NUTRITIONAL BIOCHEMISTRY

M.Sc. FOOD AND NUTRITION SCIENCE

SEMESTER-II, PAPER-I

LESSON WRITERS

Dr. D. Jalaja Kumari
Faculty
Department of FSND,
Acharya Nagarjuna University.

Dr. P. Kiranmayi
Associate Professor
Department of Biochemistry,
Acharya Nagarjuna University.

Dr. Santhi Sri, K.V.
Associate Professor
Department of FSND,
Acharya Nagarjuna University.

Dr. B. Babitha
Associate Professor
Department of FSND,
Acharya Nagarjuna University.

Dr. Ch. Manjula
Faculty
Department of FSND,
Acharya Nagarjuna University.

EDITOR

Dr. Santhi Sri, K.V
Associate Professor
Department of Food Science, Nutrition and Dietetics,
Acharya Nagarjuna University.

Academic Advisor

Dr. B. Babitha
Associate Professor
Department of FSND,
Acharya Nagarjuna University.

DIRECTOR, I/c.

Prof. V. Venkateswarlu

M.A., M.P.S., M.S.W., M.Phil., Ph.D.
Professor

CENTRE FOR DISTANCE EDUCATION
ACHARYA NAGARJUNA UNIVERSITY
NAGARJUNA NAGAR 522 510
Ph: 0863-2346222, 2346208
0863- 2346259 (Study Material)
Website www.anucde.info
E-mail: anucdedirector@gmail.com

M.Sc. FOOD AND NUTRITION SCIENCE: NUTRITIONAL BIOCHEMISTRY

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FOREWORD

Since its establishment in 1976, Acharya Nagarjuna University has been forging ahead in the path of progress and dynamism, offering a variety of courses and research contributions. I am extremely happy that by gaining 'A+' grade from the NAAC in the year 2024, Acharya Nagarjuna University is offering educational opportunities at the UG, PG levels apart from research degrees to students from over 221 affiliated colleges spread over the two districts of Guntur and Prakasam.

The University has also started the Centre for Distance Education in 2003-04 with the aim of taking higher education to the door step of all the sectors of the society. The centre will be a great help to those who cannot join in colleges, those who cannot afford the exorbitant fees as regular students, and even to housewives desirous of pursuing higher studies. Acharya Nagarjuna University has started offering B.Sc., B.A., B.B.A., and B.Com courses at the Degree level and M.A., M.Com., M.Sc., M.B.A., and L.L.M., courses at the PG level from the academic year 2003-2004 onwards.

To facilitate easier understanding by students studying through the distance mode, these self-instruction materials have been prepared by eminent and experienced teachers. The lessons have been drafted with great care and expertise in the stipulated time by these teachers. Constructive ideas and scholarly suggestions are welcome from students and teachers involved respectively. Such ideas will be incorporated for the greater efficacy of this distance mode of education. For clarification of doubts and feedback, weekly classes and contact classes will be arranged at the UG and PG levels respectively.

It is my aim that students getting higher education through the Centre for Distance Education should improve their qualification, have better employment opportunities and in turn be part of country's progress. It is my fond desire that in the years to come, the Centre for Distance Education will go from strength to strength in the form of new courses and by catering to larger number of people. My congratulations to all the Directors, Academic Coordinators, Editors and Lesson-writers of the Centre who have helped in these endeavors.

Prof. K. Gangadhara Rao
M.Tech., Ph.D.,
Vice-Chancellor I/c
Acharya Nagarjuna University.

M.Sc. FOOD AND NUTRITION SCIENCE
SEMESTER-II, PAPER-I
201FN24-NUTRITIONAL BIOCHEMISTRY
SYLLABUS

Course Objectives: To enable the students to

1) Understand the metabolism of Nutrients
2) Examine the interrelationship between metabolism of macro nutrients in normal health deficiency and diseased conditions.
3) Study the role of enzymes and hormones in the metabolism of macro and micro nutrients in normal, deficiency states and diseased conditions.

THEORY

Unit-I

- Carbohydrate Metabolism: Carbohydrates, Oxidation of glucose by Glycolysis, TCA cycle.
- Electron Transport Chain (ETC), Oxidative Phosphorylation, HMP path way.
- Glycogenesis, Glycogenolysis and Gluconeogenesis. Glycogen storage in normal and diseased states.
- Endocrinal influences on carbohydrate metabolism, Regulation of blood glucose concentration.

Unit-II

- Proteins and Amino Acids: Sources, structure, functions, digestion and absorption of proteins.
- Classification of amino acids - peptides and proteins. Metabolism of amino acids - Amino Acid decarboxylation, Tran's peptidation.
- Nucleic acid DNA, RNA, Bases - Purines and Pyrimidines, Synthesis of Nucleic Acids - Steps of replication - Initiation, Elongation and Termination. Protein biosynthesis.
- Enzymes - Classification, functions of enzymes; factors affecting enzyme activity.

Unit- III

- Fatty Acid Metabolism: Oxidation and bio synthesis of fatty acids, Ketone bodies and Ketosis
- Bio synthesis of cholesterol and their regulation, Metabolism of bilepigments. Lipids of biological significance - Lipoproteins and prostaglandins in health and disease. Metabolic Interrelationships between Carbohydrate, Lipid and Proteins.

UNIT - IV

- **Vitamins:** Fat soluble and water soluble and their sources, functions (also their role as cofactors in metabolism) deficiency states, factors influencing bioavailability and

requirements.

UNIT-V

- **Minerals:** sources, functions (also their role as cofactors in metabolism) deficiency states, factors influencing bioavailability and requirements of Calcium. Phosphorus and metabolism of Calcium and Phosphorus.
- Sources, functions (also their role as cofactors in metabolism) deficiency states. factors influencing bioavailability and requirements of Iron, Iodine. Zinc. Sodium, Potassium, Chloride and Flourine.

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Course Outcomes -After completion of this course, students will be able to:

CO1: Knowledge on metabolic pathways and disorders of metabolic pathways.

CO2: Information on functions of proteins, aminoacids, enzymes and harmones.

CO3: Understand fatty acid metabolism and interrelationships between carbohydrates. proteins and fats

CO4: Knowledge on functions, deficiencies and bioavailability of vitamins.

CO5: Acquired information on functions, deficiencies and bioavailability of minerals

(201FN24)

M.Sc. DEGREE EXAMINATION, MODEL QUESTION PAPER
FIRST SEMESTER
NUTRITIONAL BIOCHEMISTRY

Time: Three hours **Maximum: 70 marks**

Answer ONE Question From Each Unit **5 × 14 = 70M**
Each Question Carries 14 Marks.

UNIT-I

1) Explain in detail about Glycogen storage in normal and diseased states.

OR

2) Write about Endocrinal influences on carbohydrate metabolism.

UNIT-II

3) Discuss about classification of amino acids..

OR

4) Write an essay on Hormones.

UNIT-III

5) What is Bio synthesis of cholesterol and their regulation? Explain it?

OR

6) Explain about the Lipids of biological significance?

UNIT-IV

7) List out the Vitamins and write the sources of Vitamins?

OR

8) Discuss in detail about vitamin deficiencies?

UNIT-V

9) Discuss about factors Influencing bioavailability and requirements of Zinc and sodium.

OR

10) Write in detail about different sources and functions of minerals.

CONTENTS

LESSON-1

CARBOHYDRATE METABOLISM: CARBOHYDRATES, OXIDATION OF GLUCOSE BY GLYCOLYSIS, TCA CYCLE, HMP PATH WAY

1.0 OBJECTIVES:

After studying this unit, you should be able to:

- Explain how monosaccharides are catabolised to produce energy in the form of ATP through glycolysis.
- work out the energy (ATP) production when glucose is oxidized in various metabolic pathways, glycolysis, citric acid cycle etc,

STRUCTURE:

1.1 INTRODUCTION

Carbohydrates are one of the three main macronutrients (along with proteins and fats) that provide energy to the body. They are essential for proper bodily function, particularly as a primary energy source. Carbohydrate metabolism involves various biochemical reactions for the formation (anabolism), breakdown (catabolism) and inters conversion of carbohydrates in a living organism. In the present lesion we shall begin with glycolysis, universal pathway sugar catabolism. Glycolysis is central pathway of glucose catabolism. It is initial route of oxidative catabolism in both anaerobic and aerobic systems. It results in

incomplete oxidation of glucose which yields pyruvate. Complete breakdown of pyruvate takes place under aerobic conditions by first converting it to acetyl Co-A followed by an entry to the Kreb's cycle. We shall discuss the various reactions involved in this pathway. Glucose once oxidized needs to be replenished. Although, humans can't synthesize glucose from CO_2 and water, but there are reactions which replenish its levels from other sources by a process called gluconeogenesis. This specialized pathway which forms glucose from non carbohydrate sources during prolonged starvation will be explained in this lesion. Finally, the pentose phosphate pathway (PPP) and its role will be discussed.

1.2 TYPES OF CARBOHYDRATES:

Carbohydrates can be classified into two main types based on their chemical structure and function:

1) **Simple Carbohydrates (Sugars):** Simple carbohydrates consist of one or two sugar units, making them easy to digest and providing a quick source of energy.
   - Monosaccharides (Single Sugar Units)**:** These are the simplest form of carbohydrates.
     - Glucose: The primary energy source for the body, found in fruits and honey.
     - Fructose: A natural sugar found in fruits and some vegetables.
     - Galactose: Found in dairy products.
   - Disaccharides (Two Sugar Units): Formed when two monosaccharides combine.
     - Sucrose: Common table sugar, made of glucose + fructose.
     - Lactose: Found in milk and dairy products, made of glucose + galactose.
     - Maltose: Found in germinating grains, made of glucose + glucose.
     - Sources of Simple Carbohydrates: Fruits, honey, milk, candies, sugary beverages, and baked goods.
2) **Complex Carbohydrates (Starches and Fibers):** Complex carbohydrates are made up of longer chains of sugar molecules. They take longer to digest and provide sustained energy.
   a) **Starches:** Starches are polysaccharides, which consist of many glucose units linked together. They are broken down slowly by the body to provide a steady supply of energy.

      Sources of Starches: Potatoes, rice, pasta, whole grains (like oats and quinoa), legumes (beans, lentils), and starchy vegetables (corn, peas).

   b) **Fiber:** Fiber is a type of carbohydrate that the body cannot fully digest. It plays a crucial role in digestive health and helps regulate blood sugar and cholesterol levels.
      - **Soluble Fiber:** Dissolves in water and forms a gel-like substance, which helps lower cholesterol and stabilizes blood sugar (e.g., oats, beans, apples).

- **Insoluble Fiber:** Does not dissolve in water and adds bulk to stool, promoting regular bowel movements (e.g., whole grains, nuts, vegetables).
- **Sources of Fiber:** Whole grains, fruits, vegetables, legumes, nuts, and seeds.

Table: 1 Key Differences between Simple and Complex Carbohydrates

Aspect	**Simple Carbohydrates**	**Complex Carbohydrates**
Structure	1-2 sugar units (monosaccharides, disaccharides)	Long chains of sugar units (polysaccharides)
Digestion Speed	Quick digestion and absorption	Slower digestion, providing sustained energy
Examples	Glucose, sucrose, lactose	Starches, fiber (e.g., whole grains, legumes)
Sources	Fruits, honey, sugary snacks	Whole grains, beans, vegetables, nuts

1.3. OXIDATION OF GLUCOSE BY GLYCOLYSIS

Glycolysis (glykos- sweet; lysis- splitting) is a sequence of reactions which converts glucose and related hexoses into two molecules of pyruvate with net production of two ATP molecules. It is the most important pathway in energy metabolism, present in both aerobic and anaerobic organisms. The cycle is completed in ten steps with the help of enzymes present in the cytoplasm. None of the reactions are oxygen dependent. In evolutionary terms, it is regarded as a primitive pathway. The primary function of glycolysis is to convert glucose **(**$C_6H_{12}O_6$**)** into pyruvate, generating a small amount of ATP and NADH in the process.

1.3.1 Stages of Glycolysis

Glycolysis consists of 10 enzymatic steps, which can be divided into two main phases:

1.3.1.1 Preparatory Phase (Energy Investment Phase)

1.3.1.2 Payoff Phase (Energy Generation Phase)

1.3.1.3 Splitting Phase

Step-by-Step Breakdown of Glycolysis

1.3.1.1. Preparatory Phase (Steps 1-5) – Energy Investment Phase

In this phase, 2 ATP molecules are consumed to phosphorylate glucose and prepare it for cleavage into two 3-carbon molecules.

Step 1: Phosphorylation of Glucose

- Enzyme: Hexokinase (or glucokinase in the liver)
- Reaction: Glucose → Glucose-6-phosphate (G6P)

- ATP Used: 1 ATP is hydrolyzed to transfer a phosphate group to glucose.
- Significance: This step traps glucose inside the cell, as G6P cannot cross the plasma membrane.

Step 2: Isomerization of Glucose-6-Phosphate

- Enzyme: Phosphoglucose isomerase
- Reaction: Glucose-6-phosphate → Fructose-6-phosphate (F6P)
- Significance: This step converts the aldose sugar (G6P) to a ketose sugar (F6P), preparing it for the next phosphorylation step.

Step 3: Phosphorylation of Fructose-6-Phosphate (Committed Step)

- Enzyme: Phosphofructokinase-1 (PFK-1)
- Reaction: Fructose-6-phosphate → Fructose-1,6-bisphosphate
- ATP Used: 1 ATP
- Significance: This is the rate-limiting and most tightly regulated step of glycolysis. PFK-1 is allosterically activated by AMP and inhibited by ATP and citrate.

Step 4: Cleavage of Fructose-1,6-Bisphosphate

- Enzyme: Aldolase
- Reaction: Fructose-1,6-bisphosphate → Dihydroxyacetone phosphate (DHAP) + Glyceraldehyde-3-phosphate (G3P)
- Significance: This step splits the 6-carbon sugar into two 3-carbon molecules.

Step 5: Isomerization of DHAP

- Enzyme: Triose phosphate isomerase
- Reaction: Dihydroxyacetone phosphate (DHAP) → Glyceraldehyde-3-phosphate (G3P)
- Significance: This ensures that both 3-carbon molecules can proceed through the remaining steps of glycolysis.

By the end of the preparatory phase, 2 ATP have been used, and two molecules of G3P have been formed.

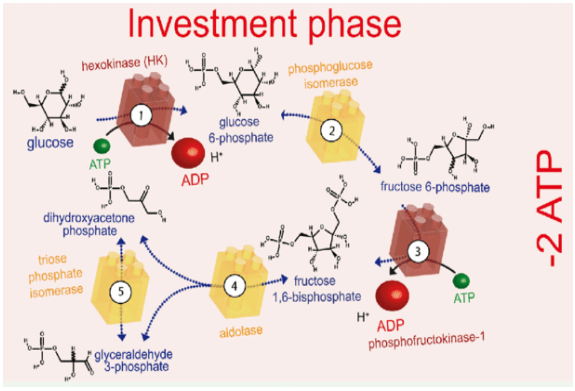

Fig. 1.1

1.3.1.2. Payoff Phase (Steps 6-10) – Energy Generation Phase

This phase generates ATP and NADH through substrate-level phosphorylation and oxidation.

Step 6: Oxidation and Phosphorylation of G3P

- Enzyme: Glyceraldehyde-3-phosphate dehydrogenase (G3PDH)
- Reaction: G3P + NAD^+ + Pi → 1,3-Bisphosphoglycerate + NADH
- Significance: This step generates NADH, which can be used in the electron transport chain under aerobic conditions.

Step 7: Substrate-Level Phosphorylation

- Enzyme: Phosphoglycerate kinase
- Reaction: 1,3-Bisphosphoglycerate + ADP → 3-Phosphoglycerate + ATP
- ATP Produced: 2 ATP (1 ATP per G3P molecule)
- Significance: This is the first step that generates ATP through substrate-level phosphorylation.

Step 8: Isomerization of 3-Phosphoglycerate

- Enzyme: Phosphoglycerate mutase
- Reaction: 3-Phosphoglycerate → 2-Phosphoglycerate
- Significance: This step prepares the molecule for dehydration.

Step 9: Dehydration of 2-Phosphoglycerate

- Enzyme: Enolase
- Reaction: 2-Phosphoglycerate → Phosphoenolpyruvate (PEP) + H_2O
- Significance: PEP is a high-energy intermediate.

Step 10: Substrate-Level Phosphorylation (Final Step)

- Enzyme**:** Pyruvate kinase
- Reaction: Phosphoenolpyruvate (PEP) + ADP → Pyruvate + ATP
- ATP Produced: 2 ATP (1 ATP per PEP molecule)
- Significance: This is the second substrate-level phosphorylation step and produces pyruvate, the end product of glycolysis.

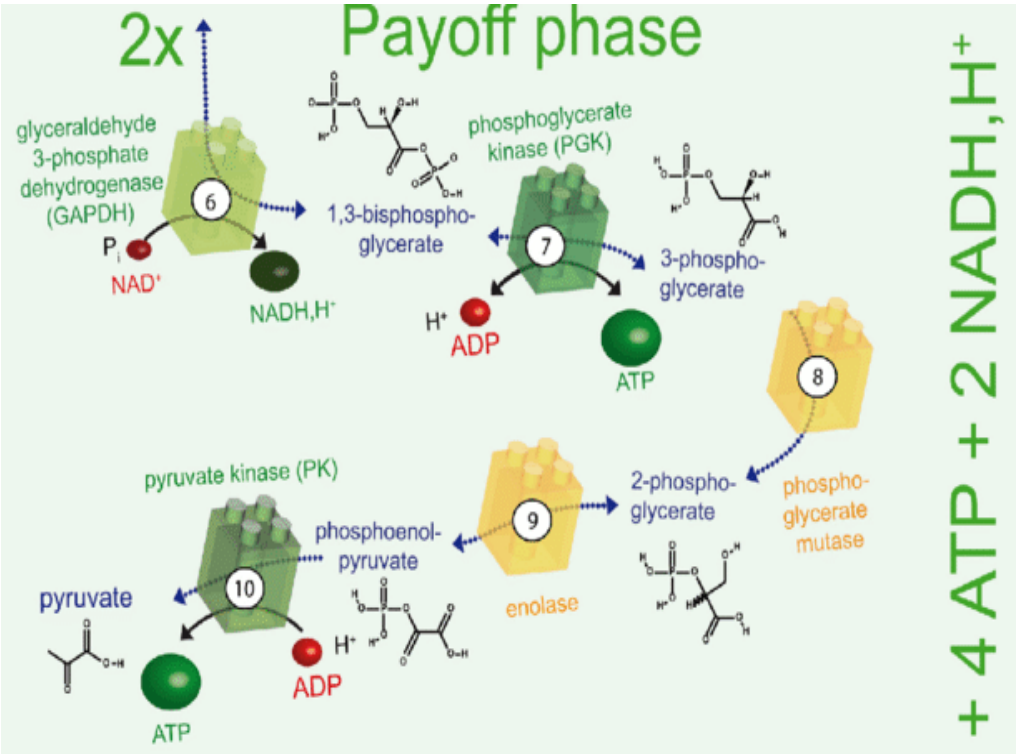

Fig. 1.2

1.3.1.3 Splitting Phase

This phase leads to splitting of high energy 6 carbons intermediate into two 3 carbon products by involving the following reactions:

1) Enzyme aldolase catalyses the splitting of fructose-1,6- bisphosphate (6-C) into glyceraldehyde 3-phosphate (3-C) and dihydroxyacetone phosphate (3-C).
2) The enzyme phosphotrioseisomerase catalyses the interconversion of glyceraldehyde 3-phosphate and dihydroxyacetone phosphate. Thus, two molecules of glyceraldehydes-3-phosphate are produced from one molecule of glucose.

1.4 TCA CYCLE

The citric acid cycle (CAC), also known as the tricarboxylic acid (TCA) cycle or the Kreb cycle – is a series of chemical reactions used by all aerobic organisms to release stored energy through the oxidation of acetyl CoA derived from carbohydrates, fats and proteins into carbon dioxide and chemical energy in the form of Adenosine triphosphate (ATP). In carbohydrate metabolism, acetyl CoA is the connecting link between glycolysis and citric acid cycle, the pyruvate produced by glycolysis is oxidized to yield two-carbon fragments in the form of the acetyl group of acetyl-coenzyme (acetyl-CoA). The cycle consumes acetyl CoA and water, reduces NAD+ to NADH and produces CO2 as a waste product. The NADH generated by citric acid cycle is fed into the oxidative phosphorylation (electron transport) pathway and the large amount of energy released is conserved in the form of ATP. It occurs in the mitochondrial matrix of eukaryotes.

TCA cycle is an amphibolic pathway because it is involved in both anabolic and catabolic processes. Anabolically, the cycle generates precursors for biosynthetic processes.

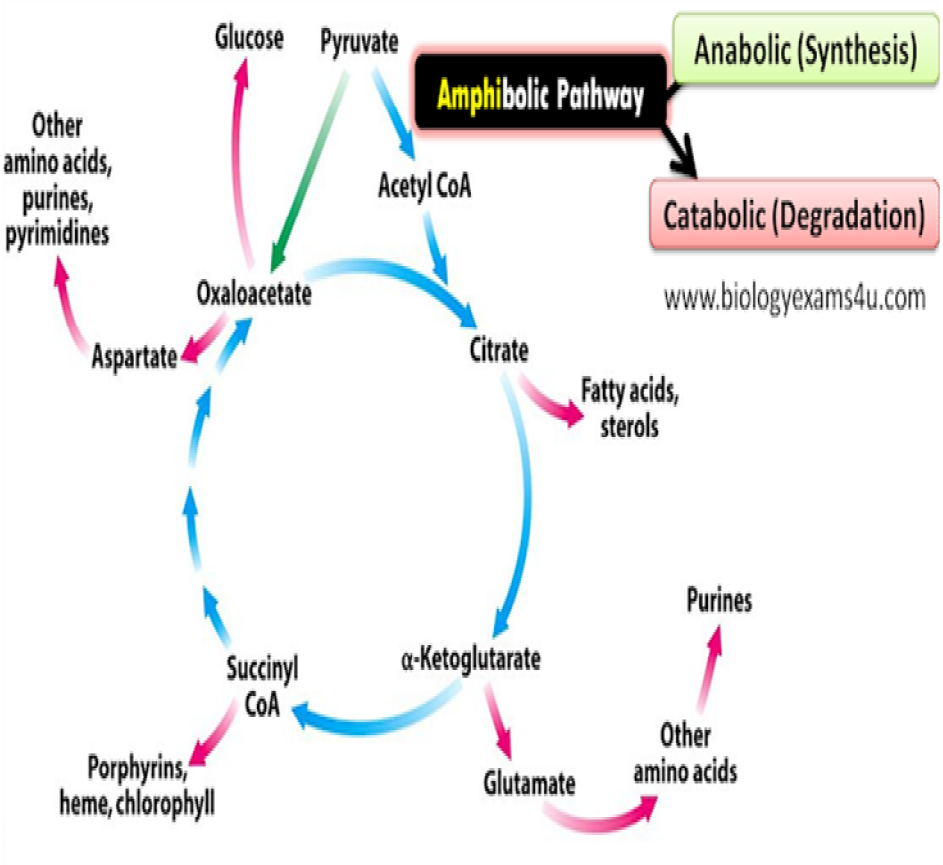

Fig. 1.3

Catabolically, the cycle serves to oxidize the acetyl group. It provides a common pathway for the final oxidation of all metabolic fuels (carbohydrates, fatty acids, amino acids and ketone bodies).

1.4.1 Sources of acetyl CoA

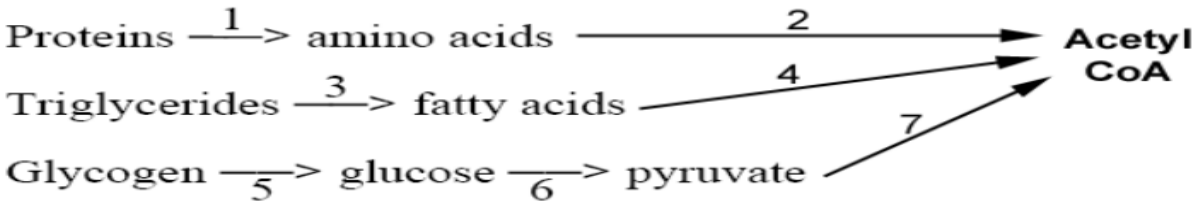

Fig. 1.4

1, proteolysis; 2, amino acid metabolism; 3, lipolysis; 4, β-oxidation; 5, glycogenolysis; 6, glycolysis; 7, oxidative decarboxylation.

Pyruvate arising from glycolysis has several fates. It can be transaminated to alanine, reduced to lactate, carboxylated to oxaloacetate or oxidatively decarboxylated to acetyl CoA.

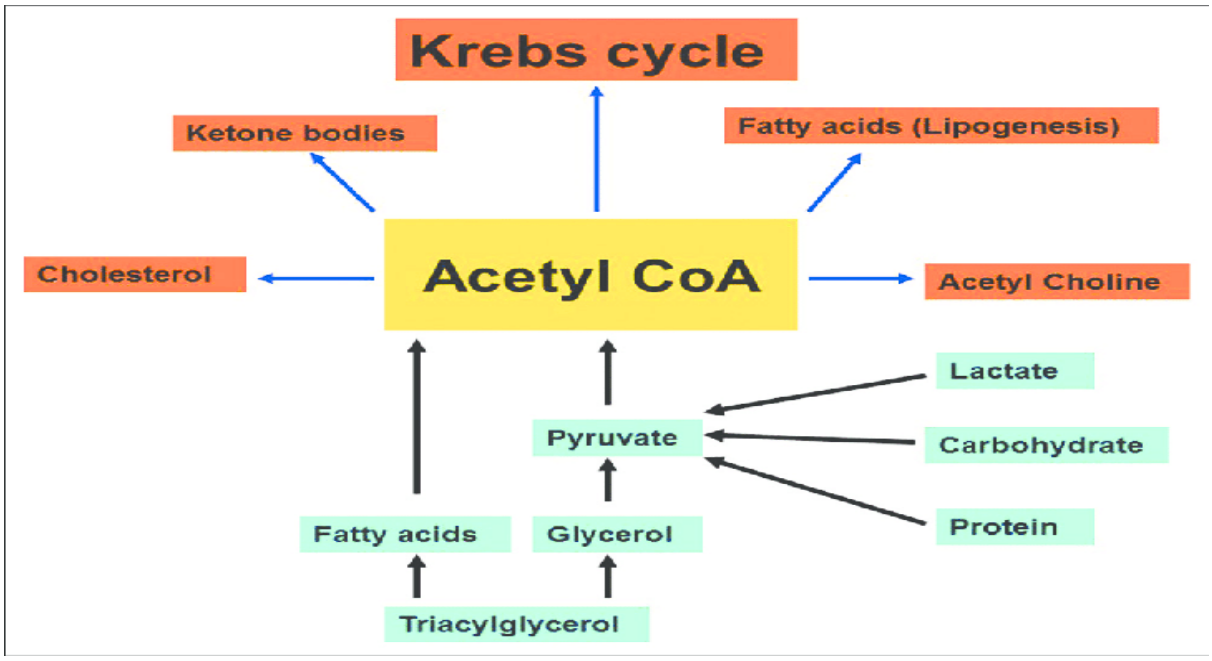

Fig. 1.5

Transamination to alanine requires pyridoxal phosphate; reduction to lactate requires NADH (niacin); conversion to oxaloacetate requires biotin; oxidative decarboxylation to acetyl CoA requires NAD+ (niacin), Coenzyme A (pantothenic acid), FAD (riboflavin), thiamine pyrophosphate, and lipoic acid.

Formation of acetyl CoA from pyruvate is not a component of the TCA cycle. But, this is one of the major routes by which acetyl CoA is generated.

Pyruvate + NAD+ + CoA —> Acetyl CoA + NADH + H+ + CO2 ΔGo = —8 kcal/mol.

Because of the high exergonic nature of this reaction, it is essentially an irreversible reaction. Therefore, the reverse reaction, i.e. the conversion of acetyl CoA to pyruvate, does not occur. Coenzyme A contains the vitamin pantothenic acid as a component. It has a thiol group (- SH) arising from β-mercaptoethylamine.

The enzyme catalyzing the reaction is called pyruvate dehydrogenase, a multienzyme complex. It consists of three different catalytic parts: pyruvate decarboxylase (E1), dihydrolipoyl transacetylase (E2), and dihydrolipoyl dehydrogenase (E3). The multienzyme complex utilizes five different coenzymes: thiamine pyrophosphate, lipoic acid, coenzyme A, FAD and NAD+ (i.e. five vitamins: thiamine, lipoic acid, pantothenic acid, riboflavin and niacin). Coenzyme A and NAD+ are free in solution whereas the other three are bound to proteins. Thiamine pyrophosphate is bound to pyruvate dehydrogenase, lipoic acid to dihydrolipoyl transacetylase, and FAD to dihydrolipoyl dehydrogenase.

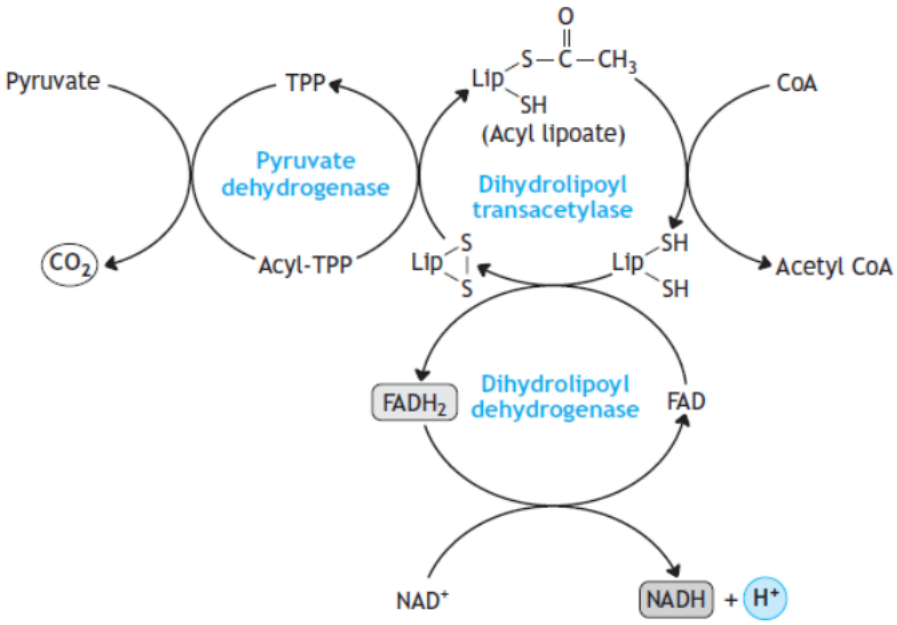

Fig. 1.6

1.4.2 Regulation of Pyruvate Dehydrogenase Complex

Product Inhibition: Acetyl CoA and NADH inhibit the complex

Covalent Modification: The pyruvate decarboxylase (E_1) component of the multienzyme complex consists of two subunits, $E_{1\alpha}$ and $E_{1\beta}$. $E_{1\alpha}$ catalyzes the decarboxylation step and is regulated by covalent modification involving a pyruvate dehydrogenase kinase and pyruvate dehydrogenase phosphatase.

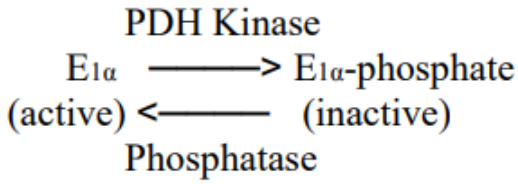

Fig. 1.7

NADH and acetyl CoA, the products of the pyruvate dehydrogenase complex, activate the PDH kinase which converts active $E_{1\alpha}$ to inactive $E_{1\alpha}$-phosphate. The substrates of the 4 pyruvate dehydrogenase complex, namely pyruvate, CoA and NAD+, inhibit the PDH kinase, thereby keeping $E_{1\alpha}$ in the active form. The PDH kinase is cAMP-independent. However, insulin activates the pyruvate dehydrogenase complex in adipose tissue and norepinephrine activates the complex in the heart by mechanisms, which do not involve cAMP. This hormonal regulation involves activation of phosphatase.

Dichloroacetate stimulates pyruvate dehydrogenase (PDH) function by inhibiting PDH kinase, which phosphorylates and inactivates PDH. Hence, in conditions that result in accumulation of lactate (lactic acidosis), dichloroacetate activates PDH, enhances pyruvate oxidation, and facilitates conversion of lactate to pyruvate. Dichloroacetate has been shown to be beneficial in patients with lactic acidosis. This compound however may not be beneficial in genetic diseases involving PDH.

Acetyl CoA formed via the pyruvate dehydrogenase complex reaction can undergo three different routes of metabolism: enter TCA cycle and get oxidized, get converted to ketone bodies (acetoacetate and β-hydroxybutyrate) or enter metabolic pathway leading to synthesis of fatty acid and sterol.

1.4.3 Reactions of the TCA Cycle

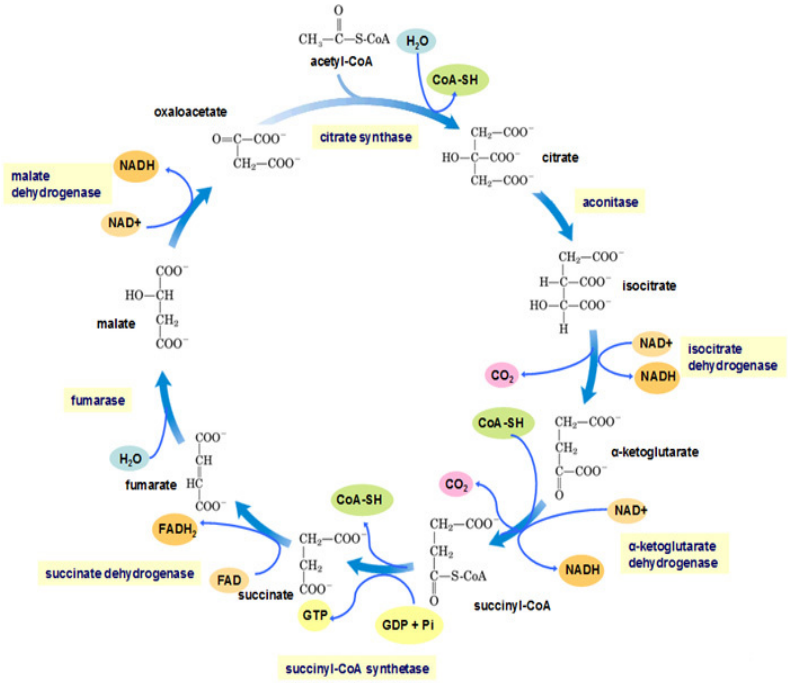

Fig. 1.8

1.4.4 Highlights of the TCA Cycle

Two carbons, in the form of acetyl CoA, are introduced into the cycle at the level of citrate synthase and two carbons are eliminated as two molecules of CO_2, one at the level of isocitrate dehydrogenase and the other at the level of α-ketoglutarate dehydrogenase. The carbon atoms in the eliminated CO_2 are not the carbon atoms introduced into the cycle as acetyl CoA. Oxaloacetate, which initiates the cycle, is regenerated at the end of the cycle.

1.5 HEXOSE MONOPHOSPHATE PATHWAY

The hexose monophosphate pathway (HMP also called the pentose phosphate pathway, or phoshogluconate pathway) consists of Mo irreversible oxidative reactions, followed by a series of reversible sugar phosphate interconversions. This is an alternate oxidative pathway for the metabolism of glucose in the liver, lactating mammary gland and adipose tissue in addition to Embden-Meyerhof pathway for glycolysis.

In this pathway, 3 molecules of ducose-6-phosphate yield 3 molecules of CO, and 3 molecules of five carbon residues (pentose sugar). The latter are converted ultimately to 2 molecules of glucose-6-phosphate and one molecule of glyceraldehyde-3- phosphate. NADP serves as a hydrogen acceptor in this pathway.

Unlike glycolysis or the citric acid cycle in which the direction of the reactions is well defined, the inter conversion reactions of the HMP pathway can function in several different

directions. The rate and direction of the reactions at any given time are determined by the supply of and demand for intermediates in the cycle. The HMP pathway like glycolysis occurs in the cytosol of the cell. However, $C0_2$ which is not F produced in glycolysis, is a characteristic product in HMP pathway. Further, in this pathway no ATP is generated, which you know, is the major product of glycolysis. Again oxidation uses $NADP^+$ unlike NAD' in glycolysis. It would be a useful exercise for you to list the similarities and differences in glycolysis and HMP pathway, later after having gone through the section of HMP pathway here. So let's get moving and get to know the metabolic reactions in the HMP pathway.

1.5.1 Metabolic Reactions in the HMP Pathway

The hexose monophosphate pathway is responsible for the generation of a substantial fraction of the cytoplasmic NADPH required for biosynthetic reactions, and for the generation of ribose-5-phosphate for nucleotide synthesis. Hence, there are the following two phases of HMP pathway: 1) In the oxidation pathway, glucose-6-phosphate is converted to ribulose-5-phosphate by dehydrogenation and decarboxylation reactions. 2) In the nonoxidative phase, ribulose-5-phosphate is converted back to glucose-6- phosphate by a series of reactions involving transketolase and transaldolase. Let us get to know more about these phases. Figure 1.8 illustrates the HMP pathway.

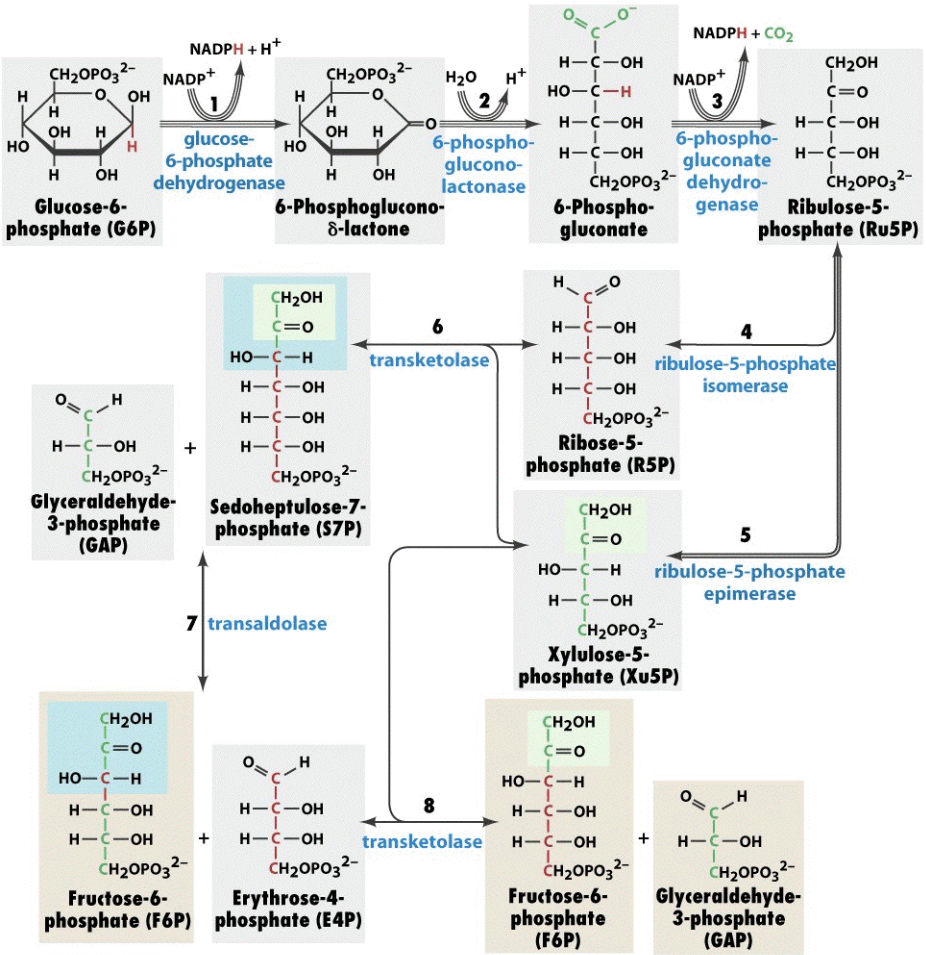

Fig. 1.9

1) The oxidative phase generates NADPH: The oxidative branch of the pathway generates NADPH and pentose-5-phosphate, through the following reactions:

   i) Glucose-6-phosphate is dehydrogenated to 6-phosphogluconate via 6-phosphoglucano-lactone by glucose-6-phosphate dehydrogenase in presence of NADP' and the cofactors Mg", Mn" or Ca++. Glucose-6-phosphate dehydrogenase deficiency is an inherited disease characterized by haemolytic anaemia if the patient is treated with an oxidant drug (such as primaquine and sulphonamide) or ingests fava beans.

   ii) 6-phosphogluconate is oxidized by 6-phosphogluconate dehydrogenase in the presence of coenzyme NADP+ and cofactors Mg", Mn++ or Ca++ to 3-keto 6 phosphogluconate which is decarboxylated to form ribulose-5 phosphate.

2) The non-oxidative phase generates ribose precursors: The non-oxidative phase of the pathway, including the following reactions, converts pentose-5-phosphate to other sugars.

   i) Ribulose-5-phosphate is acted on by ribulose-5-phosphate epimerase, which changes the configuration at carbon 3 forming xylulose-5- phosphate, and also by the enzyme ribose-5-phosphate ketoisomerase, which converts ribulose-5-phosphate to ribose-5-phosphate.

   ii) The next step involves the action of the enzyme transketolase. Transketolase with the help of TDP and Mg++ transfers carbons land 2 of xylulose-5-phosphate to ribose-5-phosphate forming sedoheptulose-7-phosphate and glyceraldehyde-3-phosphate.

   iii) Transketolase with the help of TPP and Mg++ is required again. This time it transfers carbon 1 +2 from xylulose-5-phosphate to erythrose-4-phosphate forming fructose6-phosphate and glyceraldehyde-3-phosphate.

1.5.2 Regulation of HMP Pathway

The following factors play an important role in regulation of HMP pathway:

i) The first reaction of this pathway catalyzed by glucose-6-phosphate dehydrogenase is the "rate limiting" step. This is mainly regulated by the cytoplasmic levels of NADP+ and NADPH.

ii) High carbohydrate content in the diet accelerates the rate of the pathway by activating both the dehydrogenases whereas diabetes mellitus and starvation reverses these reactions.

iii) The HMP shunt is activated by the increase in NADP' in the cytoplasm, which in Carbohydrate Metabolism turn, is due to the oxidation (utilization) of NADPH by the synthesis of fatty acids and steroids.

iv) HMP shunt is accelerated due to the stimulation of dehydrogenases by insulin.

v) Thyroid hormone acts in the same way by stimulating glucose-6-phosphate dehydrogenase.

1.5.3 Metabolic Significance of HMP Pathway

Having gone through the HMP pathway, you would have got some idea about the significance of this alternative oxidative pathway for the metabolism of glucose. Let us enumerate the significance one by one: We have seen that CO_2 is the characteristic product in the HMP pathway, which is not produced in the Embden-Meyerhof pathway. CO_2 produced in this pathway is used for the synthesis of fatty acids and purine bases. The reduced form of NADP (NADPH) is utilized for the synthesis of fatty acids, cholesterol, steroids and also in the synthesis of amino acids via glutamate dehydrogenase outside the mitochondria. In fact tissues specializing in active lipogenesis - liver, adipose tissue and the lactating mammary glands - also posses an active HMP pathway. The pentose sugars produced in HMP shunt are utilized for the synthesis of nucleic acids and nucleotides. Skeletal muscle has low activity of glucose-6-phosphate dehydogenase. Yet, like most other tissues it can synthesize ribose-5-phosphate. This is probably accomplished by a reversal of the shunt pathway utilizing fructose-6-phosphate and glyceraldehyde-3- phosphate and the enzymes transketolase and transaldolase. Both fructose-6-phosphate and glyceraldehyde-3-phosphate are utilized in Embden-Meyerhof pathway for glycolysis. Hence it is not necessary to have a completely functioning HMP pathway for a tissue to synthesize ribose-5-phosphate. The fragility of erythrocytes is impaired in the absence of NADPH generation due to the deficiency of glucose-6-phosphate dehydrogenase thereby causing haemolytic anaemia when the red blood cells are subjected to certain drugs such as primaquine and sulphonamide. An inverse correlation has been found between the activity of glucose6-phosphate dehydrogenase and the fragility of red cells (i.e. susceptibility to haemolysis).

HMP shunt in erythrocytes is of importance due to the generation of NADPH, which maintains the glutathione (G-SH) in the reduced state by glutathione reductase, a flavoprotein containing FAD. Glutathione is a tripeptide (glycine-glutamatk-cysteine), which, in the reduced state takes part in redox reactions in cells. IQ this process, two glutathione molecules combine to give the oxidized form (G-S-S-G). The reduced glutathione then removes H_2O_2 from the erythrocytes by glutathione peroxidase, an enzyme containing selenium as shown in Figure 1.9. This reaction is important because, accuinulation of H_2O_2, may decrease the life-span of erythrocytes by increasing the rate of oxidation of haemoglobin to methaemoglobin. Glutathione peroxidase is a natural antioxidant present in many tissues. Together, with

vitamin E it is part of the body's defense against lipid peroxidation. An association between the incidence of some cancers and low level of blood selenium and glutathione peroxidase activity has been reported.

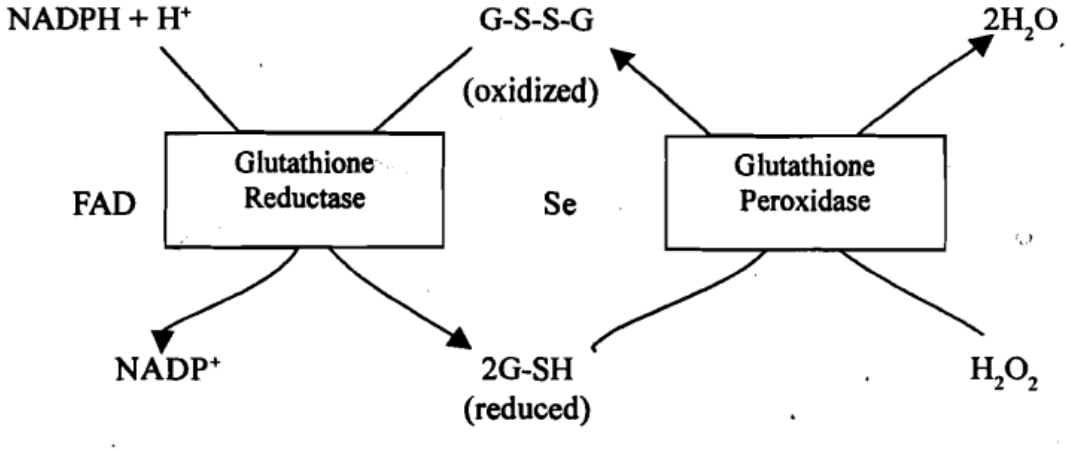

Fig. 1.10: Role of NADPH in erythrocytes

1.6 SUMMARY

Carbohydrate metabolism lies at the heart of cellular physiology: foods rich in carbohydrates are broken down into simple sugars (especially Glucose), which then follow multiple routes depending on the cell's energetic, biosynthetic and redox needs. In the early phase, glucose is converted to pyruvate via the pathway of Glycolysis in the cytosol, generating a modest amount of ATP and NADH and preparing the substrate for further oxidation or other metabolic fates. Pyruvate (and its derivative acetyl-CoA) enter the Tricarboxylic Acid Cycle (TCA cycle) in the mitochondrial matrix, where the fuel is fully oxidized: carbon dioxide is released, and high-energy electron carriers (NADH, $FADH_2$) are produced for oxidative phosphorylation. This completes the energy extraction phase. Parallel to this, the Hexose Monophosphate Pathway (HMP or pentose phosphate pathway) diverts glucose-6-phosphate into producing NADPH (for reductive biosynthesis and antioxidant defence) and ribose-5-phosphate (for nucleotide synthesis). This branch is not about maximal ATP yield, but about meeting biosynthetic & redox requirements. These pathways are tightly regulated and interconnected: depending on whether the cell needs energy, biosynthetic precursors, redox power or storage, metabolic fluxes shift. For example, when energy demand is high, flow through glycolysis + TCA increases; when biosynthetic demand is high (e.g., for fatty acid or nucleotide synthesis), flow through the HMP pathway may predominate. At the whole-organism level, proper carbohydrate metabolism allows for maintenance of blood glucose, storage of excess glucose (as glycogen), and provision of glucose when needed. When regulation fails, disorders of carbohydrate metabolism (such as insulin resistance, diabetes) can follow.

