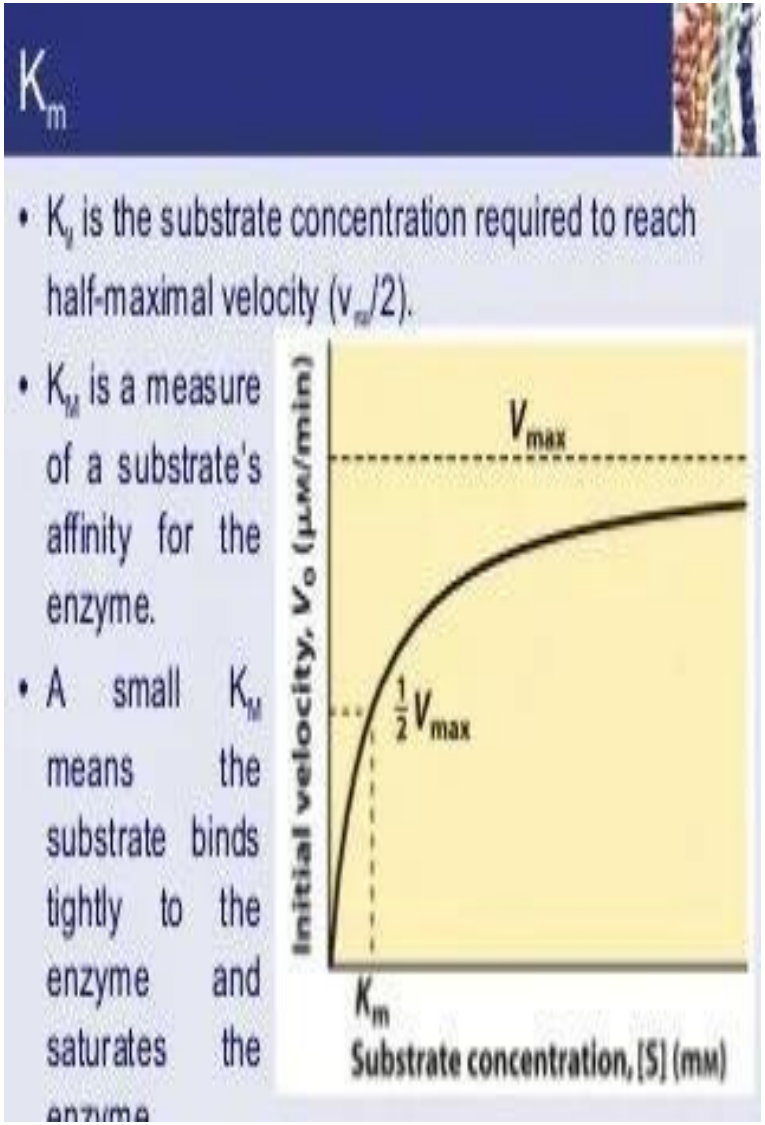
Vmax = maximal velocity

Km = Michaelis constant

The Michaelis-Menten constant (Km), the concentration of substrate ([S]) providing half of enzyme maximal activity,

Low Km means high affinity of the enzyme to the substrate.

- High Km means low affinity of the enzyme to the substrate.



The Michaelis-Menten Equation

- The basic equation derived by Michaelis and Menten to explain enzyme-catalyzed reactions is

$$V_o = \frac{V_{max}[S]}{K_m + [S]}$$

K_m - Michaelis constant;

V_o – initial velocity caused by substrate concentration, [S];

V_{max} – maximum velocity

❑ Factors Affecting enzyme activity

- The rate of the reaction is directly proportional to the enzyme concentration at all substrate concentrations.
- For example, if the enzyme concentration is halved, the initial rate of the reaction as well as that of are reduced to one half that of the original.

✓ Substrate concentration

✓ .PH

❑ Factors Affecting Reaction Velocity

1. **Substrate concentration.**
2. **Effect of PH.**
3. **Effect of Temp.**

↑temp lead to ↑rate of any reaction.
At more than 50°c most enzymes are denatured and inactivated, this lead to ↓rate of reaction.

