SHREE H. N. SHUKLACOLLEGE OF SCIENCE

(AFFILIATED TO SAURASHTRA UNIVERSITY)

Shree H.N. Shukla College Campus Nr. Lalpari lake, Behind old Marketing Yard,

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T.Y.B.SC.(MICROBIOLOGY)(CBCS)

NEW PROPOSED SYLLABUS -JUNE 2021

MB-502 BACTERIAL METABOLISM (THEORY)

UNIT :1 INTRODUCTION TO METABOLISM ,BIOENERGETICS AND ENZYME KINETICS

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Overview of metabolism

what is metabolism

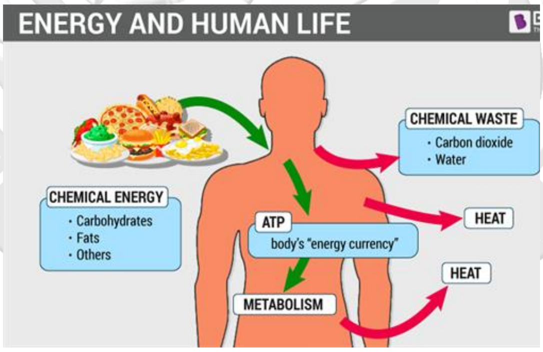
The chemical change take place in cell or organism is called **metabolism**.

OR

The chemical reaction in the body cells that change food in to energy is called metabolism.

- Metabolism consists of a series of reactions that occur within cells of living organisms to sustain life.
- The process of metabolism involves many interconnected cellular pathways to ultimately provide cells with the energy required to carry out their function.
- All of the chemical reactions that take place inside of a cell are collectively called the cell's **metabolism**.
- In the metabolic web of the cell, some of the chemical reactions release energy and can happen spontaneously (without energy input).
- However, others need added energy in order to take place.
- Just as you must continually eat food to replace what your body uses, so cells need a continual inflow of energy to power their energy-requiring chemical reactions. In fact, the food you eat is the source of the energy used by your cells!

- Metabolism is the total amount of the biochemical reactions involved in maintaining the living condition of the cells in an organism.
  All living organisms require energy for different essential processes and for producing new organic substances



- To make the idea of metabolism more concrete, let's look at two metabolic processes that are crucial to life on earth: those that build sugars, and those that break them down.

- There are two types of metabolic process :
- **catabolism**
- **Anabolism**

- **Catabolism** – This process is mainly involved in breaking down larger organic molecules into smaller molecules. This metabolic process releases energy.
- **Anabolism** – This process is mainly involved in building up or synthesizing compounds from simpler substances required by the cells.

- This metabolic process requires and stores energy.
- Metabolism is related to nutrition and the existence of nutrients.
- Bioenergetics describes the metabolism as the biochemical pathway through which the cells obtain energy. One of the major aspects is the energy formation.
- The processes of metabolism depend on the nutrients that get digested to produce energy. This energy is necessary to synthesize nucleic acids, proteins and other biomolecules in our body.
- Necessary nutrients help by supplying the required energy and other necessary chemicals that the body cannot synthesize on its own.
- Food provides different substances that are essential for the bodybuilding and repairing of tissues along with the proper functioning of the body.
- The diet requires both organic nutrients and inorganic chemical compounds.
- Organic nutrients include fats, vitamins, carbohydrates, and proteins.
- Inorganic chemical compounds include oxygen, water, and other dietary minerals.

- **Carbohydrates in Metabolism**
- Carbohydrates are supplied in three forms:
- Starch
- Sugar
- Cellulose
- Starch and sugar are the major forms of energy for humans. Metabolism of carbohydrates and sugar helps in the production of glucose.

- **Proteins in Metabolism**
- Proteins are important for building tissues.
- They help in maintaining the structure of the cells, its functions, the formation of hemoglobin, and several other body functions. The amino acids of proteins are beneficial for nutrition. Few amino acids are not synthesized by the body and are taken in from the food we eat.
- These amino acids include:
- Lysine
- Tryptophan
- Methionine
- Isoleucine

PRIMARY AND SECONDARY METABOLITES INRODUCTION

Metabolism

- Metabolism constituents all the chemical transformations occurring in the cells of living organisms and these transformations are essential for life of an organism.

Metabolites

- End product of metabolic processes and intermediates formed during metabolic processes is called metabolites.

What are Metabolites?

