Biological Chemistry Department

Biological Chemistry

Enzyme Classifications. Kinetics Mechanisms of action Specificity and Regulation

Speciality: Pharmacy for foreign students (Language of instructions – English)

Lecturer: ass. prof. Kravchenko G.B.

Lecture Plan

1. The Enzyme Structure.
2. The Enzyme Classification.
3. Mechanism of Enzyme Action.
4. Specificity of Enzymes.
5. Enzyme Kinetics.
6. Inhibition of Enzyme Activity.
7. Regulation of Enzyme Activity.

<u>Individual work</u>

1. Medical application.

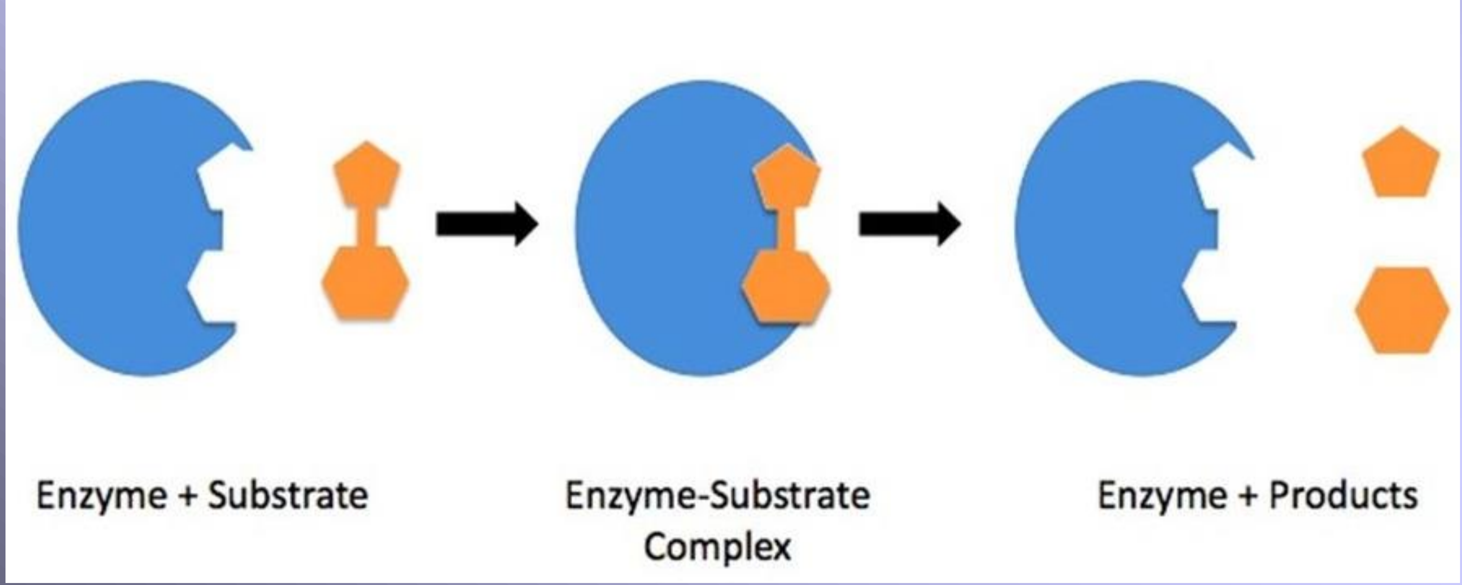
Information Resources

1. Biological Chemistry: Textbook / A.L. Zagayko, L.M. Voronina, G.B. Kravchenko, K.V. Strel`chenko. – Kharkiv: NUPh; Original, 2011. – 58-72 p.
2. Training Journal for Licensed Exam "KROK-1": Study Material in Biological Chemistry. – Kharkiv: NUPh, 2017. – 30-40 p.
3. Laboratory Manual on Biochemistry. Kharkiv: NUPh, 2017. - 36-42 p.
4. Nucleotide Metabolism: The Medical Biochemistry Page. Available on: https://themedicalbiochemistrypage.org/nucleotide-metabolism.php.
5. Enzyme Kinetics: The Medical Biochemistry Page. Available on: https://themedicalbiochemistrypage.org/enzyme-kinetics.php.

Enzymes are biological catalysts responsible for supporting almost all of the chemical reactions that maintain animal homeostasis. ***The main enzyme qualities are great effectiveness and specificity.***

The macromolecular components of almost all* enzymes are composed of protein*, except for a class of RNA known as ribozymes. Ribozymes are molecules of ribonucleic acid that catalyze reactions on the phosphodiester bond of other RNAs.

$$A + B \xrightarrow{E} AB$$



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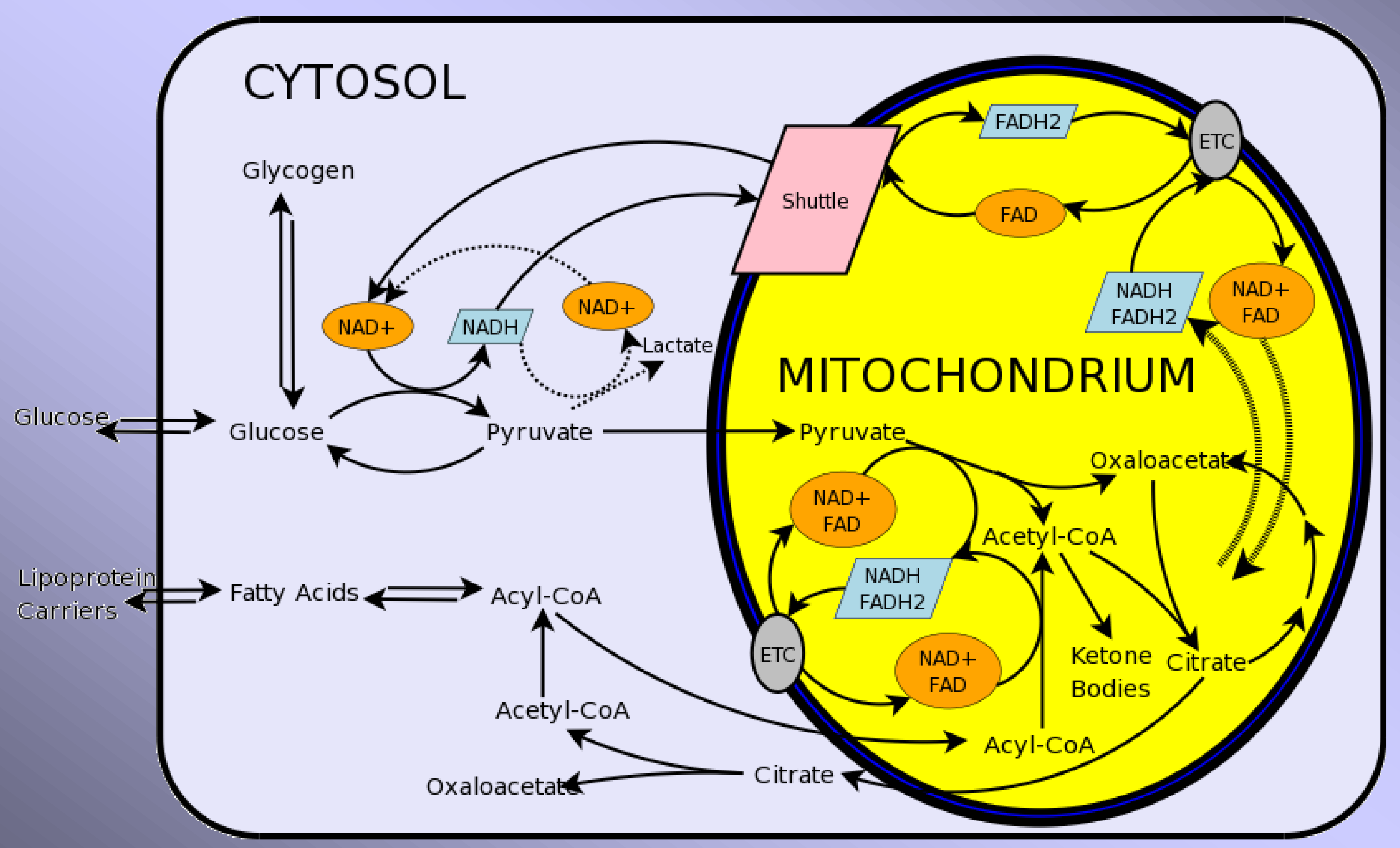
Almost every significant life process is dependent on enzyme activity. Enzymes are found in all tissues and fluids of the body. Intracellular enzymes catalyze the reactions of metabolic pathways.



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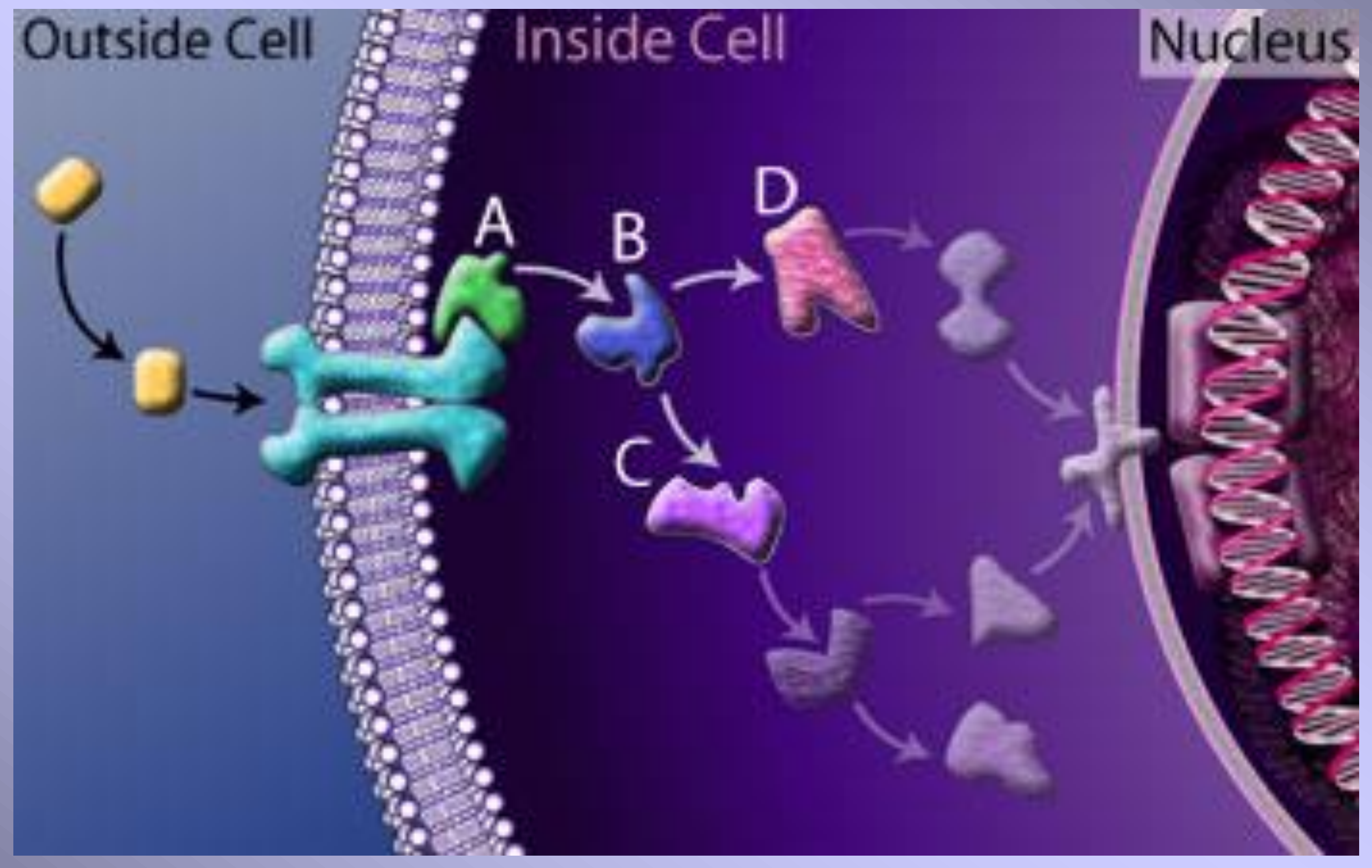
Plasma membrane enzymes regulate catalysis within cells in response to extracellular signals.