1.7 TECHNICAL TERMS

Glucose, NADH, TCA, glycolysis, Carbohydrates, ATP, HMP.

1.8 SELF ASSESSMENT QUESTIONS

1) In the TCA cycle, the first step is the condensation of acetyl-CoA with a four-carbon molecule. What is that four-carbon molecule called?
2) What are two major uses of NADPH produced by the HMP pathway in cells?
3) In carbohydrate metabolism, which form of glucose is the immediate precursor for glycogen synthesis (activated form)?

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Dr. Jalaja Kumari. Divi

LESSON-2

ELECTRON TRANSPORT CHAIN (ETC), OXIDATIVE PHOSPHORYLATION, HMP PATH WAY

2.0 OBJECTIVES:

After studying this unit, you should be able to:

- Explain the process of electron transport chain that releases free energy, which is used for ATP synthesis and heat production.
- Recognize the reactions of electron transport chain taking place in mitochondria that are coupled to oxidative phosphorylation.
- Explain the mechanism of oxidative phosphorylation.

STRUCTURE:

2.1 INTRODUCTION:

In cellular metabolism, the Electron Transport Chain (ETC), Oxidative Phosphorylation, and the Hexose Monophosphate (HMP) Pathway play crucial roles in energy production, biosynthesis, and cellular maintenance. Together, they ensure that cells can efficiently generate ATP and other essential molecules to support various biochemical processes.

2.2 ELECTRON TRANSPORT CHAIN (ETC):

The Electron Transport Chain (ETC) is a sequence of protein complexes and other molecules found in the inner mitochondrial membrane of eukaryotic cells. The primary

function of the ETC is to transfer electrons from electron donors (NADH and $FADH_2$) to electron acceptors (oxygen), coupled with the pumping of protons (H^+) across the mitochondrial membrane to create a proton gradient, which is used to generate ATP through oxidative phosphorylation.

The ETC is composed of four large protein complexes (Complexes I-IV) and two mobile electron carriers (ubiquinone (CoQ) and cytochrome c), each playing a specific role in the transfer of electrons. The entire process is essential for aerobic respiration, as it generates the proton motive force required to produce ATP.

2.2.1 ELECTRON TRANSPORT CHAIN: ORGANIZATION AND FUNCTION:

The mitochondrial electron transport chain, also known as the respiratory chain, is a vital component of aerobic respiration. It comprises four multi-subunit protein complexes embedded in the inner mitochondrial membrane: NADH-Coenzyme Q reductase (Complex I), Succinate–Coenzyme Q reductase (Complex II), Coenzyme Q-Cytochrome c reductase (Complex III), and Cytochrome c oxidase (Complex IV). The sequential arrangement of these complexes facilitates the orderly transfer of electrons, as illustrated in Figure 1.1.

Electrons derived from reduced coenzymes-NADH and $FADH_2$-are transferred through a series of electron carriers to molecular oxygen (O_2), the final electron acceptor. This electron flow drives the generation of a proton gradient across the inner mitochondrial membrane, which in turn powers ATP synthesis through oxidative phosphorylation. Notably, the electron transport chain is responsible for producing 26 of the 30 ATP molecules generated during the complete oxidation of one glucose molecule to carbon dioxide (CO_2) and water (H_2O).

In this lesion, we will explore the detailed structure and function of each component of the mitochondrial electron transport chain and its critical role in cellular energy production.

The mitochondrial electron transport chain utilizes NADH and $FADH_2$, which are energy-rich molecules generated during key metabolic pathways such as glycolysis, fatty acid oxidation, and the citric acid cycle. These molecules donate high-energy electrons, which are transferred through a series of protein complexes within the inner mitochondrial membrane to molecular oxygen (O_2), the terminal electron acceptor.

As electrons flow through the complexes, protons (H^+) are actively pumped from the mitochondrial matrix into the intermembrane space, creating an electrochemical gradient known as the proton motive force. This gradient stores potential energy, which is harnessed by ATP synthase to drive the endergonic phosphorylation of ADP to ATP, a process referred to as oxidative phosphorylation.

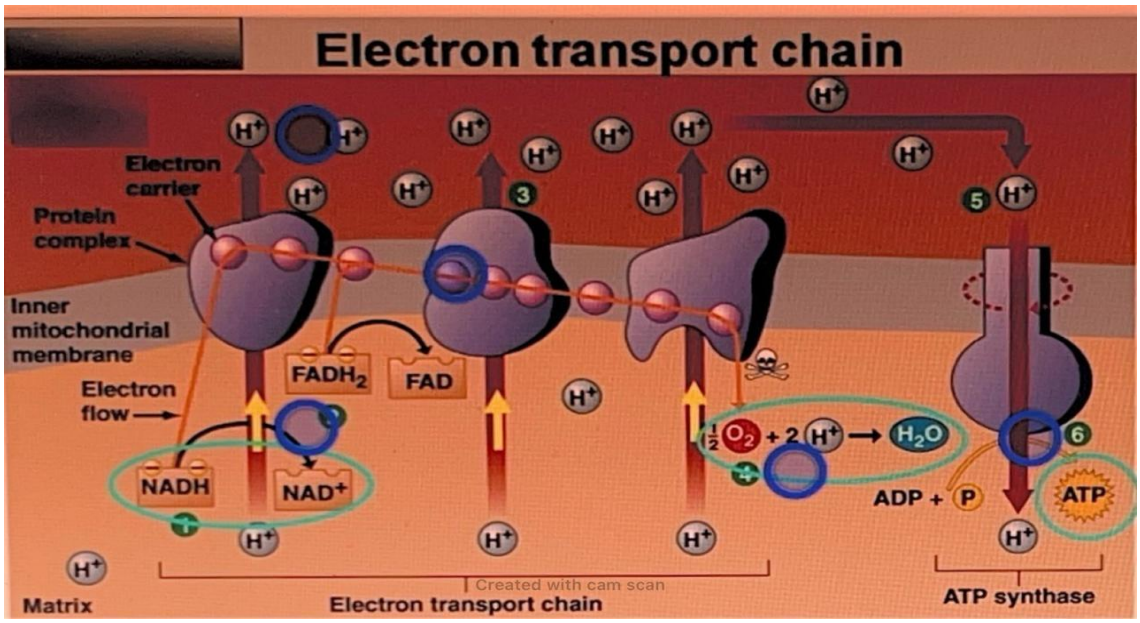


Fig. 2.1: Electron transport complexes of the inner mitochondrial membrane

Interestingly, isolated mitochondria have been shown to carry out electron transport and ATP synthesis under in vitro conditions, further supporting the autonomous and functional integrity of the electron transport system.

The inner mitochondrial membrane can be biochemically resolved into its major electron transport complexes. This resolution can be achieved in the laboratory through a combination of mechanical disruption techniques-such as sonication-and selective solubilization using biological detergents like digitonin. Following solubilization, the individual protein complexes can be separated and purified using methods such as centrifugation and chromatography.

Through such techniques, four major electron transport complexes have been successfully isolated from the inner mitochondrial membrane. These complexes function as multienzyme systems that cooperate to transport electrons from NADH to molecular oxygen (O_2) via a series of redox reactions. Each complex plays a distinct yet coordinated role in maintaining the flow of electrons and facilitating proton translocation across the membrane.

Respiratory Complex I

Complex I, also known as NADH–Coenzyme Q Reductase, is the first complex of the mitochondrial electron transport chain. It plays a critical role in catalyzing the initial step of electron transfer from NADH to coenzyme Q (CoQ), also known as ubiquinone. This large, multi-subunit complex is embedded within the inner mitochondrial membrane and is the largest of all the respiratory complexes.

Structurally, Complex I contains a molecule of flavin mononucleotide (FMN) and six to seven iron-sulfur (Fe–S) clusters, which act as successive electron carriers during the redox reactions.

The transfer of electrons through Complex I occurs in a stepwise manner involving several intermediate oxidation-reduction reactions:

1) NADH donates two electrons to FMN, forming $FMNH_2$.
2) $FMNH_2$ then passes the electrons to the series of Fe–S clusters, becoming oxidized back to FMN in the process.
3) The final electron acceptor in the complex is Coenzyme Q (ubiquinone), which accepts the electrons from the reduced Fe–S proteins and is reduced to ubiquinol ($CoQH_2$).

NADH + H+ + CoQ o NAD+ + CoQH

Importantly, this transfer of two electrons from NADH to CoQ is coupled with the translocation of four protons (H^+) from the mitochondrial matrix into the intermembrane space, contributing to the establishment of the proton motive force (as illustrated in Fig. 1.2).

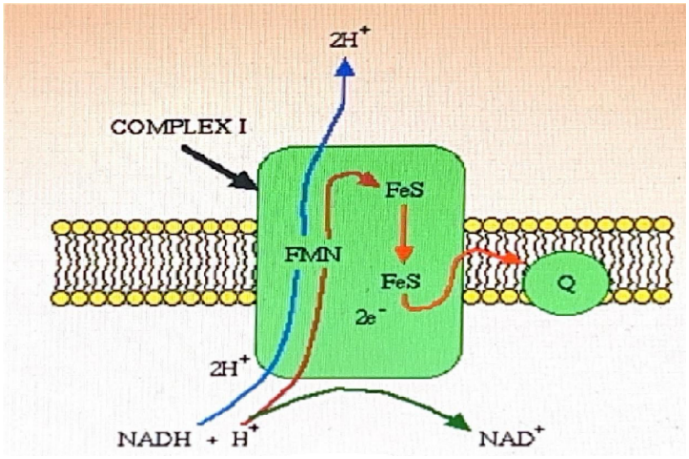


Fig. 2.2: Transfer of electrons from NADH to CoQ.

It is important to note that NADH can only participate in two-electron transfers, whereas both flavin mononucleotide (FMN) and coenzyme Q (CoQ) are capable of accepting and donating either one or two electrons. In contrast, the cytochromes-such as those found in Complex III-can only undergo single-electron (one-electron) redox reactions.

This difference in electron transfer capacity necessitates the involvement of FMN and CoQ as intermediate electron carriers, which effectively bridge the gap between the two-electron donor NADH and the one-electron acceptors (cytochromes). By facilitating stepwise electron transfer, they ensure a smooth and controlled flow of electrons through the mitochondrial electron transport chain.

Additionally, CoQ serves as a mobile electron carrier within the inner mitochondrial membrane. Its long, hydrophobic isoprenoid tail anchors it within the lipid bilayer, allowing it to diffuse freely and shuttle electrons between the respiratory complexes, particularly from Complex I and II to Complex III.

Respiratory Complex II

Complex II, also referred to as Succinate–Coenzyme Q Reductase, is the second of the four membrane-bound complexes of the mitochondrial electron transport chain. Unlike Complex I, it does not participate in proton translocation across the inner mitochondrial membrane.

This complex plays a dual role, as it contains the citric acid cycle enzyme succinate dehydrogenase, which catalyzes the oxidation of succinate to fumarate, and simultaneously transfers the resulting electrons into the electron transport chain. In addition to the dimeric succinate dehydrogenase subunit, Complex II comprises three small hydrophobic subunits embedded in the inner mitochondrial membrane.

The electron transfer pathway within Complex II proceeds as follows:

1) The oxidation of succinate to fumarate is catalyzed by the flavin-containing enzyme succinate dehydrogenase, producing $FADH_2$.
2) The covalently bound FAD (flavin adenine dinucleotide) receives electrons from succinate and becomes reduced to $FADH_2$.
3) Electrons are then transferred from $FADH_2$ to three iron-sulfur (Fe–S) clusters.
4) From the Fe–S clusters, electrons are passed to coenzyme Q (ubiquinone), reducing it to $CoQH_2$ (ubiquinol).

Complex II also contains a cytochrome b_{560} subunit, though it's exact role in electron transfer remains less clearly defined compared to the other components.

Importantly, Complex II does not contribute to the proton gradient, as it does not pump protons across the mitochondrial membrane. Nevertheless, it plays a vital role in linking the citric acid cycle with the electron transport chain and provides an alternative pathway for electron entry via $FADH_2$.

Succinate + CoQ o Fumerate + $CoQH_2$

Respiratory Complex III

Complex III, also known as Coenzyme Q–Cytochrome c Reductase, is the third integral component of the mitochondrial electron transport chain. Located within the inner mitochondrial membrane, this complex facilitates the transfer of electrons from reduced coenzyme Q ($CoQH_2$) to cytochrome c through a multi-step redox process.

Complex III comprises the following key components:

- Two cytochrome b molecules,
- One cytochrome c_1,
- One iron–sulfur (Fe–S) cluster protein, often referred to as the Rieske protein.

Structure and Function of Cytochromes

Cytochromes are redox-active proteins that contain heme prosthetic groups, enabling them to alternate between the ferrous (Fe^{2+}) and ferric (Fe^{3+}) states during electron transfer. This reversible redox cycling is critical for the passage of electrons along the respiratory chain.

The reduced form of cytochromes (Fe^{2+}) exhibits a distinctive absorption spectrum, with three prominent peaks known as D, E, and J (Soret bands). Notably, the D-peak varies among cytochrome types and serves as a distinguishing feature. This peak is absent in the oxidized (Fe^{3+}) state.

In mitochondrial membranes, three main classes of cytochromes are present:

- Cytochrome a
- Cytochrome b
- Cytochrome c

Each class may exhibit structural subtypes due to variations in the heme environment, contributing to functional diversity.

Organization and Electron Flow in Complex III

Complex III is asymmetrically embedded within the inner mitochondrial membrane:

- The cytochrome c_1 and the Rieske Fe–S protein are oriented toward the intermembrane space (outer surface),
- While cytochrome b spans the membrane and facilitates electron flow across it.

The mobile electron carrier, cytochrome c, is a small, peripheral membrane protein loosely associated with the outer surface of the inner mitochondrial membrane. It plays a critical role in shuttling electrons between Complex III (cytochrome c_1) and Complex IV (cytochrome c oxidase), by reversibly binding to each.

The net chemical reaction catalyzed by Complex III is as follows:

$$CoQH2 + 2\ Cyt\ c\ [Fe\ (III)] \text{ o } CoQ + 2Cyt\ c\ [Fe\ (II)] + 2H+$$

This reaction contributes to the proton gradient by releasing protons into the intermembrane space, further driving ATP synthesis via oxidative phosphorylation.

Respiratory Complex IV

Complex IV, also known as cytochrome c oxidase, is the terminal complex of the mitochondrial electron transport chain. It catalyzes the final step in the electron transport process, coupling the oxidation of reduced cytochrome c with the reduction of molecular oxygen (O_2) to water.

Function and Reaction Mechanism

This complex facilitates a multi-electron redox reaction, where four molecules of reduced cytochrome c each donate one electron, resulting in the four-electron reduction of one molecule of O_2 to form two molecules of H_2O:

$$\mathbf{4Cyt\ c\ [Fe\ (II)] + 4H+ + O2 \text{ o } 4Cyt\ c\ [Fe\ (III)] + 2H2O}$$

This step is highly exergonic, releasing significant free energy, which is harnessed by the complex to pump protons across the inner mitochondrial membrane. Specifically, for every molecule of O_2 reduced, four protons are translocated from the mitochondrial matrix to the intermembrane space, contributing further to the proton motive force essential for ATP synthesis.

Structural Components: Complex IV consists of multiple subunits, with the core catalytic activity being carried out by:

- Cytochromes a and a_3
- Copper centers (Cu_A and Cu_B)

The heme a_3–Cu_B center is the site of O_2 binding and reduction, whereas the Cu_A center acts as the initial electron acceptor from cytochrome c. Electrons are passed from cytochrome c → Cu_A → heme a → heme a_3–Cu_B, where O_2 is reduced.

Process	**Direct product**	**Final ATP**
Glycolysis	2NADH (cytosolic) 2 ATP	3 or 5* 2
Pyruvate oxidation (two per glucose)	2NADH (Mitochondrial matrix)	5
Acetyl – coA citric acid cycle (two per glucose)	6 NADH (Mitochondrial matrix) 2FADH2 2 ATP OR 2 GTP	15 3 2
Total yield per glucose		30 or 32

Biological Significance

The activity of Complex IV is crucial, not only for the completion of the respiratory chain but also for the regulation of cellular respiration. Since it consumes molecular oxygen, it also plays a central role in aerobic metabolism and is sensitive to changes in oxygen availability.

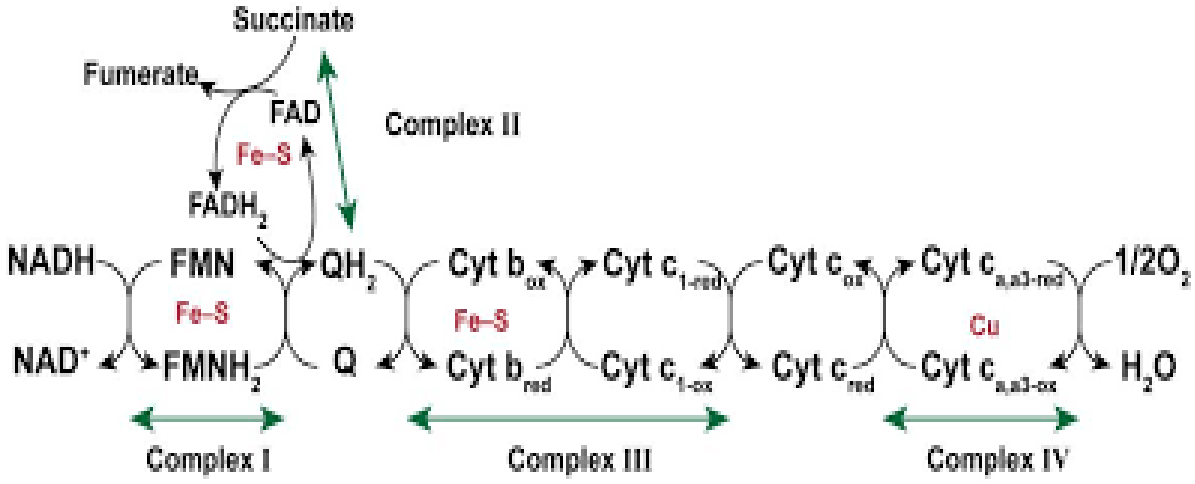


Fig. 2.3: Flow of reducing equivalents through respiratory complexes (electron transport chain) of mitochondria.

2.3 OXIDATIVE PHOSPHORYLATION:

Oxidative phosphorylation is the primary mechanism by which aerobic cells generate ATP, accounting for the majority of ATP produced during cellular respiration. The complete oxidation of one glucose molecule to carbon dioxide (CO_2) via glycolysis, the citric acid cycle, and oxidative phosphorylation yields approximately 30 to 32 molecules of ATP. In stark contrast, anaerobic glycolysis (e.g., lactate fermentation) yields only 2 ATP molecules per glucose, highlighting the evolutionary advantage and energetic efficiency provided by oxidative phosphorylation.

A particularly striking example of this efficiency is seen in the complete oxidation of palmitoyl-CoA, a derivative of the saturated fatty acid palmitate (16:0). This process, which occurs entirely in the mitochondrial matrix, yields approximately 108 ATP molecules per molecule of palmitoyl-CoA. Similar ATP yield estimates can be made for the oxidative degradation of individual amino acids.

These aerobic oxidative pathways channel high-energy electrons to molecular oxygen (O_2), the terminal electron acceptor, and couple this electron transfer with ATP synthesis through oxidative phosphorylation. Given the central role of these pathways in energy metabolism, the tight regulation of oxidative phosphorylation is essential to ensure that ATP production is matched to the cell's fluctuating energy demands.

TABLE 2.1 ATP Yield from Complete Oxidation of Glucose

*The number depends upon which shuttle system transfers reducing in equivalent

2.3.1 OXIDATIVE PHOSPHORYLATION

The efficiency of oxidative phosphorylation can be assessed by determining the percentage of total energy released during the oxidation of a substrate that is conserved in the form of ATP. This efficiency is commonly expressed using the P/O ratio, which is defined as the number of molecules of ATP synthesized per pair of electrons transferred through the mitochondrial electron transport chain (ETC).

In laboratory settings, ATP synthesis is typically estimated by measuring the incorporation of inorganic phosphate (Pi) into ATP, while the number of electron pairs transferred is inferred from the amount of O_2 consumed, which is ultimately reduced to water (H_2O). However, P/O ratio measurements are inherently prone to experimental errors, making precise values difficult to obtain.

Traditionally, the widely accepted P/O ratios have been:

- 3 ATP per NADH (electrons entering at Complex I)
- 2 ATP per $FADH_2$ (electrons entering at Complex II)

However, more recent and precise measurements suggest that these values may be somewhat overestimated. Current evidence points to:

- Approximately 2.5 ATP per NADH
- Approximately 1.5 ATP per $FADH_2$

These non-integer P/O values have important implications:

i) They reflect the complex and indirect nature of the coupling between electron transport and ATP synthesis, which does not require an exact stoichiometric relationship.

ii) They imply that oxidation and phosphorylation are not directly coupled on a one-to-one basis but are mediated by intermediate proton gradients and membrane-associated mechanisms.

Based on these updated P/O ratios, we can now recalculate the total number of ATP molecules synthesized from the complete oxidation of one molecule of glucose, considering both:

- Glycolysis
- Pyruvate oxidation
- The citric acid cyle
- Oxidative phosphorylation

Glycolysis :	Glucose + 2ADP + $2P_1$+ $2NAD^+$ → Pyruvate + 2ATP + 2NADH + $2H_2O$ + $4H^+$
Pyruvate dehydrogenase complex	2 Pyruvate + $2NAD^+$ + 2CoA-SH → 2 Acetyl-CoA + 2NADH + $2CO_2$
Citric acid cycle (including conversation of GTP into ATP) :	2 Acetyl-CoA + $6H_2O$ + $6NAD^+$ + 2FAD + 2ADP+$2P_1$ → $4CO_2$ + 6NADH + $2FADH_2$ + 2CoA-SH + 2ATP
NET :	Glucose + $10NAD^+$ + 2FAD + $4H_2O$ + 4ADP +$4P_1$ → $6CO_2$ + 10NADH +$4H^+$ + $2FADH_2$ + 4ATP

The total number of ATPs synthesized per molecule of glucose oxidized will be:

2½ ATP/NADH for 10 NADH/glucose +1% ATP/FADH, for 2 FADH./glucose + 4 ATP/glucose. i.e., 2% X 10+12X2+4= 25+3+4=32

The rate of mitochondrial respiration, as measured by oxygen (O_2) consumption, is subject to tight regulation, primarily governed by the availability of ADP, which serves as a substrate for ATP synthesis during oxidative phosphorylation. This phenomenon is known as acceptor control of respiration.

In this context, ADP functions as the phosphate acceptor, and the rate of electron transport through the respiratory chain is closely tied to its availability. The acceptor control ratio, defined as the ratio of maximal ADP-stimulated O_2 consumption to the basal rate in the

absence of ADP, can reach values of ten or higher in some animal tissues, underscoring the magnitude of this regulatory mechanism.

The intracellular concentration of ADP serves as a key indicator of the cell's energy status. A related and more precise measure is the mass-action ratio of the ATP–ADP system:

$$\frac{[ATP]}{[ADP][Pi]}$$

Under normal physiological conditions, this ratio is very high, indicating that the system remains largely in a phosphorylated (ATP-rich) state.

However, during periods of increased energy demand, such as elevated protein synthesis or muscle contraction, ATP hydrolysis accelerates, generating more ADP and inorganic phosphate (P_i). This reduces the mass-action ratio, thereby stimulating oxidative phosphorylation by providing more substrate (ADP) for ATP synthesis. As ATP is regenerated, the system gradually restores its high mass-action ratio, leading to a decrease in respiration rate once cellular ATP demands are met.

This feedback regulation ensures that ATP production is tightly coupled to its utilization, allowing minimal fluctuation in cellular [ATP]/([ADP][P_i]) ratio—even during extreme variations in energy expenditure. Thus, oxidative phosphorylation operates with remarkable sensitivity and precision, producing ATP only as rapidly as it is consumed.

2.4 THE HEXOSE MONOPHOSPHATE PATHWAY (HMP)

The Hexose Monophosphate Pathway (HMP)—also known as the Pentose Phosphate Pathway or Phosphogluconate Pathway—is an alternative oxidative route for glucose metabolism. It consists of two phases: an initial series of irreversible oxidative reactions, followed by reversible interconversions of sugar phosphates. This pathway operates in parallel with the Embden-Meyerhof pathway (glycolysis) and is especially active in the liver, lactating mammary glands, and adipose tissue.

In this pathway, three molecules of glucose-6-phosphate yield three molecules of carbon dioxide (CO_2) and three molecules of five-carbon sugars (pentose phosphates). These pentose sugars are ultimately converted into two molecules of glucose-6-phosphate and one molecule of glyceraldehyde-3-phosphate through a series of reversible reactions. $NADP^+$ acts as a hydrogen (electron) acceptor in the oxidative phase of the pathway, becoming reduced to NADPH, which is crucial for biosynthetic reactions and maintaining redox balance.

Unlike glycolysis or the citric acid cycle, where the direction of reactions is clearly defined, the interconversion reactions of the HMP pathway can proceed in multiple directions. The rate and direction of these reactions at any given time depend on the cell's supply and demand for metabolic intermediates.

The HMP pathway, like glycolysis, occurs in the cytosol of the cell. However, there are important differences. For example, carbon dioxide (CO_2)-not produced in glycolysis-is a characteristic product of the oxidative phase of the HMP pathway. Additionally, no ATP is

generated in this pathway, in contrast to glycolysis, where ATP is the primary product. Another key distinction is in the electron acceptors: the HMP pathway uses $NADP^+$ (reduced to NADPH), whereas glycolysis uses NAD^+ (reduced to NADH).

It would be a useful exercise for you to list the similarities and differences between glycolysis and the HMP pathway once you've reviewed the details of this metabolic route. So let's keep going and dive into the metabolic reactions of the HMP pathway.

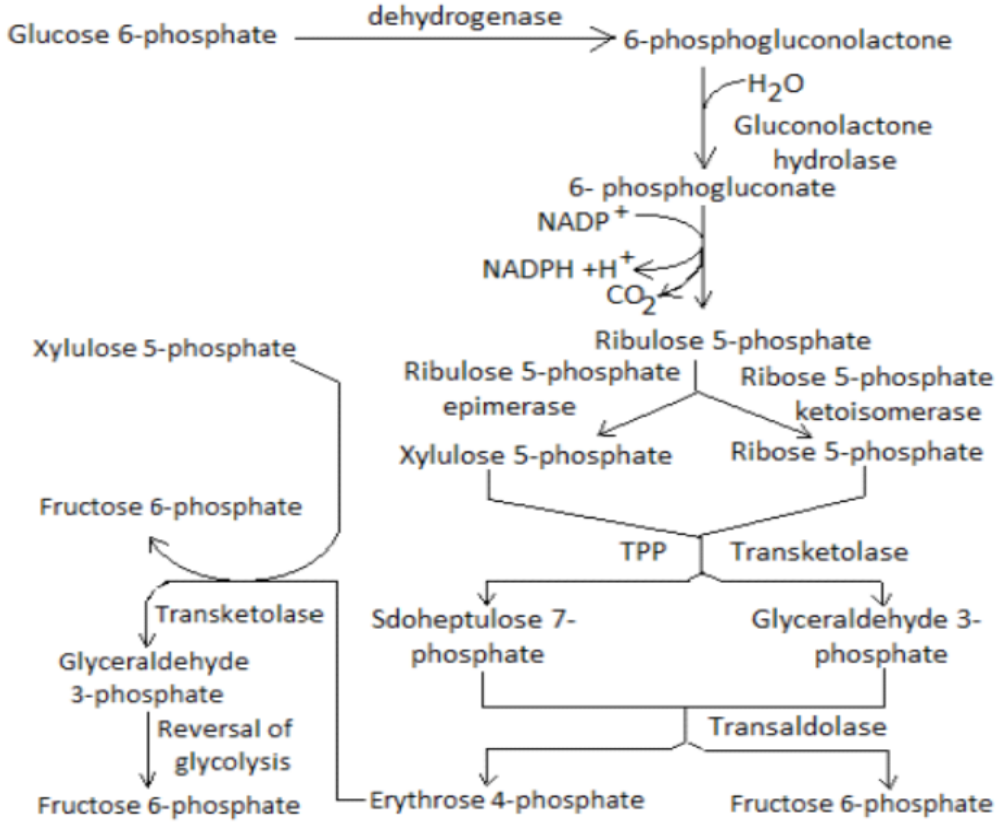
2.4.1 METABOLIC REACTIONS IN THE HMP PATHWAY

The Hexose Monophosphate Pathway (HMP) plays a crucial role in cellular metabolism by generating a significant portion of cytoplasmic NADPH, which is essential for biosynthetic (anabolic) reactions, such as fatty acid and steroid synthesis. It also produces ribose-5-phosphate, a key precursor for nucleotide and nucleic acid synthesis.

The HMP pathway is divided into two main phases:

1) Oxidative Phase: In this phase, glucose-6-phosphate is converted to ribulose-5-phosphate through a series of dehydrogenation and decarboxylation reactions, with the concurrent production of NADPH and CO_2.
2) Non-Oxidative Phase: In this phase, ribulose-5-phosphate undergoes a series of reversible reactions catalyzed by the enzymes transketolase and transaldolase, ultimately leading to the regeneration of glucose-6-phosphate and the production of glyceraldehyde-3-phosphate and fructose-6-phosphate, which can re-enter glycolysis.

Let us get to know more about these phases. Figure 2.4 Illustrates the HMP pathway.



2.4.1.1 The Oxidative Phase Generates NADPH

The oxidative branch of the Hexose Monophosphate Pathway generates NADPH and pentose-5-phosphate through a series of enzyme-catalyzed reactions. The first step is as follows:

i) Glucose-6-phosphate Dehydrogenation: Glucose-6-phosphate is dehydrogenated to 6-phosphogluconate via an intermediate, 6-phosphoglucono-δ-lactone, in a reaction catalyzed by the enzyme glucose-6-phosphate dehydrogenase (G6PD). This step requires $NADP^+$ as an electron acceptor and also depends on divalent metal cofactors such as Mg^{2+}, Mn^{2+}, or Ca^{2+}.

Glucose-6-phosphate + $NADP^+$ → 6-Phosphoglucono-δ-lactone + NADPH + H^+

This enzyme-catalyzed step is rate-limiting and highly regulated, making it the key control point of the oxidative phase.

ii) Oxidation and Decarboxylation of 6-Phosphogluconate**:** In the second major reaction of the oxidative phase, 6-phosphogluconate is oxidized by the enzyme 6-phosphogluconate dehydrogenase in the presence of the coenzyme $NADP^+$ and divalent metal ion cofactors such as Mg^{2+}**,** Mn^{2+}**,** or Ca^{2+}**.**

This reaction proceeds through the formation of an unstable intermediate, 3-keto-6-phosphogluconate, which is then decarboxylated to produce ribulose-5-phosphate and CO_2, with the concurrent reduction of $NADP^+$ to NADPH.

6-Phosphogluconate + $NADP^+$ → Ribulose-5-phosphate + CO_2 + NADPH

2.4.1.2 The Non-Oxidative Phase Generates Ribose Precursors

The non-oxidative phase of the Hexose Monophosphate Pathway involves a series of reversible reactions that convert pentose-5-phosphate into a variety of sugar phosphates. These reactions allow the cell to recycle excess pentoses or supply ribose-5-phosphate as needed for nucleotide and nucleic acid synthesis.

<u>i) Isomerization and Epimerization of Ribulose-5-Phosphate</u>

- Ribulose-5-phosphate can undergo epimerization at carbon 3, catalyzed by the enzyme ribulose-5-phosphate epimerase, to form xylulose-5-phosphate.
- It can also be converted by ribose-5-phosphate isomerase (also called ketoisomerase) into ribose-5-phosphate, a direct precursor for nucleotide biosynthesis.

These two reactions provide a mixture of ribose-5-phosphate and xylulose-5-phosphate, setting the stage for carbon rearrangements in the next steps.

<u>ii) Carbon Rearrangement by Transketolase</u>

The enzyme transketolase, which requires the cofactor thiamine diphosphate (TDP) and Mg^{2+}, catalyzes the transfer of a two-carbon unit (carbons 1 and 2) from xylulose-5-phosphate to ribose-5-phosphate**.**

2.4.2 REGULATION OF THE HEXOSE MONOPHOSPHATE (HMP) PATHWAY

Several factors influence the regulation of the HMP pathway:

1) Rate-Limiting Step: The first reaction of the HMP pathway, catalyzed by glucose-6-phosphate dehydrogenase (G6PD), is considered the rate-limiting step. This enzyme is primarily regulated by the cytoplasmic concentrations of $NADP^+$ and NADPH. High levels of $NADP^+$ stimulate the enzyme's activity, while elevated levels of NADPH inhibit it through feedback inhibition.
2) Dietary Influence: A high-carbohydrate diet increases the flux through the HMP pathway by enhancing the activity of both glucose-6-phosphate dehydrogenase and 6-phosphogluconate dehydrogenase. In contrast, conditions such as diabetes mellitus and starvation suppress these reactions, thereby reducing the activity of the pathway.
3) $NADP^+$ Availability: The HMP shunt is activated by an increase in $NADP^+$ levels in the cytoplasm. In the context of carbohydrate metabolism, this rise in $NADP^+$ is often a result of NADPH consumption, particularly during the biosynthesis of fatty acids and steroids, which utilize NADPH as a reducing agent.
4) Hormonal Regulation – Insulin: The activity of the HMP shunt is further enhanced by insulin, which stimulates the key dehydrogenase enzymes of the pathway, thereby promoting glucose utilization and biosynthetic processes in the fed state.
5) Thyroid Hormone Influence: Similarly, thyroid hormones upregulate the expression and activity of glucose-6-phosphate dehydrogenase, contributing to an increased flux through the HMP pathway.

2.4 SUMMARY

The Electron Transport Chain (ETC) and oxidative phosphorylation represent the final and most energy-efficient stage of aerobic respiration, where the majority of cellular ATP is synthesized through the transfer of electrons and the establishment of a proton gradient across the mitochondrial membrane. This tightly regulated process underscores the vital role of mitochondria as the cell's powerhouse.

In contrast, the Hexose Monophosphate (HMP) pathway, or pentose phosphate pathway, operates primarily in the cytoplasm to fulfill biosynthetic and antioxidant roles rather than energy production. It generates NADPH, essential for reductive biosynthesis and cellular defense against oxidative stress, and provides ribose-5-phosphate for nucleotide and nucleic acid synthesis.

Together, these pathways highlight the cell's remarkable metabolic versatility—while the ETC and oxidative phosphorylation optimize energy yield under aerobic conditions, the HMP pathway ensures cellular integrity and anabolic capacity. Understanding the integration of these processes is key to appreciating how cells balance energy needs with biosynthetic demand.

2.5 TECHNICAL TERMS

Electron transport chain, HMP, Electron Transport Chain, ATP and NADPH.

2.6 SELF ASSESSMENT QUESTIONS

1) With the help of reaction briefly explain the oxidative phase of the pentose phosphate pathway?
2) What is HMP pathway? Give any two points of its significance?
3) List the components of electron transport chain?

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Dr. Jalaja Kumari. Divi

LESSON-3

GLYCOGENESIS, GLYCOGENOLYSIS AND GLUCONEOGENESIS. GLYCOGEN STORAGE IN NORMAL AND DISEASED STATES

3.0 OBJECTIVES:

After studying this unit, you should be able to:

- Describe the steps of glycogenesis;
- Explain glycogenolysis and conversion of glucose 1-phosphate to glucose 6-phosphate;
- Give an overview of gluconeogenesis pathway;
- Glycogen storage in normal and diseased states

STRUCTURE:

3.1 INTRODUCTION

Glycogenesis is the biochemical process by which glucose is converted into glycogen for storage in the liver and muscle cells. It's an anabolic (building) pathway and plays a key role in maintaining blood glucose levels.

3.2 GLYCOGENESIS

Glycogenesis is the biochemical process through which glycogen is synthesized from glucose. While this process occurs in nearly all animal tissues, the liver and skeletal muscles are the primary sites.

The first step in glycogenesis is the formation of an activated glucose donor, UDP-glucose, which is synthesized from glucose 1-phosphate and UTP by the enzyme UDP-glucose pyrophosphorylase. Excess glucose entering liver and muscle cells is initially phosphorylated to glucose 6-phosphate. This is catalyzed by:

- Glucokinase in the liver
- Hexokinase in muscles

Glucose 6-phosphate is then converted to glucose 1-phosphate by the enzyme phosphoglucomutase (PGM). In the liver, gluconeogenesis can also supply glucose 6-phosphate directly, which can then enter the glycogenic pathway (Fig: 3.1).

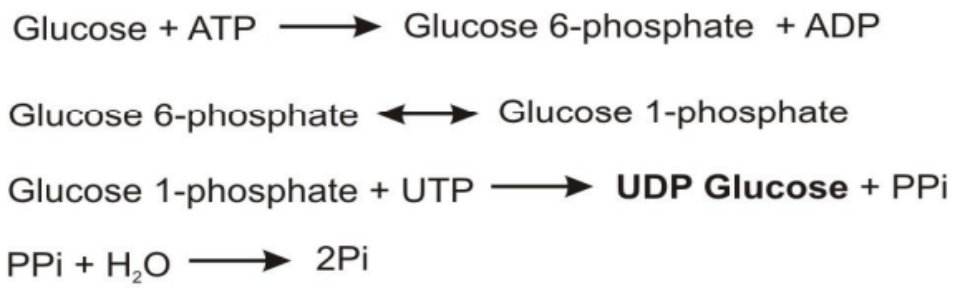


Fig. 3.1: Synthesis of UDP-glucose from glucose.

The reaction catalyzed by UDP-glucose pyrophosphorylase proceeds in the direction of UDP-glucose synthesis, driven by the hydrolysis of the by-product pyrophosphate (PPi). This hydrolysis is facilitated by a ubiquitous inorganic pyrophosphatase, which ensures the reaction remains irreversible. Similar mechanisms involving PPi hydrolysis also drive the biosynthesis of polymers like DNA and RNA in one direction.

The enzyme glycogen synthase, responsible for the elongation of glycogen chains, cannot initiate glycogen synthesis on its own—it requires a pre-existing primer.

This initiation is carried out by a specialized protein called glycogenin. Glycogenin acts both as a primer and an enzyme (glucosyl transferase). It catalyzes the sequential addition of eight glucose residues from UDP-glucose to itself. The first glucose molecule is covalently attached to a specific tyrosine residue on glycogenin.

Once this short primer chain is formed, glycogen synthase takes over to elongate the glycogen molecule by adding more glucose units via α-1,4-glycosidic bonds. Throughout this process, glycogenin remains bound to the single reducing end of the glycogen molecule.

3.2.1 GLYCOGEN SYNTHASE

Glycogen synthase catalyzes the transfer of glucose residues from UDP-glucose to the non-reducing end of the growing glycogen chain. It specifically forms α-1,4 glycosidic bonds, which are responsible for the linear structure of glycogen (Fig: 3.2).

However, glycogen synthase cannot introduce α-1, 6 linkages—the bonds required to create branch points in the glycogen molecule. The formation of these branch points is carried out by a separate enzyme known as the branching enzyme.

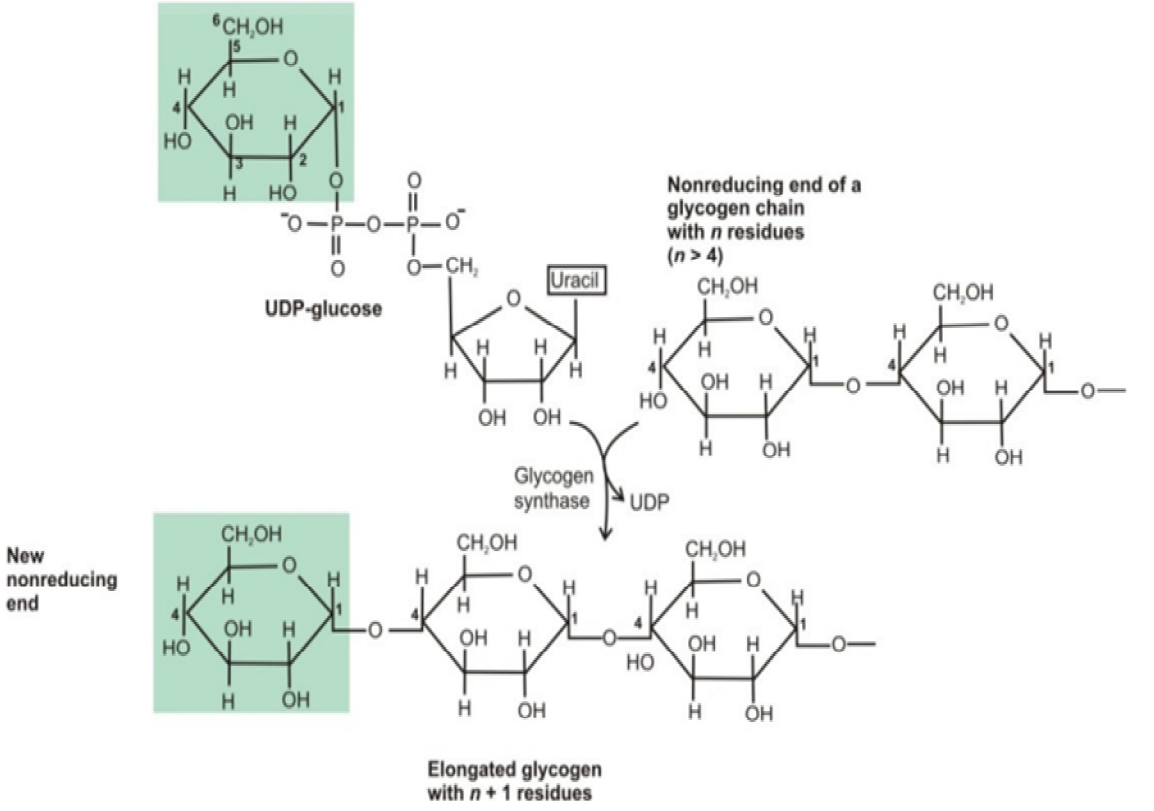


Fig. 3.2: Chain elongation by glycogen synthase.

The final stage of glycogenesis involves converting the linear glycogen chain into a branched polymer. This is catalyzed by the branching enzyme, also known as amylo-(1→4) to (1→6) transglycosylase or glycosyl-(4→6) transferase.

This enzyme functions by transferring a terminal segment of about 5 to 8 glucose residues from the non-reducing end of a glycogen chain that contains at least 11 glucose units. The transferred segment is then attached to the C-6 hydroxyl group of a glucose residue, either within the same chain or a nearby chain, forming an α-1,6 glycosidic bond. Fig. 3.3 gives overview of the complete glycogenesis pathway.

This branching increases the solubility of glycogen and creates multiple non-reducing ends, allowing rapid mobilization of glucose when needed.

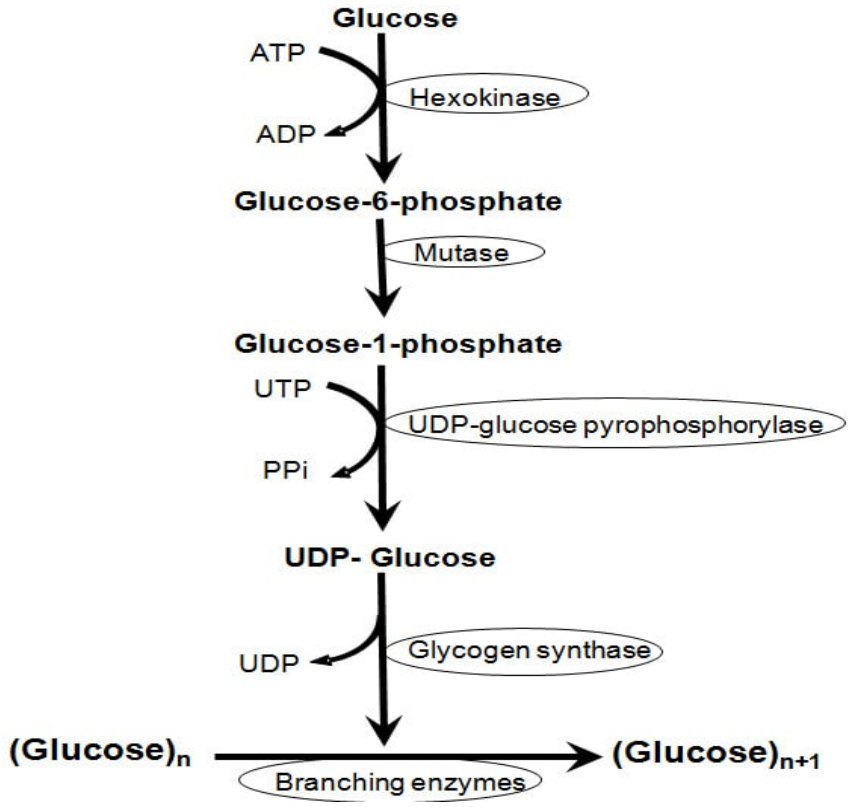


Fig. 3.3: overview of the complete glycogenesis pathway.

3.2.1.1 Overall Reaction of Glycogenesis:

(Glucose)n + Glucose + 2 ATP (Glucose)n+1 + 2ADP + 2 Pi

For each glucose molecule added to the growing glycogen chain, two molecules of ATP are consumed:

1) One ATP is used in the phosphorylation of glucose to form glucose 6-phosphate (by hexokinase or glucokinase).
2) Another ATP equivalent is used in the regeneration of UTP from UDP (via nucleoside diphosphate kinase) after UDP-glucose is formed.

This energy investment ensures the glucose is effectively stored in a stable, readily mobilizable form as glycogen.

3.3 GLYCOGENOLYSIS

Glycogenolysis is the process through which glycogen is broken down primarily into glucose-1-phosphate (90%), and to a lesser extent, into free glucose (10%). This pathway is catalyzed by a distinct set of enzymes, different from those involved in glycogenesis. The process begins with the enzyme glycogen phosphorylase, which cleaves α-1,4 glycosidic bonds at the non-reducing ends of glycogen, releasing glucose-1-phosphate.

However, glycogen phosphorylase cannot cleave near branch points; it stops about four residues away from an α-1,6 branch. To continue degradation, the branch structure must be remodelled by other enzymes, allowing phosphorylase to resume its activity.

Glycogen phosphorylase, a homodimeric enzyme, catalyzes the sequential phosphorolytic cleavage of α-1,4 glycosidic bonds from the non-reducing ends of glycogen. This reaction releases glucose-1-phosphate as the primary product (Fig 3.4). In vivo, the reaction strongly favours glycogen breakdown due to the high intracellular ratio of inorganic phosphate [Pi] to glucose-1-phosphate (typically in the range of 30–100).