Metabolites are the intermediate products produced during metabolism, catalyzed by various enzymes that occur naturally within cells. Eg., antibiotics, and pigments. The term metabolites are usually used for small molecules. The various functions of metabolites include; fuel, structure, signalling, catalytic activity, defence and interactions with other organisms

- **Primary metabolites**
- A primary metabolite is a kind of metabolite that is directly involved in normal growth, development, and reproduction.
- It usually performs a physiological function in the organism (i.e. an intrinsic function).
- A primary metabolite is typically present in many organisms or cells.
- It is also referred to as a central metabolite, which has an even more restricted meaning (present in any autonomously growing cell or organism).
- Examples of primary metabolites include alcohols such as ethanol, lactic acid, and certain amino acids.
- Within the field of industrial microbiology, alcohol is one of the most common primary metabolites used for large-scale production.
- Specifically, alcohol is used for processes involving fermentation which produce products like beer and wine.
- Additionally, primary metabolites such as amino acids– including L-glutamate and L-lysine, which are commonly used as supplements– are isolated via the mass production of a specific bacterial species, *Corynebacteria glutamicum*.

- Another example of a primary metabolite commonly used in industrial microbiology includes citric acid

- **Secondary metabolites**

- Secondary metabolites are typically organic compounds produced through the modification of primary metabolite synthases.
- Secondary metabolites do not play a role in growth, development, and reproduction like primary metabolites do, and are typically formed during the end or near the stationary phase of growth.
- Many of the identified secondary metabolites have a role in ecological function, including defense mechanism(s), by serving as antibiotics and by producing pigments.
- Examples of secondary metabolites with importance in industrial microbiology include atropine and antibiotics such as erythromycin and bactracin.

Atropine, derived from various plants, is a secondary metabolite with important use in the clinic.

Significance

- Primary metabolites are essentially involved in the growth, development, and reproduction of the microorganism.
- This type includes carbohydrate, protein, fat, nucleic acid, hormone, ethanol, and other fermentation end products that are directly involved in its growth.
- Metabolites can have a multitude of functions, including energy conversion, signaling, epigenetic influence, and cofactor activity.

Bioenergetics

- Bioenergetics is the part of biochemistry concerned with the energy involved in making and breaking of chemical bonds in the molecules found in biological organisms.
- It can also be defined as the study of energy relationships and energy transformations and transductions in living organisms.

THERMODYANAMIC

- The laws of thermodynamics are a set of scientific laws which define a group of physical quantities, such as temperature, energy, and entropy, that characterize thermodynamic systems in thermodynamic equilibrium.

Zeroth Law of Thermodynamics

- When a body, 'A', is in thermal equilibrium with another body, 'b', and also separately in thermal equilibrium with a body ', C', then body, 'B' and 'C', will also be in thermal equilibrium with each other. This statement defines the zeroth law of thermodynamics.
- The law is based on temperature measurement.

First law of thermodynamic

- The first law of thermodynamics states that the total energy of a system remains constant, even if it is converted from one form to another.
- For example, kinetic energy—the energy that an object possesses when it moves—is converted to heat energy when a driver presses the brakes on the car to slow it down.

Second law of thermodynamic

- The second law of thermodynamic explain that any spontaneously occurring process will always lead to an escalation in the entropy (s)Of the universe.
- in simple words, the law explains that an isolated system entropy will never decrease over time.

Third law of thermodynamic

- The third law of thermodynamics states that the entropy of a perfect crystal at a temperature of zero Kelvin (absolute zero) is equal to zero.

Why need in bioenergetics?

- While the first law of thermodynamics gives information about the quantity of energy transfer as a process, it fails to provide any insights about the direction of energy transfer and the quality of the energy .
- The first law cannot indicate whether a metallic bar of uniform temperature can spontaneously become warmer at one end and cooler at others.
- All that the law can state is that there will always be an energy balance if the process occurs.

It is the second law of thermodynamics that provides the criterion for the feasibility of any process. A process cannot occur unless it satisfies both the first and second laws of thermodynamics.

1. Exergonic reaction

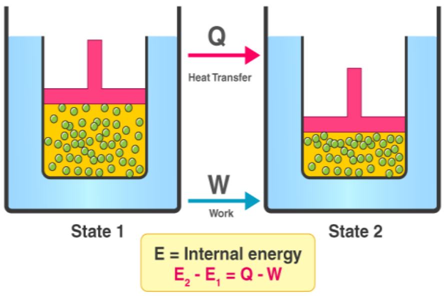
- An **exergonic** reaction is a spontaneous chemical reaction that releases energy.
- It is thermodynamically favored, indexed by a negative value of ΔG (Gibbs free energy).
- Over the course of a reaction, energy needs to be put in, and this activation energy drives the reactants from a stable state to a highly energetically unstable transition state to a more stable state that is lower in energy
- The reactants are usually complex molecules that are broken into simpler products. The entire reaction is usually catabolic.