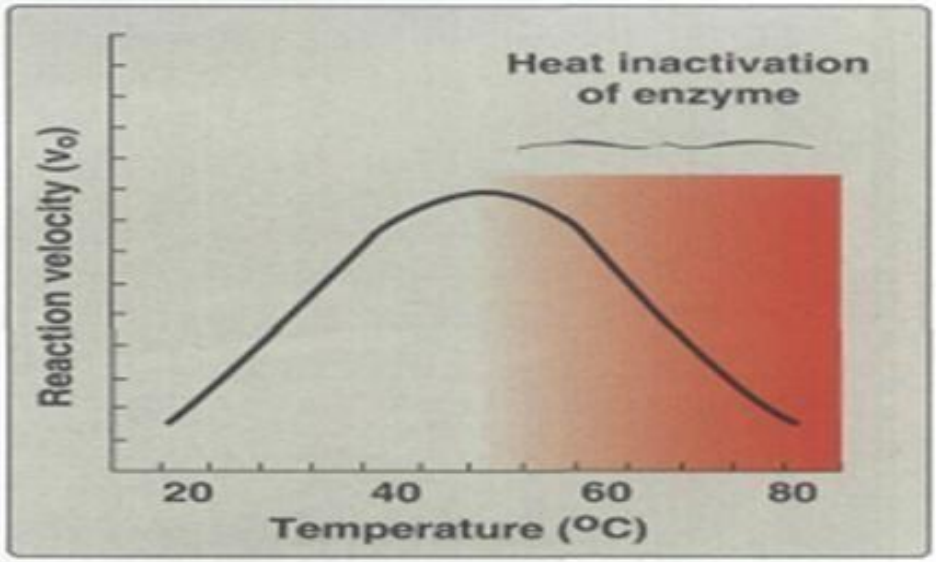


Figure 5.7
Effect of temperature on an enzyme-catalyzed reaction.

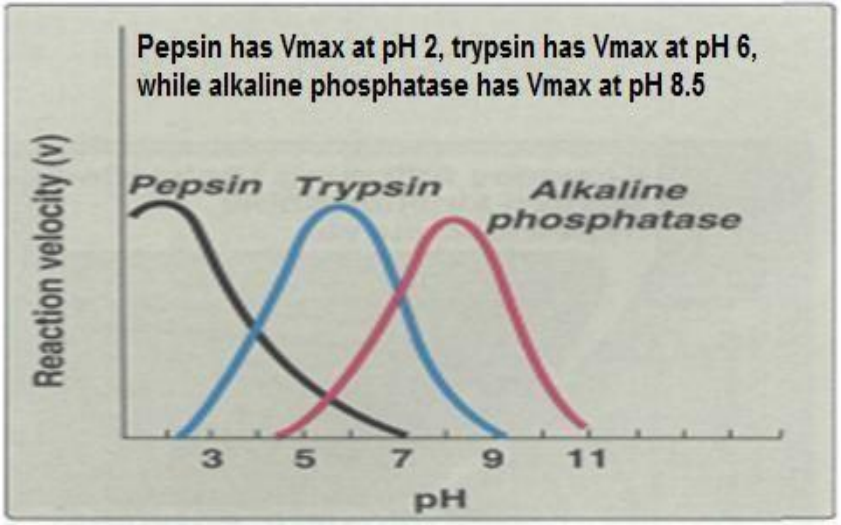


Figure 5.8
Effect of pH on enzyme-catalyzed reactions.

❑ Enzyme inhibition

- In a tissue and cell different chemical agents (**metabolites, substrate analogs, toxins, drugs, metal complexes** etc.) can inhibit the enzyme activity
- **There are two types of inhibitions:**

1/ Reversible inhibition: which includes :