A key cofactor for this enzyme is pyridoxal phosphate (PLP), a derivative of vitamin B6. PLP plays an unusual catalytic role, working alongside orthophosphate as a general acid-base catalyst.

This phosphorolytic cleavage, rather than simple hydrolysis, is energetically advantageous:

- It conserves energy by directly producing a phosphorylated sugar, which can readily enter the glycolytic or pentose phosphate pathway.
- It ensures cellular retention of glucose, as the negatively charged glucose-1-phosphate cannot easily cross the plasma membrane.

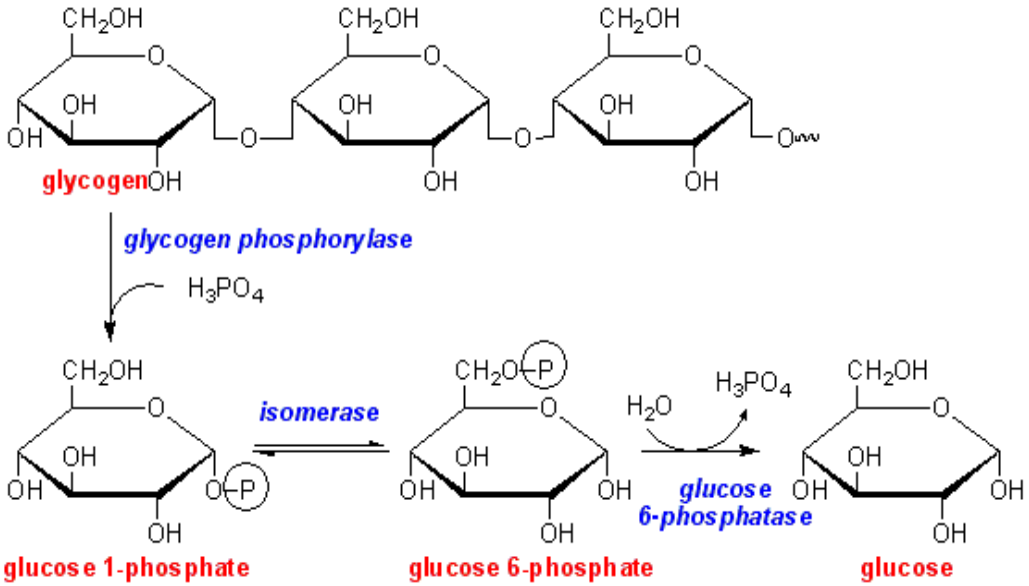


Fig. 3.4: Phosphorolytic cleavage of glycogen by glycogen phosphorylase

3.3.1 Role of Debranching Enzyme in Glycogenolysis

As glycogen phosphorylase continues to cleave α-1,4 glycosidic bonds, it eventually halts when four glucose residues remain on either side of an α-1,6 branch point. The branched structure that remains is known as a limit dextrin, which cannot be further degraded by glycogen phosphorylase alone (Fig 3.4). To proceed, eukaryotic cells employ a bifunctional debranching enzyme, which performs two critical activities using two enzymatic functions:

1. **Glycosyl Transferase Activity**
   - Transfers a trisaccharide unit (three glucose residues) from the outer branch to the non-reducing end of another linear chain.
   - This exposes the remaining single glucose at the branch point.

2. Amylo-α-1,6-glucosidase Activity

- Hydrolytically cleaves the α-1,6 glycosidic bond, releasing free glucose (not phosphorylated).
- This accounts for approximately 10% of glucose released during glycogenolysis.

In the liver, this free glucose may be directly released into the bloodstream to maintain blood glucose levels. In other tissues, it is typically phosphorylated before entering metabolic pathways like glycolysis or the pentose phosphate pathway. Once the branch is removed, glycogen phosphorylase can resume its action on the now linearized chain, continuing the production of glucose-1-phosphate.

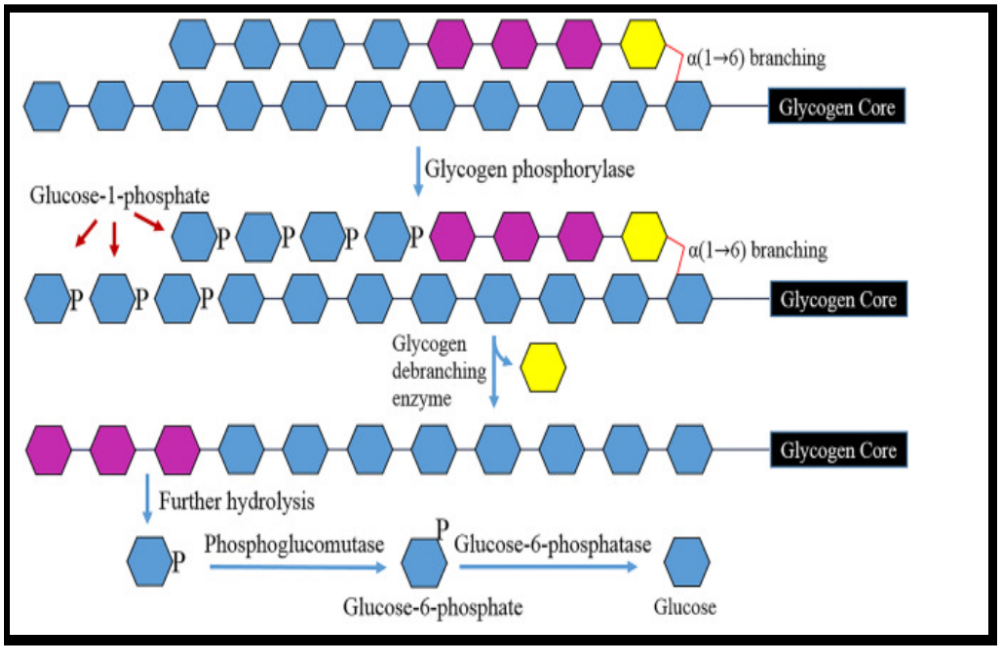


Fig. 3.4: Action of debranching enzyme on limit dextrin.

After glycogen breakdown, glucose-1-phosphate is converted to glucose-6-phosphate by the enzyme phosphoglucomutase (PGM)**.** This reaction proceeds through an enzyme-bound intermediate**,** glucose-1,6-bisphosphate (Fig: 3.5)**.** The subsequent fate of glucose-6-phosphate depends on the type of tissue:

In the Liver

- The liver contains the enzyme glucose-6-phosphatase**,** which hydrolyzes glucose-6-phosphate to free glucose**.**
- This glucose is then released into the bloodstream, serving as a major fuel for peripheral tissues, especially during fasting or muscle activity.
- Importantly, the liver does not rely heavily on glucose for its own energy needs—it functions more as a glucose supplier for the rest of the body.
- You've previously encountered glucose-6-phosphatase in the context of gluconeogenesis.

In Muscle and Adipose Tissue

- These tissues lack glucose-6-phosphatase, so free glucose cannot be produced internally.
- Instead, glucose-6-phosphate generated from glycogen enters glycolysis, where it is metabolized to produce ATP—providing direct energy for muscle contraction and other cellular activities.

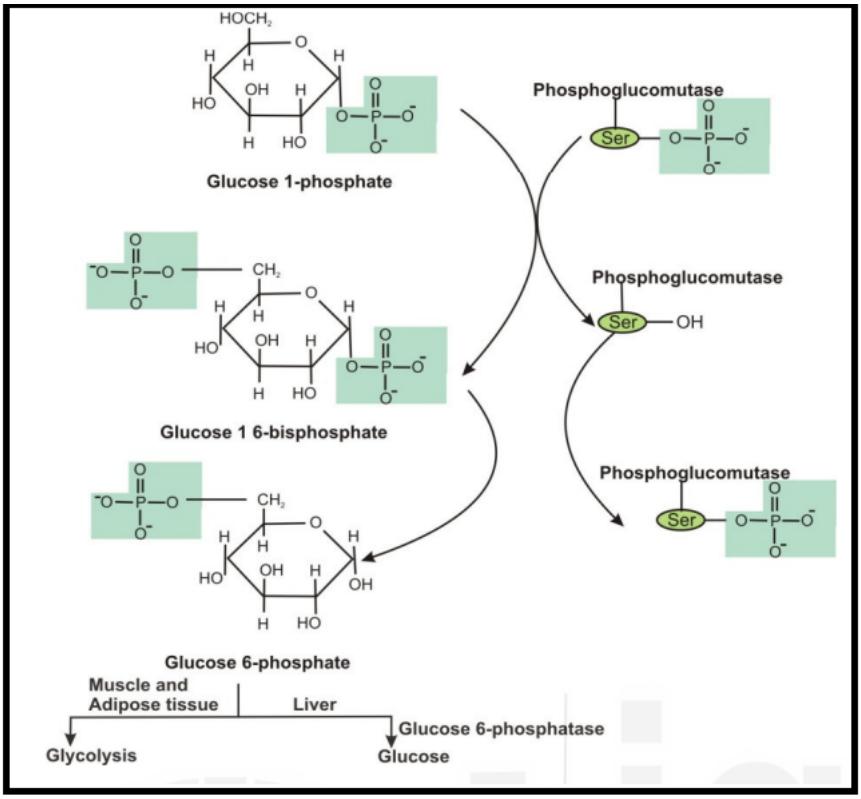


Fig. 3.5: Conversion of glucose-1-phosphate to glucose-6-phosphate by phosphoglucomutase (PGM).

3.4 GLUCONEOGENESIS

Gluconeogenesis refers to synthesis of glucose from non-carbohydrate precursors such as lactate, pyruvate, glycerol, and products derived from glucogenic amino acids. These precursors are either converted to pyruvate or they may enter as intermediates at later points in the pathway such as DHAP and OAA. You may recall that lactate is formed in skeletal muscles during vigorous exercise which is readily oxidised to pyruvate in the liver. The gluconeogenic precursors derived from partial breakdown of amino acids come from proteins in our diet or skeletal muscles during starvation. Similarly, hydrolysis of triacylglycerols yields glycerol and fatty acids.

3.4.1 GLUCONEOGENESIS FROM PYRUVATE/LACTATE

The conversion of pyruvate and other non-carbohydrate precursors to glucose is not a simple reversal of glycolysis. While glycolysis and gluconeogenesis share several steps, they differ significantly at three key points—the irreversible steps of glycolysis. These steps

account for the major negative free energy changes in the glycolytic pathway and cannot proceed in reverse under normal cellular conditions.

In gluconeogenesis, these three irreversible steps are bypassed by distinct enzymes, allowing glucose synthesis to occur efficiently without conflicting with glycolysis. These bypass reactions ensure a thermodynamically favourable and regulated pathway for glucose production.

As anticipated, these critical steps are also major sites of reciprocal regulation—ensuring that glycolysis and gluconeogenesis do not occur simultaneously in the same cell, thereby preventing a futile cycle.

Let us now explore the unique enzymatic reactions involved in bypassing the irreversible steps of glycolysis during gluconeogenesis.

3.4.1.1 Conversion of pyruvate to phosphoenolpyruvate (PEP)

The first committed step of gluconeogenesis involves the energy-dependent conversion of pyruvate to phosphoenolpyruvate (PEP). This process occurs in two enzymatic steps catalyzed by pyruvate carboxylase and phosphoenolpyruvate carboxykinase (PEPCK), which are compartmentalized in the mitochondria and cytosol, respectively.

Step 1: Pyruvate to Oxaloacetate (OAA): The substrate pyruvate may originate from:

- Transamination of alanine (within the mitochondria), or
- Glycolysis-derived pyruvate (transported into mitochondria).

Pyruvate is then converted into oxaloacetate by the biotin-dependent mitochondrial enzyme, pyruvate carboxylase. This ATP- and CO_2-dependent carboxylation proceeds via the formation of carboxyphosphate, an activated CO_2 intermediate that is transferred to biotin, covalently linked to the enzyme. Biotin thus acts as a carrier of activated CO_2, which is then transferred to pyruvate to form oxaloacetate.

Mitochondrial Export of OAA: *Since oxaloacetate cannot directly cross the mitochondrial membrane, it is reduced to malate by mitochondrial malate dehydrogenase-a reaction already familiar from the TCA cycle. Malate is transported across the inner mitochondrial membrane via a specific malate transporter. In the cytosol, malate is reoxidised to OAA by cytosolic malate dehydrogenase, generating NADH, which is required for subsequent steps of gluconeogenesis.*

This malate shuttle thus:

- Enables transfer of OAA from mitochondria to cytosol.
- Simultaneously delivers reducing equivalents (NADH) to the cytosol.

Step 2: Oxaloacetate to PEP: Cytosolic oxaloacetate is then decarboxylated and phosphorylated by phosphoenolpyruvate carboxykinase (PEPCK) using GTP to generate PEP. This step:

- Involves the release of the same CO_2 added in the previous step.

- Is energetically favorable due to decarboxylation driving the phosphorylation reaction.

Biochemical Strategy: This two-step pathway, although it consumes two high-energy phosphate bonds (ATP and GTP), is more favorable than a direct conversion because the decarboxylation step provides the thermodynamic push—an approach commonly seen in biosynthetic pathways like fatty acid synthesis.

Alternative Route: When Lactate is the Precursor: When lactate, rather than pyruvate, serves as the gluconeogenic precursor—as during vigorous exercise or in erythrocytes—it is first oxidized to pyruvate in the cytosol by lactate dehydrogenase, producing NADH in the process.

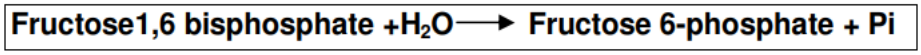
In this scenario:

- Both steps of pyruvate to PEP conversion occur in the mitochondria, as mitochondrial PEPCK catalyzes the second step.
- The malate shuttle is bypassed, since NADH is already available in the cytosol.

PEP to Fructose 1,6-Bisphosphate: Once formed, PEP progresses through the gluconeogenic pathway up to fructose 1,6-bisphosphate via the reversible reactions of glycolysis, utilizing the same enzymes working in the reverse direction.

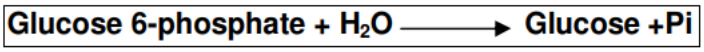
3.4.1.2 Conversion of fructose1,6-bisphosphate to fructose 6-phosphate

Fructose-1,6-bisphosphate is hydrolysed to fructose-6-phosphate and Pi by fructose-1,6-bisphosphatase.The enzyme requires Mg2+ for its activity and is absent in smooth muscles.



3.4.1.3 Conversion of glucose-6-phosphate to glucose

The last bottleneck in the generation of glucose is carried out by another hydrolytic enzyme, glucose-6-phosphatase. It converts glucose-6-phosphate to glucose.



3.4.2 GLUCONEOGENESIS FROM PRECURSORS OTHER THAN PYRUVATE

Gluconeogenesis is a universal metabolic pathway that occurs across animals, plants, fungi, and microorganisms. Despite this wide distribution, all groups use a conserved set of enzymatic reactions. Besides pyruvate, many other compounds can feed into the gluconeogenic pathway. These compounds are first converted to pyruvate, oxaloacetate (OAA), or other TCA cycle intermediates before being transformed into glucose.

Let's look at some important gluconeogenic precursors:

(a) Propionate

- **Source:**
  - β-oxidation of odd-chain fatty acids
  - Catabolism of certain amino acids like methionine and isoleucine
  - Metabolism in propionate-utilizing microorganisms
- **Pathway:**
  - Propionate is first converted to propionyl-CoA, which undergoes a three-step enzymatic conversion to succinyl-CoA, a TCA cycle intermediate.
  - Succinyl-CoA enters the TCA cycle and is ultimately converted to oxaloacetate, which serves as a gluconeogenic substrate.

(b) Glycerol

- **Source:** Released from the hydrolysis of triglycerides in adipose tissue.
- **Pathway:**
  1) Glycerol → Glycerol-3-phosphate
     (Enzyme: Glycerol kinase; requires ATP)
  2) Glycerol-3-phosphate → Dihydroxyacetone phosphate (DHAP)
     (Enzyme: Glycerol-3-phosphate dehydrogenase; uses NAD^+)
- Gluconeogenic Entry: DHAP is a glycolytic/gluconeogenic intermediate that can be directed toward glucose synthesis.

(c) Amino Acids

- Source: Partial catabolism of amino acids during protein turnover or fasting.
- Pathway:
  - Many amino acids are broken down to gluconeogenic intermediates like:
    - Pyruvate
    - Succinyl-CoA
    - Fumarate
    - α-Ketoglutarate
  - These intermediates are further oxidized in the TCA cycle to produce oxaloacetate, which can enter gluconeogenesis.
- Terminology: Such amino acids are called glucogenic amino acids.

(d) Fatty Acids and Acetyl-CoA

- **General Rule (in mammals):**
  - Fatty acids undergo β-oxidation to form acetyl-CoA.

- In humans and other mammals, acetyl-CoA cannot serve as a gluconeogenic precursor due to the irreversible nature of the pyruvate dehydrogenase step.

- **Exception (in plants, fungi, bacteria):**
  - These organisms possess the glyoxylate cycle, a modified version of the TCA cycle.
  - The glyoxylate cycle allows the conversion of two molecules of acetyl-CoA into four-carbon intermediates (like succinate), which can be converted to oxaloacetate and then glucose.

3.5 GLYCOGEN STORAGE IN NORMAL AND DISEASED STATES

3.5.1 Normal Glycogen Storage: Glycogen is a highly branched polysaccharide composed of glucose units. It serves as the main storage form of glucose in animals.

Storage Sites:

- Liver (up to 10% of liver mass): Maintains blood glucose levels, especially between meals.
- Skeletal muscles (1–2% of muscle mass): Supplies energy locally during muscle contraction.

Glycogen Metabolism:

- Glycogenesis: Formation of glycogen from glucose (activated by insulin)
- Glycogenolysis: Breakdown of glycogen to glucose (stimulated by glucagon and epinephrine)

Enzymes Involved:

- Glycogen synthase: Adds glucose units during glycogenesis.
- Glycogen phosphorylase: Removes glucose units during glycogenolysis.
- Branching and debranching enzymes: Create and remove branches to maintain glycogen structure.

3.5.2 Glycogen Storage in Diseased States (Glycogen Storage Diseases – GSDs)

Glycogen storage diseases (GSDs) are a group of inherited metabolic disorders caused by deficiencies in enzymes involved in glycogen metabolism. These result in abnormal storage and structure of glycogen in tissues (Table 3.1).

Table 3.1: Classification of GSDs

Type	Defective Enzyme	Primary Site Affected	Clinical Features
Type I (Von Gierke's)	Glucose-6-phosphatase	Liver	Hypoglycemia, hepatomegaly
Type II (Pompe's)	Lysosomal α-glucosidase	All tissues, especially heart	Cardiomegaly, muscle weakness
Type III (Cori's / Forbes')	Debranching enzyme	Liver and muscle	Mild hypoglycemia, muscle weakness
Type IV (Andersen's)	Branching enzyme	Liver	Cirrhosis, liver failure
Type V (McArdle's)	Muscle phosphorylase	Skeletal muscle	Exercise intolerance, muscle cramps
Type VI (Hers')	Liver phosphorylase	Liver	Hepatomegaly, growth retardation
Type VII (Tarui's)	Phosphofructokinase	Muscle	Similar to McArdle's, with hemolysis

Table 3.2: Normal vs Diseased Glycogen Storage

Aspect	Normal	Diseased (GSDs)
Structure	Highly branched, compact	Often abnormal (fewer branches, excessive accumulation)
Function	Maintains blood glucose, provides energy	Impaired glucose release or abnormal glycogen buildup
Enzyme activity	Fully functional	Deficient or defective enzymes
Tissue distribution	Liver and muscles	Depends on GSD type
Clinical impact	Stable metabolism	Hypoglycemia, hepatomegaly, myopathy, organ dysfunction

3.6 SUMMARY:

Glycogenesis, glycogenolysis, and gluconeogenesis are essential metabolic pathways that ensure glucose homeostasis in the body.

- Glycogenesis enables the storage of excess glucose as glycogen, primarily in the liver and muscles, providing a rapid energy reserve during times of need.
- Glycogenolysis breaks down stored glycogen to release glucose-1-phosphate, supplying energy during fasting or physical activity.
- Gluconeogenesis is crucial during prolonged fasting or carbohydrate deprivation, generating glucose from non-carbohydrate precursors such as amino acids, glycerol, and TCA cycle intermediates.

In normal physiology, these pathways are tightly regulated by hormonal signals (like insulin, glucagon, and epinephrine) to meet the dynamic energy demands of the body. However, in glycogen storage diseases (GSDs), genetic defects in enzymes involved in glycogen metabolism result in abnormal accumulation or depletion of glycogen, leading to metabolic disturbances such as hypoglycemia, hepatomegaly, muscle weakness, and organ dysfunction. Understanding these pathways is not only central to appreciating normal energy metabolism but also critical in diagnosing and managing inherited metabolic disorders that impact carbohydrate utilization.

3.7 TECHNICAL TERMS

Carbohydrate metabolism**,** Glycogenesis, Glycogenolysis, Gluconeogenesis, enzymes, and glycogen storage diseases

3.8 SELF ASSESSMENT QUESTIONS

1) What is glycogenesis? Explain its steps?
2) Name the enzymes of gluconeogenesis unique to the pathway?
3) What would you expect in a patient who has a deficiency in debranching enzyme?

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Dr. Jalaja Kumari. Divi

LESSON-4

ENDOCRINAL INFLUENCES ON CARBOHYDRATE METABOLISM, REGULATION OF BLOOD GLUCOSE CONCENTRATION

4.0 OBJECTIVES:

After studying this unit, you should be able to:

- Describe the steps of glycogenesis;
- Explain glycogenolysis and conversion of glucose 1-phosphate to glucose 6-phosphate;
- Give an overview of gluconeogenesis pathway;
- Glycogen storage in normal and diseased states

STRUCTURE:

4.1 INTRODUCTION

Carbohydrate metabolism is a vital physiological process that ensures a constant supply of energy to the body, especially to glucose-dependent organs like the brain and red blood cells. This process is intricately regulated by the endocrine system through various hormones that control the synthesis, breakdown, and utilization of carbohydrates.

The concentration of glucose in the blood is tightly maintained within a narrow range (~70–110 mg/dL in fasting state), despite changes in dietary intake, physical activity, and metabolic demands. This homeostasis is achieved by the coordinated action of hormones such as insulin, glucagon, epinephrine, cortisol, growth hormone, and thyroid hormones, which influence pathways like glycolysis, gluconeogenesis, glycogenesis, and glycogenolysis.

Any imbalance in this hormonal regulation can lead to metabolic disorders such as diabetes mellitus, hypoglycemia, or hyperglycemia, highlighting the importance of hormonal control in maintaining glucose homeostasis.

4.2 ENDOCRINAL INFLUENCES ON CARBOHYDRATE METABOLISM

Carbohydrate metabolism involves several interconnected pathways, including glycolysis, gluconeogenesis, glycogenesis, and glycogenolysis, all of which are tightly

regulated by endocrine hormones. These hormones ensure a balance between glucose production and utilization, maintaining blood glucose levels within a narrow physiological range.

Major hormones that take part in carbohydrate metabolism are described below:

4.2.1. Role of Insulin: *The principal effect of insulin on carbohydrate metabolism is to increase the utilisation of glucose by most tissues. The most important effect of insulin is to increase the rate of glycogen formation. It has been described earlier that insulin is secreted from the β-cells of the islets of Langerhans. It should be borne in mind that the degree of insulin activity and probably the actual production of insulin by the β-cells of the pancreatic islets are effected by the level of blood sugar.*

Hyperglycaemia stimulates the pancreas to produce the increased quantity of insulin and if the hyperglycaemia is maintained for a longer period then the permanent damage to the β-cells may ensue and thus permanent diabetes prevails. But it is difficult to say that the hypoglycaemia leads to decrease in insulin secretion in same level. Because during such state adrenaline is secreted and this hormone thus masks the effect of insulin on liver glycogen.

There are other factors which either suppress the production of insulin or may render its action less effective. Growth hormone, glucocorticoids (cortisone and hydrocortisone) and also thyroxine act in such process. There is evidence that growth hormone and glucocorticoids inhibit phosphorylation of glucose by affecting hexokinase activity. These two hormones have got no action on the entry of glucose into the cells. Glucagon, the α-cell hormone of pancreatic islets and also of gastro-intestinal tract seems to counteract the insulin by exhaustion atrophy of β-cells. Alloxan also counteracts the insulin by damaging the β-cells.

The insulin is mostly concerned with the utilisation of glucose by the tissues and this involves the phosphorylation in which the chain of conversions of glucose and its combination is controlled by a series of enzymes of which hexokinase is an important one. Insulin stimulates the catalytic action of hexokinase.

Insulin has been found to increase the glycogen synthetase activity in muscle. It is claimed that considerably more blood sugar is converted to fatty acids and eventually deposited in the fat depots than that which is turned into tissue glycogen. Insulin increases the conversion of sugar to fatty acids.

Furthermore, formation of liver glycogen is quantitatively higher than the formation of tissue glycogen. The influence of insulin on carbohydrate metabolism has been presented schematically in figure.

4.2.2. Role of Glucagon: *Glucagon is known as hyperglycaemic-glycogenolytic factor (HGF). Main effect of glucagon on carbohydrate metabolism is to increase the breakdown of liver glycogen to glucose and hence hyperglycaemia. It does not cause the breakdown of muscle glycogen. Glucagon is secreted from the a-cells of the islets of Langerhans, walls of duodenum and stomach. If glucose is placed in the gastro-intestinal tract then glucagon is secreted from the gastro-intestinal tract directly in the circulation.*

Glucagon raises the blood glucose level by stimulating the adenyl cyclase in the liver leading to the formation of cyclic AMP that activates the phosphorylase. Glucagon has got no effect on muscle phosphorylase. Due to action of glucagon on adenyl cyclase, cyclic AMP is formed from ATP. The cyclic AMP thus activates the phosphorylation process of liver glycogen and thus glucose is formed.

Besides this, glucagon also stimulates the process of neoglucogenesis from available amino acids in the liver. Thus increased activity of glucagon increases the blood glucose level which may indirectly stimulate the β-cells activity for the production of excess insulin. Thus prolonged treatment with glucagon causes exhaustion of β-cells and diabetes is produced. Role of glucagon on carbohydrate metabolism has been presented schematically in Fig

4.2.3. Growth Hormone: *It is established that growth hormone opposes the hexokinase mechanism, so that the phosphorylation of glucose is depressed causing hyperglycaemia. This hyperglycaemia causes secretion of insulin from the β-cells. Prolonged effect of growth hormone may eventually exhaust the β-cells. Histologically it is proved that α-cells remains unaffected when the β-cells are damaged due to prolonged glucagon therapy. Role of growth hormone on carbohydrate metabolism has been presented schematically in Fig*

4.2.4. Role of Adrenal Glucocorticoids: *Like growth hormone adrenal glucocorticoids also elevate the blood sugar level. It is claimed that these hormones produce the hyperglycaemic effect by increased neoglucogenesis in the liver. It also produces hyperglycaemia by decreasing the glucose utilisation in the liver and peripheral tissue possible through the inhibition of phosphorylation. In patients with adrenal insufficiency, the blood glucose-lowering effect of insulin is greatly enhanced. In experimental diabetes, adrenalectomy may markedly ameliorate the diabetic state.*

4.2.5. Role of Epinephrine (Adrenaline): *Epinephrine increases the blood sugar level and this is one of the most important factors in the normal organism for counteracting the hypoglycaemic action of insulin. Epinephrine causes rapid breakdown of liver glycogen to glucose with the production of hyperglycaemia. In muscle, the epinephrine causes the breakdown of glycogen to lactic acid.*

Epinephrine is released as an emergency in response to emotional excitement, injury, fright, stress, exercise, etc., and consequently augments blood sugar. Hypoglycaemia from any cause leads to secretion of epinephrine from adrenal medulla and brings the blood glucose level back to normal. Epinephrine exerts its hyperglycaemic effects by increasing the rate of glycogenolysis in the liver and muscles.

Muscle glycogen is not directly available for the replenish of glucose. By the action of epinephrine, both liver and muscle glycogen are converted into hexose phosphate. In the liver, glucose is formed by the action of phosphatase on the hexose phosphate. But the enzyme, phosphatase, is lacking in muscle and for this reason it has to complete the whole glycolytic process with the formation of lactic acid.

Some amount of lactic acid may be transformed into liver glycogen which under the action of epinephrine or glucagon, may be converted into glucose. So the ultimate action of epinephrine on the muscle glycogen is the increased deposition of liver glycogen. The

breakdown of the liver and muscle glycogen under the action of epinephrine takes place through the activation of adenyl cyclase that catalyses the formation of cyclic AMP.

Epinephrine also influences the carbohydrate metabolism indirectly by stimulating the adenophysis in releasing the ACTH. ACTH on the other hand augments the release of glucocorticoids from the adrenal cortex. This is observed in emergency, stress, fright, exercise, hypoglycaemia, etc. Insulin and epinephrine play important part in the homeostatic regulation of blood sugar. Because hypoglycaemia stimulates the secretion of epinephrine whereas hyperglycaemia stimulates the secretion of insulin.

Summarily, epinephrine elevates the blood sugar in three ways:

i) By mobilising the carbohydrate stores of the liver;

ii) By indirect formation of glucose from muscle glycogen; and

iii) By excessive formation of glucocorticoids indirectly through liberation of ACTH.

4.2.6. Role of Posterior Pituitary Hormones (Vasopressin and Oxytocin):

A large dose of vasopressin and oxytocin raise the blood sugar level temporarily. In rabbits vasopressin is more effective in raising the blood sugar level, whereas in dogs oxytocin has greater hyperglycaemic effect.

4.2.7. Role of Thyroid Hormones:

Thyroid hormones increase the glucose absorption from the intestine. The rate of glucose absorption from the intestine is decreased in hypothyroidism. The principal diabetogenic effect of thyroid hormones is possibly due to this increased absorption of glucose from the gut. The hormone also depletes some liver glycogen. Administrations of thyroid hormones to normal animals do not cause immediate effect on blood sugar but liver glycogen is depleted within six to eight hours.

In hyperthyroidism the diabetic condition is aggravated but thyroidectomy markedly decreases the intensity of the diabetes. Rate of protein catabolism is increased by excessive thyroid hormone and for this reason increased hyperglycaemia is observed due to neoglucogenesis from amino acids. Besides this, the thyroid hormones sensitise the adrenaline and the hepatic depletion of glycogen may be the indirect effect of adrenaline by thyroid hormones. Thyroid hormones also raise the renal threshold for glucose.

4.2.8. Role of Anterior Pituitary Hormones:

Like growth hormone, the anterior pituitary hormones ACTH and TSH may have some indirect role on the glucose metabolism through acting on the respective target organs. Direct role on the metabolism is possible lacking.

4.2.9. Role of Prolactin: *Has got some anti-insulin effect. It reduces the sensitivity of the animals to insulin. The diabetogenic action of prolactin is probably due to this desensitisation of animals to insulin. After hypophysectomy, the blood sugar level is reduced but administration of prolactin raises the level towards normal.*

4.2.10. Role of Sex Hormones: *Female sex hormones, oestrone and oestradiol, decrease the diabetic condition possible by stimulating the secretion of insulin. Male sex hormones, testosterone also markedly increases the severity of the diabetic condition of the castrated animals.*

The endocrine control of carbohydrate metabolism has been presented schematically in Figure.

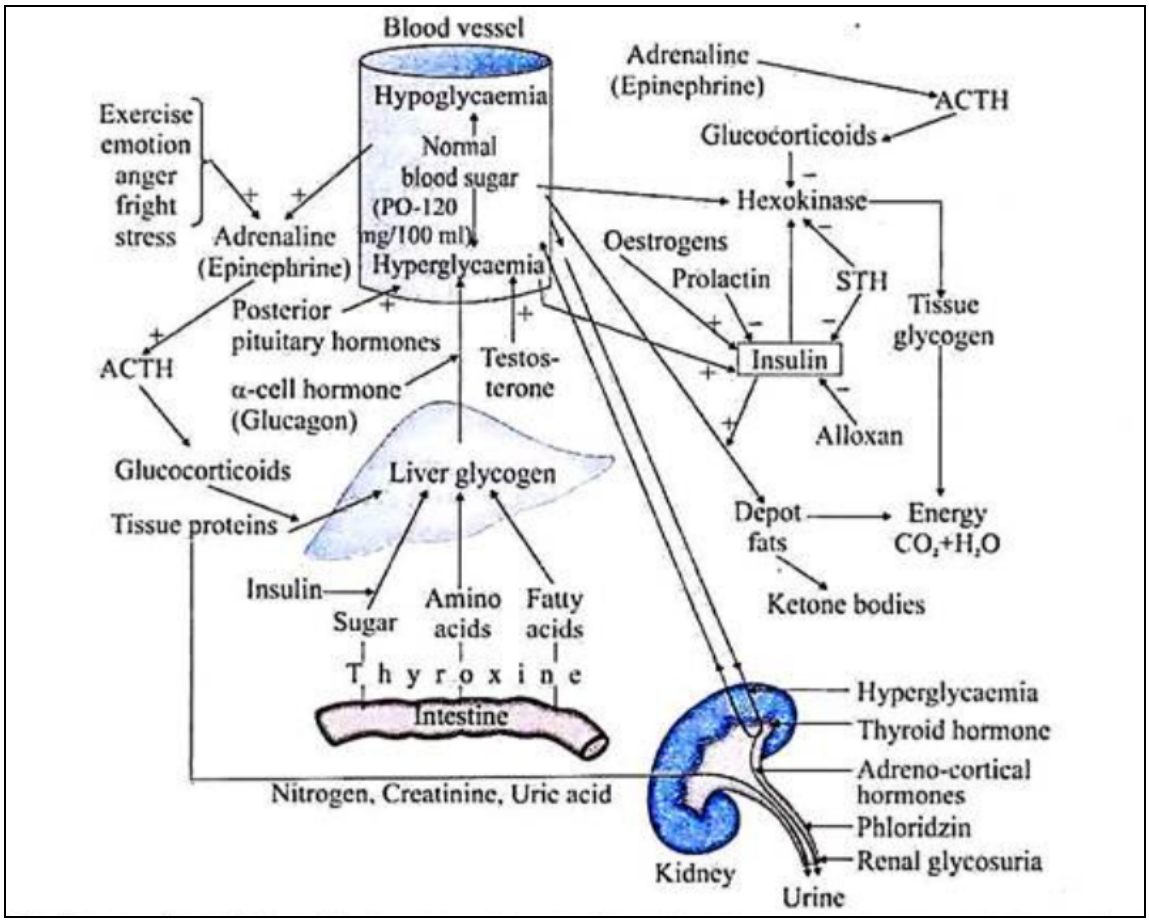

Fig. 4.1: Hormonal control of carbohydrate metabolism and their interrelationship (-) means inhibition and (+) denotes stimulation.

4.3 REGULATION OF BLOOD GLUCOSE CONCENTRATION

Maintaining blood glucose within a narrow physiological range (~70–110 mg/dL in fasting state) is critical for homeostasis. The brain, red blood cells, and kidneys depend heavily on glucose as their primary energy source. Therefore, a tightly coordinated hormonal and metabolic regulation ensures stability during feeding, fasting, and stress.

In the small intestine, glucose is absorbed into the blood and travels to the liver via the hepatic portal vein. The hepatocytes (liver cells) absorb much of the glucose and convert it into glycogen, an insoluble polymer of glucose.

This is stored in the liver and can be reconverted into glucose when blood-glucose levels fall. Other types of simple sugars in our diet such as fructose, sucrose and lactose are also fuels that contribute to the production of ATP.

All of the body's cells need to make energy and most can use other fuels such as lipids. However, neurons (nerve cells) rely almost exclusively on glucose for their energy. This is why the maintenance of blood-glucose levels is essential for the proper functioning of the nervous system.

If glucose levels fall to too low a concentration (hypoglycaemia) or rise too high (hyperglycaemia) then this situation can lead to the neurological processes in the brain being compromised. At some time, most of us will have experienced the effects of low blood glucose, a feeling of being lightheaded, weak and shaky, together with an inability to concentrate properly. Chronic hyperglycaemia, which is a common feature of diabetes mellitus, also causes neurological problems and is a contributory factor to both atherosclerosis and renal failure.

Glucose Regulation

Blood-glucose levels fluctuate as a person's intake of food varies over a 24-hour period. After meals, the body is said to be in an absorptive state as it absorbs nutrients from the gut. Blood-glucose levels rise although this is buffered by glucose storage in the liver. When digestion is complete and the absorption of nutrients decreases, the body is in a post-absorptive state and, as the body's cells use glucose to make energy, blood-glucose levels fall. Despite these fluctuations, the body needs to maintain blood-glucose levels within certain limits and the homeostatic mechanisms discussed below maintain glucose levels within these limits.

Typical Blood-Glucose Levels

During the absorptive state, glucose levels can vary with the type and quantity of food eaten. Therefore post-absorptive, fasting-state glucose levels are more reliable and are generally used by health care professionals when testing blood glucose (for example, imagine the test results just after an over-generous helping of sticky toffee pudding). Typical fasting levels of blood glucose lie between 3.3 and 6.1mmol/L. Results outside this range could indicate a dysfunction in glucose regulation such as that which occurs in patients with diabetes mellitus.

The Role of the Pancreas

The pancreas, a large gland that nestles under the stomach, plays an important part in glucose regulation and is unusual in having both an exocrine and endocrine function. As an exocrine gland it produces several digestive enzymes that are secreted into the duodenum via the pancreatic duct. Over 90 per cent of the pancreas is devoted to its exocrine, digestive function. The position of the pancreas relative to adjacent organs is shown in Fig. 4.1.

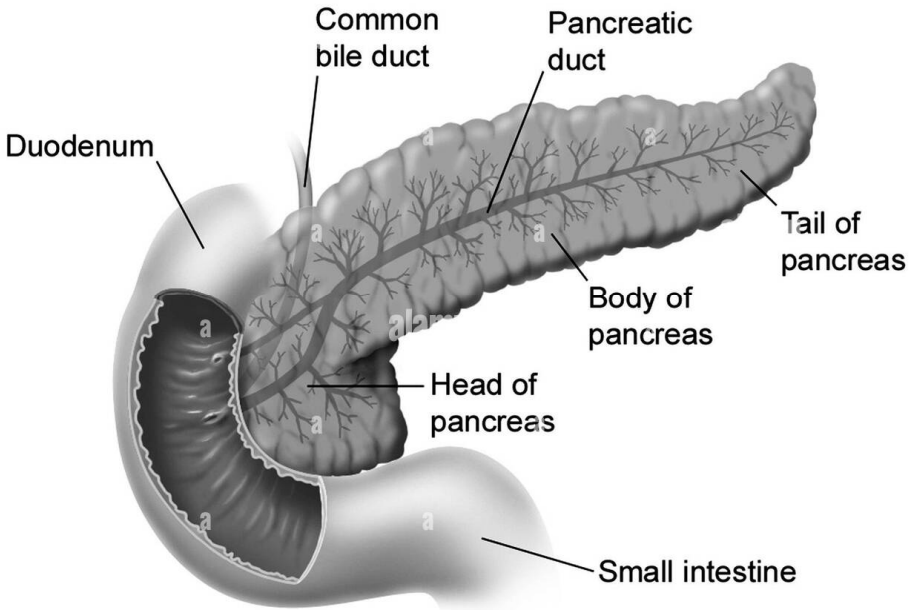

Fig. 4.1: The position of the pancreas relative to adjacent organs

As an endocrine gland, the pancreas secretes a variety of hormones that are concerned with the regulation of blood glucose, including insulin, glucagon, and somatostatin. These hormones are produced by groups of cells that under the microscope appear as small clusters, or islands. They were discovered by the German anatomist Paul Langerhans, hence they are called Islets of Langerhans, or simply pancreatic islets.

Response to an Increase in Blood Glucose

In the absorptive state, an increase in blood glucose is detected by the beta cells of the pancreatic islets, causing them to increase the release of insulin into the blood. Insulin stimulates cells, especially adipose and muscle cells, to take up glucose from the blood.

Insulin and the Transport of Glucose into Cells

To enter cells, glucose requires trans-membrane transporters and there is a family of these called GLUT (GLUcose Transporter). The most numerous is GLUT4, which is found on muscle and fat cells. When insulin binds to insulin receptors on the cell membrane, cells are stimulated to increase the number of glucose transporters. The more transporters are produced, the more glucose is transported into cells – with a corresponding drop in blood glucose.

The precise mechanism whereby insulin binds to receptors causing translocation is still to be determined (Sanger Institute, see 'websites'). Not all tissues require insulin to take up glucose, for example brain and liver cells use GLUT transporters that are not dependent on insulin.

Further effects of insulin: The hormone also has other effects on the body's cells, all of which contribute to an increase in glucose usage and storage – and therefore a reduction in blood glucose. These include:

- The promotion of glycolysis, a process that breaks down glucose for cellular energy;

- The promotion of glycogenesis, a process that converts glucose into glycogen for storage;
- The inhibition of lipolysis, a process that breaks down lipids to release energy.

These effects of insulin actively shift the metabolism away from fat and towards glucose. In other words, insulin drives the body to utilise carbohydrates as a source of energy and to spare its fat reserves.

Response to a Decrease in Blood Glucose

Several hours after eating a meal, when the body is in the post-absorptive state, insulin levels fall along with blood glucose and this results in the hormone glucagon being released by the alpha cells of the pancreas.

The role of glucagon Glucagon has the opposite effect to insulin in that it increases blood-glucose levels and promotes processes that spare glucose utilisation.

Glucagon works primarily on the hepatocytes in the liver to:

- Convert stored glycogen into glucose and release it into the blood;
- Promote gluconeogenesis, the manufacture of new glucose from lactic acid and other metabolites.

Glucagon binds to glucagon receptors, which are part of the G-protein-coupled receptor family. This stimulates a series of linked enzyme reactions, resulting in the activation of glycogen phosphorylase, the enzyme responsible for the mobilisation of glycogen reserves into free glucose. Glucagon release is inhibited by both insulin and somatostatin.

Homeostatic Control

The control of blood glucose is an excellent example of homeostatic control via negative feedback. This is where the corrective response, triggered by a deviation from normal levels, is turned off by a return to normal levels. For example, low blood glucose results in the production of glucagon and this raises blood glucose. Consequently, as glucose levels rise, the stimulation to produce glucagon is turned off. A summary of the contrasting actions of insulin and glucagon is shown in Fig 4.2.

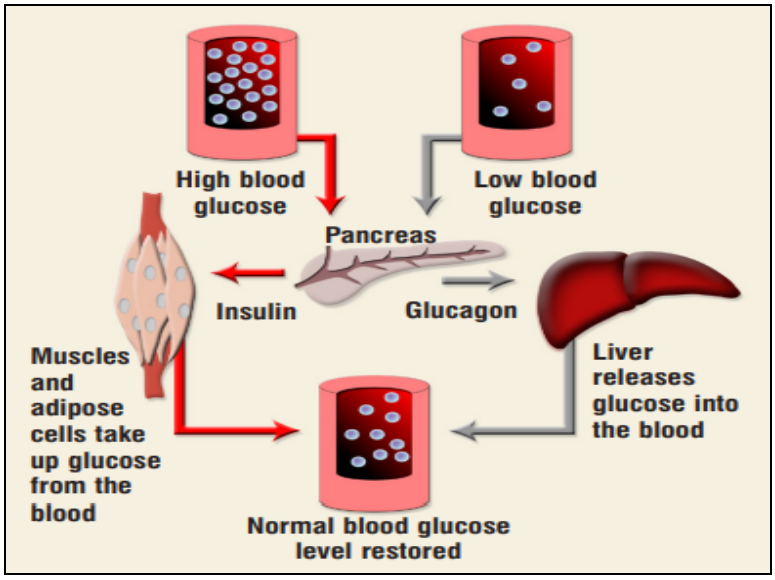

Fig. 4.2: Complementary action of insulin and glucagon responding to a rise or fall in blood-glucose levels.

The Role of Somatostatin

This is released by the delta cells located in the pancreatic islets in response to a post-prandial increase in blood glucose and amino acids. It reduces gut motility and the further absorption of nutrients as well as inhibiting pancreatic exocrine secretions.

The Function of Gastrin and Cholecystokinin

The gastrointestinal tract also releases hormones such as gastrin and cholecystokinin that stimulate the pancreas to secrete insulin in anticipation of the absorption of nutrients.

The Role of Stress Hormones

When a person is experiencing stress, neuro-endocrine mechanisms cause the release of stress hormones such as adrenaline (epinephrine). These increase blood-glucose levels by mobilising glycogen and suppressing the release of insulin.

Neuroregulation of Blood Glucose

The autonomic division of the nervous system modulates the release of insulin and glucagon. The sympathetic stimulation that occurs with exercise stimulates glucagon production and this maintains blood-glucose levels that would otherwise fall as muscles use glucose for their energy. During the periods when the body is at rest, parasympathetic activity stimulates digestion and also the release of insulin to deal with the expected rise in blood glucose.

4.4 SUMMARY

The regulation of carbohydrate metabolism and blood glucose concentration is a finely balanced process, critically governed by endocrine control. Hormones such as insulin, glucagon, cortisol, growth hormone, adrenaline, and thyroxine play pivotal roles in maintaining glucose homeostasis.

- Insulin, secreted in response to rising blood glucose, facilitates glucose uptake and storage, especially in muscle and adipose tissues.
- Glucagon and other counter-regulatory hormones act during fasting or stress to increase blood glucose via glycogenolysis and gluconeogenesis.
- These hormonal actions ensure a constant supply of glucose, particularly for glucose-dependent organs like the brain and red blood cells.
- Dysregulation of this endocrine balance can lead to metabolic disorders such as hypoglycemia or hyperglycemia, and in chronic cases, diabetes mellitus.
- Thus, the endocrinal system ensures the dynamic regulation of carbohydrate metabolism to meet both immediate and long-term energy demands of the body.

4.5 TECHNICAL TERMS:

Carbohydrate metabolism, Blood glucose concentration, Insulin, Glucagon, and Diabetes.

4.6 SELF ASSESSMENT QUESTIONS:

1) Discuss how the blood sugar level is maintained at a stable level in the well fed and fasting state.
2) Discuss the role of insulin in carbohydrate metabolism.
3) Compare the roles of insulin and glucagon in glucose homeostasis.

4.7 REFFERENCE BOOKS:

1) David L. Nelson, Michael M. Cox. Lehninger Principles of Biochemistry, 8th edition, 2021.
2) Victor W. Rodwell, David Bender, Kathleen M. Botham. Harper's Illustrated Biochemistry, 32nd edition, 2022.
3) Guyton and Hall (John E. Hall). Textbook of Medical Physiology, 14th edition, 2020.
4) U. Satyanarayana & U. Chakrapani. Biochemistry, 5th edition, 2017.

Dr. Jalaja Kumari. Divi

LESSON-5

PROTEINS AND AMINO ACIDS

5.0 OBJECTIVES:

After going through this lesson students will understand:

- Various protein sources
- Structural organization of proteins
- Functions of proteins

STRUCTURE:

5.1. INTRODUCTION

Proteins are polymers of amino acids linked together by peptide bonds. Proteins are considered as essential nutrients and are involved in various biochemical processes like catalysis, movement of muscles, immunity, cell support, transport and storage. Proteins do not accumulate in human body as reserve; rather the body excretes them during various metabolic processes especially, the urea cycle. Proteins are continuously undergoing degradation and synthesis in the body. Proteins from the food are breakdown in the gastrointestinal tract by proteolytic enzymes in to amino acids.

