U.P.Rajarshi Tandon Open University, Prayagraj

MFN-102

Advanced Nutritional Biochemistry

COURSE INTRODUCTION

The objective of this course deals basic introduction to polysaccharides, plasma proteins, intermediary metabolism and synthesis etc. in concern to their nutritional biochemistry. The aim is to provide brief introduction to nutritional biochemistry of different polysaccharides. This course is organized into following three blocks. These are as under:

Block 1 It covers the introduction of heteropolysaccharides, plasma proteins and intermediary metabolism

Block 2 It deals the purines and pyrimidines, nucleic acids and hormones

Block 3 It describes the introduction to minerals, detoxification in the Body

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Block

Heteropolysaccharides, Plasma proteins and Intermediary metabolism

MFN-102

Advanced Nutritional Biochemistry

VICE CHANCELLOR

Prof. Seema Singh Vice Chancellor UPRTOU

COURSE DESIGN COMMITTEE

Dr. Meera Pal **Director Incharge**

School of Health Sciences,
UPRTOU, Prayagraj.

Dr. Alka Gupta **Member**

Associate Professor,
(Home Science, Nutritional Sciences)

Mrs. Zoomi Singh **Member**

Assistant Professor,
Home Science, Nutritional Sciences, UPRTOU, Prayagraj (Contractual)

COURSE PREPRATION COMMITTEE

Dr. Kapil Gupta **Unit: 1-12** **Writer**

Assistant Professor
Department of Biotechnology
Siddharth University Kapilvastu, Siddharthnagar

Dr. Pramod Kumar Pandey **(All blocks and units)** **Editor**

Associate Professor,
Department of Zoology, PSM PG College, Maharajganj

COURSE COORDINATOR

Dr.Meera Pal

Associate Professor
UP Rajarshi Tandon Open University, Prayagraj

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Block Introduction

This is the first block (Heteropolysaccharides, Plasma proteins and Intermediary metabolism) of Advanced Nutritional Biochemistry. It consists of four units. The objective of this block deals basic introduction to heteropolysaccharides, plasma proteins, intermediary metabolism and synthesis respectively.

Unit 1:

In general, heteropolysaccharides (heteroglycans) contain two or more different monosaccharide units. Although a few representatives contain three or more different monosaccharides, most naturally occurring heteroglycans contain only two different ones and are closely associated with lipid or protein. The complex nature of these substances has made detailed structural studies extremely difficult. The major heteropolysaccharides include the connective-tissue polysaccharides, the blood group substances, glycoproteins (combinations of carbohydrates and proteins) such as gamma globulin, and glycolipids (combinations of carbohydrates and lipids), particularly those found in the central nervous system of animals and in a wide variety of plant gums.

The most important heteropolysaccharides are found in the connective tissues of all animals and include a group of large molecules that vary in size, shape, and interaction with other body substances. They have a structural role, and the structures of individual connective-tissue polysaccharides are related to specific animal functions; hyaluronic acid, for example, the major component of joint fluid in animals, functions as a lubricating agent and shock absorber.The connective-tissue heteropolysaccharides contain acidic groups (uronic acids or sulfate groups) and can bind both water and inorganic metal ions. They can also play a role in other physiological functions; e.g., in the accumulation of calcium before bone formation. Ion-binding ability also appears to be related to the anticoagulant activity of the heteropolysaccharide heparin.

Unit 2:

Under this unit, we have discussed plasma proteins in concern to their nature, properties and functions. The proteins in blood serum or plasma are many and are produced by various cells. The biosynthesis of the vast majority of plasma proteins takes place in the liver. A smaller part is synthesized in other cells: e.g. lymphocyte (immunoglobulins) and enterocytes (e.g. apoprotein B-48). Protein degradation takes place inhepatocytes and the mononuclear phagocytic system, where proteins are degraded predominantly after complex formation (e.g. antigen-antibody complex and hemoglobin-haptoglobin complex). Intracellularly, peptide bonds of proteins are hydrolyzed by proteases and peptidases to form amino acids. Another way serum proteins are removed is via excretion, which is facilitated by the kidneys and the gastrointestinal tract.

Unit 3:

Under this unit, we have discussed intermediary metabolism in concern to free energy changes, glycolysis, gluconeogenesis and citric acid cycle. Intermediary metabolism refers to the sum of all intracellular chemical processes by which nutritive material is converted into cellular components. It includes anabolism (synthesis of macromolecules) and catabolism (breakdown of macromolecules). Cellular energy is generated from aerobic oxidation of metabolic fuels (carbohydrates, fats, proteins) derived from digestion of a meal or from breakdown of internal stores. These metabolic fuels are broken down into basic substrates (glucose, amino acids, free fatty acids, glycerol).

This is followed by processes that remove electrons (oxidation) from these substrates at high potential and transfer them to substrates at lower potential. It is during these processes that energy is released. Reduced coenzymes (NAD+ and FADH) are intermediate energy storage compounds that aid electron (and energy) transfer from metabolic reactions (glycolysis and Krebs cycle) to the electron transport chain. During aerobic metabolism, oxygen is consumed at the end of electron transport chain producing carbon dioxide via Krebs cycle. However, energy can also be generated anaerobically via glycolysis with the production of lactate.

Unit 4:

Under this unit, we have discussed about synthesis in concern to saturated and unsaturated fatty acids, De novo synthesis of fatty acids and phospholipids. In biochemistry, fatty acid synthesis is the creation of fatty acids from acetyl-CoA and NADPH through the action of enzymes called fatty acid synthases. Fatty acid synthesis in animals is catalyzed by a single large multifunctional enzyme. The biosynthetic reaction pathway to a compound is usually not a simple opposite of its breakdown. In fatty acid synthesis, acetyl-CoA is the direct precursor only of the methyl end of the growing fatty acid chain. All the other carbons come from the acetyl group of acetyl-CoA but only after it is modified to provide the actual substrate for fatty acid synthase, malonyl-CoA.

De novo biosynthesis is the amalgamation of complex molecules to form simpler elements like sugar and acid instead of reprocessing after partial degradation. Biosynthetic components of glucose or amino acid metabolism, ammonia and carbon dioxide are employed in de novo nucleotide synthesis. The liver is the primary organ for de novo nucleotide production.

UNIT- 1 HETEROPOLYSACCHARIDES

Structure

Objectives

1.1 INTRODUCTION

A heteropolysaccharide is a polymer consisting of monosaccharide residues bonded together by glycosidic linkages. hese linkages can be between different monosaccharides, resulting in a branched polymer, or between the same monosaccharide repeating units, resulting in a linear polymer. Heteropolysaccharides found in many different places in nature, including the cell walls of bacteria, the capsules of some viruses, and also exoskeletons of some insects.

One common type of heteropolysaccharide cellulose, which is found in the cell walls of plants. Cellulose made up of repeating units of glucose, and is used to form the tough, fibrous cell walls that give plants their strength. However other heteropolysaccharides include chitin, which found in the exoskeletons of insects, and glycogen, which is used to store energy in the liver and muscles.

Objectives

This is the first block on Heteropolysaccharides, Plasma Proteins and Intermediary metabolism. It consists of following four units. Under first unit (Heteropolysaccharides) we have following objectives. These are as under:

- To understand the definition of heteropolysaccharides
- To know the introduction of heteropolysaccharides.
- To discuss the classification of heteropolysaccharides
- To discuss the properties of glycoproteins and proteoglycans

1.2 CATEGORIES OF POLYSACCHARIDES

Polysaccharides are divided into two categories:

- **Homopolysaccharides and**
- **Heteropolysaccharides.**

1.2.1 HOMOPOLYSACCHARIDES

A chain that contains only one type of monosaccharide unit is known as homopolysaccharides, whereas a heteropolysaccharide contains two or more types of monosaccharide units.The Monosaccharides may link in a linear fashion or even branch out into complex formations and this happens in both types of polysaccharides. Unlike proteins, the Polysaccharidesdo not have any fixed molecular weight. This variation is said to be due to the differences in polysaccharide assembly mechanisms. Without the use of a template, the Polysaccharide synthesis is carried out, and these depend on the intrinsic properties of enzymes.

The polysaccharides that contain multiple monosaccharide units are known as Heteropolysaccharides. Many naturally occurring heteropolysaccharides contain peptides, proteins, and lipids and these are attached to them. Some examples of heteropolysaccharides:i) Peptidoglycans, ii) Agarose, and iii) Glycosaminoglycans (GAGs).

Peptidoglycan (murein) is a part of the bacterial cell wall which is found on the outside of almost all of the bacteria's cytoplasmic membrane. The primary role of the Peptidoglycan is to be able to maintain cell integrity by resisting turgor. This is made up of linear polysaccharide strands which are connected together by short peptides. Agarose is a natural heteropolysaccharide and you can get it from red seaweed. It is a structural part of their cell wall. A linear polymer made up of agarose repeating units is what Agarose is. Agarose is ideal for the electrophoretic separation of DNA and RNA molecules in biochemistry experiments and this is due to it’s gel-forming property.

Heteropolysaccharides that are only present in animals and bacteria and not in plants are known as Glycosaminoglycans, and are found in the extracellular matrix (ECM), which binds cells together in tissues in order to provide a pathway for the nutrients and oxygen to reach individual cells in the case of multicellular animals. Some examples of Homopolysaccharide are: starch, glycogen, chitin, cellulose, and dextran. Cellulose is the most common biomaterial on the earth. Plants produce cellulose in a majority of cases, but bacteria can also produce it. The tough, fibrous, water-insoluble polysaccharide found mostly in plant cell walls is known as Cellulose and it is important for maintaining the structural integrity of the cell walls of plants. Cellulose is a -D-glucose homopolymer with -1, 4 linkages.

1.2.2 HETEROPOLYSACCHARIDES

They are a group of complex carbohydrates that composed of more than one type of monosaccharide. Heteropolysaccharides often found in plant cell walls and are responsible for the rigidity of the cell. The most common heteropolysaccharide is cellulose, which is composed of glucose monomers.

1.3 PEPTIDOGLYCAN

Peptidoglycan a glycoprotein found in the cell walls of bacteria. It composed of peptides (short chains of amino acids) and sugar molecules. The peptides cross-linked to the sugar molecules to form a tough, mesh-like structure that provides the cell wall with strength and rigidity. Peptidoglycan also helps to protect the bacteria from osmotic stress and from the action of antibiotics.

1.4 AGAROSE

Gel electrophoresis a technique used to separate DNA or RNA molecules by size. The molecules placed in a gel made of agarose, a sugar molecule found in red algae. The molecules then subjected to an electric field, which causes them to move through the gel. Larger molecules move more slowly than smaller ones, and so they separated into bands.

The agarose gel electrophoresis technique can used to determine the size of a DNA or RNA molecule. The size of a molecule can determined by comparing the distance it travels through the gel to the distance travelled by a standard molecule of known size.

1.5 GLYCOSAMINOGLYCANS

- Glycosaminoglycans (GAGs) family of linear polysaccharides that found in the extracellular matrix of all animal tissues. Therefore GAGs major component of the connective tissue scaffold and involved in a variety of biological processes including cell proliferation, cell migration, cell adhesion, and tissue repair.
- The GAGs family of linear polysaccharides that found in the extracellular matrix of all animal tissues. GAGs major component of the connective tissue scaffold and also involved in a variety of biological processes including cell proliferation, cell migration, cell adhesion, and tissue repair.
- Therefore the GAGs heterogeneous group of molecules that can divided into two main families: the heparan sulfate/chondroitin sulfate family and the hyaluronan family. The heparan sulfate/chondroitin sulfate family includes the molecules heparan sulfate, chondroitin sulfate, dermatan sulfate, and keratan sulfate. The hyaluronan family includes the molecule hyaluronan.
- The GAGs synthesized by a family of enzymes known as the glycosyltransferases. These enzymes transfer sugar moieties from nucleotide sugars to specific acceptor molecules in the GAG backbone. The GAGs then secreted into the extracellular space where they assemble into larger structures.
- Therefore the GAGs a family of linear polysaccharides that found in the extracellular matrix of all animal tissues. GAGs a major component of the connective tissue scaffold and involved in a variety of biological processes including cell proliferation, cell migration, cell adhesion, and tissue repair.

1.6 HOMOPOLYSACCHARIDE

- A homopolysaccharide a type of polymer composed of repeating monosaccharide units. The simplest homopolysaccharides composed of a single type of monosaccharide, while more complex homopolysaccharides composed of multiple types of monosaccharides.
- The most common homopolysaccharides are cellulose and glycogen. Cellulose is a structural component of plant cell walls, while glycogen is a storage molecule in animals.

Homopolysaccharide examples are starch, glycogen, chitin, cellulose, and dextran. Some of them are explained below:

1.7 STARCH

A homopolysaccharide, starch is made up of glucose monomer units linked together by glycosidic linkage. Plant cells' starch is the most essential storage polysaccharide or nutrient reservoir. The starch molecules are found in large clusters or granules within the plant cells. Humans consume more than half of their carbohydrates in the form of starch. Amylose and amylopectin are two types of starch that are both made up of glucose monomers.

1.8 GLYCOGEN

Animal cells' primary storage polysaccharide molecule is glycogen. Glycogen is structurally similar to amylopectin; the only difference is the degree of branching. In comparison to amylopectin, glycogen is highly branched, with a new branch emerging from the glycogen chain every 8-12 residues. The polymer of -D-glucose bound by glycosidic linkage (α-1, 4) is known as glycogen. (α-1, 6) linkage exists at the branching point.

1.9 CELLULOSE

One of the most common biomaterials on the earth is cellulose. Plants produce it in the majority of cases, but bacteria may also produce it. Cellulose is a tough, fibrous, water-insoluble polysaccharide found mostly in plant cell walls. It is important for maintaining the structural integrity of plant cell walls. Cellulose is a -D-glucose homopolymer with -1,4 linkages. The cellulose molecule, like amylose, is a linear, unbranched homopolysaccharide made up of 10,000-15,000 million -D-glucose units linked together by glycosidic linkage.

1.10 DIFFERENCE BETWEEN HOMOPOLY SACCHARIDES & HETEROPOLY SACCHARIDES

The difference between homopolysaccharides and heteropolysaccharides are as given below:

Homopolysaccharides	**Heteropolysaccharides**
They are chemical compounds that are made up of a single type of monomer.	They are compounds that are made up of two or more different types of monomer.
Made up of the same repeating unit.	Made up of the different repeating unit.
A single type of monomer is involved.	Different types of monomer are involved.
They are simple structures compared to heteropolysaccharide.	They are complex structures.

1.11 GLYCOPROTEINS

The cell membrane contains proteins that are free to float within or close to the membrane. They may move and engage with the surroundings of the cell. In science, the prefix "glyco" stands for "sugar." Any protein molecule with a carbohydrate attached is known as a glycoprotein. The protein's polypeptide side chains are covalently joined to the carbohydrate, an oligosaccharide chain (glycan). Either the process takes place during protein translation, or it occurs post-translationally via glycosylation.

Glycoconjugates are formed when carbohydrates are linked to proteins and lipids. They exist in three forms: glycoproteins, glycolipids and proteoglycans. Glycoproteins are formed when the protein component predominates in the combination of carbohydrates and proteins. It is referred to as a proteoglycan if the association comprises more carbohydrates than proteins. Glycolipids are formed when a carbohydrate combines with lipids. The primary site of glycoprotein and glycolipid synthesis is the Golgi apparatus.

1.12 GLYCOPROTEINS IN HEALTH & DISEASE

Glycoproteins play a vital function in the intestinal absorption and in the biliary and urine excretion of drugs while they are in the cells of the blood-brain barrier, which helps limit the entrance of certain medications into the central nervous system. Generally, transmembrane-transport proteins have been reported in the primary excretory organs, namely, liver, kidney, and gut. This step is important for the removal of substances from the body to quantify the elimination of drugs. The degree of expression and functioning of glycoprotein can be altered by inhibition and induction, which can change the effectiveness, safety, or tissue levels of glycoprotein substrates.

Glycoproteins are incredibly diverse and serve many functions in the body. Some provide structure e.g. collagens, others are involved in immunity e.g. immunoglobulins (such as IgG). Mucins are secreted into mucus of the respiratory and digestive tracts where the specific mucins can retain water thus allowing mucus to serve as an effective lubricant. Specific glycoproteins (and glycolipids) present on the surface of red blood cells determine blood group type. A-oligosaccharide for A group, B-oligosaccharide for B group, both A & B oligosaccharides for AB group, and the absence of both A & B for O group (H-oligosaccharide precursor only). The presence of Rh factor (an antigen) determines Rh^+ groups, whereas the absence of the Rh antigen leads to Rh^- groups after ABO determination.

Certain hormones are glycoproteins including follicle-stimulating hormone (FSH) – a gonadotropin hormone that has several functions in development, growth, puberty, and reproduction. Others include erythropoietin – a cytokine secreted by the kidneys that stimulate red blood cell production in bone marrow in high levels in response to hypoxia (low levels normally). Many viruses have surface glycoproteins called spike domains; S (including SARS-CoV-2; the virus causing COVID-19, discussed below)

which enable viruses to bind to their target receptors and enter cells.

Normally these surface glycoproteins can also serve as natural neutralizing targets for antibodies produced by the body in fighting off an infection and conferring some degree of future immunity. Some viruses including HIV, however, have heavily glycosylated S-domains with an abundance of glycans that interfere with antibody binding and recognition thus making viruses such as HIV more evasive and difficult to fully treat.

1.13 STRUCTURE

A sugar component (glyco) linked to a protein describes the structure of glycoproteins. Covalent bonds are used to bind the two components together. Glycoproteins have higher hydrophilicity than simple proteins due to the -OH groups of sugars. This implies that compared to other proteins, glycoproteins are more drawn towards water. The hydrophilic properties of the molecule also result in the distinctive folding of the tertiary structure of the protein.

1.14 N-LINKED GLYCOPROTEINS AND O-LINKED

Based on where the carbohydrate attaches to an amino acid in the protein, glycoproteins are divided into different groups. A carbohydrate is attached to the nitrogen (N) of the amino group (-NH2) of the R group of the amino acid asparagine in N-linked glycoproteins. The amide side chain of asparagine often serves as the R group. The process of bonding is known as N-glycosylation. The endoplasmic reticulum (ER) membrane provides sugar to N-linked glycoproteins, which are then transferred to the Golgi complex for processing. O-linked glycoproteins are those in which the carbohydrate forms a chemical bond with the hydroxyl group (-OH) of either the R group of the amino acid threonine or the R group of the amino acid serine. A hydroxylysine or hydroxyproline molecule can also form a connection with O-linked carbohydrates. The action is known as O-glycosylation. In the Golgi complex, sugar is bound to O-linked glycoproteins.

1.15 FUNCTIONS

Nearly all cellular processes involve glycoproteins. They play various roles in our body, including those related to our immune systems, physical protection, cell-to-cell communication, and reproductive systems.

- Glycoproteins are present on the lipid bilayer of cell membranes. They can operate in the aqueous environment due to their hydrophilic character, which plays a role in chemical bonding and cell-cell recognition.
- Cell surface glycoproteins are crucial for cross-linking proteins (such as collagen) and cells to strengthen and stabilise a tissue.
- Plants can resist gravity because of glycoproteins found in their cells.
- White blood cells guard the blood arteries as they search for prospective

invaders. They use lectin-type glycoproteins to adhere to the blood vessel lining.

- Glycoproteins are present in the grey matter of the brain, where they collaborate with synaptosomes and axons.
- The glycoproteins thrombin, prothrombin, and fibrinogen are necessary for blood coagulation.
- Due to their ability to facilitate sperm cell attachment to the egg's surface, glycoproteins are essential for reproduction.
- Glycoproteins called mucins are present in the mucus. The molecules protect delicate epithelial surfaces in the digestive, reproductive, urinary, and respiratory tracts.
- Glycoproteins support the immunological response. The specific antigen to which an antibody (or glycoproteins) can bind depends on the carbohydrate it contains. Surface glycoproteins on B and T cells also bind antigens.
- Glycoproteins also maintain the health of our skin. The epithelial cells that form skin have glycoproteins on their surface—these aid in bonding the skin cells in our bodies, creating a strong barrier to protect them.

1.16 EXAMPLES

There are numerous uses for the distinctive interaction between the oligosaccharide chains. Different varieties of glycoproteins with various structures and activities can be produced due to the diversity of interactions. White blood cell identification depends on glycoproteins. The immune system uses a variety of glycoproteins, including,

- Molecules that directly interact with antigens, such as antibodies (immunoglobulins).
- Major histocompatibility complex or MHC molecules, which interact with T cells as a component of the adaptive immune response, are molecules expressed on the surface of cells.
- Blood compatibility antigen H of the ABO blood type is another example of glycoprotein. A few additional examples of glycoproteins are:
- Gonadotropins (luteinizing hormone).
- Components of the zona pellucida, which protects the oocyte and is essential for sperm-egg interaction.
- Connective tissue also contains structural glycoproteins, facilitating the interaction between the connective tissue's fibres and ground substance.
- Soluble glycoproteins often exhibit a high viscosity in blood plasma and egg white.

1.17 HORMONES

Hormones that are glycoproteins include:

- Follicle-stimulating hormone
- Luteinizing hormone
- Thyroid-stimulating hormone
- Human chorionic gonadotropin
- Alpha-fetoprotein
- Erythropoietin (EPO)

1.18 DISTINCTION BETWEEN GLYCOPROTEINS AND PROTEOGLYCANS

A glycoprotein is a compound containing carbohydrate (or glycan) covalently linked to protein. The carbohydrate may be in the form of a monosaccharide, disaccharide (s), oligosaccharide (s), polysaccharide (s), or their derivatives (e.g. sulfo- or phospho-substituted). One, a few, or many carbohydrate units may be present. Proteoglycans are a subclass of glycoproteins in which the carbohydrate units are polysaccharides that contain amino sugars. Such polysaccharides are also known as glycosaminoglycans.

Frequently Asked Questions (FAQs)

Q 1. What is the function of a glycoprotein?

Glycoproteins are a class of molecules made up of carbohydrate and protein chains that play a crucial role in various physiological processes, including the immune system. Many viruses feature glycoproteins that not only facilitate their ability to infiltrate body cells but can also act as essential targets for treatment or prevention.

Q 2. What are glycoproteins derived from?

Glycoproteins are proteins with glycans affixed to the side chains of amino acids. Glycans are saccharide polymers made of oligosaccharide chains that can bind to either amino acids (glycoproteins) or lipids (glycolipids). Usually, a procedure called glycosylation generates these connections.

1.18.1 PROTEOGLYCAN

Proteoglycans are proteins that are heavily glycosylated. The basic proteoglycan unit consists of a core protein with one or more covalently attached glycosaminoglycan (GAG) chain(s). The point of attachment is a serine (Ser) residue to which the glycosaminoglycan is joined through a tetrasaccharide bridge (e.g. chondroitin sulfate-GlcA-Gal-Gal-Xyl-PROTEIN). The Ser residue is generally in the sequence -Ser-Gly-X-Gly- (where X can be any amino acid

residue but proline), although not every protein with this sequence has an attached glycosaminoglycan. The chains are long, linear carbohydrate polymers that are negatively charged under physiological conditions due to the occurrence of sulfate and uronic acid groups. Proteoglycans occur in connective tissue.

They are of a class of glycoproteins of high molecular weight that are found especially in the extracellular matrix of connective tissue (the fibrous tissue that gives support to the body structure). Proteoglycans make up a major part of the extracellular matrix, filling the spaces that occur between cells. Different from other body tissues, the extracellular matrix (ECM) is the most significant part of connective tissue.

Proteoglycans have emerged as biomacromolecules with important roles in matrix remodeling, homeostasis, and signaling in the past two decades. Due to their negatively charged glycosaminoglycan chains as well as distinct core protein structures, they interact with a variety of molecules, including matrix proteins, growth factors, cytokines and chemokines, pathogens, and enzymes. This led to the dawn of glycan therapies in the 20^{th} century, but this research was quickly overshadowed by readily available DNA and protein-based therapies. The recent development of recombinant technology and advances in our understanding of proteoglycan function have led to a resurgence of these molecules as potential therapeutics. This review focuses on the recent preclinical efforts that are bringing proteoglycan research and therapies back to the forefront. Examples of studies using proteoglycan cores and mimetics have also been included to give the readers a perspective on the wide-ranging and extensive applications of these versatile molecules. Collectively, these advances are opening new avenues for targeting diseases at a molecular level, and providing avenues for the development of new and exciting treatments in regenerative medicine.

1.18.2 CLASSIFICATION

Ways to classify

1. Nature of their GAGs chains: Proteoglycans can be classified according to the glycosaminoglycans (GAGs) attached to them. The types are chondroitin sulfate, dermatan sulfate, heparin sulfate, heparan sulfate, or keratan sulfate.
2. Proteoglycans are categorized by their relative size (large and small): Large molecules e.g. aggrecan, an important part of cartilage, versican, which is found in the blood vessels and skin. Small molecules eg decorin, biglycan, fibromodulin, and lumican.

Synthesis

Proteoglycans are synthesized in the rough endoplasmic reticulum, then reshaped in the golgi body, and are ultimately transported to the extracellular matrix by vesicles. The protein component of proteoglycans is synthesized

by ribosomes and translocated into the lumen of the rough endoplasmic reticulum. Glycosylation of the proteoglycan occurs in the Golgi apparatus in multiple enzymatic steps. First, a special link tetrasaccharide is attached to a serine side chain on the core protein to serve as a primer for polysaccharide growth. Then sugars are added one at a time by glycosyl transferase. The completed proteoglycan is then exported in secretory vesicles to the extracellular matrix of the tissue.

Diverse Functions

Proteoglycans are a major component of the animal ECM, being the filler between cells in an organism. Proteoglycans have an important role in the physiology and biomechanical function of tendons, ligaments and cardiovascular system via their involvement in regulation of assembly and maintenance of ECM, and as they participate in cell proliferation through their interactions with growth factors. Eg

- Cartilage contains a variety of proteoglycans, being essential for its normal function. These include aggrecan, decorin, biglycan, fibromodulin and lumican. Each proteoglycan serves several functions that are determinedby both its core protein and its glycosaminoglycan chains. eg Aggrecan provides cartilage with the property to bind with water to form hydrated matrices. These molecules act as fillers between the cell spaces.
- Proteoglycans play important roles in organizing the bone ECM, taking part in the structuring of the tissue itself as active regulators of collagen fibrillogenesis. The bone matrix has a lower proteoglycan content than those in the cartilage and hence takes up less water as is more brittle.

Dysfunction

An inability to break down the proteoglycans (due to absent or malfunctioning lysosomal enzymes) is characteristic of a group of genetic disorders, called mucopolysaccharidoses. Over time, these GAGs collect in the cells, blood and connective tissues. The result is permanent, progressive cellular damage which affects appearance, physical abilities, organ and system functioning.

Older Persons ECM (proteoglycan)

Forever we want to be young but our physiological systems do not allow it. The integumentary system that plays a vital role in outward appearance. Glycosaminoglycans production (named proteoglycans when attached to a protein core are part of the extracellular matrix) decrease as we age and this contributes to human skin ageing. Some of the reasons for this include:

- Reduction or absence of sexual hormonals, such as oestrogen, has been noted to contribute to a reduction in Glycosaminoglycans and proteoglycans among older adults.
- Several GAGs and PGs in the skin may explain ageing skin. In aged skin as

well as photoaging skin, a reduction in ECM components such as epidermal hyaluronan, versican, elastotic materials and dermal biglycan are related to why we have ageing skin.

It is of expert opinion that analyzing the involvement of proteoglycans and glycosaminoglycans in addition to hormonal deficiency such as a drop in the level of oestrogen or complete absence in postmenopausal women may lead us to anti-ageing skin remedies.

Functions

Proteoglycans are a major component of the animal extracellular matrix, the "filler" substance existing between cells in an organism. Here they form large complexes, both to other proteoglycans, to hyaluronan, and to fibrous matrix proteins, such as collagen. The combination of proteoglycans and collagen form cartilage, a sturdy tissue that is usually heavily hydrated (mostly due to the negatively charged sulfates in the glycosaminoglycan chains of the proteoglycans). They are also involved in binding cations (such as sodium, potassium and calcium) and water, and also regulating the movement of molecules through the matrix. Evidence also shows they can affect the activity and stability of proteins and signalling molecules within the matrix. Individual functions of proteoglycans can be attributed to either the protein core or the attached GAG chain. They can also serve as lubricants, by creating a hydrating gel that helps withstand high pressure.

Significance

Proteoglycans have a distinct spatial localization in normal skin and are essential for the correct structural development, organization, hydration, and functional properties of this tissue. The extracellular matrix (ECM) is no longer considered to be just an inert supportive material but is a source of directive, spatial and temporal, contextual information to the cells via components such as the proteoglycans. There is a pressing need to improve our understanding of how these important molecules functionally interact with other matrix structures, cells and cellular mediators in normal skin and during wound healing.

1.19 PROTEOGLYCANS IN BIOMEDICINE

Proteoglycans have emerged as biomacromolecules with important roles in matrix remodeling, homeostasis, and signaling in the past two decades. Due to their negatively charged glycosaminoglycan chains as well as distinct core protein structures, they interact with a variety of molecules, including matrix proteins, growth factors, cytokines and chemokines, pathogens, and enzymes. This led to the dawn of glycan therapies in the 20^{th} century, but this research was quickly overshadowed by readily available DNA and protein-based therapies.

The recent development of recombinant technology and advances in our understanding of proteoglycan function have led to a resurgence of these molecules as potential

therapeutics. This review focuses on the recent preclinical efforts that are bringing proteoglycan research and therapies back to the forefront. Examples of studies using proteoglycan cores and mimetics have also been included to give the readers a perspective on the wide-ranging and extensive applications of these versatile molecules. Collectively, these advances are opening new avenues for targeting diseases at a molecular level, and providing avenues for the development of new and exciting treatments in regenerative medicine.

Recent Advances

New antibodies to glycosaminoglycan side chain components of skin proteoglycans have facilitated the elucidation of detailed localization patterns within skin. Other studies have revealed important proliferative activities of proteinase-generated fragments of proteoglycans and other ECM components (matricryptins). Knockout mice have further established the functional importance of skin proteoglycans in the assembly and homeostasis of the normal skin ECM.

Critical Issues

Our comprehension of the molecular and structural complexity of skin as a complex, dynamic, constantly renewing, layered connective tissue is incomplete. The impact of changes in proteoglycans on skin pathology and the wound healing process is recognized as an important area of pathobiology and is an area of intense investigation.

Future Directions

Advanced technology is allowing the development of new artificial skins. Recent knowledge on skin proteoglycans can be used to incorporate these molecules into useful adjunct therapies for wound healing and for maintenance of optimal tissue homeostasis in aging skin.

Clinical significance

An inability to break down the proteoglycans is characteristic of a group of genetic disorders, called mucopolysaccharidoses. The inactivity of specific lysosomal enzymes that normally degrade glycosaminoglycans leads to the accumulation of proteoglycans within cells. This leads to a variety of disease symptoms, depending upon the type of proteoglycan that is not degraded. Mutations in the gene encoding the galactosyltransferase B4GALT7 result in a reduced substitution of the proteoglycans decorin and biglycan with glycosaminoglycan chains, and cause a spondylodysplastic form of Ehlers–Danlos syndrome.

1.20 SUMMARY

Under this unit we have discussed categories of polysaccharides as well as its types such as homopolysaccharides and heteropolysaccharides. Under this unit, we have dixcussed structure, properties and significance of glycoproteins and proteoglycans. Glycoproteins are molecules of oligosaccharides (glycans) linked to amino acid side

chains of proteins that serve a multitude of physiological functions. These functions vary from structural support such as collagens to determining blood group type Glycoproteins are also present on virus surfaces that enable binding to bodily receptors. SARS-CoV-2 (causes COVID-19) has a spike-domain (a glycoprotein) that binds to ACE2 receptors in the lungs and interfering with the spike domain has been a vaccine target as well as other therapeutic targets.

Proteoglycan are of a class of glycoproteins of high molecular weight that are found especially in the extracellular matrix of connective tissue (the fibrous tissue that gives support to the body structure). Proteoglycans make up a major part of the extracellular matrix, filling the spaces that occur between cells.

1.21 TERMINAL QUESTIONS

Q.1 What do you mean by polysaccharides? Define it with examples.

Answer:----------

Q.2 Explain the scopes of polysaccharides.

Answer:----------

Q. 3 Describe the types of polysaccharides with examples.

Answer:----------

Q. 4 Write short notes on the followings.

(i) Heteropolysaccharides

(ii) Homopolysaccharides

Answer:----------

Q. 5 Explain the glycoproteins with their significance.

Answer:----------

Q. 6 Explain the proteoglycans with their significance.

Answer:----------

FURTHER READINGS

- Biochemistry- Lehninger A.L.
- Textbook of Nutrition and Dietetics Ranjana Mahna
- Biochemistry fourth edition-David Hames and Nigel Hooper.
- Textbook of Biochemistry for Undergraduates - Rafi, M.D.
- Textbook of Nutrition and Dietetics- Monika Sharma

UNIT- 2 : PLASMA PROTEINS

Structure

2.1 INTRODUCTION

Plasma proteins are proteins present in the blood plasma and are produced by the liver (except for immunoglobulins). The proteins are produced by the rough ER in hepatocytes and exported into the blood via the Golgi complex. There are a number of different types of plasma proteins, each serving different specific functions: Albumins regulate the osmotic pressure of the blood (and hence moderate the osmotic pressure of

body fluids). Globulins participate in the immune system (i.e. immunoglobulins) and also act as transport proteins. Fibrinogens are involved in the clotting process (soluble fibrinogen can form an insoluble fibrin clot). Low levels of other plasma proteins have various functions (e.g. α-1-antitrypsin neutralizes digestive trypsin).

Simple and conjugated proteins that comprise plasma proteins are often referred to as blood proteins or serum proteins. Their average plasma concentration is not constant and is influenced by the presence of protein, but usually, it is 7.4% and ranges between 6.5% and 8.4% in a healthy person. As a result, they can be utilised to diagnose and predict diseases using their concentration as the criterion. Plasma proteins are classified into albumin, globulin (alpha 1 globulin, alpha 2 globulin, beta globulin), and other important plasma (Bence-jones protein, fibrinogen). Serum albumin, which constitutes 55% of blood proteins, plays a significant role in maintaining plasma at its oncotic pressure and acts as a carrier for steroid and lipids hormones.

The 38% of blood proteins are globulins that transport hormones, ions, and lipids, helping the immune system work. Aside from gamma globulins, all blood proteins are made in the liver. The conversion of fibrinogen to insoluble fibrin composes 7% of blood proteins necessary for blood clotting. Proenzymes, enzymes, and hormones comprise the remaining 1 percent of plasma proteins, which are regulatory proteins. The proteins in blood serum or plasma are many and are produced by various cells. The biosynthesis of the vast majority of plasma proteins takes place in the liver. A smaller part is synthesized in other cells: *e.g.* lymphocyte (immunoglobulins) and enterocytes (*e.g.* apoprotein B-48).

Objectives

This is the second unit plasma proteins of first block (Heteropolysaccharides, Plasma Proteins and Intermediary metabolism). Under second unit (Plasma proteins) we have following objectives. These are as under:

- To understand the definition of plasma proteins
- To know the regulation of intermediary metabolism.
- To discuss the allosteric modifications and covalent modulation
- To discuss the concept of homeostasis

2.2 PLASMA PROTEINS: DEFINITION, STRUCTURE, FUNCTIONS

Plasma proteins are the collection of intricate molecules found in blood plasma. Their roles are many and varied, and they are mostly synthesized by the liver. Albumin, globulins, and fibrinogen are the three most important plasma proteins. These proteins carry out a number of tasks, including regulating the blood's osmotic pressure, transporting hormones and other chemicals, and assisting in the formation of blood clots. The definition, purposes, obligations, activities, advantages, and disadvantages of

plasma proteins will all be covered in this unit.

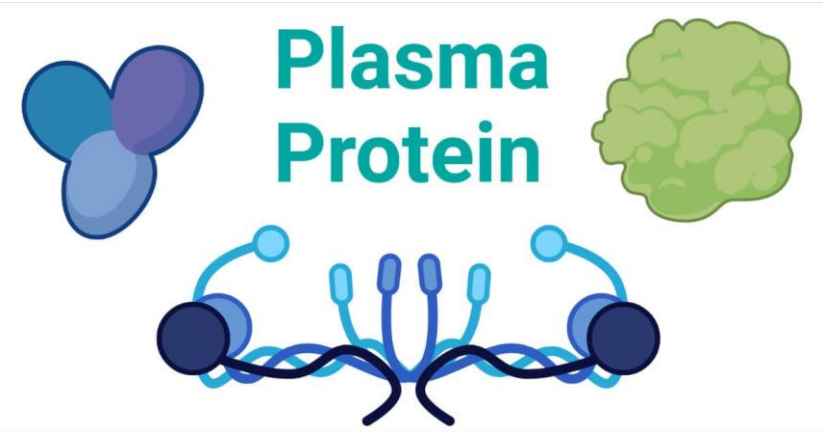


Fig. 1 Plasma Protein

Complex molecules called plasma proteins are present in blood plasma. Mostly produced by the liver, they are then released into the blood plasma. Albumin, globulins, and fibrinogen are the three primary classes into which they are divided. Each group performs and possesses some unique characteristics. Protein degradation takes place inhepatocytes and the mononuclear phagocytic system, where proteins are degraded predominantly after complex formation (*e.g.* antigen-antibody complex and hemoglobin-haptoglobin complex).

Intracellularly, peptide bonds of proteins are hydrolyzed by proteases and peptidases to form amino acids. Another way serum proteins are removed is via excretion, which is facilitated by the kidneys and the gastrointestinal tract. The total serum concentration of proteins is 65-85 g/L. Because plasma proteins are osmotically active, their physiological concentration contributes to a colloid osmotic pressure (oncotic pressure) of 3.33 to 3.52 kPa (25 to 26.4 torr). The concentration of proteins in plasma is slightly higher than in serum because plasma contains coagulation factors.

2.3 STRUCTURE OF PLASMA PROTEINS

Depending on the kind of protein, plasma proteins have different structures. Unlike globulins, which are more complicated and may include numerous chains of amino acids, albumin is a straightforward protein made up of a single chain of amino acids. The complex protein fibrinogen is made up of alpha, beta, and gamma chains, among others. The capacity of plasma proteins to attach to other molecules and take part in numerous physiological processes is determined by their structure, which is crucial for their function.

2.3.1 CATEGORIES OF PLASMA PROTEINS

A variety of intricate molecules called plasma proteins can be discovered in the blood plasma. The three primary categories are albumin, globulins, and fibrinogen.

Albumin

- Making up around 60% of all the protein in the blood, albumin is the most prevalent form of plasma protein.
- It is a simple protein made up of just one amino acid chain. Albumin is essential for preserving the blood's osmotic pressure, which is required to maintain the body's electrolyte and water balance.
- Additionally, it aids in the transportation of numerous molecules such as fatty acids, hormones, and enzymes.

Globulins

Alpha, beta, and gamma globulins are only a few of the many subtypes of globins, a class of proteins that are more complicated than albumin.

- **Alpha Globulins** – The group of proteins known as alpha globulins includes the alpha-fetoprotein, which is generated by the foetal liver and is utilised as a marker for certain cancers. Alpha-1-antitrypsin, which aids in lung damage prevention, and alpha-2-macroglobulin, which aids in immune response regulation, are other alpha globulins.
- **Beta globulins** – Beta globulins include a variety of proteins, including complement proteins and transferrin, which aid in the movement of iron throughout the body.
- **Immunoglobulins**, commonly referred to as **gamma globulins**, are essential for the immunological response. They are produced by B cells and help protect the body against infections.

2.4 FIBRINOGEN

Fibrinogen is a complex protein that is involved in the blood clotting process. It is synthesized by the liver and is converted to fibrin during the clotting process. Fibrin helps to form a clot, which is necessary to stop bleeding after an injury. In addition to these three main types of plasma proteins, there are also a number of other proteins that are found in smaller quantities in the blood plasma, including lipoproteins, which transport lipids throughout the body, and enzymes, which catalyze biochemical reactions.

2.5 PLASMA PROTEIN FUNCTIONS

Many different processes are carried out by plasma proteins, including:

- **Blood osmotic pressure maintenance**

  Albumin is the primary protein that aids in blood osmotic pressure maintenance. This pressure is required to maintain the body's electrolyte and water balance.

- The maintenance of the body's general health depends on plasma proteins. They assist in controlling the body's water balance, moving crucial chemicals around the body, and guarding the body against infections.
- For instance, albumin maintains the blood's osmotic pressure, which helps to avoid the buildup of extra fluid in the tissues.
- **Transportation**

  Hormones and other molecules are transported by globulins and albumin, which also aid in the movement of enzymes and other molecules.
- **Blood Clot Formation**

  The primary protein that aids in the formation of blood clots is fibrinogen. In order to stop excessive bleeding after an injury, they are also essential for the blood clotting process.
- **Immunity**

  Some globulins, including immunoglobulins, participate in the immunological response and aid in defending the body against infections.

2.6 PLASMA PROTEINS DEVELOPMENT PROCESS

The genes in the liver cells play a major role in controlling the production and regulation of plasma proteins. More than 90% of plasma proteins are made in the liver, and a sophisticated web of genetic pathways controls how they are made. A variety of elements, including hormones, nutrition, and illness, can affect how the genes that code for plasma proteins are expressed. Scientists are still learning more about the roles of plasma proteins and how they may be used in medicine. The use of plasma proteins in the creation of novel treatments for a variety of diseases, such as cancer and autoimmune disorders, has gained popularity in recent years. Additionally, new techniques for producing plasma proteins have been developed as a result of biotechnology advancements, including the use of recombinant DNA technology.

Advantages and Drawbacks

Advantages

One benefit of plasma proteins is that they are essential for preserving the body's general health. They aid in maintaining the proper balance of water in the body, carry vital molecules across the body, and guard against infections. Plasma proteins are also employed in a number of medical procedures, such as the therapy of the immune system and blood problems.

Drawback

However, there are some drawbacks to plasma proteins as well. For instance, the blood's plasma protein levels may become unbalanced in illnesses like liver or renal

disease, which might affect one's health. Additionally, some people may have an allergic reaction to plasma proteins, which can cause symptoms such as hives, itching, and difficulty breathing.

Genetic Control and Application

Research into the particular genes and processes involved in the production and control of these significant molecules is underway in the domain of the genetic control of plasma proteins. New pathways for modifying the genetic regulation of plasma proteins and creating novel therapies for a variety of medical illnesses may be opened up by technological advancements like gene editing and gene therapy. The study of plasma protein structure is another important topic of research, with researchers employing a variety of methods, including X-ray crystallography and NMR spectroscopy, to comprehend how these intricate molecules are put together and performed in the body.

Sequential Changes in Plasma Proteins after Surgery

Plasma proteins play a crucial role in the body's response to surgery, as they are involved in inflammation, tissue repair, and immune function. The levels and composition of plasma proteins can change in response to surgery, and understanding these changes can provide important insights into the body's response to surgical trauma. The sequential changes in plasma proteins after surgery can be divided into three phases: the acute phase response, the resolution phase, and the late phase response.

Acute Phase Response

C-reactive protein, serum amyloid A, and fibrinogen levels all quickly rise as part of the acute phase response, which is the body's initial reaction to surgical trauma. These proteins aid in mobilizing the body's immune response to the site of damage and are involved in tissue healing and inflammation. After surgery, the acute phase reaction normally lasts a few days.

Resolution and Late Phase

- The resolution phase is characterized by a reduction in the levels of acute phase proteins and an increase in the levels of proteins involved in tissue repair, such as albumin and transferrin.
- The resolution phase is a time when inflammation is waning.
- This period, which might persist for a number of weeks following surgery, is crucial for healing and tissue generation.
- After surgery, there may be a protracted period of changed plasma protein levels called the "late phase response," which might extend for several months.
- The levels of certain growth factors that are involved in tissue remodeling and scar formation, such as transforming growth factor beta, rise during this period.

 Generally speaking, the adjustments in plasma proteins following surgery reflect the

body's reaction to the trauma as well as the process of tissue regeneration and repair. Understanding these alterations can offer crucial insights into how the body reacts to surgical stress and could point to fresh treatment targets for the promotion of recovery and reduction of postoperative problems.

2.7 DEPLETION OF ABUNDANT PLASMA PROTEINS AND LIMITATIONS OF PLASMA PROTEOMICS

The goal of the quickly developing field of study known as plasma proteomics is to identify and count the proteins found in blood plasma.

- The presence of extremely abundant proteins, which might prevent the identification of important proteins with low abundance, is one of the main difficulties in plasma proteomics.
- Prior to doing a proteomic analysis, researchers frequently employ depletion techniques to take out the most prevalent proteins from plasma.
- It entails the careful removal of the sample's most prevalent proteins, sometimes with the use of antibodies or other affinity-based techniques.
- This can broaden the analysis's dynamic range and enhance the identification of proteins with lower abundances.
- However, this strategy has a number of drawbacks. Depletion strategies may not completely eliminate all highly abundant proteins, even though they can remove a sizable fraction of them.
- This may cause lingering interference with the identification of proteins with lower abundances.

2.8 INTERMEDIARY METABOLISM

Intermediary metabolism refers to the sum of all intracellular chemical processes by which nutritive material is converted into cellular components. It includes anabolism (synthesis of macromolecules) and catabolism (breakdown of macromolecules). Cellular energy is generated from aerobic oxidation of metabolic fuels (carbohydrates, fats, proteins) derived from digestion of a meal or from breakdown of internal stores. These metabolic fuels are broken down into basic substrates (glucose, amino acids, free fatty acids, glycerol). This is followed by processes that remove electrons (oxidation) from these substrates at high potential and transfer them to substrates at lower potential.

It is during these processes that energy is released. Reduced coenzymes (NAD^+ and FADH) are intermediate energy storage compounds that aid electron (and energy) transfer from metabolic reactions (glycolysis and Krebs cycle) to the electron transport chain. In the electron transport chain, electrons are transferred through a series of carriers of lower potential and energy released during this is used to form adenosine triphosphate. These electrons finally combine with the end electron acceptor oxygen, to

form water. During aerobic metabolism, oxygen is consumed at the end of electron transport chain producing carbon dioxide via Krebs cycle. However, energy can also be generated anaerobically via glycolysis with the production of lactate.

2.9 MECHANISMS OF METABOLIC REGULATION

Four mechanisms dictate the flux of metabolites through their respective pathways:

1. Substrate availability
2. Allosteric enzyme regulation
3. Covalent enzyme modification
4. Regulation of enzyme synthesis, namely through the induction or repression of transcription.