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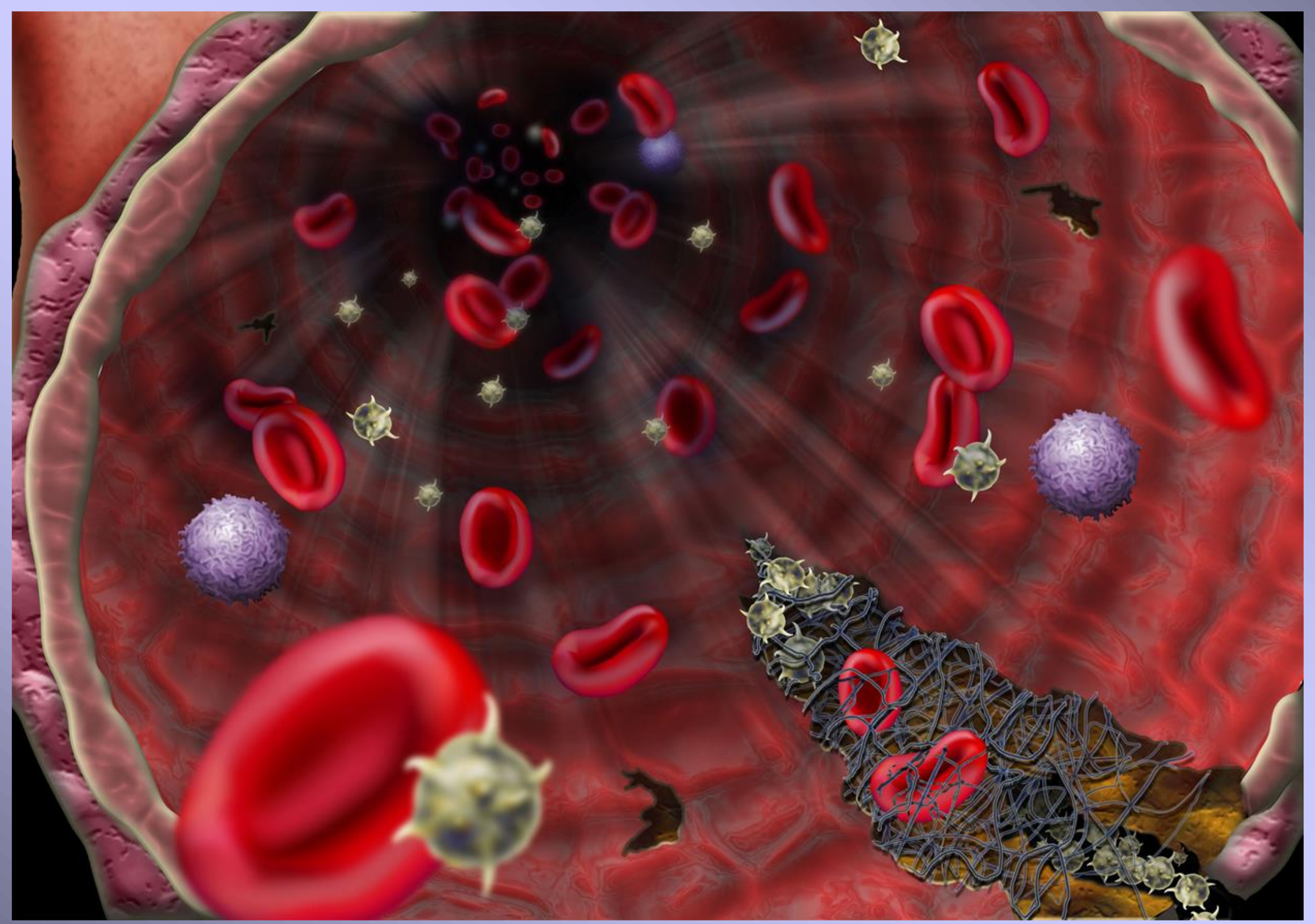
Enzymes of the circulatory system are responsible for some process regulating for example the blood clotting.



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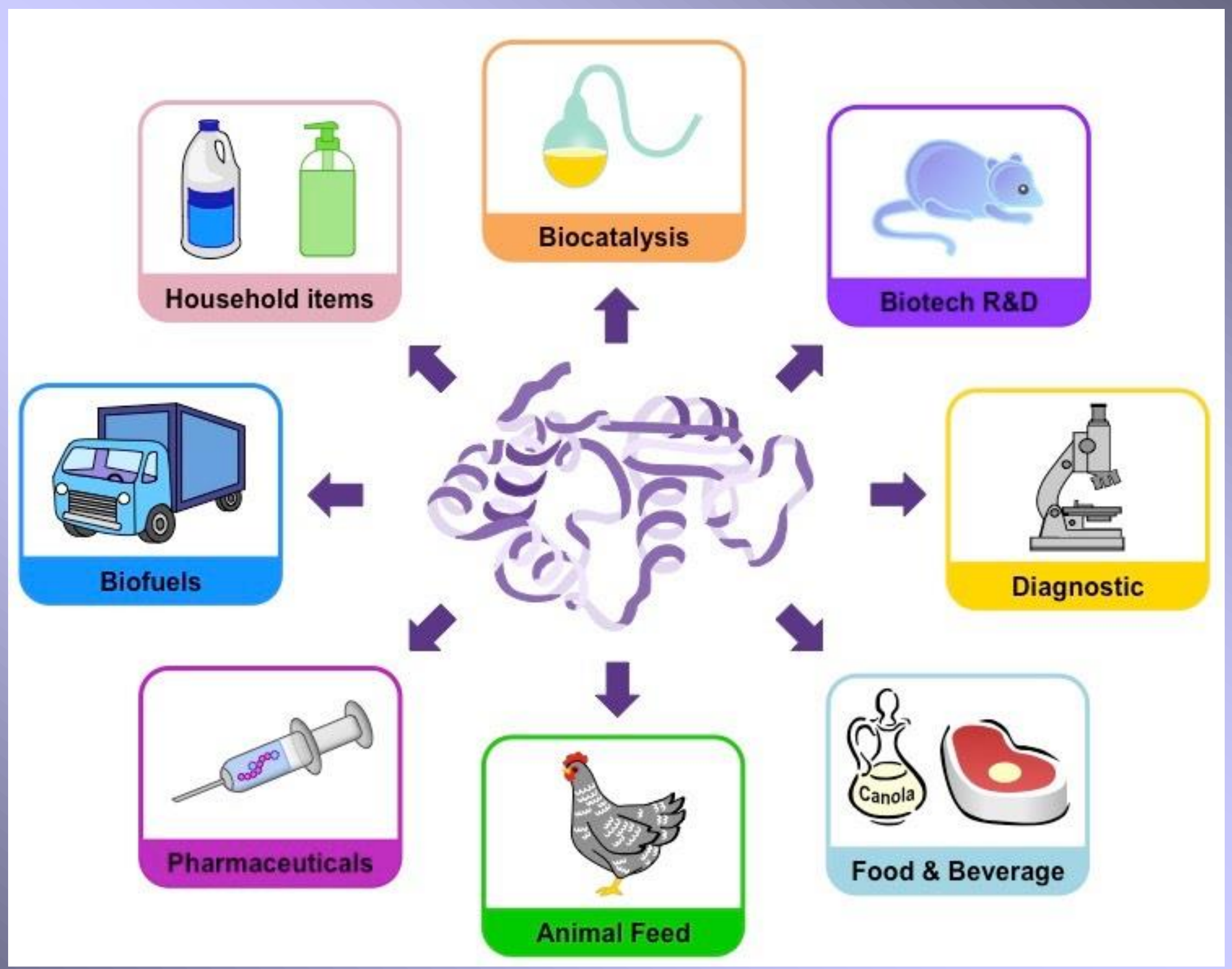

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The study of enzymes also has immense practical importance.

- ***In some diseases, especially inheritable genetic disorders, there may be a deficiency or even a total absence of one or more enzymes in the tissues.***
- ***Abnormal conditions can also be caused by the excessive activity of a specific enzyme.***
- ***Measurements of the activity of certain enzymes in the blood plasma, erythrocytes, or tissue samples are important in diagnosing disease.***

- ***Enzymes have become important practical tools, not only in medicine but also in the chemical industry, in food processing, and in agriculture.***
- ***Enzymes play a part even in everyday activities in the home such as food preparation and cleaning.***

Dairy production	Brewing	Baking	Wine and fruit juice	Meat
Rennet Lactase Protease Catalases	β-Glucanase α-Amylase Protease Amylogluco-sidase	Maltogenic amylase Glucose oxidase Pentosenase	Pectinase β-Glucanase	Protease Papain

https://image.slidesharecdn.com/enzymesinfood-161004152659/95/application-of-enzymes-in-food-industry-7-638.jpg?cb=1504358863

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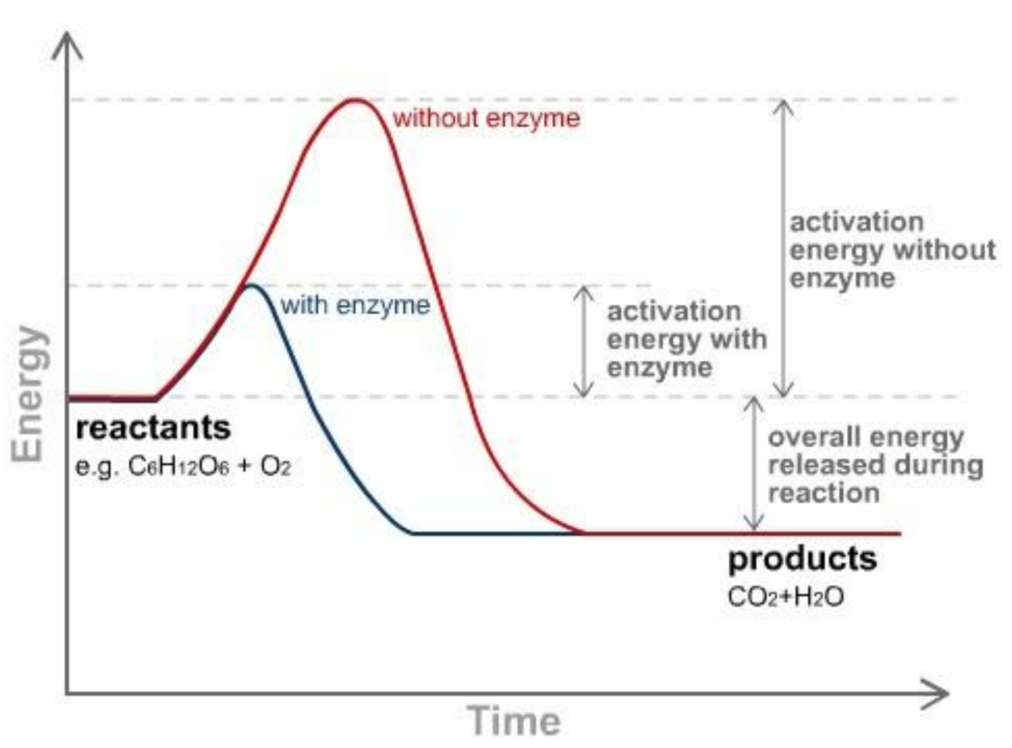
Catalyst - a substance that increases the rate of a chemical reaction by reducing the activation energy, but which is left unchanged by the reaction.

For two molecules to react they must collide with one another. They must collide in the right direction (orientation) and with sufficient energy. Sufficient energy means that between them they have enough energy to overcome the energy barrier to reaction. This is called the activation energy.

The activation energy is the minimum amount of energy required to initiate a reaction.



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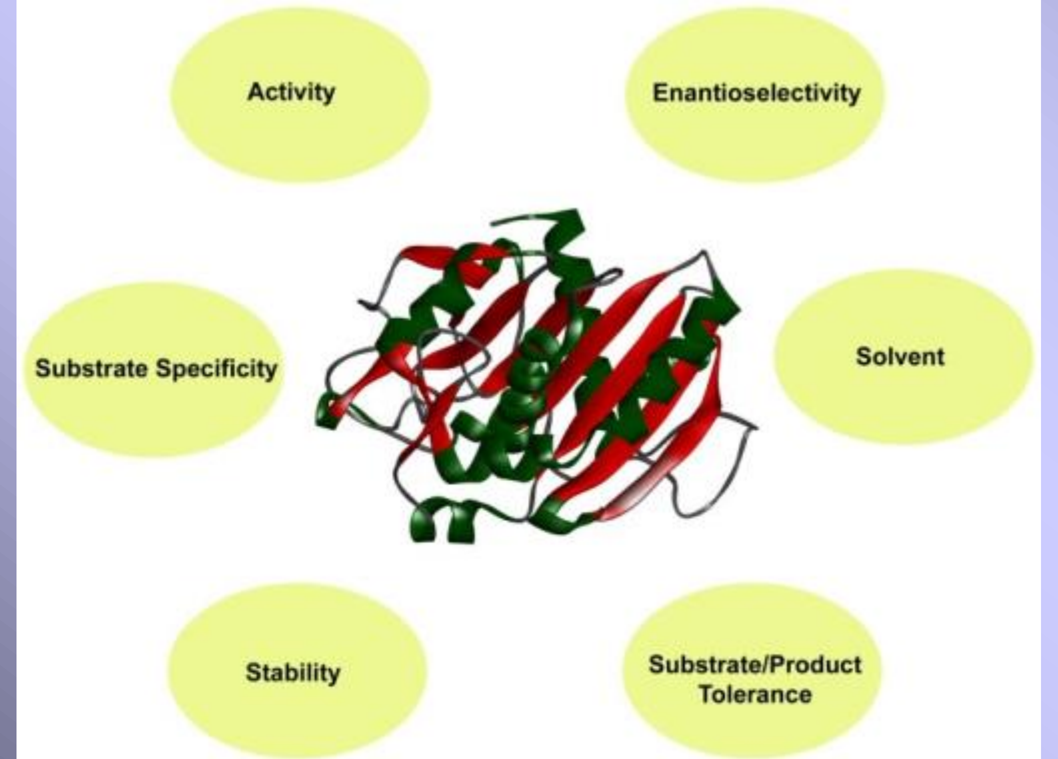
xq2c3J_P_HzXTFZeotRehVfneil0yIW5QRq7VqA=s109