The release of energy (called Gibbs free energy) is negative (i.e. $-\Delta G$) because energy is released from the reactants to the products

2. Endergonic reaction

- An **endergonic** reaction is an anabolic chemical reaction that consumes energy.
- It is the opposite of an exergonic reaction.
- It has a positive ΔG because it takes more energy to break the bonds of the reactant than the energy of the products offers, i.e. the products have weaker bonds than the reactants.
- Thus, endergonic reactions are thermodynamically unfavorable. Additionally, endergonic reactions are usually anabolic.

The mathematically expression of the first law is



The first law of thermodynamics

defines the internal energy (E) as equal to the difference of the heat transfer (Q) into a system and the work (W) done by ..

- **Free energy concept**
- **Gibbs free energy**, also known as the **Gibbs function, Gibbs energy, or free enthalpy**, is a quantity that is used to measure the maximum amount of work done in a thermodynamic system .
- when the temperature and pressure are kept constant.
- Gibbs free energy is denoted by the symbol 'G'.
- Its value is usually expressed in Joules or Kilojoules.
- Gibbs free energy can be defined as the maximum amount of work that can be extracted from a closed system.

Gibbs Free Energy Equation

- Gibbs free energy is a state function; hence it doesn't depend on the path. So, change in Gibbs free energy is equal to the change in enthalpy minus the product of temperature and entropy change of the system.
- $\Delta G = \Delta H - \Delta(TS)$
- If the reaction is carried out under constant temperature $\{\Delta T=O\}$
- $\Delta G = \Delta H - T\Delta S$
- This equation is called the Gibbs-Helmholtz equation.
- $\Delta G > 0$; the reaction is non-spontaneous and endergonic
- $\Delta G < 0$; the reaction is spontaneous and exergonic
- $\Delta G = 0$; the reaction is at equilibrium

Standard-state free energy of reaction (ΔG°)s

- The free energy of reaction at standard state conditions:
- ΔG°=ΔH°-TΔS°
- **Standard-state Conditions**

1. The partial pressure of any gases involved in the reaction is 0.1 MPa.
2. The concentrations of all aqueous solutions are 1 M.
3. Measurements are also generally taken at a temperature of 25C (298 K).
4. Pure liquids: The liquid under a total (hydrostatic) pressure of 1 atm.
5. Solids: The pure solid under 1 atm pressure.

Relationship between Free Energy and Equilibrium Constant

- The free energy change of the reaction in any state, ΔG (when equilibrium has not been attained), is related to the standard free energy change of the reaction,
- ΔG° (which is equal to the difference in the free energies of formation of the products and reactants, both in their standard states) according to the equation.
- ΔG = ΔG° + RT InQ
- Where Q is the reaction quotient.
- At equilibrium,
- ΔG = 0, and Q become equal to the equilibrium constant.
- Hence, the equation becomes,
- ΔG° = –RT In K(eq)
- ΔG° = –2.303 RT log K(eq)
- R = 8.314 J mol-1 K-1 or
- 0.008314 kJ mol-1 K-1.
- T is the temperature on the Kelvin scale

Energy rich compounds

What are high energy compounds?

- High energy compounds are also called energy-rich compounds.
- Compounds present in the biological system that when hydrolysed, produce free energy that is greater or equal to that of ATP (△G is -7.3 kcal/mol) are termed high energy compounds.
- Low-energy compounds have an energy yield of less than -7.3 kcal/mol.
- High-energy bonds are found in the majority of high-energy compounds that produce energy upon hydrolysis.
- Most of the high energy compounds contain phosphate groups and thus they are also termed high-energy phosphates.

- Types of High Energy Compounds
- These high energy compounds are mainly classified into five groups.

1. Pyrophosphates
2. Acyl phosphate
3. Enol phosphate
4. Thiol phosphate
5. Phosphagens or guanido phosphates

<u>Pyrophosphates</u>

- Pyrophosphate energy bonds are nothing but acid anhydride bonds.
- Condensation of acid groups (primarily phosphoric acid) or their derivatives results in the formation of these bonds. **ATP** (△G = -7.3 kcal/mol) is an example of a pyrophosphate. It has two phosphoanhydride diphosphate bonds.

Acyl phosphates

- The reaction between the carboxylic acid group and the phosphate group forms a high energy bond in this compound.**1,3-bisphosphoglycerate** (△G = -11.8 kcal/mol) is an example of acyl phosphate.

Enol phosphates

- The enol phosphate bond is present here.
- It is formed when a phosphate group binds to a hydroxyl group that is bound to a double-bonded carbon atom.
- As an example, consider **phosphoenolpyruvate** (△G = -14.8 kcal/mol).

Thiol phosphates

- There is no high energy phosphate bond here. Instead, a high energy thioester bond is found here.
- Thioester bonds are formed by the reaction of thiol and carboxylic acid groups.
- **Acetyl CoA** (△G = -7.7 kcal/mol) is an example.