Allosteric enzyme regulation occurs at rate-determining steps primarily. For example, following meal glycolysis in the liver is stimulated by the increase of fructose-2, 6-bisphosphate, which is an allosteric activator of phosphofructokinase-1 (PFK-1)**.** In addition, the opposing pathway of gluconeogenesis is turned off by fructose-2, 6-bisphophate allosterically inhibiting fructose-1, 6-bisphosphatase**.**

The addition or removal of phosphate groups from specific enzyme serine, threonine, or tyrosine residues allow for enzyme regulation through covalent modification. During the fed state, most of the enzymes regulated in this way will be dephosphorylated and active. Three notable exceptions to this generality are glycogen phosphorylase kinase, glycogen phosphorylase**,** and hormone-sensitive lipase**,** which are inactive when they are dephosphorylated. Note that these three enzymes play key roles in releasing stored energy, and so it makes sense to have them inactive during times when metabolites are in abundance.

Regulating enzyme synthesis by inducing or suppressing transcription allows the cell to increase or decrease the total number of key proteins of metabolic pathways, in contrast to allosteric or covalent modifications, which influence the efficiency of enzymes. This process is mediated by proteins that are typically activated or inhibited in the cytosol, usually by phosphorylation or dephosphorylation, and enter the nucleus to induce transcription of regulatory enzymes.

Example of Metabolic Regulation

For example, under fed conditions insulin induces both glycolysis and the pentose phosphate pathway. Protein phosphatase 2A (PP2A) is activated by xylulose-5-phosphate to dephosphorylate Carbohydrate response element-binding protein (ChREBP)**,** which allows it to translocate into the nucleus and bind to Max-like protein (MLX) and induces the transcription of glycolytic enzymes (Hexokinase, PFK-1, PFK-2, Pyruvate **kinase)** through interaction with carbohydrate response element (ChORE)**.** ChREBP also influences lipogenesis by enhancing the synthesis of Fatty acid synthase (FAS) **and** Stearoyl-CoA desaturase (SCD)

Equilibrium and non-equilibrium reactions

Chemical reactions involving noncovalent bond formation are discuss with regard to the equilibrium and nonequilibrium states: An equilibrium-to-equilibirum chemical reaction involves change of equilibrium states by changing the environment; a nonequilibrium-to-equilibrium reaction involves change of metastable state to equilibrium. Complex nature of the chemical reactions, especially in the latter, is shown in terms of the multiple-path nature in the microscopic molecular structure changes and macroscopic concentration changes. Irreversible and reversible nonequilibrium-to-equilibrium chemical reactions are also compared in terms of the multiple-path. Helicene oligomers, which reversibly form double-helix and random-coil by temperature changes, are discussed with regard to the reversible nonequilibrium-to-equilibrium chemical reaction with self-catalysis, where notable chemical phenomena appear under non-equilibrium conditions.

2.10 ALLOSTERIC MODULATION

Allosteric modulation is a term in pharmacology and biochemistry that refers to a group of substances that bind to a receptor to change that receptor's response to the stimulus. Some of these modulators are drugs, e.g. benzodiazepines. Allosteric site is the site that an allosteric modulator binds to. It is not the same one to which the endogenous agonist of the receptor is going to bind (this particular site is named the orthosteric site). We can call both modulators and agonists as receptor ligands.

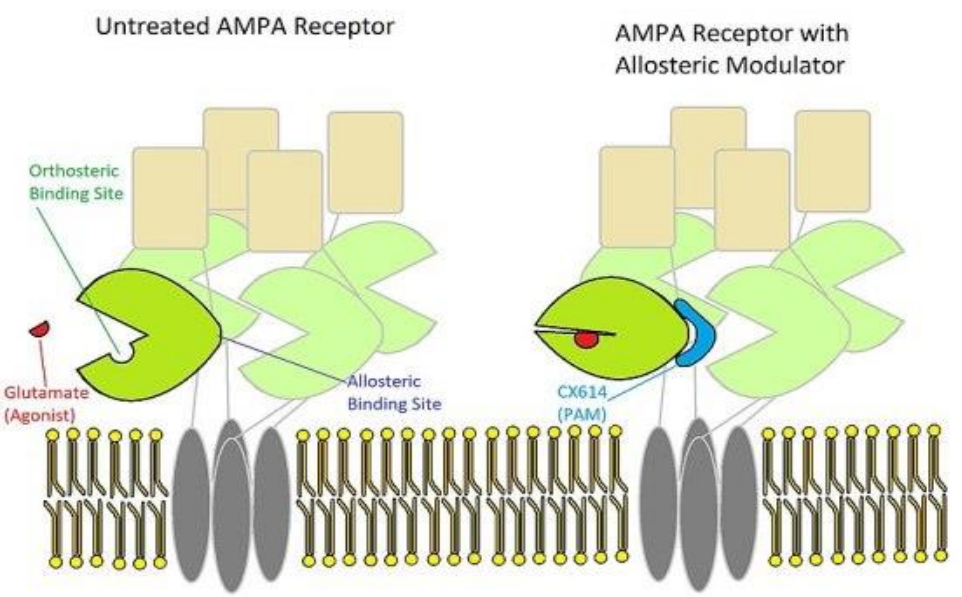


Fig. Allosteric Modulation

Moreover, there are three major types of allosteric modulators: positive, negative, and neutral modulations. The positive type can increase the response of the receptor by

increasing the probability of the agonist binding with a receptor, by increasing the ability to activate the receptor (this is called efficacy), or by both these ways. On the other hand, the negative type can decrease agonist affinity and efficacy. Finally, the neutral type does not affect the agonist activity, but it can stop other modulators from binding to an allosteric site. Moreover, some allosteric modulators work as allosteric agonists.

Generally, allosteric modulators are able to alter the affinity and efficacy of other substances that act on a receptor. A modulator can also increase the affinity and lower efficacy or vice versa. Affinity is the ability of a substance to bind to a receptor. Efficacy, on the other hand, is the ability of a substance to activate a receptor that is given as a percentage of the ability of the substance to activate the receptor in comparison to the endogenous agonist of the receptor.

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. Allostery is the process of enzyme regulation, where binding at one site influences the binding at subsequent sites.

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
- Activator increases the activity of an enzyme, whereas inhibitor decreases the activity after binding
- The velocity vs substrate concentration graph of allosteric enzymes is **S-curve** as compared to the usual hyperbolic curve

2.11 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 cooperativity, e.g. binding of oxygen to haemoglobin. Heterotropic Regulation: When the substrate and effector are different. The effector may activate or inhibit the enzyme, e.g. binding of CO_2 to haemoglobin. 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:

1. Simple Sequential Model-

It was given by Koshland. In this model, the binding of substrate induces a change in the conformation of the enzyme from T (tensed) to R (relaxed). The substrate binds according to the induced fit theory. A conformational change in one unit stimulates similar changes in other subunits. This explains the cooperative binding.The same way inhibitors and activators bind, the T form is favoured, when the inhibitor binds and R form is favoured, when the activator binds. The binding at one subunit affects the conformation of other subunits.The sequential model explains the negative cooperativity in enzymes, e.g. tyrosyl tRNA synthetase, where the binding of substrate inhibits the binding of another substrate.

2. Concerted or Symmetry Model-

According to this model, there is a simultaneous change in all the subunits of an enzyme. All the subunits are either present in R form (active form) or T form (inactive form), having less affinity to a substrate.An inhibitor shifts the equilibrium of T $\rightleftarrows$ R, towards T, and activator shifts the equilibrium towards R form and favours the binding. It explains the cooperative regulation of activators as well as inhibitors.

Allosteric Enzyme Examples

There are many allosteric enzymes that take part in the biochemical pathways so that the system is well controlled and modulated. Aspartate Transcarbamoylase (ATCase)

- 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
- This ensures the synthesis of pyrimidine nucleotide when a high concentration of purine nucleotide is present

Glucokinase

- It plays an important role in glucose homeostasis. It converts glucose to glucose-6-phosphate and enhances glycogen synthesis in the liver. It also senses the concentration of glucose for the release of insulin from pancreatic beta cells
- The glucokinase has low affinity for glucose, so it acts when more concentration of glucose is present in the liver, which should be converted to glycogen
- The activity of glucokinase is regulated by glucokinase regulatory proteins

Acetyl-CoA Carboxylase

- Acetyl-CoA carboxylase regulates the process of lipogenesis
- This enzyme is activated by citrate and inhibited by a long chain acyl-CoA molecule such as palmitoyl-CoA, which is an example of negative feedback inhibition by product
- Acetyl-CoA carboxylase is also regulated by phosphorylation/ dephosphorylation controlled by hormones such as glucagon and epinephrine

Frequently Asked Questions

Q. 1 Which are allosteric enzymes?

Allosteric enzymes are enzymes that have an additional binding site for effector molecules other than the active site.

Q. 2 Which are allosteric enzymes?

There are many allosteric enzymes that take part in the biochemical pathways. Examples include: Aspartate Transcarbamoylase, Glucokinase, Acetyl-CoA Carboxylase.

Q. 3 What are the three types of enzyme regulation?

Enzyme regulations are of the following types – Allosteric regulation, genetic and covalent modification, and enzyme inhibition

2.12 COVALENT MODULATION

Covalent modulation is an important term used in biochemistry, and it refers to a group of substances that bind covalently to a receptor, changing its response. Enzymes are

able to be regulated by the transfer of a molecule or atom from a donor to an amino acid side chain that can serve as the receptor of the transferred molecule. The other way of doing this is altering the amino acid sequence itself via proteolytic cleavage.

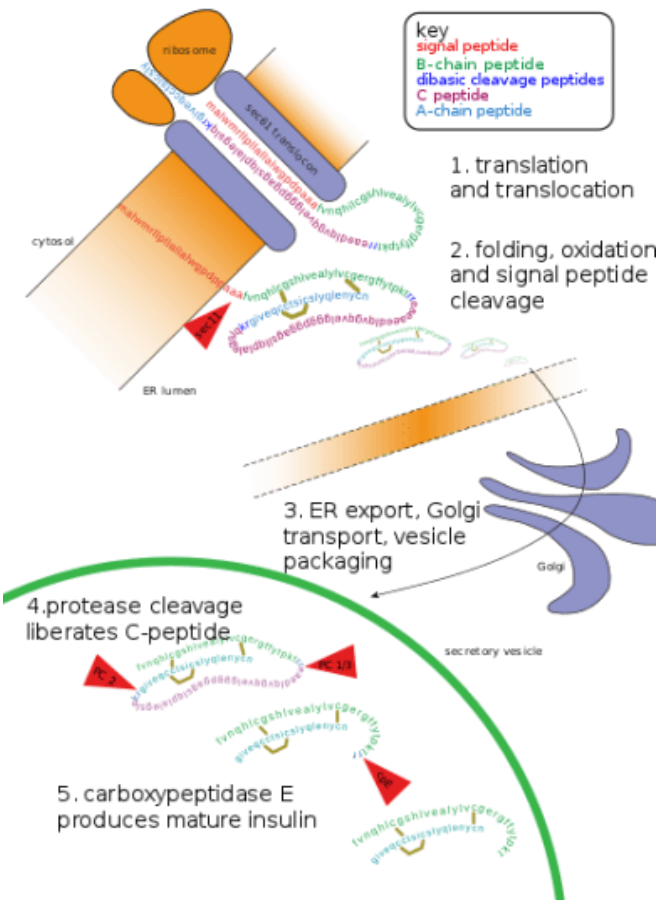


Fig. Covalent modulation

Covalent modulation involves the alteration of the shape and function of an enzyme via the covalent bonding of chemical groups to it. Moreover, this modulation is also known as post-translational modification. Usually, this modulation takes place in the endoplasmic reticulum and the Golgi apparatus. The sites that can often undergo post-translational modification are the sites having a functional group serving as a nucleophile in the reaction. These sites include hydroxyl groups of serine, threonine, and tyrosine, along with the amine forms of lysine, arginine, and histidine.

Crossing Over

The term crossing over was coined by Morgan. Crossing over is a process that produces new combinations of genes by exchanging segments between non-sister chromatids of homologous chromosomes normally reciprocally but sometimes unequally. Crossovers are chromatins resulting from crossing over i.e. interchange of chromosomal parts.

Characteristics of Crossing Over

- Occurs at two levels, at gross chromosomal level (chromosomal recombination) and at DNA level (genetic recombination).
- Occurs between non-sister chromatids of homologous chromosomes.
- Exchange is normally reciprocal but sometimes unequal.
- Frequency of crossing over is closely related to physical distance between genes located on chromosomes.

Types of Crossing Over

- Somatic or Mitotic Crossing Over
- Germinal or Meiotic Crossing Over

Somatic or Mitotic Crossing Over

When crossing over occurs in chromosomes of somatic cells of an organism during mitotic cell division, it is called as mitotic crossing over. Occurrence is rarely. It has no genetical significance.

Germinal or Meiotic Crossing Over

When crossing over occurs during meiosis, it is called as meiotic crossing over.

Pre-requirements of Crossing Over

- Replication of about 99.7% DNA and 75% of histone synthesis should be completed before prophase I.
- Attachment of all chromosomes to nuclear envelop by their both ends, during leptotene.

Kinds of Crossing Over

- Single crossing over
- Double crossing over (reciprocal and complimentary)
- Multiple crossing over

Stages of Crossing Over or Mechanism of Crossing Over

The page Mechanism or Stages of Crossing-over provides the sufficient information on the topic.

Theories about the mechanism of Crossing Over

- Duplication theory (John Belling, 1928)
- Copy choice hypothesis / Switch model (J. Laderbeg)

- Break and exchange theory
- Hybrid DNA model

Factors affecting Crossing Over

- Age
- Sex
- Temperature
- Radiations
- Chemicals
- Physical distance between genes

Significance of Crossing Over

- ✓ Crossing over is universal in occurrence, occurs in plants, animals, bacteria, viruses and moulds.
- ✓ Meiotic crossing over allows a more independent selection between the two alleles that occupy the positions of single genes, as recombination shuffles the allele content between sister chromatids.
- ✓ Helps in proving linear arrangement of genes.
- ✓ Recombination does not have any influence on the statistical probability that another offspring will have the same combination. This theory of "independent assortment" of alleles is fundamental to genetic inheritance.
- ✓ Origin of new character
- ✓ Necessary for natural selection, as it increases chances of variation.

2.13 WHAT IS HOMEOSTASIS

Homeostasis refers to the body's need to reach and maintain a certain state of equilibrium. The term was first coined by a physiologist named Walter Cannon in 1926. More specifically, homeostasis is the body's tendency to monitor and maintain internal states, such as temperature and blood sugar, at fairly constant and stable levels. Homeostasis refers to an organism's ability to regulate various physiological processes to keep internal states steady and balanced. These processes take place mostly without our conscious awareness.

How Is Homeostasis Maintained?

Your body has set points for a variety of states—including temperature, weight, sleep, thirst, and hunger. When the level is off (in either direction, too much or too little), homeostasis will work to correct it. For example, to regulate temperature, you will sweat when you get too hot or shiver when you get too cold. Another way to think of it

is like the thermostat in your house. Once set at a certain point, it works to keep the internal state at that level. When the temperature drops in your house, your furnace will turn on and warm things up to the preset temperature. In the same way, if something is out of balance in your body, a physiological reaction will kick in until the set point is once again reached. Here's how the primary components of homeostasis work:

1. **Stimulus**: A stimulus from a change in the environment kicks something out of balance in the body.
2. **Receptor**: The receptor reacts to the change by informing the control unit.
3. **Control unit**: The control unit then communicates the change needed to bring the body back into balance.
4. **Effector**: The effector receives this information and acts on the change that is needed.

A negative feedback loop will work to decrease the effect of the stimulus, whereas a positive feedback loop will increase it. In homeostasis, negative feedback loops are most common, as the body is typically attempting to decrease the effect of the stimulus to get the body back to equilibrium.

How Addiction Affects Homeostasis

Types of Homeostatic Regulation

There are three main types of homeostatic regulation that happen in the body. Though their names might be unfamiliar, you probably experience them every day.

Thermoregulation

When you think about homeostasis, temperature might come to mind first. It is one of the most important and obvious homeostatic systems. Regulating body temperature is called thermoregulation. All organisms, from large mammals to tiny bacteria, must maintain an ideal temperature in order to survive. Some factors that influence this ability to maintain a stable body temperature include how these systems are regulated as well as the overall size of the organism.

Endotherms:

Some creatures, known as endotherms or "warm-blooded" animals, accomplish this via internal physiological processes. Birds and mammals (including humans) are endotherms.

Ectotherms: Other creatures are ectotherms (aka "cold-blooded") and rely on external sources to regulate their body temperature. Reptiles and amphibians are both ectotherms.

The colloquial terms

"warm-blooded" and "cold-blooded" do not actually mean that these organisms have

different blood temperatures. These terms simply refer to *how* these creatures maintain their internal body temperatures. Thermoregulation is also influenced by an organism's size, or more specifically, the surface-to-volume ratio.

- **Large organisms**: Larger creatures have a much greater body volume, which causes them to produce more body heat.
- **Small organisms**: Smaller animals, on the other hand, produce less body heat but also have a higher surface-to-volume ratio. They lose more body heat than they produce, so their internal systems must work much harder to maintain steady body temperature. This is even true of babies, especially those born prematurely.

2.14 OSMOREGULATION

Osmoregulation strives to maintain the right amount of water and electrolytes inside and outside cells in the body. The balance of salt and water across membranes plays an important role, as in osmosis, which explains the name "osmoregulation." In this process, the kidneys are responsible for getting rid of any excess fluid, waste, or electrolytes. Osmoregulation also affects blood pressure.

Chemical Regulation

Your body regulates other chemical mechanisms as well to keep systems in balance. These use hormones as chemical signals—for example, in the case of blood sugar levels. In this situation, the pancreas would release either insulin, when blood sugar levels are high, or glucagon, when blood sugars are low, to maintain homeostasis.

Impact of Homeostasis

Homeostasis involves both physiological and behavioral responses. In terms of behavior, you might seek out warm clothes or a patch of sunlight if you start to feel chilly. You might also curl your body inward and keep your arms tucked in close to your body to keep in the heat. As endotherms, people also have a number of internal systems that help regulate body temperature. When your body temperature dips below normal, a number of physiological reactions respond to help restore balance. Blood vessels in the body's extremities constrict in order to prevent heat loss. Shivering also helps the body produce more heat.

The body also responds when temperatures go above normal. Have you ever noticed how your skin becomes flushed when you are very warm? This is your body trying to restore temperature balance. When you are too warm, your blood vessels dilate in order to give off more body heat. Perspiration is another common way to reduce body heat, which is why you often end up flushed and sweaty on a very hot day.

Homeostasis and Mental Health

Like the body, the mind seeks its own type of homeostasis and attempts to compensate when out of balance. For example, one prominent theory of human motivation, known as drive-reduction theory, suggests that homeostatic imbalances create needs. These needs, in turn,

motivate behavior in an attempt to restore homeostasis

Frequently Asked Questions

Q. 1 State homeostasis definition.

Homeostasis is the ability to maintain internal stability in an organism in response to the environmental changes. The internal temperature of the human body is the best example of homeostasis.

Q. 2 Which body systems help to maintain homeostasis?

The endocrine system and the nervous system are essential in maintaining the homeostasis of the body. However, other organs also play a role in maintaining homeostasis as well.

Q. 3 How is homeostasis essential for our body?

Homeostasis is a self-regulating process that controls internal variables necessary to sustain life.

Q. 4 What are the main components of homeostasis?

Homeostasis involves three components- the receptor, the control centre, and the effector. The receptor receives information on the changing environment, and the control centre processes the information received by the receptor. And the effector responds to the commands of the control centre by enhancing or opposing the stimulus.

Q. 5 What is the primary function of homeostasis?

The primary function of homeostasis is to maintain a balance within the body regarding its temperature, salt concentration, food intake and pH levels.

Q. 6 How does the cell maintain homeostasis in the body?

To maintain homeostasis in the body, the cells perform the following activities: Obtain and use energy, exchange materials, make new cells, and eliminate wastes.

Q. 7 What role does liver play in homeostasis?

Our liver plays a vital role in blood glucose homeostasis. When the blood glucose level rises after a meal, the liver removes glucose from the blood and stores it in the form of glycogen. When the blood glucose levels are low, it converts the stored glycogen back to glucose.

Q. 8 How does the skin help in maintaining homeostasis?

If the external temperature is high, the body tries to keep cool by producing sweat. Also, blood vessels near the skin surface dilate. This helps in decreasing body temperature. Conversely, if the external temperature is cold, the blood vessels constrict and retain body heat. Thus, the skin maintains homeostasis.

2.15 SUMMARY

Under this unit we have discussed plasma proteins and their functions in concern to intermediary metabolism. Important macromolecules known as plasma proteins are involved in a number of physiological processes, such as immune response, inflammation, and tissue repair. Proteomics has been actively researching the characterization of plasma proteins and how they alter in response to various stressors, such as surgery. Researchers frequently employ depletion techniques to get around this constraint since the presence of very abundant plasma proteins might hinder the identification of low-abundance proteins. Although depletion techniques can increase the dynamic range of proteomic analysis, they have drawbacks as well, such as incomplete depletion, information loss, sample variability, and technical constraints.

Allosteric modulation refers to a group of substances that bind to a receptor to change that receptor's response to a stimulus, while covalent modulation refers to a group of substances that bind covalently to a receptor and changes its response. The key difference between allosteric and covalent modulation is that allosteric modulation requires a phosphatase enzyme, whereas covalent modulation requires a kinase enzyme.

2.16 TERMINAL QUESTIONS

Q.1 What do you mean by plasma proteins? Define it with examples.

Answer:----------

Q.2 Explain the concept of intermediary metabolism

Answer:----------

Q.3 Explain the equilibrium and non-equilibrium reactions.

Answer:----------

Q.4 Write short notes on the followings.

(i) Allosteric modulation

(ii) Covalent modulation

Answer:----------

Q. 5 Explain the concept of homeostasis

Answer:----------

Further readings

- Biochemistry- Lehninger A.L.
- Textbook of Nutrition and Dietetics Ranjana Mahna
- Biochemistry fourth edition-David Hames and Nigel Hooper.
- Textbook of Biochemistry for Undergraduates - Rafi, M.D.
- Textbook of Nutrition and Dietetics- Monika Sharma

UNIT- 3 : INTERMEDIARY METABOLISM

Structure

Objectives

3.1 INTRODUCTION

One of the major reasons for studying Biochemistry is to understand how living organisms utilize the chemical energy in their environment to carry out their biochemical activities. It is called intermediary metabolism. This requires an understanding of the simpler principles of physical chemistry and thermodynamics as they apply to live organisms. Also required is an appreciation of the so-called "energy-rich compounds' that permit the living organism to trap and subsequentially utilize the chemical energy contained in the food materials it consumes.

The sun is the ultimate source of energy for all life on the planet Earth. That energy, like sunlight, is trapped by photosynthetic organisms and used to convert CO2 into the organisms' cellular material, composed mainly of proteins, carbohydrates, and lipids, but also smaller amounts of nucleic acids, vitamins, coenzymes, and other compounds. Some of those products of photosynthesis (carbohydrates and lipids) are, in turn, utilized by non-photosynthetic organisms, mainly animals, as a source of energy for growth, development, and reproduction

By definition, "intermediary" means "between the most complex (structure) and the least complex", whereas "metabolism" is a term derived from Greek meaning "a change or alteration." In terms of the nutrient needs of vertebrate organisms, then, the building blocks of the three major energy substrates may be arranged (synthesized, anabolized) into larger, more complex structures within the body. Also, very large (complex) organic compounds may be broken down (catabolized) into fundamental, basic building blocks. These basic units of body materials are monosaccharides (for the complex sugars or carbohydrates), amino acids (for the complex polypeptides and proteins), and glycerol and free fatty acids (for the lipid or fat moiety). Thus intermediary metabolism represents the sum total of chemical events (usually catalyzed by enzymatic proteins) occurring simultaneously in both anabolic and catabolic processes.

Objectives

This is the third unit intermediary metabolism of first block (Heteropolysaccharides, Plasma Proteins and Intermediary metabolism). Under third unit (intermediary metabolism) we have following objectives. These are as under:

- To understand the definition of metabolism
- To know the concept of intermediary metabolism and free energy.
- To discuss the concept of glycolysis and gluconeogenesis,
- To discuss the concept of citric acid cycle and hexose monophosphate pathway

3.2 TYPES OF METABOLIC REACTIONS

There are three types of reactions are present in Metabolism. They are

Exothermic Reactions

The reactions release energy and, therefore, have negative enthalpy changes. On reaction energy diagrams, the products of exothermic reactions have energy levels lower than those of starring materials.

Endothermic reactions

The reactions absorb energy and, therefore, have positive enthalpy changes. In reactions energy diagrammed, the products of endothermic reactions have higher energy levels than the starting materials.

Isothermic reaction

This type of reaction has not released any energy.

Bonds Cleavage and its types

In intermediary metabolism, a covalent bond (σ-bond) is formed with the help of two atoms by the sharing of a pair of electrons. When the two atoms are separated from each other, bond fusion (or cleavage) is said to have taken place. The cleavage process can occur in two ways:

a) homolytic cleavage and

b) Heterolytic cleavage.

a) Homolytic cleavage

When one electron of the bonding pair goes with each of the departing atoms, the fission is symmetrical (0r) and homogenous, and is called "**Homolytic cleavage**" (or) "**Homolysis**".

A-B (or) A: B –> A· + .B

- The two fragments that are produced as a result of hemolytic fission carry an odd electron each and are called "**Free Radicals**".
- These are transitory and at once react with other radicals (or) molecules by giving one more electron to restore the stable bonding pair.

b) Heterolytic Cleavage

When a covalent bond breaks in a fashion that both the bonding electrons are appropriated by one of the two departing fragments (atoms or groups), it is said to have undergone "**Heterolytic cleavage**" (or) "**Heterolysis**".

A-B (or) A: B –> $A:^{-}$ + B^{+}

- The heterolytic cleavage yields one positive & one negative ion.
- These reactions take place more readily in polar solvents like water and are catalyzed by the presence of ionic catalysts (e.g.: acidic or basic).

3.3 BOND LENGTH

Atoms involved in the formation of a bond cannot come any closer to each other than a certain distance where the potential energy is at its minimum.

Bond	**Bond Length (A^0)**	**Bond**	**Bond Length (A^0)**
C – C	1.57	C = O	1.20
C = C	1.34	C – H	1.12

C ≡ C	1.20	C – F	1.42
C – N	1.47	C – Cl	1.77
C = N	1.28	C – Br	1.91
C ≡ N	1.15	C – I	2.13
C – O	1.43	O – H	0.97

The average distance between the nuclei of two atoms bonded to each other is used under the name of bond length" or "bond distance." Thus, bond length may be defined as the average distance between the centers of the nuclei of the two bonded atoms. It is expressed in angstrom (A0) units ($1A0 = 10^{-8}$ cm).

Points to remember:

- Multiple bonds (double or triple bonds between two atoms) are always shorter than the corresponding single bond.
- Bond length decreases with the increase in "s" character, since an **s-orbital** is smaller than a p-orbital. Thus
- sp^3 **C-H** = 1.093 A^o (in alkanes)
- sp^2**C-H** = 1.087 A^o (in Alkenes)
- sp **C-H** = 1.057 A^o (in Alkynes)
- Since bond distance is the sum of the ionic or covalent (atomic) radii of the two concerned atoms, the factors, and trends observed in the ionic or atomic radii will apply on the bond distance.

3.4 BOND ANGLE

In the molecules are made up of three or more atoms, the average angle between the bonded orbitals is known as a bond angle, Φ. Fundamentally, the value of the bond angle largely depends on the nature of the bonds concerned. The bond angle in the water molecule formed by the overlapping of two s-orbitals of hydrogen atoms with one 2p orbital of an oxygen atom should be 900. The actual H-O-H bond angle is 1040 31'. Bong angles are important for analyzing the behavior of molecules in intermediary metabolism.

Points to remember

- Repulsion between atoms or groups attached to the central atoms: the positive charge, developed due to the high electronegativity of oxygen, on the two hydrogen atoms in water causes repulsion among themselves, which increases the bond angle, H-O-H from 90^0 to 105^0.

- Hybridization of bonding orbitals: hybridization of bonding orbitals also plays a very important role in determining the values of bond angles.

Bond type	sp3	sp2	sp
Bond angle	109^0 28’	120^0	180^0

- Repulsion due to non-bonded electrons: the deviation of the normal tetrahedral bond angle of 109^0 28’ in H2O (105^0), NH3 (107^0), etc. although their central atoms are in an *sp3* hybridized state.

3.5 CLASSIFICATION OF METABOLIC REAGENTS

Now let us discuss the metabolic reagents in intermediary metabolism. The presence of a charge on the reactant certainly helps the attack of the reagent on the reactant, but it is far from essential. Indeed, the requisite unsymmetrical charge distribution may be induced by the mutual polarization of the reagent and reactant on their close approach, as when bromine is added to ethylene. Thus, because of the above principle, most of the reagents can be classified into the following two types.

1. Electrophilic reagents (Electrophiles)

The name implies electrophilic (electro=electron, phile=love) reagents are electron seeking (or) loving and thus attack the substrate at the point of maximum electron density. Thus, an electrophile is a species having an electron-deficiency atom (or) center. The electrophilic reagent may be a positively charged species or a neutral molecule with an electron-deficient center. Some important electrophiles are given below:

E.g.: H^+, Br^+, NH_4^+, SO_3, R-N^+≡N,

It is interesting to note that since the electrophiles are capable of *accepting electrons pair*, they are Lewis acids. Reactions involving the attack of electrophiles are known as an electrophilic reaction

2. Nucleophilic reagents (Nucleophiles)

The reagent possessing at least one lone pair of electrons is known as nucleophilic reagents (or) nucleophiles (nucleo=nucleus; phile=love). Since they possess a higher electron density, they attack the substance at the point of minimum electron density. The nucleophilic reagent may be a negatively charged species or neutral molecule with free electron pair (s). Some important nucleophiles are given below:

E.g.: $OH^–$, $Br^–$, $CN^–$, C00$^–$, R.C≡$C^–$, $CH_3COC^–H_2$, H-O-H,

R-O-R, R-O-H, R-S-H, R-NH2, R2-NH2, :NH_3, $LiAlH_4$.

It is interesting to note that since the nucleophiles are capable of *donating electrons*

pair, they are **Lewis bases.** The reaction involving the attack of nucleophiles is referred to as a nucleophilic reaction.

Metabolic Phases

Metabolism refers to the biochemical processes that occur within living organisms to maintain life. It involves the conversion of molecules (metabolites) through various chemical reactions to produce energy, synthesize biomolecules, and carry out other essential cellular functions. Thousands of chemical reactions are taking place inside a cell in an organized, well co-organized, and purposeful manner; all these are collectively called Intermediary Metabolism. The term Metabolism came from the Greek language (*metabole*[G] = Change; ballein[G]= to throw). In living organisms, there are three different phases of metabolic phases done. These are :

1. **Primary Metabolism:** The primary metabolic state includes digestion.
2. **Secondary Metabolism:** The secondary metabolism is also called the intermediary metabolism. It includes catabolism (breakdown process of biomolecules) and anabolism. (Synthesis process of biomolecules).
3. **Tertiary Metabolism:** Biological oxidation and Oxidative phosphorylation are included in this type of metabolism.

3.6 INTERMEDIARY METABOLISM SERVES THE FOLLOWING PURPOSES

Metabolism is the overall process through which living systems acquire and utilize the free energy they need to carry out their functions. The terms "catabolism" and "anabolism" were coined by the physiologist **Gasket** in 1886.

- Chemical energy is obtained from the degradation of energy-rich nutrients**.**
- Food materials are converted into the building block precursors of cellular macromolecules. These building blocks are later made into macromolecules, such as proteins, nucleic acids, polysaccharides, etc.
- Biomolecules required for specialized functions of the cell are synthesized. Specialized functions of the cell are synthesized.
- **Metabolic pathways** are taking place with the help of sequential enzyme systems. These pathways are regulated at three levels:
- **Regulation through the action of allosteric enzymes, which** increases or decreases in the activity under the of effector molecules.
- **Hormonal regulation**: Hormones are chemical messengers secreted by different endocrine glands.
- **Regulation at the DNA level**: The concentration of the enzyme is changed by regulation at the level of synthesis of the enzyme.

Metabolism can be broadly categorized into two types of metabolic reactions: catabolic and anabolic.

a) Catabolism

It is a degradation process. A degradative process in which complex molecules are broken down into simpler ones; includes processes such as Cellular Respiration and digestion. The meaning of catabolism came from Greek (*katabole*[G] = Throwing down; ballein[G]= to throw). It is also spelled as katabolism. The energy released during this process is trapped chemical energy, usually ATP. **Eg:** Cellular Respiration The primary purpose of catabolism is to generate energy and provide building blocks for anabolic reactions. Examples of catabolic reactions include:

- **Glycolysis**: Breaking down glucose into pyruvate, producing ATP and NADH.
- **Krebs cycle (TCA cycle):** The oxidation of acetyl-CoA derived from glucose, fatty acids, or amino acids to produce ATP, NADH, FADH2, and carbon dioxide.
- **Beta-oxidation:** The breakdown of fatty acids into acetyl-CoA, generating NADH and FADH2.
- **Protein degradation:** The breakdown of proteins into amino acids, which can be used for energy production or other cellular processes.
- **Fermentation:** The anaerobic breakdown of glucose or other organic compounds to produce energy in the absence of oxygen.

b) Anabolism

Anabolic reactions involve synthesizing complex molecules from simpler molecules, consuming energy. These reactions build cellular structures, store energy, and produce biomolecules necessary for cellular function. It is a biosynthesis process. A constructive process in which complex molecules are synthesized from simpler ones; consumes rather than produces cellular energy; includes processes such as photosynthesis and assimilation; the opposite of catabolism. The meaning of the word “anabolism” comes from the Greek (*Anabole*[G] = Throwing up; ballein[G]= to throw). This needs energy. **Eg:** Photosynthesis

Examples of anabolic reactions include:

- **Protein synthesis** is assembling amino acids into polypeptide chains to form proteins.
- **Lipogenesis:** The synthesis of fatty acids and triglycerides from acetyl-CoA and other precursors.
- **Glycogenesis:** The synthesis of glycogen from glucose molecules for storage.
- **Nucleotide synthesis:** The production of nucleotides, the building blocks of

DNA and RNA.

- **Photosynthesis:** The process by which plants and some microorganisms convert sunlight, carbon dioxide, and water into glucose and oxygen.

These metabolic reactions, catabolism and anabolism, are interconnected and work harmoniously to balance energy and molecular components within cells. Catabolic reactions provide the necessary energy and building blocks for anabolic reactions, while anabolic reactions utilize the energy and building blocks to construct complex molecules essential for cellular processes. Coordinating these reactions is critical for living organisms' proper functioning and survival.

Metabolic Pathways

Metabolic pathways are a series of interconnected chemical reactions within cells to convert one molecule into another, ultimately leading to the synthesis or breakdown of various molecules. These pathways are essential for the proper functioning of cells and play a crucial role in energy production, nutrient metabolism, and the synthesis of biomolecules. An array of enzyme-catalyzed chemical reactions that bring about transformations of certain organic compounds vital to the organism, constitute "Metabolic pathways" (or) "Metabolic routes". Here are some key metabolic pathways:

Glycolysis:

- Glycolysis is the pathway by which glucose is broken down into pyruvate.
- It occurs in the cytoplasm and produces a small amount of ATP and NADH.

Citric Acid Cycle (TCA Cycle):

- Also known as the Krebs or tricarboxylic acid cycle, it occurs in the mitochondria.
- Acetyl-CoA, derived from glucose, fatty acids, or amino acids, enters the cycle and is oxidized to produce NADH, FADH2, and ATP.

Oxidative Phosphorylation:

- This pathway takes place in the inner mitochondrial membrane.
- It involves the electron transport chain, where electrons from NADH and FADH2 are passed along a series of proteins, creating a proton gradient.
- The flow of protons back across the membrane generates ATP through ATP synthase.

Beta-Oxidation:

- Beta-oxidation is the process by which fatty acids are broken down into acetyl-CoA.
- It occurs in the mitochondria and generates NADH and FADH2, which enter the

TCA cycle.

Pentose Phosphate Pathway:

- The pentose phosphate pathway operates parallel to glycolysis.
- It produces NADPH and generates intermediates for the synthesis of nucleotides.

Gluconeogenesis:

- Gluconeogenesis is the reverse process of glycolysis, occurring primarily in the liver.
- It converts non-carbohydrate precursors (lactate, amino acids, and glycerol) into glucose.

Urea Cycle:

- The urea cycle occurs in the liver and converts toxic ammonia into urea for excretion.
- It involves a series of reactions that occur between the mitochondria and cytoplasm.

Protein Synthesis:

- Protein synthesis involves the transcription of DNA into messenger RNA (mRNA) and the subsequent translation of mRNA into proteins.
- It occurs in the nucleus (transcription) and cytoplasm (translation) and requires amino acids, tRNA, ribosomes, and other factors.

These are just a few examples of metabolic pathways, and many more are involved in various other processes, including lipid synthesis, amino acid metabolism, and nucleotide synthesis. The regulation and coordination of these pathways ensure the efficient utilization of nutrients and energy to meet the needs of cells and organisms.

Three Principle characteristics of metabolic pathways, there are *Irreversible pathways, Typical irreversible metabolic pathways,* and *Branched metabolic pathways*.

1. Irreversible pathways

These are highly exergonic reactions. If two metabolites are metabolically inter-convertible, the pathway from the first to the second must differ from the pathway from the second back to the first. Example of irreversible pathways is Carbohydrate Oxidation, Fatty acid Oxidation, and Heme Biosynthesis.

2. Typical irreversible metabolic pathways

To obtain the product, a metabolic sequence should be essentially irreversible. Examples fro typical metabolic pathways are Glycolysis**,** Synthesis and Degradation of liver glycogen from (or) to Glucose.

3. Branched metabolic pathways

Some metabolic sequences may have a common path for many steps and then branch into two (or) more separate paths. Examples to the Branched metabolic pathways are, in carbohydrates metabolism, "Glucose-6-Phosphate" act as starting precursor molecule for the following pathways. Glycogen synthesis, EMP pathway (or) Glycolysis, HMP shunt.

What are the Principle characteristics of metabolic pathways?

The principal characteristics of metabolic pathways include:

1. **Interconnectedness:** Metabolic pathways are interconnected networks of chemical reactions. The products of one reaction serve as substrates for subsequent reactions, creating a chain of interlinked steps. It allows for the efficient utilization of resources and coordination of metabolic processes.

2. **Irreversibility:** Metabolic pathways are often irreversible, meaning the reactions proceed in one direction. While some reversible reactions do occur, the overall flow of the path is typically unidirectional, driven by energy considerations and regulatory mechanisms.

3. **Regulation:** Metabolic pathways are tightly regulated to ensure proper control of metabolic flux and respond to changing physiological conditions. Regulation can occur at various levels, including enzyme activity, substrate availability, and gene expression. This regulation allows cells and organisms to adapt to energy demands and nutrient availability.

4. **Energy Coupling:** Metabolic pathways are energetically coupled, meaning energy released in one reaction is often used to drive an unfavourable reaction. For example, glycolysis energy generated during glucose oxidation is used to synthesize ATP through oxidative phosphorylation.

5. **Catabolic and Anabolic Pathways:** Metabolic pathways can be categorized as catabolic or anabolic. Catabolic pathways involve breaking complex molecules, releasing energy and producing simpler molecules. Anabolic pathways, on the other hand, involve the synthesis of complex molecules, requiring energy input and building blocks.

6. **Compartmentalization:** Metabolic pathways are often compartmentalized within specific organelles or subcellular structures. This compartmentalization allows for the spatial organization and separation of incompatible reactions. For example, glycolysis occurs in the cytoplasm, while oxidative phosphorylation occurs in the mitochondria.

7. **Feedback Inhibition:** Many metabolic pathways are regulated by feedback inhibition. It occurs when the final product of a pathway acts as an inhibitor of an earlier enzyme in the pathway, regulating the rate of the pathway and preventing the over-accumulation of end products.

8. **Diversity:** Metabolic pathways exhibit tremendous diversity across different organisms and cell types. While core metabolic pathways are conserved, variations and adaptations exist to meet the specific metabolic needs of other organisms and their environments.

These characteristics collectively contribute to the efficiency, adaptability, and regulation of metabolic pathways, ensuring the proper utilization of nutrients, energy production, and maintenance of cellular homeostasis.

3.7 INTERMEDIARY METABOLISM

Metabolism is the term used to describe the interconversion of chemical compounds in the body, the pathways taken by individual molecules, their interrelationships and the mechanisms that regulate the flow of metabolites through the pathways.

Intermediary metabolism refers to the network of biochemical reactions within cells that process and convert nutrients into energy, building blocks for cellular structures, and other molecules necessary for cellular function. It involves the metabolism of carbohydrates, lipids, and proteins. Here are the key aspects of intermediary metabolism:

1. Carbohydrate Metabolism

- **Glycolysis:** Carbohydrates, mainly glucose, are broken down into pyruvate through a series of enzymatic reactions in the cytoplasm. This process generates a small amount of ATP and NADH.
- **Pyruvate Decarboxylation:** In the presence of oxygen, pyruvate enters the mitochondria and undergoes decarboxylation to form acetyl-CoA, which enters the tricarboxylic acid (TCA) cycle.
- **Tricarboxylic Acid (TCA) Cycle:** Also known as the citric acid cycle or Krebs cycle, the TCA cycle oxidizes acetyl-CoA and produces energy-rich molecules such as NADH and $FADH_2$.
- **Oxidative Phosphorylation:** NADH and $FADH_2$ are generated during glycolysis, pyruvate decarboxylation, and the TCA cycle donates electrons to the electron transport chain in the mitochondria. This process leads to the production of ATP through oxidative phosphorylation.

2. Lipid Metabolism

- **Lipolysis:** Triglycerides stored in adipose tissue are broken down into glycerol and fatty acids through the action of lipases.
- **β-Oxidation:** Fatty acids are transported into the mitochondria and undergo a series of reactions called β-oxidation, producing acetyl-CoA, NADH, and $FADH_2$.
- **Ketogenesis:** Under conditions of prolonged fasting or low carbohydrate intake,

excess acetyl-CoA generated from fatty acid breakdown enters ketogenesis, leading to the production of ketone bodies (acetoacetate, β-hydroxybutyrate, and acetone).

- **Lipogenesis:** In the fed state, when energy is abundant, excess glucose and acetyl-CoA are converted into triglycerides through lipogenesis.

3. Protein Metabolism

- **Protein Digestion:** Dietary proteins are broken down into amino acids through digestion in the stomach and small intestine.
- **Protein Synthesis:** Amino acids synthesize new proteins necessary for cellular structure, enzymes, hormones, and other functional molecules.
- **Amino Acid Metabolism:** Amino acids can also be converted into intermediates for energy production or used to synthesize non-protein molecules, such as neurotransmitters, nucleotides, and heme.

These metabolic pathways are highly interconnected, allowing for the efficient utilization of different nutrients depending on the energy demands and availability of substrates. Intermediary metabolism plays a vital role in maintaining energy balance, providing building blocks for cellular components, and regulating various physiological processes in the body.

Pathways that process the Major Products of Digestion

The nature of the diet sets the basic pattern of metabolism. There is a need to process the products of digestion of dietary carbohydrates, lipids, and protein. These are mainly glucose, fatty acids and glycerol, and amino acids, respectively. All the products o digestion are metabolized to a common product, acetyl~coA, which is then oxidized by the citric acid cycle.

Metabolism can be considered in different types based on the Biomolecule:

- Carbohydrate Metabolism
- Amino acid Metabolism
- Lipids Metabolism
- Nucleotide Metabolism
- Porphyrin Metabolism
- Vitamin Metabolism
- Mineral Metabolism

3.8 CARBOHYDRATES

Carbohydrates, or carbs, are sugar molecules. Along with proteins and fats,

carbohydrates are one of three main nutrients found in foods and drinks. Your body breaks down carbohydrates into glucose. Glucose, or blood sugar, is the main source of energy for your body's cells, tissues, and organs. Glucose can be used immediately or stored in the liver and muscles for later use.

What are the different types of carbohydrates?

There are three main types of carbohydrates:

Sugars

They are also called simple carbohydrates because they are in the most basic form. They can be added to foods, such as the sugar in candy, desserts, processed foods, and regular soda. They also include the kinds of sugar that are found naturally in fruits, vegetables, and milk.

Starches

They are complex carbohydrates, which are made of lots of simple sugars strung together. Your body needs to break starches down into sugars to use them for energy. Starches include bread, cereal, and pasta. They also include certain vegetables, like potatoes, peas, and corn.

Fiber

It is also a complex carbohydrate. Your body cannot break down most fibers, so eating foods with fiber can help you feel full and make you less likely to overeat. Diets high in fiber have other health benefits. They may help prevent stomach or intestinal problems, such as constipation. They may also help lower cholesterol and blood sugar. Fiber is found in many foods that come from plants, including fruits, vegetables, nuts, seeds, beans, and whole grains.

Which foods have carbohydrates?

Common foods with carbohydrates include:

- Grains, such as bread, noodles, pasta, crackers, cereals, and rice
- Fruits, such as apples, bananas, berries, mangoes, melons, and oranges
- Dairy products, such as milk and yogurt
- Legumes, including dried beans, lentils, and peas
- Snack foods and sweets, such as cakes, cookies, candy, and other desserts
- Juices, regular sodas, fruit drinks, sports drinks, and energy drinks that contain sugar
- Starchy vegetables, such as potatoes, corn, and peas

  Some foods don't have a lot of carbohydrates, such as meat, fish, poultry, some types of cheese, nuts, and oils.

3.9 GLYCOLYSIS

"Glycolysis is the metabolic process that converts glucose into pyruvic acid."

What is Glycolysis?

Glycolysis is the process in which glucose is broken down to produce energy. It produces two molecules of pyruvate, ATP, NADH and water. The process takes place in the cytoplasm of a cell and does not require oxygen. It occurs in both aerobic and anaerobic organisms.