- ✓*Enzymes have extraordinary catalytic power, often far greater than that of synthetic catalysts.*
- ✓*They have a high degree of specificity for their substrates;*
- ✓*they accelerate specific chemical reactions;*
- ✓*they function in aqueous solutions under very mild conditions of temperature and pH.*
- ✓*Few nonbiological catalysts show all these properties.*



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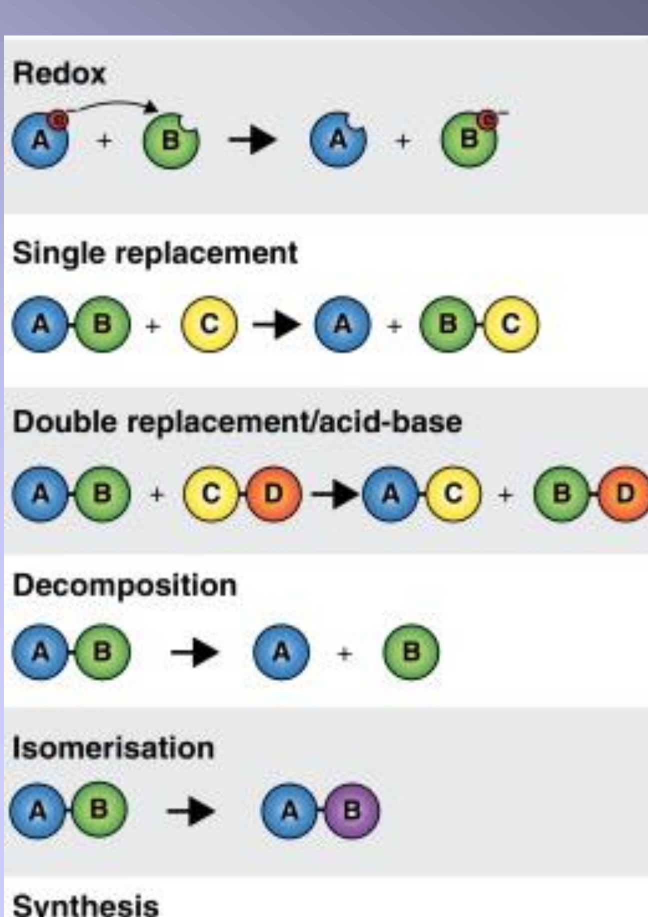
ENZYME CLASSIFICATION

Except for some of the originally studied enzymes such as pepsin, rennin, and trypsin, most enzyme names end in "ase". The International Union of Biochemistry (I.U.B.) initiated standards of enzyme nomenclature which recommend that enzyme names indicate both the substrate acted upon and the type of reaction catalyzed.

https://iubmb.org/

Enzymes can be classified by the kind of chemical reaction catalyzed.

- ✓***Addition or removal of water:*** *hydrolases - these include esterases, carbohydrases, nucleases, deaminases, amidases, and proteases*
- ✓***Transfer of electrons:*** *oxidases and dehydrogenases.*
- ***Transfer of a radical:*** *transglycosidases (monosaccharides), transphosphorylases and phosphomutases (a phosphate group), transaminases (amino group), transmethylases (a methyl group), transacetylases (an acetyl group).*
- ✓***Splitting or forming a C-C bond:*** *desmolases.*
- ✓***Changing geometry or structure of a molecule:*** *isomerases.*
- ✓***Joining two molecules through hydrolysis of pyrophosphate bond in ATP or other tri-phosphate:*** *ligases.*



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International Union of Biochemistry

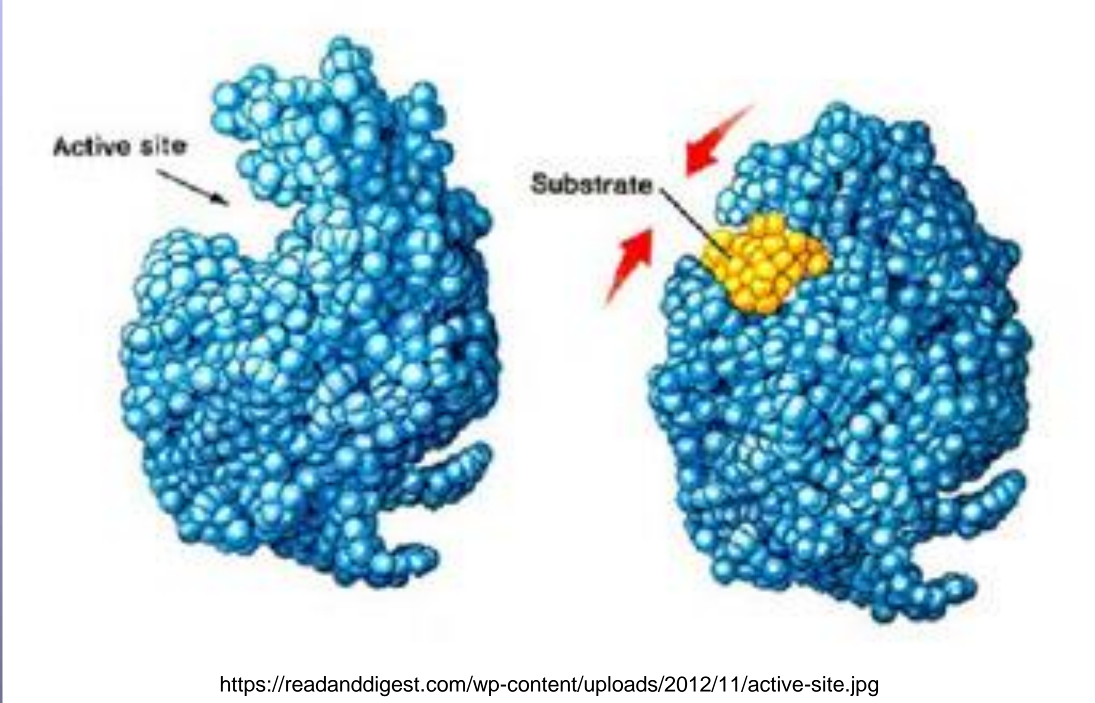
According to this classification all enzymes have a unique number which contains from four numbers. The first of them is the class number.

Class	Reaction type	Important subclasses
1 Oxidoreductases	○ = Reduction equivalent A_{red} + B_{ox} ⇌ A_{ox} + B_{red}	Dehydrogenases Oxidases, peroxidases Reductases Monooxygenases Dioxygenases
2 Transferases	A–B + C ⇌ A + B–C	C_1-Transferases Glycosyltransferases Aminotransferases Phosphotransferases
3 Hydrolases	A–B + H_2O ⇌ A–H + B–OH	Esterases Glycosidases Peptidases Amidases
4 Lyases ("synthases")	A + B ⇌ A–B	C-C-Lyases C-O-Lyases C-N-Lyases C-S-Lyases
5 Isomerases	A ⇌ Iso-A	Epimerases *cis trans* Isomerases Intramolecular transferases
6 Ligases ("synthetases")	B A + XTP (X=A,G,U,C) ⇌ A–B + XDP + P	C-C-Ligases C-O-Ligases C-N-Ligases C-S-Ligases

http://www.namrata.co/wp-content/uploads/2012/05/a.bmp

ENZYME STRUCTURE

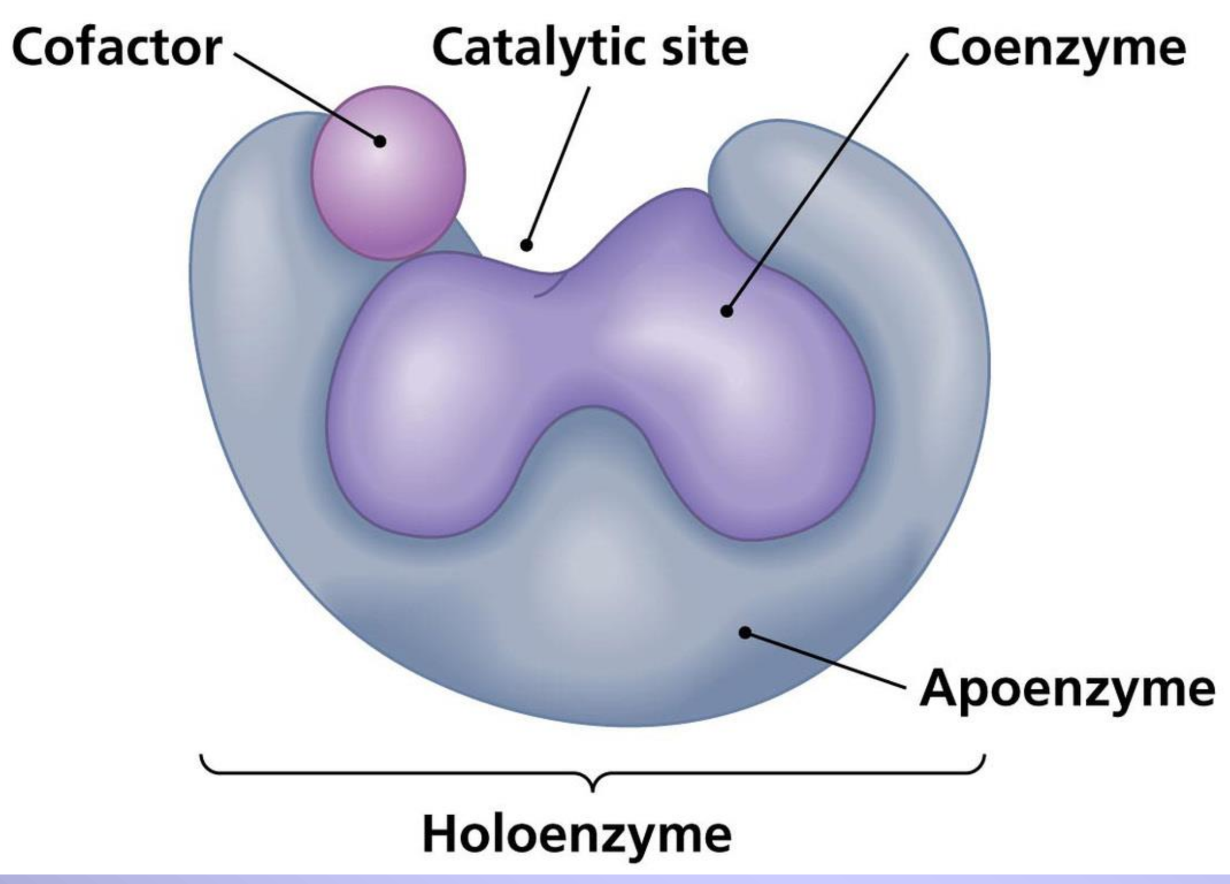
With the exception of a small group of catalytic RNA molecules, all enzymes are proteins. Their catalytic activity depends upon the integrity of their native protein conformation. If an enzyme is denatured or dissociated into subunits, catalytic activity is usually lost. If an enzyme is broken down into its component amino acids, its catalytic activity is always destroyed. Thus the primary, secondary, tertiary, and quaternary structures of protein enzymes are essential to their catalytic activity.



https://readanddigest.com/wp-content/uploads/2012/11/active-site.jpg

Non protein groups can be metal ions or a complex organic or metalloorganic molecule called a coenzyme (if they are bound with protein non covalently) or a prosthetic group (if they are bound covalently).

A complete, catalytically active enzyme together with its non-protein group is called a holoenzyme. The protein part of such an enzyme is called the apoenzyme or apoprotein and it is catalyticaly inactive.