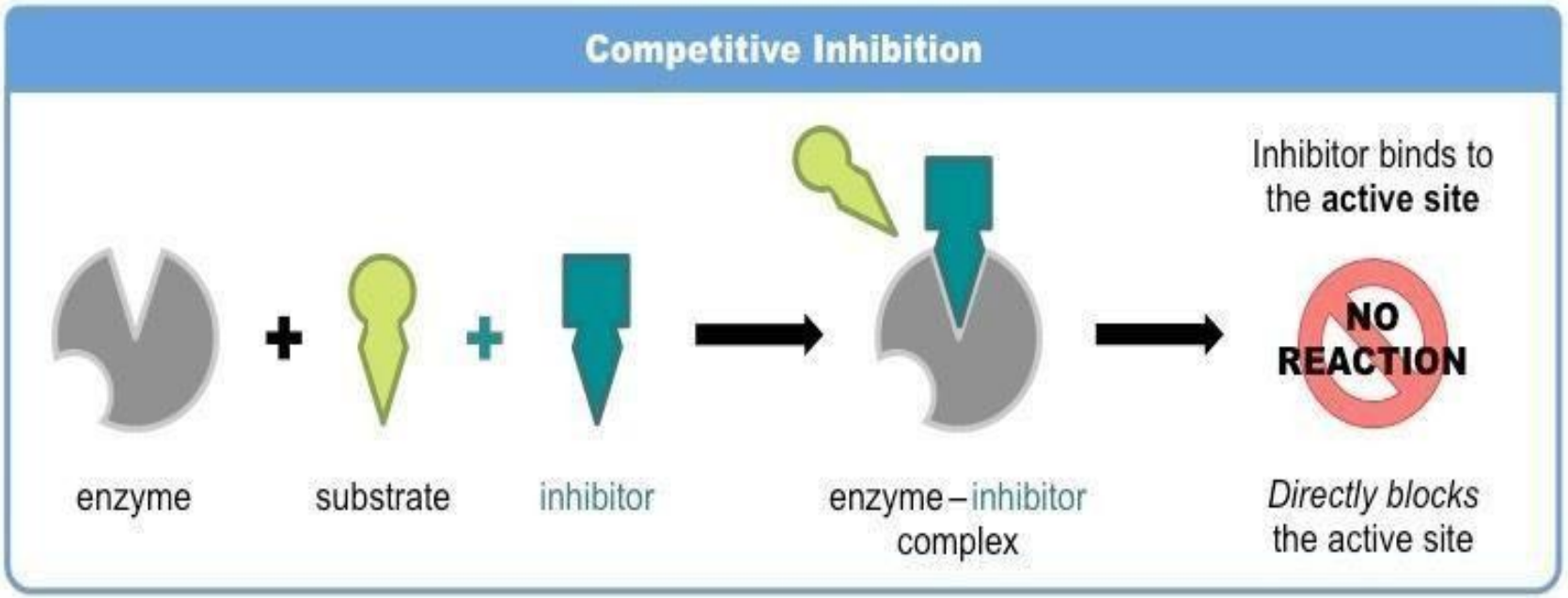
A/ Competitive inhibition: in competitive inhibition, the inhibitor and the substrate compete for the enzyme (they cannot bind at the same time) . Often competitive inhibitors strongly resemble the real substrate of the enzyme .

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.

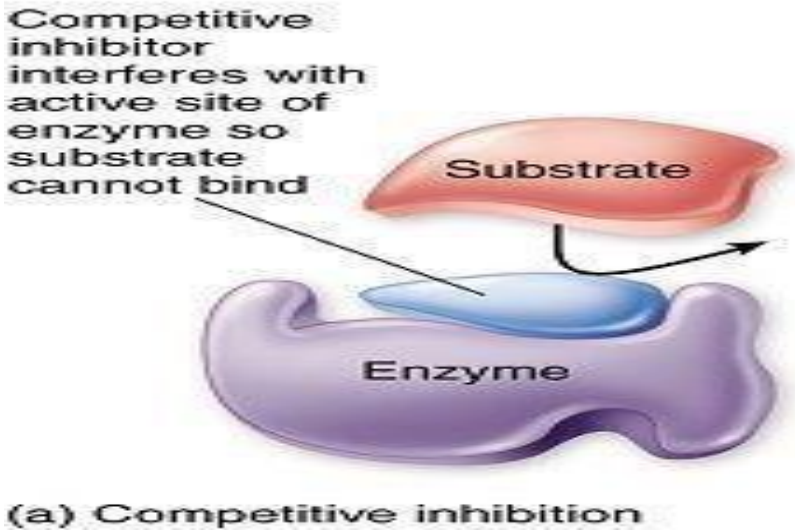
C/ noncompetitive inhibition : noncompetitive inhibitors can bind to the enzyme at the same time as the substrate . Both EI and EIS complexes are enzymatically inactive.

Reversible and irreversible inhibitors

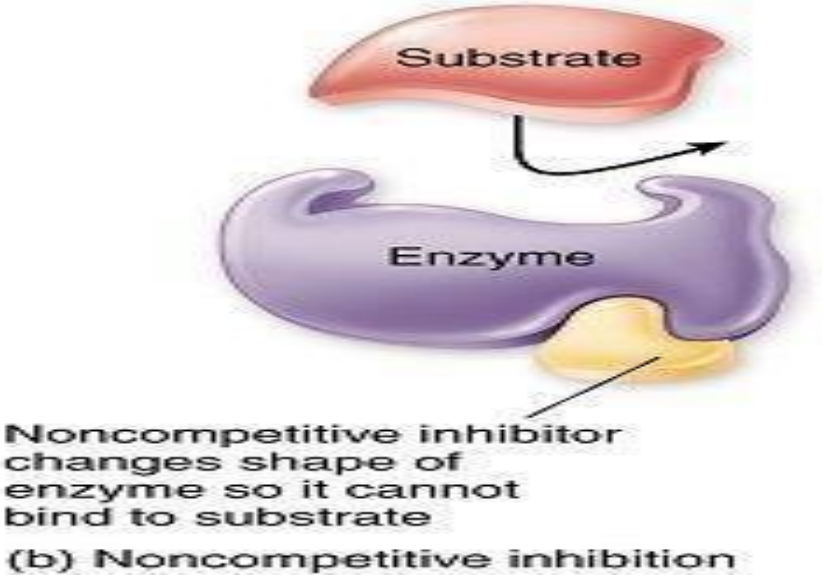
- **Reversible inhibitors**
- **Competitive inhibitors:** -Binds at the active site , Affects Km not Vmax Can be overcome by increasing the substrate concentration
- Enzyme is inactive only when bound to inhibitor