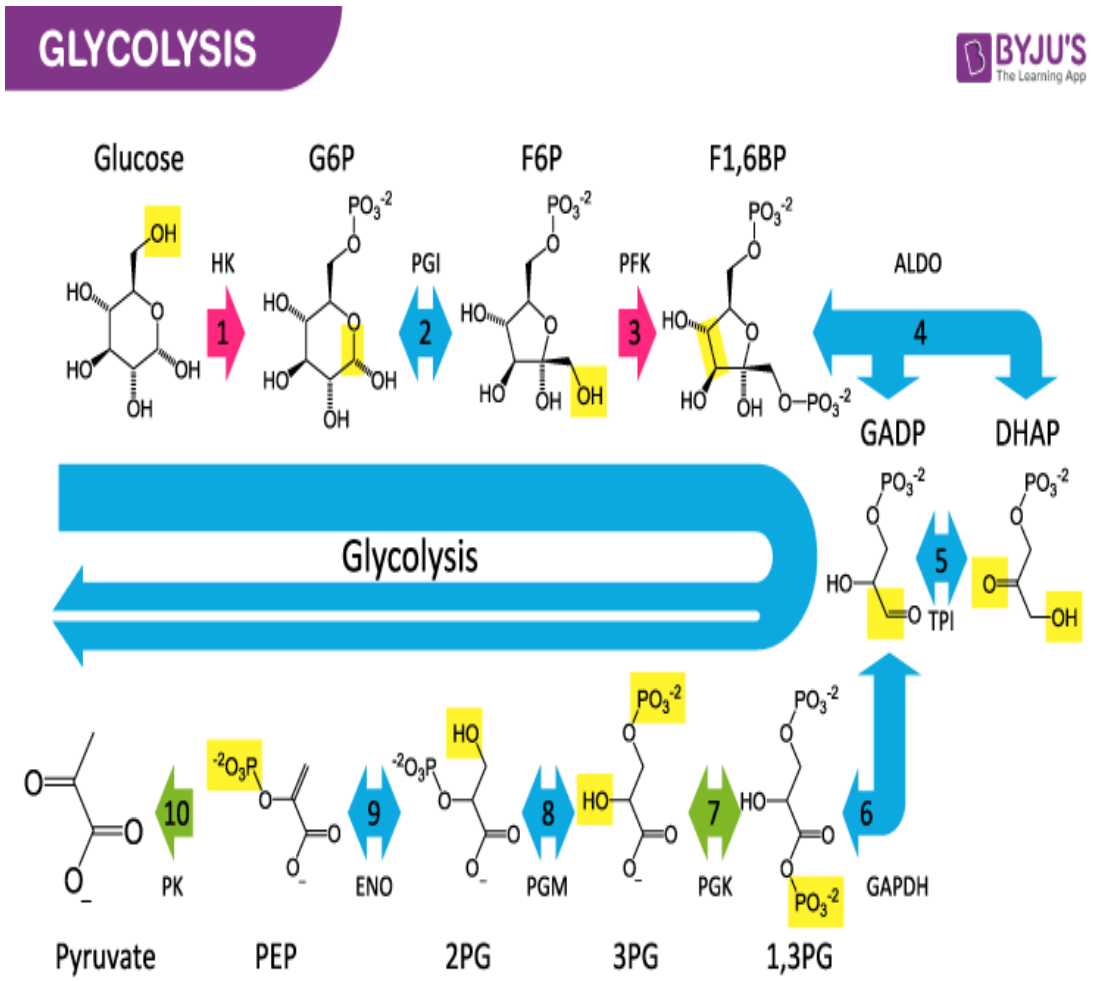


Fig. Glycolysis

Glycolysis is the primary step of cellular respiration, which occurs in all organisms. Glycolysis is followed by the Krebs cycle during aerobic respiration. In the absence of oxygen, the cells make small amounts of ATP as glycolysis is followed by fermentation. This metabolic pathway was discovered by three German biochemists-Gustav Embden, Otto Meyerhof, and Jakub Karol Parnas in the early 19th century and is known as the EMP pathway (Embden–Meyerhof–Parnas).

Glycolysis Pathway

The glycolysis pathway occurs in the following stages:

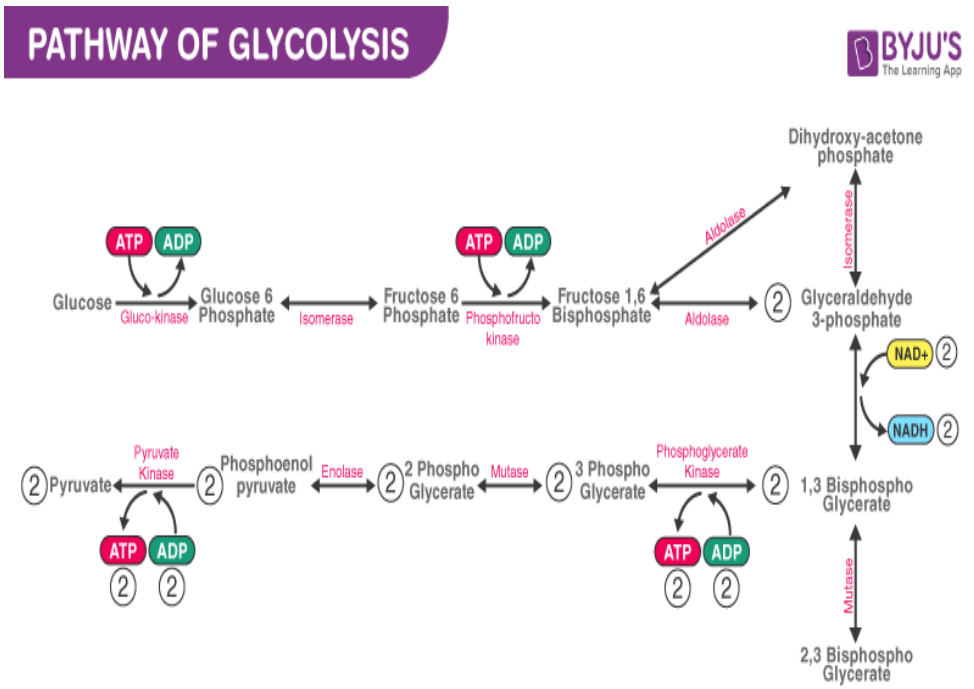


Fig. Pathway of Glycolysis

Stage 1

- A phosphate group is added to glucose in the cell cytoplasm, by the action of enzyme hexokinase.
- In this, a phosphate group is transferred from ATP to glucose forming glucose,6-phosphate.

Stage 2

Glucose-6-phosphate is isomerised into fructose,6-phosphate by the enzyme phosphoglucomutase.

Stage 3

The other ATP molecule transfers a phosphate group to fructose 6-phosphate and converts it into fructose 1,6-bisphosphate by the action of the enzyme phosphofructokinase.

Stage 4

The enzyme aldolase converts fructose 1,6-bisphosphate into glyceraldehyde 3-phosphate and dihydroxyacetone phosphate, which are isomers of each other.

Step 5

Triose-phosphate isomerase converts dihydroxyacetone phosphate into glyceraldehyde

3-phosphate which is the substrate in the successive step of glycolysis.

Step 6

This step undergoes two reactions:

- The enzyme glyceraldehyde 3-phosphate dehydrogenase transfers 1 hydrogen molecule from glyceraldehyde phosphate to nicotinamide adenine dinucleotide to form NADH + H^+.
- Glyceraldehyde 3-phosphate dehydrogenase adds a phosphate to the oxidised glyceraldehyde phosphate to form 1,3-bisphosphoglycerate.

Step 7

Phosphate is transferred from 1,3-bisphosphoglycerate to ADP to form ATP with the help of phosphoglycerokinase. Thus two molecules of phosphoglycerate and ATP are obtained at the end of this reaction.

Step 8

The phosphate of both the phosphoglycerate molecules is relocated from the third to the second carbon to yield two molecules of 2-phosphoglycerate by the enzyme phosphoglyceromutase.

Step 9

The enzyme enolase removes a water molecule from 2-phosphoglycerate to form phosphoenolpyruvate.

Step 10

A phosphate from phosphoenolpyruvate is transferred to ADP to form pyruvate and ATP by the action of pyruvate kinase. Two molecules of pyruvate and ATP are obtained as the end products.

Key Points of Glycolysis

- It is the process in which a glucose molecule is broken down into two molecules of pyruvate.
- The process takes place in the cytoplasm of plant and animal cells.
- Six enzymes are involved in the process.
- The end products of the reaction include 2 pyruvate, 2 ATP and 2 NADH molecules.

Importance of Glycolysis

Glycolysis is important because it is the metabolic pathway through which glucose generates cellular energy. Glucose is the most important source of energy for all living organisms. In the human body, glucose is the preferred fuel for the vast majority of cells:

- It is the only fuel red blood cells can use
- The preferred fuel used by the brain under non-starvation conditions

- The main fuel used by muscles during strenuous exercise.

3.10 GLUCONEOGENESIS

Gluconeogenesis is a metabolic pathway that results in the generation of glucose from non-carbohydrate carbon substrates such as lactate, glycerol and glucogenic amino acids. This unit will discuss the process of gluconeogenesis as well as relevant clinical conditions.

Overview of Gluconeogenesis

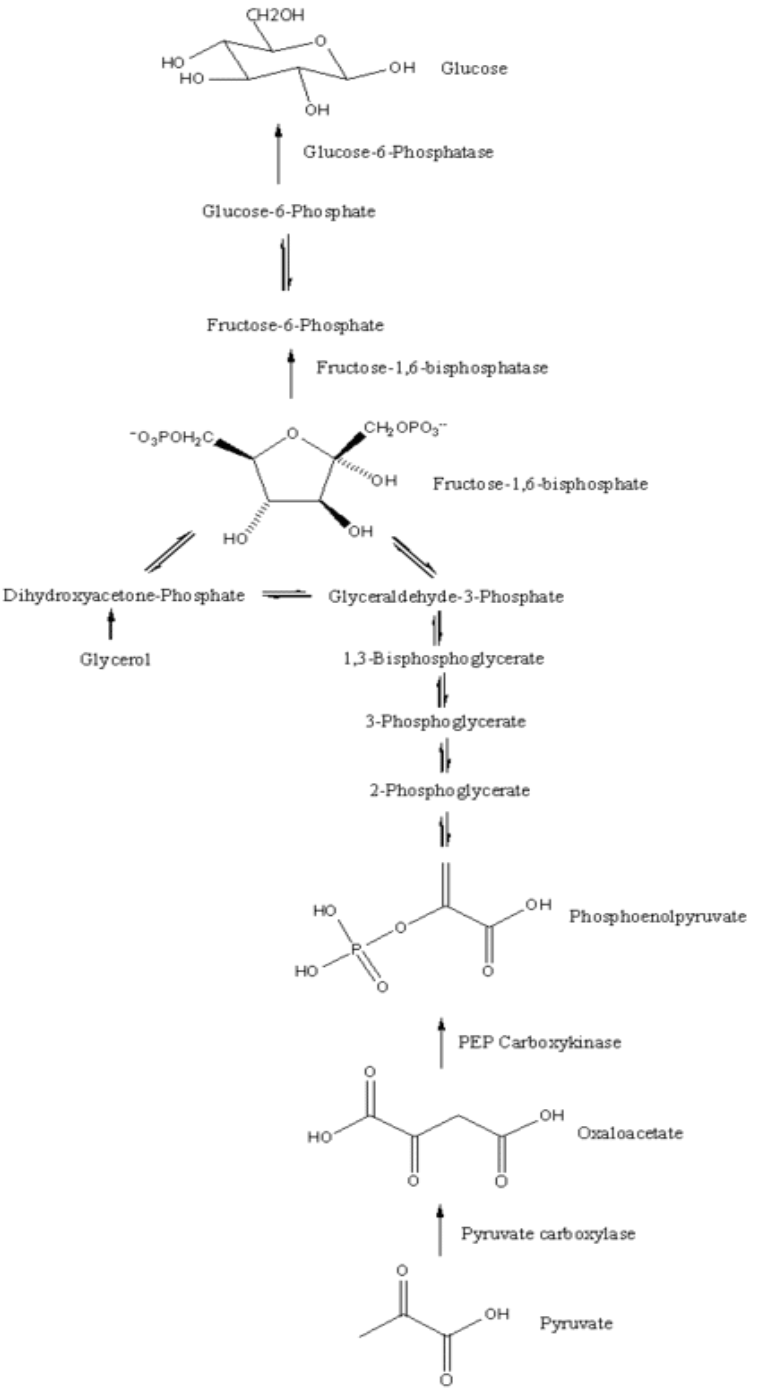


Fig Overview of the gluconeogenesis pathway

Process of Gluconeogenesis

Gluconeogenesis occurs after around 8 hours of fasting when liver glycogen stores start to deplete and an alternative source of glucose is required. It occurs mainly in the liver and to a lesser extent in the cortex of the kidney. There are three main precursors:

- **Lactate** from anaerobic glycolysis in exercising muscle and red blood cells via the Cori cycle
- **Glycerol** released from the breakdown of triglycerides in adipose tissue
- Amino acids (mainly alanine).

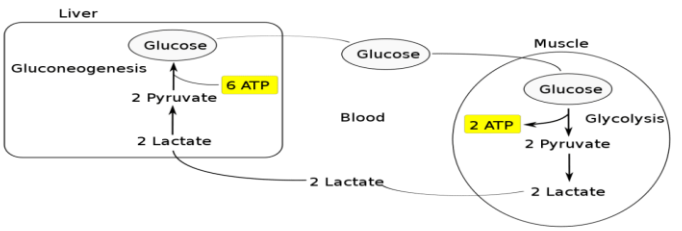


Fig. Diagram of the Cori cycle, showing how lactate is generated by muscles and then used by gluconeogenesis

Gluconeogenesis has a close relationship to glycolysis. Whilst glycolysis is the breaking of glucose, gluconeogenesis is the creation of glucose. However, it is not simply the reverse of glycolysis, as there are irreversible steps in glycolysis.

To circumvent this, some more enzymes are important in gluconeogenesis:

- Phosphoenolpyruvate carboxykinase (PEPCK) converts xaloacetate to phosphoenolpyruvate.
- Fructose 1,6-bisphosphatase converts fructose 1,6-bisphosphate to fructose 6-phosphate.
- Glucose-6-phosphatase converts glucose 6-phosphate into glucose.Fig 3 – Diagram demonstrating the 3 steps that differ in gluconeogenesis and glycolysis

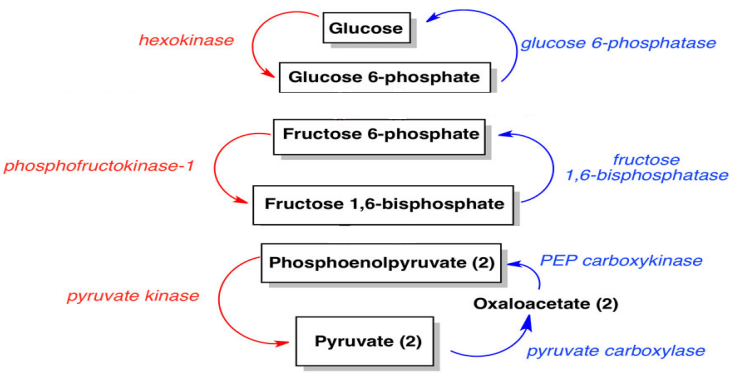


Fig. Diagram demonstrating the 3 steps that differ in gluconeogenesis and glycolysis.

Hormonal Control

Like glycolysis, this process is under the tight control of hormones to regulate blood glucose. Stress hormones such as glucagon or cortisol upregulate PEPCK and fructose 1,6-bisphosphatase in order to stimulate gluconeogenesis. However, in a fed, high-energy state gluconeogenesis decreases by inhibiting PEPCK and fructose 1, 6-bisphosphatase.

3.11 KREBS CYCLE OR TCA CYCLE (TRICARBOXYLIC ACID CYCLE) OR CITRIC ACID CYCLE

The Krebs cycle or TCA cycle (tricarboxylic acid cycle) or Citric acid cycle is a series of enzyme catalysed reactions occurring in the mitochondrial matrix, where acetyl-CoA is oxidised to form carbon dioxide and coenzymes are reduced, which generate ATP in the electron transport chain. Krebs cycle was named after Hans Krebs, who postulated the detailed cycle. He was awarded the Nobel prize in 1953 for his contribution.

It is a series of eight-step processes, where the acetyl group of acetyl-CoA is oxidised to form two molecules of CO_2 and in the process, one ATP is produced. Reduced high energy compounds, NADH and $FADH_2$ are also produced. Two molecules of acetyl-CoA are produced from each glucose molecule so two turns of the Krebs cycle are required which yields four CO_2, six NADH, two $FADH_2$ and two ATPs. **Krebs Cycle is a part of Cellular Respiration** Cellular respiration is a catabolic reaction taking place in the cells. It is a biochemical process by which nutrients are broken down to release energy, which gets stored in the form of ATP and waste products are released. In aerobic respiration, oxygen is required. Cellular respiration is a four-stage process. In the process, glucose is oxidised to carbon dioxide and oxygen is reduced to water. The energy released in the process is stored in the form of ATPs. 36 to 38 ATPs are formed from each glucose molecule. The four stages are:

1. Glycolysis: Partial oxidation of a glucose molecule to form 2 molecules of pyruvate. This process takes place in the cytosol.

2. Formation of Acetyl CoA: Pyruvate formed in glycolysis enters the mitochondrial matrix. It undergoes oxidative decarboxylation to form two molecules of Acetyl CoA. The reaction is catalysed by the pyruvate dehydrogenase enzyme.

$$2Pyruvate + 2NAD^+ + 2CoA \xrightarrow{Pyruvate\ dehydrogenase} 2AcetylCoA + 2NADH + CO_2$$

3. Krebs cycle (TCA cycle or Citric Acid Cycle): It is the common pathway for complete oxidation of carbohydrates, proteins and lipids as they are metabolised to acetyl coenzyme A or other intermediates of the cycle. The Acetyl CoA produced enters the Tricarboxylic acid cycle or Citric acid cycle. Glucose is fully oxidized in this process. The acetyl CoA combines with 4-carbon compound oxaloacetate to form 6C citrate. In this process, 2 molecules of CO_2 are released and oxaloacetate is recycled. Energy is stored in ATP and other high energy compounds like NADH and $FADH_2$.

4. Electron Transport System and Oxidative Phosphorylation: ATP is generated when electrons are transferred from the energy-rich molecules like NADH and $FADH_2$, produced in glycolysis, citric acid cycle and fatty acid oxidation to molecular O_2 by a series of electron carriers. O_2 is reduced to H_2O. It takes place in the inner membrane of mitochondria.

Krebs Cycle Steps It is an eight-step process. Krebs cycle or TCA cycle takes place in the matrix of mitochondria under aerobic condition.

Step 1: The first step is the condensation of acetyl CoA with 4-carbon compound oxaloacetate to form 6C citrate, coenzyme A is released. The reaction is catalysed by *citrate synthase*.

Step 2: Citrate is converted to its isomer, isocitrate. The enzyme *aconitase* catalyses this reaction.

Step 3: Isocitrate undergoes dehydrogenation and decarboxylation to form 5C **α**-ketoglutarate. A molecular form of CO_2 is released. *Isocitrate dehydrogenase* catalyses the reaction. It is an NAD^+ dependent enzyme. NAD^+ is converted to NADH.

Step 4: **α**-ketoglutarate undergoes oxidative decarboxylation to form succinyl CoA, a 4C compound. The reaction is catalyzed by the ***α-ketoglutarate dehydrogenase*** enzyme complex. One molecule of CO_2 is released and NAD^+ is converted to NADH.

Step 5: Succinyl CoA forms succinate. The enzyme *succinyl CoA synthetase* catalyses the reaction. This is coupled with substrate-level phosphorylation of GDP to get GTP. GTP transfers its phosphate to ADP forming ATP.

Step 6: Succinate is oxidised by the enzyme *succinate dehydrogenase* to fumarate. In the process, FAD is converted to $FADH_2$.

Step 7: Fumarate gets converted to malate by the addition of one H_2O. The enzyme catalysing this reaction is *fumarase*.

Step 8: Malate is dehydrogenated to form oxaloacetate, which combines with another molecule of acetyl CoA and starts the new cycle. Hydrogens removed, get transferred to NAD^+ forming NADH. *Malate dehydrogenase* catalyses the reaction.

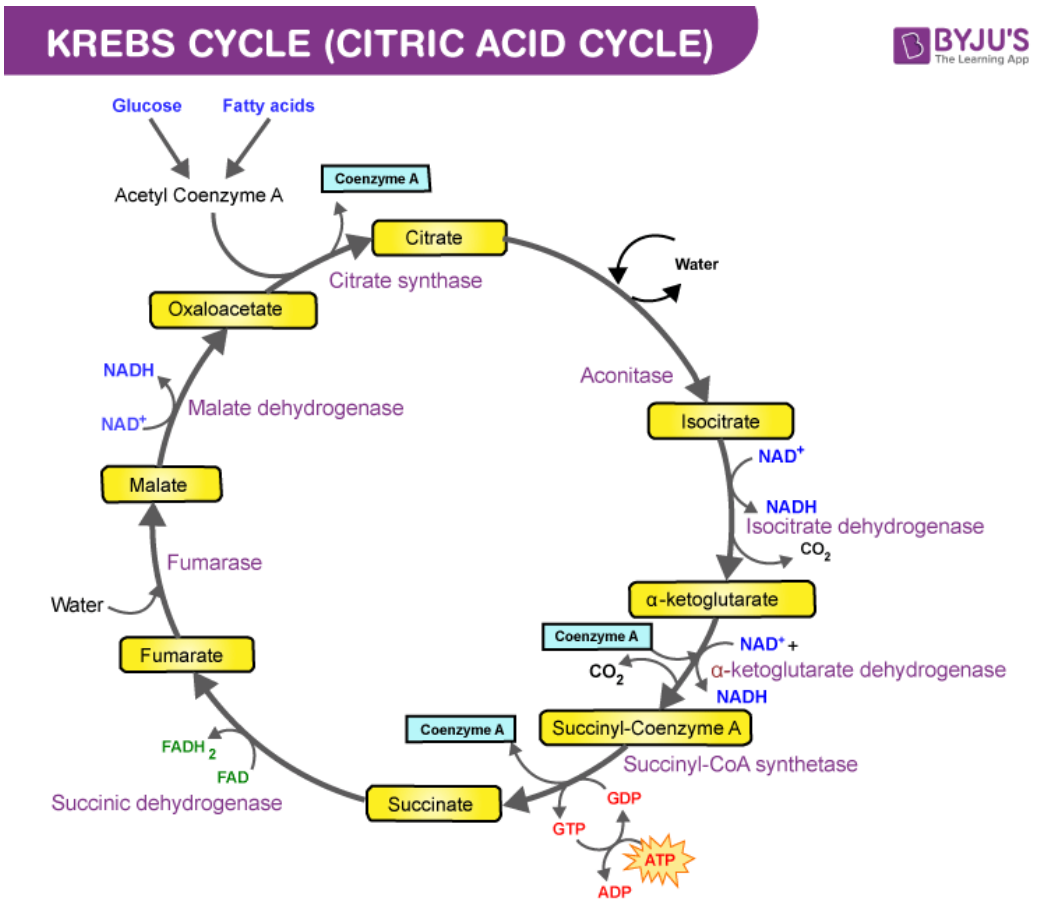


Fig. Kreb's cycle

Krebs Cycle Summary

Location: Krebs cycle occurs in the mitochondrial matrix

Krebs cycle reactants: Acetyl CoA, which is produced from the end product of glycolysis, i.e. pyruvate and it condenses with 4 carbon oxaloacetate, which is generated back in the Krebs cycle

Krebs cycle products

Each citric acid cycle forms the following products:

- 2 molecules of CO_2 are released. Removal of CO_2 or decarboxylation of citric acid takes place at two places:
    1. In the conversion of isocitrate (6C) to **α**-ketoglutarate (5C)
    2. In the conversion of **α**-ketoglutarate (5C) to succinyl CoA (4C)
- 1 ATP is produced in the conversion of succinyl CoA to succinate
- 3 NAD^+ are reduced to NADH and 1 FAD^+ is converted to $FADH_2$ in the following reactions:
    1. Isocitrate to **α**-ketoglutarate → NADH

2. **α**-ketoglutarate to succinyl CoA → NADH
3. Succinate to fumarate → $FADH_2$
4. Malate to Oxaloacetate → NADH

Note that 2 molecules of Acetyl CoA are produced from oxidative decarboxylation of 2 pyruvates so two cycles are required per glucose molecule. To summarize, for complete oxidation of a glucose molecule, Krebs cycle yields 4 CO_2, 6NADH, 2 $FADH_2$ and 2 ATPs. Each molecule of NADH can form 2-3 ATPs and each $FADH_2$ gives 2 ATPs on oxidation in the electron transport chain.

Krebs cycle equation

To Sum up

$$2Acetyl\ CoA + 6NAD^+ + 2\ FAD\ +\ 2\ ADP\ +\ 2\ P_i\ +\ 2\ H_2O \rightarrow\ 4\ CO_2\ +\ 6\ NADH\ +\ 2\ FADH_2\ +\ 2\ ATP\ +\ 2\ CoA$$

Significance of Krebs Cycle

- Krebs cycle or Citric acid cycle is the final pathway of oxidation of glucose, fats and amino acids
- Many animals are dependent on nutrients other than glucose as an energy source
- Amino acids (metabolic product of proteins) are deaminated and get converted to pyruvate and other intermediates of the Krebs cycle. They enter the cycle and get metabolised e.g. alanine is converted to pyruvate, glutamate to **α**-ketoglutarate, aspartate to oxaloacetate on deamination
- Fatty acids undergo ***β***-oxidation to form acetyl CoA, which enters the Krebs cycle
- It is the major source of ATP production in the cells. A large amount of energy is produced after complete oxidation of nutrients
- It plays an important role in gluconeogenesis and lipogenesis and interconversion of amino acids
- Many intermediate compounds are used in the synthesis of amino acids, nucleotides, cytochromes and chlorophylls, etc.
- Vitamins play an important role in the citric acid cycle. Riboflavin, niacin, thiamin and pantothenic acid as a part of various enzymes cofactors (FAD, NAD) and coenzyme A
- Regulation of Krebs cycle depends on the supply of NAD^+ and utilization of ATP in physical and chemical work
- The genetic defects of the Krebs cycle enzymes are associated with neural damage

- As most of the biological processes occur in the liver to a significant extent, damage to liver cells has a lot of repercussions. Hyperammonemia occurs in liver diseases and leads to convulsions and coma. This is due to reduced ATP generation as a result of the withdrawal of **α**-ketoglutarate and formation of glutamate, which forms glutamine

3.12 HEXOSE MONOPHOSPHATE (HMP) SHUNT: PATHWAY AND SIGNIFICANCE

The hexose monophosphate (HMP) shunt, also known as the pentose phosphate pathway or phosphogluconate pathway, is a metabolic pathway that runs parallel to glycolysis. This pathway produces NADPH and intermediates required for the synthesis of nucleic acids and amino acids. Let us study the pathway in detail.

Features of the HMP Shunt

- It is an anabolic pathway that takes place in the cytosol for most organisms. However, in plants, it takes place in plastids.
- The pathway takes place in two distinct phases: oxidative and non-oxidative phases.
- The reactions of this pathway are enzyme catalysed.
- The products obtained from the pathway include NADPH, which is used in biosynthesis in cells, ribose-5-phosphate, which is used in the synthesis of nucleic acid and nucleotides, and erythrose-4-phosphate, which is used for the synthesis of aromatic amino acids.
- In humans, this pathway is most active in mammary glands, adrenal cortex, adipose tissue, erythrocytes, testes and liver.
- The HMP shunt is a tightly controlled metabolic pathway that is connected with other pathways, such as glycolysis and gluconeogenesis, depending upon the metabolic needs of the body.
- Defects in the hexose monophosphate pathway can be linked to several disorders.

Phases of the HMP Shunt

Oxidative Phase

In this phase, NADPH is produced by the reduction of two molecules of $NADP^+$. The energy for this production is utilised by the conversion of glucose-6-phosphate to ribulose-5-phosphate. The three steps of the oxidative phase of the HMP shunt are:

- Glucose-6-phosphate is dehydrogenated to 6-phosphoglucono-δ-lactone in the

presence of glucose 6-phosphate dehydrogenase. In this reaction, one molecule of $NADP^+$ is converted into NADPH.

- 6-phosphoglucono-δ-lactone is hydrolysed into 6-phosphogluconate in the presence of 6-phosphogluconolactonase.
- 6-phosphogluconate is converted into ribulose 5-phosphate in the presence of 6-phosphogluconate dehydrogenase by oxidative decarboxylation.

Non-Oxidative Phase

The non-oxidative phase can be summarised in five steps:

- Ribulose-5-phosphate isomerises into ribose-5-phosphate in the presence of ribose-5-phosphate isomerase.
- Another enzyme, phosphopentose epimerase, isomerises ribulose-5-phosphate into xylulose 5-phosphate at the same time.
- Transketolase enzyme transfers a carbon group from ketose (xylulose-5-phosphate) to the aldose (ribose-5-phosphate), and the products obtained are glyceraldehyde 3-phosphate and sedoheptulose 7-phosphate.
- Transaldolase again transfers a carbon group from sedoheptulose 7-phosphate (ketose) to glyceraldehyde 3-phosphate (aldose), and the products obtained are erythrose 4-phosphate and fructose 6-phosphate.
- A carbon from xylulose 5-phosphate is transferred to erythrose 4-phosphate in the presence of transketolase to obtain glyceraldehyde 3-phosphate and fructose 6-phosphate.

Significance of HMP Shunt

The HMP shunt pathway is significant because it provides NADPH and important intermediated products for the synthesis of biomolecules. Some of the points of significance are:

- NADPH performs several functions in the body, such as:
- It takes part in the synthesis of steroids and fatty acids.
- It is an important component within phagolysosomes in the immune response.
- Glutathione is reduced by NADPH in the presence of glutathione reductase. This helps in quenching free oxygen radicals and peroxides from cells.
- The glyceraldehyde 3-phosphate and fructose 6-phosphate produced in the pathway are intermediates for glycolysis and gluconeogenesis.

Clinical Significance of HMP Shunt

1. **Deficiency of Glucose-6-Phosphate Dehydrogenase: The** deficiency of this enzyme which is required in the initial steps for the production of NADPH, affects the red blood cells.

   Conversely, this deficiency can provide resistance to the malarial parasite *Plasmodium falciparum*. This is possible because the cell membranes of the RBCs are weakened, and the parasite cannot continue its life cycle.

2. **Diagnosis of Thiamine Deficiency:** It is diagnosed by administering thiamine to suspected patients and observing the activity of transketolase enzymes in the RBCs. If the enzyme shows high activity, the deficiency of thiamine (vitamin B1) is confirmed.

3.13 FATTY ACID OXIDATION

Fatty acids provide highly efficient energy storage, delivering more energy per gram than carbohydrates like glucose. In tissues with high energy requirement, such as heart, up to 50–70% of energy, in the form of ATP production, comes from fatty acid (FA) beta-oxidation. During fatty acid β-oxidation long chain acyl-CoA molecules – the main components of FAs – are broken to acetyl-CoA molecules.

Pathway overview

Fatty acid transport into mitochondria

Fatty acids are activated for degradation by conjugation with coenzyme A (CoA) in the cytosol. The long-chain fatty-acyl-CoA is then modified by carnitine palmitoyltransferase 1 (CPT1) to acylcarnitine and transported across the inner mitochondrial membrane by carnitine translocase (CAT). CPT2 then coverts the long chain acylcarnitine back to long-chain acyl-CoA before beta-oxidation.

Beta-oxidation

Beta-oxidation consists of four steps:

1) Dehydrogenation catalyzed by acyl-CoA dehydrogenase, which removes two hydrogens between carbons 2 and 3.

2) Hydration catalyzed by enoyl-CoA hydratase, which adds water across the double bond.

3) Dehydrogenation catalyzed by 3-hydroxyacyl-CoA dehydrogenase, which generates NADH.

4) Thiolytic cleavage catalyzed beta-ketothiolase, which cleaves the terminal acetyl-CoA group and forms a new acyl-CoA which is two carbons shorter than the previous one.

The shortened acyl-CoA then reenters the beta-oxidation pathway.

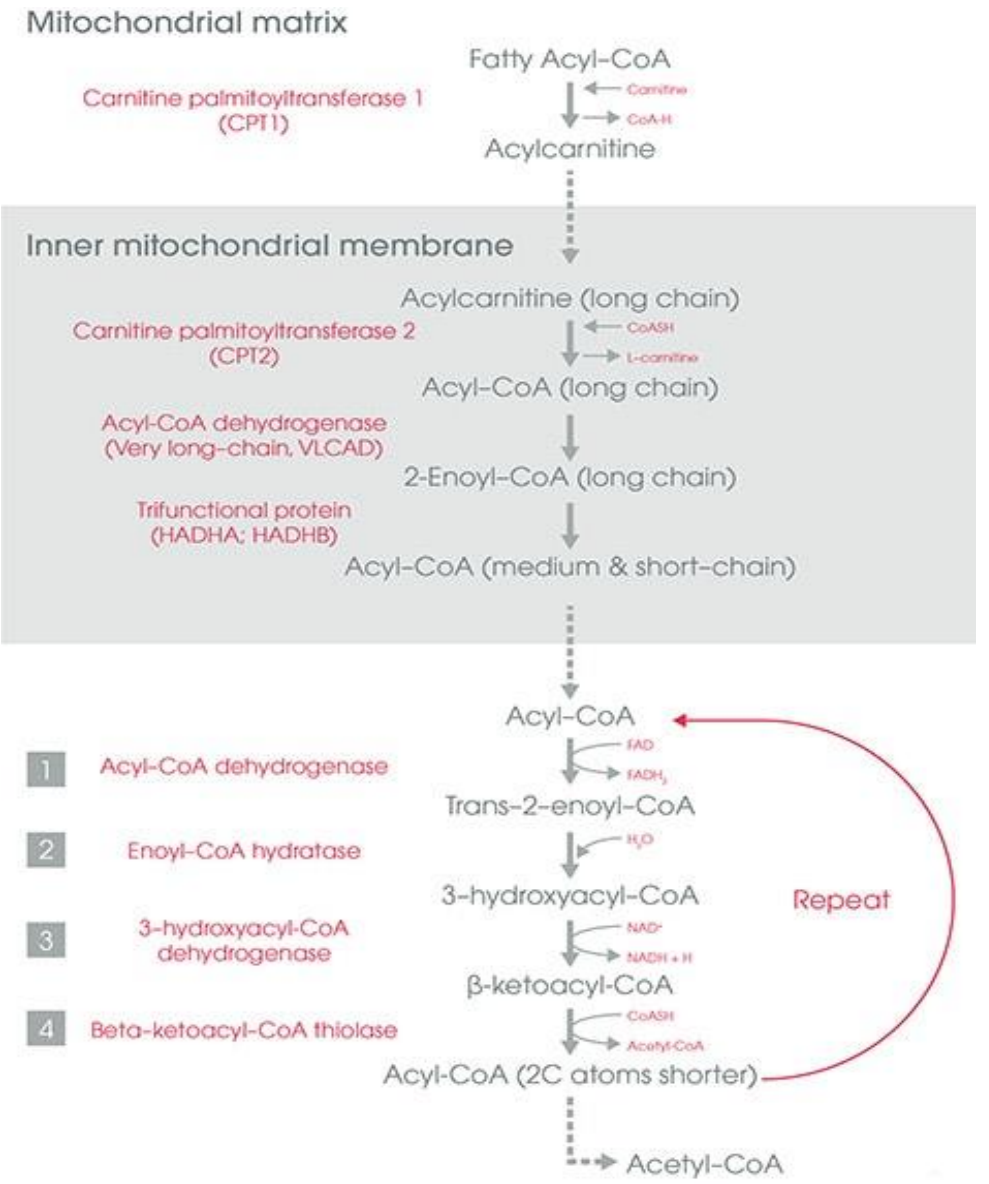


Fig. Schematic diagram of fatty acid transport and beta-oxidation in the mitochondria.

ATP synthesis

Acetyl-CoA generated by the beta-oxidation pathway enters the mitochondrial TCA cycle, where is further oxidized to generate NADH and $FADH_2$. The NADH and $FADH_2$ produced by both beta oxidation and the TCA cycle are used by the mitochondrial electron transport chain to produce ATP. Complete oxidation of one palmitate molecule (fatty acid containing 16 carbons) generates 129 ATP molecules.

3.14 SUMMARY

Under this unit we have discussed free energy in concern to intermediary metabolism. Carbohydrates constitute a group of chemically defined substances with a range of physical and physiological properties and health benefits for consumers. Their main

function is to provide energy, but they also play an important role in the structure and function of cells, tissues, and organs. Further, gluconeogenesis refers to synthesis of new glucose from noncarbohydrate precursors, provides glucose when dietary intake is insufficient or absent. It also is essential in the regulation of acid-base balance, amino acid metabolism, and synthesis of carbohydrate derived structural components.

The citric acid cycle serves as the mitochondrial hub for the final steps in carbon skeleton oxidative catabolism for carbohydrates, amino acids, and fatty acids. Each oxidative step, in turn, reduces a coenzyme such as nicotinamide adenine dinucleotide (NADH). The hexose monophosphate shunt, also known as the pentose phosphate pathway, is a unique pathway used to create products essential in the body for many reasons. The HMP shunt is an alternative pathway to glycolysis and is used to produce ribose-5-phosphate and nicotinamide adenine dinucleotide phosphate (NADPH).

3.15 TERMINAL QUESTIONS

Q.1 What do you mean by intermediary metabolism?

Answer:----------

Q.2 Write a short note on carbohydrates with its importance.

Answer:----------

Q.3 What are the 3 major enzymes in gluconeogenesis? Explain it.

Answer:----------

Q. 4 Write short notes on the followings.

(i) Citric acid cycle

(ii) Beta-oxidation

Answer:----------

Q. 5 What is the purpose of the hexose monophosphate pathway? Explain it.

Answer:----------

Further readings

- Biochemistry- Lehninger A.L.
- Textbook of Nutrition and Dietetics Ranjana Mahna
- Biochemistry fourth edition-David Hames and Nigel Hooper.
- Textbook of Biochemistry for Undergraduates - Rafi, M.D.
- Textbook of Nutrition and Dietetics- Monika Sharma

UNIT- 4 : SYNTHESIS

Structure

Objectives

4.1 INTRODUCTION

Fatty acid, important component of lipids (fat-soluble components of living cells) in plants, animals, and microorganisms. Generally, a fatty acid consists of a straight chain of an even number of carbon atoms, with hydrogen atoms along the length of the chain and at one end of the chain and a carboxyl group (—COOH) at the other end. It is that carboxyl group that makes it an acid (carboxylic acid). If the carbon-to-carbon bonds are all single, the acid is saturated; if any of the bonds is double or triple, the acid is unsaturated and is more reactive. A few fatty acids have branched chains; others contain ring structures (e.g., prostaglandins). Fatty acids are not found in a free state in nature; commonly they exist in combination with glycerol (an alcohol) in the form of triglyceride.

Among the most widely distributed fatty acids are the 16- and 18-carbon fatty acids, otherwise known as palmitic acid and stearic acid, respectively. Both palmitic and stearic acids occur in the lipids of the majority of organisms. In animals palmitic acid makes up as much as 30 percent of body fat. It accounts for anywhere from 5 to 50 percent of lipids in vegetable fats, being especially abundant in palm oil. Stearic acid is abundant in some vegetable oils (e.g., cocoa butter and shea butter) and makes up a relatively high proportion of the lipids found in ruminant tallow.

Objectives

This is the fourth unit on synthesis of first block (Heteropolysaccharides, Plasma Proteins and Intermediary metabolism). Under fourth unit (Synthesis) we have following objectives. These are as under:

- To understand the concept of de novo synthesis of fatty acids
- To know the synthesis of unsaturated fatty acids
- To discuss the breakdown of unsaturated fatty acids
- To discuss the concept of cholesterol, phospholipids and triacylglycerol.

Many animals cannot synthesize linoleic acid (an omega-6 fatty acid) and alpha-linolenic acid (an omega-3 fatty acid). Those fatty acids are required, however, for cellular processes and the production of other necessary omega-3 and omega-6 fatty acids. Thus, because they must be taken in through the diet, they are called essential fatty acids. Omega-6 and omega-3 fatty acids derived from linoleic acid and alpha-linolenic acid, respectively, are needed conditionally by many mammals—they are formed in the body from their parent fatty acids but not always at levels needed to maintain optimal health or development. Human infants, for example, are thought to have a conditionally essential need for docosahexaenoic acid (DHA), which is derived from alpha-linolenic acid, and possibly also for arachidonic acid, which is derived from linoleic acid.

Fatty acids have a wide range of commercial applications. For example, they are used not only in the production of numerous food products but also in soaps, detergents, and cosmetics. Soaps are the sodium and potassium salts of fatty acids. Some skin-care products contain fatty acids, which can help maintain healthy skin appearance and function. Fatty acids, particularly omega-3 fatty acids, are also commonly sold as dietary supplements.

4.2 DE NOVO SYNTHESIS OF FATTY ACIDS (PALMITIC ACID)

Definition:

- De novo means new way of synthesis.
- De novo synthesis of fatty acids is a set of processes that uses an acetyl CoA as a starting material to produce palmitic acid (Fatty Acids).

- Typically, De novo Lipogenesis refers to the synthesis of fatty acids from acetyl-CoA, which is the beginning of de novo lipogenesis.
- Malonyl-CoA (3 carbons) is first created by removing acetyl-CoA from the mitochondria.
- An acetyl-CoA-malonic acid complex is produced when malonyl-CoA is combined with another acetyl-CoA.
- A 16-carbon fatty acid is formed by adding 2 carbons to carbons through a similar process 7 times.

Sites:

- De novo synthesis mainly occurs in places like,
- Liver,
- Adipose tissue,
- Kidneys.

4.3 DE NOVO SYNTHESIS OF FATTY ACIDS OCCURS IN THREE STAGES

1. Production of acetyl CoA and NADPH
2. Conversion of acetyl CoA to malonyl CoA
3. Reactions of fatty acids synthase complex.

1. Production of acetyl CoA and NADPH:

- For fatty acids to be produced, acetyl CoA is essential. The main source of Acetyl CoA is pyruvate, which is oxidized in the mitochondrial matrix, as well as amino acids and ketone bodies.
- To transport **acetyl CoA**, alternative arrangements must be made because it **cannot** penetrate mitochondrial membranes.
- Oxaloacetate is formed from acetyl CoA, which is then condensed to acetyl CoA. Citrate is easily removed from the matrix and transported into the mitochondrial cytosol matrix.

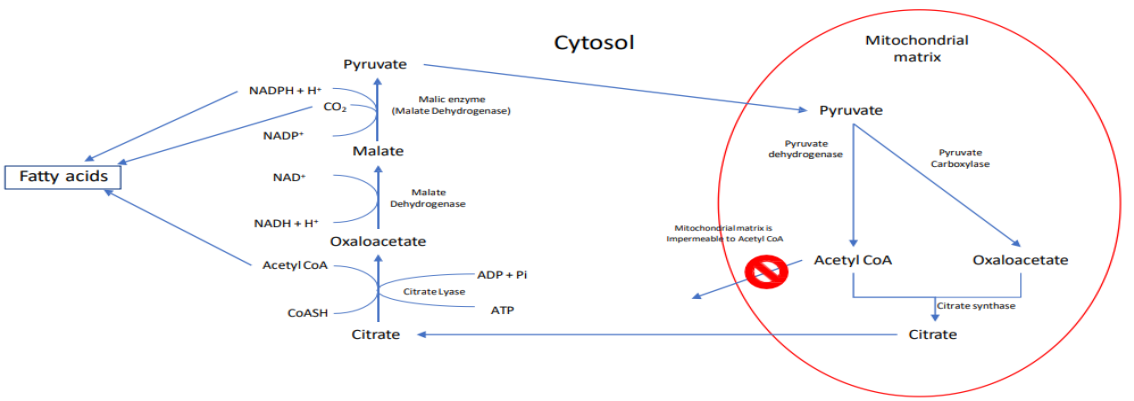


Fig. Production of acetyl CoA

2. Conversion of acetyl CoA to malonyl CoA:

- Malonyl CoA is produced by carboxylation acetyl CoA.
- This is an ATP dependent reaction and requires biotin for CO2 fixation.

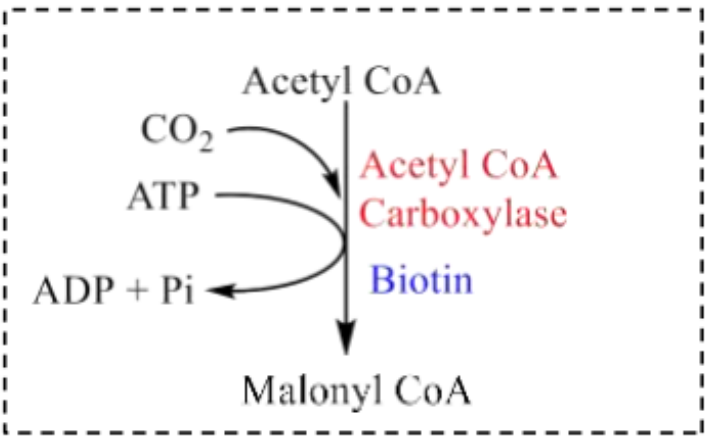


Fig. Conversion of acetyl CoA to malonyl CoA

3. Reactions of fatty acids synthase complex:

- Reactions of fatty acid synthase are catalyzed by a multifunctional enzyme known as fatty acid synthase (FAS) complex.
- Each monomer possesses the activity of a different enzyme and an acyl carrier protein (ACP).
- This sequence of reactions is as below.
- Step 1a & 1b:
  - Fatty acid synthesis starts with the formation of acetyl ACP and malonyl ACP.
  - The two enzymes involved respectively are acetyl transacylase and malonyl transacylase. In this case, acetyl CoA reacts with ACP to form acetyl ACP and coenzyme A (CoA).
  - Malonyl CoA is reacted with ACP to form malonyl ACP and CoA.
  - ACP is the acyl carrier protein. It is a protein that holds the growing fatty acid chain during its synthesis.
- **Step 2:**
  - A condensation reaction occurs between acetyl ACP and malonyl ACP to form acetoacetyl ACP.
  - One of the acyl carrier proteins is released along with a molecule of carbon dioxide.
  - Enzyme : acyl-malonyl ACP condensing enzyme.

- **Step 3: A reduction reaction**
  - Acetoacetyl ACP is reduced to D-3-hydroxybutyryl ACP using NADPH as the reducing agent.
  - Enzyme: beta-ketoacyl ACP reductase.
- **Step 4: A dehydration reaction**
  - D-3-hydroxybutyryl ACP is dehydrated to generate crotonyl ACP otherwise known as trans-Δ2-enoyl ACP.
  - Enzyme: 3-hydroxyacyl ACP dehydratase.
- **Step 5: The final step – a reduction reaction**
  - In the final step, crotonyl ACP is reduced to butyryl ACP and NADPH is the reductant.
  - Enzyme : enoyl ACP reductase.
- So we come to the end of the first elongation cycle but it is also the start of the first round of generating a fatty acid.

