

Chapter Four

Cellular Metabolism and Metabolic Disorders

Cellular metabolism

- Living cells are in a constant activity. Macromolecules are assembled and broken down, substances are transported across cell membranes, and genetic instructions are transmitted. All of these cellular activities require energy.

- Living organisms are unique in that they can extract energy from their environments and use it to carry out activities such as movement, growth and development, and reproduction.
- But the basic question is how living organisms or, their **cells extract energy** from their environments, and how cells use this energy to synthesize and assemble the components from which the cells are made.
- The answers to these questions lie in the **enzyme-mediated** chemical reactions that take place in living matter (**metabolism**). Hundreds of coordinated, **multistep reactions**, fueled by energy obtained from nutrients and/or solar energy, ultimately convert readily available materials into the molecules required for growth and maintenance.

- **Metabolism** is thus the **sum of chemical reactions** that takes place within each cell of a living organism and that **provides energy** for vital processes and synthesizing of new organic materials. Broadly, these reactions can be divided into **catabolic** reactions that convert nutrients to energy and **anabolic** reactions that lead to the synthesis of larger biomolecules.

- In metabolism, a series of chemical reactions in which the product of one reaction is the substrate for the next reaction is called a metabolic pathway.
- Catabolic pathways release energy by breaking down larger molecules into smaller molecules.
- Anabolic pathways use the energy released by catabolic pathways to build larger molecules from smaller molecules, insuring the continual flow of energy within an organism.
- The reactants and products of these chemical reactions are metabolites.

- The major classes of metabolites include proteins, carbohydrates, nucleotides, lipids, coenzymes, and cofactors.
- These classes of compounds encompass an enormous diversity of molecular structures, physicochemical properties, functions, and abundances.
- Due to the analytical challenges posed by this diversity, most studies require division into subsets of metabolites.
- The most common criteria for this distinction rely on the hydrophilic (polar) and hydrophobic (nonpolar) nature of metabolites.

- Polar metabolites are soluble in aqueous solutions and include most sugars, purines and pyrimidines, nucleotides and nucleosides, acyl carnitines, organic acids, hydrophilic acids, amino acids, and phosphorylated compounds.
- These metabolites include most of the reactants and products involved in cellular respiration (e.g., [glycolysis, the TCA cycle, or in other pathways](#)) and in the production of building blocks for synthesis of large biopolymers such as DNA, RNA, proteins, and oligosaccharides.
- The nonpolar or hydrophobic metabolites are commonly lipids. These metabolites function in energy storage, membrane structure, and signal transduction.

- At the cellular level of organization, the main chemical processes of all living matter are similar, if not identical.
- This is true for animals, plants, fungi, or bacteria; where variations occur (such as, the secretion of antibodies by some molds), the variant processes are but variations on common themes.
- Thus, all living matter is made up of large molecules called **proteins**, which provide support and coordinated movement, as well as storage and transport of small molecules, and, as catalysts, enable chemical reactions to take place rapidly and specifically under mild temperature, relatively low concentration, and neutral conditions (i.e., neither acidic nor basic).

- The chemical reactions that take place in living cells are similar as well. Green plants use the energy of sunlight to convert water (H_2O) and carbon dioxide (CO_2) to carbohydrates (sugars and starches), other organic (carbon-containing) compounds, and molecular oxygen (O_2).
- The process of photosynthesis requires energy, in the form of sunlight, to split one water molecule into one-half of an oxygen molecule (O_2 ; the oxidizing agent) and two hydrogen atoms (H ; the reducing agent), each of which dissociates to one hydrogen ion (H^+) and one electron.

- Through a series of oxidation-reduction reactions, electrons (denoted e^-) are transferred from a donating molecule (oxidation), in this case water, to an accepting molecule (reduction) by a series of chemical reactions; this “reducing power” may be coupled ultimately to the reduction of carbon dioxide to the level of carbohydrate.
- In effect, carbon dioxide accepts and bonds with hydrogen, forming carbohydrates ($C_n[H_2O]_n$).