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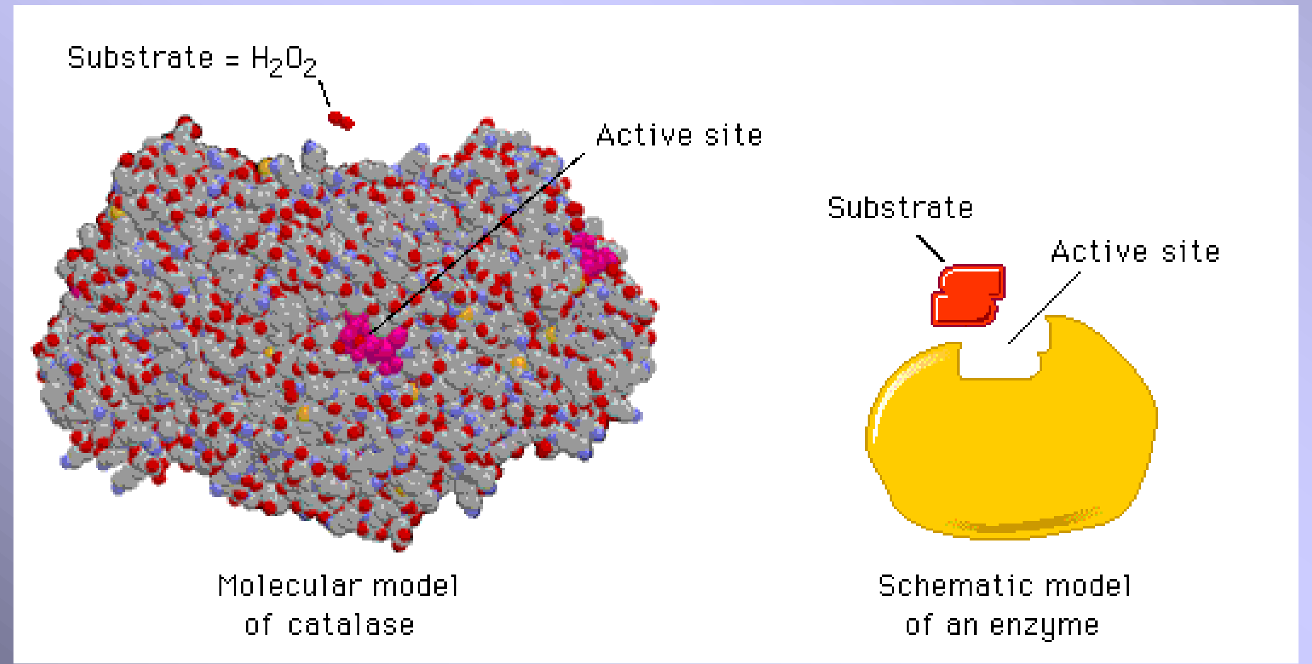
Usually the coenzymes function as transient carriers of specific functional groups. The non-protein group can also take part in substrate binding, enzyme activity regulation or stabilisation.

Some Metal Ions and Coenzymes and the Enzymes with Which They Are Associated

Metal Ion	Enzyme	Coenzyme	Enzyme
Fe^{2+} or Fe^{3+}	Cytochrome oxidase Catalase Peroxidase	Thiamine pyrophosphate (TPP)	Pyruvate dehydrogenase Succinate dehydrogenase Alcohol dehydrogenase
Cu^{2+}	Cytochrome oxidase	Flavin adenine dinucleotide (FAD)	Pyruvate dehydrogenase Succinate dehydrogenase Alcohol dehydrogenase
Zn^{2+}	DNA polymerase Carbonic anhydrase Alcohol dehydrogenase	Nicotinamide adenine dinucleotide (NAD)	Pyruvate dehydrogenase Succinate dehydrogenase Alcohol dehydrogenase
Mg^{2+}	Hexokinase Glucose-6-phosphatase	Coenzyme A (CoA)	Acetyl-CoA carboxylase

Active Site

The active site is a part of enzyme molecule where substrate binding and enzymatic reaction take place. Active site comprises only a small portion of the overall enzyme structure. The active site is part of the conformation of the enzyme molecule arranged to create a special pocket or cleft whose three-dimensional structure is complementary to the structure of the substrate.



Molecular model of catalase

Schematic model of an enzyme

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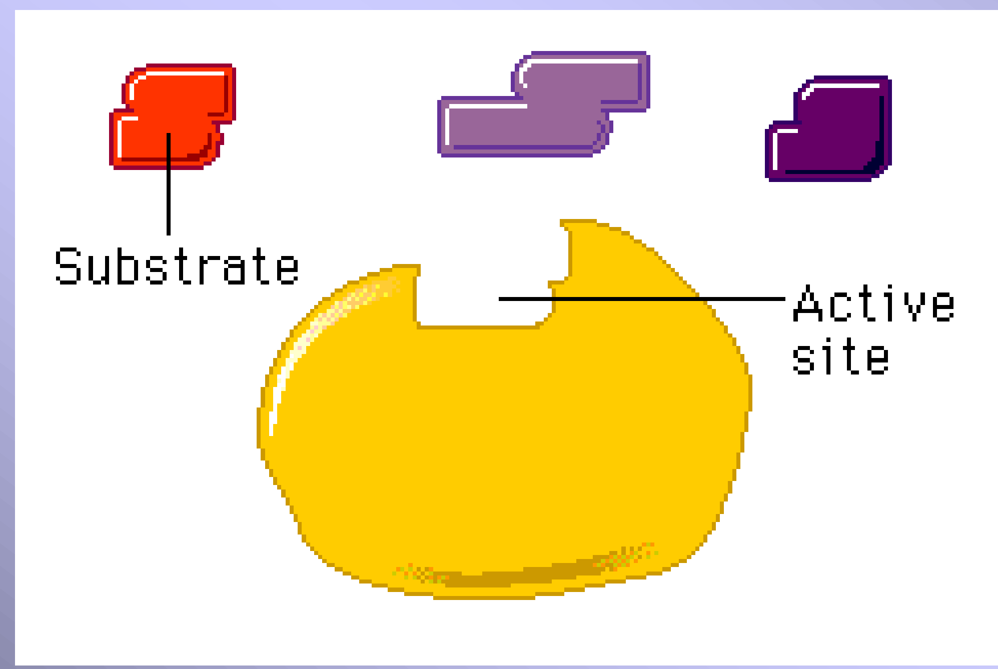
*The enzyme and the substrate molecules "recognize" each other through this **structural complementarity**. The substrate binds to the enzyme through relatively weak forces — H bonds, ionic bonds (salt bridges), and van der Waals interactions between sterically complementary clusters of atoms.*



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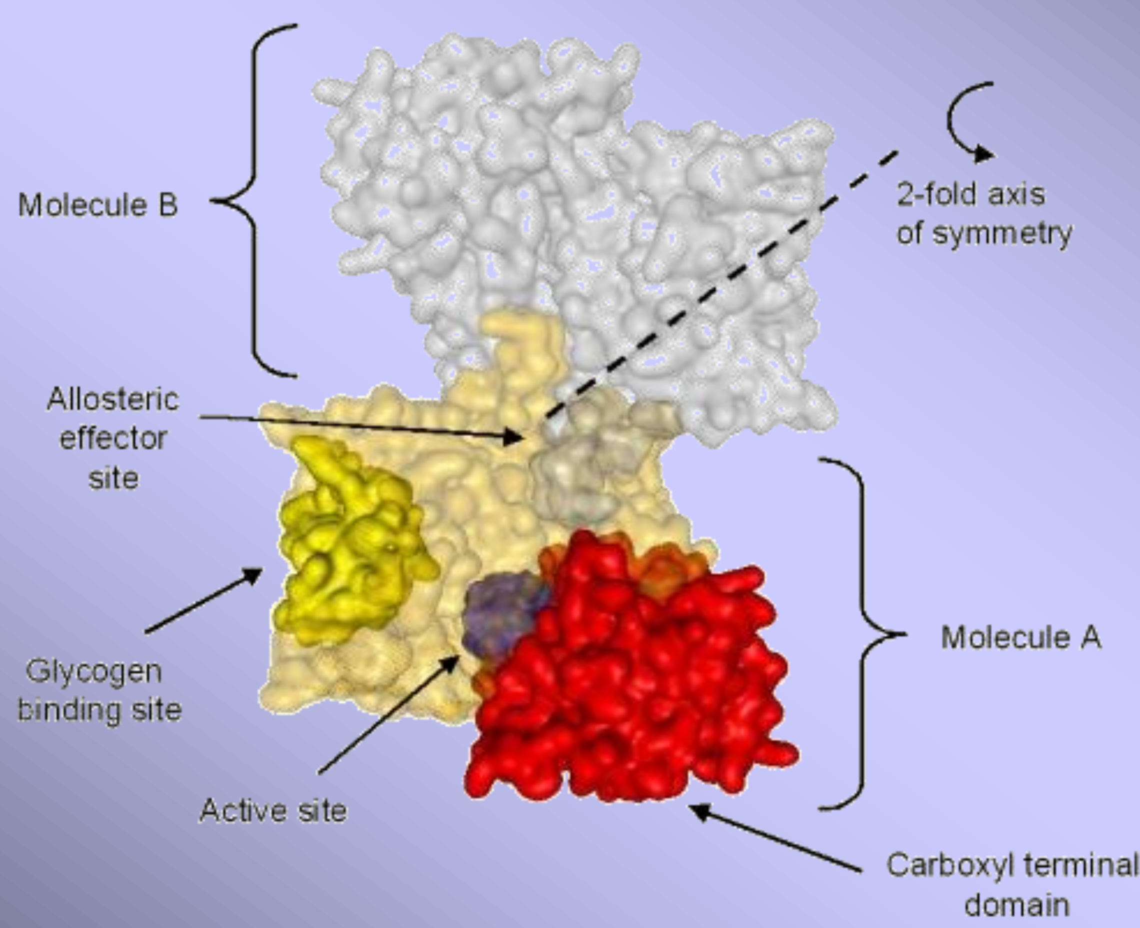
Some enzymes have an additional site - allosteric site which is separated from active site and is important for their regulation. This site interacts with special molecules, they are called the effectors, which can change the enzyme activity.



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MECHANISM OF ENZYME ACTION

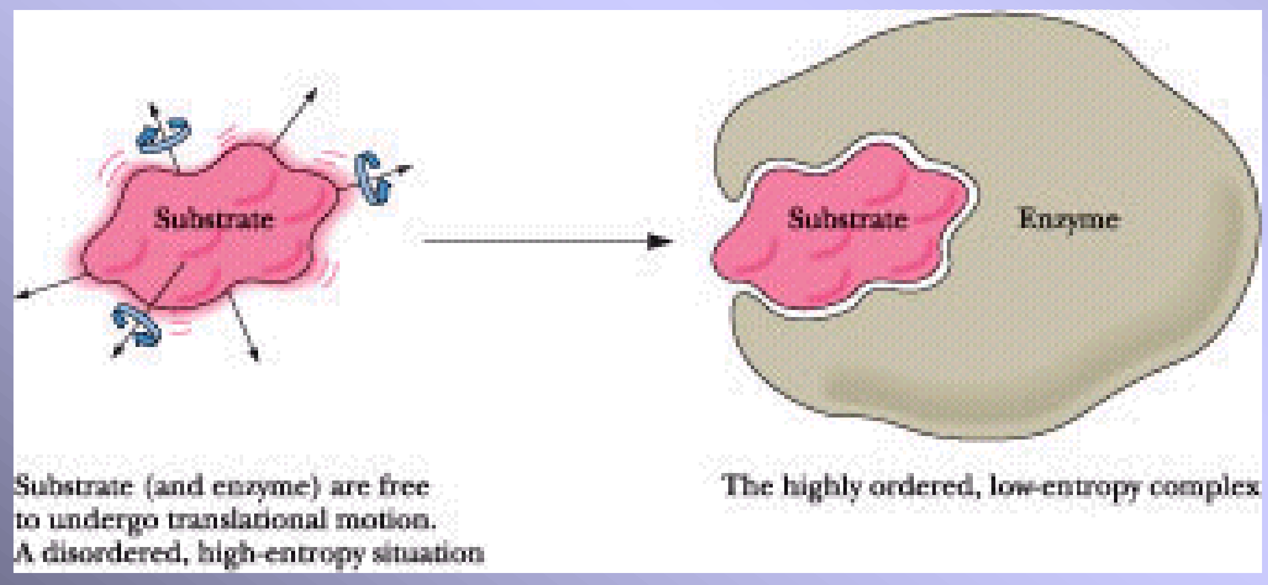
A simple enzymatic reaction might be written:

$$E + S \rightarrow ES$$

$$ES \rightarrow EP$$

$$EP \rightarrow E + P$$

where E, S, and P represent the enzyme, substrate, and product, respectively. ES and EP are complexes of the enzyme with the substrate and with the product, respectively