4.4 THE SECOND ROUND OF DE NOVO SYNTHESIS OF FATTY ACIDS

- In the second round of fatty acid synthesis, butyryl ACP condenses with another molecule of malonyl ACP to form C6-beta-ketoacyl ACP.
- A repeat of steps 2 to 5 with reduction, dehydration and reduction again produces a C-6 acyl ACP that is then ready for a 3rd round of elongation.

Termination

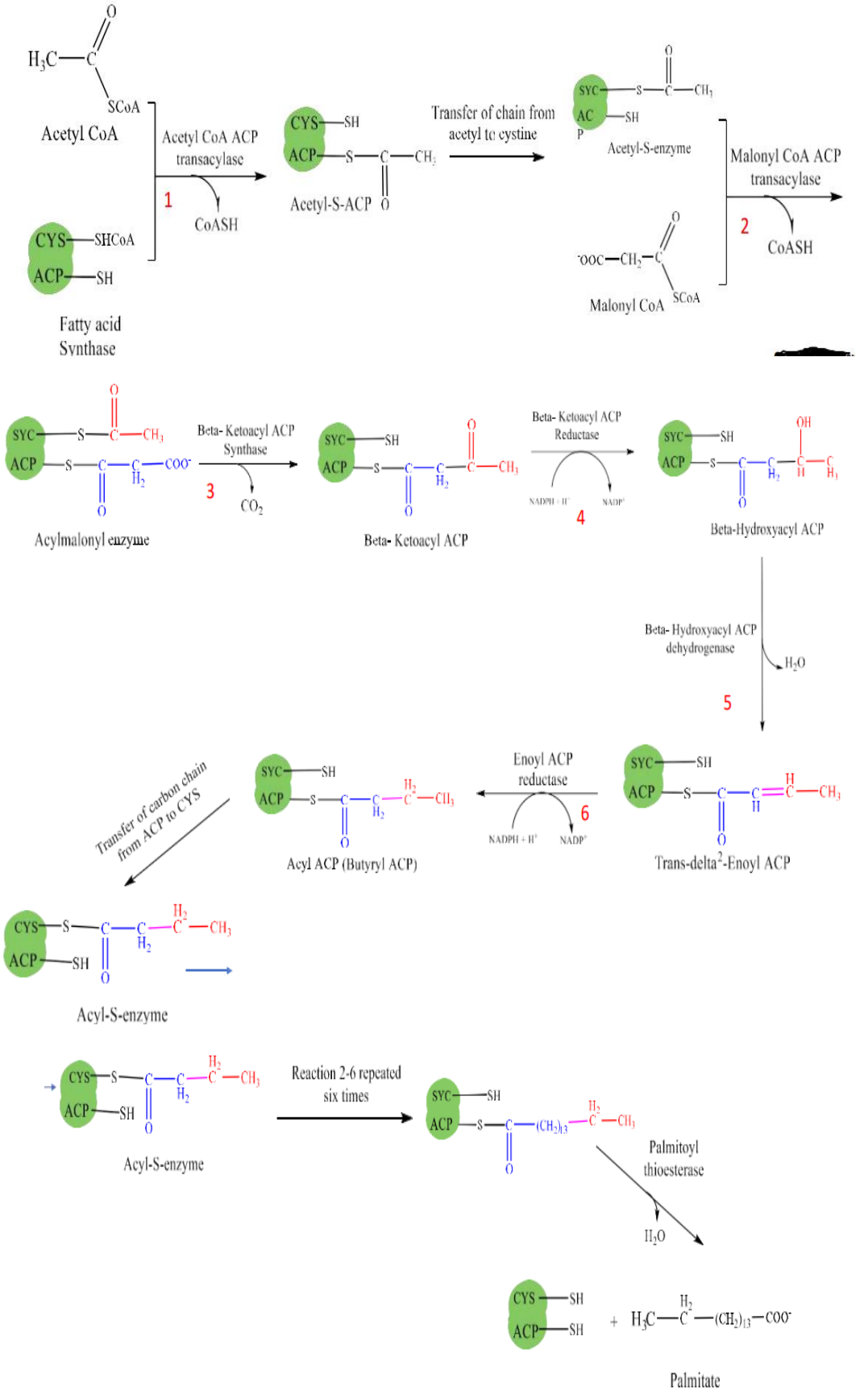
- If palmitic acid is the end product, then there are rounds of synthesis which produce a 16 carbon palmitoyl group (palmitoyl-ACP).
- This is hydrolysed using a thioesterase to generate palmitate whilst the ACP is returned to its original state with the sulfhydryl group where the fatty acid group used to be.

4.5 SUMMARY

- There are 16 carbon atoms in palmitate, and 2 of these atoms come from Acetyl CoA, and the remaining 14 atoms come from Malonyl CoA.
- The overall reaction between palmitate and the body is summarized as follows:

$$8\,\text{Acetyl CoA} + 7\text{ATP} + 14\,\text{NADPH} + 14\,\text{H}^+ \longrightarrow \text{Palmitate} + 8\,\text{CoA} + 7\text{ADP} + 7\text{Pi} + 6\text{H}_2\text{O}$$

Diagrammatic Representation:



4.6 FATTY ACID

A fatty acid is a long chain of hydrocarbon. If there are no unsaturated linkages but only single bonds between carbon atoms them the fatty acid is a saturated type. This is in contrast to an unsaturated fatty acid that contains at least one double carbon-carbon bond. A saturated fatty acid is a type of fatty acid that lacks unsaturated linkages between carbon atoms. Because of the lack of double bonds, this type of fatty acid can no longer absorb any more hydrogen; it is *saturated*. Saturated fatty acids are commonly found in animal fats. They include the 12-carbon containing fatty acid, lauric acid, the 14-carbon myristic acid, the 16-carbon palmitic acid, the 18-carbon stearic acid, the 20-carbon arachidic acid, the 22-carbon behenic acid, the 24-carbon lignoceric acid, and the 26-carbon cerotic acid.

In humans, the recommended consumption is not more than 10% of the total calories per day. Too much consumption of saturated fat is associated with heart diseases and atherosclerosis. The saturated fats increase low-density lipoprotein (LDL) and very low density lipoproteins (VLDL). Some of the dietary sources of saturated fats are butter, coconut oil, meat, peanut, butter, and cheese.

4.7 SATURATED FATS AND TRANS FATS

These are the ones that give all fats a bad reputation. Saturated fats are found in fatty pieces of meat, particularly processed meats. The American Heart Association recommends keeping your saturated fat below 6% of your daily calorie intake (for a 2000 calorie diet, this is about 12 grams). This is important because saturated fats raise LDL cholesterol levels in your blood. Those that monitor their cholesterol levels already know this increases the risk of heart disease and stroke.

The most common form of saturated fats you encounter in processed foods is ***trans fat***. These can occur naturally, but most are artificially made as they are placed in processed foods to extend their shelf life. By consuming trans fats you experience an increase in LDL cholesterol without any positive increase in “good” cholesterol (your HDL). Overall, this means trans fats *likely* increase your risk of heart disease.

4.8 UNSATURATED FATTY ACIDS

Unsaturated fatty acids are those containing one or more double bonds indicating that they can absorb additional hydrogen atoms. Unsaturated fatty acids may occur in *cis* or *trans* configuration. They may also be categorized into monounsaturated fatty acids and polyunsaturated fatty acids. Examples of unsaturated fats are myristoleic acid, palmitoleic acid, sapienic acid, oleic acid, elaidic acid, vaccenic acid, linoleic acid, linoelaidic acid, alpha-linolenic acid, arachidonic acid, erucic acid, docosahexaenoic acid, and eicosapentaenoic acid.

In humans, the recommended consumption is not more than 30% of the total calories per day. Some of the dietary sources of unsaturated fats are fish oils, walnuts, flax,

avocado, and olive oil. The unsaturated fats increase high-density lipoproteins (HDL) while decreasing low-density lipoproteins (LDL).

Benefits of Unsaturated Fats

Unsaturated fats get their name from their lack of at least two hydrogen atoms in their molecular makeup. These missing atoms make unsaturated fats easier to break down, and as a result less likely to create blockages in your arteries. Before we describe the benefits of this healthy type of fat, it is worth noting that you should not lean heavily into them as a part of your diet. The American Heart Association still recommends that less than 25% of all of your calories come from any kind of fat.

The good news is a healthy amount of unsaturated fats can play a role in lowering your bad cholesterol levels while at the same time aiding your cells and brain health. The Mayo Clinic points out that this is often largely the case because a substitution has taken place. You replace saturated fats with unsaturated fat options, resulting in benefits arguably from the unsaturated fat, but also because an unhealthy fat was removed from your diet.

4.9 CHOLESTEROL

Cholesterol is a waxy substance found in your blood. Your body needs cholesterol to build healthy cells, but high levels of cholesterol can increase your risk of heart disease. With high cholesterol, you can develop fatty deposits in your blood vessels. Eventually, these deposits grow, making it difficult for enough blood to flow through your arteries. Sometimes, those deposits can break suddenly and form a clot that causes a heart attack or stroke. High cholesterol can be inherited, but it's often the result of unhealthy lifestyle choices, which make it preventable and treatable. A healthy diet, regular exercise and sometimes medication can help reduce high cholesterol.

4.10 SYMPTOMS

High cholesterol has no symptoms. A blood test is the only way to detect if you have it. According to the National Heart, Lung, and Blood Institute (NHLBI), a person's first cholesterol screening should occur between the ages of 9 and 11, and then be repeated every five years after that. The NHLBI recommends that cholesterol screenings occur every one to two years for men ages 45 to 65 and for women ages 55 to 65. People over 65 should receive cholesterol tests annually. If your test results aren't within desirable ranges, your doctor might recommend more-frequent measurements. Your doctor might also suggest more-frequent tests if you have a family history of high cholesterol, heart disease or other risk factors, such as diabetes or high blood pressure.

Causes

Cholesterol is carried through your blood, attached to proteins. This combination of proteins and cholesterol is called a lipoprotein. There are different types of cholesterol, based on what the lipoprotein carries. They are:

- **Low-density lipoprotein (LDL).** LDL, the "bad" cholesterol, transports cholesterol particles throughout your body. LDL cholesterol builds up in the walls of your arteries, making them hard and narrow.
- **High-density lipoprotein (HDL).** HDL, the "good" cholesterol, picks up excess cholesterol and takes it back to your liver.

A lipid profile also typically measures triglycerides, a type of fat in the blood. Having a high triglyceride level also can increase your risk of heart disease. Factors you can control - such as inactivity, obesity and an unhealthy diet — contribute to harmful cholesterol and triglyceride levels. Factors beyond your control might play a role, too. For example, your genetic makeup might make it more difficult for your body to remove LDL cholesterol from your blood or break it down in the liver.

Medical conditions that can cause unhealthy cholesterol levels include:

- Chronic kidney disease
- Diabetes
- HIV/AIDS
- Hypothyroidism
- Lupus

Cholesterol levels can also be worsened by some types of medications you may be taking for other health problems, such as:

- Acne
- Cancer
- High blood pressure
- HIV/AIDS
- Irregular heart rhythms
- Organ transplants

Risk factors

Factors that can increase your risk of unhealthy cholesterol levels include:

- **Poor diet.** Eating too much saturated fat or trans fats can result in unhealthy cholesterol levels. Saturated fats are found in fatty cuts of meat and full-fat dairy products. Trans fats are often found in packaged snacks or desserts.
- **Obesity.** Having a body mass index (BMI) of 30 or greater puts you at risk of high cholesterol.
- **Lack of exercise.** Exercise helps boost your body's HDL, the "good," cholesterol.

- **Smoking.** Cigarette smoking may lower your level of HDL, the "good," cholesterol.
- **Alcohol.** Drinking too much alcohol can increase your total cholesterol level.
- **Age.** Even young children can have unhealthy cholesterol, but it's much more common in people over 40. As you age, your liver becomes less able to remove LDL cholest

Complications

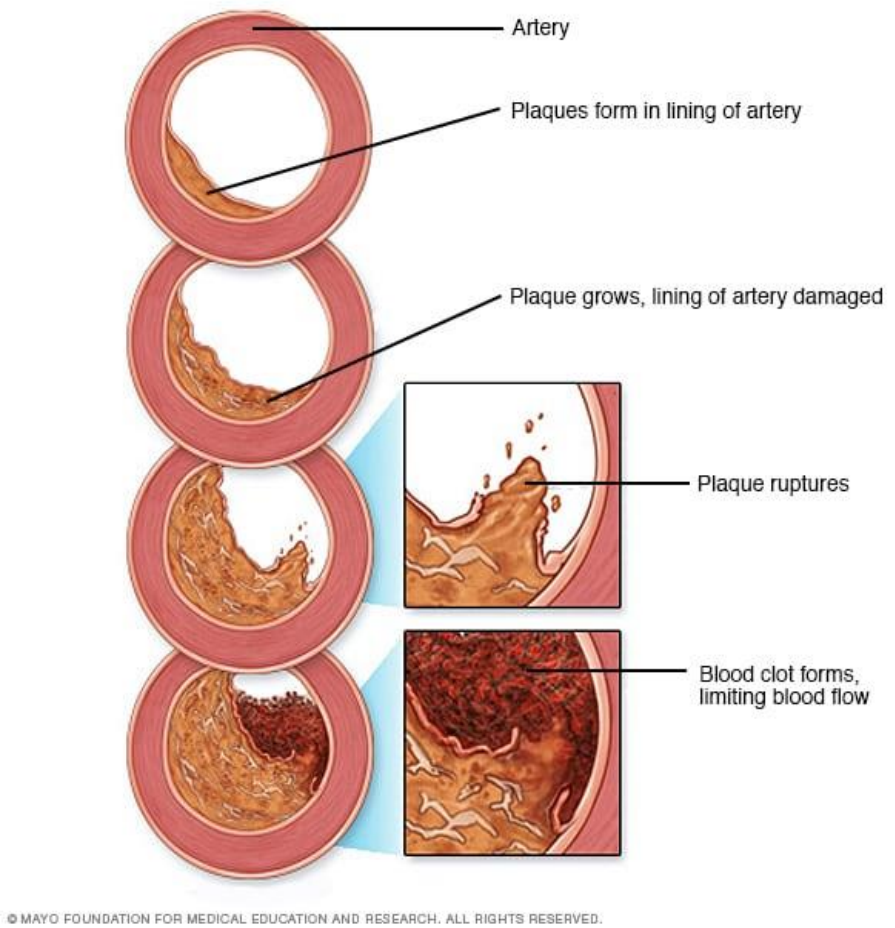


Fig. Development of atherosclerosis

High cholesterol can cause a dangerous accumulation of cholesterol and other deposits on the walls of your arteries (atherosclerosis). These deposits (plaques) can reduce blood flow through your arteries, which can cause complications, such as:

- **Chest pain.** If the arteries that supply your heart with blood (coronary arteries) are affected, you might have chest pain (angina) and other symptoms of coronary artery disease.
- **Heart attack.** If plaques tear or rupture, a blood clot can form at the plaque-rupture site -blocking the flow of blood or breaking free and plugging an artery downstream. If blood flow to part of your heart stops, you'll have a heart attack.

- **Stroke.** Similar to a heart attack, a stroke occurs when a blood clot blocks blood flow to part of your brain.

Prevention

- The same heart-healthy lifestyle changes that can lower your cholesterol can help prevent you from having high cholesterol in the first place. To help prevent high cholesterol, you can:
- Eat a low-salt diet that emphasizes fruits, vegetables and whole grains
- Limit the amount of animal fats and use good fats in moderation
- Lose extra pounds and maintain a healthy weight
- Quit smoking
- Exercise on most days of the week for at least 30 minutes
- Drink alcohol in moderation, if at all
- Manage stress

4.11 PHOSPHOLIPIDS

Phospholipid**,** also called Phosphatide**,** any member of a large class of fatlike, phosphorus-containing substances that play important structural and metabolic roles in living cells. Phospholipids are compound lipids, consisting of phosphoric acids, nitrogen base, alcohol and fatty acids. These compound lipids are major components of the cell membrane and also provide a fluid character to the membranes. In cell membranes, these phospholipids have a hydrophilic head and a hydrophobic tail, which forms the inside of the bilayer. The phospholipids, with the sphingolipids, the glycolipids, and the lipoproteins, are called complex lipids, as distinguished from the simple lipids (fats and waxes) and from other fat-soluble cell components, mostly isoprenoids and steroids. The term phosphoglyceride is used by some as a synonym for phospholipid and by others to denote a subgroup of phospholipids.

In general, phospholipids are composed of a phosphate group, two alcohols, and one or two fatty acids. On one end of the molecule are the phosphate group and one alcohol; this end is polar, *i.e.*, has an electric charge, and is attracted to water (hydrophilic). The other end, which consists of the fatty acids, is neutral; it is hydrophobic and water-insoluble but is fat-soluble. This amphipathic nature (containing both hydrophobic and hydrophilic groups) makes phospholipids important in membranes; they form a two-layer structure, called the lipid bilayer, with the polar head facing out on each surface to interact with water, and with the neutral “tails” driven inward and pointing toward one another. The lipid bilayer is the structural basis of all cell membranes and is nearly impermeable to ions and most polar molecules. Proteins embedded in the phospholipid matrix transport many substances through the membrane.

4.12 TYPES OF PHOSPHOLIPIDS

There are two types of phospholipids

- **Glycerophospholipids**

They are the major types of phospholipids, which occur in the biological membrane. It consists of glycerol-based phospholipids.

- **Sphingophospholipids**

They are the important constituents of myelin and are abundantly found in the brain and nervous tissues. It consists of sphingosine as alcohol

Properties of Phospholipids

1. They are signal mediators.
2. They are amphipathic molecules.
3. They anchor proteins within the cell membranes.
4. They are the major constituents of cell membranes.
5. They are the components of bile and lipoproteins.

Functions of Phospholipids

1. It regulates the permeability of the membrane.
2. It is also involved in the absorption of fat from the intestine.
3. It helps in ETC- Electron Transport Chain in the mitochondria.
4. Phospholipids help by preventing the accumulation of fats in the liver.
5. It plays a major role in the transportation and removal of cholesterol from the cells.
6. It forms the structural components of the cell membrane with the association of proteins.
7. They act as surfactants in the respiratory system and are also involved in the coagulation of blood cells.
8. It helps in the synthesis of different lipoproteins, prostacyclins, prostaglandins and thromboxanes.

4.13 TRIACYLGLYCEROLS

Triacylglycerols, commonly referred to as triglycerides, are composed of three fatty acids individually esterified to each carbon of a glycerol molecule. This allows for the formation of stereochemically distinct fatty acid bond positions: sn-1, sn-2, and sn-3. The fatty acid moieties of the triacylglycerol molecule account for ~90% of its molecular weight, depending on the chain length and number of double bonds of the constituent fatty acids.

Likewise, the physical form of a triacylglycerol is determined by its component fatty acids: chain length, number, position and conformation of the double bonds, and stereochemical position of each fatty acid on the triacylglycerol molecule.

Triacylglycerol is the predominant form of dietary lipid in fats and oils, whether derived from plants or animals, and the major form of lipid in the body. Triacylglycerol is composed of three fatty acids esterified to a glycerol molecule (Fig. 3). The physical properties of a triacylglycerol molecule are determined by the specific fatty acids esterified to the glycerol moiety and the actual position the fatty acids occupy. Each of the three carbons comprising the glycerol molecule allows for a stereochemically distinct fatty acid bond position: *sn*-1, *sn*-2, and *sn*-3. A triacylglycerol with three identical fatty acids is termed a simple triacylglycerol. These are exceedingly rare in nature. A triacylglycerol with two or three different fatty acids is termed a mixed triacylglycerol and make up the bulk of the triacylglycerol that occur naturally. The melting point of a triacylglycerol is determined by the physical characteristics and position of the fatty acids esterified to glycerol,—their chain length; number, position, and conformation of the double bonds; and the stereochemical position.

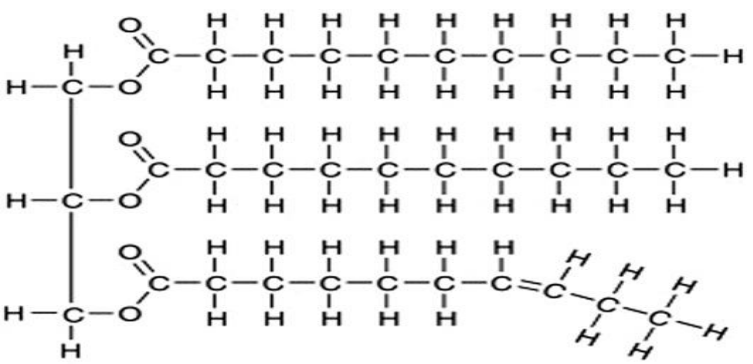


Fig. Triacylglycerol molecule

Approximately 90% of the molecular weight of triacylglycerol is accounted for by the three fatty acids. The fatty acid profile of the diet is reflected, in part, in the fatty acid profile of the adipose tissue triacylglycerol. Such data have been used to approximate long-term food intake patterns of humans. Mono- and diglycerides have one and two fatty acids, respectively, esterified to glycerol. In nature, they occur only in trace amounts. They are primarily intermediate products of triacylglycerol digestion, clearance from the bloodstream, or intracellular metabolism. They are used as emulsifiers in processed food.

Once consumed, triacylglycerol is hydrolyzed into non-esterified (free) fatty acids and monoglycerides by lipase that are synthesized in the pancreas and stored in the gallbladder until lipid in the small intestine signals for release. During absorption, these breakdown compounds enter the intestinal cells (enterocyte) and are used to resynthesize triacylglycerol. This triacylglycerol, along with intestinally derived

cholesterol and fat soluble compounds such as fat soluble vitamins, are incorporated into nascent triglyceride-rich lipoprotein particles, termed chylomicrons. Chylomicrons are first secreted into the thoracic duct (lymph) which drains into the subclavian vein (peripheral circulation). Once in circulation, fatty acids are hydrolyzed from the triacylglycerol which enables them to cross the plasma membrane of peripheral cells.

The primary enzyme that hydrolyzes triacylglycerol in plasma is lipoprotein lipase. The products of lipoprotein lipase are non-esterified fatty acids and 2-monoacylglycerol. The enzyme is attached to the luminal surface of capillary endothelial cells via a highly charged membrane-bound chain of heparin sulfate-proteoglycans. The ability of lipoprotein lipase to bind both the chylomicron particle and the cell surface ensures the cellular uptake of the liberated non-esterified fatty acids. Once inside the cell, the non-esterified fatty acids can be oxidized to provide energy, metabolized to biologically active compounds, or resynthesized into triacylglycerol for storage and subsequent use.

4.14 SUMMARY

Under this unit we have discussed De Novo Synthesis of fatty acids (Palmitic Acid), Fatty acid, phospholipids with their types and triglycerides. *De novo* fatty-acid synthesis involves two key enzymes, acetyl-CoA carboxylase (ACC) and fatty-acid synthase (FASN). ACC carboxylates acetyl-CoA to form malonyl-CoA. The malonyl-CoA product is further converted by FASN to long-chain fatty acids. Most normal human tissues preferentially use dietary (exogenous) lipid for synthesis of new structural lipids, whereas *de novo* (endogenous) fatty-acid synthesis is usually suppressed, and FASN expression is maintained at low levels. By contrast, in cancer cells, *de novo* fatty-acid synthesis is commonly elevated and the supply of cellular fatty acid is highly dependent on the *de novo* synthesis.

Therefore, deregulated *de novo* fatty-acid synthesis directly leads to cellular fatty-acid accumulation and affects fundamental cellular processes, including signal transduction and gene expression. Numerous studies have shown overexpression of FASN in various human epithelial cancers, including prostate, ovary, colon, lung, endometrium and stomach cancers. Moreover, several reports have shown that FASN and related lipogenic enzymes play important roles in tumour cell survival at multiple levels. Plasma proteins and their functions in concern to intermediary metabolism. Important macromolecules known as plasma proteins are

4.15 TERMINAL QUESTIONS

Q.1 What do you mean by De novo synthesis of fatty acids? Explain it.

Answer:----------

Q.2 Explain the concept of synthesis of unsaturated fatty acids.

Answer:----------

Q.3 Explain the concept of breakdown of unsaturated fatty acids.

Answer:----------

Q.4 Write short notes on the followings.

(i) Phospholipids

(ii) Triacylglycerol

Answer:----------

Q. 5 Explain cholesterol. Why cholesterol is important?

Answer:----------

Further readings

- Biochemistry- Lehninger A.L.
- Textbook of Nutrition and Dietetics Ranjana Mahna
- Biochemistry fourth edition-David Hames and Nigel Hooper.
- Textbook of Biochemistry for Undergraduates - Rafi, M.D.
- Textbook of Nutrition and Dietetics- Monika Sharma

U.P.Rajarshi Tandon Open University, Prayagraj

MFN-102

Advanced Nutritional Biochemistry

BLOCK

2

Purines and Pyrimidines, Nucleic acids and Hormones

Unit 5: Purines and Pyrimidines

Unit 6: Nucleic Acids

Unit 7: Mutations and gene expression

Unit 8: Hormones

MFN-102

Advanced Nutritional Biochemistry

VICE CHANCELLOR

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COURSE DESIGN COMMITTEE

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School of Health Sciences,
UPRTOU, Prayagraj.

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Associate Professor,
(Home Science, Nutritional Sciences)

Mrs. Zoomi Singh **Member**

Assistant Professor,
Home Science, Nutritional Sciences, UPRTOU, Prayagraj (Contractual)

COURSE PREPRATION COMMITTEE

Dr. Kapil Gupta **Unit: 1-12** **Writer**

Assistant Professor
Department of Biotechnology
Siddharth University Kapilvastu, Siddharthnagar

Dr. Pramod Kumar Pandey **(All blocks and units)** **Editor**

Associate Professor,
Department of Zoology, PSM PG College, Maharajganj

COURSE COORDINATOR

Dr.Meera Pal

Associate Professor
UP Rajarshi Tandon Open University, Prayagraj

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Block Introduction

This is the second block (Purines and Pyrimidines, Nucleic acids and Hormones) of Advanced Nutritional Biochemistry. It consists of four units. The objective of this block deals basic introduction to purines & pyrimidines, nucleic acids, mutation & gene expression and hormones respectively.

Unit 5 :

Under this unit, we have discussed elementary knowledge of purines and pyrimidines in concern to their structure, synthesis and breakdown. Purines have two carbon-nitrogen ring bases whereas pyrimidines have one carbon-nitrogen ring base. They are building blocks of genetic material- DNA and RNA. The synthesis of nucleotides in plants is similar to the synthesis of nucleotides in animals and microorganisms. De Novo and salvage are the two principal pathways of the synthesis of purines and pyrimidines. The de novo pathway builds these nucleotides from scratch by the usage of 5-phosphoribosyl-1-pyrophosphate (PRPP) using carbon dioxide, amino acids, and tetrahydrofolate.

Unit 6 :

Under this unit, we have discussed nucleic acids in concern to their nitrogenous bases, structure, replication and functions. Nucleic acids perform essential functions in the cell. They contain genetic information and play a key role in protein biosynthesis. They are macromolecules formed by nucleotides. Nucleotides consist of a nitrogenous base, an aldopentose and phosphoric acid. The base can be of the pyrimidine and purine type. The first include thymine (T), cytosine (C), and uracil (U); the second, adenine (A) and guanine (G)

Unit 7 :

Under this unit, we have discussed mutation, gene expression and protein biosynthesis. Mutation **is** an alteration in the genetic material (the genome) of a cell of a living organism or of a virus that is more or less permanent and that can be transmitted to the cell's or the virus's descendants. In gene expression, the information encoded in a gene is turned into a function. This mostly occurs via the transcription of RNA molecules that code for proteins or non-coding RNA molecules that serve other functions. Protein biosynthesis at the ribosome results in the conversion of nucleic acid genetic information into the polypeptides essential for cellular function. In biological systems, it involves amino acid synthesis, transcription, translation, and post-translational events

Unit 8 :

Under this unit, we have discussed hormones with types, secretions and its working mechanism. Endocrine glands make chemicals called hormones and pass them straight into the bloodstream. Hormones can be thought of as chemical messages. They are

chemical messengers that coordinate different functions in your body. Several glands, organs and tissues make and release hormones, many of which make up your endocrine system. Action Hormones are carried by the blood throughout the entire body, yet they affect only certain cells. The specific cells that respond to a given hormone have receptor sites for that hormone.

UNIT- 5 : PURINES AND PYRIMIDINES

Structure

5.1 INTRODUCTION

Nucleobases (nitrogenous bases or simply bases) are nitrogen-containing biological compounds that form nucleosides, which, in turn, are components of nucleotides, with all of these monomers constituting the basic building blocks of nucleic acids. The ability of nucleobases to form base pairs and to stack one upon another leads directly to long-chain helical structures such as ribonucleic acid (RNA) and deoxyribonucleic acid (DNA). Five nucleobases—adenine (A), cytosine (C), guanine (G), thymine (T),and uracil (U)—are called primary or canonical. They function as the fundamental units of the genetic code, with the bases A, G, C, and T being found in DNA while A, G, C, and U are found in RNA. Thymine and uracil are distinguished by merely the presence or absence of a methyl group on the fifth carbon (C5) of these heterocyclic six-membered rings. In

addition, some viruses have aminoadenine (Z) instead of adenine. It differs in having an extra amine group, creating a more stable bond to thymine.

Adenine and guanine have a fused-ring skeletal structure derived of purine, hence they are called purine bases. The purine nitrogenous bases are characterized by their single amino group ($-NH_2$), at the C6 carbon in adenine and C2 in guanine. Similarly, the simple-ring structure of cytosine, uracil, and thymine is derived of pyrimidine, so those three bases are called the pyrimidine bases. Each of the base pairs in a typical double-helix DNA comprises a purine and a pyrimidine: either an A paired with a T or a C paired with a G. These purine-pyrimidine pairs, which are called base complements, connect the two strands of the helix and are often compared to the rungs of a ladder. Only pairing purine with pyrimidine ensures a constant width for the DNA. The A–T pairing is based on two hydrogen bonds, while the C–G pairing is based on three. In both cases, the hydrogen bonds are between the amine and carbonyl groups on the complementary bases.

Objectives

This is the fifth unit on purines and pyrimidines of second block (Purines and Pyrimidines, Nucleic Acids and Hormones). Under fifth unit (purines and pyrimidines), we have following objectives. These are as under:

- To understand the definition of purine and pyrimidine basses
- To discuss the differences between purines and pyrimidines
- To know the concept of bonding between purine and pyrimidine
- To discuss the significances of purines and pyrimidines

Nitrogenous bases, also called nucleobases, are nitrogenous compounds that form an important part of the nucleotides. Nucleotides are building blocks of DNA and RNA that are composed of a sugar, nitrogenous base and a phosphate group. There are a total of five bases found in the DNA and RNA world, namely – Adenine (A), Cytosine (C), Guanine (G), Thymine (T) and Uracil (U). Let us look at the five nucleotides found in DNA and RNA.

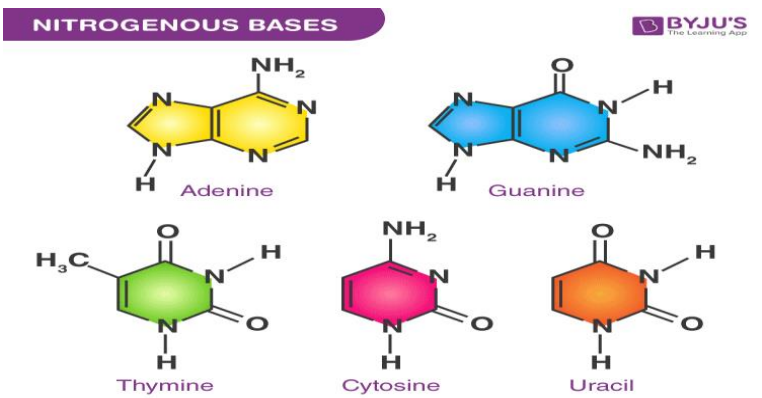


Fig. Nitrogenous bases

5.1.1 ADENINE

Adenine is a two ringed purine derived nucleobase that has an amino group attached to the C6 position. In the nucleotide structure it forms a covalent bond with the ribose/deoxyribose sugar and hydrogen bond with the adjacent nucleobase, that is either a thymine or uracil. Other compounds formed by adenine include vitamin B12, adenosine triphosphate (ATP), nicotinamide adenine dinucleotide (NAD) and flavin adenine dinucleotide (FAD).

5.1.2 GUANINE

Guanine is another two ringed purine derived nucleobase composed of a fused pyrimidine-imidazole ring system that is conjugated with double bonds. It forms hydrogen bonds with cytosine in the nucleotide sequence. Guanine combines with ribose to form guanosine and with deoxyribose to form deoxyguanosine.

5.1.3 Thymine

Thymine is an organic compound that belongs to the pyrimidine family. It forms double hydrogen bonds with adenine in the DNA helix. It is also known as 5-methyluracil because it is methylated at the C5 position in the molecule. It is not found in RNA strands.

5.1.4 CYTOSINE

Cytosine is a pyrimidine derived nitrogenous base that has an amino group at the C4 position. It forms triple hydrogen bonds with guanine in the DNA helix.

5.1.5 URACIL

Uracil is another pyrimidine derived nitrogenous base that is only found in RNA molecules in place of thymine. It is a demythlated form of thymine that is substituted with oxo groups at C2 and C4.

Adenine and guanine have a fused-ring skeletal structure derived of purine, hence they are called purine bases. The purine nitrogenous bases are characterized by their single amino group ($-NH_2$), at the C6 carbon in adenine and C2 in guanine. Similarly, the simple-ring structure of cytosine, uracil, and thymine is derived of pyrimidine, so those three bases are called the pyrimidine bases.

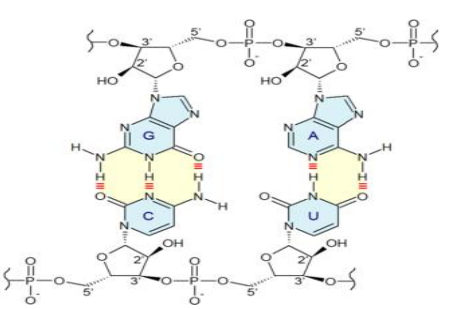


Fig. Base pairing: Two base pairs are produced by four nucleotide monomers, nucleobases are *in blue*.

Guanine (G) is paired with cytosine (C) via *three* hydrogen bonds, *in red*. Adenine (A) is paired with uracil (U) via two hydrogen bonds, in red

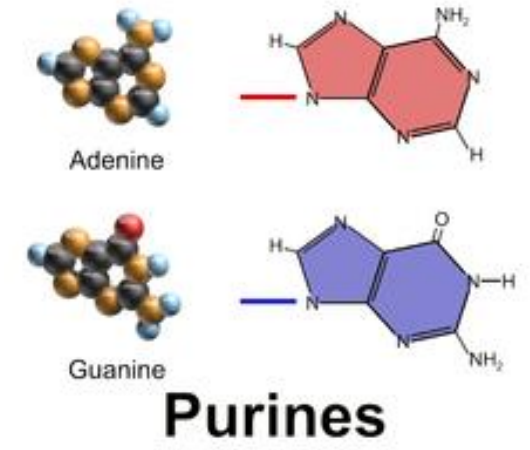


Fig. Purine nucleobases are fused-ring molecules.

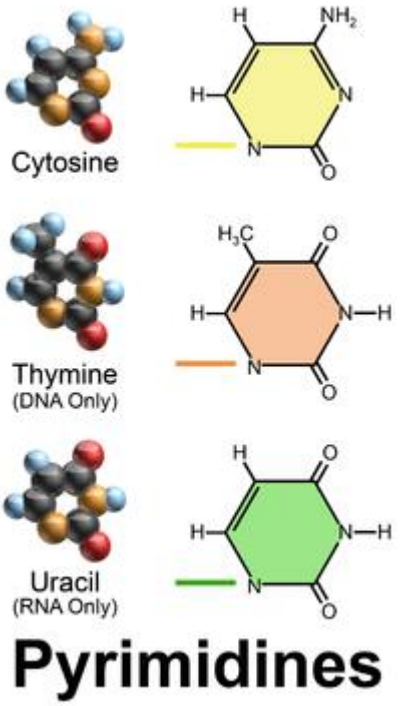


Fig. Pyrimidine nucleobases are simple ring molecules.

Each of the base pairs in a typical double-helix DNA comprises a purine and a pyrimidine: either an A paired with a T or a C paired with a G. These purine-pyrimidine pairs, which are called *base complements*, connect the two strands of the helix and are often compared to the rungs of a ladder. Only pairing purine with pyrimidine ensures a constant width for the DNA. The A–T pairing is based on two hydrogen bonds, while the C–G pairing is based on three. In both cases, the hydrogen bonds are between

the amine and carbonyl groups on the complementary bases.

Nucleobases such as adenine, guanine, xanthine, hypoxanthine, purine, 2,6-diaminopurine, and 6, 8-diaminopurine may have formed in outer space as well as on earth. The origin of the term *base* reflects these compounds' chemical properties in acid–base reactions, but those properties are not especially important for understanding most of the biological functions of nucleobases.

5.2 PURINES AND PYRIMIDINES

Purines and pyrimidines are both organic compounds that take part in the synthesis of DNA and RNA, therefore they are called as the building blocks of the genetic material; DNA and RNA. They are nitrogenous bases that make up the two different nucleotides in DNA and RNA. Purines (adenine and guanine) are two-carbon nitrogen ring bases while pyrimidines (cytosine and thymine) are one-carbon nitrogen ring bases. Given below in a tabular column are the differences between Purines and Pyrimidines.

5.2.1 PURINE VS PYRIMIDINE

Purines	**Pyrimidines**
Purine is a heterocyclic aromatic organic compound composed of a pyrimidine ring fused with imidazole ring.	Pyrimidine is a heterocyclic aromatic organic compound that is composed of carbon and hydrogen.
It comprises adenine and guanine as nucleobases.	It comprises cytosine, thymine, uracil as nucleobases
It consists of two hydrogen-carbon rings and four nitrogen atoms	It consists of one hydrogen-carbon ring and two nitrogen atoms
The melting point of purine is 214 °C	The melting point of pyrimidine is 20-22 °C
Catabolism results in the production of uric acid	Catabolism produces carbon dioxide, beta-amino acids and ammonia

Both purine and pyrimidine have similar functions. They are vital for the production of DNA and RNA, starch and proteins. They also serve as a form of energy for cells. They regulate enzymes and are necessary for cell signalling.

5.2.2 STRUCTURE

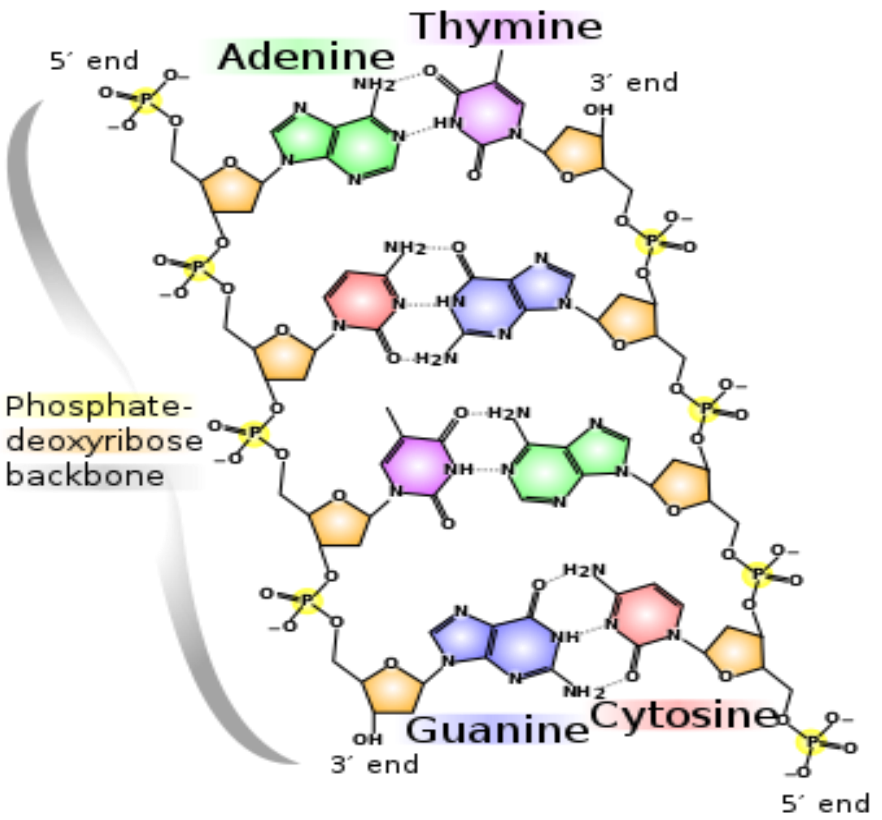


Fig. Chemical structure of DNA, showing four nucleobase pairs produced by eight nucleotides:

adenine (A) is joined to thymine (T), and guanine (G) is joined to cytosine (C)

Chemical structure of DNA, showing four nucleobase pairs produced by eight nucleotides: adenine (A) is joined to thymine (T), and guanine (G) is joined to cytosine (C). + This structure also shows the directionality of each of the two phosphate-deoxyribose backbones, or strands. The 5' to 3' (*read* "5 prime to 3 prime") directions are: *down* the strand on the left, and *up* the strand on the right. The strands twist around each other to form a double helix structure.

At the sides of nucleic acid structure, phosphate molecules successively connect the two sugar-rings of two adjacent nucleotide monomers, thereby creating a long chain biomolecule. These chain-joins of phosphates with sugars (ribose or deoxyribose) create the "backbone" strands for a single- or double helix biomolecule. In the double helix of DNA, the two strands are oriented chemically in opposite directions, which permits base pairing by providing complementarity between the two bases, and which is essential for replication of or transcription of the encoded information found in DNA.

5.3 MODIFIED NUCLEOBASES

DNA and RNA also contain other (non-primary) bases that have been modified after

the nucleic acid chain has been formed. In DNA, the most common modified base is 5-methylcytosine (m^5C). In RNA, there are many modified bases, including those contained in the nucleosides pseudouridine (Ψ), dihydrouridine (D), inosine (I), and 7-methylguanosine (m^7G). Hypoxanthine and xanthine are two of the many bases created through mutagen presence, both of them through deamination (replacement of the amine-group with a carbonyl-group). Hypoxanthine is produced from adenine, xanthine from guanine, and uracil results from deamination of cytosine.

5.4 PURINE

Purine is a heterocyclic aromatic organic compound that consists of two rings (pyrimidine and imidazole) fused together. It is water-soluble. Purine also gives its name to the wider class of molecules, purines, which include substituted purines and their tautomers. They are the most widely occurring nitrogen-containing heterocycles in nature.

Dietary sources

Purines are found in high concentration in meat and meat products, especially internal organs such as liver and kidney. In general, plant-based diets are low in purines.[2] High-purine plants and algae include some legumes (lentils and black eye peas) and spirulina. Examples of high-purine sources include: sweetbreads, anchovies, sardines, liver, beef kidneys, brains, meatextracts (e.g., Oxo, Bovril), herring, mackerel, scallops, game meats, yeast (beer, yeast extract, nutritional yeast) and gravy.

A moderate amount of purine is also contained in red meat, beef, pork, poultry, fish and seafood, asparagus, cauliflower, spinach, mushrooms, green peas, lentils, dried peas, beans, oatmeal, wheat bran, wheat germ, and haws.

Biochemistry

Purines and pyrimidines make up the two groups of nitrogenous bases, including the two groups of nucleotide bases. The purine bases are guanine (G) and adenine (A) which form corresponding nucleosides-

deoxyribonucleosides (deoxyguanosine and deoxyadenosine) with deoxyribose moiety and ribonucleosides (guanosine, adenosine) with ribose moiety. These nucleosides with phosphoric acid form corresponding nucleotides (deoxyguanylate, deoxyadenylate and guanylate, adenylate) which are the building blocks of DNA and RNA, respectively. Purine bases also play an essential role in many metabolic and signalling processes within the compounds guanosine monophosphate (GMP) and adenosine monophosphate (AMP).

In order to perform these essential cellular processes, both purines and pyrimidines are needed by the cell, and in similar quantities. Both purine and pyrimidine are self-inhibiting and activating. When purines are formed, they inhibit the enzymes required for more purine formation. This self-inhibition occurs as they also activate the enzymes needed for pyrimidine formation. Pyrimidine simultaneously self-inhibits and activates purine in a similar manner. Because of this, there is nearly an equal amount of both

substances in the cell at all times.

Properties

Purine is both a very weak acid (pK_a 8.93) and an even weaker base (pK_a 2.39). If dissolved in pure water, the pH is halfway between these two pKa values. Purine is aromatic, having four tautomers each with a hydrogen bonded to a different one of the four nitrogen atoms. These are identified as 1-H, 3-H, 7-H, and 9-H (see image of numbered ring). The common crystalline form favours the 7-H tautomer, while in polar solvents both the 9-H and 7-H tautomers predominate. Substituents to the rings and interactions with other molecules can shift the equilibrium of these tautomers.

Notable purines

There are many naturally occurring purines. They include the nucleobases adenine (2) and guanine (3). In DNA, these bases form hydrogen bonds with their complementary pyrimidines, thymine and cytosine, respectively. This is called complementary base pairing. In RNA, the complement of adenine is uracil instead of thymine.

Othernotablepurines are hypoxanthine, xanthine, theophylline, theobromine, caffeine, uric acid and isoguanine.