- ii) **Non-competitive inhibitors :** Binds at a site other than the active site
- Affects Vmax not Km
- Cannot be overcome by increasing the substrate concentration.



(a) Competitive inhibition

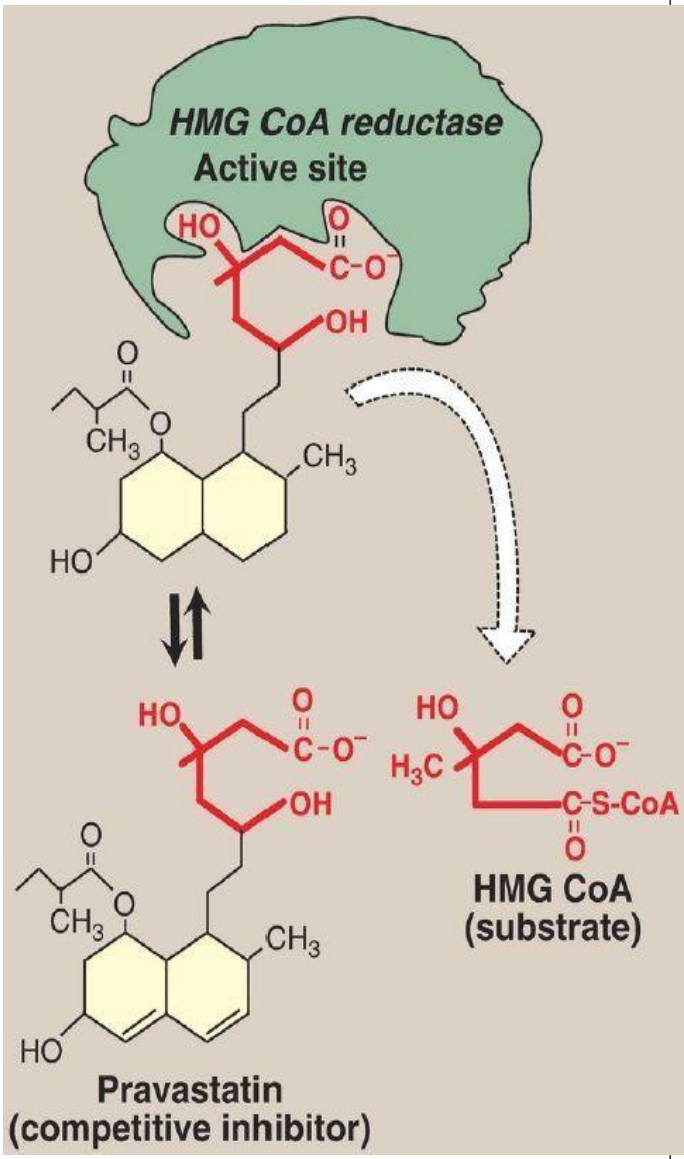


(b) Noncompetitive inhibition

Statin drugs as examples of competitive inhibitors

● **:** Antihyperlipidemic agents competitively inhibits the rate- limiting (slowest) step in cholesterol biosynthesis.

● Statins, such as atorvastatin (Lipitor) are structural analogs of the natural substrate for this enzyme :



Inhibition of enzymes

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 .

Enzyme inhibitors as drug

- **β-lactam** antibiotics, such as penicillin and amoxicillin, act by inhibiting •
- enzymes involved in bacterial cell wall synthesis
- **Angiotensin-converting enzyme** (ACE) inhibitors.
- They lower blood pressure. by blocking. the enzyme that cleaves angiotensin I to form the potent vasoconstrictor, angiotensinThese drugs, which include captopril
- **Aspirin,,**
- irreversibly inhibits for enzyme required for prostaglandin and thromboxane synthesis

A. Plasma Enzymes as diagnostic tools

- Diseases that cause tissue damage result in increased release of intracellular enzymes into the plasma.
- Determination of the level of these enzymes is used for diagnosis of heart, liver, skeletal muscle, etc.
- The level of these enzymes in plasma correlates with the extent of tissue damage.