5.2. SOURCES

The protein food group consists of foods made from meat, seafood, poultry, eggs, soy, beans, peas, and seeds. Simply put, different protein sources differ in their additional components, so it is necessary to pay attention to the whole nutrient “package.” Proteinrich animalbased foods commonly have high amounts of B vitamins, vitamin E, iron, magnesium, and zinc. Seafood generally contains healthy fats, and plant sources of protein contain a high

amount of fiber. Some animal based protein rich foods have an unhealthy amount of saturated fat and cholesterol. When choosing dietary sources of protein, take note of the other nutrients and also the non nutrients, such as cholesterol, dyes, and preservatives, in order to make good selections that will benefit your health.

For instance, a hamburger patty made from 80 % lean meat contains 22 gm of protein, 5.7 gm of saturated fat, and 77 mg of cholesterol. A burger made from 95 % lean meat also contains 22 gm of protein, but has 2.3 gm of saturated fat and 60 mg of cholesterol. A cup of boiled soybeans contains 29 gm of protein, 2.2 gm of saturated fat, and no cholesterol. For more comparisons of protein rich foods

5.3 STRUCTURAL ORGANIZATION OF PROTEINS

Amino Acids are linked together by Peptide Bonds

Alpha carboxyl group of one amino acid reacts with alpha amino group of another amino acid to form a peptide bond or CO-NH bridge. Proteins are made by polymerization of amino acids through peptide bonds. Two amino acids are combined to form a dipeptide; three amino acids form a tripeptide; a few amino acids together will make an oligopeptide; and combination of 10 to 50 amino acids is called as a polypeptide. By gathering, big polypeptide chains containing more than 50 amino acids are called proteins.

- **Primary structure** of protein means the order of amino acids in the polypeptide chain and the location of disulfide bonds, if any.
- **Secondary Structure** is the steric relationship of amino acids, close to each other.
- **Tertiary Structure** denotes the overall arrangement and interrelationship of the various regions, or domains of a single polypeptide chain.
- **Quaternary Structure** results when the proteins consist of two or more polypeptide chains held together by non-covalent forces.

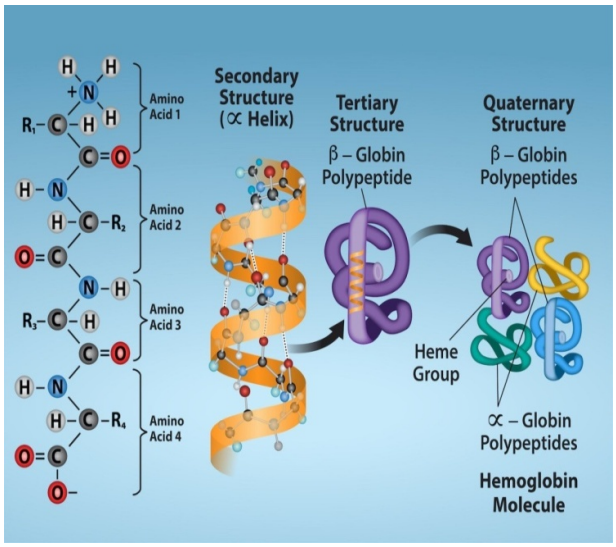

Fig. 5.1: Levels of Organization of Proteins

https://raider.pressbooks.pub/biology1/chapter/21-protein-structure-and-function

Proteins have different levels of structural organization; primary, secondary, tertiary and quaternary.

5.3.1. Primary Structure

Primary structure denotes the number and sequence of amino acids in the protein. The higher levels of organization are decided by the primary structure. Each polypeptide chain has adistinctive amino acid sequence decided by the genes. The primary structure is maintained by the covalent peptide bonds.

Characteristics of a Peptide Bond

- The peptide bond is a partial double bond.
- The C–N bond is ‘trans' in nature and there is no freedom of rotation because of the partial double bond character. The distance is 1.32Å which is midway between single bond (1.49 Å) and double bond (1.27Å). The side chains are free to rotate on either side of the peptide bond.
- The angles of rotation known as Ramachandran angles, therefore determine the spatial orientation of the peptide chain. Dr. G.N. Ramachandran did pioneer work on the structural aspects of proteins during 1950s and1960s.

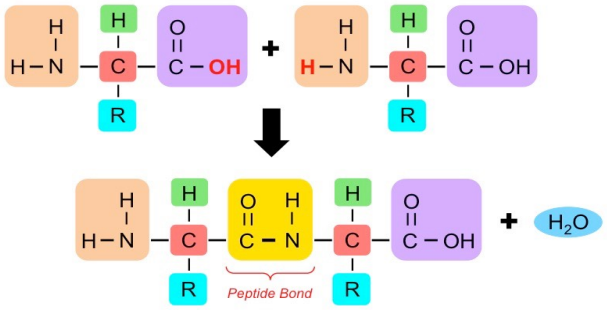

Fig. 5.2: Peptide Bond

Source: https://old-ib.bioninja.com.au/standard-level/topic-2-molecular-biology/24-proteins/peptide-bonds.html

Numbering of Amino Acids in Proteins

In a polypeptide chain, at one end there willbe one free alpha amino group. This end is called the amino terminal (N-terminal) end and the amino acid contributing the alpha amino group is named as the first amino acid. Usually the N-terminal amino acid is written on the left-hand side when the sequence of the protein is denoted. Incidentally, the biosynthesis of the protein also starts from the amino terminal end. The other end of the polypeptide chain is the carboxy terminal end (C-terminal), where there is a free alpha carboxyl group which is contributed by the last amino acid. All other alpha amino and alpha carboxyl groups are involved in peptide bond formation. Amino acid residues in polypeptides are namedby changing the suffix "-ine" to "-yl", for example, Glycine to Glycyl. Thus, peptide bonds formed by carboxyl group of glycine with amino group of Alanine, and then

carboxyl group of Alaninewith amino group of Valine and is called glycylalanyl-valine and abbreviated asNH_2-Gly-Ala-Val-COOHor Gly-Ala-Val.

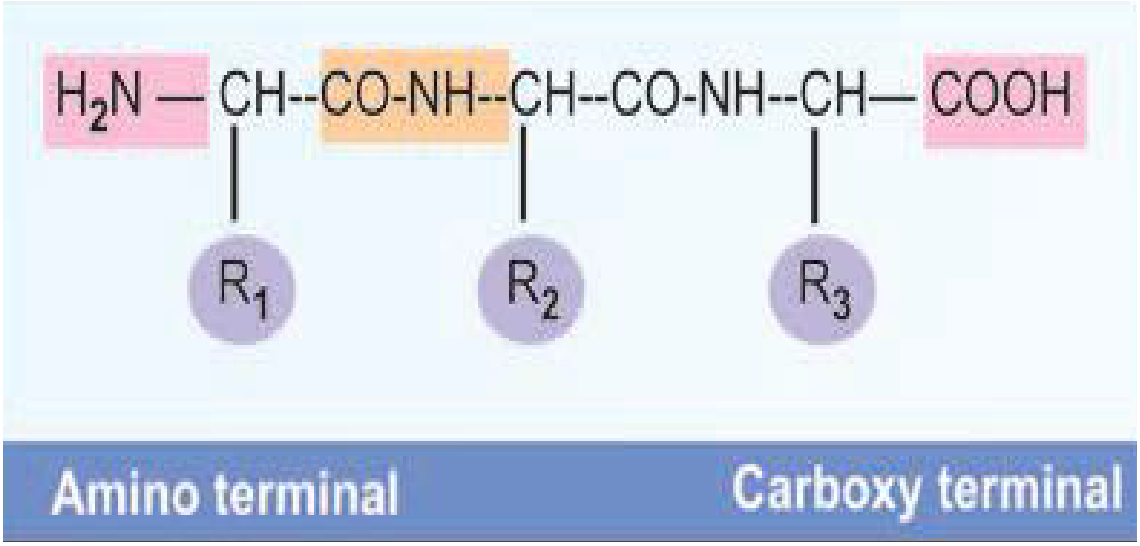

Fig. 5.3: End Groups of Polypeptide Chain

5.3.2 Secondary Structure of Proteins

The term "secondary structure" denotes the configurational relationship between residues which are about 3-4 amino acids apart in the linear sequence. Secondary and tertiary levels of protein structure are preserved by non covalent forces or bonds like hydrogen bonds, electrostatic bonds, hydrophobic interactions and Vander Waals forces.

5.3.2 Hydrogen Bond is a weak electrostatic attraction between one electronegative atom like O or N and a hydrogen atom covalently linked to a second electronegative atom. Hydrogen atoms can be donated by –NH (imidazole, indole, and peptide); -OH (serine, threonine) and -NH2 (arginine, lysine). Hydrogen accepting groups are COO- (aspartic, glutamic) C=O (peptide); and S–S (disulphide).

Electrostatic Bonds (Ionic Bonds): Positive charges are donated by ε-amino group of lysine, guanidinium group of arginine and imidazolium group of histidine. Negative charges are provided by β and γ carboxyl groups of aspartic and glutamic acids.

Hydrophobic Bonds are formed by interactions between nonpolar hydrophobic side chains by eliminating water molecules. This serves to hold lipophilic side chains together.

The **Vander Waals Forces** are very weak, but collectively contribute maximum towards the stability of protein structure.

Alpha Helix

Pauling and Corey described the alpha-helix and beta-pleated sheet structures of polypeptide chains in 1951.

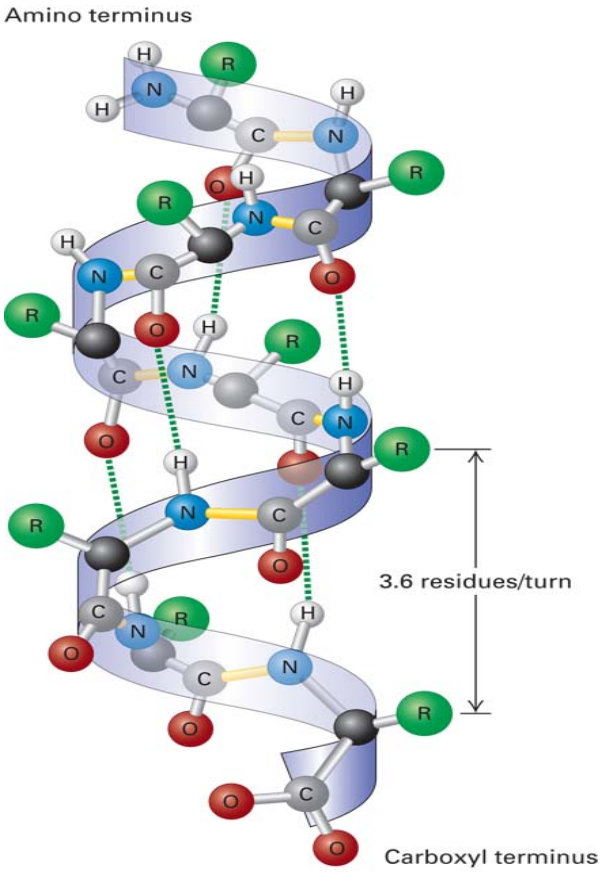

Fig. 5.4: Alpha helix

https://digfir-published.macmillanusa.com/lodish8e/lodish8e_ch3_4.html

The alpha-helix is the most common and stable conformation for a polypeptide chain. In proteins like hemoglobin and myoglobin, the alpha-helix is abundant, whereas it is virtually absent in chymotrypsin. The alpha helix is a spiral structure. The polypeptide bonds form the back-boneand the side chains of amino acids extend outward. The structure is stabilized by hydrogen bonds between NH and C=O groups of the main chain. Each turn is formed by 3.6 residues. The distance between each amino acid residue is 1.5 Å. The alpha-helix is generally right handed. Left handed alpha helix is rare, because amino acids found in proteins are of L-variety, which exclude left handedness. Proline and hydroxy proline will not allow the formation of alpha-helix.

Beta-pleated sheet

The polypeptide chains in beta-pleated sheet are almost fully extended. The distance between adjacent amino acids is 3.5Å.It is stabilized by hydrogen bonds between NH and C=O groups of neighboring polypeptide segments. Adjacent strands in a sheet can run in the same direction with regard to the amino and carboxy terminal ends of the polypeptide chain (parallel) or in opposite direction (anti parallel beta sheet). Beta-pleated sheet is the major structural motif in proteins like silk Fibroin (antiparallel), Flavodoxin (parallel) and Carbonicanhydrase (both). **iv.** Beta bends may be formed in many proteins by the abrupt U-turn folding of the chain. Intra chain disulfide bridges stabilize these bends.

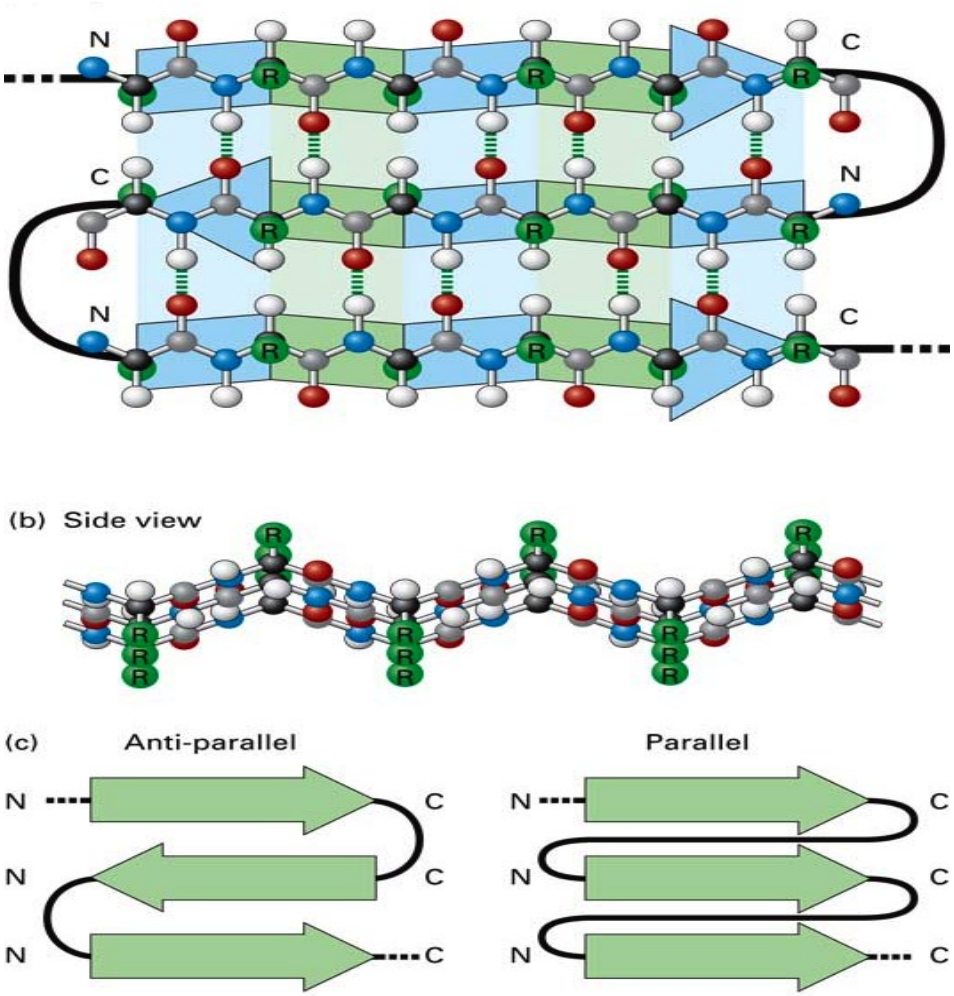

Fig. 5.5: Beta-Pleated Sheet

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5.3.3 Tertiary Structure

Secondary structure denotes the configurational relationship between residues which are about 3-4 amino acids apart or secondary level defines the organization at immediate vicinity of amino acids. The tertiary structure denotes three-dimensional structure of the whole protein. The tertiary structure defines the steric relationship of amino acids which are far apart from each other in the linear sequence, but are close in the three-dimensional aspect. ii. The tertiary structure is maintained by non covalentinte ractions such as hydrophobic bonds, electrostatic bonds and vander Waals forces. The tertiary structure acquired by native protein is always thermodynamically most stable.

Domain is the term used to denote a compact globular functional unit of a protein. A domain is a relatively independent region of the protein, and may represent a functional unit. The domains are usually connected with relatively flexible areas of protein. Phenyl alanine hydroxylase enzyme contains 3 domains, one regulatory, one catalytic and one protein-protein interaction domains.

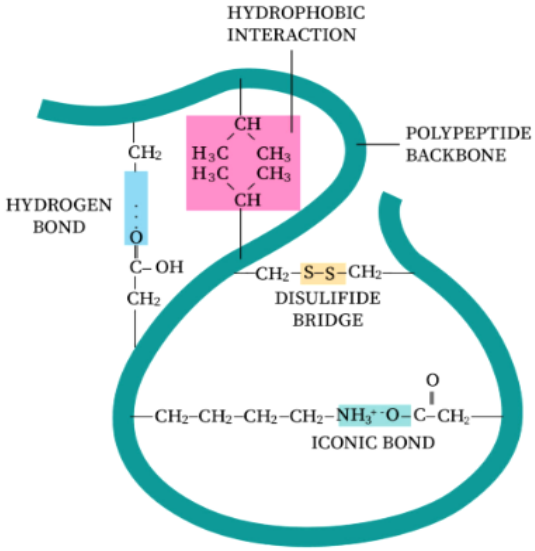


Fig. 5.6: Tertiary Structure

https://studymind.co.uk/notes/protein-structures-tertiary-and-quaternary-structures/

5.3.4 Quaternary Structure

Certain polypeptides will aggregate to form one functional protein. This is referred to as the quaternary structure. The protein will lose its function when the levels of organizations of proteins subunits are dissociated. The forces that keep the quaternary structure are hydrogen bonds, electrostatic bonds, hydrophobic bonds and vander Waals forces. iv. Depending on the number of polypeptide chain, the protein may be termed as monomer (1 chain), dimer (2 chains), tetramer (4 chains) and so on. Each polypeptide chain is termedas subunit or monomer. Homodimer contains two copies of the same polypeptide chain.Heterodimer contains two different types ofpolypeptides as a functional unit.v. For example, 2 alpha-chains and 2 beta-chains form the Hemoglobin molecule. Similarly, 2 heavy chains and 2 light chains form one molecule of immunoglobulin G. Creatinekinase (CK) is a dimer. Lactate dehydrogenase (LDH) is a tetramer.

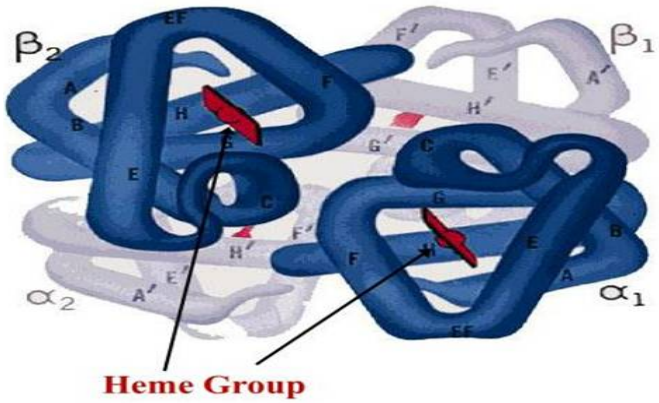


Fig. 5.7: Quaternary Structure: Haemoglobin

Source: https://www.slideserve.com/preston/hemoglobin-quaternary-structurequaternary-structure

5.4 FUNCTIONS:

- **Becoming a Source of Energy**

Apart from carbohydrates and fats, protein also serves as one of the body's energy sources. In essence, the body will use energy from carbohydrates and fats. Nevertheless, when the body does not get adequate intake of both for 18–48 hours, it will break down stored protein as amino acids into additional energy. This process usually occurs when you are exercising or fasting.

- **Building and Maintaining Body Tissues**

Protein is a nutrient that plays a significant role in building almost all body cells, including bones, muscles, lungs, hair, and skin. Protein functions to maintain or repair damaged body tissues. Normally, the necessary protein to build and maintain body tissues remains the same every day. However, there are some conditions that sometimes cause the body to require more protein, such as pregnancy, breastfeeding, or certain diseases.

- **Accelerating Chemical Reactions**

Enzymes are a type of protein that functions to accelerate thousands of chemical reactions, both inside and outside the body's cells. This function of protein is supported by a combination of molecules in cells called substrates.Some enzymes also require other molecules, such as vitamins and minerals, to carry out chemical reactions. Some processes that depend on enzymes include food digestion, blood clotting, muscle contraction, and energy production.

- **Sending Signals to the Body**

In addition to enzymes, proteins can be hormones that function to send signals and control biological processes between cells, tissues, and organs. For example, insulin sends signals to body cells to absorb sugar into muscle and liver cells.

- **Forming Antibodies**

One of the functions of protein for the body is to form antibodies in the immune system. Antibodies are essential components in the body that function to combat viruses, bacteria, and other foreign objects that can cause infections.

- **Forming Hemoglobin and Blood Plasma**

In addition to forming antibodies, the benefit of protein for the body is to aid in the formation of hemoglobin, which is an important blood component for binding oxygen and distributing it to every body tissue. Nonetheless, this function can only occur when protein combines with hemeiron. Furthermore, protein also functions to form blood plasma. The types of proteins that form blood plasma are globulin and albumin. Blood plasma itself is a component responsible for carrying electrolytes, vitamins, glucose, and amino acids throughout the body.

- **Storing Nutrients**

Protein also functions in transporting nutrients, such as vitamins, blood sugar, minerals, oxygen, and cholesterol, throughout the bloodstream. Protein is also beneficial for storing nutrients, one of which is ferritin, a type of protein that stores the body's iron needs.

- **Maintaining Body Strength and Flexibility**

Some types of proteins, such as collagen, elastin, and keratin, play a role in maintaining the strength and flexibility of the body. Collagen is useful for maintaining bone density, muscles, tendons, and ligaments. On the other hand, elastin is essential to maintain the body's flexibility so that it can be moved freely.Meanwhile, keratin is beneficial for keeping the strength of the skin, hair, and nails. If you experience hair loss, dry skin, or brittle nails, then one of the causes may be protein deficiency.

- **Maintaining Acid-Base Balance and Body Fluids**

Another function of protein is to maintain the body's acid-base balance. Proteins work by taking or releasing hydrogen so that the body's acidity remains balanced. Moreover, proteins named albumin and globulin can also balance body fluids by drawing and retaining water levels in the blood. Protein plays an important role in maintaining the function of body organs. Therefore, it is best to properly meet daily protein needs.

5.6 DIGESTION AND ABSORPTION OF PROTEINS

The proteolytic enzymes secreted in pancreatic juice and also present in the intestinal mucosa cause the hydrolysis of proteins in the intestinal tract. In the stomach pepsin is present in gastric juice and hydrolyzes the peptide bonds in the interior of the protein molecule. Pepsin hydrolyzes the dietary protein into a mixture of polypeptides:

$$\textbf{Dietary protein} \xrightarrow{\textbf{pepsin}} \textbf{Polypeptides}$$

Renin has a strong action on milk. This is very important in the digestion of milk proteins in infants. The polypeptides formed in the stomach are digested in the intestine by trypsin, chhymotrypsin and carboxy peptidases secreted in pancreatic juice and amino peptidases present in the intestinal mucosa. Trypsin hydrolyzes peptide linkages containing arginine or lysine and chymotrypsin hydrolyzes peptide linkages containing tyrosine or phenylalanine

$$\textbf{Polypeptides} \xrightarrow[\textbf{Chymotrypsin}]{\textbf{Trypsin}} \textbf{peptides + aminoacids}$$

Carboxypeptidase A hydrolyzes the end group of peptides containing aromatic or aliphatic aminoacid and releases free aminoacids. Carboxypeptidase B hydrolyzes peptides

containing arginine and lysine residues. The intestinal mucosa also contains tripeptidase, dipeptidase etc which hydrolyze tri and dipeptides.

Carboxypeptidase

Peptides ⟶ Aminoacids

Aminopeptidase

Peptides ⟶ Aminoacids

Dipeptidase

Dipeptides ⟶ Aminoacids

Tripeptidase

Tripeptides ⟶ Aminoacids

The final products of digestion of proteins are amino acids which are absorbed.

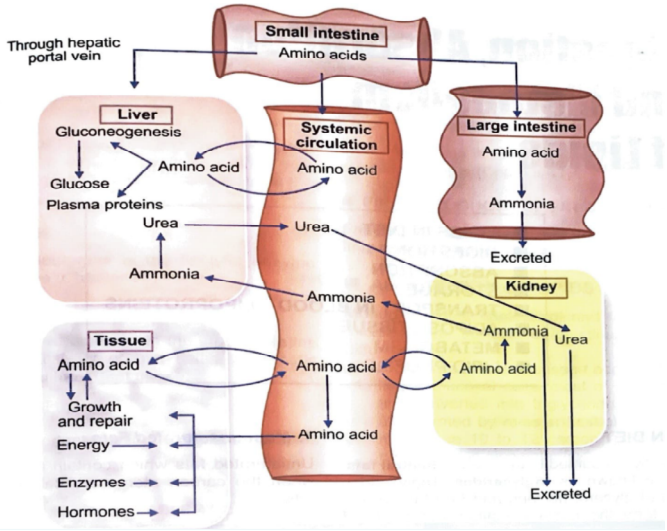


Fig. 5.8: Metabolism of Proteins

Source: https://www.jaypeedigital.com/book/9789350259368/chapter/ch46

Absorption

Three different active processes are involved in the transport of amino acids. One process involves cystine and the basic amino acids, another the amino acids proline and hydroxyproline and the third the neutral (L-) amino acids.

D-amino acids are absorbed by simple diffusion. But the neutral (L-) amino acids require a carrier system in the absorption. Na^+ is also required. This is similar to that of active transport of glucose. Vitamin B_6 is also involved in the process. The amino acid associates with the carrier and Na^+ in the microvilli and the complex travels to the inner side of the membrane where it dissociates, releasing the amino acid Na^+ in to the cytosol. The carrier returns back and functions repeatedly. Na^+ is then actively transported out of the cell. If one amino acid is fed in excess, it retards the absorption of another. This is similar to those made

with respect to reabsorption of amino acids by the renal tubules. Sometimes the whole protein is absorbed into the blood. A protein is antigenic and accounts for food allergies. In the young animal, the permeability of the mucosa, in this respect is greater than that in the adult.

Food proteins are generally readily digested 90-97%) under normal conditions, very little escapes in the faeces. The insoluble fibrous protein, keratin, is not hydrolyzed by enzymes of the human digestive tract. These are altered by heating to coagulation and hydrolyzed by superheated steam. The biological values of these proteins are not affected by such procedures. Cooked egg albumin is digested more readily than raw. The nutritional value of cereal proteins is lowered by overheating or toasting.

5.7. SUMMARY:

Proteins are considered as essential nutrients and are involved in various biochemical processes like catalysis, movement of muscles, immunity, cell support, transport and storage.

Protein-rich animal-based foods commonly have high amounts of B vitamins, vitamin E, iron, magnesium, and zinc. Seafood generally contains healthy fats, and plant sources of protein contain a high amount of fiber. Proteins have different levels of structural organization; primary, secondary, tertiary and quaternary. The proteolytic enzymes secreted in pancreatic juice and also present in the intestinal mucosa cause the hydrolysis of proteins in the intestinal tract. Food proteins are generally readily digested (90-97%) under normal conditions, very little escapes in the faeces. The insoluble fibrous protein, keratin, is not hydrolyzed by enzymes of the human digestive tract.

5.8. TECHNICAL TERMS:

Peptide bond, alpha helix, beta pleated sheet, heamoglobin, digestion, absorption.

5.9 SELF ASSESSMENT QUESTIONS:

1) Write an essay on sources and functions of proteins.
2) Explain in detail about structural organization of proteins.
3) Discuss in detail about digestion and absorption of proteins.

5.10 REFERENCE BOOKS:

1) D.M. Vadudevan, S.Sree Kumari and Kannan Vaidyanathan Text Book of Biochemistry for Medical Students, Sixth Edition.
2) Ahern, Rajagopal and TAN Biochemistry Free for All, Version 1.3.
3) K.Sembulingam, Prema Sembulingam, Medical Physiology, 6th Edition.

Dr. P. Kiranmayi

LESSON-6

AMINO ACIDS

6.0 OBJECTIVES:

After going through this lesson students will understand:

- Amino Acid Classification
- Role of Peptides
- Decarboxylation and Transpeptidation Reactions

STRUCTURE:

6.1. INTRODUCTION:

All of the proteins on the earth are made up of the same 20 amino acids. Linked together in long chains called polypeptides, amino acids are the building blocks for the vast assortment of proteins found in all living cells. All amino acids have the same basic structure.

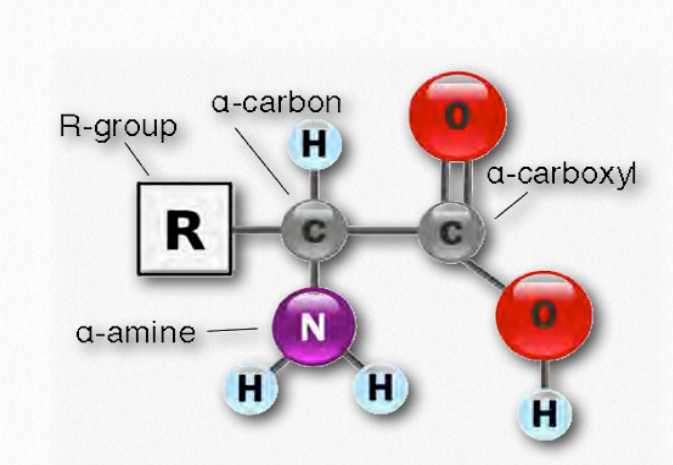


Fig. 6.1: General Structure of Amino Acid
Source: Ahern et al Biochemistry free for all Verson 1.3

At the "center" of each amino acid is a carbon called the α carbon and attached to it are four groups - a hydrogen, an α carboxyl group, an α-amine group, and an R-group, sometimes referred to as a side chain. The α carbon, carboxyl, and amino groups are common to all amino acids, so the R-group is the only unique feature in each amino acid. (A minor exception to this structure is that of proline, in which the end of the R-group is attached to the α-amine.) With the exception of glycine, which has an R-group consisting of a hydrogen atom, all of the amino acids in proteins have four different groups attached to them and consequently can exist in two mirror image forms, L and D. With only very minor exceptions, every amino acid found in cells and in proteins is in the L configuration. There are 22 amino acids that are found in proteins and of these, only 20 are specified by the universal genetic code.

6.2 CASSIFICATION OF AMINOACIDS

Amino Acids are classified in to

Non-Polar	Carboxyl	Amine	Aromatic	Hydroxyl	Other
Alanine	Aspartic Acid	Arginine	Phenylalanine	Serine	Asparagine
Glycine	Glutamic Acid	Histidine	Tryptophan	Threonine	Cysteine
Isoleucine		Lysine	Tyrosine	Tyrosine	Glutamine
Leucine					Selenocysteine
Methionine					Pyrrolysine
Proline					
Valine					

Fig. 6.2: Amino Acid Categories (Based on R-Group Properties)
Source: Ahern et al Biochemistry free for all Verson 1.3

6.2.1 Essential and Non Essential Amino Acids

Essential and non-essential Nutritionists divide amino acids into two groups – Essential amino acids (must be in the diet because cells can't synthesize them) and non-essential amino acids (can be made by cells). Essential amino acids vary considerable from one organism to another and even differ in humans, depending on whether they are adults or children.

Essential	Non-Essential
Histidine	Alanine
Isoleucine	Arginine
Leucine	Asparagine
Lysine	Aspartic acid
Methionine	Cysteine
Phenylalanine	Glutamic acid
Threonine	Glutamine
Tryptophan	Glycine
Valine	Proline
	Selenocysteine
	Serine
	Tyrosine

Fig. 6.3
Source: Ahern et al Biochemistry free for all Verson 1.3

Essential and Non Essential Amino Acids

Some amino acids that are normally non essential, may need to be obtained from the diet in certain cases. Individuals who do not synthesize sufficient amounts of arginine, cysteine, glutamine, proline, selenocysteine, serine, and tyrosine, due to illness, for example, may need dietary supplements containing these amino acids.

6.2.2 Nonprotein Amino Acids

There are also α-amino acids found in cells that are not incorporated into proteins. Common ones include ornithine and citrulline.

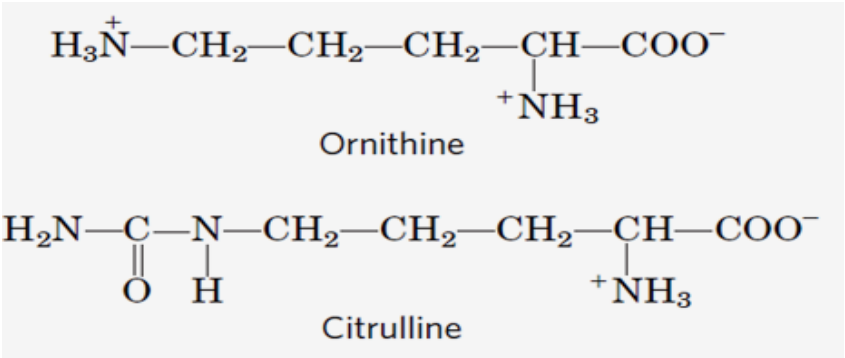


Fig. 6.3: Non Proteins Amino Acids
Source: Ahern et al Biochemistry free for all Verson 1.3

6.2.3 Nonpolar Amino Acids

Non polar amino acids include alanine, Glycine, leucine, isoleucine, methionine, proline and valine.

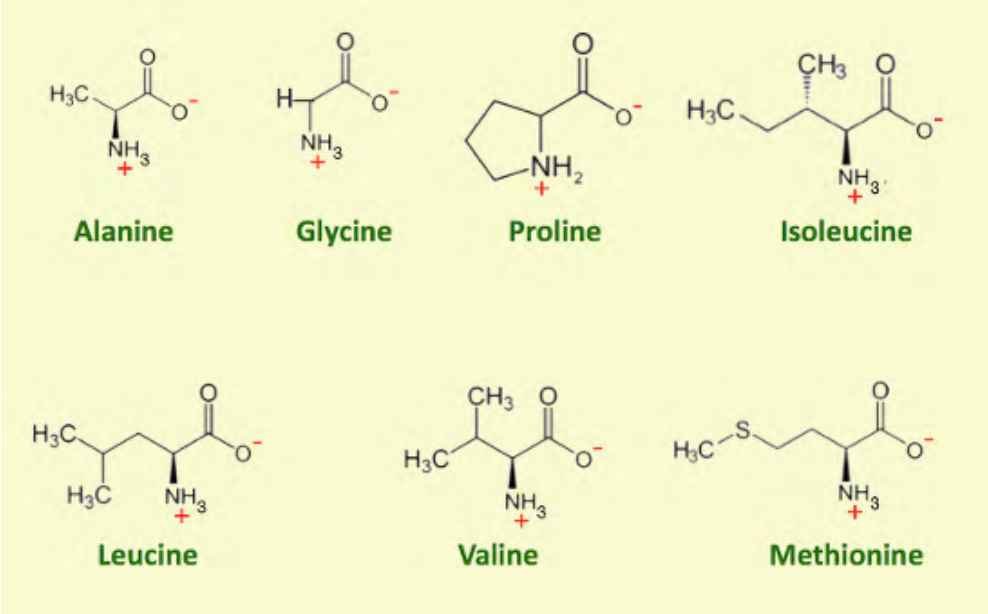


Fig. 6.4: Non Polar Amino Acids

Source: Ahern et al Biochemistry free for all Verson 1.3

6.2.4 Aromatic Amino Acids

Phenylalanine (Phe/F) is a non-polar, essential amino acid coded by UUU and UUC. It is a metabolic precursor of tyrosine. Inability to metabolize phenylalanine arises from the genetic disorder known as phenylketonuria.

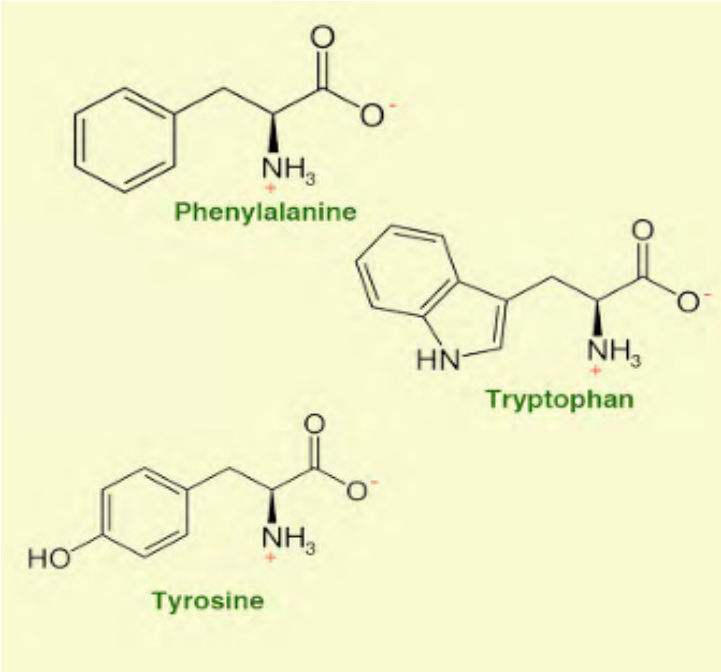


Fig. 6.5: Aromatic Amino Acids

Source: Ahern et al Biochemistry free for all Verson 1.3

Phenylalanine is a component of the aspartame artificial sweetener. Tryptophan (Trp/W) is an essential amino acid containing an indole functional group. It is a metabolic precursor of serotonin, niacin, and (in plants) the auxinphytohormone. Though reputed to serve as a sleep aid, there are no clear research results Tyrosine (Tyr/Y) is a non-essential amino acid coded by UAC and UAU. It is a target for phosphorylation in proteins by tyrosine protein kinases and plays a role in signaling processes. In do paminergic cells of the brain, tyrosine hydroxy lase converts tyrosine to l dopa, an immediate precursor of dopamine. Dopa mine, in turn, is a precursor of norepinephrine and epinephrine. Tyrosine is also a precursor of thyroid hormones and melanin.

6.2.5 Carboxyl Amino Acids

Carboxyl Amino Acids are aspartic acid and glutamic acid

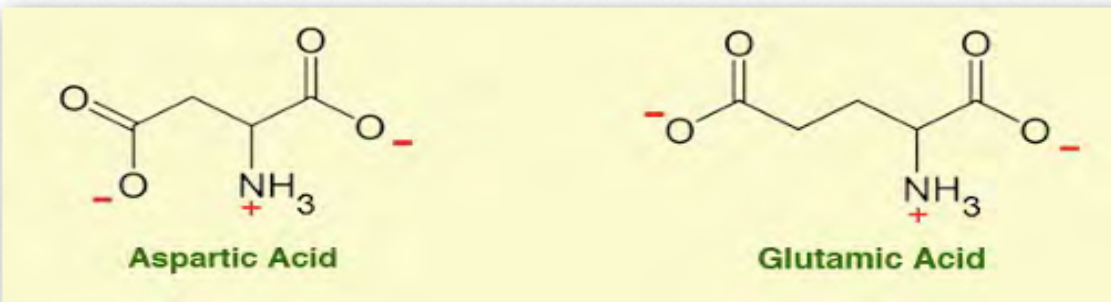


Fig. 6.6: Carboxyl amino acids

Source: Ahern et al Biochemistry free for all Verson 1.3

6.2.6 Amine amino acids

Amine amino acids are arginine, histidine and lysine.

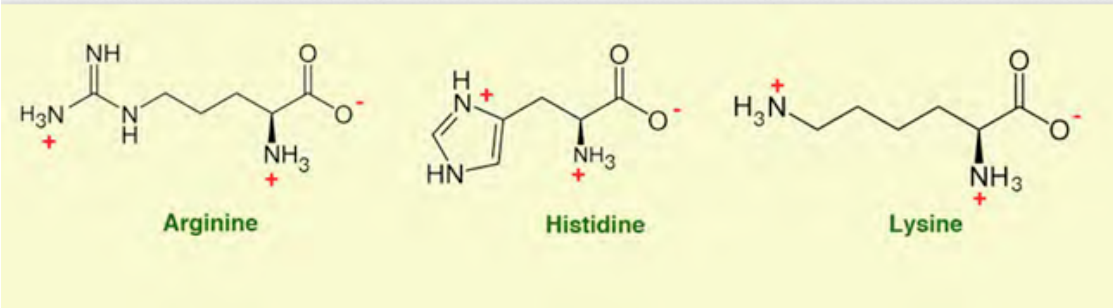


Fig. 6.7: Amine amino acids

Source: Ahern et al Biochemistry free for all Verson 1.3

6.2.7 Hydroxyl Amino Acids

Serine (Ser/S) is one of three amino ac ids having an R-group with a hydroxyl in it (threonine and tyrosine are the others). Being able to hydrogen bond with water, it is classified as a polar amino acid. It is not essential for humans. Serine is pre cursor of many important cellular com pounds, including purines, pyrimidines, sphingolipids, folate, and of the amino acids glycine, cysteine, and Tyrosine (Tyr/Y) is a non-essential amino acid. It is a target for phosphorylation in pro teins by tyrosine protein kinases and plays a role in signaling processes. In do paminergic cells of the brain, tyrosine hydroxy lase converts tyrosine to l dopa, an immediate precursor of dopamine. Dopa mine, in turn, is a precursor of norepinephrine and epinephrine. Tyrosine is also a precursor of thyroid hormones and melanin.

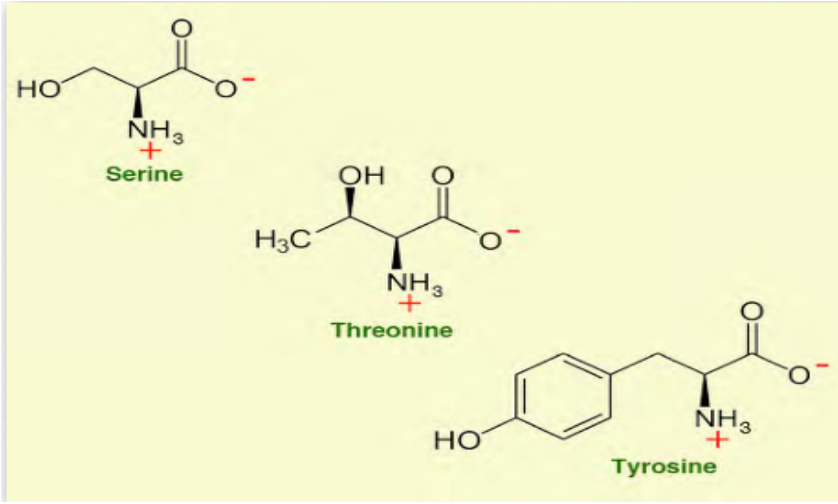


Fig. 6.8: Hydroxyl Amino Acids
Source: Ahern et al Biochemistry free for all Verson 1.3

6.3 PEPTIDES AND PROTEINS

Although amino acids serve other functions in cells, their most important role is as constituents of proteins. Proteins, as we noted earlier, are polymers of amino acids. Amino acids are linked to each other by peptide bonds, in which the carboxyl group of one amino acid is joined to the amino group of the next, with the loss of a molecule of water. Additional amino acids are added in the same way, by formation of peptide bonds between the free carboxyl on the end of the growing chain and the amino group of the next amino acid in the sequence. A chain made up of just a few amino acids linked together is called an oligopeptide (oligo-few) while a typical protein, which is made up of many amino acids is called a polypeptide (poly-many). The end of the peptide that has a free amino group is called the N-terminus (for NH_2), while the end with the free carboxyl is termed the C terminus (for carboxyl).

6.4 METABOLISM OF AMINO ACIDS

Amino acid metabolism in contrast to some of the metabolic path ways described to this point, amino acid metabolism is not a single pathway. The 20 amino acids have some parts of their metabolism that overlap with each other, but others are very different from the rest. In discussing amino acid metabolism, we will group metabolic pathways according to common metabolic features they possess.

General reactions of amino acid metabolism are Decarboxylation, Transamination and deamination.

6.4.1 Decarboxylation

Decarboxylation Decarboxylation is the reaction by which CO_2 is removed from the COOH group of an amino acid as a result an amine is formed. The reaction is catalysed by the enzyme decarboxylase, which requires pyridoxal-P (B_6-PO_4) as coenzyme. Tissues like liver, kidney, brain possess the enzyme decarboxylase and also by microorganisms of intestinal tract. The enzyme removes CO_2 from COOH and converts the amino acid to corresponding amine.

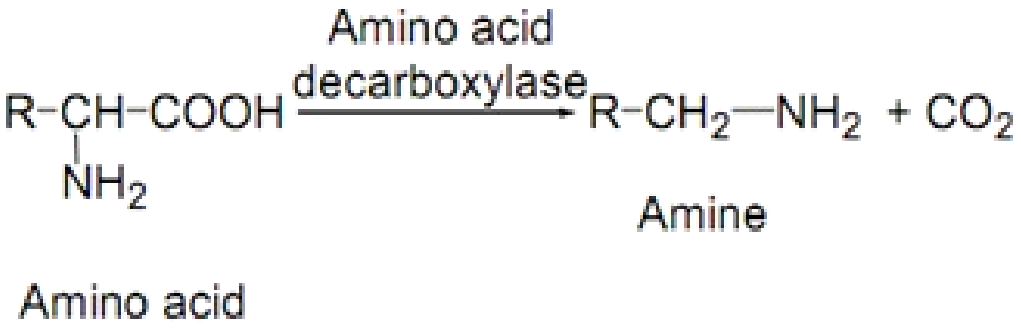
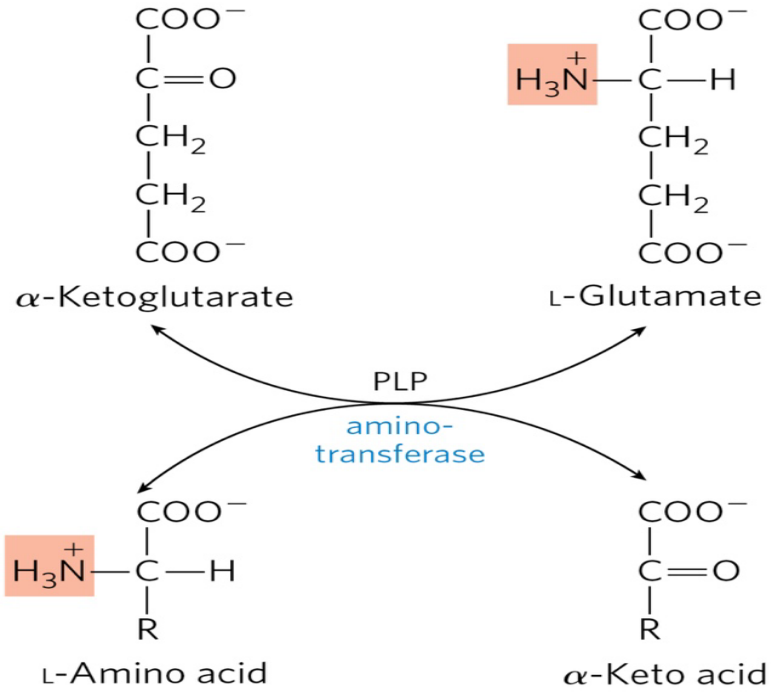


Fig. 6.8

6.4.2 Transamination

The first step in the catabolism of most L-amino acids is tramsamination. It occurs in most tissues. It is promoted by enzymes called aminotransferases or transaminases. The α-amino group is transferred to the α-carbon atom of α- ketoglutarate, leaving behind the corresponding α-keto acid analog of the amino acid.