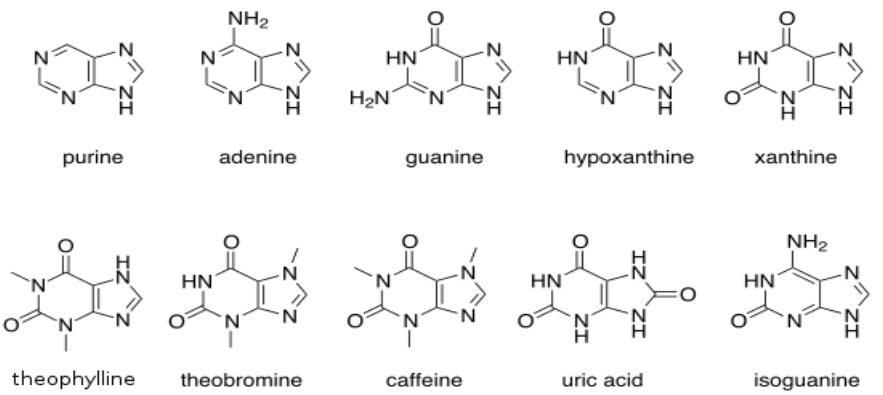


Fig. Structure of Purines

Functions

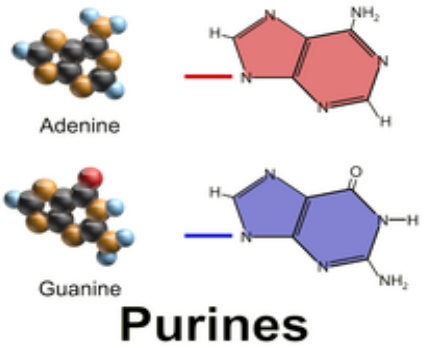
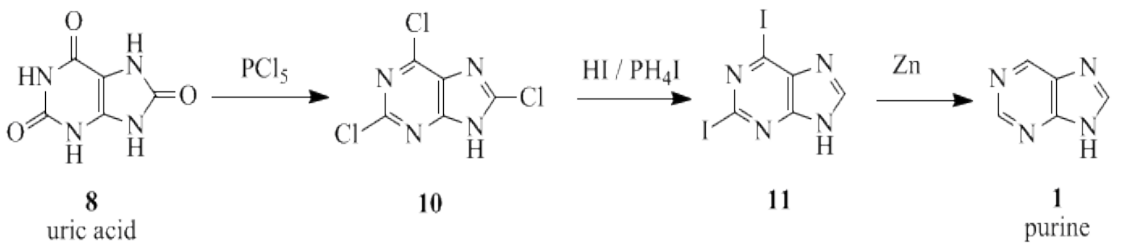


Fig. The main purine-derived nucleobases

Aside from the crucial roles of purines (adenine and guanine) in DNA and RNA, purines are also significant components in a number of other important biomolecules, such as ATP, GTP, cyclic AMP, NADH, and coenzyme A. Purine (1) itself, has not been found in nature, but it can be produced by organic synthesis. They may also function directly as neurotransmitters, acting upon purinergic receptors. Adenosine activates adenosine receptors.

History

The word *purine* (*pure urine*) was coined by the German chemist Emil Fischer in 1884. He synthesized it for the first time in 1898. The starting material for the reaction sequence was uric acid (8), which had been isolated from kidney stones by Carl Wilhelm Scheele in 1776. Uric acid (8) was reacted with PCl_5 to give 2, 6, 8-trichloropurine (10), which was converted with HI and PH_4I to give 2,6-diiodopurine (11). The product was reduced to purine (1) using zinc dust.



8 uric acid **10** **11** **1** purine

5.5 METABOLISM

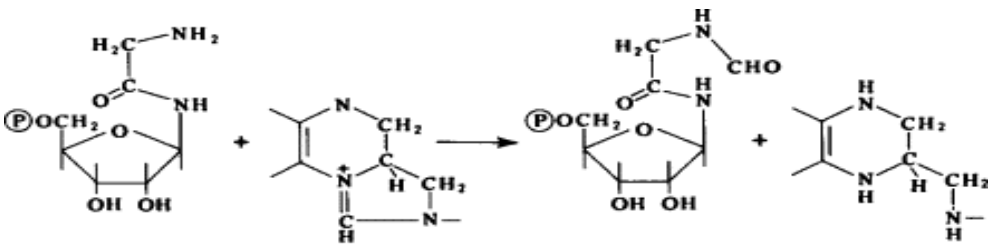
Many organisms have metabolic pathways to synthesize and break down purines. Purines are biologically synthesized as nucleosides (bases attached to ribose). Accumulation of modified purine nucleotides is defective to various cellular processes, especially those involving DNA and RNA. To be viable, organisms possess a number of deoxypurine phosphohydrolases, which hydrolyze these purine derivatives removing them from the active NTP and dNTP pools. Deamination of purine bases can result in accumulation of such nucleotides as ITP, dITP, XTP and dXTP. Defects in enzymes that control purine production and breakdown can severely alter a cell's DNA sequences, which may explain why people who carry certain genetic variants of purine metabolic enzymes have a higher risk for some types of cancer.

Purine biosynthesis in the three domains of life

Organisms in all three domains of life, eukaryotes, bacteria and archaea, are able to carry out de novo biosynthesis of purines. This ability reflects the essentiality of purines for life. The biochemical pathway of synthesis is very similar in eukaryotes and bacterial species, but is more variable among archaeal species. A nearly complete, or complete, set of genes required for purine biosynthesis was determined to be present in 58 of the 65 archaeal species studied. However, also identified were seven archaeal species with entirely, or nearly entirely, absent purine encoding genes. Apparently the archaeal species unable to synthesize purines are able to acquire exogenous purines for growth.,[14] and are thus analogous to purine mutants of eukaryotes, e.g. purine mutants of the Ascomycete

fungus *Neurospora crassa*, that also require exogenous purines for growth.

Purine biosynthesis *de novo* was one of the first areas of metabolism in which a folic acid derivative was specifically identified as a cofactor in an enzymatic reaction. The ability of pigeon liver extracts to add formate to phosphoribosyl glycineamide was impaired by treatment with charcoal, but was restored by addition of H_4-folate. Although the complicated interconversions of the H_4-folate coenzymes caused confusion for some time, the specific one-carbon donor for this reaction was eventually identified as 5, 10-methenyl H_4-folate. The phosphoribosyl glycineamide formyltransferase reaction itself is irreversible.



Recent studies using *Salmonella typhimurium* suggest either that its formyltransferase is atypical, or that it is not an obligate enzyme for purine biosynthesis in this organism. Mutants lacking this enzyme could not be found, nor could a folate coenzyme requirement for phosphoribosyl formylgycineamide synthesis be demonstrated

5.6 PURINES VS. PYRIMIDINES

While both purines and pyrimidines are heterocyclic aromatic compounds, they can be differed from each other based on the chemical structure. A purine has *two* carbon rings whereas a pyrimidine has *one* carbon ring. The purine has a *pyrimidine ring* fused to an *imidazole ring*. The pyrimidine has only a *pyrimidine ring*. Thus, the purine has four nitrogen atoms whereas the pyrimidine has two.

Pyrimidines include cytosine, thymine, and uracil whereas purines include *adenine* and *guanine*. These five nitrogenous bases are regarded as *primary* or *canonical* since they are the fundamental units of the genetic code. The nucleobases that make up the nucleic acid are used to distinguish DNA from RNA molecules. In DNA, thymine complementary pairs with adenine whereas in RNA, uracil matches with adenine. The thymine differs from uracil in having a methyl group, which the uracil lacks. The pairings of nucleobases C-G and A-T (or A-U in RNA) are referred to as *base complements*.

Properties of Pyrimidines

Pyrimidine is a heterocyclic aromatic organic compound with a chemical formula of $C_4H_4N_2$. It has a single ring (called a *pyrimidine ring*) with alternating carbon and nitrogen atoms. The molar mass of pyrimidine is 80.088 g/mol and its melting point is at 20-22 °C.

Cytosine, Thymine, and Uracil

Cytosine, thymine, and uracil are pyrimidine nucleobases. Cytosine can be distinguished from the other pyrimidines by having a keto group at position 2 and an amine group at position 4 in its heterocyclic aromatic ring. It has a chemical formula of $C_4H_5N_3O$. In DNA and RNA, cytosine matches with guanine forming three hydrogen bonds. When phosphorylated with three phosphoric acid groups, they become cytidine triphosphate (CTP) and deoxycytidine triphosphate (dCTP), which are nucleotides that build up RNA and DNA molecules, respectively. A cytidine triphosphate is a nucleotide that forms part of DNA or RNA. It may also serve as a co-factor to enzymes. It can transfer its phosphate to convert ADP to ATP.

Thymine has a chemical formula of $C_5H_6N_2O_2$. It has two keto groups at positions 2 and 4, and a methyl group at position 5 in its heterocyclic aromatic ring. Thymine complementary base pairs with adenine by two hydrogen bonds. However, unlike cytosine that is present in both DNA and RNA, thymine is present only in the DNA molecule because it is replaced by uracil in RNA. Thymine that is attached to a deoxyribose (a pentose sugar) is referred to as *deoxythymidine* (or thymidine). When phosphorylated with three phosphoric acid groups, the deoxythymidine becomes *deoxythymidine triphosphate* (dTTP), which is one of the nucleotide mono meric units that buildup DNA.

Uracil is similar to thymine in terms of structure except for the methyl group at position 5 in the heterocyclic aromatic ring present in thymine. It has a chemical formula of $C_4H_4N_2O_2$. In complementary base pairing, uracil pairs with adenine. In general, uracil occurs in RNA, not in DNA. Instead of uracil, DNA has thymine that pairs with adenine.

One of the possible explanations why DNA has thymine instead of uracil is associated with the conversion of cytosine into uracil by spontaneous deamination. Cytosine can turn into uracil when it loses its amine group. This deamination of cytosine is a common occurrence. Nevertheless, the error is corrected through an inherent DNA repair systems. If not repaired though, it could lead to point mutation. If uracil is present in the DNA, the repair systems may not be able to distinguish the original uracil from the cytosine-turned-uracil and therefore may fail to discern which uracil to correct.

The presence of methyl group in thymine (which is absent in uracil) helps avert this from happening, thereby, preserving the integrity and stability of the genetic code. Uracil that is attached to a deoxyribose (a pentose sugar) is referred to as *uridine*. When phosphorylated with three phosphoric acid groups, uridine becomes *uridine triphosphate* (UTP), which is one of the nucleotide monomeric units that build up RNA.

5.7 COMMON BIOLOGICAL REACTIONS

In pyrimidine biosynthesis, the ring forms by a series of steps that begins in the formation of carbamoyl phosphate. First, carbamoyl phosphate is produced from biochemical reaction involving bicarbonate, glutamine, ATP (for phosphorylation), and water molecule. The enzyme that catalyzes the reaction is carbamoyl phosphate

synthetase II located in the cytosol. Next, the carbamoyl phosphate is converted into carbamoyl aspartate by the enzyme aspartate transcarbamylase.

Then, the ring closes through intramolecular condensation, converting carbamoyl phosphate into dihydroorotate by the enzyme dihydroorotase. Lastly, the dihydroorotate is oxidized by dihydroorotate dehydrogenase (an integral membrane protein in the inner mitochondrial membrane) to convert into orotate. As a result, C2 of the pyrimidine ring comes from the bicarbonate ion (HCO_3^-), N3 comes from glutamine, and the rest of the atoms in the rings are derived from aspartate.

After the pyrimidine ring forms, 5-phospho-α-D-ribosyl 1-pyrophosphate (PRPP), a ribose phosphate, reacts to orotate to form orotidine-5-monophosphate (OMP). OMP is then decarboxylated by the enzyme OMP decarboxylase to yield uridine monophosphate (UMP). Eventually, uridine diphosphate (UDP) and uridine triphosphate (UTP) are produced down the biosynthetic pathway by kinases and dephosphorylation of ATPs. UTP can be converted into cytidine triphosphate (CTP) by amination of UTP via the enzyme CTP synthetase.

Pyrimidine biosynthesis differs from purine biosynthesis in a way that purines are synthesized as a nucleotide first whereas pyrimidines form initially as a free base. In humans, pyrimidines are synthesized in various tissues, especially in spleen, thymus, and gastrointestinal tract. Pyrimidines that are degraded can be recycled by a *salvage pathway*. Nucleobases are recovered for re-use post-RNA and DNA degradations. Pyrimidine salvage pathways are as follows:

- Cytosine is converted into uracil by deamination. By *uridine phosphorylase*, uracil is converted into uridine by reacting with ribose-1-phosphate. Through the enzyme *nucleoside kinase*, uridine is converted into uridine monophosphate (UMP).
- Thymine is converted into thymidine by reacting with *deoxyribose-1-phosphate* and by the enzyme *thymidine phosphorylase*. Thymidine is then converted into *thymidine monophosphate* by the enzyme *nucleoside kinase*.

5.8 BIOLOGICAL FUNCTIONS

Pyrimidines as one of the nucleobases are important structural components of nucleic acids. Nucleic acids such as DNA and RNA molecules contain the genetic information important for all cellular functions and heredity. Apart from the nucleic acids, nucleobases are also important components of certain proteins and starches. Thus, their functions are not just to serve as structural constituents of DNA and RNA but they are also involved in the regulation of enzymes and cell signaling.

5.9 SUMMARY

Under this unit we have discussed different types of nitrogenous bases, purines and pyrimidines, common biological reactions and biological functions. Several chemicals

with a similar cyclic structure, each known as a nitrogenous base, play several important roles in biology. Not only is a nitrogenous base the building blocks for genetic information carrying molecules like DNA and RNA, but different forms of the nitrogenous base serve in various cellular roles from *signal transduction* to growing microtubules. In DNA and RNA, a nitrogenous base forms a bond with a 5-sided carbon sugar molecule, which forms a "backbone" for the entire molecule. A nitrogenous base plus this sugar backbone is known as a *nucleotide*, and forms the building blocks of DNA and RNA. Purines act as metabolic signals, provide energy, control cell growth, are part of essential coenzymes, contribute to sugar transport and donate phosphate groups in phosphorylation reactions.

Pyrimidines are biologically very important heterocycles and represent by far the most ubiquitous members of the diazine family with uracil (**6**) and thymine (**7**) being constituents of ribonucleic acid (RNA) and deoxyribonucleic acid (DNA) and with cytosine. In addition to this, pyrimidines skeleton is also present in many natural products such as vitamin B_1 (thiamine) and many synthetic compounds, such as barbituric acid (**9**) and Veranal (**10**) which are used as hypnotics

5.10 TERMINAL QUESTIONS

Q. 1 What do you know about purine and pyrimidine bases? Define it with examples.

Answer:----------

Q. 2 What are the significances of purines and pyrimidines? Explain it.

Answer:----------

Q.3 What are the differences between purines and pyrimidines? Distinguish it.

Answer:----------

Q.4 Write short notes on the followings.

(i) Purine bases

(ii) Pyrimidine bases

Answer:----------

Q. 5 How do purine and pyrimidine bases bond together? Describe it.

Answer:----------

Q. 6 Why does purine always pair with pyrimidine?

Answer:----------

Further readings

- Biochemistry- Lehninger A.L.
- Textbook of Nutrition and Dietetics Ranjana Mahna
- Biochemistry fourth edition-David Hames and Nigel Hooper.
- Textbook of Biochemistry for Undergraduates - Rafi, M.D.
- Textbook of Nutrition and Dietetics- Monika Sharma

UNIT- 6 NUCLEIC ACIDS

Structure

Objectives

Further readings

6.1 INTRODUCTION

Nucleic acids, and DNA in particular, are key macromolecules for the continuity of life. DNA bears the hereditary information that's passed on from parents to children, providing instructions for how (and when) to make the many proteins needed to build and maintain functioning cells, tissues, and organisms. How DNA carries this information, and how it is put into action by cells and organisms, is complex, fascinating, and fairly mind-blowing, and we'll explore it in more detail in the section on molecular biology. Here, we'll just take a quick look at nucleic acids from the macromolecule perspective.

Nucleic acid**,** naturally occurring chemical compound that is capable of being broken down to yield phosphoric acid, sugars, and a mixture of organic bases (purines and pyrimidines). Nucleic acids are the main information-carrying molecules of the cell, and, by directing the process of protein synthesis, they determine the inherited characteristics of every living thing. The two main classes of nucleic acids are deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). DNA is the master blueprint for life and constitutes the genetic material in all free-living organisms and most viruses. RNA is the genetic material of certain viruses, but it is also found in all living cells, where it plays an important role in certain processes such as the making of proteins. This unit covers the chemistry of nucleic acids, describing the structures and properties that allow them to serve as the transmitters of genetic information.

Objectives

This is the sixth unit on nucleic acids of second block (Purines and Pyrimidines, Nucleic Acids and Hormones). Under sixth unit (Nucleic acids), we have following objectives. These are as under:

- To understand the concept of nucleic acids
- To distinguish between DNA and RNA
- To discuss the structure of nucleic acids
- To discuss the important functions of nucleic acids
- To know the applications of nucleic acid

Roles of DNA and RNA in cells

Nucleic acids**,** macromolecules made out of units called nucleotides, come in two naturally occurring varieties: deoxyribonucleic acid **(**DNA**)** **and** ribonucleic acid **(**RNA**).** DNA is the genetic material found in living organisms, all the way from single-celled bacteria to multicellular mammals like you and me. Some viruses use RNA, not DNA, as their genetic material, but aren't technically considered to be alive (since they cannot reproduce without help from a host).

DNA in cells

In eukaryotes, such as plants and animals, DNA is found in the **nucleus**, a specialized, membrane-bound vault in the cell, as well as in certain other types of organelles (such as mitochondria and the chloroplasts of plants). In prokaryotes, such as bacteria, the DNA is not enclosed in a membranous envelope, although it's located in a specialized cell region called the **nucleoid**.

In eukaryotes, DNA is typically broken up into a number of very long, linear pieces called **chromosomes**, while in prokaryotes such as bacteria, chromosomes are much smaller and often circular (ring-shaped). A chromosome may contain tens of thousands of **genes**, each providing instructions on how to make a particular product needed by the cell.

From DNA to RNA to proteins

Many genes encode protein products, meaning that they specify the sequence of amino acids used to build a particular protein. Before this information can be used for protein synthesis, however, an RNA copy (transcript) of the gene must first be made. This type of RNA is called a **messenger RNA** (**mRNA**), as it serves as a messenger between DNA and the ribosomes, molecular machines that read mRNA sequences and use them to build proteins. This progression from DNA to RNA to protein is called the "central dogma" of molecular biology.

Importantly, not all genes encode protein products. For instance, some genes specify **ribosomal RNAs** (**rRNAs**), which serve as structural components of ribosomes, or **transfer RNAs** (**tRNAs**), cloverleaf-shaped RNA molecules that bring amino acids to the ribosome for protein synthesis. Still other RNA molecules, such as tiny **microRNAs** (**miRNAs**), act as regulators of other genes, and new types of non-protein-coding RNAs are being discovered all the time.

6.2 NUCLEOTIDES

DNA and RNA are polymers (in the case of DNA, often very long polymers), and are made up of monomers known as **nucleotides**. When these monomers combine, the resulting chain is called a **polynucleotide** (*poly-* = "many"). Each nucleotide is made up of three parts: a nitrogen-containing ring structure called a nitrogenous base, a five-carbon sugar, and at least one phosphate group. The sugar molecule has a central position in the nucleotide, with the base attached to one of its carbons and the phosphate group (or groups) attached to another. Let's look at each part of a nucleotide in turn.

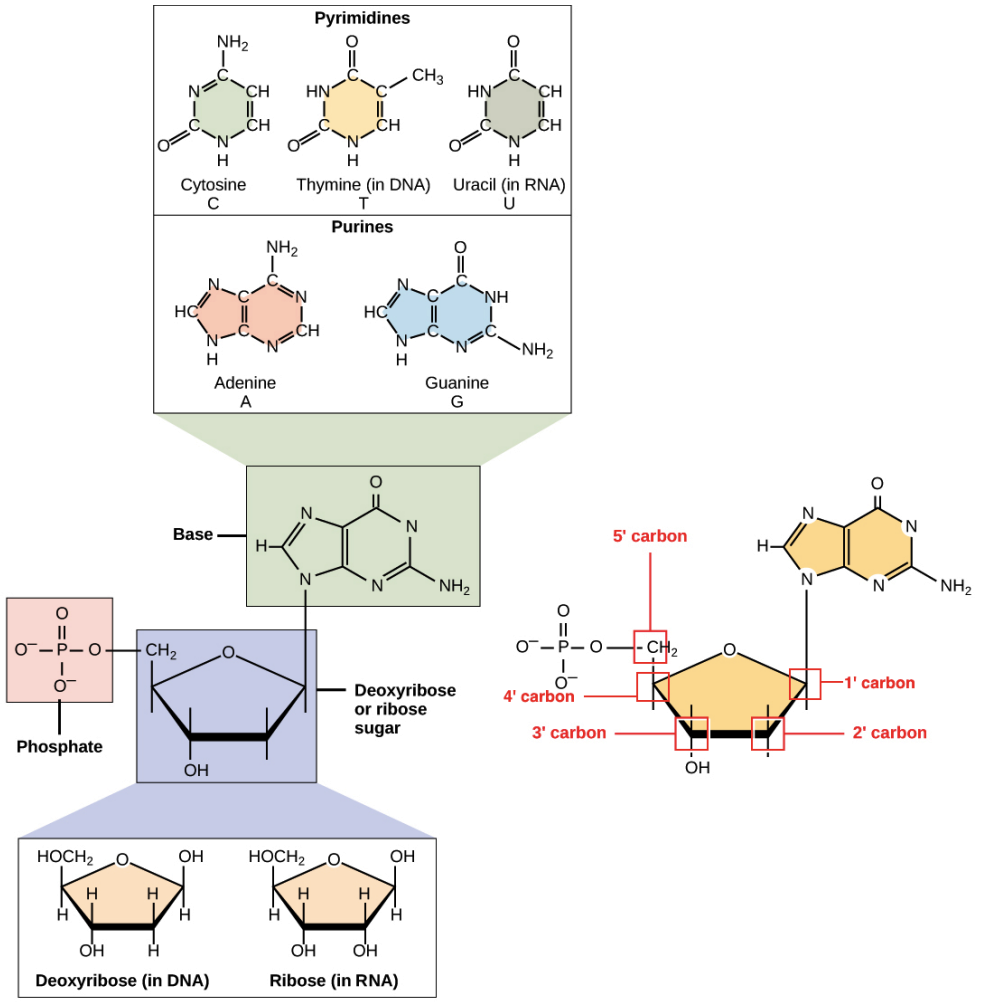


Fig. Structure of Nucleotides

Image of the components of DNA and RNA, including the sugar (deoxyribose or ribose), phosphate group, and nitrogenous base. Bases include the pyrimidine bases (cytosine, thymine in DNA, and uracil in RNA, one ring) and the purine bases (adenine and guanine, two rings). The phosphate group is attached to the 5' carbon. The 2' carbon bears a hydroxyl group in ribose, but no hydroxyl (just hydrogen) in deoxyribose.

6.3 NITROGENOUS BASES

The nitrogenous bases of nucleotides are organic (carbon-based) molecules made up of nitrogen-containing ring structures. Each nucleotide in DNA contains one of four possible nitrogenous bases: adenine (A), guanine (G) cytosine (C), and thymine (T). Adenine and guanine are **purines**, meaning that their structures contain two fused carbon-nitrogen rings. Cytosine and thymine, in contrast, are **pyrimidines** and have a single carbon-nitrogen ring. RNA nucleotides may also bear adenine, guanine and cytosine bases, but instead of thymine they have another pyrimidine base called uracil (U). As shown in the figure above, each base has a unique structure, with its own set of functional groups attached to the ring structure. In molecular biology shorthand, the nitrogenous bases are often just referred to by their one-letter symbols, A, T, G, C, and U. DNA contains A, T, G, and C, while RNA contains A, U, G, and C (that is, U is swapped in for T).

6.3.1 SUGARS

In addition to having slightly different sets of bases, DNA and RNA nucleotides also have slightly different sugars. The five-carbon sugar in DNA is called **deoxyribose**, while in RNA, the sugar is **ribose**. These two are very similar in structure, with just one difference: the second carbon of ribose bears a hydroxyl group, while the equivalent carbon of deoxyribose has a hydrogen instead. The carbon atoms of a nucleotide's sugar molecule are numbered as 1′, 2′, 3′, 4′, and 5′ (1′ is read as "one prime"), as shown in the figure above. In a nucleotide, the sugar occupies a central position, with the base attached to its 1′ carbon and the phosphate group (or groups) attached to its 5′ carbon.

6.3.2 PHOSPHATE

Nucleotides may have a single phosphate group, or a chain of up to three phosphate groups, attached to the 5' carbon of the sugar. Some chemistry sources use the term "nucleotide" only for the single-phosphate case, but in molecular biology, the broader definition is generally accepted11start superscript, 1, end superscript In a cell, a nucleotide about to be added to the end of a polynucleotide chain will bear a series of three phosphate groups. When the nucleotide joins the growing DNA or RNA chain, it loses two phosphate groups. So, in a chain of DNA or RNA, each nucleotide has just one phosphate group.

6.3.3 POLYNUCLEOTIDE CHAINS

A consequence of the structure of nucleotides is that a polynucleotide chain has directionality – that is, it has two ends that are different from each other. At the **5'** end**,** or beginning, of the chain, the 5' phosphate group of the first nucleotide in the chain sticks out. At the other end, called the **3'** end, the 3' hydroxyl of the last nucleotide added to the chain is exposed. DNA sequences are usually written in the 5' to 3' direction, meaning that the nucleotide at the 5' end comes first and the nucleotide at the 3' end comes last.

As new nucleotides are added to a strand of DNA or RNA, the strand grows at its 3' end, with the 5′ phosphate of an incoming nucleotide attaching to the hydroxyl group at the 3' end of the chain. This makes a chain with each sugar joined to its neighbors by a set of bonds called a phosphodiester linkage**.**

6.4 DNA STRUCTURE

DNA consists of instructions that monitor the performance of all cell functions. It is a cellular molecule that is organized into chromosomes. They are present in the nucleus of the cells and contain cellular activities.

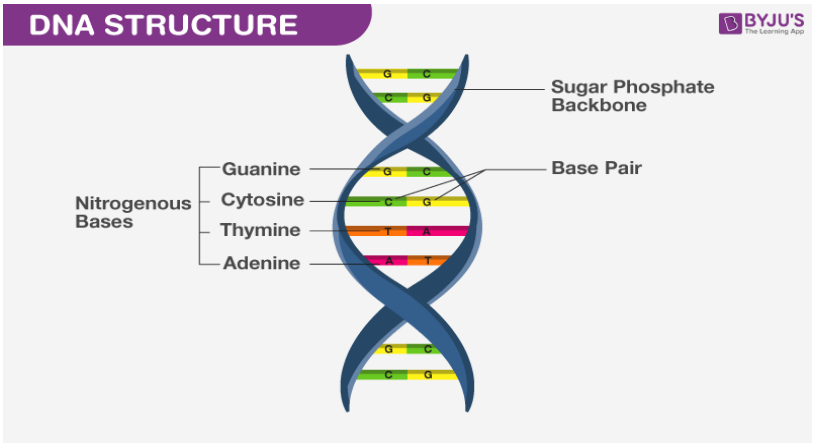


Fig. DNA Structure

It is a double helix formed by 2 polynucleotide chains that are twisted. There are 2 strands of DNA which are parallel to each other. Hydrogen bond binds two helices and the bases are bundled within the helix. Due to the presence of phosphate groups, DNA is negatively charged.

Chemically, DNA is composed of a pentose sugar, phosphoric acid and some cyclic bases containing nitrogen. The sugar moiety present in DNA molecules is β-D-2-deoxyribose. The cyclic bases that have nitrogen in them are adenine (A), guanine (G), cytosine(C) and thymine (T). These bases and their arrangement in the molecules of DNA play an important role in the storage of information from one generation to the next one.

RNA Structure

RNA plays a vital role in the synthesis of proteins that mainly involves decoding and translation of genetic code and transcription to produce proteins. RNA molecules are also composed of phosphoric acid, a pentose sugar and some cyclic bases containing nitrogen. RNA has β-D-ribose in it as the sugar moiety. The heterocyclic bases present in RNA are adenine (A), guanine (G), cytosine(C) and uracil (U). In RNA the fourth base is different from that of DNA. The RNA generally consists of a single strand which sometimes folds back.

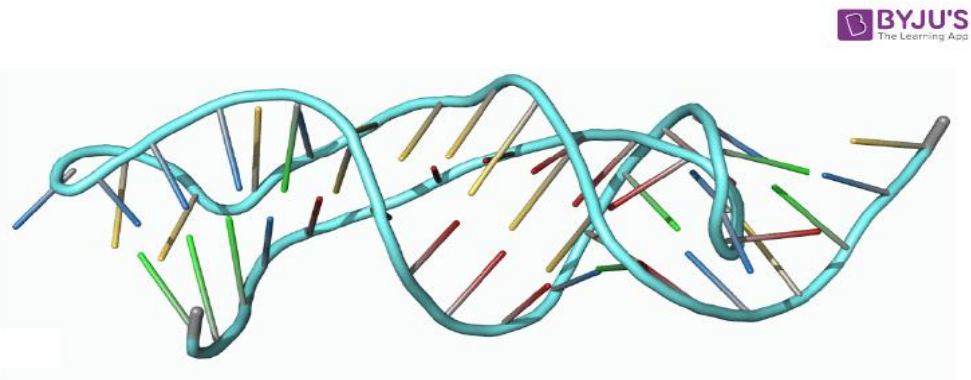


Fig. RNA Structure

There are several different types of RNA and each has a specific function.

- **Ribosomal RNA** – It is one of the components of ribosomes that are involved in protein synthesis.
- **Transfer RNA** – It is essential for the translation of mRNA in protein synthesis.
- **Micro RNAs** – It is the smallest among all RNA that helps in regulating gene expressions.
- **Messenger RNA** – It is the RNA transcript that is produced during DNA transcription.

Functions of Nucleic Acids

- Nucleic Acid is responsible for the synthesis of protein in our body
- RNA is a vital component of protein synthesis.
- Loss of DNA content is linked to many diseases.
- DNA is an essential component required for transferring genes from parents to offspring.
- All the information of a cell is stored in DNA.
- DNA fingerprinting is a method used by forensic experts to determine paternity. It is also used for the identification of criminals. It has also played a major role in studies regarding biological evolution and genetics.

6.5 PROPERTIES OF DNA

Deoxyribonucleic acid, or DNA, chains are typically found in a **double helix**, a structure in which two matching (complementary) chains are stuck together, as shown in the diagram at left. The sugars and phosphates lie on the outside of the helix, forming the backbone of the DNA; this portion of the molecule is sometimes called the **sugar-phosphate** backbone. The nitrogenous bases extend into the interior, like the steps of a staircase, in pairs; the bases of a pair are bound to each other by hydrogen bonds.

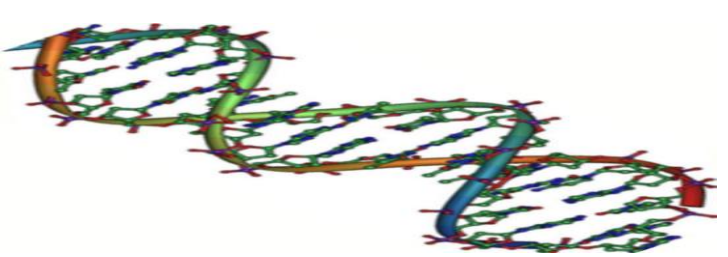
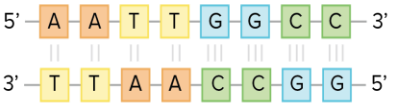


Fig. Structural model of a DNA double helix.

The two strands of the helix run in opposite directions, meaning that the 5′ end of one

strand is paired up with the 3′ end of its matching strand. (This is referred to as antiparallel orientation and is important for the copying of DNA.) So, can any two bases decide to get together and form a pair in the double helix? The answer is a definite no. Because of the sizes and functional groups of the bases, base pairing is highly specific: A can only pair with T, and G can only pair with C, as shown below. This means that the two strands of a DNA double helix have a very predictable relationship to each other.

For instance, if you know that the sequence of one strand is 5'-AATTGGCC-3', the complementary strand must have the sequence 3'-TTAACCGG-5'. This allows each base to match up with its partner:



5'-AATTGGCC-3' 3'-TTAACCGG-5'

These two strands are complementary, with each base in one sticking to its partner on the other. The A-T pairs are connected by two hydrogen bonds, while the G-C pairs are connected by three hydrogen bonds. When two DNA sequences match in this way, such that they can stick to each other in an antiparallel fashion and form a helix, they are said to be complementary**.**

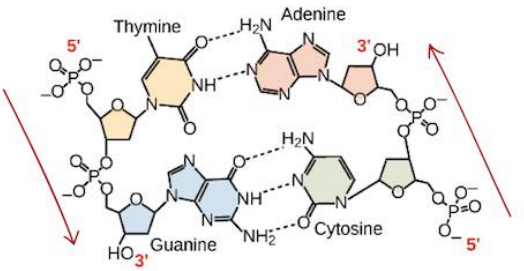


Fig. Hydrogen bonding between complementary bases holds DNA strands together in a double helix of antiparallel strands. Thymine forms two hydrogen bonds with adenine, and guanine forms three hydrogen bonds with cytosine.

Q. 1 Comment on the stability of DNA on its stability towards heat denaturation.

Answer: On heating, the hydrogen bond holding the two DNA strands gets weaken up and finally breaks off leading the two DNA strands to uncurl.

Q. 2 Do DNA and RNA have the same constituting units? If not, name the different units.

Answer: Both DNA and RNA are polymeric units made from nucleotides. The nucleotides are monomer units which consist of three constituents namely: 5-carbon sugar, a phosphate group (PO_4^{3-}) and a nitrogenous base. The DNA and RNA differ in terms of constituting sugar molecules; the RNA contains the ribose sugar and the DNA

contains the deoxyribose sugar.

Q. 3 Which fragment moves most quickly during the gel electrophoresis?

1. Large fragments
2. Small fragments
3. Large genome
4. None of the above

Answer: (b.)

Explanation: All the DNA fragments have equal charge/mass ratio. This is why the smaller fragments move faster during the gel electrophoresis.

Q. 4 Which pyrimidine base contains an amino acid group at C4?

Answer: Cytosine contains an amino group at C4.

Q. 5 At what wavelength do the nucleotides absorb light?

Answer: Nucleotides absorb light at 260 nm.

Q. 6 What is the function of glycosidic bonds in DNA and RNA?

Answer: The glycosidic bonds connect the sugar to the base.

Q. 7 Which of the following is useful in nucleic acid (NA) analysis?

1. Molecular weight of the nucleic acids
2. Absorption of UV light
3. Absorption of visible light
4. None of the above

Answer: (b.)

Explanation: The double bonds present within the purine and pyrimidine rings in the nucleic acids absorb strongly at a maximum wavelength of 260 nm. Thus, absorption of UV light is useful in NAs analysis.

Q. 7 What are the helical structures in the DNA and RNA made of?

Answer: The helical structure backbone in the DNA and RNA is made of the alternating sugars and the phosphate groups. Each sugar molecule is connected to a base.

Q. 8 Which of the 5 canonical nucleobases occurs only in

1. DNA, and
2. RNA

Answer: There are 5 primary nucleobases namely Uracil, Adenine, Thymine, Guanine

and Cytosine. Out of these, Thymine is found only in DNA and Uracil is found only in RNA.

Q. 9 How is the base-pair sequencing significant in DNA and RNA?

Answer: During the protein synthesis, the base-pair sequencing enables the DNA to store and transmit the coded information. This coded information is known as genes. While in RNA, the base-pair sequencing is essential for most of the chemical processes of all life forms.

Q. 10 Who proposed the double-helix model of DNA?

Answer: Watson and Crick in 1953 proposed the double-helical structure of DNA.

Q. 11 Where were the nucleic acids discovered first?

Answer: The nucleic acids were first discovered in the nucleus of the Eukaryotic cells.

Q. 12 The viruses are under a constant debate of whether they are living or non-living things. Give a reason to support this statement.

Answer: The cells in all living beings consist of both- the DNA and the RNA. Only the viruses contain either DNA or RNA. It is very rare to find the DNA and RNA both in a virus. This is why the viruses are always under the debate whether they are living or non-living.

Q. 13 What is solid-phase chemical synthesis? Give 1 use of this method in terms of nucleic acids.

Answer: The solid-phase synthesis is a method in which a solid-state material is taken in a reaction vessel and the molecules are covalently bonded to it in stepwise manner. This is a highly efficient reaction that takes place in a single vessel.

6.6 BIOCHEMICAL PROPERTIES

6.6.1 DENATURATION

The strands of the DNA double helix are held together by hydrogen bonding interactions between the complementary base pairs. Heating DNA in solution easily breaks these hydrogen bonds, allowing the two strands to separate—a process called denaturation or melting. The two strands may reassociate when the solution cools, reforming the starting DNA duplex—a process called renaturation or hybridization. These processes form the basis of many important techniques for manipulating DNA. For example, a short piece of DNA called an oligonucleotide can be used to test whether a very long DNA sequence has the complementary sequence of the oligonucleotide embedded within it. Using hybridization, a single-stranded DNA molecule can capture complementary sequences from any source. Single strands from RNA can also reassociate. DNA and RNA single strands can form hybrid molecules that are even more stable than double-stranded DNA. These molecules form the basis of a technique that is used to purify and characterize messenger

RNA (mRNA) molecules corresponding to single genes.

6.6.2 ULTRAVIOLET ABSORPTION

DNA melting and reassociation can be monitored by measuring the absorption of ultraviolet (UV) light at a wavelength of 260 nanometres (billionths of a metre). When DNA is in a double-stranded conformation, absorption is fairly weak, but when DNA is single-stranded, the unstacking of the bases leads to an enhancement of absorption called hyperchromicity. Therefore, the extent to which DNA is single-stranded or double-stranded can be determined by monitoring UV absorption.

6.6.3 CHEMICAL MODIFICATION

After a DNA molecule has been assembled, it may be chemically modified—sometimes deliberately by special enzymes called DNA methyltransferases and sometimes accidentally by oxidation, ionizing radiation, or the action of chemical carcinogens. DNA can also be cleaved and degraded by enzymes called nucleases.

6.6.4 METHYLATION

Three types of natural methylation have been reported in DNA. Cytosine can be modified either on the ring to form 5-methylcytosine or on the exocyclic amino group to form N^4-methylcytosine. Adenine may be modified to form N^6-methyladenine. N^4-methylcytosine and N^6-methyladenine are found only in bacteria and archaea, whereas 5-methylcytosine is widely distributed. Special enzymes called DNA methyltransferases are responsible for this methylation; they recognize specific sequences within the DNA molecule so that only a subset of the bases is modified. Other methylations of the bases or of the deoxyribose are sometimes induced by carcinogens. These usually lead to mispairing of the bases during replication and have to be removed if they are not to become mutagenic.

Natural methylation has many cellular functions. In bacteria and archaea, methylation forms an essential part of the immune system by protecting DNA molecules from fragmentation by restriction endonucleases. In some organisms, methylation helps to eliminate incorrect base sequences introduced during DNA replication. By marking the parental strand with a methyl group, a cellular mechanism known as the mismatch repair system distinguishes between the newly replicated strand where the errors occur and the correct sequence on the template strand.

In higher eukaryotes, 5-methylcytosine controls many cellular phenomena by preventing DNA transcription. Methylation is also believed to signal imprinting, a process whereby some genes inherited from one parent are selectively inactivated. Correct methylation may also repress or activate key genes that control embryonic development. On the other hand, 5-methylcytosine is potentially mutagenic because thymine produced during the methylation process converts C:G pairs to T:A pairs. In mammals, methylation takes place selectively within the dinucleotide

sequence CG—a rare sequence, presumably because it has been lost by mutation. In many cancers, mutations are found in key genes at CG dinucleotides.

6.6.5 NUCLEASES

Nucleases are enzymes that hydrolytically cleave the phosphodiester backbone of DNA. Endonucleases cleave in the middle of chains, while exonucleases operate selectively by degrading from the end of the chain. Nucleases that act on both single- and double-stranded DNA are known. Restriction endonucleases are a special class that recognize and cleave specific sequences in DNA. Type II restriction endonucleases always cleave at or near their recognition sites. They produce small, well-defined fragments of DNA that help to characterize genes and genomes and that produce recombinant DNAs. Fragments of DNA produced by restriction endonucleases can be moved from one organism to another. In this way it has been possible to express proteins such as human insulin in bacteria.

6.6.6 MUTATION

Chemical modification of DNA can lead to mutations in the genetic material. Anions such as bisulfite can deaminate cytosine to form uracil, changing the genetic message by causing C-to-T transitions. Exposure to acid causes the loss of purine residues, though specific enzymes exist in cells to repair these lesions. Exposure to UV light can cause adjacent pyrimidines to dimerize, while oxidative damage from free radicals or strong oxidizing agents can cause a variety of lesions that are mutagenic if not repaired. Halogens such as chlorine and bromine react directly with uracil, adenine, and guanine, giving substituted bases that are often mutagenic. Similarly, nitrous acid reacts with primary amine groups—for example, converting adenosine into inosine—which then leads to changes in base pairing and mutation. Many chemical mutagens, such as chlorinated hydrocarbons and nitrites, owe their toxicity to the production of halides and nitrous acid during their metabolism in the body.

6.6.7 SUPERCOILING

Circular DNA molecules such as those found in plasmids or bacterial chromosomes can adopt many different topologies. One is active supercoiling, which involves the cleavage of one DNA strand, its winding one or more turns around the complementary strand, and then the resealing of the molecule. Each complete rotation leads to the introduction of one supercoiled turn in the DNA, a process that can continue until the DNA is fully wound and collapses on itself in a tight ball. Reversal is also possible. Special enzymes called gyrases and topoisomerases catalyze the winding and relaxation of supercoiled DNA. In the linear chromosomes of eukaryotes, the DNA is usually tightly constrained at various points by proteins, allowing the intervening stretches to be supercoiled. This property is partially responsible for the great compaction of DNA that is necessary to fit it within the confines of the cell. The DNA in one human cell would have an extended length of between two and three metres, but

it is packed very tightly so that it can fit within a human cell nucleus that is 10 micrometres in diameter.

Sequence determination

Methods to determine the sequences of bases in DNA were pioneered in the 1970s by Frederick Sanger and Walter Gilbert, whose efforts won them a Nobel Prize in 1980. The Gilbert-Maxam method relies on the different chemical reactivities of the bases, while the Sanger method is based on enzymatic synthesis of DNA in vitro. Both methods measure the distance from a fixed point on DNA to each occurrence of a particular base—A, C, G, or T. DNA fragments obtained from a series of reactions are separated according to length in four "lanes" by gel electrophoresis. Each lane corresponds to a unique base, and the sequence is read directly from the gel. The Sanger method has now been automated using fluorescent dyes to label the DNA, and a single machine can produce tens of thousands of DNA base sequences in a single run.

6.7 Ribonucleic acid (RNA)

RNA is a single-stranded nucleic acid polymer of the four nucleotides A, C, G, and U joined through a backbone of alternating phosphate and ribose sugar residues. It is the first intermediate in converting the information from DNA into proteins essential for the working of a cell. Some RNAs also serve direct roles in cellular metabolism. RNA is made by copying the base sequence of a section of double-stranded DNA, called a gene, into a piece of single-stranded nucleic acid. This process, called transcription (*see below* RNA metabolism), is catalyzed by an enzyme called RNA polymerase.

6.8 PROPERTIES OF RNA

Ribonucleic acid (RNA), unlike DNA, is usually single-stranded. A nucleotide in an RNA chain will contain ribose (the five-carbon sugar), one of the four nitrogenous bases (A, U, G, or C), and a phosphate group. Here, we'll take a look at four major types of RNA: messenger RNA (mRNA), ribosomal RNA (rRNA), transfer RNA (tRNA), and regulatory RNAs.

6.9 MESSENGER RNA (MRNA)

Messenger RNA **(**mRNA**)** is an intermediate between a protein-coding gene and its protein product. If a cell needs to make a particular protein, the gene encoding the protein will be turned "on," meaning an RNA-polymerizing enzyme will come and make an RNA copy, or transcript, of the gene's DNA sequence. The transcript carries the same information as the DNA sequence of its gene. However, in the RNA molecule, the base T is replaced with U. For instance, if a DNA coding strand has the sequence 5'-AATTGCGC-3', the sequence of the corresponding RNA will be 5'-AAUUGCGC-3'.

Once an mRNA has been produced, it will associate with a ribosome, a molecular machine that specializes in assembling proteins out of amino acids. The ribosome uses the information in the mRNA to make a protein of a specific sequence, "reading out"

the mRNA's nucleotides in groups of three (called **codons**) and adding a particular amino acid for each codon.

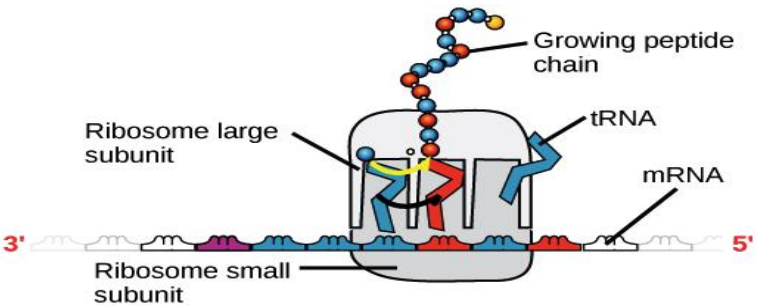


Fig. Structure of Messenger RNA (mRNA)

Image of a ribosome (made of proteins and rRNA) bound to an mRNA, with tRNAs bringing amino acids to be added to the growing chain. The tRNA that binds, and thus the amino acid that's added, at a given moment is determined by the sequence of the mRNA that is being "read" at that time.

6.10 RIBOSOMAL RNA (RRNA) AND TRANSFER RNA (TRNA)

Ribosomal RNA **(**rRNA**)** is a major component of ribosomes, where it helps mRNA bind in the right spot so its sequence information can be read out. Some rRNAs also act as enzymes, meaning that they help accelerate (catalyze) chemical reactions – in this case, the formation of bonds that link amino acids to form a protein. RNAs that act as enzymes are known as ribozymes. Transfer RNAs **(**tRNAs**)** are also involved in protein synthesis, but their job is to act as carriers – to bring amino acids to the ribosome, ensuring that the amino acid added to the chain is the one specified by the mRNA. Transfer RNAs consist of a single strand of RNA, but this strand has complementary segments that stick together to make double-stranded regions. This base-pairing creates a complex 3D structure important to the function of the molecule.

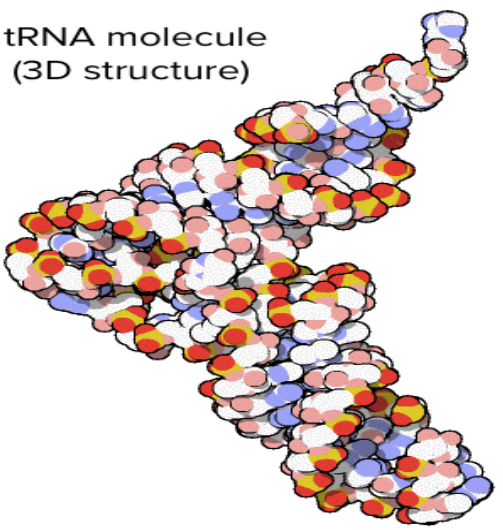


Fig. Structure of a tRNA. The overall molecule has a shape somewhat like an L.