Phosphagens

- Guanidine phosphate bonds are present in phosphagens or guanido phosphates.
- The phosphate group is attached to the guanidine group to form it.
- **Phosphocreatine** (△G = -10.3 kcal/mol) is the most important compound with this type of bond.

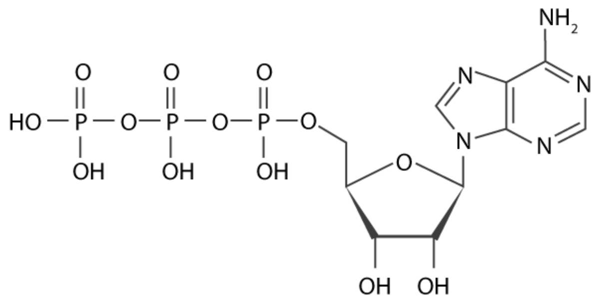
Energy metabolism

Role of ATP in metabolism

What is ATP-Adenosine Triphosphate?

- ATP – Adenosine triphosphate is called the energy currency of the cell.
- It is the organic compound composed of the phosphate groups, adenine, and the sugar ribose.
- These molecules provide energy for various biochemical processes in the body.
- Therefore, it is called “Energy Currency of the Cell”.

- These ATP molecules are synthesized by Mitochondria; therefore it is called powerhouse of the cell.
- The ATP molecule was discovered in the year 1929 by German chemist Karl Lohmann.
- Later in the year 1948, Scottish biochemist Alexander Todd was the first person to synthesized the ATP molecule.
- These organic molecules function by capturing the chemical energy obtained from the digested food molecules and are later released for different cellular processes.



- ATP hydrolysis provides the energy needed for many essential processes in organisms and cells.
- These include intracellular signaling, DNA and RNA synthesis, Purinergic signaling, synaptic signaling, active transport, and muscle contraction.
- The hydrolysis of ATP produces ADP, together with an inorganic phosphate ion (P_i), and the release of free energy.
- To carry out life processes, ATP is continuously broken down into ADP, and, like a rechargeable battery, ADP is continuously regenerated into ATP by the reattachment of a third phosphate group

ROLE OF REDUCING POWER IN METABOLISM

- Reducing power is defined as the potential or power of any substance to reduce another substance
- That can be either by addition or removal of hydrogen or by loss or gain of electrons.
- free energy change are not only related to the equilibria of "regular''chemical reaction but also to the equilibria of oxidation –reduction reaction .

- the release of energy normally involves oxidation –reduction reaction.

Oxidation –reduction

- **Oxidation** describes chemical reactions where electrons are lost, whereas **reduction** refers to reactions where electrons are gained.
- Electrons are stable atomic particles that are negatively charged, and the transfer of electrons between molecules produces energy.
- Electrons do not exist by themselves; they are always associated with an atom.
- A **redox reaction** occurs when an electron is transferred between molecules, and describes the summation of the oxidation and reduction reaction(s).
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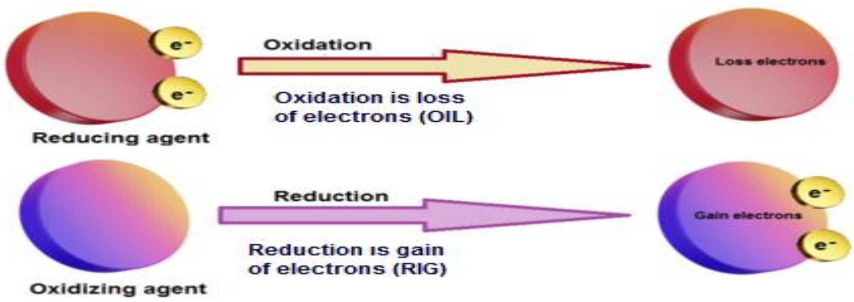
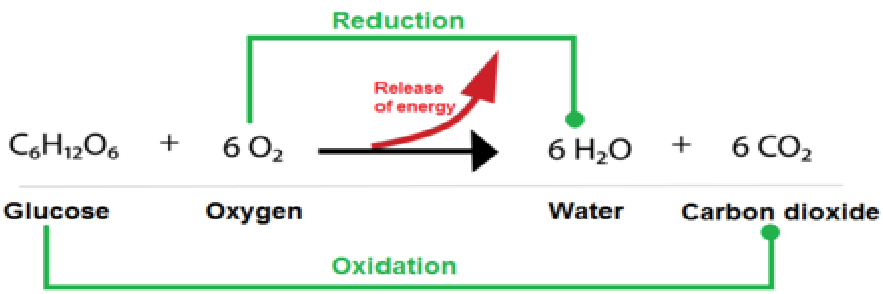