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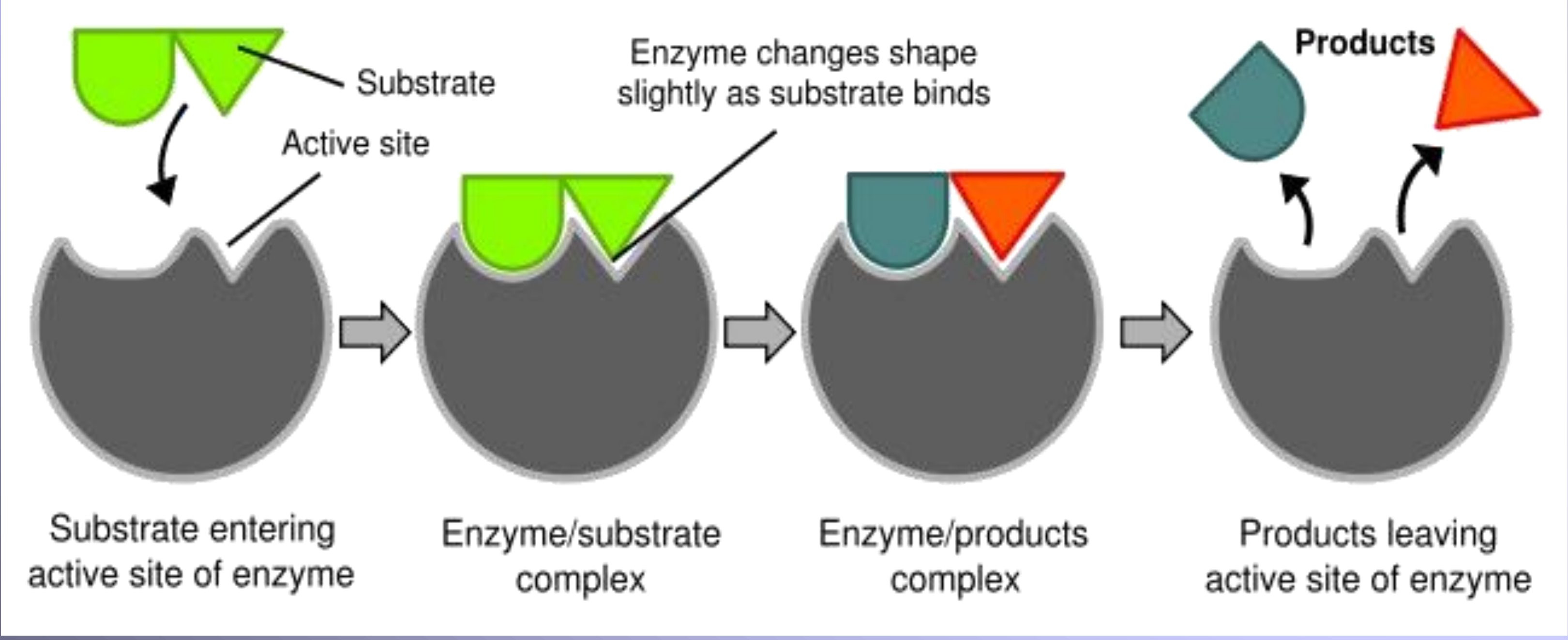
The stages of enzyme action

Mechanism for a single substrate enzyme catalyzed reaction. The enzyme (E) binds a substrate (S) and produces a product (P).

Catalytic step

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

Substrate binding



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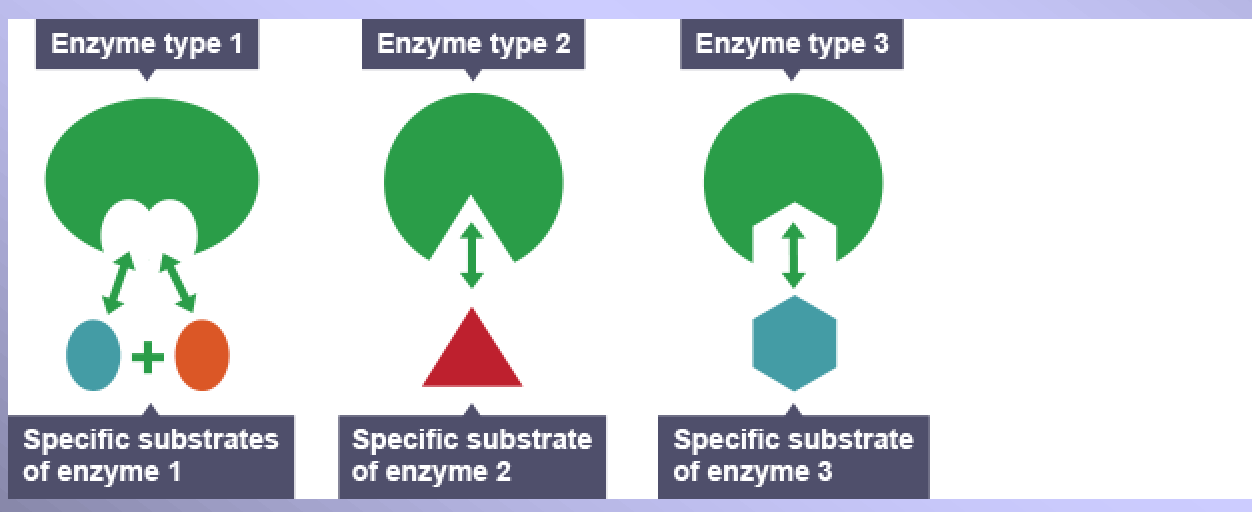
ENZYME SPECIFICITY

The extraordinary ability of an enzyme to catalyze only one particular reaction is a quality known as specificity. Specificity means an enzyme acts only on a specific substance, its substrate, invariably transforming it into a specific product. That is, an enzyme binds only certain compounds, and then, only a specific reaction ensues. Some enzymes show absolute specificity, catalyzing the transformation of only one specific substrate to yield a unique product. Other enzymes carry out a particular reaction but act on a class of compounds. For example, hexokinase (ATP : hexose-6-phosphotransferase) will carry out the ATP-dependent phosphorylation of a number of hexoses at the 6-position, including glucose.



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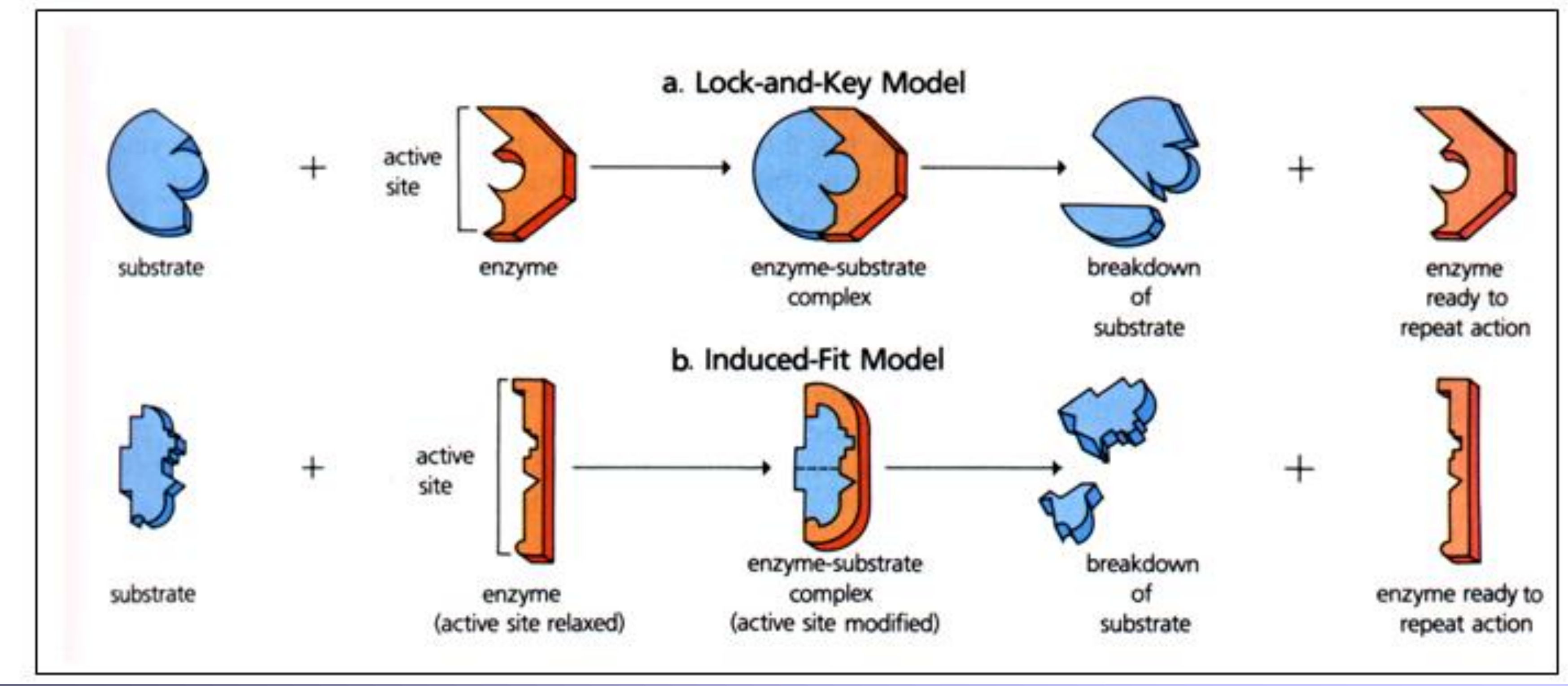
Specificity is the result of molecular recognition.

There were some hypothesis explaining the enzyme specificity.

The "Lock and Key" Hypothesis

Pioneering enzyme specificity studies at the turn of the century by the great organic chemist Emil Fischer led to the notion of an enzyme resembling a "lock" and its particular substrate the "key." This analogy captures the essence of the specificity that exists between an enzyme and its substrate, but enzymes are not rigid templates like locks.



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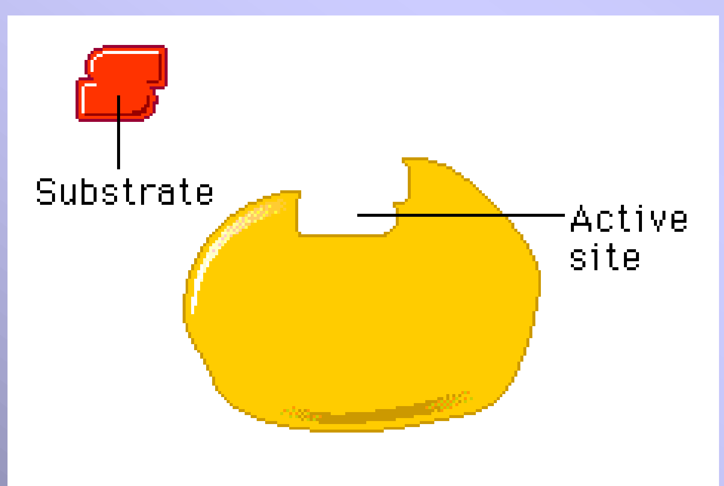
The "Induced Fit" Hypothesis

Enzymes are highly flexible, conformationally dynamic molecules, and many of their remarkable properties, including substrate binding and catalysis, are due to their structural pliancy. Realization of the conformational flexibility of proteins led Daniel Koshland to hypothesize that the binding of a substrate (S) by an enzyme is an interactive process. That is, the shape of the enzyme's active site is actually modified upon binding S, in a process of dynamic recognition between enzyme and substrate aptly called induced fit.

This idea also helps to explain some of the mystery surrounding the enormous catalytic power of enzymes: In enzyme catalysis, precise orientation of catalytic residues comprising the active site is necessary for the reaction to occur; substrate binding induces this precise orientation by the changes it causes in the protein's conformation.



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Types of Specificity

A few enzymes exhibit absolute specificity; that is, they will catalyze only one particular reaction. Other enzymes will be specific for a particular type of chemical bond or functional group. In general, there are four distinct types of specificity:

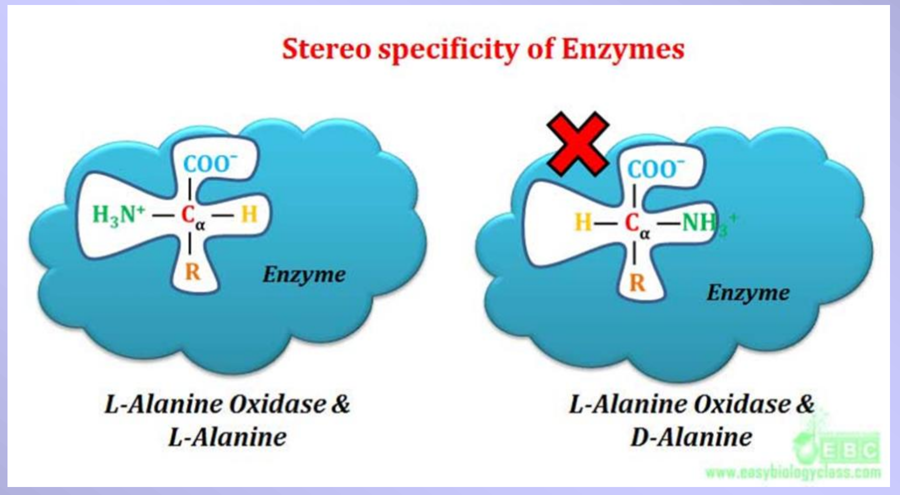
Absolute specificity - the enzyme will catalyze only one reaction.

Group specificity - the enzyme will act only on molecules that have specific functional groups, such as amino, phosphate and methyl groups.

Linkage specificity - the enzyme will act on a particular type of chemical bond regardless of the rest of the molecular structure.

Stereochemical specificity - the enzyme will act on a particular steric or optical isomer.