Regulatory RNA (miRNAs and siRNAs)

Some types of non-coding RNAs (RNAs that do not encode proteins) help regulate the expression of other genes. Such RNAs may be called regulatory RNAs. For example, microRNAs **(**miRNAs**)** **and** small interfering RNAs siRNAs are small regulatory RNA molecules about 22 nucleotides long. They bind to specific mRNA molecules (with partly or fully complementary sequences) and reduce their stability or interfere with their translation, providing a way for the cell to decrease or fine-tune levels of these mRNAs. These are just some examples out of many types of noncoding and regulatory RNAs. Scientists are still discovering new varieties of noncoding RNA.

6.11 DIFFERENCES BETWEEN DNA AND RNA

	DNA	**RNA**
Function	Repository of genetic information	Involved in protein synthesis and gene regulation; carrier of genetic information in some viruses
Sugar	Deoxyribose	Ribose
Structure	Double helix	Usually single-stranded
Bases	C, T, A, G	C, U, A, G

6.12 SUMMARY

Under this unit we have discussed nucleic acids in concern to DNA replication, its biochemical properties, RNA, its properties and types etc. Nucleic acids are molecules made up of nucleotides that direct cellular activities such as cell division and protein synthesis. Each nucleotide is made up of a pentose sugar, a nitrogenous base, and a phosphate group. There are two types of nucleic acids: DNA and RNA. Deoxyribonucleic acid (abbreviated DNA) is the molecule that carries genetic information for the development and functioning of an organism. DNA is made of two linked strands that wind around each other to resemble a twisted ladder — a shape known as a double helix.

On the other hand, Ribonucleic acid (RNA) is a molecule that is present in the majority of living organisms and viruses. It is made up of nucleotides, which are ribose sugars attached to nitrogenous bases and phosphate groups. Nucleic acid isolation may be required from human cells of different types or free circulating NA. When pathogens

are of interest, viruses, bacteria, protozoans, and fungi must be considered. Multiplex testing may depend on simultaneous isolation of NA from some or all of these sources.

6.13 TERMINAL QUESTIONS

Q.1 What do you mean by nucleic acids? Define it with examples.

Answer:----------

Q. 2 Describe the differences between DNA and RNA.

Answer:----------

Q. 3 Describe RNA with its different types.

Answer:----------

Q. 4 Write short notes on the followings.

(i) t-RNA (transfer RNA)

(ii) r-RNA (Ribosomal RNA)

Answer:----------

Q. 5 Describe different functions of nucleic acids.

Answer:----------

Q. 6 Describe different functions of nucleic acids.

Answer:----------

Further readings

- Biochemistry- Lehninger A.L.
- Textbook of Nutrition and Dietetics Ranjana Mahna
- Biochemistry fourth edition-David Hames and Nigel Hooper.
- Textbook of Biochemistry for Undergraduates - Rafi, M.D.
- Textbook of Nutrition and Dietetics- Monika Sharma

UNIT- 7 MUTATION & GENE EXPRESSION

Structure

7.1 INTRODUCTION

Mutation, an alteration in the genetic material (the genome) of a cell of a living organism or of a virus that is more or less permanent and that can be transmitted to the cell's or the virus's descendants. (The genomes of organisms are all composed of DNA, whereas viral genomes can be of DNA or RNA; see heredity: The physical basis of heredity.) Mutation in the DNA of a body cell of a multicellular organism (somatic mutation) may be transmitted to descendant cells by DNA replication and hence result in a sector or patch of cells having abnormal function, an example being cancer. Mutations in egg or sperm cells (germinal mutations) may result in an individual offspring all of whose cells carry the mutation, which often confers some serious malfunction, as in the case of a human genetic disease such as cystic fibrosis. Mutations result either from accidents during the normal chemical transactions of DNA, often during replication, or from exposure to high-energy electromagnetic radiation (e.g., ultraviolet light or X-rays) or particle radiation or to highly reactive chemicals in the environment. Because mutations are random changes, they are expected to be mostly deleterious, but some may be beneficial in

certain environments. In general, mutation is the main source of genetic variation, which is the raw material for evolution by natural selection.

The genome is composed of one to several long molecules of DNA, and mutation can occur potentially anywhere on these molecules at any time. The most serious changes take place in the functional units of DNA, the genes. A mutated form of a gene is called a mutantallele. A gene is typically composed of a regulatory region, which is responsible for turning the gene's transcription on and off at the appropriate times during development, and a coding region, which carries the genetic code for the structure of a functional molecule, generally a protein. A protein is a chain of usually several hundred amino acids. Cells make 20 common amino acids, and it is the unique number and sequence of these that give a protein its specific function.

Objectives

This is the seventh unit on mutation & gene expression of second block (Purines and Pyrimidines, Nucleic Acids and Hormones). Under seventh unit (Mutation & gene expression), we have following objectives. These are as under:

- To understand the definition of mutation
- To discuss the concept of gene expression.
- To know the regulation of gene expression.
- To discuss the concept of protein biosynthesis

Each amino acid is encoded by a unique sequence, or codon, of three of the four possible base pairs in the DNA (A–T, T–A, G–C, and C–G, the individual letters referring to the four nitrogenous bases adenine, thymine, guanine, and cytosine). Hence, a mutation that changes DNA sequence can change amino acid sequence and in this way potentially reduce or inactivate a protein's function. A change in the DNA sequence of a gene's regulatory region can adversely affect the timing and availability of the gene's protein and also lead to serious cellular malfunction. On the other hand, many mutations are silent, showing no obvious effect at the functional level. Some silent mutations are in the DNA between genes, or they are of a type that results in no significant amino acid changes.

Mutations are of several types. Changes within genes are called point mutations. The simplest kinds are changes to single base pairs, called base-pair substitutions. Many of these substitutes an incorrect amino acid in the corresponding position in the encoded protein, and of these a large proportion result in altered protein function. Some base-pair substitutions produce a stop codon. Normally, when a stop codon occurs at the end of a gene, it stops protein synthesis, but, when it occurs in an abnormal position, it can result in a truncated and nonfunctional protein. Another type of simple change, the deletion or insertion of single base pairs, generally has a profound effect on the protein because the protein's synthesis, which is carried out by the reading of triplet codons in a linear fashion from one end of the gene to the other, is thrown off.

This change leads to a frameshift in reading the gene such that all amino acids are incorrect from the mutation onward. More-complex combinations of base substitutions, insertions, and deletions can also be observed in some mutant genes.

Mutations that span more than one gene are called chromosomal mutations because they affect the structure, function, and inheritance of whole DNA molecules (microscopically visible in a coiled state as chromosomes). Often these chromosome mutations result from one or more coincident breaks in the DNA molecules of the genome (possibly from exposure to energetic radiation), followed in some cases by faulty rejoining. Some outcomes are large-scale deletions, duplications, inversions, and translocations. In a diploid species (a species, such as human beings, that has a double set of chromosomes in the nucleus of each cell), deletions and duplications alter gene balance and often result in abnormality. Inversions and translocations involve no loss or gain and are functionally normal unless a break occurs within a gene. However, at meiosis (the specialized nuclear divisions that take place during the production of gametes—i.e., eggs and sperm), faulty pairing of an inverted or translocated chromosome set with a normal set can result in gametes and hence progeny with duplications and deletions.

Loss or gain of whole chromosomes results in a condition called aneuploidy. One familiar result of aneuploidy is Down syndrome, a chromosomal disorder in which humans are born with an extra chromosome 21 (and hence bear three copies of that chromosome instead of the usual two). Another type of chromosome mutation is the gain or loss of whole chromosome sets. Gain of sets results in polyploidy—that is, the presence of three, four, or more chromosome sets instead of the usual two. Polyploidy has been a significant force in the evolution of new species of plants and animals. Most genomes contain mobile DNA elements that move from one location to another. The movement of these elements can cause mutation, either because the element arrives in some crucial location, such as within a gene, or because it promotes large-scale chromosome mutations via recombination between pairs of mobile elements in different locations.

7.2 GENETIC MUTATIONS

Genetic mutations are changes to your DNA sequence that happen during cell division when your cells make copies of themselves. Your DNA tells your body how to form and function. Genetic mutations could lead to genetic conditions like cancer, or they could help humans better adapt to their environment over time.

A genetic mutation is a change in a sequence of your DNA. Your DNA sequence gives your cells the information they need to perform their functions. If part of your DNA sequence is in the wrong place, isn’t complete or is damaged, you might experience symptoms of a genetic condition.

7.3 WHEN DO GENETIC MUTATIONS HAPPEN?

Genetic mutations occur during cell division when your cells divide and replicate. There are two types of cell division:

- **Mitosis**: The process of making new cells for your body. During mitosis, your genes instruct your cells to split into two by making a copy of your chromosomes.
- **Meiosis**: The process of making egg and sperm cells for the next generation. During meiosis, chromosomes copy themselves with half the amount of chromosomes as the original (from 46 to 23). That's how you're able to get your genetic material equally from each parent.

How do genetic mutations happen?

Genetic mutations occur during cell division. When your cells divide, they hand-write your body's instruction manual by copying the original document word for word. There's a lot of room for error during cell division because your cells might substitute (replace), delete (remove) or insert (add) letters while they're copying. If you have an error (genetic mutation), your genetic instruction manual for your cells may not be readable by the cells, or may have missing parts or unnecessary parts added. All of this can mean that your cells can't function as they normally should.

7.4 FUNCTIONS

How do genetic mutations affect other organs?

A genetic mutation changes the information your cells need to form and function. Your genes are responsible for making proteins that tell your body what physical characteristics you should have. If you have a genetic mutation, you could experience symptoms of a genetic condition because your cells are doing a different job than they should be. Symptoms of genetic conditions depend on which gene has a mutation. There are many different diseases and conditions caused by mutations. The signs and symptoms you experience could include:

- Physical characteristics like facial abnormalities, a cleft palate, webbed fingers and toes, or short stature.
- Problems with cognitive (intellectual) function and developmental delays.
- Vision or hearing loss.
- Breathing problems.
- Increased risk of developing cancer.

Are genetic mutations bad?

Not all genetic mutations lead to genetic disorders. Some genetic mutations don't have

any effect on your health and well-being. This is because the change in the DNA sequence doesn't change how your cell functions. Your body also has enzymes, which are a substance that creates chemical reactions in our body. These enzymes help your body protect itself from disease. Enzymes can repair a variety of genetic mutations before they affect how a cell functions. Some genetic mutations even have a positive effect on humans. Changes in how cells work can sometimes improve the proteins that your cells produce and allow them to adapt to changes in your environment. An example of a positive genetic mutation is one that can protect a person from acquiring heart disease or diabetes, even with a history of smoking or being overweight.

7.5 HOW DO GENETIC MUTATIONS LEAD TO GENETIC VARIATIONS?

A genetic mutation is a change to a gene's DNA sequence to produce something different. It creates a permanent change to that gene's DNA sequence. Genetic variations are important for humans to evolve, which is the process of change over generations. A sporadic genetic mutation occurs in one person. That person passes their genetic mutation onto their children (hereditary), and it continues for generations. If the mutation improves that person's chance of survival, or freedom from disease, then it begins being passed through generations and spread through the population. As the mutation passes from generation to generation, it becomes a normal part of the human genome and evolves from a gene variant into a normal gene.

7.6 ANATOMY

Where are genes in my body?

Genes reside on thread-like structures in your body called chromosomes. Chromosomes are in each cell in your body. There are trillions of cells in your body that make you who you are.

What are the different types of genetic mutations?

There are different types of genetic mutations based on where they form. Types of genetic mutations include:

- **Germline mutation**: A change in a gene that occurs in a parent's reproductive cells (egg or sperm) that affects the genetic makeup of their child (hereditary).
- **Somatic mutation**: A change in a gene that occurs after conception in the developing embryo that may become a baby. These occur in all cells in the developing body — except the sperm and egg. Somatic mutations can't pass from parents to their children (hereditary) because traits are passed only from the sperm and egg.

Can I inherit genetic mutations?

Yes, you can inherit germline genetic mutations, while somatic mutations occur with no

previous history of the mutation in your family. There are several patterns that genetic mutations can pass from the parent to a child (hereditary).

What are genetic disorders?

A genetic disorder is a condition caused by changes in your genome, or the genetic material present in a human. It includes your DNA, genes and chromosomes. Several factors cause genetic conditions, including:

- Mutation of one gene (monogenic).
- Mutation of multiple genes (multifactorial inheritance).
- Mutation of one or more chromosomes.
- Environmental factors (chemical exposure, UV rays) that change your genetic makeup.

You can inherit the genetic condition from your parents (if it's germ cell DNA in the sperm or egg) or the genetic condition can happen randomly, without having a history of the genetic condition in your family.

7.7 WHAT ARE COMMON GENETIC DISORDERS?

There are thousands of genetic conditions that exist. Some of the most common genetic conditions are:

- Alzheimer's disease.
- Alzheimer's disease.
- Some cancers.
- Cystic fibrosis.
- Down syndrome.
- Sickle cell disease.

7.8 Gene expression

Gene expression is the process by which information from a gene is used in the synthesis of a functional gene product that enables it to produce end products, proteins or non-coding RNA, and ultimately affect a phenotype. These products are often proteins, but in non-protein-coding genes such as transfer RNA (tRNA) and small nuclear RNA (snRNA), the product is a functional non-coding RNA. Gene expression is summarized in the central dogma of molecular biology first formulated by Francis Crick in 1958, further developed in his 1970 article, and expanded by the subsequent discoveries of reverse transcription and RNA replication. The process of gene expression is used by all known life—eukaryotes (including multicellular organisms), prokaryotes (bacteria and archaea), and utilized by viruses-to generate the macromolecular machinery for life.

In genetics, gene expression is the most fundamental level at which the genotype gives rise to the phenotype, *i.e.* observable trait. The genetic

information stored in DNA represents the genotype, whereas the phenotype results from the "interpretation" of that information. Such phenotypes are often displayed by the synthesis of proteins that control the organism's structure and development, or that act as enzymes catalyzing specific metabolic pathways.

All steps in the gene expression process may be modulated (regulated), including the transcription, RNA splicing, translation, and post-translational modification of a protein. Regulation of gene expression gives control over the timing, location, and amount of a given gene product (protein or ncRNA) present in a cell and can have a profound effect on the cellular structure and function. Regulation of gene expression is the basis for cellular differentiation, development, morphogenesis and the versatility and adaptability of any organism. Gene regulation may therefore serve as a substrate for evolutionary change.

This amazing artwork shows a process that takes place in the cells of all living things: the production of proteinsno post. This process is called **protein synthesis**, and it actually consists of two processes — transcription and translation. In eukaryotic cells, transcription takes place in the nucleus. During transcription, DNA is used as a template to make a molecule of messenger RNA (mRNA). The molecule of mRNA then leaves the nucleus and goes to a ribosome in the cytoplasm, where translation occurs. During translation, the genetic code in mRNA is read and used to make a polypeptide. These two processes are summed up by the central dogma of molecular biology:

DNA → RNA → Protein.

7.9 TRANSCRIPTION

Transcription is the first part of the central dogma of molecular biology: **DNA → RNA**. It is the transfer of genetic instructions in DNA to mRNA. During transcription, a strand of mRNA is made to complement a strand of DNA. You can see how this happens in given figure.

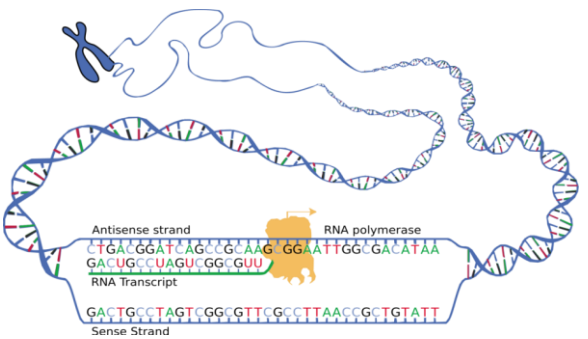


Fig.Transcription uses the sequence of bases in a strand of DNA to make a complementary strand of mRNA. Triplets are groups of three successive nucleotide bases in DNA. Codons are complementary groups of bases in mRNA.

Transcription begins when the enzyme RNA polymerase binds to a region of a gene called the promoter sequence. This signals the DNA to unwind so the enzyme can “read” the bases of DNA. The two strands of DNA are named based on whether they

will be used as a template for RNA or not. The strand that is used as a template is called the template strand, or can also be called the antisense strand. The sequence of bases on the opposite strand of DNA is called the non-coding or sense strand. Once the DNA has opened, and RNA polymerase has attached, the RNA polymerase moves along the DNA, adding RNA nucleotides to the growing mRNA strand. The template strand of DNA is used as to create mRNA through complementary base pairing. Once the mRNA strand is complete, and it detaches from DNA. The result is a strand of mRNA that is nearly identical to the coding strand DNA – the only difference being that DNA uses the base thymine, and the mRNA uses uracil in the place of thymine

7.10 PROCESSING MRNA

In eukaryotes, the new mRNA is not yet ready for translation. At this stage, it is called pre-mRNA, and it must go through more processing before it leaves the nucleus as mature mRNA. The processing may include splicing, editing, and polyadenylation. These processes modify the mRNA in various ways. Such modifications allow a single gene to be used to make more than one protein.

- **Splicing** removes introns from mRNA, as shown in given figure. **Introns** are regions that do not code for the protein. The remaining mRNA consists only of regions called **exons** that do code for the protein. The ribonucleoproteins in the diagram are small proteins in the nucleus that contain RNA and are needed for the splicing process.

- **Editing** changes some of the nucleotides in mRNA. For example, a human protein called APOB, which helps transport lipids in the blood, has two different forms because of editing. One form is smaller than the other because editing adds an earlier stop signal in mRNA.

- **5′ Capping** adds a methylated cap to the "head" of the mRNA. This cap protects the mRNA from breaking down, and helps the ribosomes know where to bind to the mRNA

- **Polyadenylation** adds a "tail" to the mRNA. The tail consists of a string of As (adenine bases). It signals the end of mRNA. It is also involved in exporting mRNA from the nucleus, and it protects mRNA from enzymes that might break it down.

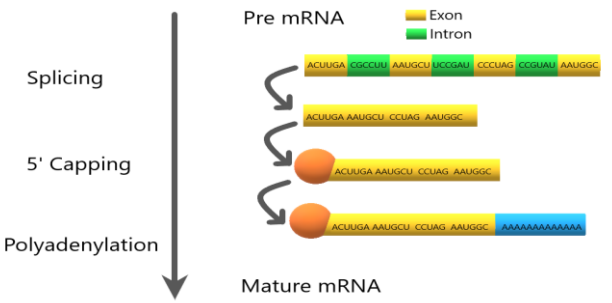


Fig. Pre mRNA processing. mRNA requires processing before it leaves the nucleus.

Translation

Translation is the second part of the central dogma of molecular biology: **RNA → Protein**. It is

the process in which the genetic code in mRNA is read to make a protein. Translation is illustrated in Figure 5.7.4. After mRNA leaves the nucleus, it moves to a ribosome, which consists of rRNA and proteins. The ribosome reads the sequence of codons in mRNA, and molecules of tRNA brin g amino acids to the ribosome in the correct sequence. Translation occurs in three stages: Initiation, Elongation and Termination.

Initiation:

After transcription in the nucleus, the mRNA exits through a nuclear pore and enters the cytoplasm. At the region on the mRNA containing the methylated cap and the start codon, the small and large subunits of the ribosome bind to the mRNA. These are then joined by a tRNA which contains the anticodons matching the start codon on the mRNA. This group of molecues (mRNA, ribosome, tRNA) is called an initiation complex.

Elongation:

tRNA keep bringing amino acids to the growing polypeptide according to complementary base pairing between the codons on the mRNA and the anticodons on the tRNA. As a tRNA moves into the ribosome, its amino acid is transferred to the growing polypeptide. Once this transfer is complete, the tRNA leaves the ribosome, the ribosome moves one codon length down the mRNA, and a new tRNA enters with its corresponding amino acid. This process repeats and the polypeptide grows.

Termination:

At the end of the mRNA coding is a stop codon which will end the elongation stage. The stop codon doesn't call for a tRNA, but instead for a type of protein called a release factor, which will cause the entire complex (mRNA, ribosome, tRNA, and polypeptide) to break apart, releasing all of the components.

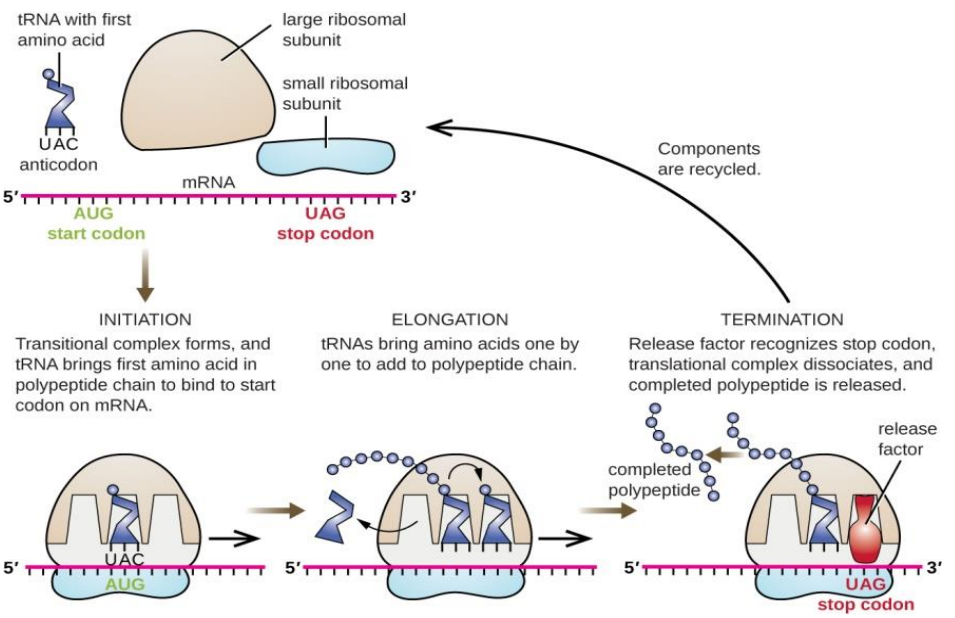


Fig. Translation takes place in three stages: Initiation, Elongation and Termination

7.11 SUMMARY

Under this unit we have discussed mutation and its types, gene expression and its regulation as well as protein biosynthesis. Mutation is the alteration in the genetic material of a cell that is transmitted to the cell's offspring. Mutations may be spontaneous or induced by outside factors (mutagens). They take place in the genes, occurring when one base is substituted for another in the sequence of bases that determines the genetic code, or when one or more bases are inserted or deleted from a gene. Many mutations are harmless, often masked by the presence of a dominant normal gene. Some have serious consequences; for example, a particular mutation inherited from both parents results in sickle-cell anemia. Only mutations that occur in the sex cells (eggs or sperm) can be transmitted to the individual's offspring. Alterations caused by these mutations are usually harmful. In the rare instances in which a mutation produces a beneficial change, the percentage of organisms with this gene will tend to increase until the mutated gene becomes the norm in the population. In this way, beneficial mutations serve as the raw material of evolution.

Protein synthesis is the process in which cells make proteins. It occurs in two stages: transcription and translation. Transcription is the transfer of genetic instructions in DNA to mRNA in the nucleus. It includes three steps: initiation, elongation, and termination. After the mRNA is processed, it carries the instructions to a ribosome in the cytoplasm. Translation occurs at the ribosome, which consists of rRNA and proteins. In translation, the instructions in mRNA are read, and tRNA brings the correct sequence of amino acids to the ribosome. Then, rRNA helps bonds form between the amino acids, producing a polypeptide chain. After a polypeptide chain is synthesized, it may undergo additional processing to form the finished protein.

7.12 TERMINAL QUESTIONS

Q.1 What do you mean by mutation? Explain it with examples.

Answer:----------

Q.2 Explain the gene expression.

Answer:----------

Q.3 Explain the regulation of gene expression.

Answer:----------

Q.4 Write short notes on the followings.

(i) Gene expression

(ii) Protein biosynthesis

Answer:----------

Q. 5 Describe

mutation with its types.

Answer:----------

Further readings

- Biochemistry- Lehninger A.L.
- Textbook of Nutrition and Dietetics Ranjana Mahna
- Biochemistry fourth edition-David Hames and Nigel Hooper.
- Textbook of Biochemistry for Undergraduates - Rafi, M.D.
- Textbook of Nutrition and Dietetics- Monika Sharma

UNIT- 8 HORMONES

Structure

Objectives

8.1 INTRODUCTION

Hormones are chemical substances that act like messenger molecules that stream through the bloodstream. Hormones carry chemical messages from the glands where they are produced to cells in different parts of the human body. These chemical messages help to turn on or turn off cellular processes that control stress, appetite, growth, sleep cycles, blood sugar, sex drive, and sexual function. The importance of hormones in the proper functioning of the human body is immense. They control the functions of organs and influence their growth, reproduction and sexual characteristics. Moreover, hormones also affect the way

a human body stores and uses energy and regulates the volume of fluids as well as the level of sugar and salt in the blood. Thus, a small amount of hormone can trigger a significant response in the human body.

Objectives

This is the eighth unit on hormones of second block (Purines and Pyrimidines, Nucleic Acids and Hormones). Under sixth unit (hormones), we have following objectives. These are as under:

- To know the definition and general features of hormones
- To discuss characteristics and functions of hormones
- To discuss the different endocrine glands and their hormones
- To discuss therapeutic uses of hormones and their comparison with neurotransmitters

8.2 HORMONES

Hormones are chemical messengers that are secreted directly into the blood, which carries them to organs and tissues of the body to exert their functions. They are various chemicals released within the human body that regulate and control the activities of multiple organs. The introduction of hormones to the blood takes place via endocrine glands. There are many types of hormones that act on different aspects of bodily functions and processes. Some of these include:

- Development and growth
- Metabolism of food items
- Sexual function and reproductive growth and health
- Cognitive function and mood
- Maintenance of body temperature and thirst

8.3 GENERAL FEATURES

Relationships between endocrine and neural regulation

Hormonal regulation is closely related to that exerted by the nervous system, and the two processes have generally been distinguished by the rate at which each causes effects, the duration of these effects, and their extent; i.e., the effects of endocrine regulation may be slow to develop but prolonged in influence and widely distributed through the body, whereas nervous regulation is typically concerned with quick responses that are of brief duration and localized in their effects. Advances in knowledge, however, have modified these distinctions.

Nerve cells are secretory, for responses to the nerve impulses that they propagate depend

upon the production of chemical transmitter substances, or neurotransmitters, such as acetylcholine and norepinephrine (noradrenaline), which are liberated at nerve endings in minute amounts and have only a momentary action. It has been established, however, that certain specialized nerve cells, called neurosecretory cells, can translate neural signals into chemical stimuli by producing secretions called neurohormones. These secretions, which are often polypeptides (compounds similar to proteins but composed of fewer amino acids), pass along nerve-cell extensions, or axons, and are typically released into the bloodstream at special regions called neurohemal organs, where the axon endings are in close contact with blood capillaries. Once released in this way, neurohormones function in principle similar to hormones that are transmitted in the bloodstream and are synthesized in the endocrine glands.

The distinctions between neural and endocrine regulation, no longer as clear-cut as they once seemed to be, are further weakened by the fact that neurosecretory nerve endings are sometimes so close to their target cells that vascular transmission is not necessary. There is good evidence that hormonal regulation occurs by diffusion in plants and (although here the evidence is largely indirect) in lower animals (e.g., coelenterates), which lack a vascular system.

8.4 THE EVOLUTION OF HORMONES

Hormones have a long evolutionary history, knowledge of which is important if their properties and functions are to be understood. Many important features of the vertebrate endocrine system, for example, are present in the lampreys and hagfishes, modern representatives of the primitively jawless vertebrates (Agnatha), and these features were presumably present in fossil ancestors that lived more than 500 million years ago. The evolution of the endocrine system in the more advanced vertebrates with jaws (Gnathostomata) has involved both the appearance of new hormones and the further evolution of some of those already present in agnathans; in addition, extensive specialization of target organs has occurred to permit new patterns of response.

The factors involved in the first appearance of the various hormones is largely a matter for conjecture, although hormones clearly are only one mechanism for chemical regulation, diverse forms of which are found in living things at all stages of development. Other mechanisms for chemical regulation include chemical substances (so-called organizer substances) that regulate early embryonic development and the pheromones that are released by social insects as sex attractants and regulators of the social organization. Perhaps, in some instances, chemical regulators including hormones appeared first as metabolic by-products. A few such substances are known in physiological regulation: carbon dioxide, for example, is involved in the regulation of the respiratory activity of which it is a product, in insects as well as in vertebrates. Substances such as carbon dioxide are called parahormones to distinguish them from true hormones, which are specialized secretions.

Where are they secreted from?

Hormones are secreted from the endocrine glands in the body. The glands are ductless, so hormones are secreted directly into the blood stream rather than by way of ducts. Some of the major endocrine glands in the body include:

- Pituitary gland
- Pineal gland
- Thymus
- Thyroid
- Adrenal glands
- Pancreas
- Testes
- Ovaries

These organs secrete hormone in microscopic amounts and it takes only very small amounts to bring about major changes in the body. Even a very slight excess of hormone secretion can lead to disease states, as can the slightest deficiency in a hormone.

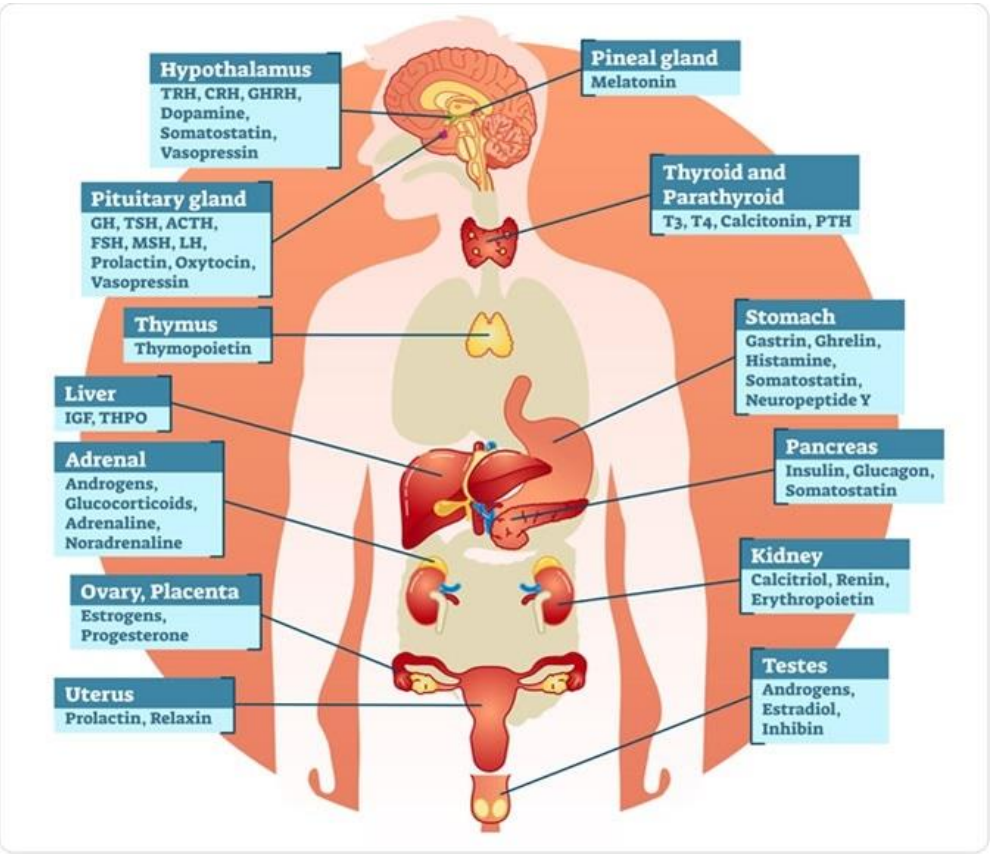


Fig. Different hormones of human body

Our body contains two different kinds of glands.

Endocrine Glands:

These glands, such as the pituitary and adrenal glands, do not have ducts and deliver their secretions through the blood straight to the site of action.

Exocrine Glands:

These glands have ducts by which their secretions are transported. Example: sweat and liver, Endocrine glands secrete "Hormones".

8.5 WHAT IS THE FUNCTION OF HORMONES?

Hormones act as a messenger which is released into the blood. Blood transmits them to various organs and tissues of the human body. After reaching a target site, hormones bind to the receptors. Once this process is complete, hormones then transmit the message which causes an organ or tissue to perform a specific action.

The following are some important functions of hormones:

- Regulating mood and cognitive functions
- Growth and development
- Food metabolism
- Maintaining body temperature
- Controlling thirst and hunger
- Initiating and maintaining sexual development and reproduction

Hormone Regulation

Hormones may be regulated by glands and organs, by a negative feedback mechanism, or by other hormones. Hormones that regulate the release of other hormones are defined as tropic hormones, which are secreted by the anterior pituitary in the brain.

Hormones During Pregnancy

Many hormone levels are affected in the body during pregnancy. Several hormones play major roles during pregnancy such as Estrogen, Progesterone, human chorionic gonadotropin hormone (hCG), and Human placental lactogen (hPL).

Chemical Nature of Hormones

Hormones may be chemically classified as either proteins or steroids. All of the hormones in the human body, except the sex hormones and those from the adrenal cortex, are proteins or protein derivatives.

What are The Properties of Hormones?

The significant properties of hormones are –

1. They have a low molecular weight; thus, they can easily pass through capillaries.
2. Hormones always act in low concentration.
3. They are soluble in water so that they can be transported via blood.
4. The importance of hormones is that they are non-antigenic. They are organic catalysts. Hormones act as coenzymes of other enzymes in the human body.
5. Hormones, in their first action, cause a limited number of reactions and do not influence any metabolic activities of a cell directly.
6. A significant characteristic of hormones is that, after their function is over, they are readily destroyed, excreted or inactivated.
7. Hormonal activities are not hereditary.

8.6 CHARACTERISTICS OF HORMONES

Hormones possess the following characteristics:

- Endocrine cells release hormones into the body.
- Circulating in bodily fluids, hormones are chemical messengers.
- They act on one portion of the body after being secreted in another.
- Unlike enzymes, hormones do not catalyse any reactions.
- They are not stored beforehand and are only secreted in minute amounts when necessary.
- The nervous system uses the feedback effect to control hormone secretion.
- The majority of the time, hormones have long-lasting impacts such as altered behaviour, growth, etc.

8.7 CLASSIFICATION OF HORMONES

The hormones produced in the human body are classified based on their chemical structure and nature as follows:

a. Peptide/Protein Hormones:

These hormones are made of polypeptide chains—linked chains of amino acids. The secretory vesicles serve as both a place for peptide hormone synthesis and

storage. They are located in the membrane of the cell and are expelled from the parent cell through exocytosis. After being stored in vesicles, the substance is released when a stimulus causes a reaction, such as when high blood glucose levels cause the release of insulin. These hormones are water soluble but not fat soluble. The cell membrane comprises a phospholipid bilayer that prevents any fat-insoluble compounds from diffusing into the cell, preventing peptide hormones from passing through the membrane. Since the peptide hormones are unable to pass through the cell's plasma membrane, the receptors are present on the target's cell surface.

ADH (antidiuretic hormone), which is produced in the brain and released into the circulation by the posterior pituitary gland, is one example along with oxytocin and vasopressin.

b. Steroid Hormones:

These hormones are lipid-derived hormones that are obtained from cholesterol. On-demand, they are synthesised from precursors and released from the parent cell by a simple diffusion process. These hormones typically have the goal response of inducing the synthesis of new proteins because they bind to proteins while being transported through the blood. Steroid hormones, in contrast to peptide hormones, are fat-soluble and may pass through the cell membranes. Steroid hormones comprise sex hormones including progesterone, estrogen, and testosterone.

8.8 FUNCTIONS OF HORMONES

The following are a few important functions that hormones perform:

- Metabolism of food.
- Development and growth.
- Controlling hunger and thirst.
- Preserving one's body's temperature.
- Maintain Homeostasis
- Regulating sleep and wake cycle
- Regulating mental and emotional functions.
- Establishing and sustaining sexual development and reproduction

8.9 ENDOCRINE GLANDS AND THE HORMONES SECRETED BY THEM

Endocrine Gland	Hormone	Target Tissue/Organ	Function
Anterior Pituitary Gland	Growth Hormone	Most Tissues	Influences development and growth, activate the synthesis of proteins and modifies the distribution of fat
	Thyroid-Stimulating Hormone (TSH)	Thyroid Gland	Promotes the synthesis and release of thyroid hormones
	Adrenocorticotropic Hormone (ACTH)	Adrenal Cortex	Promote secretion of glucocorticoid hormones.
	Melanocyte-Stimulating Hormone (MSH)	Melanocytes In Skin	Promotes melanin production in the melanocytes present in the skin
	Luteinizing Hormone (LH)	Ovaries In Females	Stimulates ovulation and production of progesterone in ovaries
	Follicle-Stimulating Hormone (FSH)	Follicles Present In The Ovaries Of A Female	Helps in follicle maturation and oestrogen production in ovaries
	Prolactin	Mammary Glands And Ovaries In Female	Promotes milk production in breasts
Posterior Pituitary Gland	Antidiuretic Hormone (ADH)	Kidney	Influences kidney water retention and regulates blood pressure
	Oxytocin	Uterus, Mammary Gland	Stimulates uterine and breast milk duct contraction
Thyroid Gland	Thyroid Hormone	Most Cells Of The Body	Regulates metabolism and has a corresponding impact on development, maturation, nervous system activity, and metabolism

	Calcitonin	Primarily Bone	Reduces rate of bone decomposition and prevents the increase in calcium ions in the blood.
Parathyroid Gland	Parathyroid Hormone (PTH)	Bone, Kidney	a key factor in controlling blood calcium levels
Adrenal Gland	Epinephrine	Blood Vessels, Liver, Heart, Fat Cells	Increases blood flow, heart rate, and oxygen intake.
	Norepinephrine	Blood Vessels, Liver, Heart, And Fat Cells	Regulate blood pressure
	Aldosterone	Kidneys, Sweat Glands, And Intestine	regulates blood pressure, water balance, and salt levels.
	Corticosteroid	Most Tissues	controls important bodily processes, reduces inflammation, keeps blood sugar, blood pressure, and muscular strength stable, and manages salt and water balance.
Pancreas, more specifically Islets of Langerhans	Insulin	Liver, Skeletal Muscle, Adipose Tissue	lowers blood sugar levels and accelerates protein, lipid, and glucose metabolism
	Glucagon	Primarily Liver	Increases blood sugar level
Thymus	Thymosin	Immune Cells/Tissues	Helps in the development and proper functioning of the immune system
Pineal Gland	Melatonin	Hypothalamus And Many Other Tissues	releases melatonin during the night to promote sleep
Ovaries	Oestrogen	Most Tissues	vital for the health of the uterus and breasts, has an impact on the development of female sexual characteristics and maintains bone health.

	Progesterone	Most Tissues	stimulate uterine lining for conception and get the breasts prepared for producing milk
Testes	Testosterone	Most Tissues	enhancement of male sexual characteristics and maturation
Hypothalamus	Gonadotropin-releasing hormone (GnRH)	Pituitary Gland	controls the release LH/FSH from the pituitary gland.
	Corticotropin-releasing hormone (CRH)	Pituitary Gland	controls the release of adrenocorticotropic from the pituitary gland.
	Thyrotropin-releasing hormone (TRH)	Pituitary Gland	controls the release of thyroid-stimulating hormone from the pituitary gland.
	Growth hormone-releasing hormone (GHRH)	Pituitary Gland	controls the release of growth hormone from the pituitary gland.

8.10 WHAT ARE HORMONES MADE OF?

Hormones are made of a diverse range of chemicals, but they are classified into three classes –

1. Eicosanoids
2. Amino acid/protein derivatives (amines, proteins, and peptides)
3. Steroids

8.11 IMPORTANT HORMONES OF THE HUMAN BODY

- **Melatonin:** It primarily controls the circadian rhythm or sleep cycles.
- **Estrogen**: This is the main sex hormone present in women which bring about puberty, prepares the uterus and body for pregnancy and even regulates the menstrual cycle. Estrogen level changes during menopause because of which women experience many uncomfortable symptoms.
- **Cortisol**: It has been named the "stress hormone" as it helps the body in responding to stress. This is done by increasing the heart rate, elevating blood sugar levels etc.
- **Progesterone:** It is a female sex hormone also responsible for the

menstrual cycle, pregnancy and embryogenesis.

- **Testosterone**: This is the most important sex hormone synthesized in men, which cause puberty, muscle mass growth, and strengthen the bones and muscles, increase bone density and controls facial hair growth.

  Some hormones, such as serotonin and dopamine, also function as neurotransmitters, which are chemicals that relay messages between nerve cells in the brain and from neurons to muscles.

Frequently Asked Questions

Q1. What is a hormone? What does it do?

Hormones are the chemicals that are responsible for controlling and regulating the activities of certain cells and organs. These hormones are secreted by ductless glands known as endocrine glands.

Q2. List the types of Hormones.

Hormones are classified into two types, namely: Peptide hormones and steroid hormones.

Q3. Name 3 diseases caused by hormonal imbalance.

- Diabetes.
- Osteoporosis.
- Hyperthyroidism.

Q4. What are hormones made of?

Hormones are made of either proteins or steroids.

Q5. Name the hormone produced by the adrenal glands.

The hormone released by the adrenal glands is called Epinephrine. It is also called adrenaline.

Q6. Name the hormone produced by the pineal gland.

The hormone produced by the pineal gland is Melatonin. It regulates the body's sleep cycle.

Q7. Which are the hormones produced by the thyroid gland?

The thyroid gland is responsible for producing thyroxine, triiodothyronine, and calcitonin.

Q8. Name the glands responsible for producing Testosterone.

In males, testosterone is produced by the testes while ovaries produce the same hormone in females.

Q9. Name the glands responsible for producing Progesterone.

Progesterone is produced by the ovaries.

Q10. Name the hormone responsible for Gigantism.

The hormone responsible for gigantism is growth hormones, which are released by the pituitary gland.

Q11. What causes Acromegaly?

Acromegaly is the result of excess production of the growth hormone by the pituitary gland, commonly as a result of a benign tumour.

8.12 HOW MANY TYPES OF HORMONES ARE THERE IN A HUMAN BODY?

Even though there are several types of hormones in a human body, they are primarily classified into three categories based on their chemical structure. These are –

1. **Lipid-Derived Hormones**

   Lipid-derived hormones are primarily derived from cholesterol, and they share a similarity in terms of their structure. Steroid hormones are the primary lipid hormones in the human body, and chemically they are either ketones or alcohols. Examples of steroid hormones are cortisol and aldosterone.

2. **Amino Acid-Derived Hormones**

- These classes of hormones originate from amino acids, tyrosine and tryptohan. Examples of such hormones as norepinephrine and epinephrine. The medulla section of the adrenal glands produces these. Moreover, the pineal gland in the brain synthesizes melatonin, which controls the sleep cycle.

3. **Peptide Hormones**

   The structure of the peptide hormone is similar to that of the polypeptide chain (chain of amino acids). A popular example of peptide hormone is insulin produced by the pancreas.

8.13 NAME OF HORMONES AND THEIR FUNCTIONS

Here is a list of some important hormones and their functions –

- **Insulin:** Produced by the pancreas, this hormone helps the human body to synthesize glucose from food intake for energy. Additionally, it controls the blood sugar level in the human body.
- **Cortisol:** It is a steroid hormone synthesized in the cortex of adrenal glands. Furthermore, this hormone is also called stress hormone as it helps the human

body to deal with any pressure.

- **Melatonin:** The pineal gland in the human brain produces this hormone. It primarily controls the sleep cycle.
- **Progesterone:** This female hormone is responsible for embryogenesis, menstrual cycle, and pregnancy. It is produced in the corpus luteum section of the ovary.

Examples of Hormones

- Insulin is a hormone that's made by the beta cells in the pancreas. When it is released into the blood, insulin helps regulate how the cells of the body use glucose (a type of sugar) for energy.
- Androgens are responsible for male sex characteristics. Testosterone, the sex hormone produced by the testicles, is an androgen.
- Estrogens are the group of hormones responsible for female sexual development. They are produced primarily by the ovaries and in small amounts by the adrenal glands.
- The thyroid gland secretes two main hormones, thyroxine and triiodothyronine, into the bloodstream. These thyroid hormones stimulate all the cells in the body and control biological processes such as growth, reproduction, development, and metabolism.

8.14 THERAPEUTIC USE

Many hormones and their structural and functional analogs are used as medication. The most commonly prescribed hormones are estrogens and progestogens (as methods of hormonal contraception and as HRT), thyroxine (as levothyroxine,for hypothyroidism) and steroids (for autoimmune diseases and several respiratory disorders). Insulin is used by many diabetics. Local preparations for use in otolaryngology often contain pharmacologic equivalents of adrenaline, while steroid and vitamin D creams are used extensively in dermatological practice.

A "pharmacologic dose" or "supraphysiological dose" of a hormone is a medical usage referring to an amount of a hormone far greater than naturally occurs in a healthy body. The effects of pharmacologic doses of hormones may be different from responses to naturally occurring amounts and may be therapeutically useful, though not without potentially adverse side effects. An example is the ability of pharmacologic doses of glucocorticoids to suppress inflammation.

8.15 COMPARISON WITH NEUROTRANSMITTERS

There are various clear distinctions between hormones and neurotransmitters:

- A hormone can perform functions over a larger spatial and temporal scale than can a neurotransmitter, which often acts in micrometer-scale distances.
- Hormonal signals can travel virtually anywhere in the circulatory system, whereas neural signals are restricted to pre-existing nerve tracts.
- Assuming the travel distance is equivalent, neural signals can be transmitted much more quickly (in the range of milliseconds) than can hormonal signals (in the range of seconds, minutes, or hours). Neural signals can be sent at speeds up to 100 meters per second.
- Neural signalling is an all-or-nothing (digital) action, whereas hormonal signalling is an action that can be continuously variable as it is dependent upon hormone concentration.