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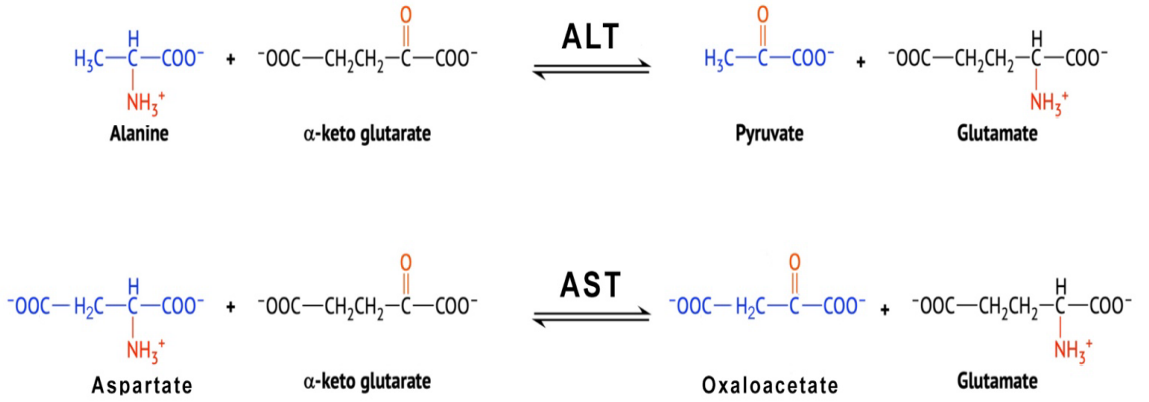
Many are specific for α-ketoglutarate as the amino group acceptor but differ in their specificity for the L-amino acid. These reactions are freely reversible so they can be used to resynthesize amino acids. All aminotransferases have pyridoxal phosphate (PLP), the coenzyme form of pyridoxine (vitamin B6). Pyridoxal phosphate functions as an intermediate carrier of amino groups at the active site of aminotransferases. The 2 most clinically important aminotransferases are ALT (GPT) and AST (GOT):



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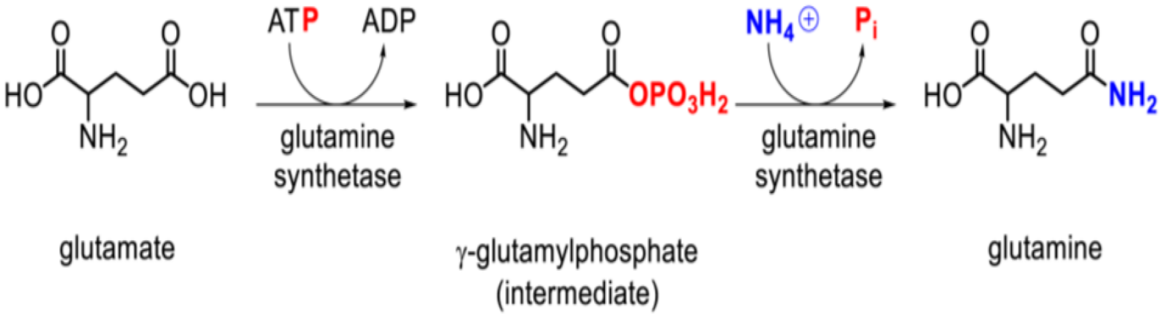
All amino acids undergo transamination except lysine, threonine, proline and hydroxyproline which they bypass transamination and undergo direct oxidative deamination.

6.4.3 Oxidative deamination

Occurs in hepatocytes. Glutamate is transported from the cytosol into mitochondria, where it undergoes oxidative deamination catalyzed by L-glutamate dehydrogenase to produce NH^{4+} and α- ketoglutarate. The combined action of an aminotransferase and glutamate dehydrogenase is referred to as transdeamination.

Glutamine synthesis: In many tissues, including the brain, some processes such as nucleotide degradation and termination of neurotransmitter signals generate free ammonia. The free ammonia produced in tissues is combined with glutamate to yield glutamine by the action of glutamine synthetase. This reaction requires ATP and occurs in two steps:



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Excess glutamine is transported in the blood to the intestine, liver, and kidneys where the enzyme glutaminase converts glutamine to glutamate and NH4+. The NH4+ from intestine and kidney is transported in the blood to the liver.

6.5 Transpeptidation Reaction

The chemical reaction that forms the peptide cross-links or bonds during the synthesis of peptidoglycan (murein) in a bacterial cell wall. Peptidoglycan or murein is a polysaccharide molecule that consists mainly of alternating repeats of **N-acetylglusamine (NAG)** and **N-acetylmuramic acid (NAM)**. Murein is a bacterial cell wall polymer that contains short peptide molecules which forms glycan tetrapeptide during the Transpeptidation reaction.

NAG and NAM are two sugar derivative molecules with some amino acids (e.g. D-glutamic acid, L-alanine and D-alanine) attached to them both. NAG, NAM and the amino acids join together in a chemical reaction to form glycan tetrapeptide. To each molecule of NAM and NAG is attached a tetrapeptide consisting of alternating D- and L- amino acids (L-alanine and D-glutamic acid) to form a glycan tetrapeptide molecule.

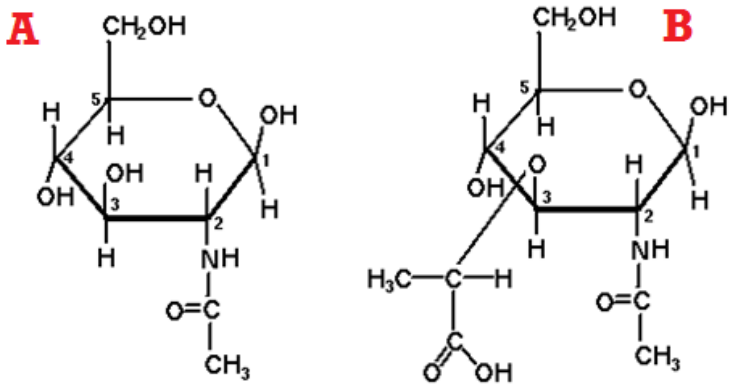


Fig. 6.9: Transpeptidation Reaction

https://microbiologyclass.net/transpeptidation-reaction/

The glycan tetrapeptide repeat unit is cross-linked to adjacent glycan chains either through a direct peptide linkage or peptide interbridge (as is the case for Gram-positive bacteria). But in Gram-negative bacteria, cross-linking of peptidoglycan usually occurs by the formation of peptide bond from lysine or diaminopimelic acid (DAP) of one glycan chain to the carboxyl group of the terminal amino acid (D-alanine) on the adjacent glycan chain. These processes culminate to the formation of peptidoglycan (murein) layer in both Gram-positive and Gram-negative bacteria.

In Gram positive bacteria, it should be noted that the murein layer is usually composed of several sheets of peptidoglycan, and they form a larger proportion of the cell wall of Gram-positive organisms. But in Gram-negative bacteria, the murein layer is only but a single sheet of peptidoglycan. Though Gram-negative bacteria have a thin peptidoglycan layer as opposed to Gram-positive bacteria with a much thicker peptidoglycan layer, the cell wall of the former is much more complex than that of the later. And this is because of the presence of OM which lies outside the thin peptidoglycan layer and the presence of LPS amongst other cell wall constituents that are unique to the Gram-negative bacteria.

6.6. SUMMARY:

Amino acids are the building blocks for the vast assortment of proteins found in all living cells. All amino acids have the same basic structure. At the “center” of each amino acid is a carbon called the α carbon and attached to it are four groups - a hydrogen, an α-carboxyl group, an α-amine group, and an R-group, sometimes referred to as a side chain. The α carbon, carboxyl, and amino groups are common to all amino acids, so the R-group is the only unique feature in each amino acid. Amino acid metabolism In contrast to some of the metabolic path ways described to this point, amino acid metabolism is not a single pathway. The 20 amino acids have some parts of their metabolism that overlap with each other, but others are very different from the rest.

6.7. TECHNICAL TERMS

Peptide bond, carboxylation, transpeptidation

6.8 SELF ASSESSMENT QUESTIONS

1) Write an account on classification of amino acids
2) Explain about decarbodylation
3) Write an essay on transpeptation reaction

6.9. REFERENCE BOOKS:

1) D.M. Vadudevan, S.Sree kumari and Kannan Vaidyanathan Text Book of Biochemistry for Medical Students, Sixth Edition.
2) Ahern, Rajagopal and TAN Biochemistry Free for All, Version 1.3
3) A.C.D.E.B., Fundamentals of Biochemistry.

Dr. P. Kiranmayi

LESSON-7

NUCLEIC ACIDS

7.0 OBJECTIVES:

After going through this lesson students will understand:

- Nucleic acid classification
- DNA replication
- Proteins Biosynthesis

STRUCTURE:

7.1 INTRODUCTION

Nucleic acids are macromolecules. The repeating units in nucleic acids are nucleotides. Nucleic acids derive their names because of their primary occurrence in the nucleus. Elements constituting nucleic acids are C, H, O, N and P. Most of the nucleic acids have approximately 15 to 16% nitrogen and 9 to 12% phosphorus. Nucleic acids are colourless complex compounds which are made up of three units: bases (purine or pyramidine), sugar and phosphoric acid. These are obtained by the careful hydrolysis of nucleoproteins.

7.2 CLASSIFICATION OF NUCLEIC ACIDS

The nucleic acids, DNA and RNA, may be thought of as the information molecules of the cell. DNA is the hereditary information in every cell that is copied and passed on from generation to generation. DNA was discovered in 1869 by Friedrich Miescher, and was identified as the genetic material in experiments in the 1940s led by Oswald Avery, Colin MacLeod, and Maclyn McCarty. X-ray diffraction work of Rosalind Franklin and the observations of Erwin Chargaff were combined by James Watson and Francis Crick to form a model of DNA.

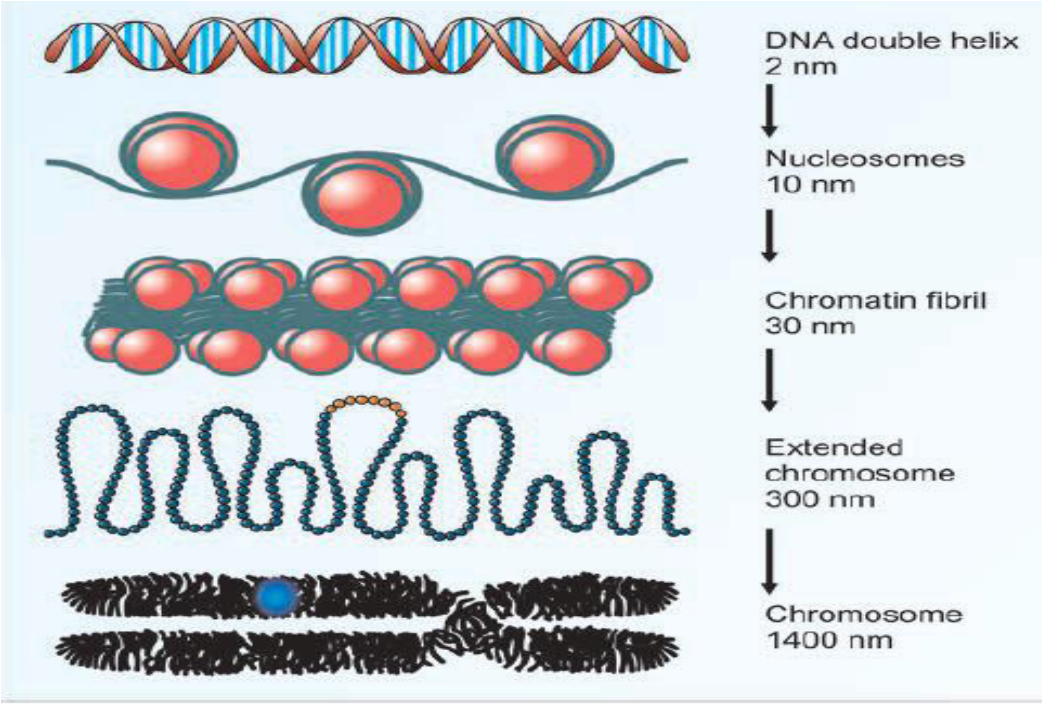


Fig.7.1: DNA condenses to form chromosome

Source: DM. Vasudevan et al 7 edition Text book of biochemistry for medical students

Two types of nucleic acids have been known for a long time: deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). DNA is found predominantly in the nucleus while RNA is predominant in the cytoplasm. The genetic information contained in the DNA molecule is essentially a set of coded instructions for the synthesis of proteins by living cells. DNA also synthesizes RNA and RNA in turn is responsible for the synthesis of proteins. In this way, the nucleic acids determine the ultimate form and function of all living organisms

These are defined as polynucleotides in which repeating units are ribonucleotides (in RNA) or deoxy ribonucleotides (in DNA). The difference between the two structures is that in deoxy ribonucleotides there is no -OH group in position 2^1. The presence of three esterifiable –OH groups in the ribose portion or two in the deoxy ribose portion gives rise to several possible phosphor esters.

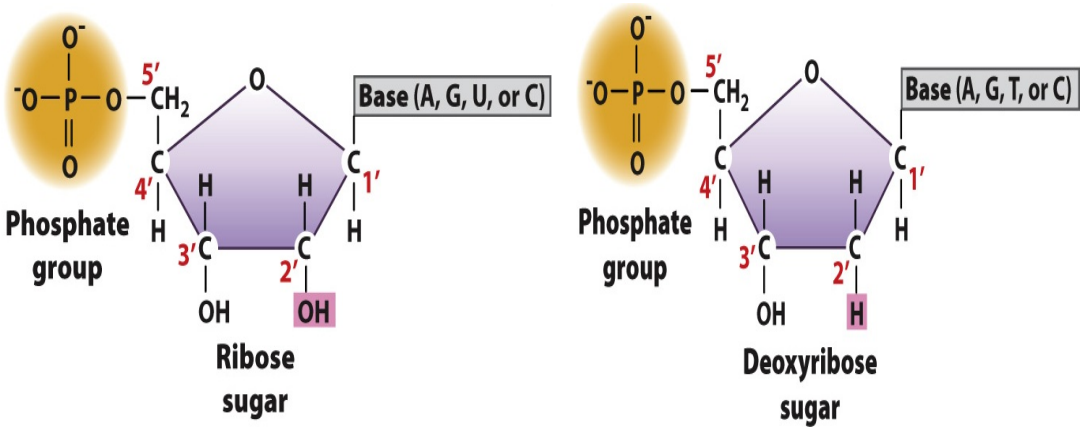


Fig.7.2

Ribonucleotide **Deoxyribonucleotide**

https://digfir-published.macmillanusa.com/morris2e/morris2e_ch2_22.html

Nucleotides are building blocks of large molecules. They serve three crucial functions in cells. Some are energy carriers, other are coenzymes and still others are carriers of hereditary information.

7.2.1 Nucleotides

Structurally, a nucleotide can be regarded as a phosphor ester of a nucleoside. In turn, a nucleoside is a N-glycoside in which the sugar component is ribose or deoxy ribose and aglucon is a pyrimidine or purine base. Thus, nucleotide is composed of three units: a phosphate group derived from phosphoric acid (H_3PO^4), attached to a pentose sugar, attached to a nitrogenous base (either purine or pyramidine). A nucleotide is formed by the reaction of the sugar portion of a nucleoside with phosphoric acid through dehydration synthesis.

Nucleoside + Phosphoric acid →nucleotide + H_2O

The four nucleotides found in DNA are combination of adenine, guanine, cytosine or thymine with deoxy ribose and phosphate.

Nucleosides: A nucleoside is a chemical combination of a pentose sugar and pyrimidine or a purine base. The attachment of the two components is a general dehydration synthesis reaction in which a molecule of water is removed from between the base and sugar.

Nitrogenous base+ Pentose sugar → Nucleoside + H_2O

Thus, a nucleoside is a N-glycoside in which the sugar component is ribose or deoxyribose and the aglucon is a pyrimidine or purine base. Nucleosides containing ribose are called ribonucleosides. Those containing deoxy ribose are called deoxy ribonucleosides.

Nitrogenous bases: there are two types of nitrogenous bases. Pyrimidines and purines. The pyrimidines are single ring compounds, with nitrogen in positions 1 and 3 of a 6 membered benzene ring. The two most common pyrimidines of DNA are cytosine (C) and thymine (T).

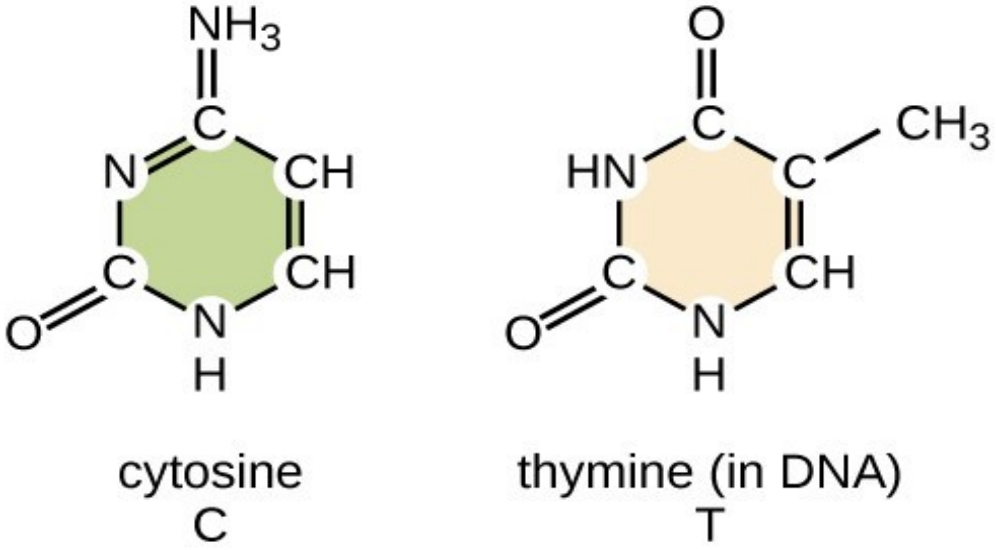


Fig.7.3: Pyrimidines

https://www.nursinghero.com/study-guides/lcc-ctc-microbiology/structure-and-function-of-dna

The purines are double ring compounds. A purine molecule consists of a 5-membered imidazole ring joined to a pyrimidine ring at positions 4 and 5. The two most common purines of DNA are adenine (A) and guanine (g).

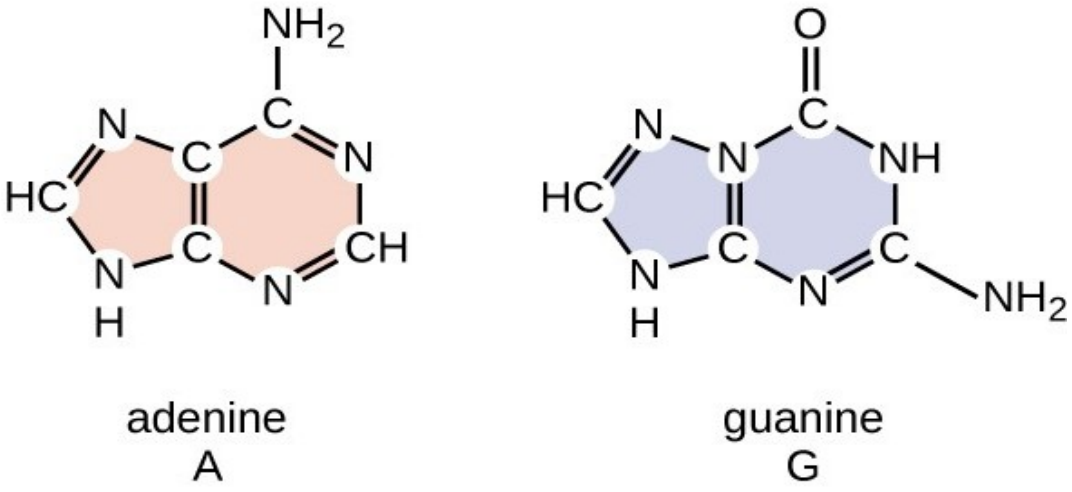


Fig.7.4: Purines

https://www.nursinghero.com/study-guides/lcc-ctc-microbiology/structure-and-function-of-dna

7.3 STRUCTURE OF DNA

DNA is present in the cells of all plants, animals, prokaryotes and in a number of viruses. In eukaryotes it is combined with proteins to form nucleoproteins. In prokaryotes the genetic material consists of a single giant molecule of DNA about 1,000 microns in length, without any associated proteins. DNA is present mainly in the chromosomes. It has also been reported in cytoplasmic organelles like mitochondria and chloroplasts. The DNA of all plants and animals and many viruses is double stranded.

The widely accepted molecular model of DNA is the double helix structure proposed by Watson and Crick (1953). The DNA molecule consists of two helically twisted strands connected together by 'steps'. Each strand consists of alternating molecules of deoxy ribose and phosphate groups. Each step is made up of a double ring purine base and single ring pyrimidine base. The purine and pyrimidine bases are connected to deoxy ribose sugar molecules. The two strands are interwined in a clockwise direction *i.e.,* in a right hand helix and run in opposite directions. The strand completes a turn each 34 A^0. Each nucleotide occupies 3.4A^0. Thus, there are 10 nucleotides per turn. Each successive nucleotide turns 36 degrees in the horizontal plane. The width of the DNA molecule is 20 A^0. The twisting of the strands results in the formation of deep and shallow spiral grooves. The DNA molecule is a polymer consisting of several thousand pairs of nucleotide monomers. Each nucleotide consists of the pentose sugar deoxy ribose, a phosphate group and nitrogenous base which may be either a pruine or a pyrimidine. Deoxy ribose and nitrogenous base together form a nucleoside. A nucleoside and a phosphate together form a nucleotide.

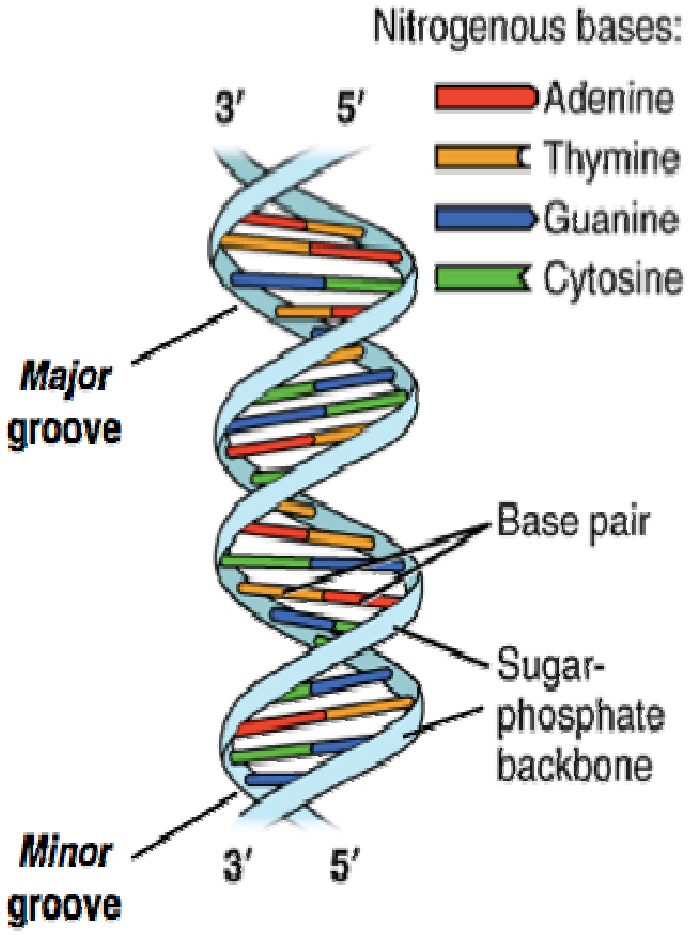


Fig.7.5: Structure of DNA

https://www.khanacademy.org/science/ap-biology/gene-expression-and-regulation/replication/a/hs-dna-structure-and-replication-review

7.3.1 Base pairing

Each step of the DNA ladder is made up of a purine and a pyrimidine pair *i.e.,* of a double ring and a single ring compound.

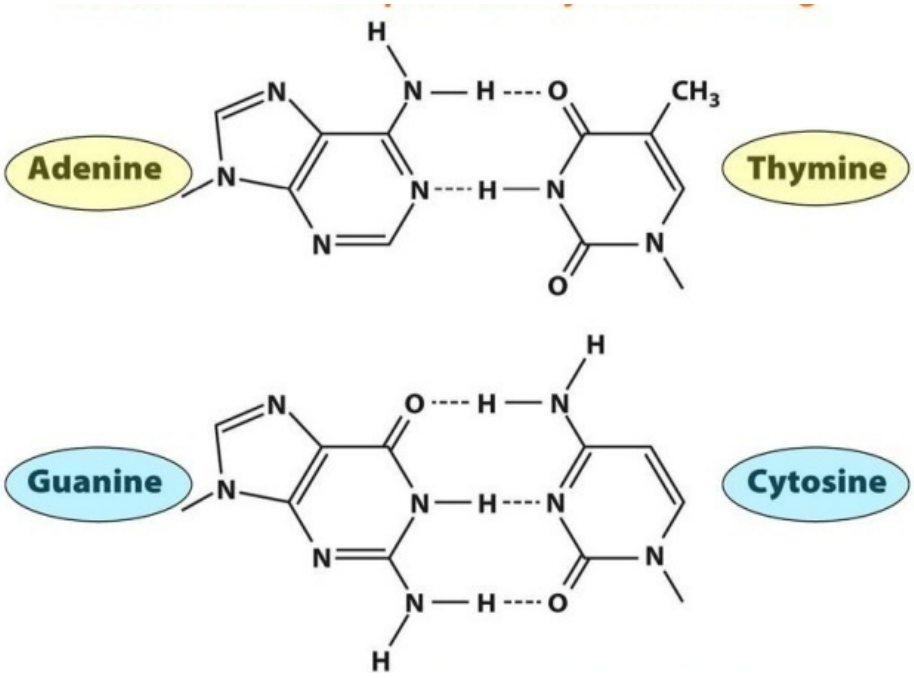


Fig.7.6: Complementary base pairing: Double helix

https://slideplayer.com/slide/16130952/95/images/11/Double-Helix%3A+Complementary+Base+Pairing.jpg

Two purines would occupy too much space, while two pytimidines would occupy too little. Because of the purine-pyrimidine pairing the total number of purines in a double stranded DNA molecule is equal to the total number o pyrimidines. Thus A/T=1 and G/C=1 or A+G=C+T. The ratio A+T/G+C, however, rarely equals 1 , and varies with different species from 0.4 to 1.9. This ratio is commonly low in micro organisms and high in higher animals.

7. 4 STRUCTURE OF RNA

RNA is also a polynucleotide but the pentose ribose has a hydroxyl group in position 2^1. It is a long chain polynucleotide which does not exist in a regular conformation like a double stranded DNA although some viruses have double stranded RNA. The single RNA strand is folded upon itself, either entirely or in certain regions. In the folded region a majority of the bases are complementary and are joined by hydrogen bonds. This helps in the stability of the molecule. In the unfolded region the bases have no complements. Due to this, RNA is not having the purine-pyramidine quality that is found in DNA. It is understandable that on a single chain of RNA the molar proportion of purines and pyrimidines can vary considerably.

RNA does not contain the pyrimidine base thymine but the pyrimidine uracil instead. In regions where purine-pyrimidine pairing takes place, adenine pairs with uracil and guanine with cytosine. This base pairing is of importance when RNA is being synthesized by DNA and RNA is involved in protein synthesis. In addition to the four bases mentioned above, RNA has also some unusual bases; there are more unusual bases in RNA than in DNA. All normal RNA chains either start with adenine or guanine.

7.4.1 Types of RNA

There are three types of RNA: messenger RNA (m RNA), ribosomal RNA (r RNA) and transfer RNA (t RNA).

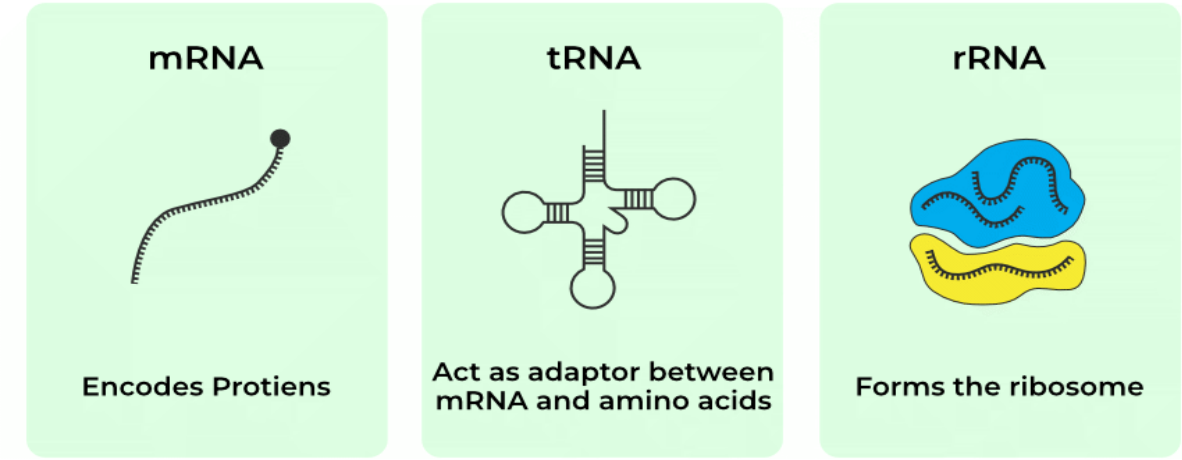


Fig.7.7: Types of RNA

Source: https://microbenotes.com/rna-ribonucleic-acid/

m RNA: this is so named because it carries information for protein synthesis from the DNA to the sites of protein formation (ribosomes). Only about 5% of total cellular content of RNA is m RNA. Messenger RNA is always single stranded. It contains mostly the bases adenine, guanine, cytosine and uracil. The sequence of bases n m RNA molecules is complementary to the bases that constitute the genetic code.

Ribosomal RNA: it occurs in combination with protein as ribonucleoprotein in the minute round particles called ribosomes which are attached to the surfaces of intra cellular membrane system called endoplasmic reticulum. It constitutes about 80% of the total RNA of the cell.

Transfer RNA: it plays an important role in transfer of amino acids in the process of protein synthesis. Each amino acid is carried by a specific t RNA. It is the smallest of the RNA species containing about 15 to 80 nucleotides.

The structure of t RNA is conventionally represented in the form of a clover leaf. The t RNA molecule has four recognition sites

- Amino acid attachment site: it is the 3^1 terminal- CCA sequence
- Anticodon site: it consists of the middle three bases on the anticodonn loop which forms the anticodon
- Ribosome recognition site: this is common to all t RNA and consists of G-T-Ψ-C-R sequence o the TΨC loop.

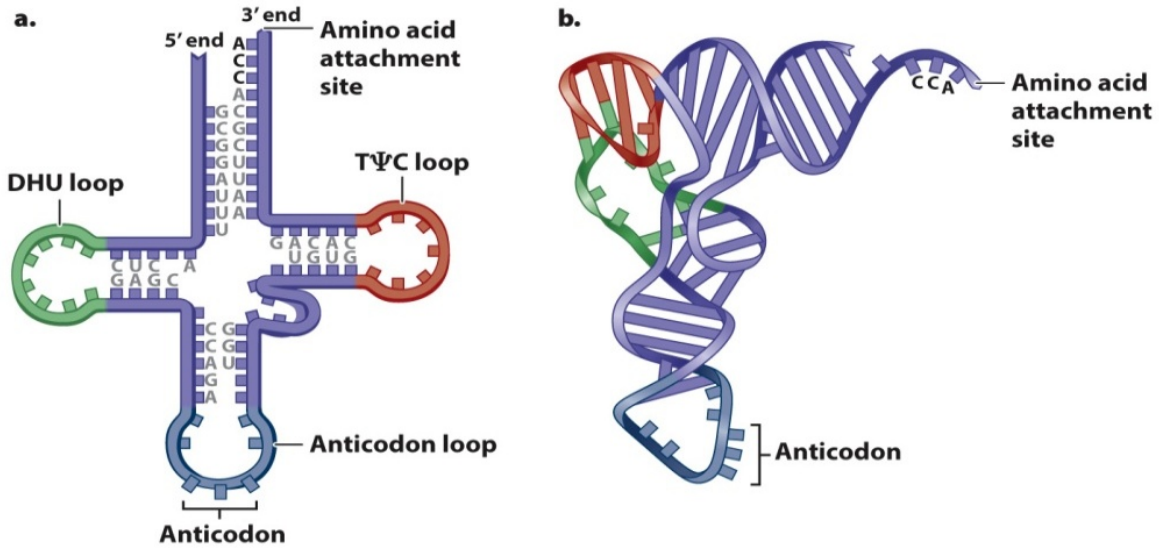


Fig.7.8: Structure of t RNA

https://digfir-published.macmillanusa.com/morris2e/morris2e_ch4_11.html

7.5 SYNTHESIS OF NUCLEIC ACIDS

7.5.1 DNA REPLICATION

New cells are synthesized by the division of pre existing cells. Each time the cell divides, its DNA must be copied so that a copy of this information passed on to the daughter cells. This process is known as DNA replication. DNA replication takes place in three stages- initiation, elongation and termination.

Initiation:

- Replication begins at specific initiation point and this is a unique sequence of bases called *Ori*.
- In *Ori* there are two series of short repeats such as three repeats of a 13 base pair sequence and four repeats of a 9 base pair sequence.
- In this process about 20 Dna A protein molecule each with a bound ATP, bind at the four repeats of 9 base pair sequence, DNA is wrapped around the complex.
- With the help of ATP and histone like protein HU, the three 13 base pair repeats are denatured to give open cimpled.
- With the help of Dna C protein ATP Dna B protein binds to the open complex to form prepriming complex. As a result, unwinding of DNA occurs and priming replication starts.

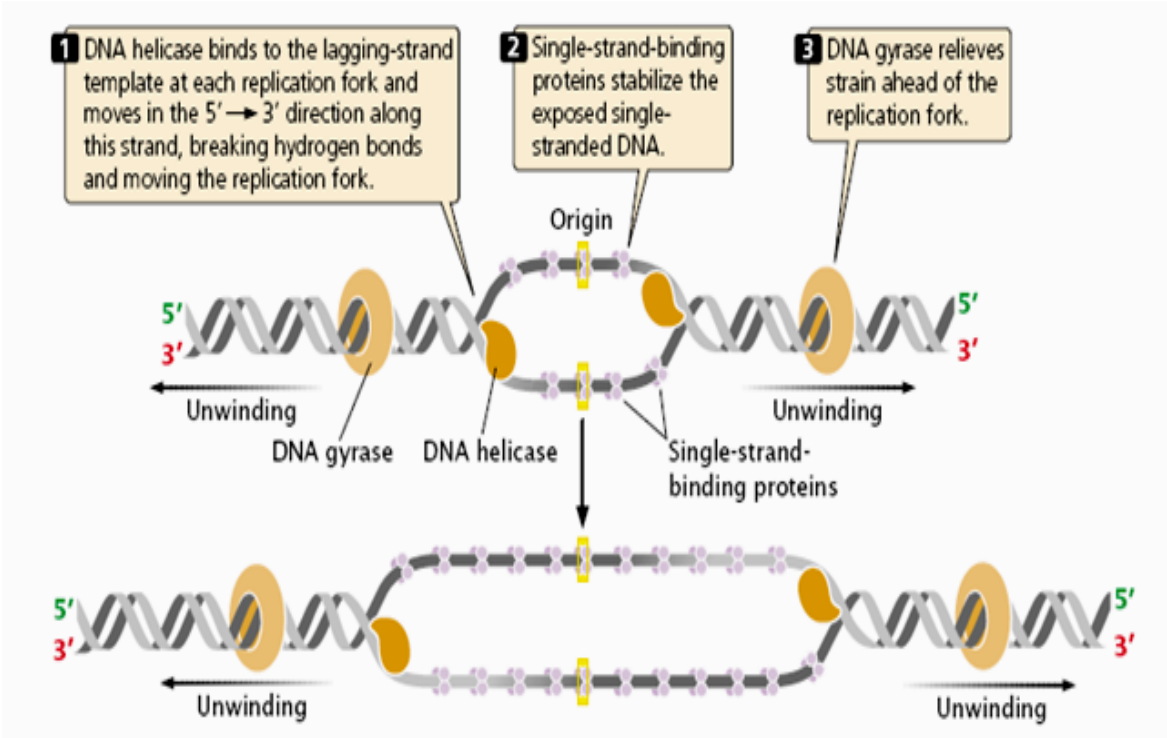


Fig.7.9: Initiation

Source: https://www.biologyexams4u.com/2013/04/steps-involved-in-dna-replication-in.html

Elongation:

- In the elongation process of replication two operations occur such as leading strand synthesis and aging strand synthesis.

i) Leading strand synthesis

a) Leading strand synthesis begins with the synthesis of RNA pimer by Dna G protein at the replication origin

b) Deoxyribonucleotides are then added to this primer by DNA polymerase III.

c) SSB proteins help to stabilize the separated strand

d) Helicases separate the two DNA strands at the fork

e) Toposiomerase II (DNA gyrase) acts to relieve the stress generated by helicases.

f) This leading strand is replicated in a continuous manner in the 5^1 to 3^1 direction.

ii) Lagging strand synthesis

a) Lagging strand is replicated discontinuously and must b e accomplished in short fragments (okzaki fragments) synthesized in the direction opposite to fork movement.

b) Synthesis of okazaki gragments

The multiprotein primosome complex travels in the same direction as the replication fork. At intervals, Dna G protein synthesizes RNA primer for a new okazaki fragment. The synthesis proceeds in the direction opposite to fork movement. Ech primer s extended by DNA Polymerse III

c) When the new okazaki fragment is complete, the RNA primer is removed by DNA polymerase I. The remaining nick is sealed by DNA ligase.

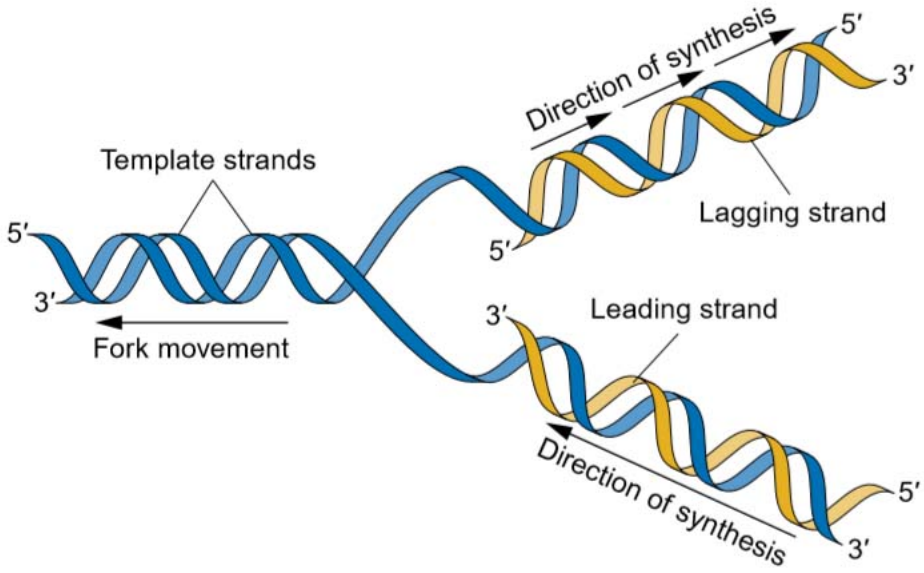


Fig.7.10: Elongation

Source: https://ncstate.pressbooks.pub/organicchem/chapter/replication-of-dna/

Termination

Very little is known about this process, it is assumed that DNA topoisomerase IV appears to be necessary for final separation of the two completed circular DNA molecules.

7.6 PROTEIN BIOSYNTHESIS

It is a process by which information in mRNA is used to direct the synthesis of proteins. The mRNA nucleotide sequence is translated into the sequence of aminoacids of the specified protein. The translation of the m RNA starts near its 5^1 terminal with the formation of the corresponding amino terminal of the protein molecule. In eukaryotic organisms, the process of transcription is a nuclear one; m RNA translation occurs in the cytoplasm. Protein biosynthesis can be explained by initiation, elongation and termination.

Initiation

There are three initiation factors namely IF_1, IF_2, IF_3

- $IF_1$and IF_3 bind with free 30s ribosomal subunit.
- m RNA attach to 30s ribosomal subunit.
- IF_2 and N-formyl methionine t-RNA bind 30s ribosomal subunit along with GTP, binding takes place between 30s ribosomal subunits, IF_2 and N-formyl methionine t RNA in the presence of GTP.
- The specific sequence of nucleotide bases 5^1end; namely Shine-Dalgarno sequence.
- Ribosomes with 30s subunit selects the proper initiation codon AUG. This AUG is responsibe for the initiation of protein synthesis at the 5^1 end which is close to Shine Dalgarno sequence.

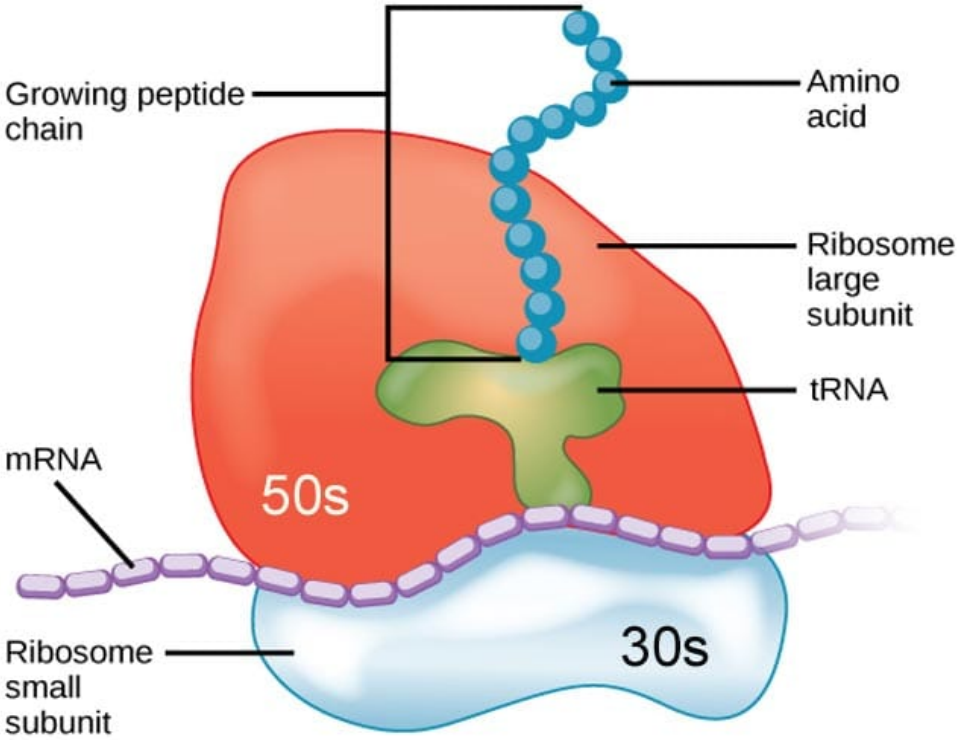


Fig.7.11: Prokaryotic ribosomes

Source: https://www.bioexplorer.net/ribosomes-function.html/

Elongation

- The polypeptide chain elongates by sequential additions of amino acid at carboxyl end. The approximate rate of addition is about 40 amino acids per second to growing polypeptide chain 5' to 3' end GTP facilitates elongation.
- Initiation of tRNa occupies P site while incoming aminoacy tRNA is deposited at A site. The process is dependent on the elongation factor and energy available from GTP hydrolysis.
- In the first step $IF_1$and IF_3 bind to the 30s ribosomal subunit. This is followed by attachment of mRNA followed IF_2 and N- formyl RNA.
- In the presence of Mg^{++} ions 30s subunit combined with 50s subunit form 70s ribosome.

30s+ 50s→70s

- Initiation codon is AUG which initiates proteins synthesis. In the next step 50s ribosomal subunit is added along with GTP which is hydrolysed to GDP + Pi. All these factors IF_1, IF_2 and IF_3 are released and 70s initiation complex is formed.
- Peptidyl transferase catalyses the formation of peptide bond t-RNA is attributed as ribozyme which is responsible for peptide formation. In this way elongation of peptide chain occurs every time with the addition of new codon with three bases. This process is called as translocation. Elongation process continues till termination signal is received.

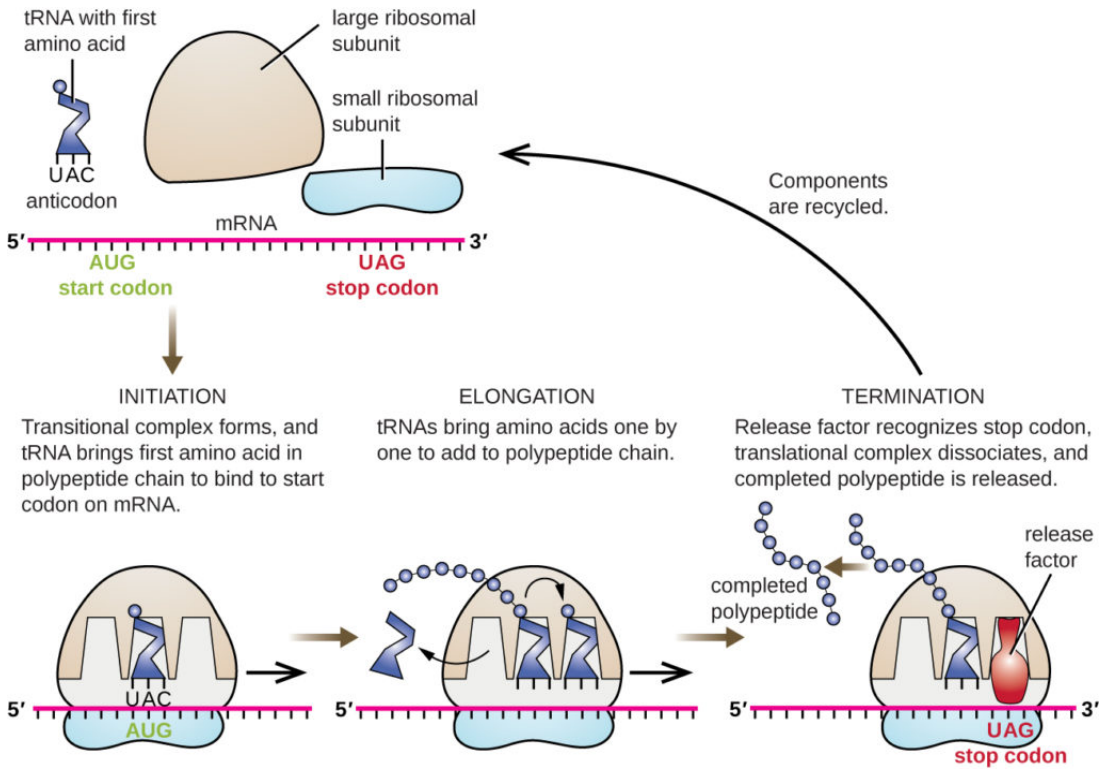


Fig.7.12: Steps in Protein biosynthesis

https://teachmephysiology.com/biochemistry/protein-synthesis/dna-translation/

Termination

- Elongation process is stopped on receiving a signal from one of the three codons UAA, UAG and UGA.
- With the help of release factors RF_1, RF_2 and RF_3 the termination codon occupies the ribosomal A site and thereby arrest the growth. The release factors brings about the hydrolytic break down of peptidyl t-RNA and release the newly synthesized protein which is brought about by the releasing factor.