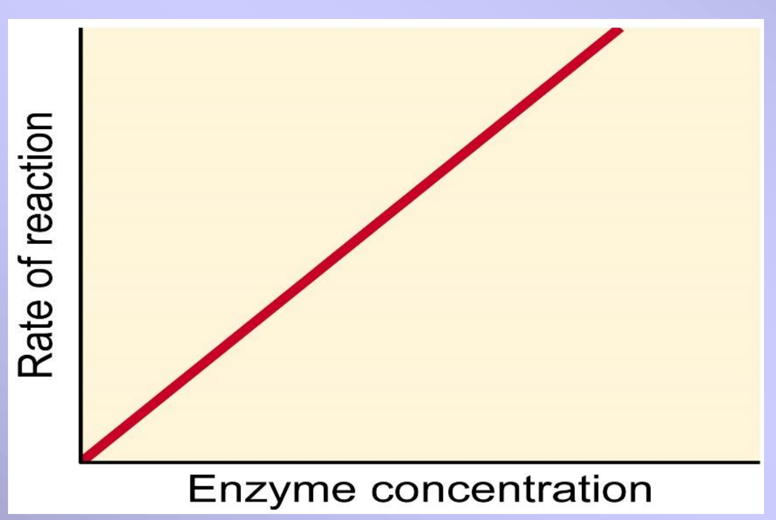
Though enzymes exhibit great degrees of specificity, cofactors may serve many apoenzymes. For example, nicotinamide adenine dinucleotide (NAD) is a coenzyme for a great number of dehydrogenase reactions in which it acts as a hydrogen acceptor. Among them are the alcohol dehydrogenase, malate dehydrogenase and lactate dehydrogenase reactions.

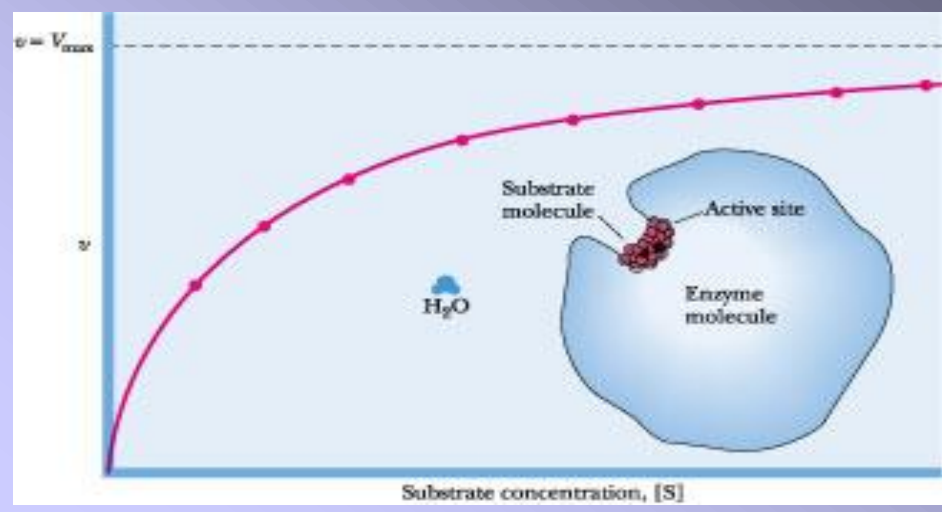


http://www.easybiologyclass.com/wp-content/uploads/2015/05/Enzyme-specificity-stereo-specificity-l-d-alanine-oxidase-easybiologyclass.jpg

Factors affecting catalytic activity of enzymes

- *Concentration of enzyme and substrate*





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

For a given enzyme concentration, 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 enzyme molecules at any given moment are virtually saturated with substrate. The enzyme/substrate complex has to dissociate before the active sites are free to accommodate more substrate.

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•pH *An enzyme possesses an array of ionizable side chains and prosthetic groups that not only determine its secondary and tertiary structure but may also be intimately involved in its active site. Further, the substrate itself often has ionizing groups, and one or another of the ionic forms may preferentially interact with the enzyme. Enzymes in general are active only over a limited pH range and most have a particular pH at which their catalytic activity is optimal.*

Optimum pH of Some Enzymes

Enzyme	Optimum pH
Pepsin	1.5
Catalase	7.6
Trypsin	7.7
Fumarase	7.8
Ribonuclease	7.8
Arginase	9.7

The pH activity profiles of four different enzymes. Trypsin, an intestinal protease, has a slightly alkaline pH optimum, whereas pepsin, a gastric protease, acts in the acidic confines of the stomach and has a pH optimum near 2. Papain, a protease found in papaya, is relatively insensitive to pHs between 4 and 8. Cholinesterase activity is pH-sensitive below pH 7 but not between pH 7 and 10. The cholinesterase pH activity profile suggests that an ionizable group with a pK' near 6 is essential to its activity. Might it be a histidine residue within the active site?

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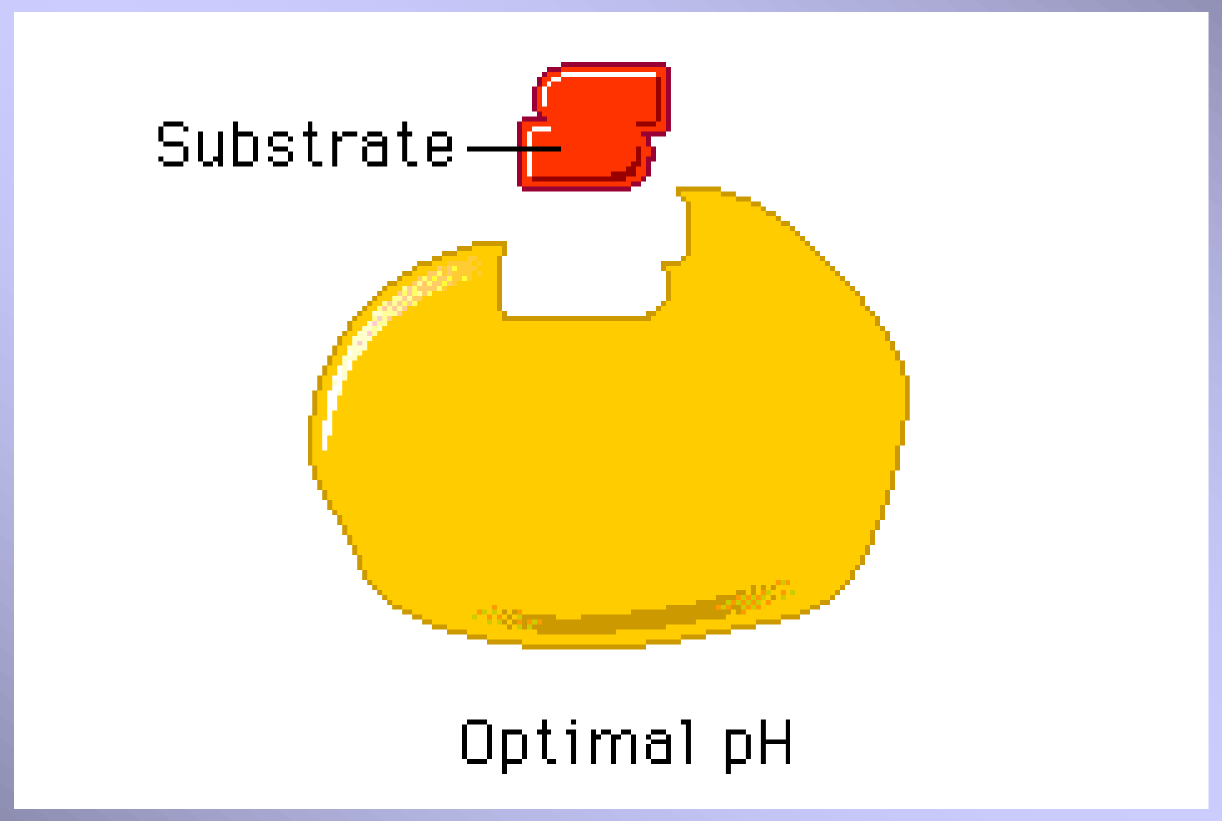
The Effect of pH on Enzyme Activity



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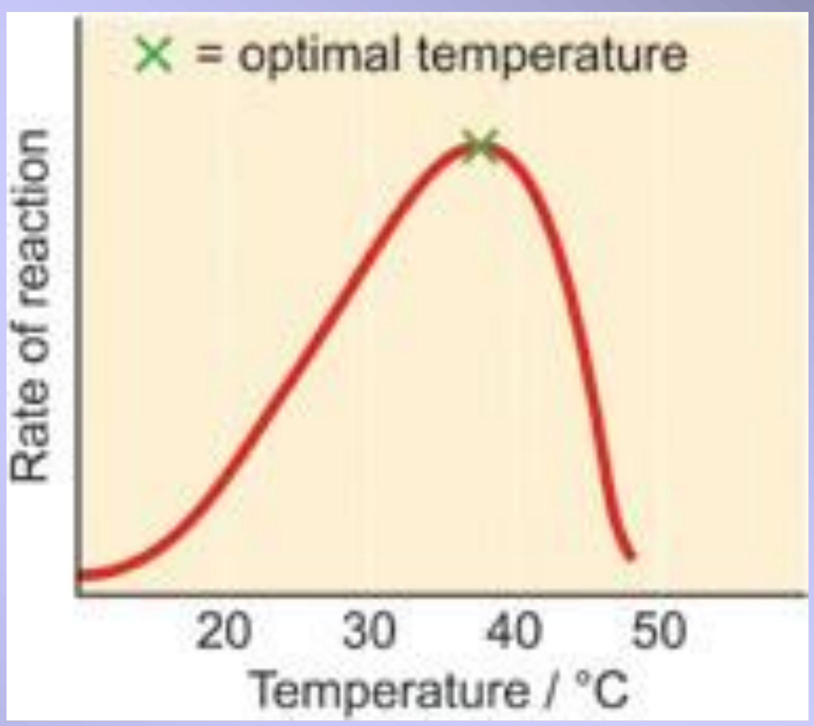
•Temperature



Like most chemical reactions, the rates of enzyme-catalyzed reactions generally increase with increasing temperature. However, at temperatures above 50° to 60°C, enzymes typically show a decline in activity. Two effects are operating here: (a) the characteristic increase in reaction rate with temperature, and (b) thermal denaturation of protein structure at higher temperatures.

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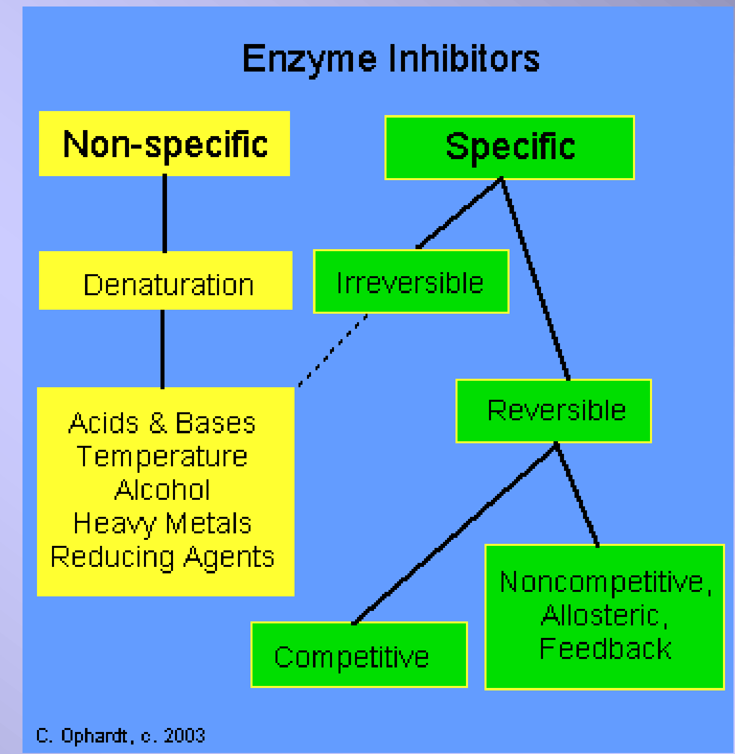
ENZYME INHIBITION

If the velocity of an enzymatic reaction is decreased or inhibited, the kinetics of the reaction obviously have been perturbed. Systematic perturbations are a basic tool of experimental scientists; much can be learned about the normal workings of any system by inducing changes in it and then observing the effects of the change. The study of enzyme inhibition has contributed significantly to our understanding of enzymes.

Reversible Versus Irreversible Inhibition

Enzyme inhibitors are classified in several ways. The inhibitor may interact either reversibly or irreversibly with the enzyme. Reversible inhibitors interact with the enzyme through noncovalent association/dissociation reactions. In contrast, irreversible inhibitors usually cause stable, covalent alterations in the enzyme. That is, the consequence of irreversible inhibition is a decrease in the concentration of active enzyme.



http://chemistry.elmhurst.edu/vchembook/images/573inhibitors.gif

Irreversible Inhibition

If the inhibitor combines irreversibly with the enzyme—for example, by covalent attachment—the kinetic pattern seen is like that of noncompetitive inhibition, because the net effect is a loss of active enzyme.