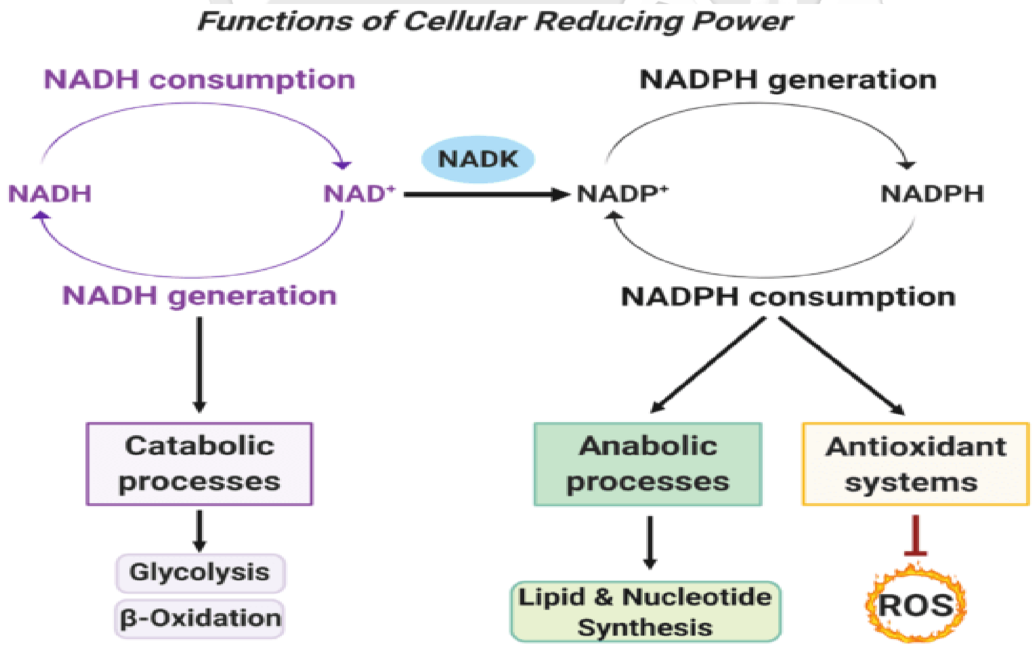


- **Reducing Power** - Many steps in a catabolic pathway involve oxidation (loss of electrons)/reduction (gain of electrons) reactions.

  The electrons (along with hydrogens) are usually transferred from the molecule being oxidized to the coenzymes NAD or NADP, to form NADH & NADPH. NADH & NADPH are used to reduce other molecules or are used to generate new ATP molecules.

  NAD (Nicotinamide adenine dinucleotide)

- The cellular respiration processes of all living cells make use of the coenzyme Nicotinamide adenine dinucleotide (NAD). It plays a key role in energy metabolism by accepting and donating electrons.
- NAD^+ is mostly used in catabolic pathways, such as glycolysis, that break down energy molecules to produce ATP. The ratio of NAD^+ to NADH is kept very high in the cell, keeping it readily available to act as an oxidizing agent.
- NADH is used in the electron transport chain to provide energetic electrons.



ROLE OF PRECURSOR METABOLITES IN METABOLISM

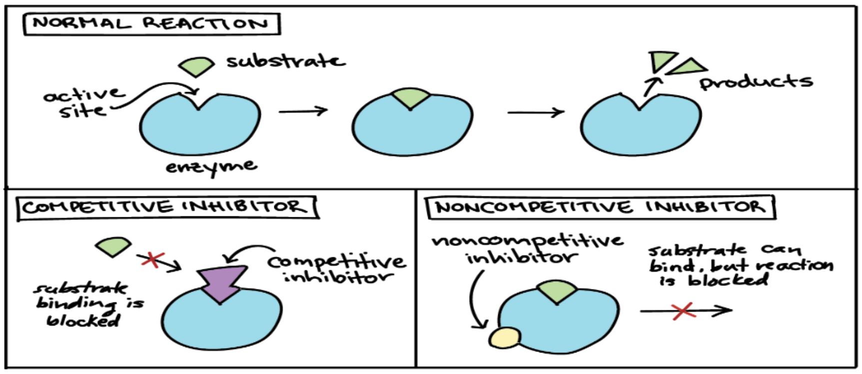
- Precursor metabolites are intermediate molecules in catabolic and anabolic pathways that can be either oxidized to generate ATP or can be used to synthesize macromolecular subunits such as amino acids, lipids, and nucleotides.
- The generation of the precursor metabolites is a critical step in anabolism.
- Precursor metabolites are carbon skeleton used as the starting substrates for the synthesis of monomers and other building blocks needed for the synthesis of macromolecules .
- The precursor metabolites are molecules used in essential chemical reactions within organisms.
- These chemical reactions either result in the formation of large molecules that are useful to the body (such as polysaccharides, lipids, proteins, and DNA) and/or create ATP (energy molecule). In this way, the precursor metabolites are like building blocks.
- The precursor metabolites are formed from the breakdown of molecules like proteins, but can be used to create more macromolecules. Therefore, the precursor metabolites link catabolism and anabolism in the body.