- Living organisms that require oxygen reverse this process: they consume carbohydrates and other organic materials, using oxygen synthesized by plants to form water, carbon dioxide, and energy.
- The process that removes hydrogen atoms (containing electrons) from the carbohydrates and passes them to the oxygen is an energy-yielding series of reactions.
- In plants, all but two of the steps in the process that converts carbon dioxide to carbohydrates are the same as those steps that synthesize sugars from simpler starting materials in animals, fungi, and bacteria.

- Similarly, the series of reactions that take a given starting material and synthesize certain molecules will be used in other synthetic pathways are similar, or identical, among all cell types.
- For instance, from a metabolic point of view, the cellular processes that take place in a lion are only marginally different from those that take place in a dandelion.

Enzymes and their role in metabolism

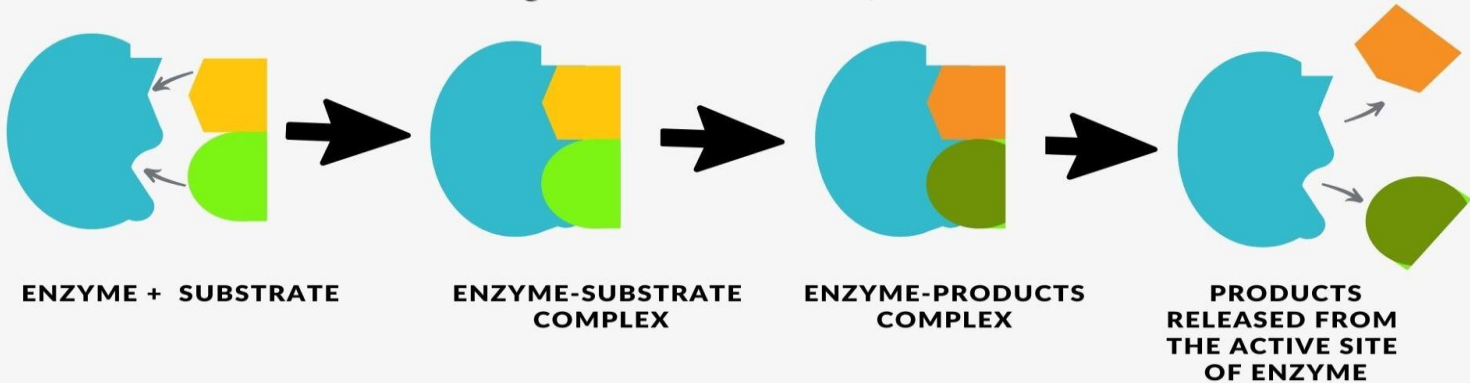
- Most chemical reactions within cells do not occur spontaneously. Instead, they need a catalyst to get them started.
- In many cases, heat may be a catalyst, but this is inefficient because heat cannot be applied to molecules in a controlled fashion. Thus, most chemical reactions require biological catalyst called **enzymes**.

- Enzymes are protein catalysts that speed biochemical reactions by **facilitating the molecular rearrangements that support cell function.**
- Enzymes speed up (catalyze) chemical reactions; in some cases, enzymes can make a chemical reaction millions of times faster than it would have been without it. **Almost all** metabolic processes in the cell need enzyme catalysis in order to occur at rates fast enough to sustain life

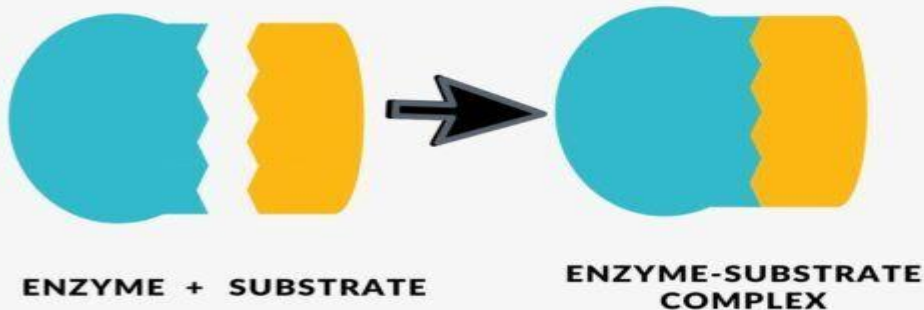
- Enzymes bind with particular reactants until the chemical reaction occurs, then free themselves. Thus, at any given time, the numerous pathways involved in building up and breaking down cellular components **must be monitored and balanced** in a coordinated fashion. To achieve this goal, cells organize reactions into various enzyme-powered pathways.
- **Enzymes speed up reactions by lowering activation energy.** Many enzymes change shape when substrates bind. This is termed "**induced fit**", meaning that the precise orientation of the enzyme required for catalytic activity can be induced by the binding of the substrate.