Neurohormones are a type of hormone that share a commonality with neurotransmitters. They are produced by endocrine cells that receive input from neurons, or neuroendocrine cells. Both classic hormones and neurohormones are secreted by endocrine tissue; however, neurohormones are the result of a combination between endocrine reflexes and neural reflexes, creating a neuroendocrine pathway. While endocrine pathways produce chemical signals in the form of hormones, the neuroendocrine pathway involves the electrical signals of neurons. In this pathway, the result of the electrical signal produced by a neuron is the release of a chemical, which is the neurohormone**.** Finally, like a classic hormone, the neurohormone is released into the bloodstream to reach its target.

8.16 SUMMARY

Under this unit we have discussed different hormones with their general features, characteristics, classification, functions and their therapeutic. The existence of humans depends heavily and fundamentally on hormones. As you have seen throughout this unit, endocrine hormones can have a wide variety of effects on the body, including the regulation of metabolism, reproductive functions, homeostasis of different ions and molecules, and mediating responses to stressful situations. Different hormones have different effects, but even a single hormone can have multiple effects. Hormones travel throughout the bloodstream and affect any cells that have the appropriate receptors for them, known as target cells. Many hormones have target cells in multiple types of organs and tissues, or they regulate molecules, such as blood glucose, that affect many organ systems. These are some of the reasons why changes in the normal level of an endocrine hormone -either hypersecretion or hyposecretion - can result in a wide variety of symptoms, such as is seen in Cushing’s syndrome, diabetes, and PCOS. By understanding what goes wrong in these disorders, you can better appreciate how important the endocrine system is for regulating the many diverse functions of the human body.

8.17 TERMINAL QUESTIONS

Q.1 What do you mean by hormone? Write any four characteristics of hormones in humans.

Answer:----------

Q.2 Name the important glands of the endocrine system and the hormones secreted by these glands.

Answer:----------

Q.3 Which hormones are produced by ovary and testis?

Answer:----------

Q.4 Write short notes on the followings.

(i) Animal hormones

(ii) Plant hormones

Answer:----------

Q. 5 How hormones act as chemical messenger and how they help in conserving water

Answer:----------

Further readings

- Biochemistry- Lehninger A.L.
- Textbook of Nutrition and Dietetics Ranjana Mahna
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U.P.Rajarshi Tandon Open University, Prayagraj

MFN-102

Advanced Nutritional Biochemistry

BLOCK

3

Minerals, Detoxification in the body

Unit 9: Minerals

Unit 10: Detoxification in the body

Unit 11: Major Alterations

Unit 12: Metabolism

MFN-102

Advanced Nutritional Biochemistry

VICE CHANCELLOR

Prof. Seema Singh Vice Chancellor UPRTOU

COURSE DESIGN COMMITTEE

Dr. Meera Pal **Director Incharge**

School of Health Sciences,
UPRTOU, Prayagraj.

Dr. Alka Gupta **Member**

Associate Professor,
(Home Science, Nutritional Sciences)

Mrs. Zoomi Singh **Member**

Assistant Professor,
Home Science, Nutritional Sciences, UPRTOU, Prayagraj (Contractual)

COURSE PREPRATION COMMITTEE

Dr. Kapil Gupta **Unit: 1-12** **Writer**

Assistant Professor
Department of Biotechnology
Siddharth University Kapilvastu, Siddharthnagar

Dr. Pramod Kumar Pandey **(All blocks and units)** **Editor**

Associate Professor,
Department of Zoology, PSM PG College, Maharajganj

COURSE COORDINATOR

Dr.Meera Pal

Associate Professor
UP Rajarshi Tandon Open University, Prayagraj

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Block Introduction

This is the second block (Minerals, Detoxification in the body) of Advanced Nutritional Biochemistry. It consists of four units. The objective of this block deals basic introduction to minerals, detoxification in the body, major alterations and metabolism.

Unit 9

Under this unit, we have discussed minerals, sources, types and their biological significance. Some minerals are essential to our health and essential minerals are divided into macromineral and microminerals. The body contains many different minerals. Minerals by themselves are inactive chemical elements, like the iron in a pan or calcium in a rock. But in the body, calcium is used to make the bones and teeth, and iron is used to make the hemoglobin in red blood cells. The body uses this iron to carry oxygen to its cells

Unit 10

Under this unit, we have discussed the concept of detoxification in our body. Detoxification is a set of interventions aimed at managing acute intoxication and withdrawal. It denotes a clearing of toxins from the body of the patient who is acutely intoxicated. Detoxification seeks to minimize the physical harm caused by the abuse of substances. Metabolism is usually known for a detoxification method through which endogenous chemicals and xenobiotics are transformed into highly hydrophilic components to expedite removal from the body.

Unit 11

Under this unit, we have discussed major alterations such as carbohydrates and fat metabolism in chronic nutrition-related degenerative diseases Throughout life span, the human body is differentially adjusted and maintained by a complex and connected network of biochemical reactions embedded in pathways that are involved in both energy balance and the interconversion of metabolites to meet ever-changing physiologic needs. This process, known as metabolism, uses energy to sustain the body's vital functions. It utilizes the favorable thermodynamics of biochemical reactions to carry out the physiologic processes of the body in a systematic and tissue-specific manner. . Excess nutrition without compensatory energy expenditure leads to many diseases and may also make the body more susceptible to pathogens.

Unit 12

Under this unit, we have discussed protein metabolism in chronic nutrition-related degenerative diseases and their consequences. Protein metabolism entails the creation of proteins and amino acids, known as anabolism, as well as the breakdown of proteins into amino acids, known as catabolism. In this process, transcription, translation, and post-translational modifications are all dietary proteins are first broken down to individual amino acids by various enzymes and hydrochloric acid present in the

gastrointestinal tract. These amino acids are absorbed into the bloodstream to be transported to the liver and onward to the rest of the body. Absorbed amino acids are typically used to create functional proteins, but may also be used to create energy. They can also be converted into glucose.

UNIT- 9 MINERALS

Structure

Objectives

9.1 INTRODUCTION

In geology and mineralogy, a mineral or mineral species is, broadly speaking, a solid substance with a fairly well-defined chemical composition and a specific crystal structure that occurs naturally in pure form. The geological definition of mineral normally excludes compounds that occur only in living organisms. However, some minerals are often biogenic (such as calcite) or organic compounds in the sense of chemistry (such as mellite). Moreover, living organisms often synthesize inorganic minerals (such as hydroxylapatite) that also occur in rocks.

The concept of mineral is distinct from rock, which is any bulk solid geologic material that is relatively homogeneous at a large enough scale. A rock may consist of one type of mineral or may be an aggregate of two or more different types of minerals, spacially segregated into distinct phases. Some natural solid substances without a definite crystalline structure, such as opal or obsidian, are more properly called mineraloids. If a chemical

compound occurs naturally with different crystal structures, each structure is considered a different mineral species. Thus, for example, quartz and stishovite are two different minerals consisting of the same compound, silicon dioxide.

Objectives

This is the ninth unit on minerals of third block (Minerals, Detoxification in the Body). Under ninth unit (minerals), we have following objectives. These are as under:

- To understand the definition of minerals
- To know the resources of minerals, classification and their uses
- To discuss the differences between metallic and non-metallic minerals
- To discuss the multivitamin/mineral supplements and RDA

The International Mineralogical Association (IMA) is the generally recognized standard body for the definition and nomenclature of mineral species. As of July 2023, the IMA recognizes 5,955 official mineral species. The chemical composition of a named mineral species may vary somewhat due to the inclusion of small amounts of impurities. Specific varieties of a species sometimes have conventional or official names of their own.

Besides the essential chemical composition and crystal structure, the description of a mineral species usually includes its common physical properties such as habit, hardness, lustre, diaphaneity,colour, streak, tenacity, cleavage, fracture, parting, specific gravity, magnetism, fluorescence, radioactivity, as well as its taste or smell and its reaction to acid. Minerals are classified by key chemical constituents; the two dominant systems are the Dana classification and the Strunz classification. Silicate minerals comprise approximately 90% of the Earth's crust. Other important mineral groups include the native elements, sulfides, oxides, halides, carbonates, sulfates, and phosphates.

9.2 WHAT ARE MINERALS?

- The elements in the earth’s crust are rarely found exclusively but are usually combined with other elements to make various substances. These substances are recognized as minerals.
- Thus, a mineral is a naturally occurring organic and inorganic substance.
- It has an orderly atomic structure and a definite chemical composition and physical properties.
- A mineral is composed of two or more elements. But sometimes single element minerals like sulfur, copper, silver, gold, graphite etc. are also found.
- Though the number of elements making up the lithosphere are limited they are combined in many different ways to make up many varieties of minerals.
- There are at least 2,000 minerals that have been named and identified in the earth crust; but almost all the commonly occurring ones are related to six major

mineral groups that are known as major rock forming minerals.

- The basic source of all minerals is the hot magma in the interior of the earth.
- When magma cools, crystals of minerals appear, and a systematic series of minerals are formed in sequence to solidify so as to form rocks.
- Minerals such as coal, petroleum and natural gas are organic origin found in solid, liquid and gaseous forms respectively.

9.3 WHAT ARE MINERAL RESOURCES?

A mineral is a naturally occurring substance, representable by a chemical formula, that is usually solid and inorganic, and has a crystal structure. Mineral resources are the key material basis for socio-economic development. Statistical results show that more than 95% of energy used by mankind, 80% of industrial raw materials and 70% of raw materials for agricultural production are from mineral resources.

Fig. Different types of minerals

A mineral is a pure inorganic substance that occurs naturally in the earth's crust. More than two-thousand minerals have been identified and most of these are inorganic, which are formed by the various combination of elements. However, a small proportion of the earth's crust contains organic materials, consisting of single elements such as gold, silver, diamond, and sulfur.

What are the Elements Found on Earth?

- The earth is composed of various kinds of elements. These elements are found in solid form in the outer layer of the earth and in hot and molten form in the interior. About 98 per cent of the total crust of the earth is composed of eight elements.
    - Oxygen, Silicon, Aluminum, Iron, Calcium, Sodium, Potassium and Magnesium.
    - The rest is composed of titanium, hydrogen, phosphorus, manganese, sulfur, carbon, nickel and other elements.

9.4 WHAT ARE THE PHYSICAL CHARACTERISTICS OF MINERALS?

- **External crystal form:**
    - Determined by internal arrangement of the molecules: Cubes, Octahedrons, Hexagonal prisms, etc.
- **Cleavage:**
    - Tendency to break in given directions producing relatively plane surfaces
    - Result of internal arrangement of the molecules
    - May cleave in one or more directions and at any angle to each other
- **Fracture:**
    - Internal molecular arrangement is so complex
    - There are no planes of molecules
    - The crystal will break in an irregular manner, not along planes of cleavage
- **Luster:**
    - Appearance of a material without regard to color.
    - Each mineral has a distinctive luster like metallic, silky, glossy etc.
- **Color:**
    - Some minerals have characteristic color determined by their molecular structure: malachite, azurite, chalcopyrite etc. and some minerals are coloured by impurities. For example, because of impurities quartz may be white, green, red, yellow etc.
- **Streak:**
    - Color of the ground powder of any mineral.
    - It may be of the same color as the mineral or may differ
        - Malachite is green and gives a green streak, fluorite is purple or green but gives a white streak.
- **Transparency:**
    - Transparent: Light rays pass through so that objects can be seen plainly
    - Translucent: Light rays pass through but will get diffused so that objects cannot be seen
    - Opaque: Light will not pass at all.
- **Structure:**
    - Particular arrangement of the individual crystals:
        - Fine, medium or coarse grained.
        - Fibrous: Separable, divergent, radiating.

- **Hardness:**
    - Relative resistance being scratched.
- **Specific gravity:**
    - The ratio between the weight of a given object and the weight of an equal volume of water; object weighed in air and then weighed in water and divide weight in air by the difference of the two weights.

9.5 CATEGORIES OF MINERAL RESOURCES

Mineral resources can be divided into two major categories.

- Metallic Mineral Resources
- Non-metallic Mineral Resources

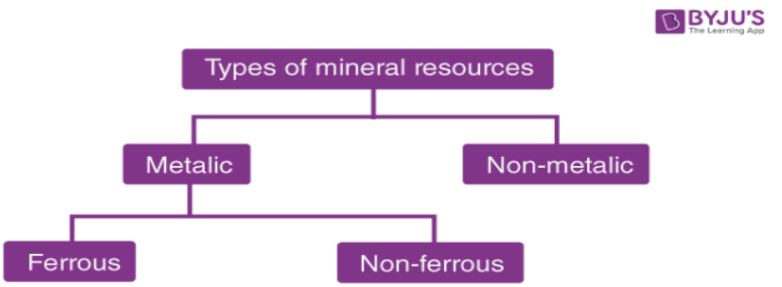


Fig. Types of minerals

There are metals that are hard and conduct electricity and heat with characteristics of lustre or shine. Such metals are called metallic minerals. For example Silver, Chromium, Tin, Nickel, Copper, Iron, Lead, Aluminum, Gold, and Zinc.

1. Characteristics of Metallic Minerals

- Metallic Minerals show a metallic shine in their appearance.
- The potential source of the metal can be got through mining.
- Contains metals in their chemical composition.
- Metallic minerals contain metal in raw form.

2. Characteristics of Nonmetallic Mineral Resources

- Minerals appear with a non-metallic shine or lustre
- Do not contain extractable metals in their chemical composition

9.6 CLASSIFICATION OF METALLIC MINERALS

1. Ferrous metallic minerals
2. Nonferrous metallic minerals

Minerals that contain iron are called ferrous minerals**.** Example of ferrous minerals is Chromites, Iron ore, and manganese. Minerals that do not contain iron are called **non-**ferrous minerals**.** Examples of nonferrous minerals are lead, silver, gold, and copper. There is a group of chemical elements that when melted do not generate a new product. Such special groups are called Nonmetallic minerals. Example: Dimension stone, halite, sand, gypsum, uranium metal, gravel.

9.7 USES OF MINERALS

The use of minerals depends upon their deposits. Some countries are rich in mineral deposits, while others have no deposits. The greatest use of minerals depends on their properties. For instance, Aluminum is light, strong and durable in nature, so it is used for aircraft, shipping, and car industries. Minerals are used in almost all industries. Gold, silver, and platinum metal are used in the jewellery industry. Copper is used in the coin industry and for making pipes and wires. Silicon obtained from quartz is used in the computer industry. Mineral elements give fireworks colour. Barium produces glossy greens; strontium yields dark reds; copper yields blues; and zinc yields sodium. Mixing elements can make many colours: strontium and sodium create bright orange; titanium, zirconium, and magnesium alloys create silvery white; copper and strontium make lavender blue.

Examples of Minerals

Minerals are compounds naturally produced on Earth. They have a clear structure and chemical composition. There are more than 3000 known minerals. Some, like gold and diamond, are rare and precious, while others, like quartz, are more ordinary. Minerals are composed of atoms as are all compounds. There are just only a hundred components around us, and they are the fundamental building blocks in everything of us. They can be found in their pure form, or chemically combined with other compound-making elements. A compound is composed of two or more chemically united elements.

Over 99 per cent of the minerals that make up the surface of the Earth consists of only eight elements. Some of such elements are found as complexes in conjunction with other elements. Minerals are naturally occurring elements or compounds in the Earth's crust. Rocks are minerally shaped mixtures. Much as the building blocks of rocks are elements, the rocks form the rock building blocks. The mineral biotite has basal cleavage which means that it has a complete cleavage. The cleavage plane on top of this sample is visible on the smooth, reflective surface. The flat surface at the bottom, in line with the top of the bowl, is similar to the rim and thus reflects the same cleavage axis.

9.8 CONSERVATION OF MINERAL RESOURCES

The total volume of consumable mineral resources is just 1% of all the minerals present in the earth's crust. However, the consumption rate is so high that these mineral resources which are non-renewable will get exhausted very soon. Here are some measures to conserve minerals:

- Use of minerals in a planned and sustainable manner.

- Recycling of metals
- Use of alternative renewable substitutes.
- Technology should be improved to use the low-grade ores profitably.

Any minerals usually occur as well-developed crystals and are treated in their crystal types. A detailed nomenclature has emerged to classify crystal types and may be familiar with some common names. Different properties aid in the detection of other minerals. For certain minerals, these properties may not be distinguishable enough to aid in their detection. And, they can only be found in some mineral.

Frequently Asked Questions – FAQs

Q 1 What is the importance of mineral resources?

Mineral resources are among the most important natural resources that determine a country's industrial and economic growth by supplying raw materials to the economy's primary, secondary and tertiary sectors.

Q 2 What are the uses of minerals?

Calcium provides bones and teeth with stability and endurance. It also aids in blood coagulation, enzyme regulation, nervous system processing of signals, etc. In transporting oxygen from the lungs to other parts of the body, iron is needed.

Q 3 How minerals are found?

Minerals can be found all over the world in the crust of the earth, but generally in such small quantities that they are not worth extracting. Minerals are found in economically viable deposits only with the aid of certain geological processes. Just where they are located will mineral deposits be collected.

Q4 What defines a mineral?

A mineral is an inorganic solid which occurs naturally, with certain chemical composition and an ordered atomic arrangement. This may sound a bit mouthful, but it becomes clearer if you break it down. There are minerals that occur naturally. They're not made by people.

Q5 What are the characteristics of minerals?

Minerals are identified with eight main properties: crystal habit, lustre, hardness, cleavage, break, colour, line, and specific gravity. There is usually no specific diagnostic property that can be used to classify a mineral sample on its own.

9.9 DIFFERENCE BETWEEN METALLIC AND NON-METALLIC MINERALS

Energy Minerals are studied under the category of fossil fuels. They are quite visibly different from Metallic and Non-Metallic Minerals. But generally, students get confused between Metallic and Non-Metallic Minerals so for your clear understanding

we are providing here key differences between Metallic and Non-Metallic Minerals

Metallic Mineral	Non-Metallic Mineral
These Minerals contain metals in their chemical composition.	These Minerals do not contain metals in their chemical composition.
These Minerals have a shiny appearance of their own.	These Minerals don't have a shiny appearance of their own.
These are generally obtained from igneous rocks.	These are generally obtained from sedimentary rocks.
These are ductile.	These are not ductile or brittle.
By the melting process, metals can be obtained from Metallic Minerals.	These Minerals do not yield any new product on melting.
These are malleable.	These are non-malleable.
Ores of iron, aluminum, gold, silver are examples of Metallic Minerals.	Diamond, slat, potash etc. are examples of non-Metallic Minerals.

So, this was brief on Minerals, their types, and their uses.

9.10 ANTIOXIDANTS

Antioxidants are substances that may prevent or delay some types of cell damage. Examples include beta-carotene, lutein, lycopene, selenium, and vitamins C and E. They are found in many foods, including fruits and vegetables. They are also available as dietary supplements. Most research has not shown antioxidant supplements to be helpful in preventing diseases.

Calcium

Calcium is a mineral found in many foods. Almost all calcium is stored in bones and teeth to help make and keep them strong. Your body needs calcium to help muscles and blood vessels contract and expand, and to send messages through the nervous system. Calcium is also used to help release hormones and enzymes that affect almost every function in the human body.

Daily Value (DV)

The Daily Value (DV) tells you what percentage of a nutrient one serving of that food or supplement provides compared to the recommended amount.

Dietary Supplements

A dietary supplement is a product you take to supplement your diet. It contains one or

more dietary ingredients (including vitamins; minerals; herbs or other botanicals; amino acids; and other substances). Supplements do not have to go through the testing that drugs do for effectiveness and safety.

Electrolytes

Electrolytes are minerals in body fluids. They include sodium, potassium, magnesium, and chloride. When you are dehydrated, your body does not have enough fluid and electrolytes.

Iodine

Iodine is a mineral found in some foods. Your body needs iodine to make thyroid hormones. These hormones control your body's metabolism and other functions. They are also important for bone and brain development during pregnancy and infancy.

Iron

Iron is a mineral. It is also added to some food products and is available as a dietary supplement. Iron is a part of hemoglobin, a protein that transports oxygen from the lungs to the tissues. It helps provide oxygen to muscles. Iron is important for cell growth, development, and normal body functions. Iron also helps the body make some hormones and connective tissue.

Magnesium

Magnesium is a mineral naturally present in many foods, and is added to other food products. It is also available as a dietary supplement and present in some medicines. It helps your body regulate muscle and nerve function, blood sugar levels, and blood pressure. It also helps your body make protein, bone, and DNA.

Minerals

Minerals are those elements on the earth and in foods that our bodies need to develop and function normally. Those essential for health include calcium, phosphorus, potassium, sodium, chloride, magnesium, iron, zinc, iodine, chromium, copper, fluoride, molybdenum, manganese,andselenium.

9.11 MULTIVITAMIN/MINERAL SUPPLEMENTS

Multivitamin/mineral supplements contain a combination of vitamins and minerals. They sometimes have other ingredients, such as herbs. They are also called multis, multiples, or simply vitamins. Multis help people get the recommended amounts of vitamins and minerals when they cannot or do not get enough of these nutrients from food.

Phosphorus

Phosphorus is a mineral that helps keep your bones healthy. It also helps keep blood vessels and muscles working. Phosphorus is found naturally in foods rich in protein, such as meat, poultry, fish, nuts, beans, and dairy products. Phosphorus is also added to many processedfoods.

Potassium

Potassium is a mineral that your cells, nerves, and muscles need to function properly. It helps your body regulate your blood pressure, heart rhythm and the water content in cells. It also helps with digestion. Most people get all the potassium they need from what they eat and drink. It is also available as a dietary supplement.

9.12 RECOMMENDED DIETARY ALLOWANCE (RDA)

Recommended Dietary Allowance (RDA) is the amount of a nutrient you should get each day. There are different RDAs based on age, gender, and whether a woman is pregnant or breast feeding.

Selenium

Selenium is a mineral that the body needs to stay healthy. It is important for reproduction, thyroid function, and DNA production. It also helps protect the body from damage caused by free radicals (unstable atoms or molecules that can damage cells) and infections. Selenium is present in many foods, and is sometimes added to other foods. It is also available as a dietary supplement.

Sodium

Table salt is made up of the elements sodium and chlorine - the technical name for salt is sodium chloride. Your body needs some sodium to work properly. It helps with the function of nerves and muscles. It also helps to keep the right balance of fluids in your body.

Zinc

Zinc, a mineral that people need to stay healthy, is found in cells throughout the body. It helps the immune system fight off invading bacteria and viruses. The body also needs zinc to make proteins and DNA, the genetic material in all cells. During pregnancy, infancy, and childhood, the body needs zinc to grow and develop properly. Zinc also helps wounds heal and is important for our ability to taste and smell. Zinc is found in a wide variety of foods, and is found in most multivitamin/mineral supplements.

9.13 SUMMARY

Under this unit we have discussed minerals, its resources, characteristics, conservation and their uses. Some minerals are more essential than others, in the sense that they have few if any substitutes capable of providing similar functionality at similar costs. The availability of these minerals is a function of geologic, technical, environmental and social, political, and economic factors. Minerals are important for your body to stay healthy. Your body uses minerals for many different jobs, including keeping your bones, muscles, heart, and brain working properly. Minerals are also important for making enzymes and hormones. There are two kinds of minerals: macrominerals and trace minerals. You need larger amounts of macrominerals.

They include calcium, phosphorus, magnesium, sodium, potassium, chloride and sulfur. You only need small amounts of trace minerals. They include iron, manganese, copper, iodine, zinc, cobalt, fluoride and selenium. Most people get the amount of minerals they

need by eating a wide variety of foods. In some cases, your doctor may recommend a mineral supplement. People who have certain health problems or take some medicines may need to get less of one of the minerals. For example, people with chronic kidney disease need to limit foods that are high in potassium.

9.14 TERMINAL QUESTIONS

Q.1 What do you mean by minerals? Explain it with examples.

Answer:----------

Q.2 Explain the physical characteristics of minerals.

Answer:----------

Q.3 Explain the differences between metallic and non-metallic minerals.

Answer:----------

Q.4 Write short notes on the followings.

(i) Uses of minerals

(ii) Antioxidants

Answer:----------

Q. 5 Explain the multivitamins/minerals supplements in nutritional sciences.

Answer:----------

Further readings

- Biochemistry- Lehninger A.L.
- Textbook of Nutrition and Dietetics Ranjana Mahna
- Biochemistry fourth edition-David Hames and Nigel Hooper.
- Textbook of Biochemistry for Undergraduates - Rafi, M.D.
- Textbook of Nutrition and Dietetics- Monika Sharma

UNIT- 10 DETOXIFICATION IN THE BODY

Structure

Objectives

10.1 INTRODUCTION

Detoxification or detoxication (detox for short) is the physiological or medicinal removal of toxic substances from a living organism, including the human body, which is mainly carried out by the liver. Additionally, it can refer to the period of drug withdrawal during which an organism returns to homeostasis after long-term use of an addictive substance. In medicine, detoxification can be achieved by decontamination of poison ingestion and the use of antidotes as well as techniques such as dialysis and (in a limited number of cases) chelation therapy. Many alternative medicine practitioners promote various types of detoxification such as detoxification diets. Scientists have described these as a "waste of time and money". Sense about Science, a UK-based charitable trust, determined that most such dietary "detox" claims lack any supporting evidence.

The liver and kidney are naturally capable of detox, as are intracellular (specifically, inner membrane of mitochondria or in the endoplasmic reticulum of cells) proteins such as CYP enzymes. In cases of kidney failure, the action of the kidneys is mimicked by dialysis; kidney and liver transplants are also used for kidney and liver failure, respectively.

Objectives

This is the tenth unit on detoxification in the body of third block (Minerals, detoxification in the body). Under tenth unit (detoxification in the body), we have following objectives. These are as under:

- To understand the concept of detoxification
- To discuss different types of detoxification
- To discuss the metabolism of foreign compounds
- To discuss the industrial chemicals, pesticides and barbiturates

Indus Valley Ayurvedic Centre India (IVAC) is a distinguished Ayurvedic centre in India that offers authentic Panchakarma, detoxification, rejuvenation, weight loss, and yoga programs. Nestled amid lush landscapes in Mysore, IVAC is a stone's throw from the sacred Chamundi Hills. The resort features flourishing gardens and awe-inspiring vistas of the grand Lalitha Mahal Palace and vibrant Mysore City. IVAC has won multiple accolades and is NABH-certified as the "Best Authentic Ayurvedic Clinic & Panchakarma Centre in India" by Assocham India. IVAC's Panchakarma program is the ultimate cleanse, detox, de-stress, and rejuvenation program. It is a comprehensive and holistic treatment that addresses the physical, mental, and spiritual dimensions of well-being. The program includes a variety of Ayurvedic treatments, such as massage, oil therapy, herbal therapy, and panchakarma.

IVAC's Panchakarma program is designed to help you achieve optimal health and well-being. It can help you to:

- Cleanse your body of toxins

- Improve your digestion
- Boost your immune system
- Reduce stress and anxiety
- Improve your sleep
- Promote weight loss
- Increase your energy levels
- Enhance your overall sense of well-being

If you are looking for a holistic and effective way to improve your health and well-being, then IVAC's Panchakarma program is the perfect choice.

10.2 WHAT ARE "DETOXES" AND "CLEANSES

A variety of "detoxification" diets, regimens, and therapies—sometimes called "detoxes" or "cleanses"—have been suggested as ways to remove toxins from your body, lose weight, or promote health. "Detoxification" programs may involve a single process or a variety of approaches. These include:

- Drinking only juices or similar beverages
- Eating only certain foods
- Using dietary supplements or other commercial products
- Using herbs
- Cleansing the colon (lower intestinal tract) with enemas, laxatives, or colon hydrotherapy (also called "colonic irrigation" or "colonics")
- Reducing environmental exposures
- Using a sauna.
- These programs may be advertised commercially, offered at health centers, or part of naturopathic treatment. Some "detoxification" programs can be unsafe and falsely advertised. (The Centers for Disease Control and Prevention recommends chelation therapy, a type of chemical detoxification procedure, for removing toxic metals from the body in some specific serious cases. This page does not address that type of detoxification.)

10.3 WHAT DOES THE RESEARCH SAY ABOUT "DETOXES" AND "CLEANSES"?

There have been only a small number of studies on "detoxification" programs in people. While some have had positive results on weight and fat loss, insulin resistance, and blood pressure, the studies themselves have been of low quality—with study design problems,

few participants, or lack of peer review (evaluation by other experts to ensure quality). A 2015 review concluded that there was no compelling research to support the use of "detox" diets for weight management or eliminating toxins from the body. A 2017 review said that juicing and "detox" diets can cause initial weight loss because of low intake of calories but that they tend to lead to weight gain once a person resumes a normal diet. There have been no studies on long-term effects of "detoxification" programs.

What about safety?

- The U.S. Food and Drug Administration (FDA) and Federal Trade Commission (FTC) have taken action against several companies selling detox/cleansing products because they (1) contained illegal, potentially harmful ingredients; (2) were marketed using false claims that they could treat serious diseases; or (3) in the case of medical devices used for colon cleansing, were marketed for unapproved uses.
- Some juices used in "detoxes" and "cleanses" that haven't been pasteurized or treated in other ways to kill harmful bacteria can make people sick. The illnesses can be serious in children, elderly people, and those with weakened immune systems.
- Some juices are made from foods that are high in oxalate, a naturally occurring substance. Two examples of high-oxalate foods are spinach and beets. Drinking large quantities of high-oxalate juice can increase the risk for kidney problems.
- People with diabetes should follow the eating plan recommended by their health care team. If you have diabetes, consult your health care providers before making major changes in your eating habits, such as going on a "detox" diet or changing your eating patterns.
- Diets that severely restrict calories or the types of food you eat usually don't lead to lasting weight loss and may not provide all the nutrients you need.
- Colon cleansing procedures may have side effects, some of which can be serious. Harmful effects are more likely in people with a history of gastrointestinal disease, colon surgery, severe hemorrhoids, kidney disease, or heart disease.
- "Detoxification" programs may include laxatives, which can cause diarrhea severe enough to lead to dehydration and electrolyte imbalances.
- Drinking large quantities of water and herbal tea and not eating any food for days in a row could lead to dangerous electrolyte imbalances.

Take charge of your health—talk with your health care providers about any complementary health approaches you use, including any "detoxes" or "cleanses." Together, you and your health care providers can make shared, well-informed decisions.

10.4 ARE ALL FASTING PROGRAMS CONSIDERED "DETOXES" AND "CLEANSES"?

Although some fasting programs are advertised with "detoxification" claims, other fasting programs—including intermittent fasting and periodic fasting—are being researched for health promotion, disease prevention, improved aging, and in some cases weight loss. But there are no firm conclusions about their effects on human health. Also, fasting can cause headaches, fainting, weakness, and dehydration.

10.5 TYPES OF DETOXIFICATION

10.5.1 ALCOHOL DETOXIFICATION

Alcohol detoxification is a process by which a heavy drinker's system is brought back to normal after being habituated to having alcohol in the body continuously for an extended period of substance abuse. Serious alcohol addiction results in a downregulation of GABA neurotransmitter receptors. Precipitous withdrawal from long-term alcohol addiction without medical management can cause severe health problems and can be fatal. Alcohol detox is not a treatment for alcoholism. After detoxification, other treatments must be undergone to deal with the underlying addiction that caused alcohol use.

10.5.2 DRUG DETOXIFICATION

Clinicians use drug detoxification to reduce or relieve withdrawal symptoms while helping an addicted person adjust to living without drug use; drug detoxification does not aim to treat addiction but rather represents an early step within long-term treatment. Detoxification may be achieved drug-free or may use medications as an aspect of treatment. Often drug detoxification and treatment will occur in a community program that lasts several months and takes place in a residential setting rather than in a medical center. Drug detoxification varies depending on the location of treatment, but most detox centers provide treatment to avoid the symptoms of physical withdrawal from alcohol and from other drugs. Most also incorporate counseling and therapy during detox to help with the consequences of withdrawal.

10.5.3 METABOLIC DETOXIFICATION

An animal's metabolism can produce harmful substances which it can then make less toxic through reduction, oxidation (collectivelyknownas redox reactions), conjugation and excret ion of molecules from cells or tissues. This is called xenobiotic metabolism. Enzymes that are important in detoxification metabolism include cytochrome P450 oxidases, UDP-glucuronosyltransferases, and glutathione *S*-transferases. These processes are particularly well-studied as part of drug metabolism, as they influence the pharmacokinetics of a drug in the body.

10.6 ALTERNATIVE MEDICINE

Certain approaches in alternative medicine claim to remove "toxins" from the body through herbal, electrical or electromagnetic treatments. These toxins are undefined and have no scientific basis, making the validity of such techniques questionable. There is little evidence for toxic accumulation in these cases, as the liver and kidneys automatically detoxify and excrete many toxic materials including metabolic wastes. Under this theory, if toxins are too rapidly released without being safely eliminated (such as when metabolizing fat that stores toxins), they can damage the body and cause malaise.

10.7 METABOLISM

Metabolism**,** the sum of the chemical reactions that take place within each cell of a living organism and that provide energy for vital processes and for synthesizing new organic material. 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 how do living organisms—or, their cells—extract energy from their environments, and how do 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. The physical and chemical properties of the components of living things dealt with in this article are found in the unit carbohydrate; cell; hormone; lipid; photosynthesis; and protein.

10.8 METABOLISM OF FOREIGN COMPOUNDS

Foreign compounds that humans ingest or inhale can be classified into two categories, hydrophiles (soluble in water) and lipophiles (soluble in lipid medium), basing on their solubilities in water. Membrane lipid bilayers serve as physical barriers for xenobiotics transporting across cell membranes. Transport mechanism for hydrophilic compounds is distinctive from lipophilic substances. Xenobiotics are transported across cell membranes through mechanisms such as passive diffusion, facilitated diffusion, and active transport. Metabolic pathways consist of activation metabolism and detoxification metabolism. Metabolites are transported to external cell compartments before excretion from the body by renal, hepatic and skin.

Biotransformation can occur in any of several tissues and organs. Some compounds are transformed chemically in the intestine, some in the lungs, the kidneys, or the skin, but the greatest number of these chemical reactions are carried out in the liver which metabolizes not only drugs but also most of the other foreign substances. Biotransformation in the liver is therefore a critical factor not only in drug therapy but also in defending the body against the toxic effects of a wide variety of substances. All the blood that has absorbed digested food and other substances from the intestines, enters the liver through the large portal vein

which ramifies into fine channels through which the blood perfuses slowly among the liver cells. Here, nutrients and other foreign substances are removed, metabolized in some cases, stored and then released into the general circulation. For example, amino acids are converted to proteins, glucose is converted into glycogen and stored for conversion back into glucose whenever required. Drugs and other toxic substances are detoxified.

The biotransformation of foreign compounds in the liver is accomplished by several remarkable enzyme systems which are built into the membranes of the endoplasmic reticulum of the liver cells. The endoplasmic reticulum is of two kinds-rough and smooth, and they differ both in form and function. The surface of the rough membranes are studded with ribosomes, small granules that translate the genetic code into the sequences of amino acids constituting proteins. The smooth membranes have no ribosomes. In the liver, the main function of both kinds of membranes is to assemble the enzymatic complexes that transform foreign substances, and then to serve as the site of those transformations. Biotransformation is carried out by four basic reactions: (1) Oxidation, (2) Reduction, (3) Hydrolysis and (4) Conjugation. Oxidation, which is the central step involved is of two types-microsomal and non-microsomal.

10.9 MICROSOMAL OXIDATION

The mechanism of microsomal oxidation has been the subject of much investigation, and at least the overall details are now clear. Studies with labelled oxygen have shown that the oxygen atom incorporated into the molecule of foreign compound during microsomal oxidation is derived entirely from molecular oxygen and not from water. Microsomes are known to contain cytochromes which differ from those found in mitochondria. Several different cytochromes have been described and may be involved in the oxidation of particular classes of foreign compounds. Cyto chrome P-450 is the most abundant microsomal cytochrome and is present in tissues like liver, which are actively involved in the metabolism of these compounds, but is absent from the tissues like brain which are not concerned with this type of metabolism. The amount of cytochrome P-450 present in the liver is significantly increased following exposure to foreign compounds and this increase is abolished if actinomycin-D, an inhibitor of messenger RNA formation, is simultaneously administered.

Like many other cytochromes, P-450 reacts with molecular oxygen to form an unstable complex. This oxygen molecule is available for foreign compounds. As only the reduced form of cytochrome P-450 reacts with molecular oxygen, a mechanism for the continuous regeneration of this form is present within the microscomes. The mechanism is in many ways analogous to the electron transport pathway of the mitochondria. The process requires $NADPH_2$ specifically and $NADH_2$ is not used. The transfer of electrons from $NADPH_2$ to cytochrome P-450 is accomplished by an enzyme known as $NADPH_2$ - cytochrome-c-oxido-reductase and is the same enzyme present in mitochondria. This enzyme has at least two components, a flavoprotein (FAD) and o protein containing non-haem iron. Like cytochrome P-450, the amount of the microsomal oxido-reductase also increases greatly following exposure to foreign compounds.

Cytochrome P-450 is present within microsomes in a protein-bound form and it is presumably

the nature of protein that determines the specificity of the oxygen transfer reaction to the foreign compound. In fact these microsomal oxidation represent the class of enzymic reaction with the lowest degree of substrate specificity. A very large range of chemically different substances get oxidised by the active form of oxidized cytochrome P-450. Phenobarbital, aminopyrine, steroid hormones and aromatic hydrocarbons all appear to be oxidized by the same system.

Presence of several other microsomal cytochromes help to determine what specificity there is in microsomal oxidations. Hexobarbital is oxidized by a system that will not oxidize tyramine and is true the other way. Some foreign compounds may be oxidized by two different pathways by the microsomes. If the compound is given alone, the oxidized products may be quite different from those when it is given in the presence of a second foreign compound. For example, when the polycyclic aromatic hydrocarbon, 7-12-dimethyl benzanthracene (DMBA) is given alone to rats the major metabolite is formed by oxidation of the 7-methyl group which has potent necrotic effects on adrenals. Now, if the rats are pretreated with some other hydrocarbon, like naphthalene or with steroids like betamethasone, these substances cause a different type of enzyme induction than that induced by DMBA alone. If DMBA is now given, the major metabolites are ring hydroxylated compounds which do not cause adrenal necrosis. A somewhat similar effect can be seen in the interaction between certain drug: and the metabolism of endogenous steroid hormones. Phenobarbitone has beer Lund to increase the rate of turnover of several steroids including cortisol and testosterone.

10.10 NON-MICROSOMAL OXIDATION

While the microsomes are the most important sub cellular fractions involved in the metabolism of foreign compounds, a number of reactions also occur catalysed by soluble enzymes of the cell sap. An important nonmicrosomal enzyme is alcohol dehydrogenase which catalyses the reversible inter-conversion of primary alcohols and aldehydes. Another important soluble enzyme is aldehyde dehydrogenase which catalyses the conversion of primary aldehydes to the corresponding carboxylic acids.

Oxidation accounts for most of the metabolic transformations. The alkyl side-chains of barbiturates and some other drugs are oxidized to form alcohols. In the case of compounds incorporating aromatic rings including polycyclic hydrocarbons, for example in cigarette smoke and many drugs, a hydroxyl group is inserted into the ring. In other cases; alkyl groups are removed from either nitrogen or oxygen atoms, amino groups are removed or sulfoxides are formed.

10.10 EXAMPLESO FDRUG METABOLISM

With this outline of general principles of mechanisms of metabolism, some examples of biotransformation of different classes of chemical compounds are considered to illustrate the reactions involved and the products formed.

10.10.2 SALICYLATES

All commonly used esters of salicylic acid are hydrolysed within the body to release the free acid. This then undergoes microsomal oxidation to form gentisic acid and trihydroxybenzoic acid, both of which appear in the urine, together with salicylic acid mainly as the glucuronide. *20%* of salicylate is metabolized and excreted in this way and the remaining 80% is metabolized to the glycine conjugate-salicyluric acid.

10.10.3 PHENOTHIAZINE TRANQUILLIZERS

More than 30 individual metabolites of chlorpromazine appear in the urine. Thiorida zine and imipramine are metabolised in a similar way but the structural differences alter the pattern. Thioridazine has 2 sulphur atoms, both of which can undergo oxidation to the corresponding sulfoxides or even the sulphone in the case of the S in the side chain. In Imipramine which lacks an S-atom the ethylene bridge can be hydroxylated on either carbon. Oxidation of the N-side chain gives monoand di-demethylated derivatives so that the range of metabolites in human beings is analogous to thoseforCPZ.

10.10.4 BARBITURATES

Chemically three types of processes can be recognized in metabolism of the barbiturates: ring scission, oxidation and addition or removal of substituents.

10.10.5 INDUSTRIAL CHEMICALS

Benzene is widely used in many industries but is among the most difficult of foreign compounds for the human body to detoxify. It presents a uniformly hydrophobic molecule with no substituent or grouping that may be acted upon by enzymes. A small amount is metabolized by the body in a variety of ways, but it is a very toxic compound, difficult to remove from tissues, and may eventually induce aplastic anaemia and liver damage. The principal metabolite is phenol which is excreted in urine both as the glucuronate and sulphate. In contrast to benzene, toluene (methyl benzene), is much less toxic and about 80% is rapidly excreted in urine as hippuric acid, the remaining being excreted unchanged via the lungs. As ring hydroxylation does not occur phenols are not formed. Oxidation of the methyl group to yield benzoic acid takes place through the intermediates benzoyl alcohol and benzaldehyde.

Xylol, which is a mixture of three isomeric dimethyl benzenes, is extensively metabolized to corresponding toluic acids which are excreted in urine as glycine and glucuronide conjugates.Naphthalene is widely used in many industries and has been shown to be capable of inducing cataract. This toxic action is due to its metabolite 1-2-dihydroxynaphthalene, which is formed via its 1-2 epoxide. Tetralin (tetrahydronaphthalene), which is widely used in polishes and paints as a turpentine substitute, is readily metabolised by hydroxylation of the saturated ring to α-tetralol and β-tetralol.

Like benzene, chlorinated aliphatic hydrocarbons, present a difficult metabolic problem to body tissues. Over 80%, of the dose of carbontetrachloride and over 90%, of chloroform or tetrachlorethylene, appear unchanged in expired air. Toxic actions, particularly on liver, of all these compounds are well known. About 1% of carbontetrachloride and 4% of chloroform are converted to CO_2, presumably through reductive dechlorination and then oxidation.

10.10.6 PESTICIDES

Large amounts of phenoxyacetic acids are used as herbicides, which are strong, water soluble acids and are rapidly eliminated. DDT is used most widely as an insecticide. It is fat soluble and metabolised very poorly by humans. Consequently, ingested DDT is absorbed with dietary lipids and deposited largely unchanged in adipose tissues. Two metabolic pathways operate in humans. The first is a reductive dechlorination to the corresponding dichloro-ethane (DDD) which then undergoes hydrolytic dechlorination and oxidation to a carboxylic acid (DDA) which is conjugated with the amino acids serine and aspartic acid. The second pathway is an oxidative dechlorination to yield dichloroethylene (DDE) which is a major metabolite in adipose tissue. Aldrin and dialdrin differ only by an epoxide group, which can be added to aldrin by metabolism. The reaction is difficult and aldrin is largely unmetabolised. Dialdrin is metabolised by opening the epoxide to the corresponding dihydroxy derivative; several other metabolites have also been detected.

Organophosphorus insecticides, parathion and malathion, are readily metabolised in *vivo* to paraoxon and maloxon. Both of these metabolites are potent anticholinesterases-an example of lethal synthesis. Further metabolism of parathion yields diethyl phosphate and p-nitrophenol, which is reduced to p-aminophenol and excreted in urine. Like organophosphorus compounds carbamate insecticides act as anticholinesterases, but do not require metabolic activation. All the metabolites are less active than the parent compounds. Most compounds in this series are aromatic carbamates and are subject to microsomal oxidation.

10.10.7 FOOD ANUTRIENTS

Many anutrients of plant foods occur as glycosides and extensive hydrolysis occurs by intestinal bacteria, to release aglycones. The extent of further metabolism depends on the particular substance. Oily compounds like terpenes, may be metabolised by enzymes of important metabolic pathways, such as fatty acid B-oxidation. Methyl purines like caffeine are subjected to demethylation and then excreted in urine as monoor dimethyl-uric acids.

10.10.8 METABOLISM IN NEONATES

So far as the neonatal metabolism is concerned, the presence of metabolites in the urine gives evidence that infants have an active enzyme system and cytochrome P-450 for carrying out aliphatic and aromatic hydroxylations and allylic and aromatic epoxidations from the first day, for example the metabolites dihydroxy secobarbital and dihydrodiol of dilantin have been detected. Caffeine is excreted unchanged in the urine of neonates, suggesting that the rate of N-demethylation is much slower in the infant than in mother.

Though there is evidence that the metabolising enzyme system is present in the neonate, the rate of metabolism is very slow and that causes the prolonged action of active drugs, and this may be important from the toxicological point of view. However, the glucuronate conjugating mechanism is not well developed in infants upto 3 months of age.

10.10.9 INTERACTIONS BETWEEN FOREIGN COMPOUNDSINTHEBODY

Patients are often given several drugs at the same time. Certain combinations can have unpredictable and sometimes undesirable effects if one drug inhibits or stimulates the metabolism of another or competes with it. For example, phenylbutazone and chloramphenicol compete with the metabolic inactivation of tolbutamide, which can lead to excessive tolbutamide activity causing serious hypoglycemia.

Enzyme induction with phenobarbitone is well known and sudden withdrawal causes toxicity of other drugs given concomitantly like phenylbutazone, antipyrine, coumarin, anticoagulants, etc. Heavy alcohol drinkers are found to have an increased concentration of cytochrome P-450 and therefore stimulate the metabolism of a wide variety of drugs. Besides drug interactions, the ability of environmental pollutants to modify drug action is now under active investigation. It is clear that insecticides stimulate drug metabolising enzymes and heavy metals like lead and methyl mercury inhibit the enzymes.

The process of metabolism is complex and many enzymes are involved in it. II due to some genetic defect a particular enzyme is absent, it will affect the metabolism of certain substances; for example succinylcholine is rapidly inactivated it normal people by cholinesterase of lives and plasma. In a small number of people who lack this enzyme, succinylcholine is metabolised very slowly and they may develop prolonged muscular paralysis and apnoea. Isoniazid is another example Some individuals metabolise it rapidly and some very slowly depending upon the ability of the liver to produce acetylcoenzyme-A.