Here is an example

- Glucose 6 phosphate (G6P) can be formed from the breakdown of glycogen (glycogenolysis).
- It is also constructed from simple glucose which organisms either get from consuming complex sugars and breaking them down, or by photosynthesis in plants.
- chemo organoheterotrophs: produced by the central metabolic pathways.
- autotrophs use CO_2 fixation pathways and other pathways such as gluconeogenesis to make precursor metabolites

Non regulatory enzyme

- A non-regulatory enzyme is one in which the catalytic activity solely depends on the availability of the substrate and is not affected by the concentration of the final product.
- The enzyme catalyzed reaction will continue as long as the substrate is available.



Michaelis-Menten equation

- Michaelis-Menten equation is a mathematical equation that relates the rates of enzyme-catalyzed reaction with the concentration of both substrate and enzyme.
- This equation/model was given derived by two scientists Leonor Michaelis and Maud Leonora Menten in the 20th century to describe the variation of rate of the chemical reaction catalyzed by enzymes.

Assumptions of the Michaelis Menten equation

To derive the Michaelis Menten equation, the following principle features of many enzymes catalyzed are considered.

1. For a given initial concentration of substrate $[S]_o$, the initial rate of product formation is proportional to the total concentration of enzyme $[E]_o$.
2. At low concentrations of substrate $[S]_o$, the rate of product formation varies linearly with substrate concentration i.e. rate is proportional to $[S]_o$.
3. At a high concentration of substrate, the rate of product formation becomes independent of substrate concentration reaching a maximum value known as the **maximum velocity, Vmax.**
4. The Michaelis-Menten equation arises from the general equation for an enzymatic reaction: $E + S \leftrightarrow ES \leftrightarrow E + P$, where E is the enzyme, S is the substrate, ES is the enzyme-substrate complex, and P is the product.

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ES \xrightarrow{k_2} E + P$$

Rate of formation of ES = $k_1[E][S]$
Rate of breakdown of ES = $(k_{-1} + k_2)$ [ES]

and set equal to each other (Note that the brackets represent concentrations). Therefore:

$k_1[E][S] = (k_{-1} + k_2)$ [ES]

Rearranging terms,

$[E][S]/[ES] = (k_{-1} + k_2)/k_1$

The fraction [E][S]/[ES] has been coined K_m, or the Michaelis constant

According to Michaelis-Menten's kinetics equations, at low concentrations of substrate, [S], the concentration is almost negligible in the denominator as $K_M >> [S]$, so the equation is essentially

$V_0 = V_{max} [S]/K_M$

which resembles a first order reaction.

At High substrate concentrations, $[S] >> K_M$, and thus the term $[S]/([S] + K_M)$ becomes essentially one and the initial velocity approached V_{max}, which resembles zero order reaction.

The **Michaelis-Menten** equation is:

$$V_0 = V_{max}\left(\frac{[\text{Substrate}]}{[\text{Substrate}] + K_m}\right)$$

In this equation:

V_0 is the initial velocity of the reaction.

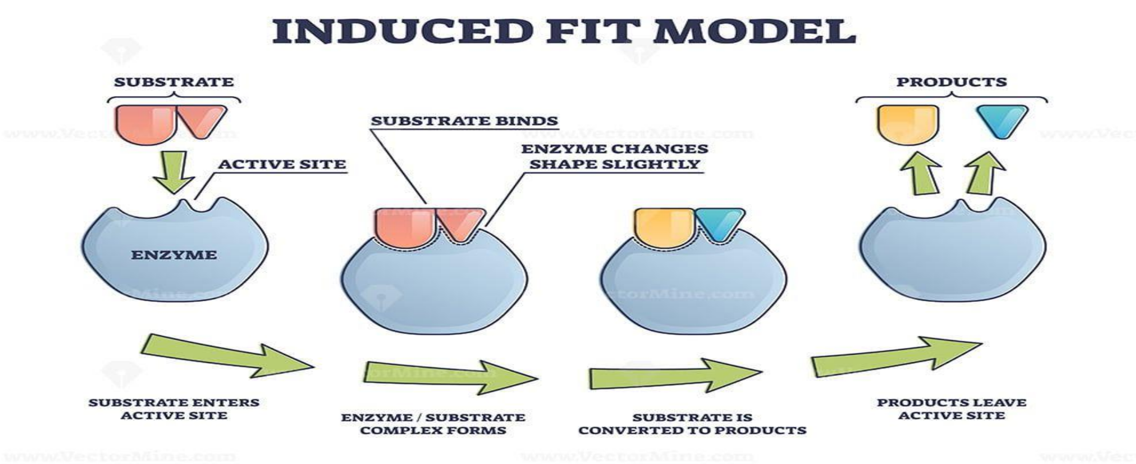
V_{max} is the maximal rate of the reaction.