Induced fit model

The induced fit model is a model depicting the enzyme-substrate interaction. In this model, the substrate and the active site of the enzyme undergo changes to attain an optimal fit.



Lock-and-key model

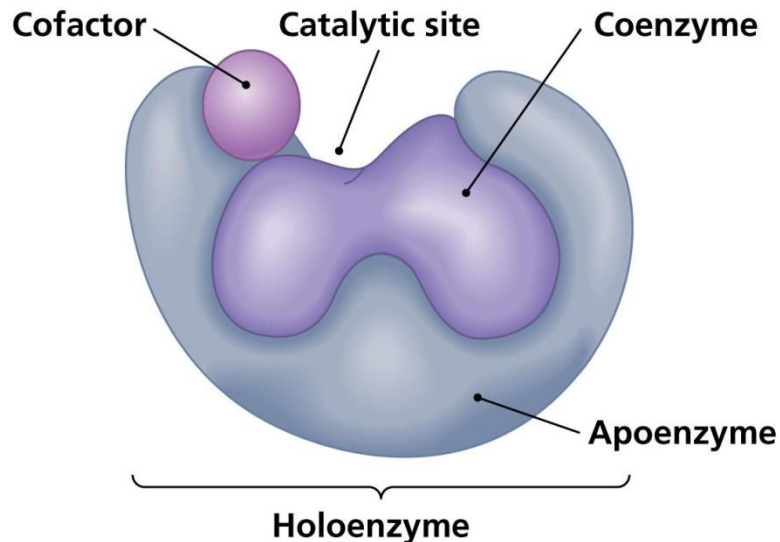


Lock-and-key model is a model used to represent enzyme-substrate interaction.

Chemical nature and classification of enzymes

- All known enzymes are proteins with the exception of recently discovered RNA enzymes.
- Some enzymes may additionally contain a non-protein group. Enzymes are high molecular weight compounds made up principally of chains of amino acids linked together by peptide bonds.

- Many enzymes require the presence of other compounds (**cofactors**) before their catalytic activity can be exerted. This entire active complex is referred to as the **holoenzyme**; i.e., apoenzyme (protein portion) plus the cofactor (coenzyme, prosthetic group or metal-ion activator).



- on the basis of differences in chemical nature, the enzymes may be described as follows:
 - **Simple enzymes**: Simple enzymes are made up of only protein (polypeptide). They contain no chemical groups other than amino acid residues. Digestive enzymes such as pepsin, and trypsin are of this nature.
 - **Conjugate Enzymes**: It is an enzyme which is formed of two parts – a protein part called apoenzyme (e.g., flavoprotein) and a non-protein part named cofactor. The complete conjugate enzyme, consisting of an apoenzyme and a cofactor, is called holoenzyme. There can be an enzymatic activity only when both components (apoenzyme and cofactor) are present together. The cofactor is sometimes a simple divalent metallic ion (e.g. Ca, Mg, Zn, Co, etc), and sometimes a nonprotein organic compound.

- However, some enzymes require both kinds of cofactors. If the cofactor is firmly bound to the apoenzyme, it is called **prosthetic group**. For example, cytochromes are the enzymes that possess porphyrins as their prosthetic groups.
- If, instead of being more or less permanently bound to the apoenzyme the cofactor attaches itself to the apoenzyme only at the time of reaction, it is called a **coenzyme**.