7.7 SUMMARY:

The repeating units in nucleic acids are nucleotides. Nucleic acids derive their names because of their primary occurrence in the nucleus. Elements constituting nucleic acids are C, H, O, N and P. Most of the nucleic acids have approximately 15 to 16% nitrogen and 9 to 12% phosphorus. Two types of nucleic acids have been known for a long time: deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). DNA is found predominantly in the nucleus while RNA is predominant in the cytoplasm. New cells are synthesized by the division of pre existing cells. Each time the cell divides, its DNA must be copied so that a copy of this information passed on to the daughter cells. This process is known as DNA replication. It is a process by which information in mRNA is used to direct the synthesis of proteins. The mRNA nucleotide sequence is translated into the sequence of aminoacids of the specified protein.

7.8 TECHNICAL TERMS:

DNA, RNA, Nucleotides, DNA replication, Protein Biosynthesis

7.9 SELF ASSESSMENT QUESTIONS:

1) Write an account on classification of nucleic acids
2) Explain in detail about steps in DNA replication
3) Discuss in detail about protein biosynthesis

7.10 REFERENCE BOOKS:

1) A.C.DEB, fundamentals of Biochemistry
2) Lippincott's Illustrated Reviews: Biochemistry Sixth Edition, Denise R.Feerrier
3) Campbell and Farrell, Biochemistry, 6th Edition

Dr. P. Kiranmayi

LESSON-8

ENZYMES

8.0. OBJECTIVES:

After going through this lesson students will understand:

- Classification of enzymes
- Functions of enzymes
- Factors affecting enzyme activity

STRUCTURE:

8.1 INTRODUCTION

All enzymes are proteins which enhance the rates of the various chemical reactions which occur in biological systems under thermodynamically unfavourable conditions. A catalyst is a substance which participates in a chemical reaction to accelerate the rate of reaction without modification during the reaction. Enzymes promote and control the

conversion of the complex carbohydrates, fats and proteins of our body into simple substances which the intestines can absorb and also the various reactions by which these simple substances are used in the body for building up new tissues or production of energy. The enzymes are not broken down or changed in the process; they are as potent at the end of the reaction as at the beginning and very small amounts can affect the conversion of large quantity of material.

Enzymes are soluble, colloidal organic catalysts formed by living cells, specific in action, protein in nature, inactive at 0^0C and destroyed by moist heat at 100^0C. Enzymes which are used in the cells are called to be intracellular enzymes. Enzymes which are produced by other cells and are secreted to other parts of the body are called extracellular enzymes. An enzyme which is secreted in inactive form and ultimately activated by an agent secreted by other cell is said to be zymogen secretion. E.g. Trypsinogen (pancreatic juice) activated by enterokinase (intestinal mucosa) to give active trypsin, prothrombin (blood) activated by thrombopastin(tissues to give active thrombin. Zymogen secretion is probably a protective mechanism to prevent digestion of cell walls and ducts, since it is most frequently found with protein- splitting enzymes.

The substance on which the enzyme acts is called the substrate. Except the enzyme's pepsin, trypsin, ptyalin and erepsin, enzymes are usually named by adding the suffix- ase to the main part of the name of the substrate on which they act. Some examples are maltase acts on maltose, lactase acts on lactose, lipases act on lipids. But there are many substances which are acted on by some enzymes in different ways. A dipeptide can be attacked by three enzymes. These enzymes are named by their function. A dipeptide can be hydrolysed by dipeptidase in to aminoacids. The free amino group of the aminoacid is removed by anther enzyme nd the free carboxyl group is also removed by another enzyme. So, the names of these three enzymes acting on a dipeptide are dipeptidase, deaminase and decarboxlase. Some enzymes are named by their functions only. Examples: transferases, dehydrogenases, hydrolases, oxydases and reductases. Some enzymes acting on the substrates are freely described by the adjectives.

Example: Amylolytic, Lipolytic, Proteolytic.

Chemical Nature of Enzymes

Enzymes are regarded as proteins. This is now generally accepted with some exceptions. The enzymes are soluble to some extent in water, glycerol and dilute alcohol. They are precipitated from solutions by protein precipitation agents such as acids, alkalies, salt and TCA. They are non-dialyzable because of colloidal nature, although certain enzymes contain small dissociable and dialyzable molecule, known as prosthetic groups. Enzymes are more stable in concentrated solutions.

Characteristics of Enzymes

All enzymes are proteins. Enzymes follow the physical and chemical reactions of proteins. They are heat labile. They are water soluble. They can be precipitated by protein precipitating reagents. They contain 16% weight as nitrogen.

Coenzymes

Many enzymes have been shown to be conjugated proteins and the prosthetic groups of some of them are readily detached. These are termed as Co enzymes.

Protein Nature of Enzymes

All the enzymes are protein in nature with large molecular weight with exception of ribozymes which are few RNA molecules with enzymatic activity. Few enzymes are simple proteins having a protein part which is called as Apo enzyme and nonprotein part which is called as prosthetic part.

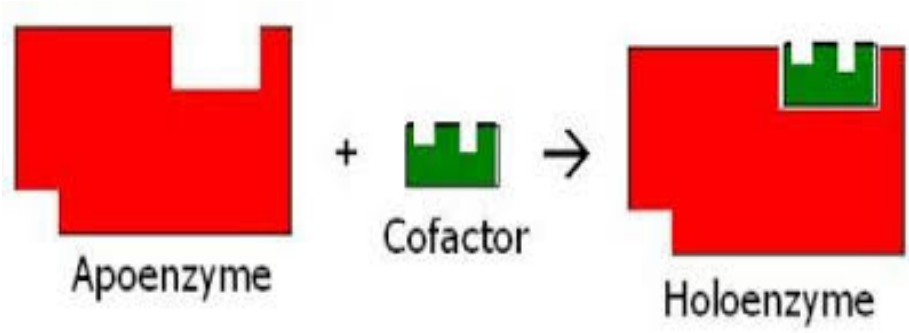


Fig. 8.1: Apoenzyme + Cofactor = Holoenzyme

https://en.wikibooks.org/wiki/Structural_Biochemistry/Enzyme/Apoenzyme_and_Holoenzyme

8.2 CLASSIFICATION OF ENZYMES

Enzymes are classified as per the IUB system and are expressed as enzyme code number (EC number) of four digits. The first digit represents the class; second digit stands for the subclass; third digit is the sub-subclass or subgroup; and the fourth digit gives the number of the particular enzyme in the list. The enzymes are classified in to 6 major classes

8.2.1 Oxidoreductases (EC 1):

Enzymes catalyzing oxidoreductions between two substrates A and B:

$$\mathbf{A_{reduced} + B_{oxidized} = A_{oxidized} + B_{reduced}}$$

These enzymes can be grouped in many different ways. Three main groups can be explained in order to get the simpler expression:

Oxidases: The enzymes which use oxygen as hydrogen acceptor,

e.g.: Tyrosinase, cytochrome oxidase

Anaerobic Dehyrogenases: the enzymes which use some other substance as hydrogen acceptor.

e.g.: Malate dehydrogenase, succinate dehydrogenase, lactate dehydrogenase.

Hydroperoxidases: The enzymes which use hydrogen peroxide as substrate.

e.g.: Peroxidase, Catalase

Aerobic Dehydrogenises: The enzymes which use either oxygen or another substance as hydrogen acceptor.

e.g: D and L - aminoacid oxidases, xanthine oxidase, aldehyde oxidase

Oxygenases: The enzymes which act on single hydrogen donors with incorporation of oxygen.

e.g.: Tryptophan oxygenase

Hydroxylases: The enzymes which act on paired donors with incorporation of oxygen into one donor.

e.g: Steroid hydroxylases

8.2.2 Transferases (EC 2): They catalyse the transfer of some group or radical, R, from one molecule A, to another molecule, B:

A. R+B ↔ A+B.R

The groups include

- Transphosphorylases: Hexokinase, phosphoglucomutases, phospoglycerate kinase
- Transglycosidases: Pohosphorylase
- Transaminases: Aspartate amino transferase
- Transacylase: Choline acetyl transferase

8.2.3 Hydrolases (EC 3): Enzymes catalyzing hydrolysis of ester, ether, peptide, glycosyl, acid anhydride by the addition of water.

The group includes the extracellular digestive enzyme and many intracellular enzymes. Enzymes acting on glycosyl compounds (β-galactosidase), enzymes acting on peptide bonds (pepsin, rennin, chymotrysin), eserases (lipase, phosphatases, sulphatases), hydrolytic deaminases (guanine deaminase).

8.2.4 Lyases (EC 4**):** Enzymes that catalyze removal of groups from substrates by mechanisms other than hydrolysis leaving double bonds. Eg. Aldolase, Fumerase

8.2.5 Isomerases (EC 5**):** Enzymes catalyzing interconversion of optical, geometric, or positional isomers.

- Racemases and epimerases, eg., Alanine racemase.
- Cis – trans isomerases eg. Retinene isomearase
- Enzymes catalyzing interconversion of aldoses and ketoses, eg. Triose phosphate isomerises.

8.2.6. Ligases (EC 6): Enzymes catalyzing the lining together of two compounds couple to the breaking of a pyrophosphate bond in ATP or a similar compound

- Enzymes catalyzing formation of C-S bonds, eg: succinate thiokinase
- Enzymes catalyzing formation of C-N bonds eg., glutamine synthetase
- Enzymes catalyzing formation of C-C bonds eg.Acetly-CoA carboxylase

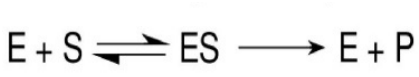
Complete enzyme along with prosthetic group is called as Holoenzyme. Certain enzymes with only one polypeptide chain are called as monomeric enzymes. Eg: Ribonuclease. Several enzymes possess more than on polypeptide chain are called as oligomeric enzymes. Ex: Lactate dehydrogenase. Some vitamins of B complex group exhibit co enzyme activity.

B Vitamins and their Coenzymes

Vitamin	Coenzyme
Vitamin B_1(thiamine)	Thiamine pyrophosphate (TPP)
Vitamin B_2 (riboflavin)	Flavin mononucleotide (FMN) or flavin adenine dinucleotide (FAD)
Vitamin B_3 (niacin)	Nicotinamide adenine dinucleotide, nicotinamide adenine dinucleotide phosphate
Vitamin B_6 (pyridoxine)	Pyridoxal phosphate
Vitamin B_{12} (cyanocobalamin)	Methycobalamin or deoxyadenosylcobalamin
Biotin	Biotin
Folic Acid	Tetrahydrofolate
Pantothenic Acid	Coenzyme A

Mechanism of Enzyme Action

According to Michaelis and Menten, enzyme (E) first combines with substrate (S) to form an Enzyme substrate complex (ES) which further dissociates to form the product (P) and enzyme (E) is set free. The same enzyme E could be reused to combine with another molecule of substrate and from product again and again.



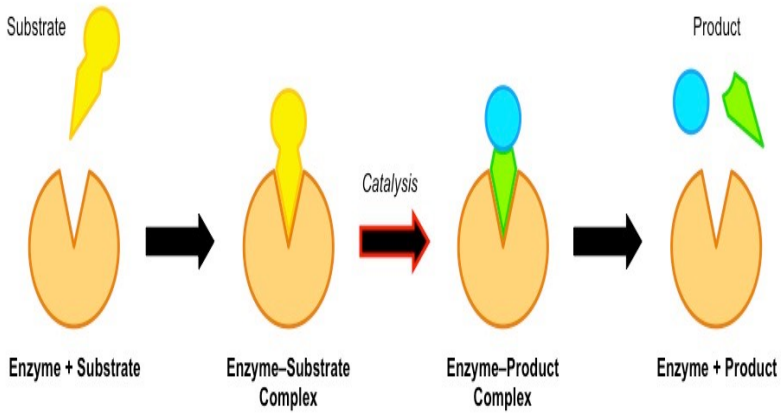


Fig. 8.2: Mechanism of enzyme catalysis

https://old-ib.bioninja.com.au/standard-level/topic-2-molecular-biology/25-enzymes/enzyme-catalysis.html

The concentration of products formed depends on the concentration of the unstable complex [ES] which is expressed as molar concentration. The enzyme substrate complex [ES] formation has been explained in many ways of which the following two hypothesis have been widely accepted

Lock and Key Model

This model was originally proposed by Fisher which states that the active site already exists in proper conformation even in absence of substrate. Thus, the active site by itself provides a rigid, preshaped fitting with the size and shape of the substrate as the key fits into the lock and hence is called Lock and Key Model. This model proposes that the substrates bind with rigid preexisting shape of the active site, provides additional groups for binding other ligands.

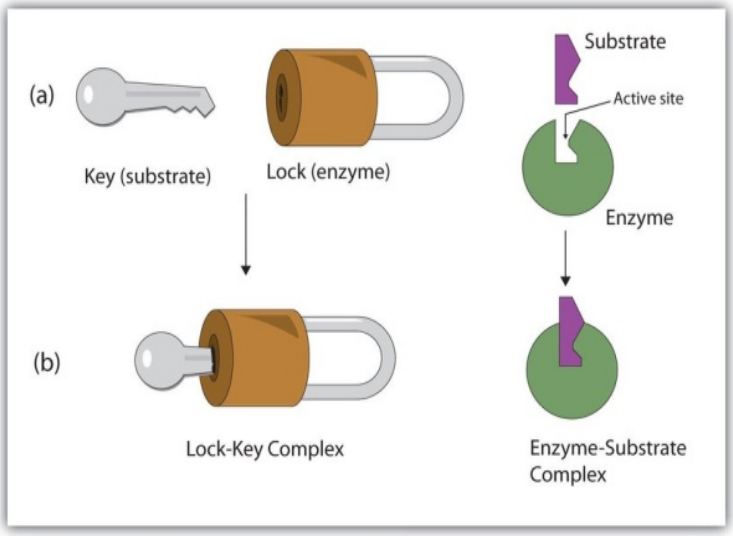


Fig. 8.3: Lock and Key Model

https://www.researchgate.net/figure/Lock-and-key-model-that-explains-the-selectivity-of-enzymes-Picture-is-taken-from-2_fig4_344298011

Induced Fit Model:

Lock and key model had restrictive features therefore Koshland in 1963 suggested an induced fit model. The important features of this model are the flexibility of region of active site.

According to this the active site does not possess a rigid, preformed structure on enzyme to fit the substrate. On the contrary the substrate during its binding induces conformational changes in the active site to attain the final catalytic shape and form.

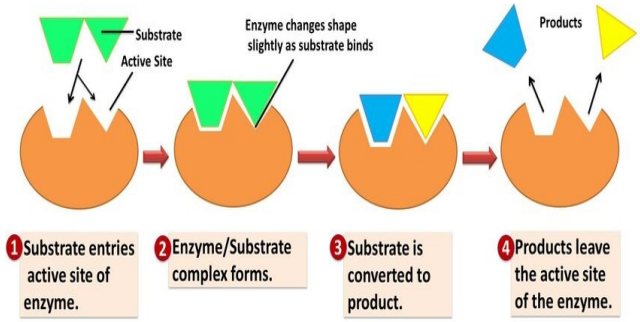


Fig. 8.4: Induced Fit Model

https://www.researchgate.net/figure/According-to-the-induced-fit-model-both-enzyme-and-substrate-undergo-dynamic_fig6_354597569

8.3. FACTORS AFFECTING ENZYME ACTIVITY

Enzymes functions effectively under the optimal conditions. Enzyme activity can be influenced by various factors such as

a) Enzyme Concentration:

The velocity of an enzyme reaction is directly proportional to the concentration of enzyme i.e. the more the enzyme, the faster the reaction. If one double the amount of the enzyme, the rate of reaction is usually double.

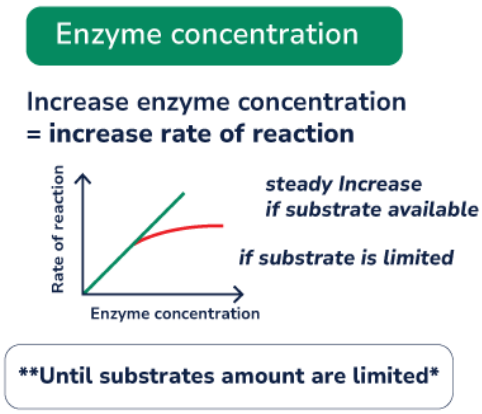


Fig. 8.5: Factors Affecting Enzyme Activity

https://www.geeksforgeeks.org/biology/factors-affecting-enzyme-activity/

b) Hydrogen Ion Concentration (pH):

Enzyme reactions are influenced by varying the pH of reaction mixture.

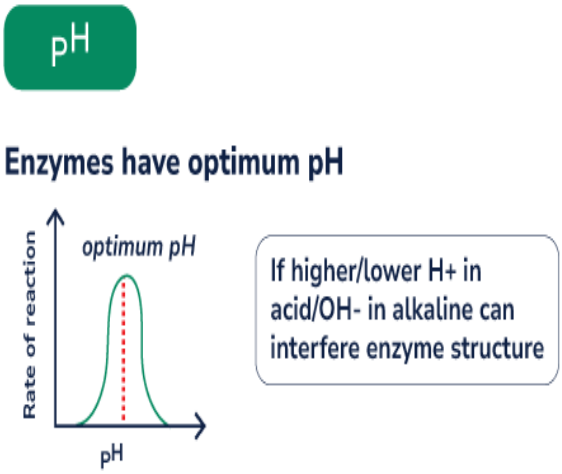


Fig. 8.6: Factors Affecting Enzyme Activity

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The optimum pH is the pH at which certain enzyme will cause a reaction to progress most rapidly and yield thereby maximum product concentration. On either side of optimum pH the rates of reactions will be diminished. The optimum pH depends on kind of buffer, the particular substrate and source of enzyme. The optimum pH of certain enzymes: Pepsin 1.4, Trypsin 7.8, Amylase 6.9, Pancreatic enzymes 7.0, Maltase 5.2, Alkaline phosphatise 9.5.

c) Substrate Concentration:

The velocity of enzyme reaction increases as the concentration of substrate increases. At first the curve of enzyme velocity to substrate concentration is almost linear but as per Michaelis - Menten hypothesis the reaction curve flattens and assumes a hyperbolic pattern.

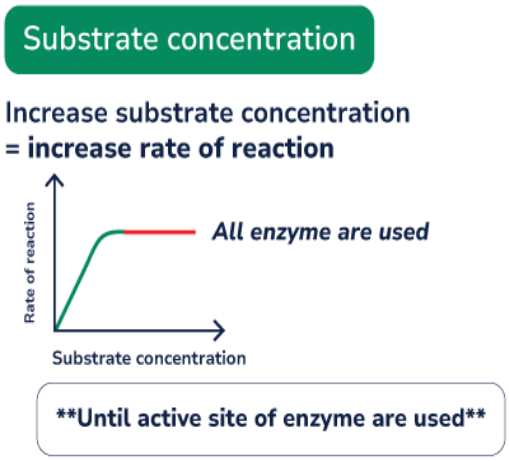

Fig. 8.7: Factors Affecting Enzyme Activity

https://www.geeksforgeeks.org/biology/factors-affecting-enzyme-activity/

d) Temperature:

The rise in temperature enhances the rate of enzyme reaction but at the same time causes inactivation of the enzymes due to denaturation of the protein. At optimum temperature the activity is maximum. If the temperature is lowered, the rate of an enzyme reaction is diminished. At the temperature 0^0C, most enzymes are practically inactive.

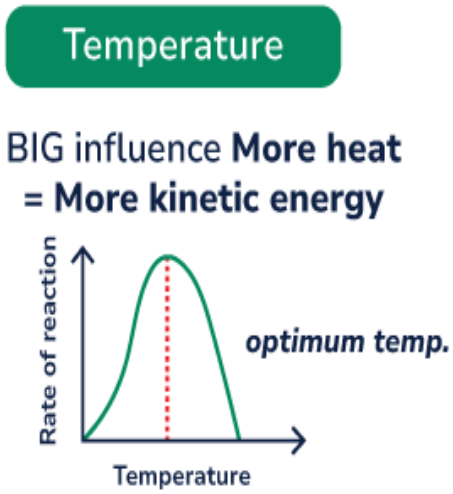

Fig. 8.8: Factors Affecting Enzyme Activity

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e) Coenzymes and activators:

In the absence of coenzymes and activators the enzymes may be inactive. The activators (cl^-,Mg^{++}, Ca^{++}, Mn^{++} etc. may take part in the formation of enzyme substrate complex. Mn^{++} in the action of some peptidases may prevent the inactivation of the enzyme by inhibitors. Some enzymes which are activators are called kineses. eg., enterokinase converts trypsinogen to trypsin by removing hexapeptide from trysinogen.

8.5. SUMMARY

Enzymes are soluble, colloidal organic catalysts formed by living cells, specific in action, protein in nature, inactive at 0^0C and destroyed by moist heat at 100^0C. Enzymes which are used in the cells are called to be intracellular enzymes. Enzymes are regarded as proteins. This is now generally accepted with some exceptions. The enzymes are soluble to some extent in water, glycerol and dilute alcohol. They are precipitated from solutions by protein precipitation agents such as acids, alkalies, salt and TCA. Enzymes are classified as per the IUB system and are expressed as enzyme code number (EC number) of four digits. According to Michaelis and Menten, enzyme (E) first combines with substrate (S) to form an Enzyme substrate complex (ES) which further dissociates to form the product (P) and enzyme (E) is set free.

All the enzymes are protein in nature with large molecular weight with exception f ribozymes which are few RNA molecules with enzymatic activity. Few enzymes are simple proteins having a protein part which is called as Apo enzyme and nonprotein part which is called as prosthetic part. The same enzyme E could be reused to combine with another molecule of substrate and from product again and again Enzyme activity can be influenced by various factors such as temperature, substrate concentration, pH, time etc.

8.6. TECHNICAL TERMS:

Ligases, Hydorlases, Isomerases, Substrate Concentration, Active Site.

8.7. SELF ASSESSMENT QUESTIONS:

1) Write in detail about classification of enzymes
2) Add a note on chemical nature of enzymes
3) Explain about lock and key theory of enzymes
4) Discuss in detail about factors effecting enzyme action

8.8. REFERENCE BOOKS:

1) A.C.D.E.B., Fundamentals of Biochemistry.
2) Lippincott's Illustrated Reviews: Biochemistry Sixth Edition, Denise R.Feerrier.
3) Campbell and Farrell, Biochemistry, 6^{th} Edition.
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Dr. P. Kiranmayi

LESSON-9

FATTY ACID METABOLISM: OXIDATION AND BIOSYNTHESIS OF FATTY ACIDS, KETONE BODIES AND KETOSIS

9.0. OBJECTIVES:

After going through this lesson students will understand:

- Understand the physiological need for fatty acid synthesis, particularly in the liver and adipose tissue.
- Identify the sources of carbon, ATP, and reducing power in synthesis.
- Explain the transport of acetyl-CoA from mitochondria to the cytoplasm via the citrate shuttle.
- Recognize the clinical relevance of fatty acid metabolism (e.g., obesity, non-alcoholic fatty liver disease).

STRUCTURE:

9.1 INTRODUCTION

Fatty acids are building block of most lipids, made of long chain organic acids having one polar carboxyl group (head) and a non-polar hydrocarbon chain (tail). The latter makes them water insoluble. They are not found free in nature but found as esterified forms. Most naturally occurring fatty acids have got even number of carbons. They may be saturated or unsaturated, with one or more double bonds. Mostly the double bond occurs at the 9^{th} carbon as we count from the carboxyl group end.

There are two systems of numbering the carbon atoms in a fatty acid n 3 2 1

$CH_3 (CH_2)_n CH = CH CH_2 CH_2 CH_2 COOH$

ω β α

1) Numbering starts from carboxyl carbon. The last carbon is the "n" carbon

2) The second carbon is the "α" "and the third the "β" Carbon. The last carbon atom is omega.

Eg:- $CH_3 (CH_2)_7 CH_2CH_2 (CH_2)_7 COOH$ stearic acid (saturated fatty acid)

Eg:- $CH_3 (CH_2)_7 CH=CH (CH_2)_7 COOH$ oleic acid (Unsaturated fatty acid)

Fatty acids can be represented as shown below where the delta indicates the position of the double bond and the next number shows the number of carbon atoms and the last number indicates the number of double bonds. In a different way the position of the double bond(s) can be indicated as shown in the second expression without the delta.

C18:1, $^{9}\Delta$ or 18:1(9)

C18 indicates 18 carbons, 1 indicates the number of double bonds, delta 9($^{9}\Delta$) indicates the position of double bond between 9^{th} and 10^{th} carbon atoms.

- Double bonds in naturally occuring fatty acids are in the cis- configuration and saturated fatty acids of C_{12} to C_{24} are solids at body temperature but the unsaturated once are liquids.

PUFA (Polyunsaturated fatty acids): They have two or more double bonds .they are called as essential fatty acids because they are required in the body and cannot be synthesized. So they need to be include in the diet.

18	Linoleic acid	18: 2; 9 (12)
18	Linolenic acid	18: 2; 9 (12, 15)

These two are called essential fatty acids.

20	Arachidonic acid	20: 4; (5, 8, 11, 14)

Arachidonic acid is semi essential fatty acid because it can be synthesized from the above two essential fatty acids.

Functions:

1) The fluidity of membrane depends on length and degree of unsaturated fatty acids.
2) Membrane PL contains essential fatty acids. In case of deficiency of EFA, other fatty acids replace them in the membrane; as a result membrane gets modified structurally and functionally.
3) They are required for the synthesis of PL, cholesterol ester and lipoproteins
4) Poly unsaturated fatty acids are released from membranes, diverted for the synthesis of prostaglandins, leukotriens and thromboxanes.
5) They act as fat mobilizing agents in liver and protect liver from accumulating fats (fatty liver).

9.2 FATTY ACID METABOLISM

Fatty acids are a major source of energy and play an essential role in biological membranes and signalling pathways. The body manages fatty acids through two interrelated processes: fatty acid oxidation and fatty acid biosynthesis.

Fatty acid oxidation is the process of breaking down long-chain fatty acids into acetyl-CoA, which then enters the Krebs cycle to produce ATP. This pathway is essential during fasting, prolonged exercise, and starvation when glucose availability is low.

Conversely, fatty acid biosynthesis occurs when energy and carbohydrate levels are high. In this state, excess glucose is converted into acetyl-CoA, which serves as the substrate for fatty acid synthesis. The newly formed fatty acids are stored as triglycerides in adipose tissue or incorporated into cellular membranes.

These metabolic pathways are compartmentalized within the cell: oxidation takes place in the mitochondria, while biosynthesis occurs in the cytoplasm. This separation ensures that these opposing pathways do not occur simultaneously. Hormonal control and feedback regulation maintain energy homeostasis.

Understanding fatty acid metabolism is critical for exploring metabolic disorders such as obesity, insulin resistance, diabetes mellitus, and non-alcoholic fatty liver disease (NAFLD).

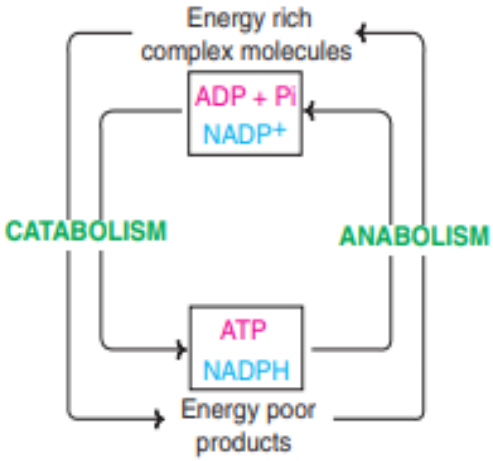

Fig. 9.1: An outline of catabolism and anabolism.

Fatty acid metabolism includes:

1) Fatty Acid Oxidation (Catabolic)
2) Fatty Acid Biosynthesis (Anabolic)

9.3 OXIDATION OF FATTY ACIDS (B-OXIDATION)

Fatty acids are primarily oxidized via β-oxidation to generate energy, especially during fasting or starvation when glucose is limited. This process occurs in mitochondria and produces acetyl-CoA, which enters the citric acid cycle (TCA cycle) for ATP production. Tissues like muscle and liver perform β-oxidation, but brain and erythrocytes cannot utilize fatty acids directly.

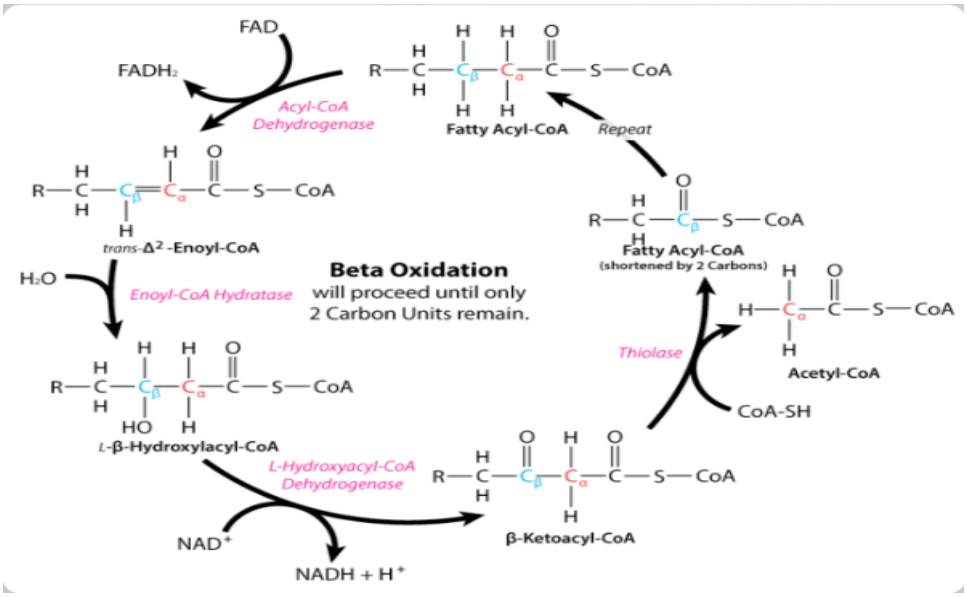

Fig. 9.2: Beta Oxidation of fatty acid

Stages of β-Oxidation:

β-Oxidation involves three main stages:

1. **Activation of Fatty Acids (in Cytosol):**
    - Fatty acids are activated to acyl-CoA by acyl-CoA synthetases (thiokinases).
    - Reaction: Fatty acid + CoA + ATP + Mg^{2+} → Acyl-CoA + AMP + PPi.
    - PPi is hydrolyzed to 2Pi by pyrophosphatase, making the reaction irreversible.
    - Energy cost: Equivalent to 2 ATP (high-energy bonds used).
    - Different synthetases activate short-, medium-, and long-chain fatty acids.
2. **Transport into Mitochondria (Carnitine Shuttle):**
    - Acyl-CoA cannot cross the inner mitochondrial membrane directly.
    - Carnitine shuttle transports it:
        - Carnitine acyltransferase I (CAT-I, outer membrane): Acyl-CoA + Carnitine → Acyl-carnitine + CoA.
        - Translocase moves acyl-carnitine across the membrane.
        - Carnitine acyltransferase II (CAT-II, inner membrane): Acyl-carnitine + CoA → Acyl-CoA + Carnitine.
    - Regulation: Malonyl-CoA (from fatty acid synthesis) inhibits CAT-I, preventing futile cycles.
3. **β-Oxidation Proper (in Mitochondrial Matrix):**
    - A cycle of four reactions removes 2-carbon units (acetyl-CoA) from the β-carbon.
    - For even-chain saturated fatty acids (e.g., palmitate, C16):
        - Dehydrogenation: Acyl-CoA dehydrogenase (FAD) → trans-Δ^2-enoyl-CoA + $FADH_2$.
        - Hydration: Enoyl-CoA hydratase → L-β-hydroxyacyl-CoA.
        - Dehydrogenation: β-Hydroxyacyl-CoA dehydrogenase (NAD^+) → β-ketoacyl-CoA + NADH.
        - Thiolysis: Thiolase (CoA) → Acetyl-CoA + Shortened acyl-CoA.
    - Cycle repeats until full degradation (7 cycles for palmitate → 8 acetyl-CoA).

Energetics

- Each cycle: 1 $FADH_2$ (1.5 ATP) + 1 NADH (2.5 ATP) + Acetyl-CoA (10 ATP via TCA).
- For palmitate (C16): 7 cycles → 7 $FADH_2$ (10.5 ATP) + 7 NADH (17.5 ATP) + 8 acetyl-CoA (80 ATP) = 108 ATP gross.
- Net: 106 ATP (subtract 2 ATP for activation).
- Efficiency: ~40% of palmitate's energy (2340 kcal) conserved as ATP.

Variations

- Odd-Chain Fatty Acids: Final product is propionyl-CoA → Succinyl-CoA (via biotin-dependent carboxylation, racemase, and B_{12}-dependent mutase).
- Unsaturated Fatty Acids: Require isomerase (for cis-trans conversion) and epimerase; yield less energy.
- Peroxisomal Oxidation: For very long-chain fatty acids (VLCFAs); produces H_2O_2 (cleaved by catalase); no ATP from $FADH_2$.
- α-Oxidation: Minor pathway for branched fatty acids (e.g., phytanic acid in Refsum's disease); removes α-carbon as CO_2.
- ω-Oxidation: In ER; oxidizes ω-carbon to dicarboxylic acids; minor.

Regulation

- Increased by glucagon/epinephrine (via cAMP, lipolysis).
- Inhibited by insulin (reduces lipolysis).
- Malonyl-CoA inhibits carnitine shuttle.

Biomedical/Clinical Concepts

- MCAD Deficiency: Causes sudden infant death syndrome (SIDS); blocks medium-chain oxidation.
- Jamaican Vomiting Sickness: Hypoglycin A inhibits β-oxidation.
- Refsum's Disease: Defect in α-oxidation; phytanic acid accumulation; avoid chlorophyll-rich foods.
- Zellweger Syndrome: Absent peroxisomes; VLCFA accumulation in brain/liver.

9.4 BIOSYNTHESIS OF FATTY ACIDS

Stages of Biosynthesis

1. **Production of Acetyl-CoA and NADPH:**
   - Acetyl-CoA from mitochondria (pyruvate oxidation) is shuttled to cytosol via citrate shuttle.
   - Citrate lyase: Citrate → Acetyl-CoA + Oxaloacetate.
   - Oxaloacetate → Malate (malate dehydrogenase) → Pyruvate (malic enzyme, produces NADPH).
   - Additional NADPH from HMP shunt (50-60%).
2. **Formation of Malonyl-CoA:**
   - Acetyl-CoA carboxylase (ACC): Acetyl-CoA + CO_2 + ATP + Biotin → Malonyl-CoA + ADP + Pi.
   - ACC is rate-limiting; activated by citrate, inhibited by palmitoyl-CoA.
3. **Reactions of Fatty Acid Synthase (FAS) Complex:**
   - FAS is a multifunctional dimer (7 enzymes + ACP with pantetheine-SH).
   - Steps (repeat 7 times for palmitate):
     - Loading: Acetyl-CoA to ACP (acetyl transacylase); Malonyl-CoA to ACP (malonyl transacylase).
     - Condensation: β-Ketoacyl-ACP synthase → β-Ketoacyl-ACP + CO_2.
     - Reduction: β-Ketoacyl-ACP reductase (NADPH) → β-Hydroxyacyl-ACP.
     - Dehydration: β-Hydroxyacyl-ACP dehydratase → trans-Δ^2-Enoyl-ACP.
     - Reduction: Enoyl-ACP reductase (NADPH) → Acyl-ACP (2 carbons longer).
     - Release: Palmitoyl thioesterase → Palmitate.

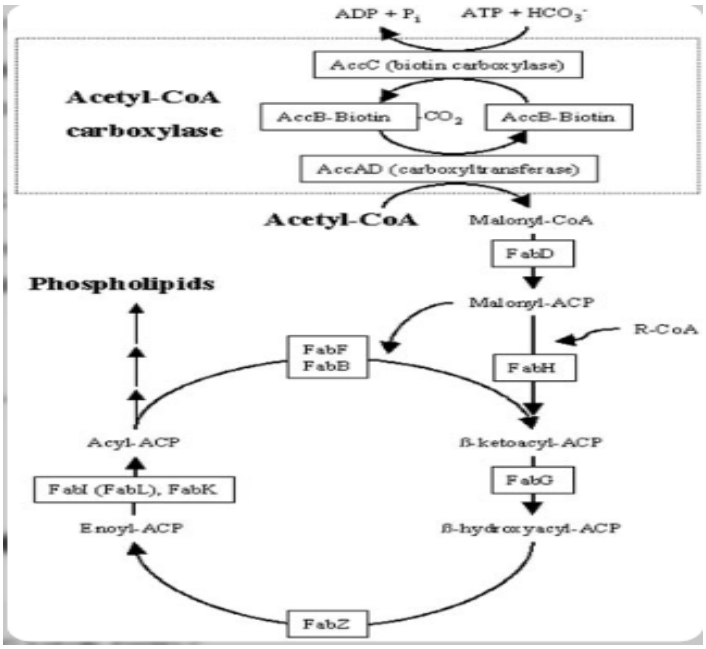

Fig. 9.3: Fatty acid Biosynthesis

Summary Reaction

8 Acetyl-CoA + 7 ATP + 14 NADPH + 14 H^+ → Palmitate + 8 CoA + 7 ADP + 7 Pi + 6 H_2O.

Chain Elongation and Desaturation

- Elongation: Beyond C16; microsomal (malonyl-CoA, NADPH) or mitochondrial (acetyl-CoA, NADPH).
- Desaturation: Fatty acyl-CoA desaturase (cytochrome b_5, NADPH, O_2) introduces double bonds up to Δ^9.
- Essential fatty acids: Linoleic (ω-6) and linolenic (ω-3) cannot be synthesized; arachidonic from linoleic.

Regulation

- Short-Term: ACC phosphorylation (inactive by glucagon/epinephrine via AMPK); dephosphorylation (active by insulin).
- Long-Term: High-carb diet induces ACC/FAS; fasting/high-fat diet represses.
- Hormones: Insulin promotes; glucagon inhibits.
- NADPH supply from HMP shunt.

Biomedical/Clinical Concepts

- Obesity: Excessive synthesis due to high insulin/glucagon ratio.
- Essential Fatty Acid Deficiency: Leads to skin lesions, poor wound healing.

DIFFERENCES BETWEEN OXIDATION & BIOSYNTHESIS

Feature	Fatty Acid Oxidation	Fatty Acid Biosynthesis
Purpose	Energy Production	Energy Storage, Membrane Synthesis
Site	Mitochondria	Cytoplasm
Starting Molecule	Fatty acyl-CoA	Acetyl-CoA
End Product	Acetyl-CoA, NADH, FADH2	Palmitic acid (C16:0)
Cofactors	NAD+, FAD	NADPH
Carrier Molecule	Coenzyme A (CoA)	Acyl Carrier Protein (ACP)
Key Enzyme	Acyl-CoA Dehydrogenase	Fatty Acid Synthase, ACC
Regulation	Glucagon, AMP	Insulin, Citrate

This table helps clearly differentiate between the two processes based on structure, function, and regulation.

9.5 KETONE BODIES

Ketone bodies (acetoacetate, β-hydroxybutyrate, acetone) are produced in liver mitochondria from acetyl-CoA when carbohydrates are scarce. They serve as water-soluble fuels for extrahepatic tissues.

The metabolism of Ketone Bodies

When the level of acetyl CoA from β-oxidation increases in excess of that required for entry into the citric acid cycle, It undergoes ketogenesis in the mitochondria of liver (ketone body synthesis). The three compounds viz., acetoacetate, β-hydroxybutyrate, and acetone are collectively known as ketone bodies. The synthesis of ketone bodies takes place during severe starvation or severe diabetes mellitus. During such conditions, the body totally depends on the metabolism of stored triacylglycerols to fulfill its energy demand.

In the synthesis, two molecules of acetyl CoA condense together to form acetoacetyl CoA, a reaction catalyzed by thoilase. Another molecule of acetyl CoA reacts with the acetoacetyl CoA to form 3-Hydroxy-3-methyl glutaryl CoA (HMGCoA). This step is the rate limiting step and the reaction is catalyzed by HMGCoA synthase enzyme. Note that this compound is also an intermediate in the synthesis of cholesterol in the liver cell cytosol but the mitochondrial HMGCoA goes to ketone body synthesis.

The HMGCoA formed in the hepatocytes mitochondria by the action of the enzyme HMGCoA lyase is changed to acetoacetate.

The acetoacetate, when its concentration is very high in blood is spontaneously decarboxylated to acetone.

Acteoacetate can be converted to β-hydroxy butyrate by a dehydrogenase enzyme. It is a reversible reaction. See the figure

The odor of acetone may be detected in the breath of a person who has a high level of acetoacetate, like diabetic patients. During starvation and severe diabetes mellitus peripheral tissues fully depend on ketone bodies. Even tissues like the heart and brain depend mainly on ketone bodies during such conditions to meet their energy demand.

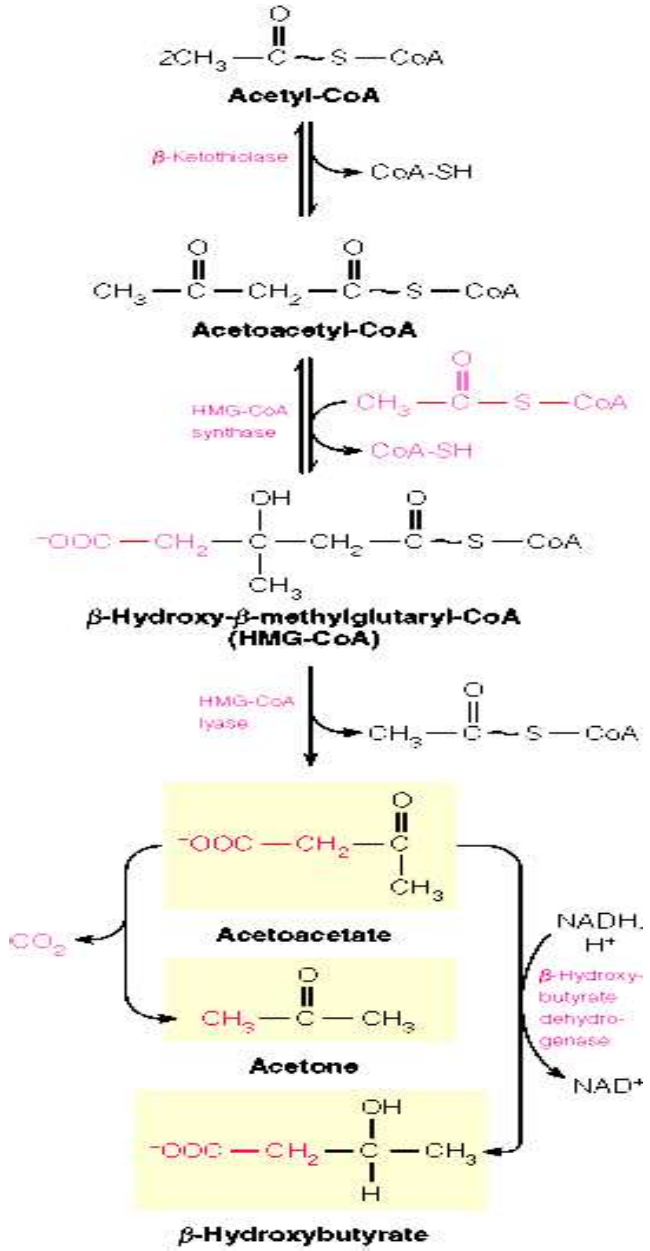

Fig. 9.4: Synthesis of Ketone Bodies

Ketogenesis (in Liver)

- Excess acetyl-CoA from β-oxidation.
- Steps:
  - Thiolase: 2 Acetyl-CoA → Acetoacetyl-CoA.
  - HMG-CoA synthase: Acetoacetyl-CoA + Acetyl-CoA → HMG-CoA.
  - HMG-CoA lyase: HMG-CoA → Acetoacetate + Acetyl-CoA.
  - β-Hydroxybutyrate dehydrogenase: Acetoacetate → β-Hydroxybutyrate (NADH).
  - Spontaneous: Acetoacetate → Acetone + CO_2.
- Regulation: Increased by high acetyl-CoA (low oxaloacetate in TCA); glucagon promotes.

Utilization of Ketone Bodies

The ketone bodies, being water-soluble, are easily transported from the liver to various tissues. The two ketone bodies-acetoacetate and b-hydroxybutyrate serve as important sources of energy for the ***peripheral tissues*** such as skeletal muscle, cardiac muscle, renal cortex etc. The tissues which lack mitochondria (e.g. erythrocytes) however, cannot utilize ketone bodies. The production of ketone bodies and their utilization become more significant when glucose is in short supply to the tissues, as observed in ***starvation***, and ***diabetes mellitus***.

During prolonged ***starvation***, ketone bodies are the major ***fuel source for the brain*** and other parts of central nervous system. It should be noted that the ability of the brain to utilize fatty acids for energy is very limited. The ketone bodies can meet 50-70% of the brain's energy needs. This is an adaptation for the survival of the organism during the periods of food deprivation.

Reactions of ketone bodies : b-Hydroxy- butyrate is first converted to acetoacetate (reversal of synthesis) and metabolized. Acetoacetate is activated to acetoacetyl CoA by a mitochondrial enzyme ***thiophorase*** (succinyl CoA acetoacetate CoA transferase). The coenzyme A is donated by succinyl CoA, an intermediate in citric acid cycle. ***Thiophorase is absent in liver***, hence ketone bodies are not utilized by the liver. Thiolase cleaves acetoacetyl CoA to two moles of acetyl CoA

9.6 KETOSIS

- Ketosis: Overproduction > utilization → Ketonemia (blood ketones >1 mg/dL) + Ketonuria + Acetone breath.
- Causes: Starvation (adaptive, no acidosis); uncontrolled diabetes (insulin deficiency → lipolysis → excess acetyl-CoA).

- **Ketoacidosis:** In diabetes; ketones lower blood pH (pKa ~4) → Acidosis, coma, death if untreated.Both acetoacetate and b-hydroxybutyrate are strong acids. Increase in their concentration in blood would cause acidosis. The carboxyl group has a p^{Ka} around 4. Therefore, the ketone bodies in the blood dissociate and release H^+ ions which lower the pH. Diabetic ketoacidosis is dangerous—may result in coma, and even death, if not treated. Ketosis due to starvation is not usually accompanied by ketoacidosis.