[Substrate] is the concentration of the substrate.

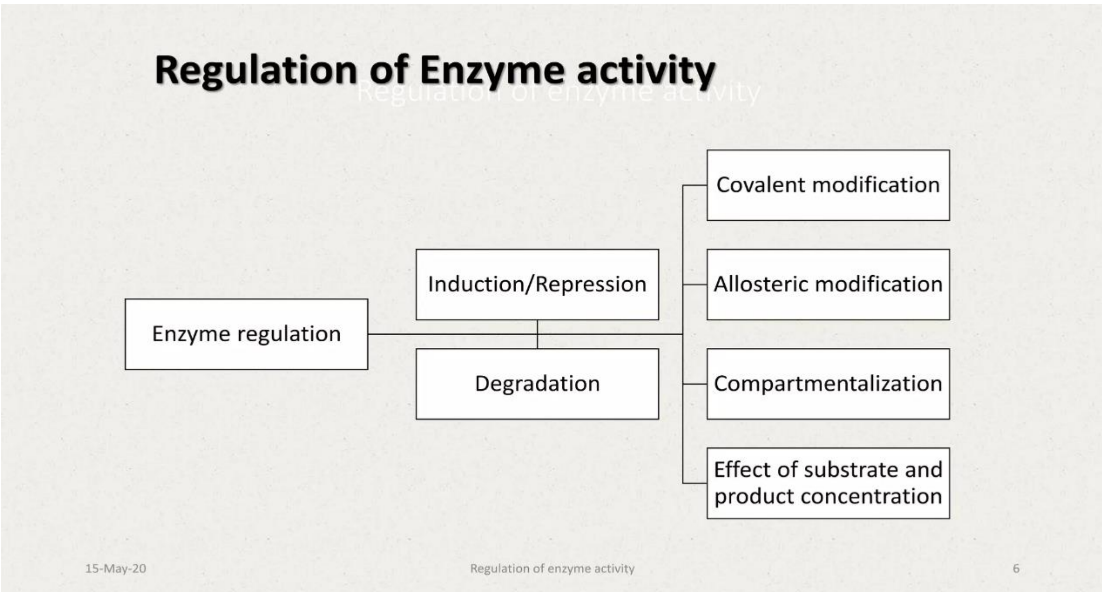
Regulatory enzyme

- Regulatory molecules. Enzyme activity may be turned "up" or "down" by activator and inhibitor molecules that bind specifically to the enzyme.
- 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.

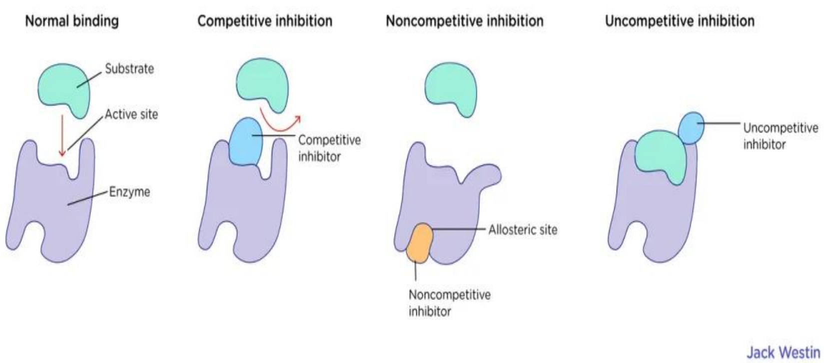
Feedback inhibition. Key metabolic enzymes are often inhibited by the end product of the pathway they control (feedback inhibition).



INDUCED FIT MODEL
SUBSTRATE
ACTIVE SITE
ENZYME
SUBSTRATE BINDS
ENZYME CHANGES SHAPE SLIGHTLY
PRODUCTS
SUBSTRATE ENTERS ACTIVE SITE
ENZYME / SUBSTRATE COMPLEX FORMS
SUBSTRATE IS CONVERTED TO PRODUCTS
PRODUCTS LEAVE ACTIVE SITE



Regulation of Enzyme activity
Enzyme regulation
Induction/Repression
Degradation
Covalent modification
Allosteric modification
Compartmentalization
Effect of substrate and product concentration
15-May-20
Regulation of enzyme activity
6



Normal binding
Competitive inhibition
Noncompetitive inhibition
Uncompetitive inhibition
Substrate
Active site
Enzyme
Competitive inhibitor
Allosteric site
Noncompetitive inhibitor
Uncompetitive inhibitor
Jack Westin

Allosteric enzymes

Allosteric enzymes are enzymes that have an additional binding site for effector molecules other than the active site. The binding brings about conformational changes, thereby changing its catalytic properties. The effector molecule can be an inhibitor or activator. All the biological systems are well regulated. There are various regulatory measures in our body, that control all the processes and respond to the various inside and outside environmental changes. Whether it is gene expression, cell division, hormone secretion, metabolism or enzyme activity, everything is regulated to ensure proper development and survival.