Irreversible inhibitors are those that combine with or destroy a functional group on the enzyme that is essential for its activity. Formation of a covalent link between an irreversible inhibitor and an enzyme is common. Irreversible inhibitors are very useful in studying reaction mechanisms. Amino acids with key catalytic functions in the active site can sometimes be identified by determining which amino acid is covalently linked to an inhibitor after the enzyme is inactivated.

$$\underset{(Ser^{195})}{Enz{-}CH_2{-}OH} + \underset{\text{DIFP}}{F{-}\overset{\overset{O}{\|}}{P}(O{-}CH(CH_3)_2){-}O{-}CH(CH_3)_2} \xrightarrow{H^+ + F^-} Enz{-}CH_2{-}O{-}\overset{\overset{O}{\|}}{P}(O{-}CH(CH_3)_2){-}O{-}CH(CH_3)_2$$

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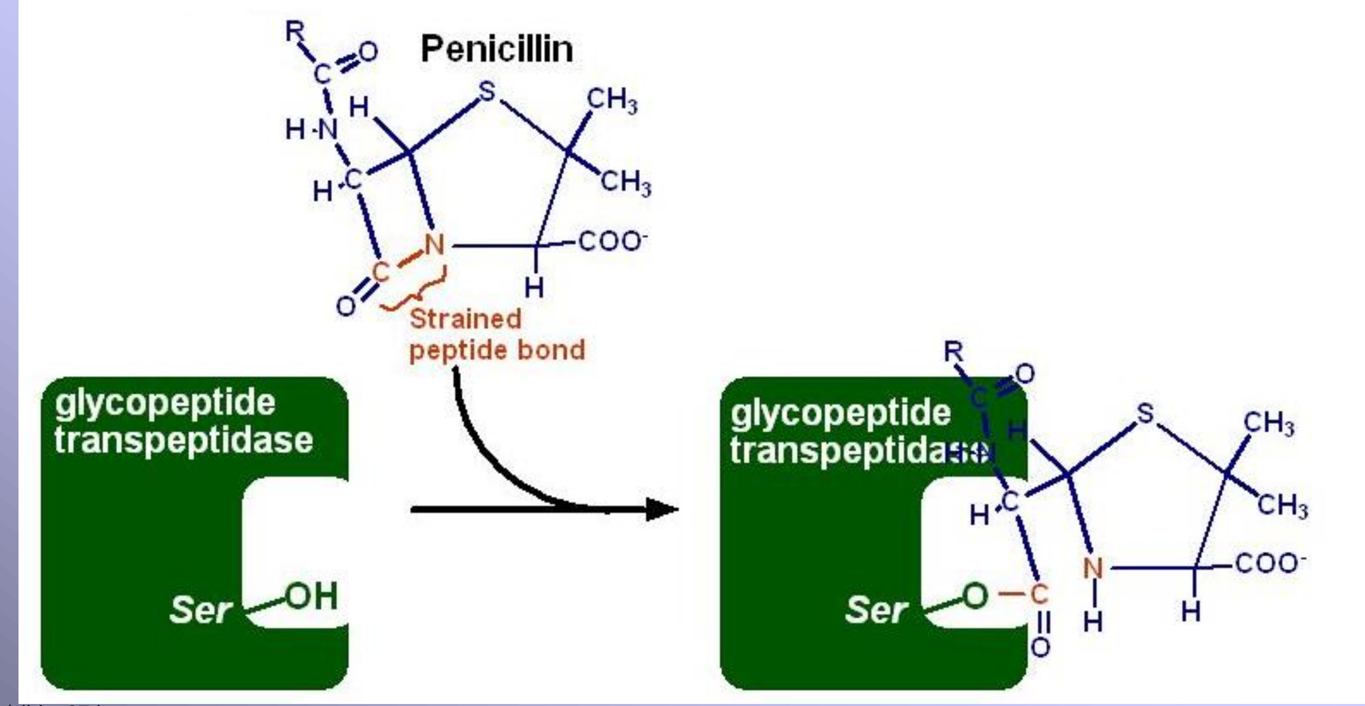
Suicide Substrates—Mechanism-Based Enzyme Inactivators

Suicide substrates are inhibitory substrate analogies designed so that, via normal catalytic action of the enzyme, a very reactive group is generated. This reactive group then forms a covalent bond with a nearby functional group within the active site of the enzyme, thereby causing irreversible inhibition. Suicide substrates bind with specificity and high affinity to the enzyme active site; in their reactive form, they become covalently bound to the enzyme. This covalent link effectively labels a particular functional group within the active site, identifying the group as a key player in the enzyme's catalytic cycle.

5-fluorouracil (which is converted in the body to 5F-dUMP) is a suicide inhibitor of thymidylate synthase, and prevents DNA synthesis in cancerous cells.

Penicillin—A Suicide Substrate

Several drugs in current medical use are mechanism-based enzyme inactivators. For example, the antibiotic penicillin exerts its effects by covalently reacting with an essential serine residue in the active site of glycoprotein peptidase, an enzyme that acts to cross-link the peptidoglycan chains during synthesis of bacterial cell walls. Once cell wall synthesis is blocked, the bacterial cells are very susceptible to rupture by osmotic lysis, and bacterial growth is halted.



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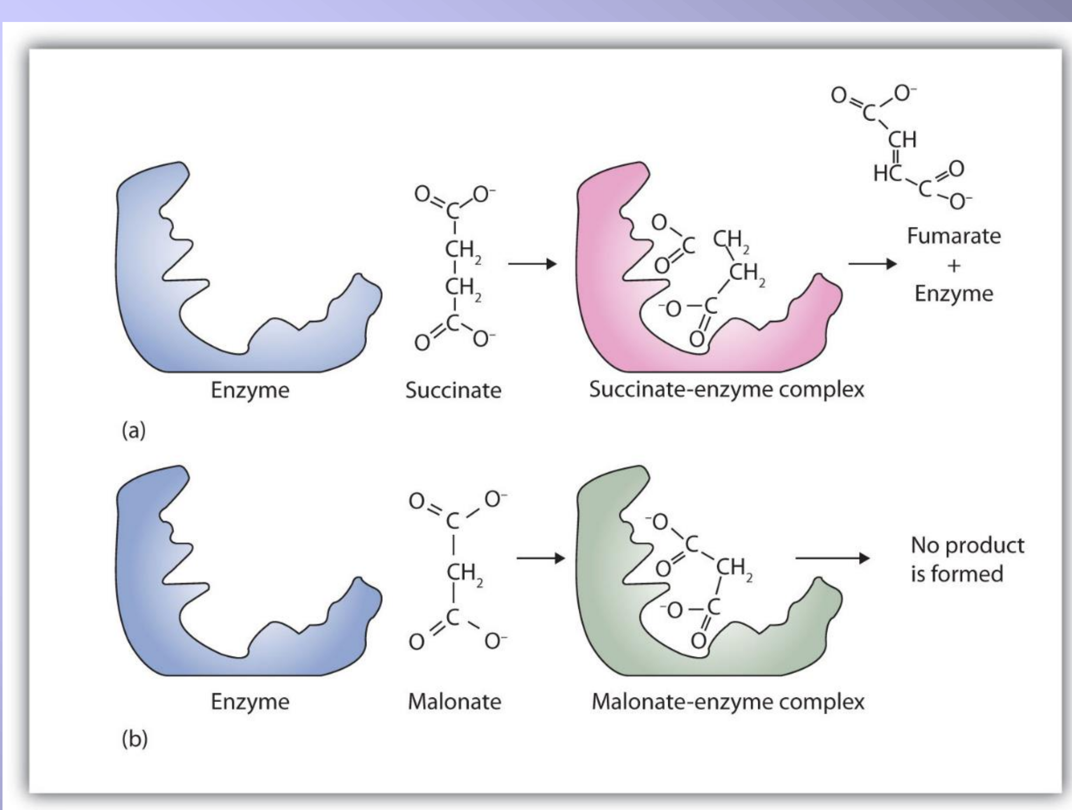
Reversible Inhibition

Reversible inhibitors fall into two major categories: competitive and noncompetitive (although other more unusual and rare categories are known). Competitive inhibitors are characterized by the fact that the substrate and inhibitor compete for the same binding site on the enzyme, the so-called active site or S-binding site.

Succinate dehydrogenase — a classic example of competitive inhibition. The enzyme succinate dehydrogenase (SDH) is competitively inhibited by malonate. The structural similarity between them is obvious and is the basis of malonate's ability to mimic succinate and bind at the active site of SDH. However, unlike succinate, which is oxidized by SDH to form fumarate, malonate cannot lose two hydrogens; consequently, it is unreactive.



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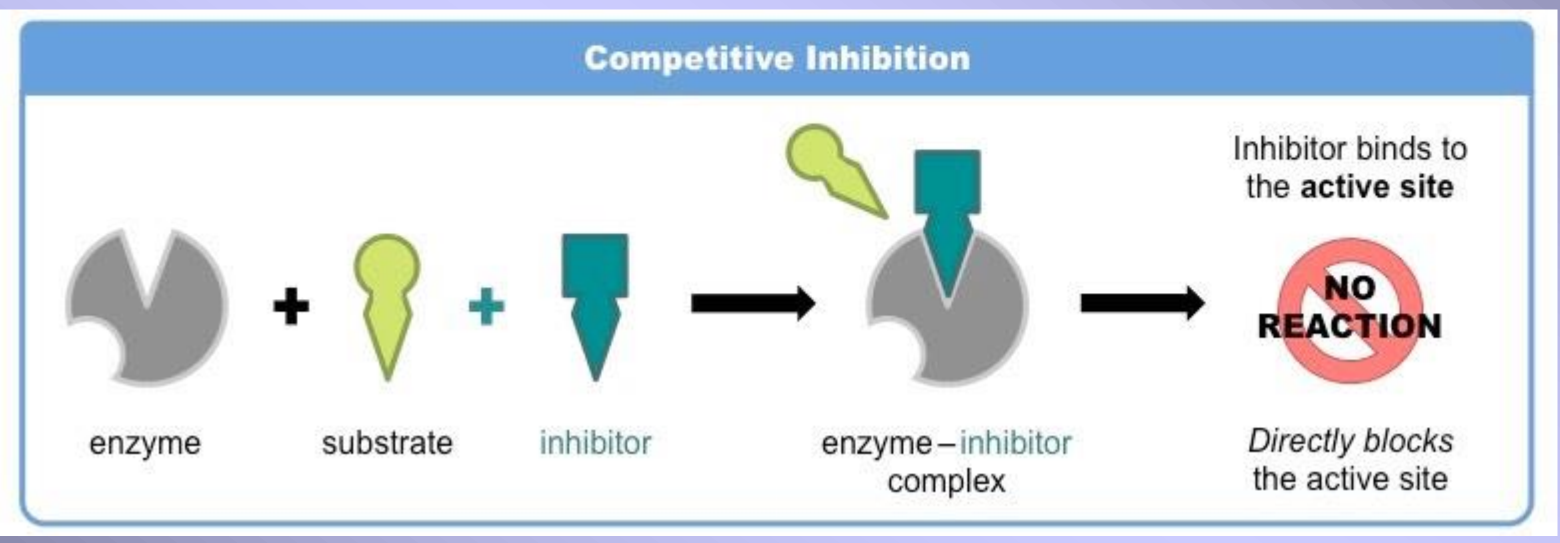
In competitive inhibition enzymes can form ES complexes or enzyme-inhibitor (EI) complexes. In order to form an enzyme-inhibitor complex, many inhibitors take on a shape that is very similar to the substrates. They then bind to the enzyme at the active site which prevents the substrate from binding at the site.



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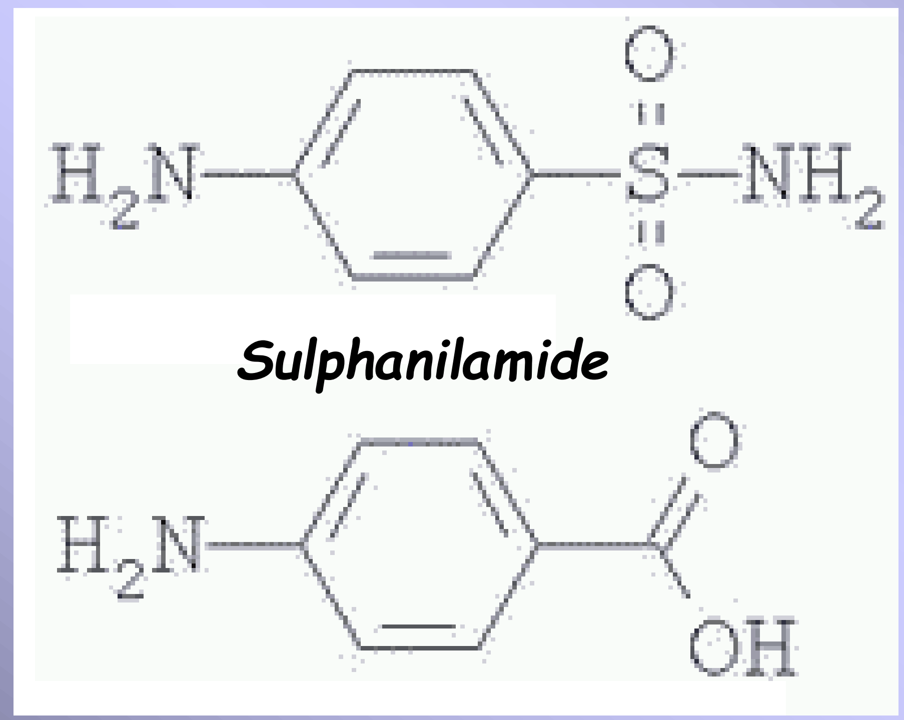
Para-aminobenzoic acid

Essential growth factor for micro-organisms. It forms part of the molecule of folic acid and is therefore required for the synthesis of this vitamin. Mammals cannot synthesize folic acid, and PABA has no other known function; there is no evidence that it is a human dietary requirement. Sulphanilamides (sulpha drugs) are chemical analogues of PABA, and exert their antibacterial action by antagonizing PABA utilization.