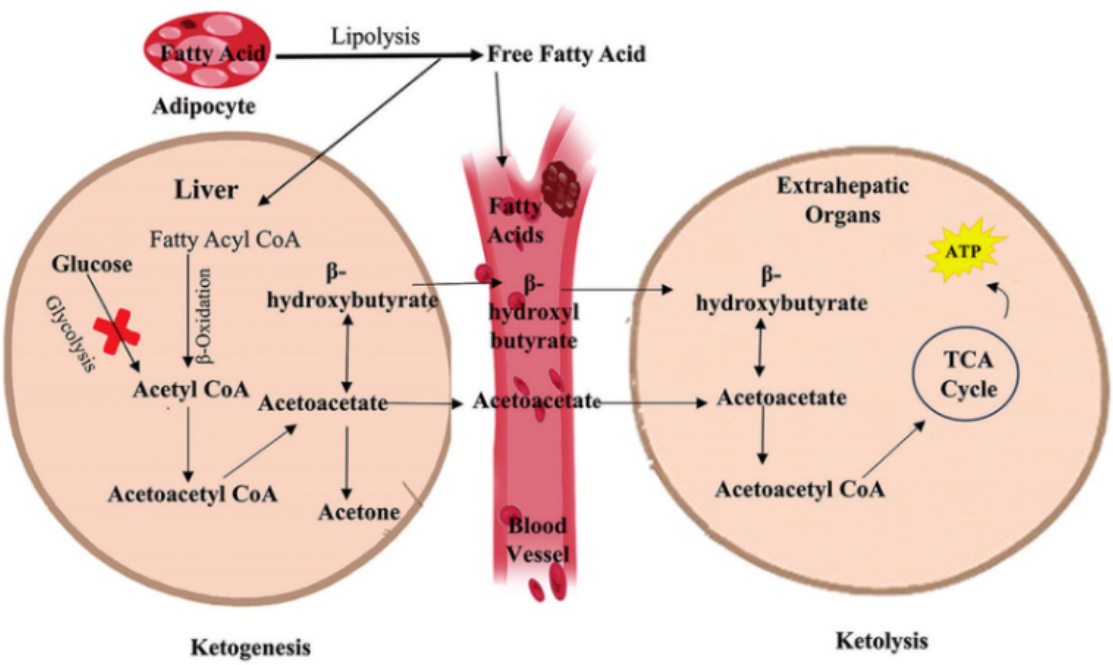

Fig. 9.5: Ketogenesis and Ketolysis

Biomedical/Clinical Concepts

- Diabetic Ketoacidosis (DKA): High ketones (100 mg/dL blood); fruity breath; treat with insulin/fluids.
- Starvation Ketosis: Mild; brain spares glucose by using ketones.
- Detection: Rothera's test (purple ring with acetoacetate/acetone).

9.7 SUMMARY:

Fatty acid metabolism encompasses the breakdown and synthesis of fats for energy regulation. The body uses fatty acid oxidation during energy scarcity and fatty acid synthesis when energy is in excess.

These processes are not only essential for maintaining physiological homeostasis but also serve as targets for managing metabolic diseases. Regulation is tightly controlled through hormones (insulin, glucagon) and metabolites (malonyl-CoA).

Furthermore, ketone bodies serve as an alternative fuel source during prolonged fasting or carbohydrate deprivation. While ketosis is a normal adaptive response, unregulated ketone body production can lead to dangerous conditions like ketoacidosis.

9.8. TECHNICAL TERMS

- Acetyl-CoA: A central molecule in energy metabolism.
- Malonyl-CoA: An intermediate in fatty acid synthesis.
- Fatty Acid Synthase (FAS): A multi-enzyme protein for fatty acid chain elongation.
- Carnitine Shuttle: Transports fatty acids into mitochondria.
- Beta-Oxidation: Cyclical breakdown of fatty acids for ATP production.
- Ketone Bodies: Alternative fuel during carbohydrate deficiency.
- Ketoacidosis: A pathological state of excessive ketone accumulation.

9.9 SELF-ASSESSMENT QUESTIONS:

- What are the key differences between fatty acid oxidation and biosynthesis?
- Explain the steps and regulation of the carnitine shuttle system.
- Describe how palmitic acid is synthesized from acetyl-CoA.
- How is fatty acid metabolism regulated by insulin and glucagon?
- What are the causes and symptoms of MCAD deficiency?
- Explain how ketone bodies are formed and utilized in the body.
- Why is malonyl-CoA important in coordinating fatty acid metabolism?

9.10 REFERENCE BOOKS:

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Dr. Santhi Sri, K.V

LESSON-10

BIOSYNTHESIS OF CHOLESTEROL AND REGULATIONS, METABOLISM OF BILE PIGMENTS

10.0. OBJECTIVES:

After going through this lesson students will :

- Understand the pathway of cholesterol biosynthesis in the human body
- Explain how cholesterol biosynthesis is regulated
- Describe the metabolism of bile pigments, especially bilirubin and biliverdin
- Identify clinical significance of disorders related to cholesterol and bile pigment metabolism
- Link the importance of these pathways in health and disease (e.g., jaundice, atherosclerosis

STRUCTURE:

10.1 INTRODUCTION

Cholesterol is found exclusively in animals, hence it is often called as ***animal sterol***. The total body content of cholesterol in an adult man weighing 70 kg is about 140 g i.e., around 2 g/kg body weight. Cholesterol is ***amphipathic*** in nature, since it possesses both hydrophilic and hydrophobic regions in the structure.

Compounds containing 27 carbon cyclopentanoperhydrophenanthrene structures with four rings labeled A to D. Steroids are complex fat-soluble molecules, which are present in the plasma lipoproteins and outer cell membrane. Cholesterol is one of the important non fatty acid lipid that is grouped with steroids.

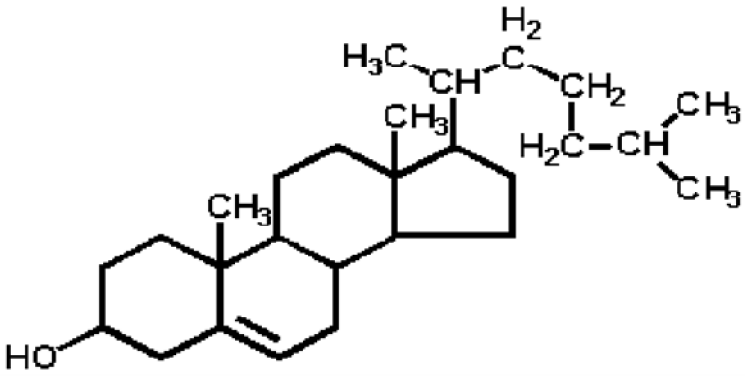

Fig. 10.1: Structure of Cholesterol.

Cholesterol is essential to life, as it performs a number of important functions

1) It is a ***structural component*** of cell membrane.
2) Cholesterol is the precursor for the ***synthesis of all other steroids*** in the body. These include steroid hormones, vitamin D and bile acids.
3) It is an essential ingredient in the structure of ***lipoproteins*** in which form the lipids in the body are transported.
4) Fatty acids are transported to liver as cholesteryl esters for oxidation.

10.2 BIOSYNTHESIS OF CHOLESTEROL

- Cholesterol is an essential lipid molecule in the human body. It is a structural component of cell membranes, a precursor for bile acids, steroid hormones, and vitamin D.
- Cholesterol is synthesized in the cell cytosol and endoplasmic reticulum from acetylCoA. Liver and intestine account each for 10% of the total cholesterol synthesized in the body. Almost all tissues containing nucleated cells can synthesize cholesterol. The synthesis follows five major steps which include:
- Acetyl CoA is converted to HMG CoA.
- HMG CoA is reduced to Mevalonate by a reductase.
- Mevalonate undergoes three times Phosphorylation, in the presence of 3 ATPs and various kinases.The product is 3- phosphor-5 pyrophospho mevalonate.
- Dephosphorylation, decarboxylation converts it to Isopentenyl pyrophosphate. It is isomerised to dimethyl allyl pyrophosphate by isomeras.
- Isopentenyl pyrophosphate and dimethyl allyl pyrophosphate form Geranyl PP(10C). Geranyl PP and one more molecule of Isopentenyl PPFarnesyl PP(15C).
- Two of Farnesyl PP join to form Squalene (30C).
- Squalene undergoes cyclization, loses three carbon atoms,aquire a double bond,forms cholesterol

- **The pathway requires:**
  - Acetyl-CoA (building block)
  - ATP (energy)
  - NADPH (reducing agent from the pentose phosphate pathway

Cholesterol biosynthesis is a complex and multi-step anabolic process carried out primarily in the liver but also in other tissues like the adrenal glands, intestines, and reproductive organs. This process occurs in the cytoplasm and smooth endoplasmic reticulum of cells. It begins with a molecule called acetyl-CoA, which is produced from the breakdown of carbohydrates, fats, and proteins.

Stages of Biosynthesis

1) Synthesis of HMG-CoA (6C): Two acetyl-CoA → acetoacetyl-CoA (thiolase). Acetoacetyl-CoA + acetyl-CoA → HMG-CoA (HMG-CoA synthase). Cytosolic enzyme (distinct from mitochondrial for ketogenesis).
2) Formation of Mevalonate (6C, Rate-Limiting): HMG-CoA reductase (ER) reduces HMG-CoA to mevalonate (2 NADPH). Statins inhibit here.
3) Production of Isoprenoid Units (5C): Mevalonate → 3-phospho-5-pyrophosphomevalonate (3 ATP, kinases). Decarboxylation → isopentenyl pyrophosphate (IPP). Isomerization → dimethylallyl pyrophosphate (DPP).
4) Synthesis of Squalene (30C): IPP + DPP → geranyl pyrophosphate (GPP, 10C). GPP + IPP → farnesyl pyrophosphate (FPP, 15C). Two FPP → squalene (squalene synthase, 2 NADPH).
5) Conversion to Cholesterol (27C): Squalene → squalene epoxide (monooxygenase, O_2, NADPH) → lanosterol (cyclase). Lanosterol → cholesterol (19 steps: demethylations at C4/C14, double bond shift C8→C5, reduction C24-C25). Intermediates: 14-desmethyl lanosterol, zymosterol, cholestadienol, desmosterol, 7-dehydrocholesterol.

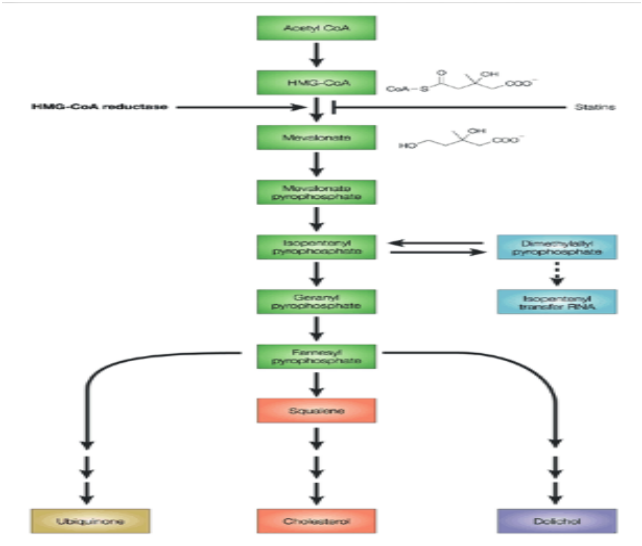

Fig. 10.2: Biosynthesis of Cholesterol

Catabolism of Cholesterol:

Intestinal Bacteria converts cholesterol to coprostanol which is excreted in feces. Cholesterol breaks down to cholic acid and chenodeoxycholic acid. Both are bile acids. They combine with sodium, Potassium to form bile salts. The key enzyme -hydroxylase is inhibited by high concentration of bile acids.

Functions of Bile Salts

- **They lower** surface tension, emulsify fats ,a pre requisite for the action of pancreatic lipase They activate Lipase.
- They shift the pH from 9 to 6
- They form micelles with fatty acid, a mono, di, triglyceride and help in absorption Promote absorption of fat soluble vitamins
- Bile salts keep cholesterol in soluble form in gall bladder. They regulate the breakdown of cholesterol

Cholelitiasis (Gall stones):

Absence of bile salts precipitate cholesterol as gall stones.Solublity of cholesterol depends on the ratio of phospholipids, bile salts to cholesterol.Due to infections bile acids are destroyed which leads to decreases solubility of cholesterol.

Decrease of bile salts can be due to:

a) Failure in enterohepatic circulation

b) Cirrhosis of Liver

c) Disease of ileum.

The patients are treated with chenodeoxycholic acid to solublize the cholesterol or the stones are removed by surgical intervention.

Hypercholesterolemia:

- Normal cholesterol level is 150-250mg% in blood. High concentration leads to hyper cholesterolemia.
- Excess cholesterol gets deposited under the skin, tendons as Xanthomas.
- In some cases the regulatory enzyme HMG-CoA reductase is not sensitive to feed back regulation. Such people suffer from familial hypercholesterolemia.

Atherosclerosis:

- Deposition of lipids in the connective tissues of intima of arteries is called atherosclerosis. It causes obstruction to blood flow, leading coronary heart disease, stroke, myocardial infarction etc.
- The process is initiated when there is injury to endothelial cells of blood vessels. A number of factors are responsible for injury .The condition is compounded by hyper lipidemia.

- **Atherogenesis** is the process by which **atherosclerotic plaques** form, a critical step in the disease, **atherosclerosis**.
- Low-density lipoprotein complexes (**LDLs**), which are the primary means of transporting
- **cholesterol** in the blood, are readily oxidized.

A class of white blood cells recognizes the oxidation and absorbs the LDL through its scavenger receptor. They becomes engorged and is referred to as a foam cell.

Foam cells attract other white blood cells, which leads to accumulation of more cholesterol.

Ultimately, this accumulation of cholesterol becomes one of the chief chemical constituents of the **atherosclerotic plaque** that forms at the site.

Circulating monocytes accumulate at the site of injury, ingest excess of lipids. If the damage to the intima continues, there is infiltration of platelets at the site.

Foam cells and platelets aggregate, and release substances resulting in atheromatic plaque.

Hypercholesterolemic Drugs

- **Compactin** inhibits HMG CoA reductase.Cholesterol synthesis decreases.
- **Mevinolin** Competes for Mevalonate ,Cholesterol synthesis decreases
- **Cholsetepol,** cholesteyramine (Resins) combine with bile salts and inhibit their reabsorption. Here Bile salts are lost in feces. As a result more cholesterol breaks down to bile salts.
- **Diatery fiber** is not a drug, better than a drug because
- Bile salts gets trapped in fiber and lost in feces.
- More cholesterol breaks down
- Cholesterol absorption is decreased because of indigestible fiber
- All other lipids are absorbed less.

DEGRADATION OF CHOLESTEROL

- The steroid nucleus (ring structure) of the cholesterol cannot be metabolized in humans.***function*** as surfactants. In the bile, the conjugated bile acids exist as sodium and potassium salts which are known as ***bile salts***.
- Cholesterol (50%) is converted to bile acids,excreted in feces

Synthesis of bile Acids:

- The bile acids possess 24 carbon atoms, 2 or 3 hydroxyl groups in the steroid nucleus and a side chain ending in carboxyl group. The bile acids are amphipathic in nature since they possess both polar and non-polar groups. They serve as emulsifying agents in the intestine and actively participate in the digestion and absorption of lipids.

- The synthesis of primary bile acids takes place in the liver and involves a series of reactions . The step catalysed by **7** a-***hydroxylase*** is inhibited by bile acids and this is the ***rate limiting*** reaction. Cholic acid and chenodeo- xycholic acid are the primary bile acids and the former is found in the largest amount in bile. . On conjugation with glycine or taurine, ***conjugated bile acids*** (glycocholic acid, taurocholic acid etc.) are formed which are more ***efficient in their function*** as surfactants. In the bile, the conjugated bile acids exist as sodium and potassium salts which are known as ***bile salts***.
- In the intestine, a portion of primary bile acids undergoes deconjugation and dehydroxylation to form ***secondary bile acids*** (deoxycholic acid and lithocholic acid). These reactions are catalysed by bacterial enzymes in the intestine.

10.3 REGULATION OF CHOLESTEROL BIOSYNTHESIS:

Cholesterol is both essential and potentially harmful in excess, its biosynthesis is tightly regulated. The rate-limiting step in this process is the reduction of HMG-CoA to mevalonate, catalyzed by the enzyme HMG-CoA reductase. This step is the main control point for cholesterol synthesis, and its regulation is multi-layered.

- Acetyl CoA is converted to Mevalonate. It is the committed step in the synthesis of cholesterol.
- Almost 800 mg of cholesterol is synthesized in our body .HMG CoA reductase is the regulatory enzyme.
    - Dietary cholesterol inhibits endogenous synthesis.
    - Fasting leads to low levels of the key enzyme.
    - Insulin activates protein phosphatase which converts it to active enzyme. Glucagon decreases its activity through c AMP dependent protein kinase.
    - Whenever ATP levels are low, the enzyme is switched off by AMP activated protein kinase.
    - m RNA for HMG CoA reductase is under the control of sterols . High concentration of sterols inhibits the synthesis of m RNA, there by the synthesis of enzyme.
    - High levels of degradation products lead to rapid degradation of HMG CoA reductase.

Feedback regulation is one of the primary mechanisms. When there is an adequate or excessive amount of cholesterol in the cell, the activity and synthesis of HMG-CoA reductase are suppressed. This prevents unnecessary cholesterol production.

- Hormonal regulation also plays a key role. The enzyme HMG-CoA reductase is activated by insulin and suppressed by glucagon, which reflects the body's energy and nutritional status. Insulin, for example, signals a well-fed state and promotes anabolic processes like cholesterol synthesis. Conversely, glucagon signals a fasting state and suppresses energy-consuming processes.

- There is also transcriptional regulation via a protein called SREBP (Sterol Regulatory Element-Binding Protein). When cholesterol levels are low, SREBP is activated and moves to the nucleus, where it binds to specific DNA sequences and promotes the transcription of genes involved in cholesterol synthesis, including the HMG-CoA reductase gene. When cholesterol levels are high, SREBP remains inactive, and gene transcription is halted.

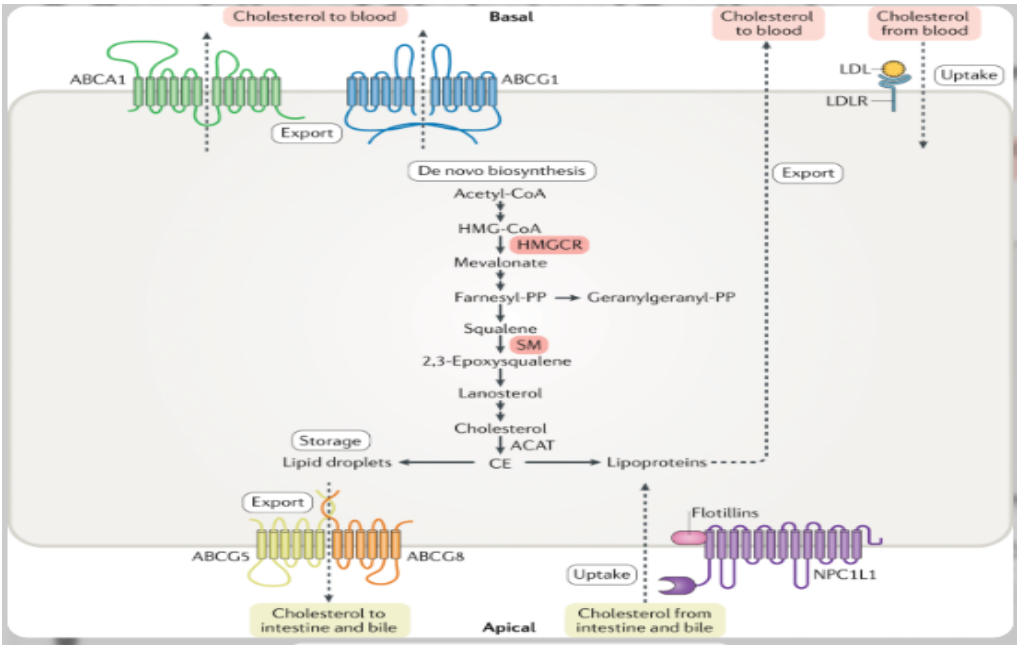

Fig. 10.3: Regulation of Cholesterol

Post-translational modification also plays a role. HMG-CoA reductase can be phosphorylated by AMP-activated protein kinase (AMPK), which renders the enzyme inactive. This mechanism links cholesterol synthesis to the energy status of the cell.

In addition to physiological control, pharmacological regulation is highly relevant. Statin drugs, commonly used to treat high cholesterol, are competitive inhibitors of HMG-CoA reductase. They effectively reduce endogenous cholesterol synthesis, which lowers plasma LDL cholesterol levels and reduces the risk of atherosclerosis and cardiovascular disease.

10.4 METABOLISM OF BILE PIGMENTS

Bile pigments are primarily derived from the breakdown of heme, which is released when old or damaged red blood cells are destroyed in the spleen, liver, and bone marrow. The first step in bile pigment formation is the degradation of heme by the enzyme heme oxygenase. This reaction breaks open the porphyrin ring of heme, releasing iron (which is reused), carbon monoxide (which has signaling functions), and a green pigment called biliverdin.

Biliverdin is then reduced to bilirubin, a yellow-orange pigment, by the enzyme biliverdin reductase. This bilirubin is initially unconjugated, meaning it is not water-soluble. It circulates in the bloodstream bound to albumin, a plasma protein that transports it to the liver.

In the liver, conjugation occurs, where bilirubin is made water-soluble by attaching it to glucuronic acid, a reaction catalyzed by the enzyme UDP-glucuronyl transferase. This conjugated bilirubin is now ready for excretion and is secreted into the bile. From the bile, it enters the small intestine.

In the intestine, bacterial enzymes act on conjugated bilirubin to convert it into urobilinogen. A small portion of this urobilinogen is reabsorbed into the bloodstream and taken to the kidneys, where it is excreted in urine as urobilin, giving urine its characteristic yellow color. The majority of the urobilinogen is oxidized in the intestine to form stercobilin, which is excreted in feces and gives stools their brown color.

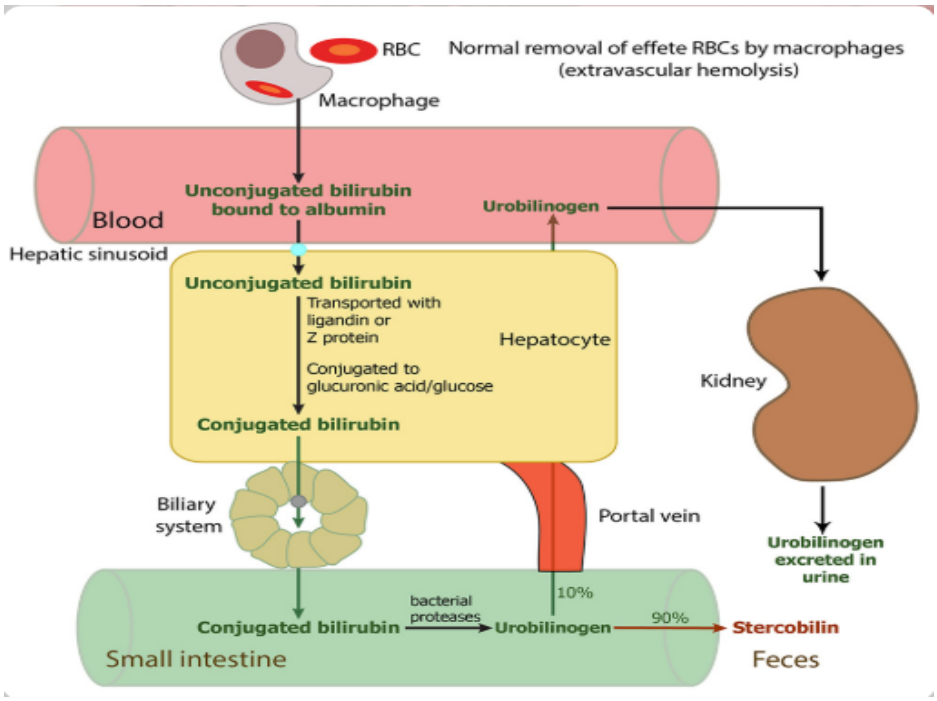

Fig. 10.4: Metabolism of Bile Pigments

Bile Pigment Metabolism Pathway

Stages of Heme Degradation

1) Heme to Biliverdin: In RE macrophages: Heme oxygenase (NADPH, O_2) cleaves heme → biliverdin (green) + Fe^{3+} + CO. Heme induces enzyme.
2) Biliverdin to Bilirubin: Biliverdin reductase (NADPH) reduces biliverdin → unconjugated bilirubin (yellow, lipophilic).
3) Transport to Liver: Unconjugated bilirubin-albumin complex (high-affinity site; drugs displace it, risking kernicterus in neonates).
4) Conjugation in Liver: Uptake by hepatocytes (ligandin/Z-protein). Bilirubin glucuronyltransferase (ER) adds 1-2 glucuronides (UDP-glucuronate) → bilirubin mono/diglucuronide (water-soluble). Induced by phenobarbital.
5) Excretion into Bile: Active transport of conjugated bilirubin into bile canaliculi (rate-limiting; impaired in liver dysfunction).

6) Intestinal Fate: Bacterial β-glucuronidases hydrolyze → bilirubin → urobilinogen (reabsorbed 10%, enterohepatic circulation). Urobilinogen → urobilin (urine) or stercobilin (feces; brown color).

Jaundice (Hyperbilirubinemia >2 mg/dL)

- Hemolytic (Prehepatic): ↑Unconjugated bilirubin (e.g., hemolysis, malaria). ↑Urobilinogen urine, dark feces. van den Bergh: Indirect positive.
- Hepatic (Hepatocellular): Liver damage (e.g., hepatitis, cirrhosis). ↑Both conjugated/unconjugated bilirubin, ↑ALT/AST. Pale stools, dark urine. Biphasic van den Bergh.
- Obstructive (Posthepatic): Bile duct block (e.g., gallstones). ↑Conjugated bilirubin, ↑ALP. Clay stools, dark urine. Direct positive van den Bergh.

10.5 SUMMARY

The biosynthesis and regulation of cholesterol, as well as the metabolism of bile pigments, are fundamental processes that illustrate the body's biochemical sophistication and its need to maintain internal balance. Cholesterol is vital for structural, hormonal, and metabolic functions, and its synthesis is finely tuned through feedback, hormonal, genetic, and pharmacological controls. Bile pigments, although they are by-products of heme degradation, have significant diagnostic importance, especially in liver and hematologic disorders.

Understanding these pathways not only provides deep insight into normal physiological functions but also forms the basis for diagnosing and managing conditions such as cardiovascular disease, hyperlipidemia, jaundice, and liver dysfunction. Therefore, a strong grasp of these metabolic pathways is essential for students of biochemistry, medicine, and health sciences.

10.6 TECHNICAL TERMS:

- Acetyl-CoA: A two-carbon molecule key to metabolic processes.
- HMG-CoA Reductase: Enzyme that regulates cholesterol synthesis.
- Squalene: Linear intermediate in cholesterol synthesis.
- Bilirubin: Yellow bile pigment formed from heme breakdown.
- Conjugated Bilirubin: Bilirubin bound to glucuronic acid.
- Urobilinogen: Colorless pigment formed in the intestine.
- Stercobilin: Pigment that gives feces its brown color.

10.7 SELF-ASSESSMENT QUESTIONS:

1) Outline the key steps involved in cholesterol biosynthesis.
2) Describe how cholesterol synthesis is regulated.

3) What is the significance of HMG-CoA reductase?
4) Explain the process of bilirubin formation and excretion.
5) Differentiate between conjugated and unconjugated bilirubin.
6) What are the different types of jaundice and their causes?
7) How do statins help in managing cholesterol levels?

10.8 REFERENCE BOOKS:

- Harper's Illustrated Biochemistry – Murray et.al..
- Lehninger Principles of Biochemistry – Nelson & Cox.
- Lippincott's Illustrated Reviews: Biochemistry – Ferrier.
- Textbook of Medical Physiology – Guyton & Hall.
- Biochemistry – Satyanarayana & Chakrapani.

Dr. Santhi Sri, K.V

LESSON-11

LIPIDS OF BIOLOGICAL SIGNIFICANCE - LIPOPROTEINS AND PROSTAGLANDINS IN HEALTH AND DISEASE

11.0. OBJECTIVES:

After going through this lesson students will:

- Understand the structure and classification of biologically significant lipids.
- Describe the composition, types, and physiological roles of lipoproteins.
- Explain the functions and biosynthesis of prostaglandins.
- Discuss the roles of lipoproteins and prostaglandins in health and disease.
- Analyse lipid-related disorders, including hyperlipidaemia, atherosclerosis, and inflammatory conditions.
- Appreciate the clinical significance of lipid profile testing and lipid-lowering therapies.

STRUCTURE:

11.1 INTRODUCTION:

Lipids are a diverse group of hydrophobic biomolecules that play crucial roles in energy storage, cell membrane structure, and signalling. Among these, lipoproteins and prostaglandins are of significant biological and clinical importance.

Lipoproteins are complexes of lipids and proteins that transport hydrophobic lipids like cholesterol and triglycerides through the aqueous environment of blood. They are essential for lipid metabolism and energy distribution, but are also closely linked to cardiovascular diseases such as atherosclerosis when present in abnormal levels.

Prostaglandins, on the other hand, are a type of eicosanoid derived from fatty acids, particularly arachidonic acid. They act as local hormones and mediate a wide range of physiological processes, including inflammation, fever, pain, blood clotting, and smooth muscle contraction. Imbalances or overproduction of prostaglandins are implicated in various pathological conditions such as arthritis, asthma, and cancer.

Thus, understanding the roles of lipoproteins and prostaglandins provides insight into their dual significance in maintaining health and contributing to disease mechanisms.

11.2 LIPIDS OF BIOLOGICAL SIGNIFICANCE: LIPOPROTEINS AND PROSTAGLANDINS

Lipids are essential biomolecules that serve as energy reserves, structural components of cell membranes, and signalling molecules. Among the various classes of biologically significant lipids, lipoproteins and prostaglandins play key roles in maintaining health and are also involved in several disease conditions.

11.2.1. LIPOPROTEINS

Lipoproteins are conjugated proteins that transport insoluble lipids (e.g., triacylglycerols, cholesterol) in plasma, preventing aggregation and enabling delivery to tissues. They are essential for lipid homeostasis but imbalances lead to cardiovascular diseases (CVD).

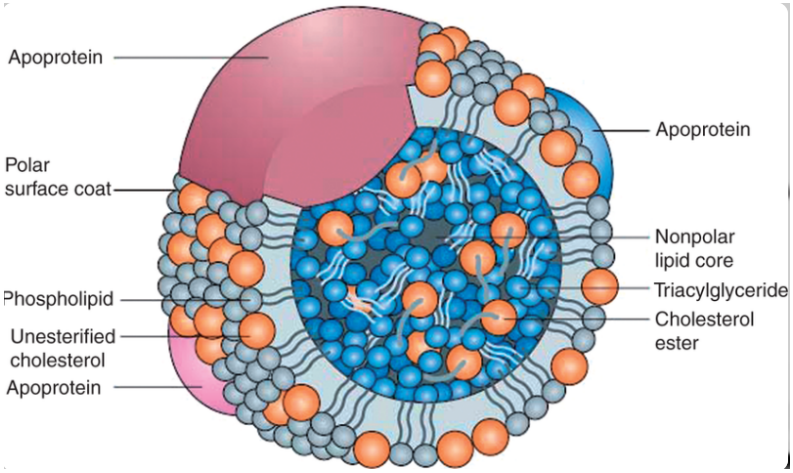

Fig. 11.1

Structure

General Structure: Neutral lipid core (triacylglycerols, cholesteryl esters) surrounded by a shell of phospholipids, free cholesterol, and apoproteins (Fig. 14.33 in textbook). The amphiphilic shell ensures solubility in plasma.

Classification:

Based on Density (Ultracentrifugation) and Electrophoretic Mobility:

- Chylomicrons: Largest (100-1000 nm), lowest density (<0.96 g/mL); origin at pre-β; 88% triacylglycerols, 2% protein (apo B-48 main); transport dietary lipids.

- VLDL: 30-90 nm, density 0.96-1.006 g/mL; pre-β; 55% triacylglycerols, 10% protein (apo B-100); transport endogenous triacylglycerols.
- IDL: Intermediate; formed from VLDL; β mobility.
- LDL: 20-25 nm, density 1.006-1.063 g/mL; β; 59% cholesterol, 20% protein (apo B-100); "bad cholesterol," delivers cholesterol to tissues.
- HDL: Smallest (10-20 nm), highest density (1.063-1.21 g/mL); α; 40% protein (apo A main); "good cholesterol," reverse cholesterol transport.
- FFA-Albumin: Non-electrophoretic; transports free fatty acids bound to albumin (Table 14.5 for details).

Apolipoproteins (Apoproteins)

- Proteins (1-40% of lipoprotein) that stabilize structure, recognize receptors, and activate enzymes.
- Key Types: Apo A (HDL structural), Apo B-48 (chylomicrons), Apo B-100 (VLDL/LDL recognition), Apo C-II (activates lipoprotein lipase), Apo E (receptor binding for remnants).

Metabolism

Lipoprotein metabolism integrates dietary and endogenous lipid transport.

Lipoproteins in Disease:

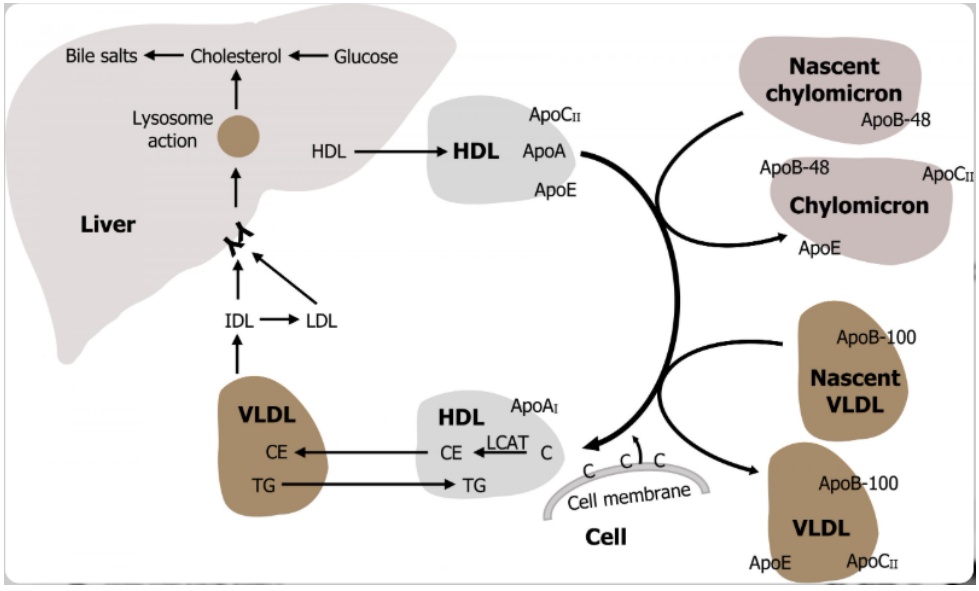

Fig. 11.2

- Chylomicrons: Synthesized in intestines (nascent with apo B-48); acquire apo C-II/E from HDL; lipoprotein lipase (LPL, activated by apo C-II) hydrolyzes triacylglycerols in adipose/muscle; remnants (with apo E) cleared by liver receptors.
- VLDL: Liver synthesis (nascent with apo B-100); acquires apo C-II/E from HDL; LPL hydrolysis forms IDL, then LDL (loses apo E/C-II).

- LDL: Supplies cholesterol to tissues via LDL receptors (apo B-100 mediated endocytosis); excess LDL oxidizes, forms foam cells, promotes atherosclerosis.
- HDL: Liver/intestine synthesis (nascent discoidal); LCAT (activated by apo A) esterifies cholesterol; CETP exchanges cholesteryl esters for triacylglycerols with VLDL/LDL; mature HDL delivers cholesterol to liver for bile acid synthesis/excretion (cardioprotective).
- Regulation: LPL in capillaries; LCAT for esterification; CETP for lipid exchange.

11.2.2 PROSTAGLANDINS

Prostaglandins (PGs)and their related compounds-prostacyclins (PGI), thromboxanes (TXA), leukotrienes (LT) and lipoxins are collectively known as ***eicosaniods***, since they all contain 20 carbons (*Greek*: eikosi-twenty). Eicosanoids are considered as locally acting hormones with a wide range of biochemical functions.

Prostaglandins (PGs) were first discovered in human semen by Ulf von Euler (of Sweden) in 1930. These compounds were found to stimulate uterine contraction and reduce blood pressure. von Euler presumed that they were synthesized by prostate gland and hence named them as prostaglandins. It was later realized that PGs and other eicosanoids are synthesized in almost all the tissues (exception– erythrocytes). By then, however, the name prostaglandins was accepted worldwide, and hence continued.

The prostaglandins E and F were first isolated from the biological fluids. They were so named due to their solubility in ether (PGE) and phosphate buffer (PGF, F for fosfat, in Swedish). All other prostaglandins discovered later were denoted by a letter—PGA, PGH etc.

All cells with the exception of the red blood cell have the capacity to synthesize prostaglandins. Arachidonic acid is an unsaturated fatty acid prevalent in high concentrations in the phospholipid of the cell membrane, which is precursor for synthesis of prostaglandins.

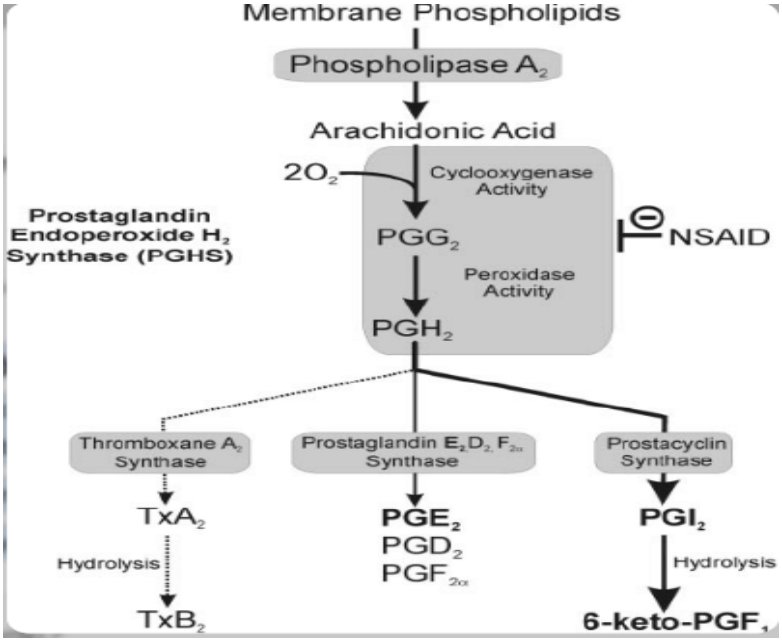

Fig. 11.3

Structure and Types:

- Parent Structure: Prostanoic acid (cyclopentane ring + two chains); variations in ring substituents/double bonds.
- Key PGs: PGE (keto at C9, OH at C11), PGF (OH at C9/C11), etc.
- Related: Prostacyclins (PGI2, extra ring); thromboxanes (TXA2, oxane ring); leukotrienes (linear, no ring).

Synthesis:

- Precursor: Arachidonic acid (20:4 Δ5,8,11,14) from membrane phospholipids via phospholipase A2 (stimulated by epinephrine/bradykinin).
- Cyclic Pathway: Cyclooxygenase (COX) forms PGG2/PGH2; synthases produce PGs (e.g., PGE2, PGF2α), PGI2, TXA2.
    - COX-1 (constitutive, housekeeping); COX-2 (inducible, inflammation).
- Inhibition: Aspirin (irreversible COX acetylator); NSAIDs (reversible); corticosteroids (block phospholipase A2).
- Degradation: Rapid (lung/liver); 15-hydroxy PG dehydrogenase oxidizes C15 OH to keto, then reduces double bond.
- Linear Pathway: Lipoxygenase forms leukotrienes (e.g., LTA4 → LTB4/LTC4) and lipoxins.

Biochemical Actions

PGs act locally via cAMP/cGMP; effects vary by tissue/type.

- Blood Pressure: PGE/PGA/PGI2 vasodilate, lower BP; treat hypertension.
- Inflammation: PGE1/E2 cause redness/swelling; mediate arthritis/psoriasis; corticosteroids inhibit.
- Reproduction: PGE2/F2α induce labor/abortion; promote estrus/fertilization.
- Pain/Fever: PGE2 (with histamine/bradykinin) causes pain; pyrogens increase PGE2 in hypothalamus; aspirin relieves.
- Gastric Secretion: PGE inhibits HCl; treat ulcers; diarrhea from increased motility.
- Immune System: PGE suppresses B/T-lymphocytes.
- Respiratory: PGE bronchodilates; PGF constricts; treat asthma.
- Renal: PGE increases GFR, Na+/K+ excretion.
- Metabolism: PGE increases cAMP (lipolysis/glycogenolysis/Ca2+ mobilization).
- Platelet Aggregation/Thrombosis: PGI2 inhibits; TXA2/PGE2 promote; balance regulates hemostasis.
- Leukotrienes: Contract smooth muscle; implicated in asthma/allergy (SRS-A 100-1000x potent than histamine).

11.3 LIPOPROTEINS IN HEALTH AND DISEASE

Lipoproteins are ***molecular complexes*** that consist ***of lipids and proteins*** (conjugated proteins). They function as transport vehicles for lipids in blood plasma. Lipoproteins deliver the lipid components (cholesterol, triacylglycerol etc.) to various tissues for utilization.

Inherited disorders of lipoproteins are encountered in some individuals resulting in ***primary*** hyper- or hypolipoproteinemias. These are due to genetic defects in lipoprotein metabolism and transport. The ***secondary*** acquired lipoprotein disorders are due to some other diseases (e.g. diabetes mellitus, nephrotic syndrome, atherosclerosis, hypothyrodism etc.), resulting in abnormal lipoprotein pattern which often resembles the primary inherited condition.

TABLE ; Classification and characteristics of hyperlipoproteinemias (hyperlipidemias)

Hyperlipoproteinemia Type	Increased plasma lipoprotein(s)	Increased plasma lipid (most)	Probable metabolic defect	Risk of atherosclerosis	Suggested treatment
I	Chylomicrons	Triacylglycerols	Deficiency of lipoprotein lipase	May increase	Low fat diet
IIa	LDL	Cholesterol	Deficiency of LDL receptors	Very high (mostly in coronary artery)	Low cholesterol fat diet; cholestyramine
IIb	LDL and VLDL	Triacylglycerols and cholesterol	Overproduction of apo-B	do	do
III	IDL	Triacylglycerols and cholesterol	Abnormality in apo-E	Very high (mostly in peripheral vessels)	Low fat and low caloric diet; clofibrate
IV	VLDL	Triacylglycerols	Overproduction of TG	May or may not increase	Low fat and low caloric diet; niacin
V	Chylomicrons and VLDL	Triacylglycerols		do	do

- **Health Roles:** Efficient lipid transport; HDL's reverse transport protects against CVD (anti-atherogenic); LDL delivers cholesterol for membranes/hormones.
- **Disorders** (Hyperlipoproteinemias, Fredrickson's Classification):

- Type I: Lipoprotein lipase deficiency; elevated chylomicrons/triacylglycerols; treat with low-fat diet.
- TypeIIa: LDL receptor defect (familial hypercholesterolemia); high LDL/cholesterol; high CHD risk; treat with statins/cholestyramine.
- Type IIb: Apo B overproduction; high LDL/VLDL; similar to IIa.
- Type III: Apo E abnormality; high IDL; peripheral atherosclerosis.
- Type IV: VLDL overproduction; high triacylglycerols; associated with obesity/diabetes.
- Type V: High chylomicrons/VLDL; secondary to diabetes/alcohol.

- **Hypolipoproteinemias:**

- **Familial hypobetalipoproteinemia :** It is an inherited disorder probably due to an impairment in the synthesis of apoprotein B. The plasma LDL concentration in the affected individuals is between 10 to 50% of normal values. This disorder is harmless, and the individuals have healthy and long life.
- **Abetalipoproteinemia :** This is a rare disorder due to a defect in the synthesis of apoprotein B. It is characterized by a total absence of b-lipoprotein (LDL) in plasma. Triacylglycerols are not found in plasma, but they accumulate in liver and intestine. Serum cholesterol level is low. Abetalipoproteinemia is associated with decreased absorption of fat and fat-soluble vitamins. Impairment in physical growth and mental retardation are commonly observed.
- **Familial alpha-lipoprotein deficiency (Tangier disease):** The plasma HDL particles are almost absent. Due to this, the reverse transport of cholesterol is severely affected leading to the accumulation of cholesteryl esters in tissues. An absence of apoprotein C II-which activates lipoprotein lipase-is also found. The plasma triacylglycerol levels are elevated. The affected individuals are at an increased risk for atherosclerosis.

Fatty Liver:

The normal concentration of lipid (mostly phospholipid) in liver is around 5%. Liver is not a storage organ for fat, unlike adipose tissue. However, in certain conditions, lipids- especially the ***triacylglycerols-accumulate*** excessively in liver, resulting in fatty liver.In the normal liver, Kupffer cells contain lipids in the form of droplets. In fatty liver, droplets of triacylglycerols are found in the entire cytoplasm of hepatic cells. This causes impairment in metabolic functions of liver. Fatty liver is associated with fibrotic changes and cirrhosis, Fatty liver may occur due to two main causes.

1) Increased synthesis of triacylglycerols
2) Impairment in lipoprotein synthesis.

1) **Increased triacylglycerol synthesis:** Mobilization of free fatty acids from adipose tissue and their influx into liver is much higher than their utilization. This leads to the overproduction of triacylglycerols and their accumulation in liver. ***Diabetes mellitus***, ***starvation***, ***alcoholism*** and ***high fat diet*** are associated with increased mobilization of fatty acids that often cause fatty liver. Alcohol also inhibits fatty acid oxidation and, thus, promotes fat synthesis and its deposition.

2) **Impaired synthesis of lipoproteins:** The synthesis of very low density lipoproteins (VLDL) actively takes place in liver. VLDL formation requires phospholipids and apoprotein B. Fatty liver caused by impaired lipoprotein synthesis may be due to :

   a) A defect in phospholipid synthesis;

   b) Ablock in apoprotein formation;

   c) A failure in the formation/secretion of lipo- protein.

   Among the three causes, fatty liver due to impairment in phospholipid synthesis has been studied in some detail. This is usually associated with the dietary ***deficiency of lipotropic factors*** such as choline, betaine, inositol etc. (more details given later). Deficiency of essential fattyacids leads to a decreased formation of phospholipids. Further, excessive consumption of cholesterol competes with essential fatty acids and impairs phospholipid synthesis.

Certain chemicals (e.g. puromycin, ethionine, carbon tetrachloride, chloroform, lead, phosphorus etc.) that inhibit protein synthesis cause fatty liver. This is due to a blockade in the synthesis of apoprotein B required for VLDL production.

Lipoprotein synthesis and their secretion require ATP. Decrease in the availability of ATP, sometimes found in pyridoxine and pantothenic acid deficiency, impairs lipoprotein formation. The action of ethionine in the development of fatty liver is believed to be due to a reduction in the availability of ATP. Ethionine competes with methionine and traps the available adenosine (as adenosylethionine)—thereby reducing ATP levels.

Deficiency of vitamin E is associated with fatty liver. Selenium acts as a protective agent in such a condition.

Endocrine Factors: Certain hormones like ACTH, insulin, thyroid hormones, adreno-corticoids promote deposition of fat in liver.

- **Clinical Concepts:** High LDL risks atherosclerosis/CHD; low HDL correlates with CVD. Tests: Lipid profile (cholesterol <200 mg/dL, LDL <100, HDL >60, triacylglycerols <150). Treatments: Statins inhibit HMG-CoA reductase; lifestyle changes.

11.4 PROSTAGLANDINS IN HEALTH AND DISEASE

Prostaglandins perform diversified functions. And for this reason, PGs (or other derivatives) are the most exploited in therapeutic applications. They are used in the ***treatment of gastric ulcers***, ***hypertension***, ***thrombosis***, ***asthma*** etc. Prostaglandins are also employed in the medical termination of pregnancy, prevention of conception, induction of labor etc.

Inhibitors of prostaglandin synthesis (e.g. aspirin, ibuprofen) are utilized in controlling fever, pain, migraine, inflammation etc.