It is indeed fascinating how the human organism is capable of handling such a vast spectrum of chemical agents. The metabolism of numerous foreign substances has not been fully explored, and as more and more new compounds come into existence the metabolic load on human beings will increase, as also considerations of benefit versus risk produced by them. The use of sophisticated methods like gas chromatography, especially that coupled to mass spectrometry with computerisation have opened up new avenues in understanding metabolism of chemicals. However, what is undoubtedly most important to those concerned with human welfare is to be aware of the problems posed by exposure of the population to foreign compounds.

10.11 Summary

Under this unit we have discussed detoxification and its types, metabolism of foreign compounds as well as interaction of foreign compounds in the body. Many diets and supplements claim to 'detoxify' the body from these substances, but they are typically unsupported by research. A full-body detox is part of regular organ function, with the body naturally eliminating harmful substances through the kidneys, liver, digestive system, skin, and lungs. This unit discusses the many misconceptions around detox diets, and notes ways that you can support the body's natural detoxification processes.

Certain approaches in alternative medicine claim to remove "toxins" from the body through herbal, electrical or electromagnetic treatments. These toxins are undefined and have no scientific basis, making the validity of such techniques questionable. There is little evidence for toxic accumulation in these cases, as the liver and kidneys automatically detoxify and excrete many toxic materials including metabolic wastes. Under this theory, if toxins are too rapidly released without being safely eliminated (such as when metabolizing fat that stores toxins), they can damage the body and cause malaise. Therapies include contrast showers, detoxification foot pads, oil pulling, Gerson therapy, snake-stones, body cleansing, Scientology's Purification Rundown, water fasting, and metabolic therapy.

10.12 TERMINAL QUESTIONS

Q.1 What do you mean by detoxification? Define it with examples.

Answer:----------

Q.2 What do you mean by detoxes and cleanses? Explain it.

Answer:----------

Q.3 Explain drug metabolism with examples.

Answer:----------

Q.4 Write short notes on the followings.

(i) Alcohol detoxification

(ii) Drug detoxification

Answer:----------

Q. 5 Describe interactions between foreign compounds in the body.

Answer:----------

Further readings

- Biochemistry- Lehninger A.L.
- Textbook of Nutrition and Dietetics Ranjana Mahna
- Biochemistry fourth edition-David Hames and Nigel Hooper.
- Textbook of Biochemistry for Undergraduates - Rafi, M.D.
- Textbook of Nutrition and Dietetics- Monika Sharma

UNIT- 11 MAJOR ALTERATIONS

Structure

11.1 INTRODUCTION

The term is most common in biochemistry, where it is a synonym of saccharide (from Ancient Greek *(sákkharon)* 'sugar, a group that includes sugars, starch, and cellulose. The saccharides are divided into four chemical groups: monosaccharides, disaccharides, oligosaccharides, and polysaccharides. Monosaccharides and disaccharides, the smallest (lower molecular weight) carbohydrates, are commonly referred to as sugars. While the scientific nomenclature of carbohydrates is complex, the names of the monosaccharides and disaccharides very often end in the suffix *-ose*, which was originally taken from the word glucose (from Ancient Greek *(gleûkos)* 'wine, and is used for almost all sugars, e.g. fructose (fruit sugar), sucrose (cane or beet sugar), ribose, lactose (milk sugar), etc.

Carbohydrates perform numerous roles in living organisms. Polysaccharides serve as an energy store (e.g. starch and glycogen) and as structural components (e.g. cellulose in plants and chitin in arthropods). The 5-carbon monosaccharide ribose is an important component of coenzymes (e.g. ATP, FAD and NAD) and the backbone of the genetic molecule known as RNA. The related deoxyribose is a component of DNA. Saccharides and their derivatives include many other important biomolecules that play key roles in the immune system, fertilization, preventing pathogenesis, blood clotting, and development.

Objectives

This is the eleventh unit on major alterations of third block (Minerals, detoxification in the body). Under tenth unit (major alterations), we have following objectives. These are

as under:

- To understand the definition and sources of carbohydrates
- To know the concept of fat metabolism
- To know the chronic or degenerative conditions
- To discuss the different types of degenerative diseases.

Carbohydrates are central to nutrition and are found in a wide variety of natural and processed foods. Starch is a polysaccharide and is abundant in cereals (wheat, maize, rice), potatoes, and processed food based on cereal flour, such as bread, pizza or pasta. Sugars appear in human diet mainly as table sugar (sucrose, extracted from sugarcane or sugar beets), lactose (abundant in milk), glucose and fructose, both of which occur naturally in honey, many fruits, and some vegetables. Table sugar, milk, or honey are often added to drinks and many prepared foods such as jam, biscuits and cakes.

Cellulose, a polysaccharide found in the cell walls of all plants, is one of the main components of insoluble dietary fiber. Although it is not digestible by humans, cellulose and insoluble dietary fiber generally help maintain a healthy digestive system by facilitating bowel movements. Other polysaccharides contained in dietary fiber include resistant starch and inulin, which feed some bacteria in the microbiota of the large intestine, and are metabolized by these bacteria to yield short-chain fatty acids.

A carbohydrate is a biomolecule consisting of carbon (C), hydrogen (H) and oxygen (O) atoms, usually with a hydrogen–oxygen atom ratio of 2:1 (as in water) and thus with the empirical formula $C_m(H_2O)_n$ (where *m* may or may not be different from *n*), which does not mean the H has covalent bonds with O (for example with CH_2O, H has a covalent bond with C but not with O). However, not all carbohydrates conform to this precise stoichiometric definition (e.g., uronic acids, deoxy-sugars such as fucose), nor are all chemicals that do conform to this definition automatically classified as carbohydrates (e.g. formaldehyde and acetic acid).

What's most important is the type of carbohydrate you choose to eat because some sources are healthier than others. The amount of carbohydrate in the diet – high or low – is less important than the type of carbohydrate in the diet. For example, healthy, whole grains such as whole wheat bread, rye, barley and quinoa are better choices than highly refined white bread or French fries. Many people are confused about carbohydrates, but keep in mind that it's more important to eat carbohydrates from healthy foods than to follow a strict diet limiting or counting the number of grams of carbohydrates consumed.

11.2 WHAT ARE CARBOHYDRATES

Carbohydrates are found in a wide array of both healthy and unhealthy foods—bread, beans, milk, popcorn, potatoes, cookies, spaghetti, soft drinks, corn, and cherry pie. They also come in a variety of forms. The most common and abundant forms are

sugars, fibers, and starches. Foods high in carbohydrates are an important part of a healthy diet. Carbohydrates provide the body with glucose, which is converted to energy used to support bodily functions and physical activity. But carbohydrate quality is important; some types of carbohydrate-rich foods are better than others**:**

- The healthiest sources of carbohydrates—unprocessed or minimally processed whole grains, vegetables, fruits and beans—promote good health by delivering vitamins, minerals, fiber, and a host of important phytonutrients.
- Unhealthier sources of carbohydrates include white bread, pastries, sodas, and other highly processed or refined foods. These items contain easily digested carbohydrates that may contribute to weight gain, interfere with weight loss, and promote diabetes and heart disease.

The Healthy Eating Plate recommends filling most of your plate with healthy carbohydrates – with vegetables (except potatoes) and fruits taking up about half of your plate, and whole grains filling up about one fourth of your plate.

11.3 WHAT ARE THE DIFFERENT TYPES OF CARBOHYDRATES

There are three main types of carbohydrates:

- **Sugars.** They are also called simple carbohydrates because they are in the most basic form. They can be added to foods, such as the sugar in candy, desserts, processed foods, and regular soda. They also include the kinds of sugar that are found naturally in fruits, vegetables, and milk.
- **Starches.** They are complex carbohydrates, which are made of lots of simple sugars strung together. Your body needs to break starches down into sugars to use them for energy. Starches include bread, cereal, and pasta. They also include certain vegetables, like potatoes, peas, and corn.
- **Fiber.** It is also a complex carbohydrate. Your body cannot break down most fibers, so eating foods with fiber can help you feel full and make you less likely to overeat. Diets high in fiber have other health benefits. They may help prevent stomach or intestinal problems, such as constipation. They may also help lower cholesterol and blood sugar. Fiber is found in many foods that come from plants, including fruits, vegetables, nuts, seeds, beans, and whole grains.

11.4 WHICH FOODS HAVE CARBOHYDRATES

Common foods with carbohydrates include:

- Grains, such as bread, noodles, pasta, crackers, cereals, and rice
- Fruits, such as apples, bananas, berries, mangoes, melons, and oranges
- Dairy products, such as milk and yogurt

- Legumes, including dried beans, lentils, and peas
- Snack foods and sweets, such as cakes, cookies, candy, and other desserts
- Juices, regular sodas, fruit drinks, sports drinks, and energy drinks that contain sugar
- Starchy vegetables, such as potatoes, corn, and peas

11.5 TRY THESE TIPS FOR ADDING HEALTHY CARBOHYDRATES TO YOUR DIET

1. Start the day with whole grains.

Try a hot cereal, like steel cut or old fashioned oats (not instant oatmeal), or a cold cereal that lists a whole grain first on the ingredient list and is low in sugar. A good rule of thumb: Choose a cereal that has at least 4 grams of fiber and less than 8 grams of sugar per serving.

2. Use whole grain breads for lunch or snacks.

Confused about how to find whole-grain bread? Look for bread that lists as the first ingredient whole wheat, whole rye, or some other whole grain —and even better, one that is made with only whole grains, such as 100 percent whole wheat bread.

3. Also look beyond the bread aisle.

Whole wheat bread is often made with finely ground flour, and bread products are often high in sodium. Instead of bread, try a whole grain in salad form such as brown rice or quinoa.

4. Choose whole fruit instead of juice.

An orange has two times as much fiber and half as much sugar as a 12-ounce glass of orange juice.

5. Pass on potatoes, and instead bring on the beans.

Rather than fill up on potatoes – which have been found to promote weight gain – choose beans for an excellent source of slowly digested carbohydrates. Beans and other legumes such as chickpeas also provide a healthy dose of protein.

11.6 FAT METABOLISM

Metabolism is the process your body uses to make energy from the food you eat. Food is made up of proteins, carbohydrates, and fats. Chemicals in your digestive system (enzymes) break the food parts down into sugars and acids, your body's fuel. Your body can use this fuel right away, or it can store the energy in your body tissues. If you have a metabolic disorder, something goes wrong with this process.

Lipid metabolism disorders, such as gaucher disease and Tay-Sachs disease, involve

lipids. Lipids are fats or fat-like substances. They include oils, fatty acids, waxes, and cholesterol. If you have one of these disorders, you may not have enough enzymes to break down lipids. Or the enzymes may not work properly and your body can't convert the fats into energy. They cause a harmful amount of lipids to build up in your body. Over time, that can damage your cells and tissues, especially in the brain, peripheral nervous system, liver, spleen, and bone marrow. Many of these disorders can be very serious, or sometimes even fatal.

These disorders are inherited. Newborn babies get screened for some of them, using blood tests. If there is a family history of one of these disorders, parents can get genetic testing to see whether they carry the gene. Other genetic tests can tell whether the fetus has the disorder or carries the gene for the disorder.

Enzyme replacement therapies can help with a few of these disorders. For others, there is no treatment. Medicines, blood transfusions, and other procedures may help with complications.

Fat metabolism is a biological metabolic process that breaks down ingested fats into fatty acids and glycerol after which into simpler compounds that can be used with the aid of cells of the body. These compounds ultimately gets processed and broken down to produce energy to the body cells. Fat metabolism is controlled by hormones such as insulin, growth hormone, adrenocorticotropic hormone, and glucocorticoids. The rate of fat catabolism is inversely related to the rate of carbohydrate catabolism, and in someconditions, such as diabetes mellitus, the secretion of these hormones increases to counter a decrease in carbohydrate catabolism

Chronic conditions are diseases of long-term duration and may result from a combination of genetic, physiological, environmental, and behavioural factors. The main types of chronic disease include cardiovascular diseases (which account for 17.9 million deaths globally every year), cancers (which are responsible for 9 million deaths annually), chronic respiratory diseases (3.9 million deaths/year), and diabetes (1.6 million deaths/year). In addition, mortality resulting from dementia more than doubled between 2000 and 2016, and it was the fifth leading cause of death worldwide in 2016. The increasing prevalence of these diseases is having a huge financial impact on healthcare systems globally and is arousing the attention and interest of researchers and policymakers at all levels of governance. With respect to diabetes, there were about 422 million adults who were living with the condition in 2014. This is significantly higher than the 108 million in 1980, representing a worldwide increase in diabetes prevalence from 4.7% in 1980 to 8.5% in 2014 among the adult population.

Strategies for managing these chronic conditions are usually multidimensional, and at the centre of these approaches are nutritional and/or dietary interventions, regular physical activity, and lifestyle modifications. The role of nutrition in chronic disease management is particularly crucial as diet is a modifiable risk factor for most chronic conditions that exist either as single conditions or in comorbid states.

In this regard, Ojo et al. conducted a systematic review and meta-analysis of randomised controlled trials with the aim of evaluating the effect of dietary glycaemic index (GI) on glycaemia in patients with type 2 diabetes. Six studies that met the inclusion criteria were selected for the meta-analysis. The results showed that, for the meta-analysis and sensitivity tests, there were significant differences, between the low-GI diet and the higher-GI diet with respect to glycated haemoglobin in patients with type 2 diabetes. Significant differences were also observed in relation to fasting blood glucose between the low-GI diet and the higher-GI diet. Therefore, it was concluded that a low-GI diet is more effective in managing blood glucose parameters (glycated haemoglobin and fasting blood glucose) than a higher-GI diet in patients with type 2 diabetes. This conclusion is in line with the findings of an earlier systematic review by Thomas and Elliot which showed that low-GI diets may promote glycaemic control in patients with diabetes. It is possible that because low-GI foods—including legumes, lentils, and oats—are made up of carbohydrates, which break down slowly in the gut and are absorbed slowly, may explain the findings of these reviews.

11.7 CHRONIC OR DEGENERATIVE CONDITIONS

- A chronic condition is one that has been present for six months or longer.
- Not all chronic conditions will lead to disability.
- Care options will depend on the type and severity of your condition.
- Ask your doctor about setting up a chronic disease management plan.

A chronic condition is one that has been present for 6 months or longer. Not all chronic conditions will lead to disability. However, there are a number of chronic or degenerative conditions that can have a significant effect on a person’s ability to get around and take care of themselves. Common chronic and degenerative conditions that can lead to disability include:

- multiple sclerosis
- Arthritis
- Parkinson’s disease
- Muscular dystrophy
- Huntington’s disease.

If you or someone you are caring for has a chronic or degenerative condition, you may need to make some changes to make life easier.

These might include:

- Making modifications around the home to make everyday tasks simpler
- Moving closer to family

- Purchasing speech and mobility aids
- Planning for a future where you have limited mobility.

How much care you need will depend on the type and severity of your condition. Some serious degenerative conditions will mean that you eventually require a high level of care, while others can be managed through help in the home or through regular visits to healthcare professionals. Ask your doctor about setting up a chronic disease management plan. This means that your doctor can plan and coordinate your care with a multidisciplinary team, which includes two or more healthcare professionals, such as a physiotherapist, occupational therapist and speech therapist. In this unit, some of the more common degenerative conditions that lead to limited mobility or motor control. Follow the links to find information on diagnosis, treatment and local disability support services.

Arthritis

There are more than 100 different arthritis and other musculoskeletal conditions that affect the muscles, bones and joints. Management techniques can include medical treatment and medication, physiotherapy, exercise and self-management techniques.

Rheumatoid arthritis

Rheumatoid arthritis is a disease in which inflammation (pain, heat and swelling) affects the joints, particularly the hands, feet and knees and sometimes other organs of the body. Joint stiffness is common, especially in the morning. There is no cure for rheumatoid arthritis but there are effective ways to manage it.

Osteoarthritis

Osteoarthritis is a disease of the joints. The two bones of a joint are normally protected by smooth, cushioning material called cartilage. In osteoarthritis, cartilage breaks down, causing pain and stiffness in the joint. Osteoarthritis is one of the most common forms of arthritis.

Friedreich ataxia

Friedreich ataxia is a rare inherited disease of the nervous system characterised by the gradual loss of balance, coordination and muscular control. The affected person has increasing difficulty with coordination leading to an unsteady gait and slurred speech, which may look like being drunk to an outsider observer. There is no cure, but some symptoms can be managed with medication and physical therapy.

Huntington’s disease

Huntington's disease is a neurological (nervous system) condition caused by an altered gene. The death of brain cells in certain areas of the brain result in a gradual loss of cognitive (thinking), physical and emotional function. Symptoms can appear when the person is in their thirties or forties. The most common symptom is jerky movements of the arms and legs (called 'chorea'). A person with Huntington's disease may also have

difficulties with speech, swallowing and concentration.

Kennedy's disease

Kennedy's disease is a rare inherited neuromuscular disorder that causes progressive weakening and wasting of the muscles, particularly the arms and legs. Kennedy's disease is also known as X-linked spinal bulbar muscular atrophy (SBMA). The disorder only affects men. There is no cure yet, and treatment can only ease some of the symptoms.

Marfan syndrome

Marfan syndrome is caused by a faulty gene that affects connective tissue. It can affect the skeletal, cardiovascular, ocular, pulmonary and nervous systems. The most serious defects include those of the heart valves and aorta. There is no cure, but the syndrome and its complications can be managed.

Multiple sclerosis

Multiple sclerosis (MS) is a disease of the central nervous system. Its symptoms are varied and unpredictable. The cause of MS is unknown and there is no cure. Treatments are available to ease symptoms and slow down the course of the disease.

Motor neurone disease (MND)

Motor neurone disease (MND) is a rapidly progressing, neurological disease. Motor neurones are nerve cells that control the voluntary muscles of the trunk and limbs, and affect speech, swallowing and breathing. Damage to these nerves causes muscle weakness and wasting. People with MND become increasingly disabled, and may lose speech, have difficulty swallowing and eventually die from respiratory (breathing) failure.

Muscular dystrophy

Muscular dystrophy is the name given to a group of inherited muscle diseases that cause progressive degeneration and weakness of the muscles. Muscular dystrophy can occur at any age. People affected by neuromuscular disorders have different degrees of independence, mobility and carer needs. Each of the approximately 60 neuromuscular disorders has a separate cause.

Myasthenia gravis

Myasthenia gravis is an autoimmune disease that causes muscle weakness. The symptoms are caused by the immune system interfering with the transmission of messages from the nerves to the muscles. There is no cure, but treatment is usually successful in managing the symptoms.

Parkinson's disease

Parkinson’s disease affects one in 100 people over the age of 60. Symptoms range from tremor, rigidity and slow movements to lethargy, masked face and sleep disturbance. Although we do not know what causes Parkinson’s disease, treatments and therapies include medication, surgery and multidisciplinary therapy, including exercise

Polio and post-polio syndrome

Poliomyelitis (polio) is caused by a virus that affects the digestive system and, in some cases, the nervous system. Symptoms vary from mild, flu-like symptoms to life-threatening paralysis and possibly death. Post-polio syndrome occurs years after an initial bout of polio, with new symptoms of weakness, joint and muscle pain and fatigue. If you are not immunized, you could contract polio if your food, water or hands are contaminated with the faeces of an infected person.

11.8 SUMMARY

Under this unit we have discussed carbohydrates with its resources, metabolism of fat and various degenerative diseases. Carbohydrates, a large group of biological compounds containing carbon, hydrogen, and oxygen atoms, include sugars, starch, glycogen, and cellulose. All carbohydrates contain alcohol functional groups, and either an aldehyde or a ketone group (or a functional group that can be converted to an aldehyde or ketone). The simplest carbohydrates are monosaccharides.

Metabolism is a balancing act involving two kinds of activities that go on at the same time: building up body tissues and energy stores (called anabolism) breaking down body tissues and energy stores to get more fuel for body functions (called catabolism).Fat is an important fuel for low and moderate exercise intensity, especially if the exercise is prolonged. The regulation of fat metabolism in skeletal muscle during exercise is complex and involves many sites of control.

More research is needed to determine the importance of fat as a fuel during the recovery from a single bout of exercise and the rest and lower power outputs that occur between bouts of high intensity exercise common to stop-and-go sports. Degenerative disease is the result of a continuous process based on degenerative cell changes, affecting tissues or organs, which will increasingly deteriorate over time. In neurodegenerative diseases, cells of the central nervous system stop working or die via neurodegeneration.

11.9 TERMINAL QUESTIONS

Q.1 What do you mean by carbohydrates? Define it with examples.

Answer:----------

Q.2 Explain the concept of fat metabolism.

Answer:----------

Q.3 Describe the degenerative diseases with their types.

Answer:----------

Q.4 Write short notes on the followings.

(i) Carbohydrates

(ii) Degenerative diseases

Answer:---

Q. 5 Explain the structure of carbohydrates.

Answer:---

Further readings

- Biochemistry- Lehninger A.L.
- Textbook of Nutrition and Dietetics Ranjana Mahna
- Biochemistry fourth edition-David Hames and Nigel Hooper.
- Textbook of Biochemistry for Undergraduates - Rafi, M.D.
- Textbook of Nutrition and Dietetics- Monika Sharma

UNIT- 12 PROTEIN METABOLISM

Structure

Objectives

12.1 INTRODUCTION

Proteins are large biomolecules and macromolecules that comprise one or more long chains of amino acid residues. Proteins perform a vast array of functions within organisms, including catalysing metabolic reactions, DNA replication, responding to stimuli, providing structure to cells and organisms, and transporting molecules from one location to another. Proteins differ from one another primarily in their sequence of amino acids, which is dictated by the nucleotide sequence of their genes, and which usually results in protein folding into a specific 3D structure that determines its activity.

A linear chain of amino acid residues is called a polypeptide. A protein contains at least one long polypeptide. Short polypeptides, containing less than 20–30 residues, are rarely considered to be proteins and are commonly called peptides. The individual amino acid residues are bonded together by peptide bonds and adjacent amino acid residues. The sequence of amino acid residues in a protein is defined by the sequence of a gene, which is encoded in the genetic code. In general, the genetic code specifies 20 standard amino acids; but in certain organisms the genetic code can include selenocysteine and—in certain archaea—pyrrolysine. Shortly after or even during synthesis, the residues in a protein are often chemically modified by post-translational modification, which alters the physical and chemical properties, folding, stability, activity, and ultimately, the function of the proteins. Some proteins have non-peptide groups attached, which can be called prosthetic groups or cofactors. Proteins can also work together to achieve a particular function, and they often associate to form

stable protein complexes.

Objectives

This is the twelfth unit on protein metabolism of third block (Minerals, detoxification in the body). Under twelfth unit (protein metabolism), we have following objectives. These are as under:

- To know the definition and function of proteins
- To know the concept of protein metabolism
- To know the chronic or degenerative conditions
- To discuss different types of degenerative diseases.

Once formed, proteins only exist for a certain period and are then degraded and recycled by the cell's machinery through the process of protein turnover. A protein's lifespan is measured in terms of its half-life and covers a wide range. They can exist for minutes or years with an average lifespan of 1–2 days in mammalian cells. Abnormal or misfolded proteins are degraded more rapidly either due to being targeted for destruction or due to being unstable.

Like other biological macromolecules such as polysaccharides and nucleic acids, proteins are essential parts of organisms and participate in virtually every process within cells. Many proteins are enzymes that catalyze biochemical reactions and are vital to metabolism. Proteins also have structural or mechanical functions, such as actin and myosin in muscle and the proteins in the cytoskeleton, which form a system of scaffolding that maintains cell shape. Other proteins are important in cell signaling, immune responses, cell adhesion, and the cell cycle. In animals, proteins are needed in the diet to provide the essential amino acids that cannot be synthesized. Digestion breaks the proteins down for metabolic use.

Proteins may be purified from other cellular components using a variety of techniques such as ultracentrifugation, precipitation, electrophoresis, and chromatography; the advent of genetic engineering has made possible a number of methods to facilitate purification. Methods commonly used to study protein structure and function include immunohistochemistry, site-directedmutagenesis, X-ray crystallography, nuclear magnetic resonance and mass spectrometry.

Most microorganisms and plants can biosynthesize all 20 standard amino acids, while animals (including humans) must obtain some of the amino acids from the diet. The amino acids that an organism cannot synthesize on its own are referred to as essential amino acids. Key enzymes that synthesize certain amino acids are not present in animals—such as aspartokinase, which catalyses the first step in the synthesis of lysine, methionine, and threonine from aspartate. If amino acids are present in the environment, microorganisms can conserve energy by taking up the amino acids from their surroundings and down regulating their biosynthetic pathways.

In animals, amino acids are obtained through the consumption of foods containing protein. Ingested proteins are then broken down into amino acids through digestion, which typically involves denaturation of the protein through exposure to acid and hydrolysis by enzymes called proteases. Some ingested amino acids are used for protein biosynthesis, while others are converted to glucose through gluconeogenesis, or fed into the citric acid cycle. This use of protein as a fuel is particularly important under starvation conditions as it allows the body's own proteins to be used to support life, particularly those found in muscle.

In animals such as dogs and cats, protein maintains the health and quality of the skin by promoting hair follicle growth and keratinization, and thus reducing the likelihood of skin problems producing malodours. Poor-quality proteins also have a role regarding gastrointestinal health, increasing the potential for flatulence and odorous compounds in dogs because when proteins reach the colon in an undigested state, they are fermented producing hydrogen sulfide gas, indole, and skatole. Dogs and cats digest animal proteins better than those from plants, but products of low-quality animal origin are poorly digested, including skin, feathers, and connective tissue.

12.2 GENERAL STRUCTURE AND PROPERTIES OF PROTEINS

12.3 THE AMINO ACID COMPOSITION OF PROTEINS

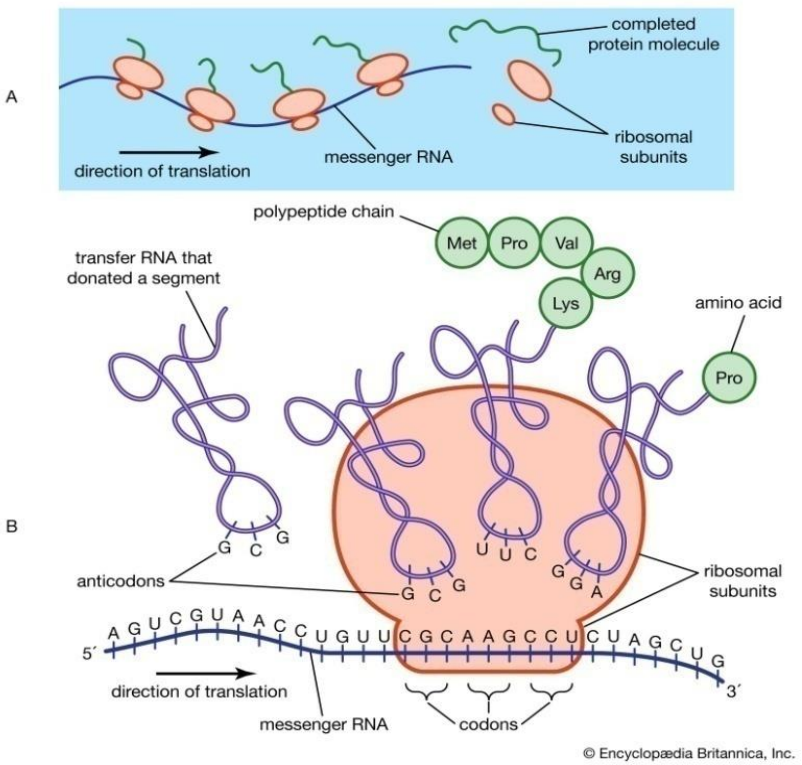
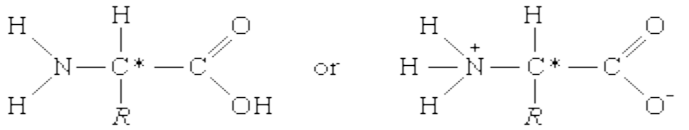


Fig. protein synthesis

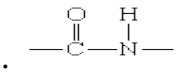
The common property of all proteins is that they consist of long chains of α-amino (alpha amino) acids. The general structure of α-amino acids is shown in . The α-amino acids are so called because the α-carbon atom in the molecule carries an amino group

(—NH_2); the α-carbon atom also carries a carboxyl group (—COOH).



In acidic solutions, when the pH is less than 4, the —COO groups combine with hydrogen ions (H^+) and are thus converted into the uncharged form (—COOH). In alkaline solutions, at pH above 9, the ammonium groups (—NH^+_3) lose a hydrogen ion and are converted into amino groups (—NH_2). In the pH range between 4 and 8, amino acids carry both a positive and a negative charge and therefore do not migrate in an electrical field. Such structures have been designated as dipolar ions, or zwitterions (i.e., hybrid ions).

Although more than 100 amino acids occur in nature, particularly in plants, only 20 types are commonly found in most proteins. In protein molecules the α-amino acids are linked to each other by peptide bonds between the amino group of one amino acid and the carboxyl group of its neighbor



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The condensation (joining) of three amino acids yields the tripeptide.

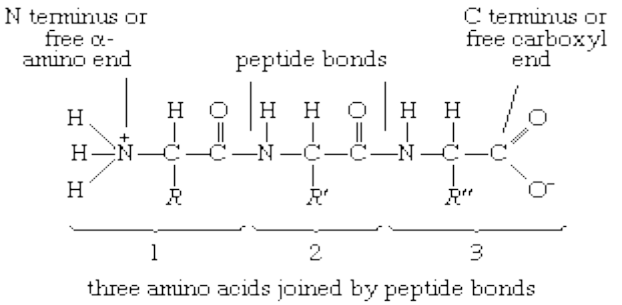

Fig. Three amino acids joined by peptide bonds

It is customary to write the structure of peptides in such a way that the free α-amino group (also called the N terminus of the peptide) is at the left side and the free carboxyl group (the C terminus) at the right side. Proteins are macromolecular polypeptides—i.e., very large molecules (macromolecules) composed of many peptide-bonded amino acids. Most of the common ones contain more than 100 amino acids linked to each other in a long peptide chain. The average molecular weight (based on the weight of a hydrogen atom as 1) of each amino acid is approximately 100 to 125; thus, the molecular weights of proteins are usually in the range of 10,000 to 100,000 daltons (one dalton is the weight of one hydrogen atom). The species-specificity and organ-specificity of proteins result from differences in the number and sequences of amino acids. Twenty different amino acids in a chain 100 amino acids long can be arranged in far more than 10^{100} ways (10^{100} is the number one followed by 100 zeroes).

12.4 STRUCTURES OF COMMON AMINO ACIDS

The amino acids present in proteins differ from each other in the structure of their side (*R*) chains. The simplest amino acid is glycine, in which *R* is a hydrogen atom. In a number of amino acids, *R* represents straight or branched carbon chains. One of these amino acids is alanine, in which *R* is the methyl group (—CH_3). Valine, leucine, and isoleucine, with longer *R* groups, complete the alkyl side-chain series. The alkyl side chains (*R* groups) of these amino acids are nonpolar; this means that they have no affinity for water but some affinity for each other. Although plants can form all of the alkyl amino acids, animals can synthesize only alanine and glycine; thus valine, leucine, and isoleucine must be supplied in the diet.

Two amino acids, each containing three carbon atoms, are derived from alanine; they are serine and cysteine. Serine contains an alcohol group (—CH_2OH) instead of the methyl group of alanine, and cysteine contains a mercapto group (—CH_2SH). Animals can synthesize serine but not cysteine or cystine. Cysteine occurs in proteins predominantly in its oxidized form (oxidation in this sense meaning the removal of hydrogen atoms), called cystine. Cystine consists of two cysteine molecules linked by the disulfide bond (—S—S—) that results when a hydrogen atom is removed from the mercapto group of each of the cysteines. Disulfide bonds are important in protein structure because they allow the linkage of two different parts of a protein molecule to—and thus the formation of loops in—the otherwise straight chains. Some proteins contain small amounts of cysteine with free sulfhydryl (—SH) groups.

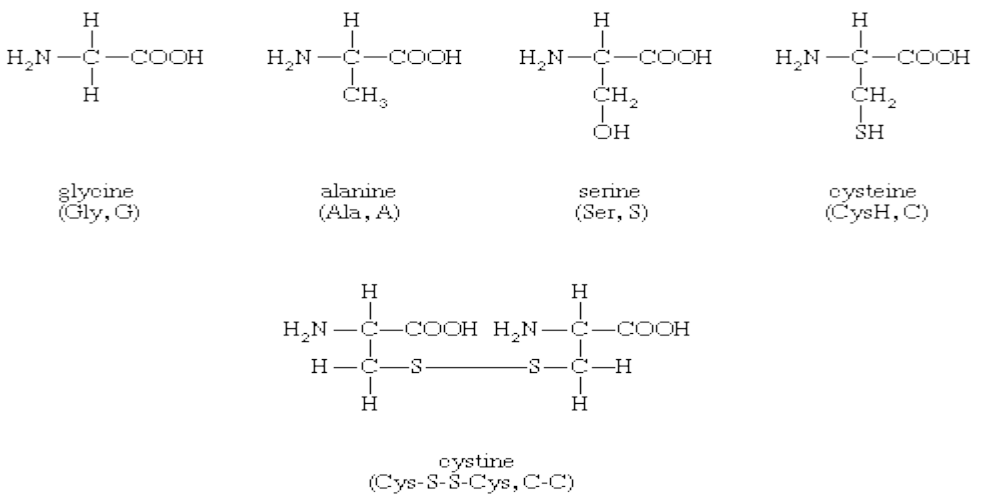

Fig. Structure of amino acids

Four amino acids, each consisting of four carbon atoms, occur in proteins; they are aspartic acid, asparagine, threonine, and methionine. Aspartic acid and asparagine, which occur in large amounts, can be synthesized by animals. Threonine and methionine cannot be synthesized and thus are essential amino acids; i.e., they must be supplied in the diet. Most proteins contain only small amounts of methionine.

Proteins also contain an amino acid with five carbon atoms (glutamic acid) and a secondary amine (in proline), which is a structure with the amino group (—NH_2) bonded to the alkyl side chain, forming a ring. Glutamic acid and aspartic acid are

dicarboxylic acids; that is, they have two carboxyl groups (—COOH).

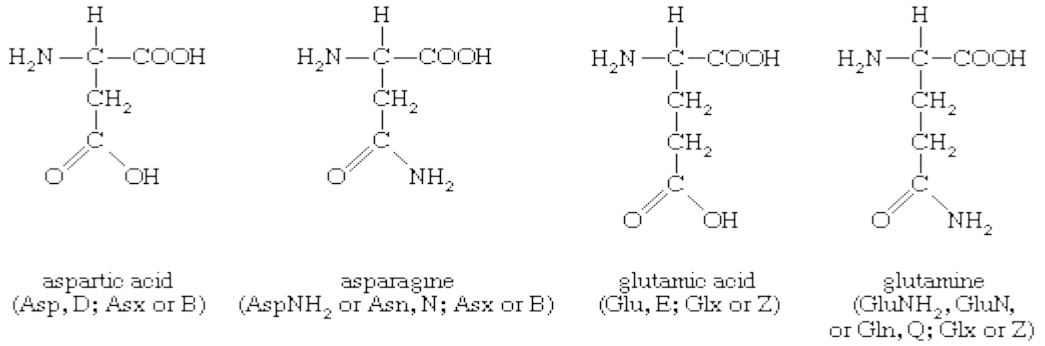

Fig. Structure of amino acids

Glutamine is similar to asparagine in that both are the amides of their corresponding dicarboxylic acid forms; i.e., they have an amide group (—$CONH_2$) in place of the carboxyl (—COOH) of the side chain. Glutamic acid and glutamine are abundant in most proteins; e.g., in plant proteins they sometimes comprise more than one-third of the amino acids present. Both glutamic acid and glutamine can be synthesized by animals.

Milk proteins

Milk contains the following: an albumin, α-lactalbumin; a globulin, beta-lactoglobulin; and a phosphoprotein, casein. If acid is added to milk, casein precipitates. The remaining watery liquid (the supernatant solution), or whey, contains α-lactalbumin and β-lactoglobulin. Both have been obtained in crystalline form; in bovine milk, their molecular weights are approximately 14,000 and 18,400, respectively. Lactoglobulin also occurs as a dimer of molecular weight 37,000. Genetic variations can produce small variations in the amino acid composition of lactoglobulin. The amino acid composition and the tertiary structure of lactalbumin resemble that of lysozyme, an egg protein.

Casein is precipitated not only by the addition of acid but also by the action of the enzyme rennin, which is found in gastric juice. Rennin from calf stomachs is used to precipitate casein, from which cheese is made. Milk fat precipitates with casein; milk sugar, however, remains in the supernatant (whey). Casein is a mixture of several similar phosphoproteins, called α-, β-, γ–, and κ-casein, all of which contain some serine side chains combined with phosphoric acid. Approximately 75 percent of casein is α-casein. Cystine has been found only in κ-casein. In milk, casein seems to form polymeric globules (micelles) with radially arranged monomers, each with a molecular weight of 24,000; the acidic side chains occur predominantly on the surface of the micelle, rather than inside.

Egg proteins

About 50 percent of the proteins of egg white are composed of ovalbumin, which is easily obtained in crystals. Its molecular weight is 46,000 and its amino acid composition differs from that of serum albumin. Other proteins of egg white are conalbumin, lysozyme,

ovoglobulin, ovomucoid, and avidin. Lysozyme is an enzyme that hydrolyzes the carbohydrates found in the capsules certain bacteria secrete around themselves; it causes lysis (disintegration) of the bacteria. The molecular weight of lysozyme is 14,100. Its three-dimensional structure is similar to that of α-lactalbumin, which stimulates the formation of lactose by the enzyme lactose synthetase. Lysozyme has also been found in the urine of patients suffering from leukemia, meningitis, and renal disease.

Avidin is a glycoprotein that combines specifically with biotin, a vitamin. In animals fed large amounts of raw egg white, the action of avidin results in "egg-white injury." The molecular weight of avidin, which forms a tetramer, is 16,200. Egg-yolk proteins contain a mixture of lipoproteins and livetins. The latter are similar to serum albumin, α-globulin, and β-globulin. The yolk also contains a phosphoprotein, phosvitin. Phosvitin, which has also been found in fish sperm, has a molecular weight of 40,000 and an unusual amino acid composition; one third of its amino acids are phosphoserine.

12.5 PROTEIN METABOLISM

The main sources of amino acids for the human body are the proteins in our diet, the non-essential amino acids synthesized by the liver plus the amino acids that come from the own's body protein, which are being constantly degraded and resynthesized. Protein digestion begins in the stomach, where the action of gastric juice hydrolyzes about 10% of the peptide bonds. Gastric juice is a mixture of water (more than 99%), inorganic ions, hydrochloric acid, and various enzymes and other proteins. The pain of a gastric ulcer is at least partially due to irritation of the ulcerated tissue by acidic gastric juice.

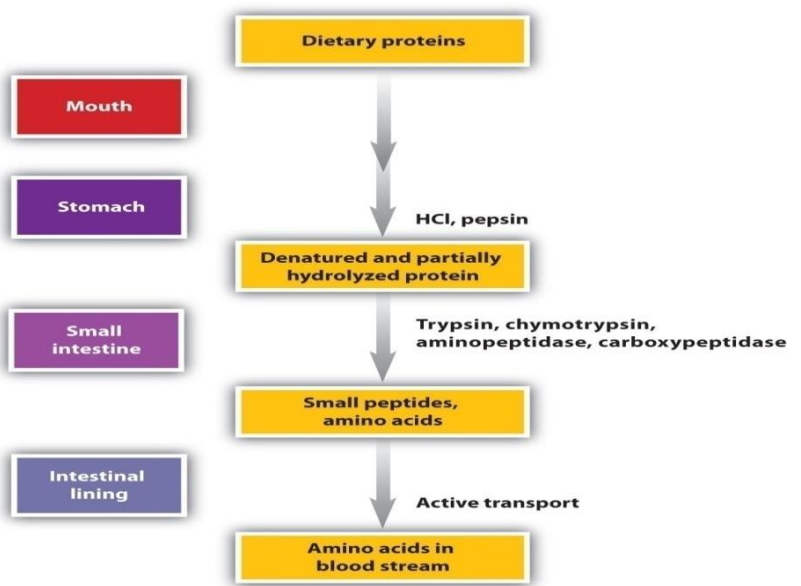

Fig. The principal events and Sites of Protein Digestion

The hydrochloric acid (HCl) in gastric juice is secreted by glands in the stomach lining. The pH of freshly secreted gastric juice is about 1.0, but the contents of the stomach may raise the pH to between 1.5 and 2.5. HCl helps to denature food proteins; that is, it unfolds the protein molecules to expose their chains to more efficient enzyme action.

The principal digestive component of gastric juice is pepsinogen, an inactive enzyme produced in cells located in the stomach wall. When food enters the stomach after a period of fasting, pepsinogen is converted to its active form—pepsin—in a series of steps initiated by the drop in pH. Pepsin catalyzes the hydrolysis of peptide linkages within protein molecules. It has a fairly broad specificity but acts preferentially on linkages involving the aromatic amino acids tryptophan, tyrosine, and phenylalanine, as well as methionine and leucine. Protein digestion is completed in the small intestine.

Protein metabolism denotes the various biochemical processes responsible for the synthesis of proteins and amino acids (anabolism), and the breakdown of proteins by catabolism. The steps of protein synthesis include transcription, translation, and post translational modifications. During transcription, RNA polymerase transcribes a coding region of the DNA in a cell producing a sequence of RNA, specifically messenger RNA (mRNA). This mRNA sequence contains codons: 3 nucleotide long segments that code for a specific amino acid. Ribosomes translate the codons to their respective amino acids. In humans, non-essential amino acids are synthesized from intermediates in major metabolic pathways such as the Citric Acid Cycle. Essential amino acids must be consumed and are made in other organisms. The amino acids are joined by peptide bonds making a polypeptide chain. This polypeptide chain then goes through post translational modifications and is sometimes joined with other polypeptide chains to form a fully functional protein.

Dietary proteins are first broken down to individual amino acids by various enzymes and hydrochloric acid present in the gastrointestinal tract. These amino acids are absorbed into the bloodstream to be transported to the liver and onward to the rest of the body. Absorbed amino acids are typically used to create functional proteins, but may also be used to create energy. They can also be converted into glucose. This glucose can then be converted to triglycerides and stored in fat cells. Proteins can be broken down by enzymes known as peptidases or can break down as a result of denaturation. Proteins can denature in environmental conditions the protein is not made for.

12.6 NEURODEGENERATIVE DISEASES

Neurodegenerative diseases such as Alzheimer's or Parkinson's are associated with the prion-like propagation and aggregation of toxic proteins. A long standing hypothesis that amyloid-beta drives Alzheimer's disease has proven the subject of contemporary controversy; leading to new research in both the role of tau protein and its interaction with amyloid-beta. Conversely, recent work in mathematical modeling has demonstrated the relevance of nonlinear reaction-diffusion type equations to capture essential features of the disease. Such approaches have been further simplified, to network-based models, and offer researchers a powerful set of computationally tractable tools with which to investigate neurodegenerative disease dynamics. Here, we propose a novel, coupled network-based model for a two-protein system that includes an enzymatic interaction term alongside a simple model of aggregate transneuronal damage. We apply this theoretical model to test the possible interactions between tau

proteins and amyloid-beta and study the resulting coupled behavior between toxic protein clearance and proteopathic phenomenology. Our analysis reveals ways in which amyloid-beta and tau proteins may conspire with each other to enhance the nucleation and propagation of different diseases, thus shedding new light on the importance of protein clearance and protein interaction mechanisms in prion-like models of neurodegenerative disease.

Many neurodegenerative diseases involve the misfolding and aggregation of specific proteins into abnormal, toxic species. Therapeutic targeting of protein misfolding has generated unique challenges for drug discovery and development for several reasons, including 1) the dynamic nature of the protein species involved, 2) uncertainty about which forms of a given disease protein (monomers, oligomers, or insoluble aggregates) are primarily responsible for cellular toxicity, 3) our still limited understanding about which components of the cellular proteostatic machinery these disease proteins interact with and 4) lack of well-validated biomarkers for clinical trials.

However, as we continue to gain knowledge of disease mechanisms, improve our abilities to model disease states in vitro and in vivo, and identify new biomarkers, there is increasing optimism that we will discover novel therapeutics that prevent, reverse, or delay the progression of neurodegenerative diseases. In concert with the scientific advances in the past several decades, the field of neurodegenerative disease research is undergoing significant change with respect to how various stakeholders engage each other and share information with the entire community. Increasing collaboration between scientists from the pharmaceutical industry disease foundations, academic researchers, contract research organizations, and patient advocacy group, and increasing communication between groups studying different diseases, has spurred promising initiatives in basic, translational, and clinical research in neurodegenerative disease.

12.7 SUMMARY

Under this unit we have discussed different types of proteins, protein metabolism, degenerative diseases. Proteins are large, complex molecules that play many critical roles in the body. They do most of the work in cells and are required for the structure, function, and regulation of the body's tissues and organs. Proteins are built as chains of amino acids, which then fold into unique three-dimensional shapes. Bonding within protein molecules helps stabilize their structure, and the final folded forms of proteins are well-adapted for their functions.

Protein metabolism denotes the various biochemical processes responsible for the synthesis of proteins and amino acids (anabolism), and the breakdown of proteins by catabolism. The steps of protein synthesis include transcription, translation, and post translational modifications. During transcription, RNA polymerase transcribes a coding region of the DNA in a cell producing a sequence of RNA, specifically messenger RNA (mRNA). This mRNA sequence contains codons: 3 nucleotide long segments that code for a specific amino acid. Ribosomes translate the codons to their respective amino acids.[1] In humans, non-essential amino acids are synthesized from

intermediates in major metabolic pathways such as the Citric Acid Cycle. Essential amino acids must be consumed and are made in other organisms. The amino acids are joined by peptide bonds making a polypeptide chain. This polypeptide chain then goes through post translational modifications and is sometimes joined with other polypeptide chains to form a fully functional protein.

12.8 TERMINAL QUESTIONS

Q.1 What do you mean by proteins? Explain it with examples.

Answer:----------

Q.2 Explain protein metabolism.

Answer:----------

Q.3 Explain degenerative diseases with examples.

Answer:----------

Q.4 Write short notes on the followings.

(i) Protein metabolism

(ii) Structure of proteins

Answer:----------

Q. 5 Describe various types of proteins. Classify them.

Answer:----------

Further readings

- Biochemistry- Lehninger A.L.
- Textbook of Nutrition and Dietetics Ranjana Mahna
- Biochemistry fourth edition-David Hames and Nigel Hooper.
- Textbook of Biochemistry for Undergraduates - Rafi, M.D.
- Textbook of Nutrition and Dietetics- Monika Sharma

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