Para-aminobenzoic acid

	Competitive	Non-competitive	Uncompetitive
Cartoon Guide	Substrate; Inhibitor; Compete for active site	Different site	
Equation and Description	E + S ⇄ ES → E + P + *I* ⇅ E*I*	E + S ⇄ ES → E + P + + *I* *I* ⇅ ↓↑ E*I* + S → E*I*S	E + S ⇄ ES → E + P + *I* ⇅ E*I*S
	[*I*] binds to free [E] only, and competes with [S]; increasing [S] overcomes Inhibition by [*I*].	[*I*] binds to free [E] or [ES] complex; Increasing [S] can not overcome [*I*] inhibition.	[*I*] binds to [ES] complex only, increasing [S] favors the inhibition by [*I*].

Juang RH (2004) BCbasics

Controls Over Enzymatic Activity

The activity displayed by enzymes is affected by a variety of factors, some of which are essential to the harmony of metabolism.

- ✓The availability of substrates and cofactors will determine the enzymatic reaction rate.
- ✓There are genetic controls over the amounts of enzyme synthesized (or degraded) by cells. Induction, which is the activation of enzyme synthesis, and repression, which is the shutdown of enzyme synthesis, are important mechanisms for the regulation of metabolism.
- ✓Enzymatic activity can also be activated or inhibited through noncovalent interaction of the enzyme with small molecules (metabolites) other than the substrate. This form of control is termed allosteric regulation
- ✓Enzymes can be regulated by covalent modification, the reversible covalent attachment of a chemical group. For example, a fully active enzyme can be converted into an inactive form simply by the covalent attachment of a functional group, such as a phosphoryl moiety.

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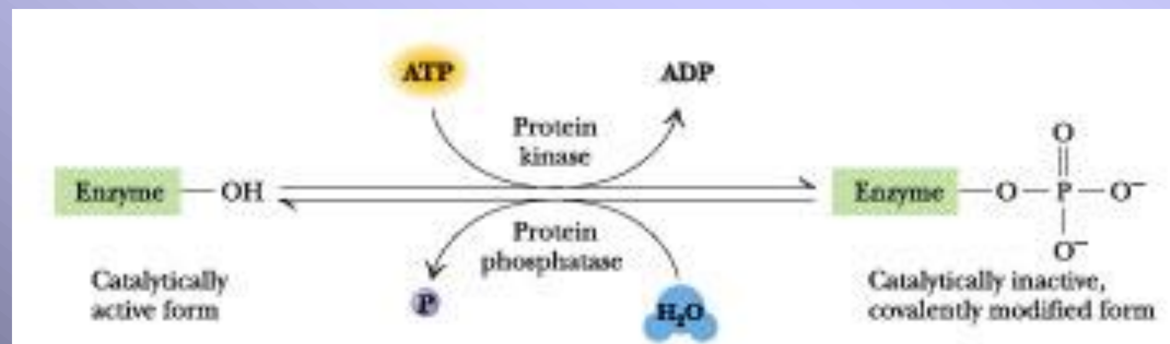
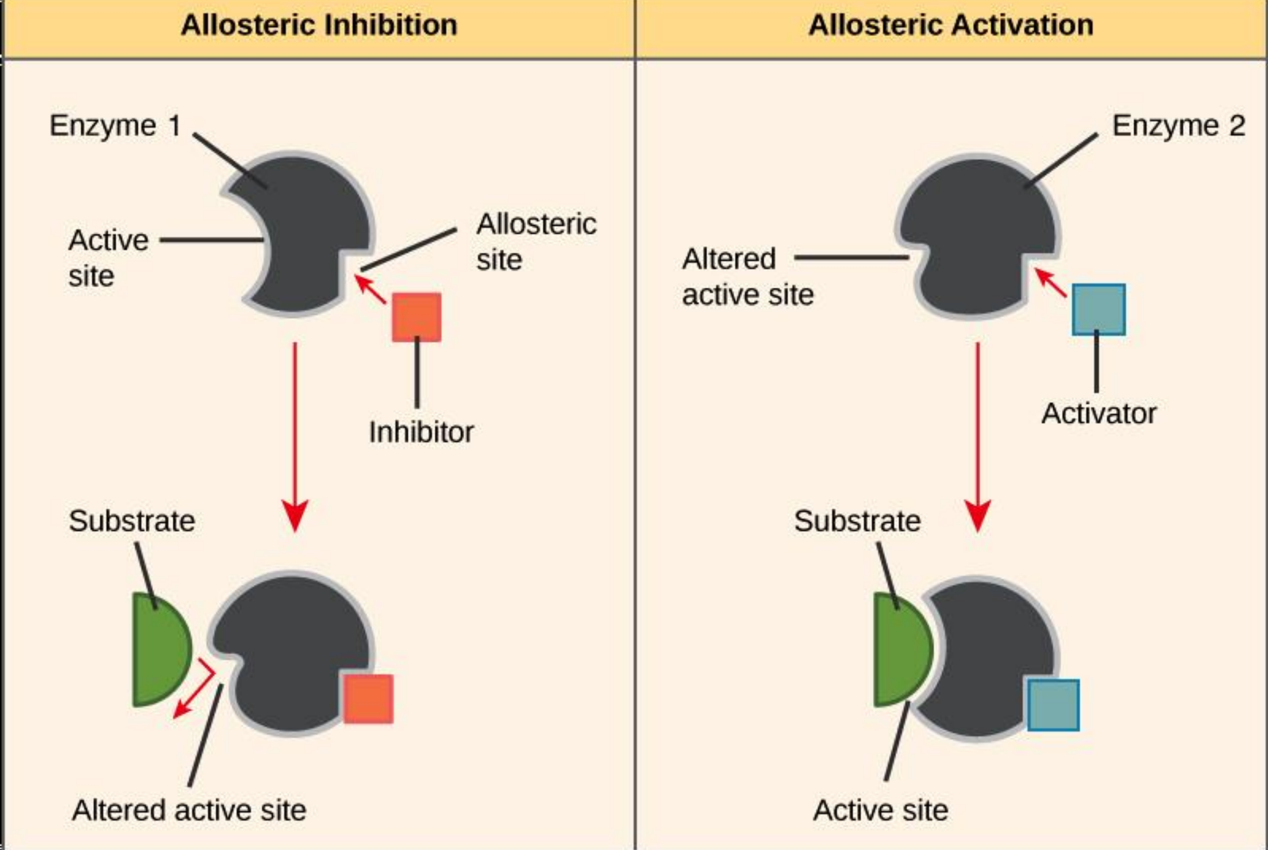


Allosteric Regulation

Some enzymes regulate the rate of metabolic pathways in cells. In feedback inhibition, the end product of a pathway inhibits the first enzyme of that pathway. The activity of some regulatory enzymes, called allosteric enzymes, is adjusted by reversible, noncovalent binding of a specific modulator to a regulatory or allosteric site. Such modulators may be inhibitory or stimulatory and may be either the substrate itself or some other metabolite.



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Isozymes *A number of enzymes exist in more than one quaternary form, differing in their relative proportions of structurally equivalent but catalytically distinct polypeptide subunits. A classic example is mammalian lactate dehydrogenase (LDH), which exists as five different isozymes, depending on the tetrameric association of two different subunits, A and B: A_4, A_3B, A_2B_2, AB_3, and B_4. The kinetic properties of the various LDH isozymes differ in terms of their relative affinities for the various substrates and their sensitivity to inhibition by product. Different tissues express different isozyme forms, as appropriate to their particular metabolic needs. By regulating the relative amounts of A and B subunits they synthesize, the cells of various tissues control which isozymic forms are likely to assemble, and, thus, which kinetic parameters prevail.*

LDH isoforms

H M

Isoenzymes of lactate dehydrogenase	Highest levels found in the following:
H_4 (LDH_1)	Heart, kidneys
H_3M (LDH_2)	Red blood cells, heart, kidney, brain
H_2M_2 (LDH_3)	Brain, lung, white blood cells
HM_3 (LDH_4)	Lung, skeletal muscle
M_4 (LDH_5)	Skeletal muscle, liver

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Creatine kinase (CK) isoenzymes

Isoenzyme name	Composition	Present in	Elevated in
CK-1	BB	Brain	CNS diseases brain tumors
CK-2	MB	Heart	Acute myocardial infarction
CK-3	MM	Skeletal muscle	Skeletal muscle diseases

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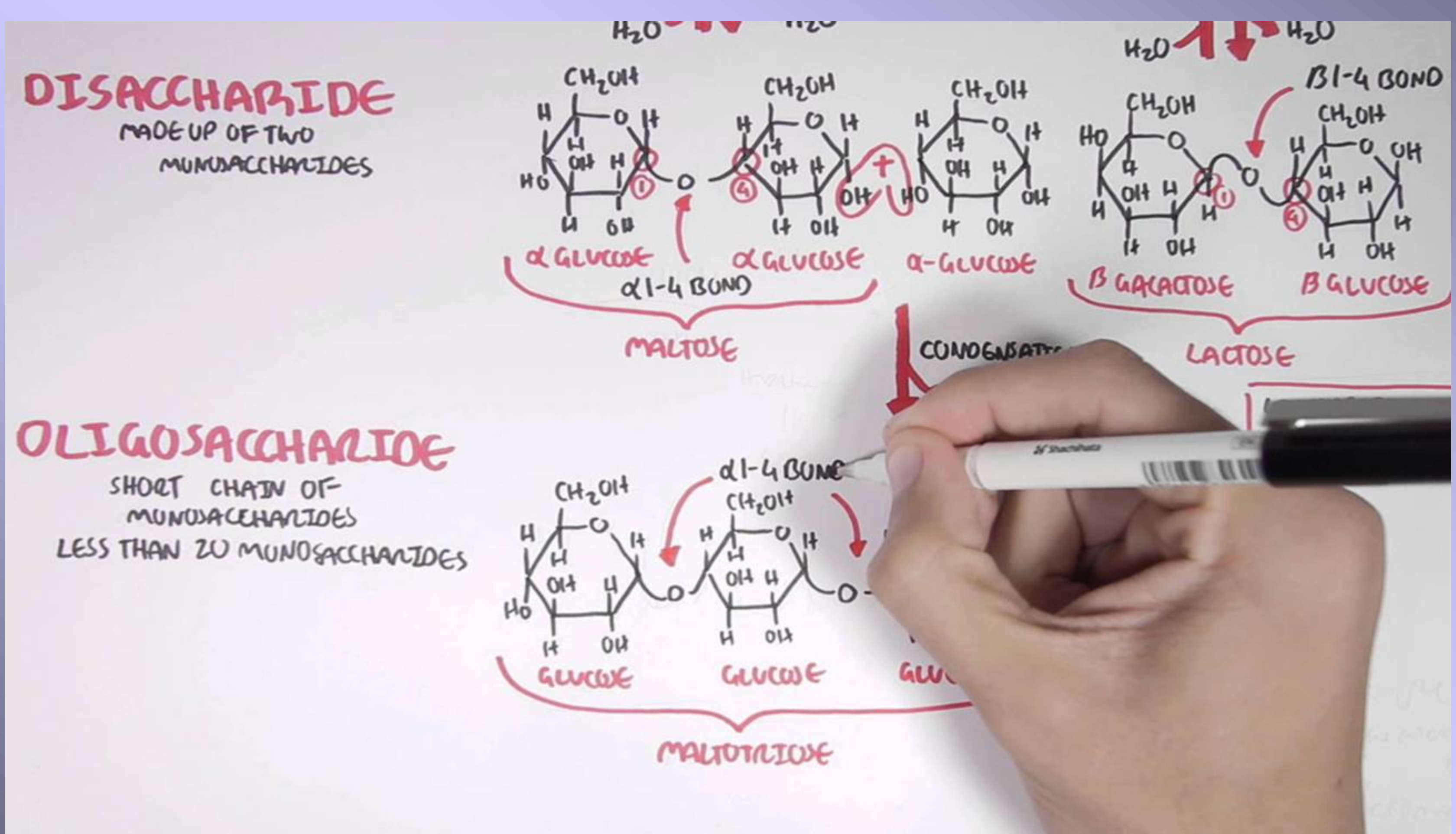
Conclusions

1. As enzymes are involved in so many aspects off living process, any understanding of biochemistry depends on an appreciation of these remarkable compounds.
2. The remarkable properties of enzymes include enormous catalytic power and a high degree of the reaction specificity.
3. Enzyme catalytic activities can be precisely regulated.
4. The measurement of serum activity (a level) of numerous enzymes has been shown to be of diagnostic significance.

Do you have any questions?

Thank you for your attention!



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