Enzymes are helpful as diagnostic in different .

- diseases, namely:
- Myocardial infarction .
- Liver diseases.
- Muscle diseases.
- Bone diseases.
- Cancers .

Table 7–2. Principal Serum Enzymes Used in Clinical Diagnosis

	Serum Enzyme	Major Diagnostic Use
	Aminotransferases	
	Aspartate aminotransferase (AST, or SGOT)	Myocardial infarction, but also in Liver
*	Alanine aminotransferase (ALT, or SGPT)	Viral hepatitis
*	Amylase	Acute pancreatitis
	Ceruloplasmin	Hepatolenticular degeneration (Wilson's disease)
*	Creatine kinase	Muscle disorders and myocardial infarction
	γ-Glutamyl transferase	Various liver diseases
*	Lactate dehydrogenase isozyme 5	Liver diseases
*	Lipase	Acute pancreatitis
*	Phosphatase, acid	Metastatic carcinoma of the prostate
*	Phosphatase, alkaline (isozymes)	Various bone disorders, obstructive liver diseases

Note: Many of the above enzymes are not specific to the disease listed.

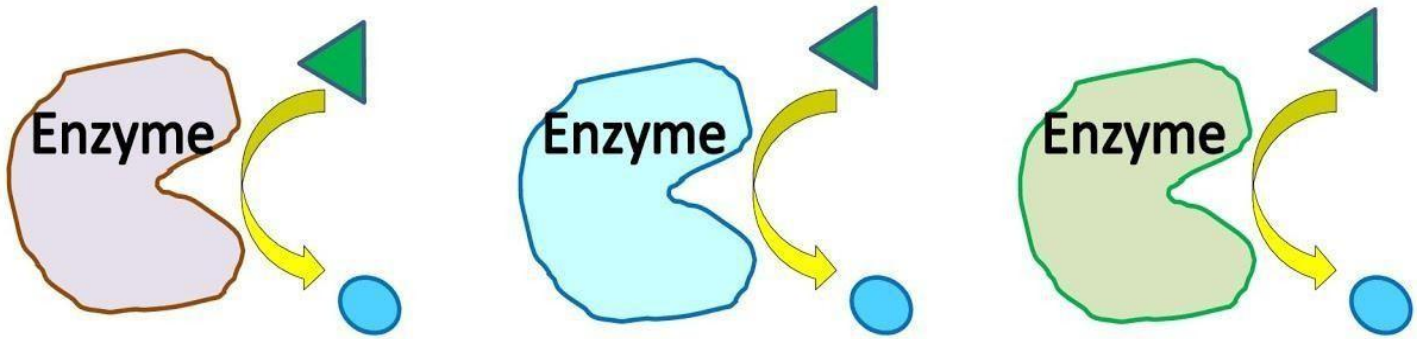
Know the enzymes marked by * and their principal use.

❑Isoenzymes

- Forms of the same enzyme
- Catalyse the same chemical reaction Different in terms of physical forms

Quickly understand

Isoenzymes



Isoenzymes and Diseases

- The pattern of isoenzymes found in the plasma may, therefore, serve as a means of identifying the site of tissue damage. For example, Increase in total LDH level is seen in hemolytic anemias, hepatocellular damage, muscular dystrophy, carcinomas, and leukemias.
- Since total LDH is increased in many conditions, the study of isoenzymes of LDH is of more significance.
- LDH enzyme is a tetramer with 4 subunits.
- But the subunit may be either **H (heart)** or **M (muscle)** polypeptide chains.
- Although both of them have the same molecular weight (32 kD), there are minor amino acid variations. So combinations of H and M chains are possible; H4, H3M, H2M2, M3H and M4, forming 5 iso- enzymes **(LDH1, LDH2, LDH3, LDH4, LDH5).**
- All these 5 forms are seen in all persons. M4 form is seen in skeletal muscles while H4 form is seen in heart.

- **Isoenzymes are multiple enzyme, isomers of enzyme. • There are five isoenzymes of LDH.**

- LDH-1 found in heart and in RBC as well as in brain.
- LDH-2 found in the reticuloendothelial system.
- LDH-3 found in the lungs.
- LDH-4 found in the kidneys,placenta and pancrease.
- LDH-5 found in the liver and striated muscle


THANK YOU
FOR YOUR
ATTENTION