- **Metallo-enzymes**: The metal cofactors involved in enzymic reactions are monovalent (K^+) and divalent cations (Mg^{++} , Mn^{++} and Cu^{++}). These may be loosely held by the enzyme, or as in some cases, go into the composition of the molecule itself. If the metal forms part of the molecule, as iron of haemoglobin or cytochrome, the enzymes are called **metallo-enzymes**.
- **Isoenzymes (Isozymes)**: At one time it was believed that an organism has only a single enzyme for a given step of a metabolic reaction. It was later discovered that a substrate may be acted upon by a number of variants of an enzyme producing the same product.

- Classes of enzymes based on the substrate they act up on

S.No.	Type of reaction	Description of reaction	Enzyme class
1.	Oxidation – reduction	Transfer of electrons.	Oxidoreductases
2.	Group transfer	Transfer of a functional group from one molecule to another.	Transferases
3.	Hydrolysis	Cleavage of bonds by the addition of water.	Hydrolases
4.	Nonhydrolytic cleavage	Cleaving/splitting a molecule by nonhydrolytic processes.	Lyases
5.	Isomerization & rearrangements	Rearrangement of atoms to form isomers.	Isomerases
6.	Ligation using energy from ATP	Formation of Carbon and other bonds with energy from ATP.	Ligases

Mechanisms of enzyme action

- Mechanisms of enzyme catalysis vary, but are all similar in principle to other types of chemical catalysis in that the crucial factor is a reduction of energy barrier(s) separating the reactants from the products.
- The reduction of activation energy increases the fraction of reactant molecules that can overcome this barrier and form the product.
- An important principle is that since they only reduce energy barriers between products and reactants, enzymes always catalyze reactions in both directions, and cannot drive a reaction forward or affect the equilibrium position.

- An enzyme attracts substrates to its active site, catalyzes the chemical reaction by which products are formed, and then allows the products to dissociate (separate from the enzyme surface).
- The combination formed by an enzyme and its substrates is called the **enzyme– substrate complex**.
- The substrates are attracted to the active site **by electrostatic and hydrophobic forces**, which are called **noncovalent** bonds because they are physical attractions and not chemical bonds.

Factors affecting enzymatic activities

- The activity of an enzyme is affected by its environmental conditions such as temperature and pH. Changing these alter the rate of reaction caused by the enzyme. In nature, organisms adjust the conditions of their enzymes to produce an optimum rate of reaction, where necessary, or they may have enzymes which are adapted to function well in extreme conditions where they live.

Temperature

- Increasing temperature increases the kinetic energy that molecules possess. In a fluid, this means that there are more random collisions between molecules per unit time. Since enzymes catalyse reactions by randomly colliding with substrate molecules, increasing temperature increases the rate of reaction, forming more product.

- However, increasing temperature also increases the **vibrational energy** that molecules have, specifically (in this case enzyme molecules), which puts strain (damage) on the bonds that hold them together.
- As temperature increases, more bonds, especially the weaker hydrogen and ionic bonds, will break as a result of this strain. breaking bonds within the enzyme will cause the **active site** to change shape.
- This change in shape means that the Active Site is less complementary to the shape of the Substrate, so that it is less likely to catalyse the reaction. Eventually, the enzyme will become denatured and will no longer function.
- The temperature at which the maximum rate of reaction occurs is called the **enzyme's Optimum Temperature**. This is different for different enzymes.

pH - Acidity and Basicity

- pH is a measure of the hydrogen ion (H^+) concentration, and therefore a good indicator of the hydroxide ion (OH^-) concentration.
- Lower pH values mean higher H^+ concentrations and lower OH concentrations. H^+ and OH ions are charged and therefore interfere with hydrogen and ionic bonds that hold together an enzyme, since they will be attracted or repelled by the charges created by the bonds. This interference causes a change in shape of the enzyme, and importantly, its active site.

- Different enzymes have different optimum pH values. This is the pH value at which the bonds within them are influenced by H^+ and OH^- ions in such a way that the shape of their active site is the most complementary to the shape of their substrate.
- At the optimum pH, the rate of reaction is at an optimum. Any change in pH above or below the optimum will quickly cause a decrease in the rate of reaction, since more of the enzyme molecules will have active sites whose shapes are not (or at least are less) complementary to the shape of their substrate.