Allosteric Enzyme Properties

- Enzymes are the **biological catalyst,** which increases the rate of the reaction.
- Allosteric enzymes have an additional site, other than the active site or substrate binding site. The substrate-binding site is known as C-subunit and effector binding site is known as R-subunit or regulatory subunit
- There can be more than one allosteric sites present in an enzyme molecule
- They have an ability to respond to multiple conditions, that influence the biological reactions
- The binding molecule is called an effector, it can be inhibitor as well as activator.
- The binding of the effector molecule changes the conformation of the enzyme.

Allosteric Regulation Mechanism

- There are two types of allosteric regulation **on the basis of substrate and effector molecules**:
- **Homotropic Regulation:** Here, the substrate molecule acts as an effector also. It is mostly enzyme activation and also called**Allosteric Regulation Mechanism** cooperativity,
- e.g., binding of oxygen to hemoglobin.
- **Heterotopic Regulation:** When the substrate and effector are different. The effector may activate or inhibit the enzyme, e.g., binding of CO_2 to hemoglobin.
- **On the basis of action performed by the regulator**, allosteric regulation is of two types, inhibition and activation.

Allosteric Inhibition

- When an inhibitor binds to the enzyme, all the active sites of the protein complex of the enzyme undergo conformational changes so that the activity of the enzyme decreases.
- In other words, an allosteric inhibitor is a type of molecule which binds to the enzyme specifically at an allosteric site.

Allosteric Activation

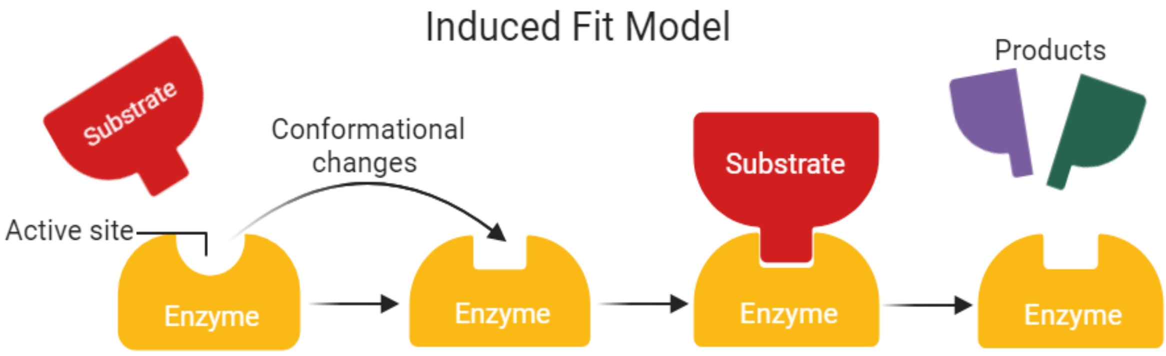
- When an activator binds, it increases the function of active sites and results in increased binding of substrate molecules.
- There are two models proposed for the mechanism of regulation of allosteric enzymes:

Allosteric Enzyme Examples

- ATCase catalyses the biosynthesis of pyrimidine
- Cytidine triphosphate (CTP) is the end product and also inhibits the reaction.
- It is known as feedback regulation.
- ATP (adenosine triphosphate), a purine nucleotide activates the process, high concentration of ATP can overcome inhibition by CTP

Conformational changes in regulatory enzyme

- In biochemistry, a **conformational change** is a change in the shape of a macromolecule, often induced by environmental factors.
- Its shape can change in response to changes in its environment or other factors; each possible shape is called a conformation, and a transition between them is called a *conformational change*.
- Factors that may induce such changes include temperature, ph, voltage, light in chromophores, concentration of ions, phosphorylation, or the binding of a ligand.



- Enzymes must allow substrates to bind and products to be released efficiently. The conformational changes undergone by the enzyme during substrate binding, conversion of substrate to product and product release, is the subject of this review.
- the most prominent examples of proteins that undergo large-scale conformational changes to regulate cell processes are guanine and adenine nucleotide triphosphatases (NTPases).
- These ubiquitous enzymes function as conformational switches and regulators fuleled by nucleotide binding and hydrolysis
- Protein conformational switches alter their shape upon receiving an input signal, such as ligand binding, chemical modification, or change in environment.