- Small changes in pH above or below the optimum do not cause a permanent change to the enzyme, since the bonds can be reformed.
- However, extreme changes in pH can cause enzymes to denature and permanently lose their function. Enzymes in different locations of our body have different optimum pH values since their environmental conditions may be different. For example, the enzyme pepsin functions best at around pH-2 and is found in the stomach, which contains hydrochloric acid.
- Because enzymes are sensitive to changes in acidity, most living systems are highly buffered; i.e., they have mechanisms that enable them to maintain a constant acidity

Substrate and enzyme concentration

- Changing the enzyme and substrate concentrations affect the rate of reaction of an enzyme catalysed reaction.
- Controlling these factors in a cell is one way that an organism regulates its enzyme activity and so its metabolism.
- Changing the concentration of a substance only affects the rate of reaction if it is the **limiting factor**.
- If it is the limiting factor, increasing concentration will increase the rate of reaction up to a point, after which any increase will not affect the rate of reaction.
- This is because it will no longer be the limiting factor and another factor will be limiting the maximum rate of reaction.

Substrate concentration

- Increasing substrate concentration increases the rate of reaction. This is because more substrate molecules will be colliding with enzyme molecules, so more product will be formed.
- However, after a certain concentration, any increase will have no effect on the rate of reaction, since substrate concentration will no longer be the limiting factor. The enzymes will effectively become saturated, and will be working at their maximum possible rate.

Enzyme concentration

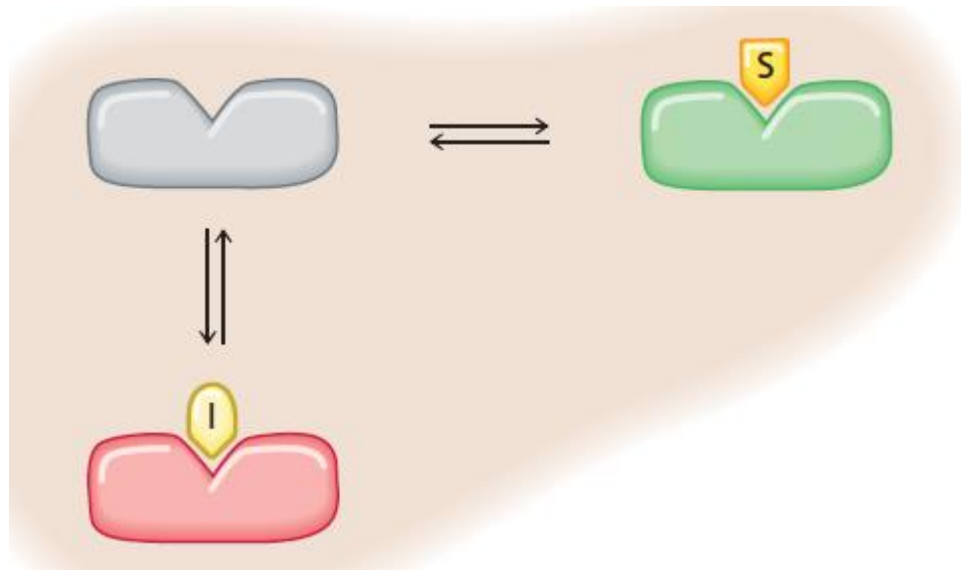
- Increasing enzyme concentration will increase the rate of reaction, as more enzymes will be colliding with substrate molecules.
- However, this too will only have an effect up to a certain concentration, where the enzyme concentration is no longer the limiting factor.

Enzyme inhibitors

- Enzyme activity can be inhibited in various ways. Inhibition could be reversible or irreversible.

Reversible inhibition

- **Competitive inhibition**: occurs when molecules very similar to the substrate molecules bind to the active site and prevent binding of the actual substrate. Penicillin, for example, is a competitive inhibitor that blocks the active site of an enzyme that many bacteria use to construct their cell walls.

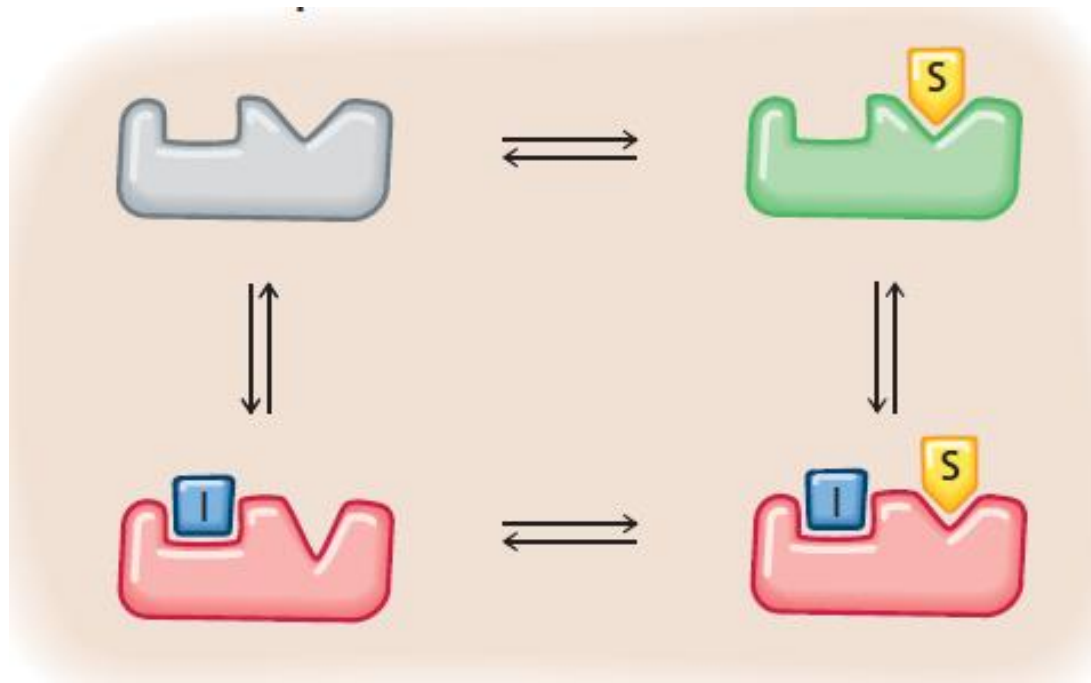


Competitive inhibition

- **Noncompetitive inhibition:** occurs when an inhibitor binds to the enzyme at a location other than the active site.
- In some cases of noncompetitive inhibition, the inhibitor is thought to bind to the enzyme in such a way as to physically block the normal active site.
- In other instances, the binding of the inhibitor is believed to change the shape of the enzyme molecule, thereby deforming its active site and preventing it from reacting with its substrate.

- This latter type of noncompetitive inhibition is called **allosteric inhibition**; the place where the inhibitor binds to the enzyme is called the **allosteric site**.
- Frequently, an end-product of a metabolic pathway serves as an allosteric inhibitor on an earlier enzyme of the pathway. This inhibition of an enzyme by a product of its pathway is a form of **negative feedback**.

- **Activators:** Allosteric control can involve stimulation of enzyme action as well as inhibition.
 - An activator molecule can be bound to an allosteric site and induce a reaction at the active site by changing its shape to fit a substrate that could not induce the change by itself.
- Common activators include hormones and the products of earlier enzymatic reactions.
- Allosteric stimulation and inhibition allow production of energy and materials by the cell when they are needed and inhibit production when the supply is adequate.



Noncompetitive inhibition

Irreversible inhibition

- Irreversible inhibitors usually covalently modify an enzyme, and inhibition can therefore **not be reversed**.
- Irreversible inhibitors often contain reactive functional groups. Irreversible inhibition is different from reversible enzyme inactivation. Irreversible inhibitors are generally specific for one class of enzyme and do not inactivate all proteins; they do not function by destroying protein structure but by specifically altering the active site of their target.

Thank You!