- **Health Roles:** Local signaling for homeostasis (e.g., PGI2 prevents thrombosis, PGE gastric protection).
- **Disease Associations:** Overproduction causes pain/fever/inflammation (e.g., migraine, arthritis); low marine lipids (EPA) reduce TXA2, lower heart attacks (Eskimos).
- **Biomedical Applications:** PGE2/F2α for abortion/labor; misoprostol for ulcers; alprostadil for impotence; inhibitors (aspirin/ibuprofen) for pain/fever/migraine.

PGs play important roles in the regulation of many basic physiologic processes within the human body. Each organ system has its own specific site of synthesis and PG mediator(s). In some systems such as the musculoskeletal system, for example, the primary effects are more complex, ie, demonstrating both bone resorption and bone formation. Ultimately, the specific impairment of these regulatory controls in various organ systems can often lead to significant short- and long-term dysfunction and disease. These include but are not limited to acute and chronic renal failure, gastrointestinal inflammation and hemorrhage, and others.

11.5 SUMMARY:

Lipoproteins and prostaglandins are critical lipids with distinct but interconnected roles in human health. While lipoproteins manage lipid transport and energy distribution, prostaglandins act as potent local mediators of inflammation and physiological balance. Abnormalities in their functions can contribute to a wide range of diseases, making them key targets in medical diagnosis and treatment.

11.6 TECHNICAL TERMS:

- **Apolipoprotein**: Protein component of lipoproteins
- **Eicosanoids**: Lipid mediators derived from 20-carbon fatty acids
- **Cyclooxygenase (COX)**: Enzyme that catalyzes prostaglandin synthesis
- **Hyperlipidemia**: Elevated levels of lipids in the blood
- **Statins**: Cholesterol-lowering drugs

11.7 SELF-ASSESSMENT QUESTIONS:

1) What are the different types of lipoproteins and their functions?
2) Explain the biosynthesis and biological roles of prostaglandins.
3) How do lipoproteins contribute to cardiovascular disease?
4) What is the role of NSAIDs in prostaglandin regulation?
5) Differentiate between the roles of LDL and HDL.

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Dr. Santhi Sri, K.V

LESSON-12

METABOLIC INTERRELATIONSHIPS BETWEEN CARBOHYDRATES, LIPIDS AND FATS

12.0. OBJECTIVES:

After going through this lesson students will understand:

- To understand the conversion pathways between macronutrients
- To explore energy production from different macronutrients
- To examine hormonal regulation of nutrient metabolism
- To highlight the importance of metabolic balance and health implications

STRUCTURE:

12.1 INTRODUCTION

Metabolic Interrelationships between Carbohydrates, Lipids, and Proteins

The human body maintains energy balance and nutrient supply through a complex network of interconnected metabolic pathways involving carbohydrates, lipids, and proteins. These macronutrients, though distinct in structure and primary functions, are interconvertible under metabolic control.

Carbohydrates serve as the primary and most immediate source of energy. When carbohydrate intake is limited or energy demands are high, the body turns to lipids, which provide a more concentrated energy source. Proteins, although primarily used for growth and repair, can also be broken down for energy during prolonged fasting or starvation.

These metabolic interrelationships are regulated by hormones such as insulin, glucagon, cortisol, and epinephrine, ensuring that the body can adapt to changing energy requirements. The integration and coordination of these pathways are essential for maintaining homeostasis, especially during fasting, exercise, or illness.

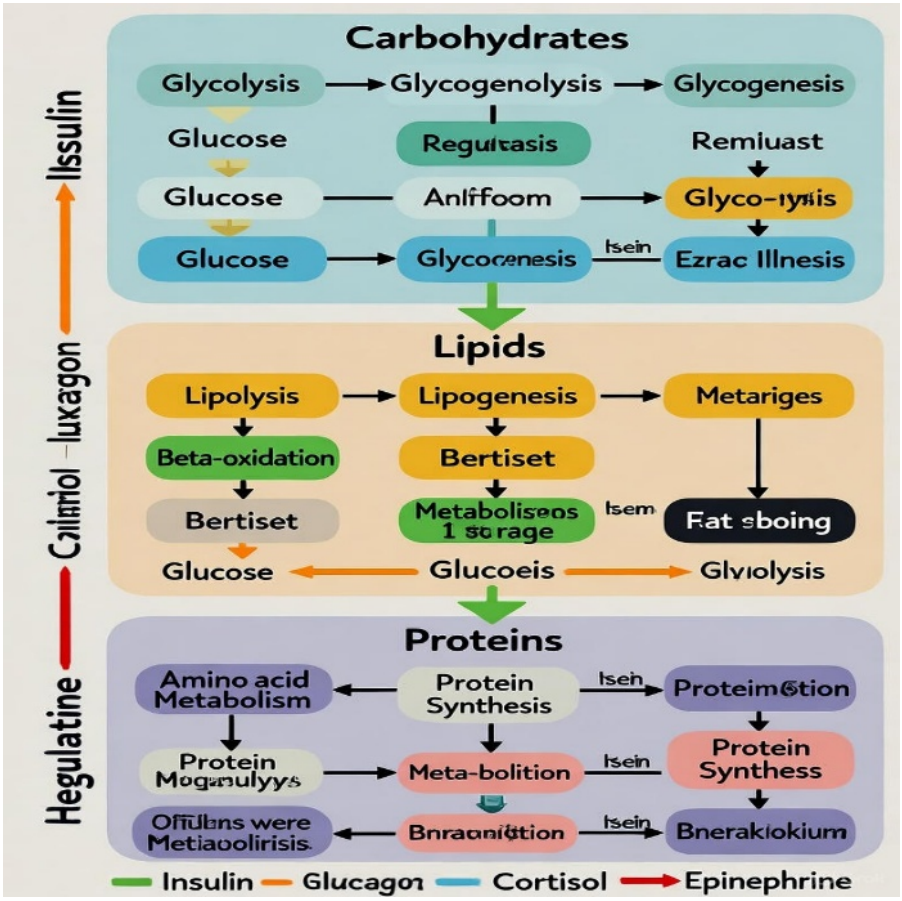


Fig. 12.1

12.2 OVERVIEW:

The metabolism of carbohydrates, lipids, and proteins is intricately connected. The body maintains a dynamic metabolic balance to ensure a continuous energy supply, cellular repair, and biosynthesis, regardless of external conditions (e.g., fed vs. fasting state). These macronutrients can be converted into each other, either for energy production, storage, or structural and functional roles.

All three macronutrients ultimately feed into common metabolic hubs such as:

- Acetyl-CoA
- Pyruvate
- Krebs (TCA) Cycle
- Electron Transport Chain

Carbohydrate Metabolism in Interrelationship

Carbohydrates are the primary and most readily available source of energy. Glucose is the central molecule in carbohydrate metabolism and acts as a major fuel for the brain, muscles, and red blood cells.

In the fed state, glucose is:

- Oxidized via glycolysis → ATP

- Stored as glycogen (liver and muscle)
- Converted into fatty acids through lipogenesis if in excess

In the fasting state, glucose is:

- Maintained by glycogenolysis (early fasting)
- Produced by gluconeogenesis from amino acids, lactate, and glycerol (prolonged fasting)
- Glucose is the source of pyruvate, which is a central link between carbohydrates, lipids, and amino acids.

Lipid Metabolism in Interrelationship

Lipids (especially triglycerides) are the most energy-dense molecules and are used as a major energy source during fasting or energy demands.

Fatty acids undergo β-oxidation to form acetyl-CoA, which enters the TCA cycle or forms ketone bodies.

The glycerol backbone of triglycerides can enter gluconeogenesis.

In the fed state, excess glucose can be converted into fatty acids via acetyl-CoA in the cytoplasm of liver/adipose cells.

However, fatty acids cannot be converted to glucose due to the irreversible nature of the pyruvate dehydrogenase reaction (acetyl-CoA cannot form pyruvate).

Protein Metabolism in Interrelationship

Proteins are not primarily used for energy, but they become important during:

- Starvation
- Prolonged fasting
- Intense exercise

Amino acids can be classified as:

- Glucogenic → converted into glucose (via pyruvate or TCA intermediates)
- Ketogenic → converted into ketone bodies or acetyl-CoA
- Mixed → both glucogenic and ketogenic

Proteins from body tissues (muscles) are broken down into amino acids to provide substrates for:

- Gluconeogenesis (glucose production)
- Ketogenesis (in limited amino acids)
- Energy production (via Krebs cycle)

Tissue-Specific Metabolic Roles

Liver:

- Central organ for metabolic integration
- Regulates gluconeogenesis, glycogenesis, lipogenesis, ketogenesis
- Synthesizes non-essential amino acids, cholesterol, lipoproteins

Adipose Tissue:

- Stores triglycerides
- Releases free fatty acids during fasting
- Responds to insulin for fat storage

Muscle:

- Uses glucose, fatty acids, and ketone bodies as energy
- Provides amino acids during fasting (muscle protein breakdown)

Brain:

- Uses glucose as primary fuel
- Uses ketone bodies during prolonged fasting
- Cannot use fatty acids directly (blood-brain barrier)

Hormonal Control of Interrelationships

Hormone	State	Effects on Metabolism
Insulin	Fed	Promotes glucose uptake, glycogen & fat synthesis, inhibits gluconeogenesis
Glucagon	Fasting	Stimulates glycogenolysis, lipolysis, and gluconeogenesis
Epinephrine	Stress/Exercise	Promotes glycogenolysis, lipolysis
Cortisol	Chronic stress	Enhances protein breakdown, gluconeogenesis

12.3. METABOLIC CONDITIONS HIGHLIGHTING INTERRELATIONSHIPS

Diabetes Mellitus:

Impaired insulin function → excess glucose in blood

Body uses fats and proteins for energy → ketosis, muscle wasting

Starvation:

Initially uses glycogen → shifts to gluconeogenesis → then to lipolysis and ketogenesis

Preserves protein by shifting to fat metabolism

Obesity:

Excess carbohydrate → converted to fat

Disrupted metabolic regulation → fat accumulation

Key Concepts:

- Acetyl-CoA is a central molecule in lipid and carbohydrate metabolism.
- Glucose can be stored, used, or converted to fat.
- Fatty acids are a dense energy source but cannot be converted to glucose.
- Proteins serve as a backup energy source and are converted to glucose or fat when needed.
- The liver is the hub of metabolic interconversion.

The metabolism of carbohydrates, lipids, and proteins is not isolated but interdependent, ensuring the body adapts to varying energy demands. These interrelationships are vital for homeostasis, especially during metabolic stress, fasting, or illness. Hormonal control plays a crucial role in determining which pathways are activated. Understanding these interactions is key to diagnosing and managing metabolic diseases such as diabetes, obesity, and malnutrition.

1. Carbohydrate Metabolism:

- Carbohydrates are primarily broken down into glucose, the main energy source for the body.
- Glucose is metabolized through glycolysis to form pyruvate.
- Under aerobic conditions, pyruvate is converted to acetyl-CoA, which enters the TCA cycle to produce ATP.

Excess glucose can be stored as glycogen or converted into fatty acids via lipogenesis.

1) Carbohydrate metabolism refers to the chemical processes involved in the breakdown, conversion, and utilization of carbohydrates in the body.
2) The main source of carbohydrate is glucose, derived from dietary intake (starch, sugar).
3) **Major pathways include:**
    - Glycolysis – breakdown of glucose into pyruvate with ATP production.
    - Gluconeogenesis – synthesis of glucose from non-carbohydrate sources.

- Glycogenesis – conversion of glucose into glycogen for storage (in liver and muscles).
- Glycogenolysis – breakdown of stored glycogen into glucose.

Pentose Phosphate Pathway (HMP shunt) – produces NADPH and ribose for biosynthesis.

4) Insulin and glucagon are the main hormones regulating carbohydrate metabolism.
5) Final energy is released through the Krebs cycle and Electron Transport Chain (ETC).
6) Carbohydrate metabolism is vital for energy supply, especially for the brain, muscles, and red blood cells.

Carbohydrate metabolism encompasses all biochemical processes responsible for the breakdown and conversion of carbohydrates into usable energy. The central molecule is glucose, which undergoes glycolysis to form pyruvate and generate ATP. When energy is needed quickly, stored glycogen is mobilized through glycogenolysis, while excess glucose is stored via glycogenesis. In times of fasting, the body can also produce glucose from non-carbohydrate sources through gluconeogenesis. The pentose phosphate pathway diverts glucose to produce NADPH and ribose sugars. These pathways are tightly regulated by hormones like insulin (promotes glucose storage) and glucagon (promotes glucose release). Overall, carbohydrate metabolism plays a critical role in maintaining energy homeostasis, especially for high-demand organs like the brain and muscles.

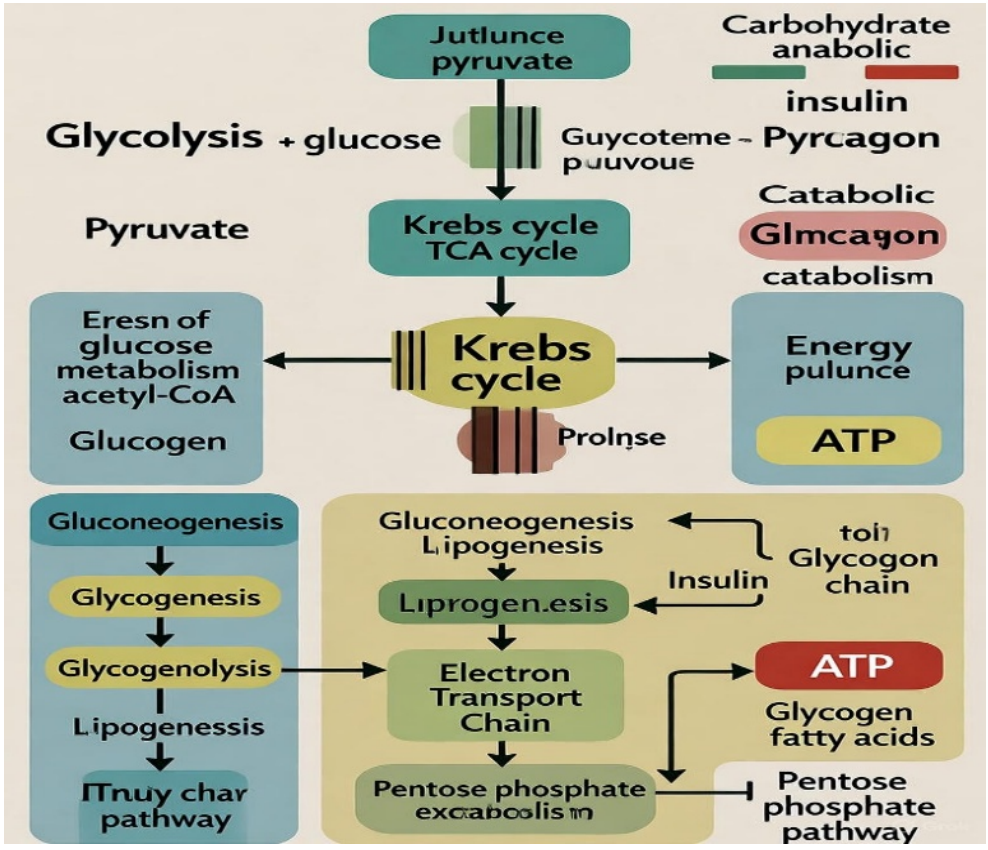


Fig. 12.2

2. Lipid Metabolism

Lipids are broken down into fatty acids and glycerol.

Fatty acids undergo β-oxidation to generate acetyl-CoA, which enters the TCA cycle for ATP production.

In times of energy surplus, acetyl-CoA from carbohydrates or amino acids can be used to synthesize fatty acids and stored as triglycerides.

Glycerol can enter the glycolytic pathway after conversion to glyceraldehyde-3-phosphate.

Lipid metabolism refers to the processes of breaking down and synthesizing lipids (fats) for energy production, storage, and structural roles in the body.

1. Breakdown of Lipids (Catabolism)

- Lipids (mainly triglycerides) are broken down into:
- Glycerol
- Free fatty acids (FFAs)

This process is called lipolysis and occurs in adipose tissue.

Enzyme involved: Hormone-sensitive lipase, activated during fasting or stress.

2. Fatty Acid β-Oxidation (in Mitochondria)

- Fatty acids are transported into the mitochondria via the carnitine shuttle.
- Undergo β-oxidation, which is a cyclic process that:
- Removes two-carbon units per cycle
- Produces acetyl-CoA, NADH, and $FADH_2$
- Acetyl-CoA then enters the TCA (Krebs) cycle for complete oxidation and ATP generation via the Electron Transport Chain (ETC).

3. Glycerol Utilization

- Glycerol released from triglycerides is converted into:
- Glycerol-3-phosphate, then to
- Glyceraldehyde-3-phosphate (G3P)
- G3P enters the glycolytic pathway, contributing to glucose metabolism or energy production.

4. Lipogenesis (Fat Synthesis)

- In times of excess energy (postprandial state):
- Glucose or amino acids are converted into acetyl-CoA
- Acetyl-CoA is used for fatty acid synthesis in the cytoplasm (mainly in liver and adipose tissue).
- Fatty acids are esterified with glycerol to form triglycerides (TG) and stored in adipose tissue.

5. Ketogenesis (in Liver)

- When carbohydrate availability is low (e.g., fasting, starvation, diabetes):
- Excess acetyl-CoA from fatty acid β-oxidation is converted to ketone bodies (acetoacetate, β-hydroxybutyrate, acetone).
- These ketone bodies serve as alternative energy sources for brain, muscle, and heart.

6. Regulation of Lipid Metabolism

State	Hormonal Control	Effect
Fasting	↑ Glucagon, ↑ Epinephrine	Stimulates lipolysis and β-oxidation
Fed state	↑ Insulin	Stimulates lipogenesis, inhibits lipolysis

7. Importance of Lipid Metabolism

- Provides more ATP per gram than carbohydrates.
- Essential during fasting, prolonged exercise, or low-carb diets.
- Helps maintain energy balance, body temperature, and membrane structure.

Lipid metabolism involves the breakdown and synthesis of fats to meet the body's energy demands. Triglycerides are hydrolyzed into glycerol and fatty acids. Fatty acids are oxidized via β-oxidation in the mitochondria to produce acetyl-CoA, which enters the TCA cycle for ATP generation. Glycerol is converted into glyceraldehyde-3-phosphate, entering the glycolytic pathway. When energy intake exceeds demand, acetyl-CoA derived from carbohydrates or amino acids is used for fatty acid synthesis (lipogenesis), and excess fat is stored as triglycerides in adipose tissue. In prolonged fasting, the liver converts fatty acids into ketone bodies (ketogenesis), which serve as alternative fuels. Lipid metabolism is tightly regulated by hormones such as insulin, glucagon, and epinephrine, ensuring energy availability under various physiological conditions.

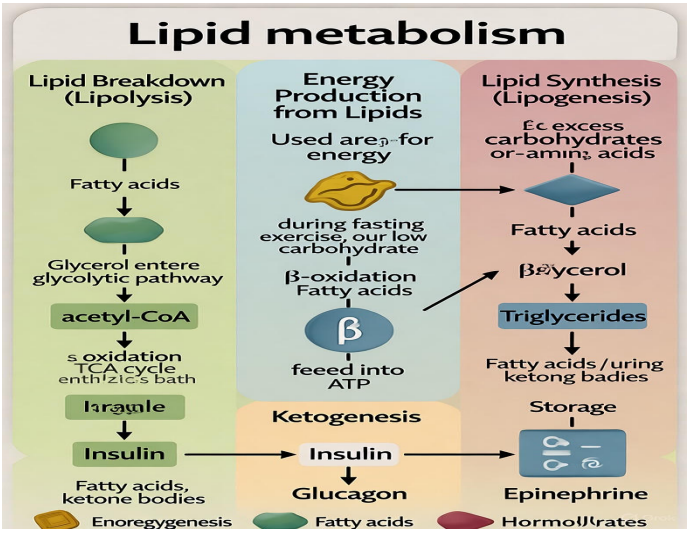


Fig. 12.3

3. Protein Metabolism

Proteins are hydrolyzed into amino acids.

Amino acids undergo transamination and deamination, producing carbon skeletons that can be converted into:

- Pyruvate
- Acetyl-CoA
- TCA cycle intermediates
- The nitrogen part is converted to urea and excreted.

During fasting or starvation, proteins can serve as a significant source of gluconeogenesis and energy.

1. Shared Metabolic Intermediates

- Amino acids, after deamination, produce carbon skeletons that are converted into:
- Pyruvate (link to glycolysis)
- Acetyl-CoA (common to fatty acid metabolism and TCA cycle)
- TCA cycle intermediates (e.g., oxaloacetate, α-ketoglutarate)

2. Gluconeogenesis from Glucogenic Amino Acids

- In fasting or carbohydrate-deficient states, glucogenic amino acids are used to produce glucose.
- Key gluconeogenic amino acids: alanine, glutamine, serine.

3. Ketogenic Amino Acids and Lipid Connection

- Ketogenic amino acids (e.g., leucine, lysine) are metabolized into acetyl-CoA, which can:
- Enter the TCA cycle for energy
- Be converted into ketone bodies (especially during prolonged fasting)
- Participate in fatty acid synthesis under energy surplus conditions

4. Protein Catabolism Supports Energy Needs

- During prolonged starvation, protein breakdown provides:
- Substrates for gluconeogenesis (carbohydrate synthesis)
- Precursors for ketone body formation (lipid metabolism)
- This shift spares blood glucose for brain and red blood cells.

5. Insulin and Hormonal Control

- Insulin promotes protein synthesis and inhibits proteolysis, alongside promoting glucose and fat storage.
- In insulin-deficient states (e.g., diabetes), increased proteolysis supports gluconeogenesis and lipolysis.

6. Interconversion and Energy Balance

- Excess protein intake can be converted into fat (lipogenesis) via acetyl-CoA.
- Insufficient carbohydrate intake increases reliance on protein and fat catabolism for maintaining ATP and glucose levels.

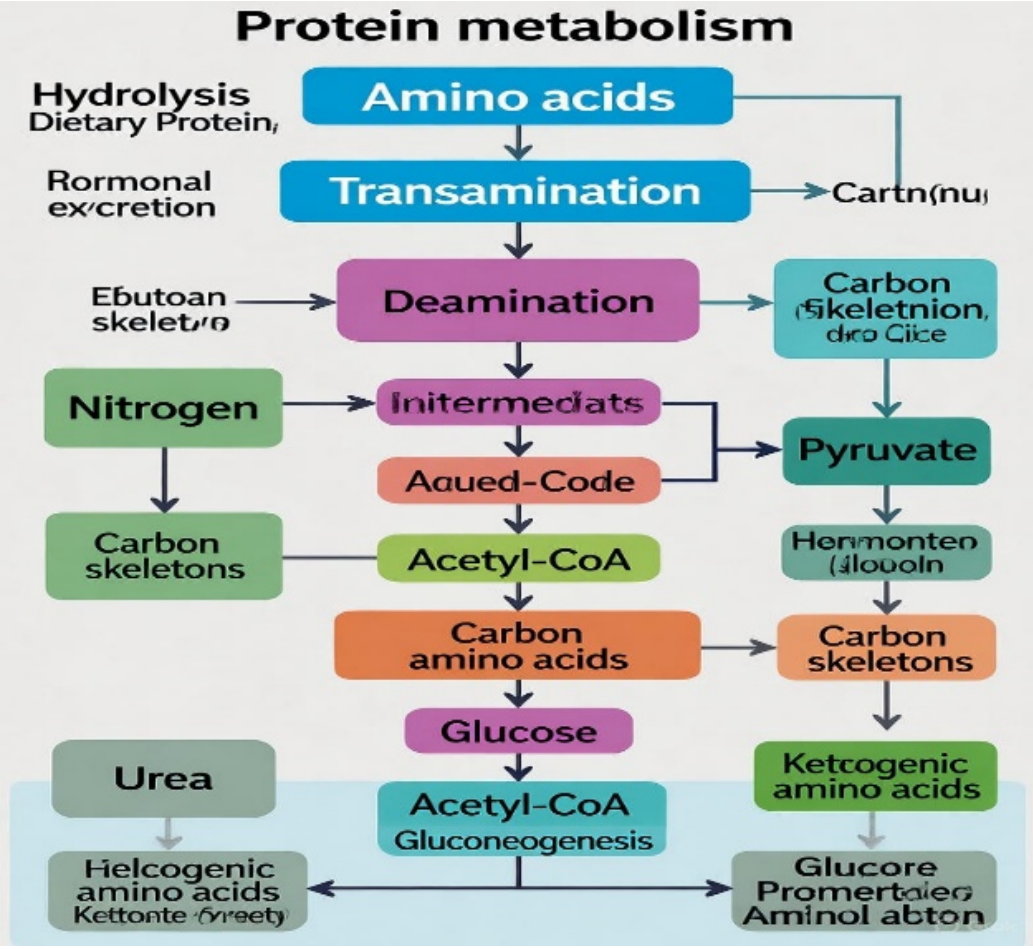


Fig. 12.4

Protein Metabolism in Interrelation with Carbohydrate Metabolism

Protein metabolism is closely interlinked with carbohydrate metabolism through shared intermediates and energy pathways. Dietary proteins are first broken down into amino acids by proteolytic enzymes during digestion. These amino acids are then absorbed and enter various metabolic pathways based on the body's energy and biosynthetic needs. Amino acids do not serve as a primary energy source under normal, fed conditions, but during fasting,

prolonged exercise, or carbohydrate deficiency, they become a significant substrate for gluconeogenesis - the generation of glucose from non-carbohydrate sources.

After transamination (transfer of amino groups), the remaining carbon skeletons of amino acids can be converted into key metabolic intermediates such as pyruvate, acetyl-CoA, and citric acid (TCA) cycle intermediates like α-ketoglutarate, oxaloacetate, and fumarate. These intermediates can either enter the gluconeogenic pathway (to form glucose) or be oxidized for ATP production via the TCA cycle. Meanwhile, the amino (nitrogen) group is removed via deamination, producing ammonia, which is toxic and thus converted to urea in the liver and excreted via urine. This metabolic integration allows amino acids to serve dual purposes: energy generation and maintenance of blood glucose levels during nutrient stress.

Thus, the interconnection between protein and carbohydrate metabolism is vital for maintaining glucose homeostasis, particularly during fasting or catabolic states. When glycogen stores are depleted, the glucogenic amino acids (like alanine and glutamine) are mobilized from muscle and other tissues to support hepatic gluconeogenesis. In reverse, when dietary carbohydrate is sufficient, excess amino acids can be directed toward anabolic processes or converted to fat. This interdependence emphasizes the metabolic flexibility of the body and highlights how disturbances in one pathway, such as in uncontrolled diabetes, can lead to increased protein catabolism to support glucose synthesis.

Interrelationship Overview:

Common Entry Point – Acetyl-CoA:

All three nutrients can be converted into acetyl-CoA, which feeds into the TCA cycle.

Acetyl-CoA is a key intermediate in energy production, fatty acid synthesis, and ketone body formation.

Energy Production:

Regardless of the source (carbs, lipids, proteins), they all eventually contribute to ATP synthesis via the TCA cycle and oxidative phosphorylation.

Storage and Conversion:

Excess carbohydrates can be converted into fat.

Proteins can be converted into glucose (gluconeogenesis) or even fat under certain conditions.

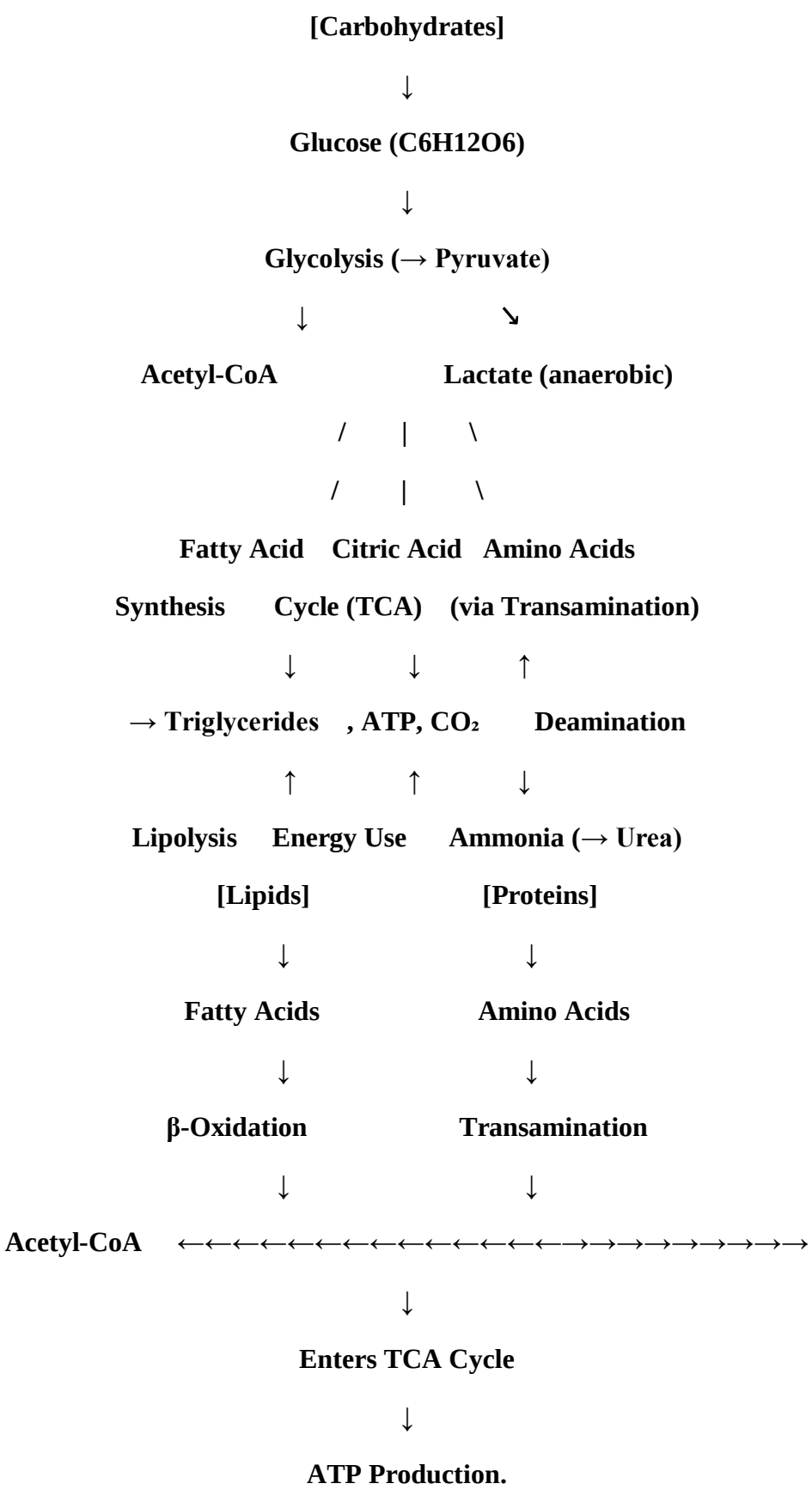
Fat cannot be converted back to glucose due to the irreversible nature of the pyruvate to acetyl-CoA conversion.

Fasting and Starvation:

The body shifts from using carbohydrates to fats, and later to proteins as energy sources.

Ketone bodies are formed from excess acetyl-CoA during prolonged fasting.

12.4. METABOLIC INTERRELATIONSHIPS BETWEEN CARBS, LIPIDS AND PROTEINS FLOW CHART:



12.5 SUMMARY:

The metabolism of carbohydrates, lipids, and proteins is intricately linked. They interact through shared intermediates like acetyl-CoA and TCA cycle compounds, enabling the body to adapt to different dietary conditions and energy demands. Understanding these interrelationships is crucial in fields like nutrition, medicine, and biochemistry, as it explains how the body maintains energy homeostasis and responds to metabolic stress.

12.6 TECHNICAL TERMS:

- **Lipogenesis**: Conversion of carbohydrates into fats
- **Gluconeogenesis**: Formation of glucose from non-carbohydrate sources
- **Ketogenesis**: Production of ketone bodies from fatty acids
- **Transamination**: Transfer of an amino group from one amino acid to a keto acid
- **Acetyl-CoA**: A key metabolic intermediate linking carbohydrate, fat, and protein metabolism

12.7 SELF-ASSESSMENT QUESTIONS:

1) Describe the metabolic changes that occur during the fed and fasting states.
2) How are carbohydrates converted into fats?
3) Why can't fatty acids be converted into glucose?
4) Explain the role of acetyl-CoA in metabolic interrelationships.
5) What are the hormonal regulators of metabolism during exercise?

12.8 REFERENCE BOOKS:

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Dr. Santhi Sri, K.V

LESSON-13

VITAMIN A, D, E AND K

13.0. OBJECTIVES:

After reading this chapter students will summarize:

- Identify the dietary sources of vitamins A, D, E, and K.
- Describe the deficiency disorders associated with inadequate intake of these vitamins.

STRUCTURE:

13.1 INTRODUCTION

Vitamins are organic compounds needed in small amounts to support metabolic functions and overall health. They are essential for processes such as energy production, immunity, tissue repair and the maintenance of vision, skin and bones. Since the body cannot synthesize most vitamins adequately, they must be obtained through diet or supplements. Based on solubility, vitamins are classified into two groups. Fat-soluble vitamins are vitamin A (Retinol), D (Calciferol), E (Tocopherol), and K (Phylloquinone) dissolve in fat and are stored in the liver and fatty tissues for later use. Water-soluble vitamins including Vitamin C (Ascorbic acid) and the B-complex group Thiamine (B1), Riboflavin (B2), Niacin (B3), Pantothenic acid (B5), Pyridoxine (B6), Biotin (B7), Folic acid (B9) and Cobalamin (B12) dissolve in water, are not stored in large amounts, and therefore require regular intake.

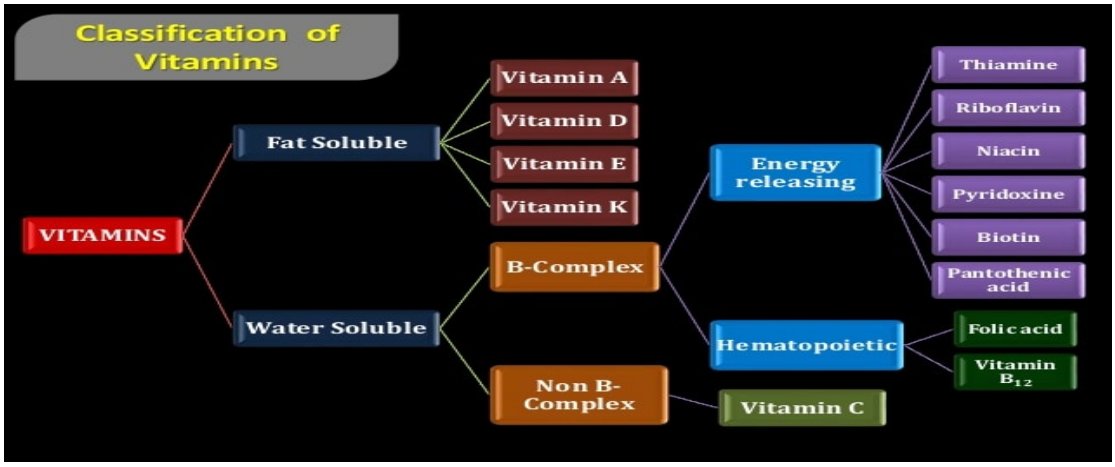

Fig. 13.1: Classification of Vitamins

13.2. VIATAMIN A

Vitamin A is a fat-soluble nutrient found in animal foods, while its precursor β-carotene occurs in plants. As early as 500 B.C., Hippocrates treated night blindness with ox liver now known to be vitamin A-rich. The term "vitamin A" refers to a group of related compounds called retinoids including retinol, retinal, and retinoic acid. Retinol (alcohol form) is stored in animal tissues as retinyl esters, retinal interconvert with retinol and was once called retinine and retinoic acid is formed by oxidation of retinal cannot revert to other forms but regulates important biological functions. Plant derived β-carotene acts as a **provitamin**, converting to retinal in the gut. Because this conversion is inefficient, β-carotene has only about one-sixth the biological activity of retinol.

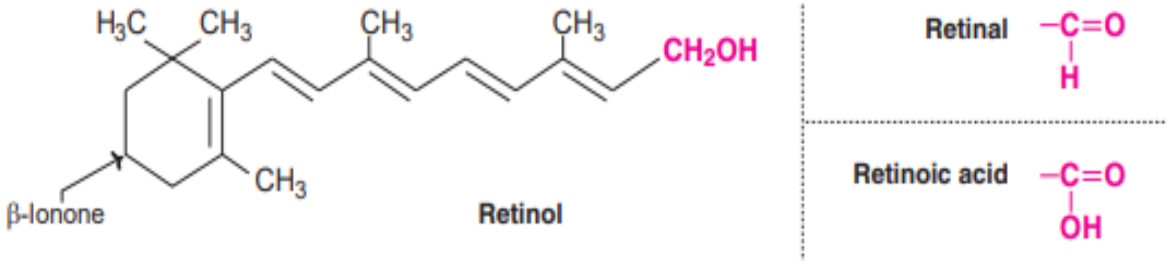

Fig. 13.2: Structure of Retinol, Retinal, Retinoic acid

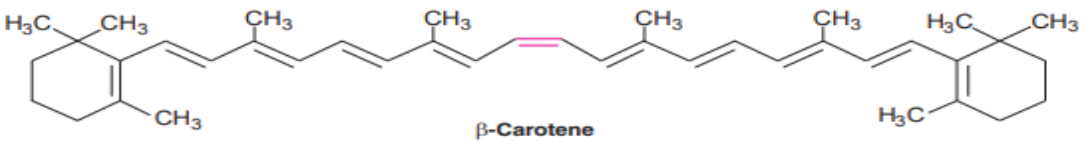

Fig. 13.3: Structure of β-Carotene

13.2.1 SOURCES

Vitamin A in its preformed state is found in animal derived foods, with the richest sources being liver, kidney, egg yolk, milk, cheese, and butter. Fish liver oil such as those from cod or shark is particularly high in vitamin A.

Plant based foods on the other hand, provide provitamin A in the form of carotenes. Vibrant yellow and dark green vegetables and fruits including carrot, spinach, pumpkin, mango and papaya are excellent sources of these carotenes.

13.3.2. ABSORPTION AND TRANSPORT

Dietary retinyl esters are hydrolyzed by pancreas or intestinal brush border hydrolases in the intestine into retinol and free fatty acids, while carotenes are hydrolyzed by β-carotene 15-15'- dioxygenase of intestinal cells to release 2 moles of retinal which is reduced to retinol. Retinol is re-esterified and it incorporated into chylomicrons and transferred to the lymph, then taken up by the liver and stored. Whenever the body needs, liver releases retinol. Retinol release aided by zinc and it is transported by retinol-binding protein (RBP) with pre-albumin. The retinol-RBP complex enters target cells where, cellular RBP carries retinol to the nucleus and binding chromatin to act like a steroid hormone.

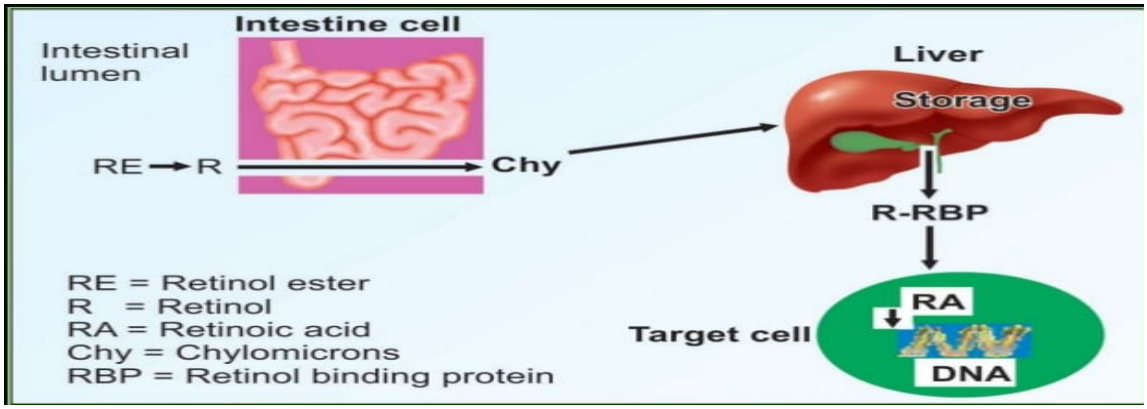

Fig. 13.4: Absorption and transport of Vitamin A

13.2.3 FUNCTIONS OF VITAMIN A

Vitamin A is necessary for a variety of functions such as vision, proper growth and differentiation, reproduction and maintenance of epithelial cells. In recent years, each form of vitamin A has been assigned specific functions.

- **Vitamin A and vision**: The biochemical function of vitamin A in the process of vision was first elucidated by George Wald (Nobel Prize 1968). The events occur in a cyclic process known as Rhodopsin cycle or Wald's visual cycle.

- **Colour vision:** Cones are specialized in bright and colour vision. Visual cycle comparable to that present in rods is also seen in cones. The colour vision is governed by colour sensitive pigments– porphyropsin (red), iodopsin (green) and cyanopsin (blue). All these pigments are retinalopsin complexes. When bright light strikes the retina, one or more of these pigments are bleached, depending on the particular colour of light. The pigments dissociate to all-trans-retinal and opsin, as in the case of rhodopsin. And this reaction passes on a nerve impulse to brain as a specific colored when porphyropsin splits, green when iodopsin splits or blue for cyanopsin. Splitting of these three pigments in different proportions results in the perception of different colours by the brain.

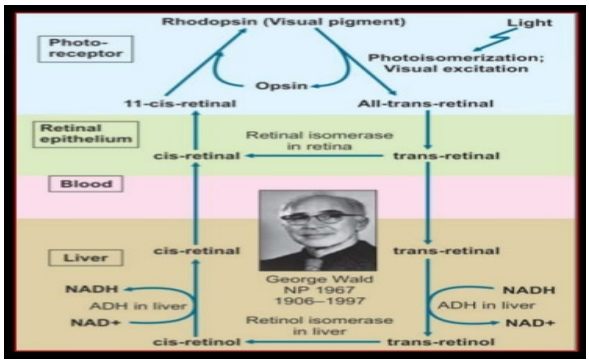

Fig. 13.5: Wald's Visual Cycle

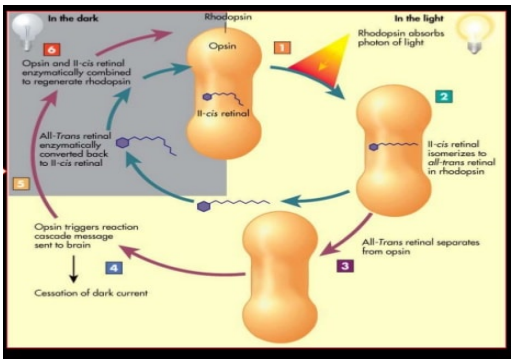

Fig. 13.6: Visual Cycle

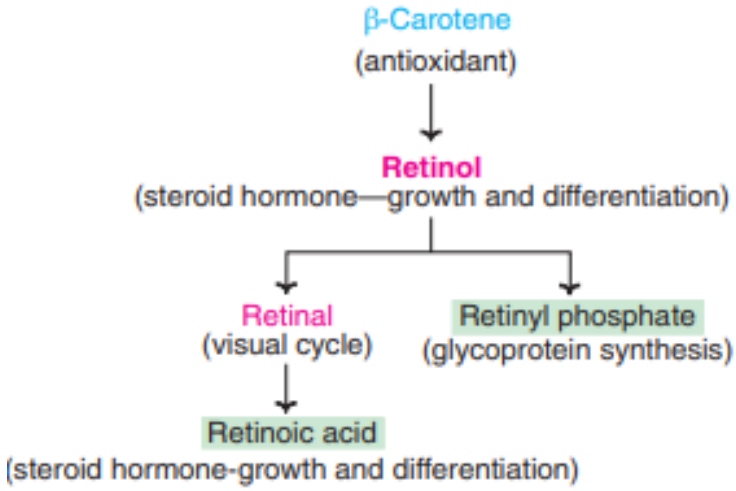

Fig. 13.7: Functions of vitamin A compounds

- Retinol and retinoic acid function almost like steroid hormones. They regulate the protein synthesis and thus are involved in the cell growth and differentiation.
- Vitamin A is essential to maintain healthy epithelial tissue. This is due to the fact that retinol and retinoic acid are required to prevent keratin synthesis (responsible for horny surface).
- Retinyl phosphate synthesized from retinol is necessary for the synthesis of certain glycoproteins, and mucopolysaccharides which are required for growth and mucus secretion.

- Retinol is necessary for normal reproduction. It acts like a hormone and regulates gene expression.
- Vitamin A is considered to be essential for the maintenance of proper immune system to fight against various infections.
- Cholesterol synthesis requires vitamin A. Mevalonate, an intermediate in the cholesterol biosynthesis, is diverted for the synthesis of coenzyme Q in vitamin A deficiency. It is pertinent to note that the discovery of coenzyme Q was originally made in vitamin A deficient animals.
- Carotenoids (most important E-carotene) function as antioxidants and reduce the risk of cancers initiated by free radicals and strong oxidants. E-Carotene is found to be beneficial to prevent heart attacks. This is also attributed to the antioxidant property.

13.2.4. DEFICIENCY STATE OF VITAMIN A

The vitamin A deficiency may be due to inadequate dietary intake, impaired intestinal absorption, reduced storage in liver and chronic alcholism. The deficiency symptoms are not immediate, since the hepatic stores can meet the body requirements for quite some time (2-4 months). The deficiency manifestations are related to the eyes, skin and growth.

- **Night Blindness (Nyctalopia)**: is one of the earliest symptoms of vitamin A deficiency. The individuals have difficulty to see in dim light since the dark adaptation time is increased. Prolonged deficiency irreversibly damages a number of visual cells.
- **Xerophthalmia:** Severe deficiency of vitamin A leads to xerophthalmia. This is characterized by dryness in conjunctiva and cornea, and keratinization of epithelial cells. In certain areas of conjunctiva, white triangular plaques known as Bitot's spots are seen. If, xerophthalmia persisits for a long time, corneal ulceration and degeneration occur. This result in the destruction of cornea, a condition referred to as keratomalacia, causing total blindness. Therefore, adequate intake of vitamin A is necessary for the prevention of blindness.
- **Effect on Growth:** Vitamin A deficiency results in growth retardation due to impairment in skeletal formation.
- **Effect on Reproduction**: The reproductive system is adversely affected in vitamin A deficiency. Degeneration of germinal epithelium leads to sterility in males.
- **Effect on Skin and Epithelial Cells**: The skin becomes rough and dry. Keratinization of epithelial cells of gastrointestinal tract, urinary tract and respiratory tract is noticed. This leads to increased bacterial infection. Vitamin A deficiency is associated with formation of urinary stones. The plasma level of retinol binding protein is decreased in vitamin A deficiency.
- **Hypervitaminosis A:** Excessive consumption of vitamin A leads to toxicity. The symptoms of hypervitaminosis A include dermatitis raised intracranial tension, enlargement of liver, skeletal decalcification, tenderness of long bones, loss of weight, irritability, loss of hair, joint pains etc. Elderly people are more susceptible to vitamin A toxicity; hence overdoses should be avoided.

Total serum vitamin A level (normal 20–50 Pg/dl) is elevated in hypervitaminosis A. Free retinol or retinol bound to plasma lipoproteins is actually harmful to the body. It is now believed that the vitamin A toxicosis symptoms appear only after retinol binding capacity of retinol binding protein exceeds.

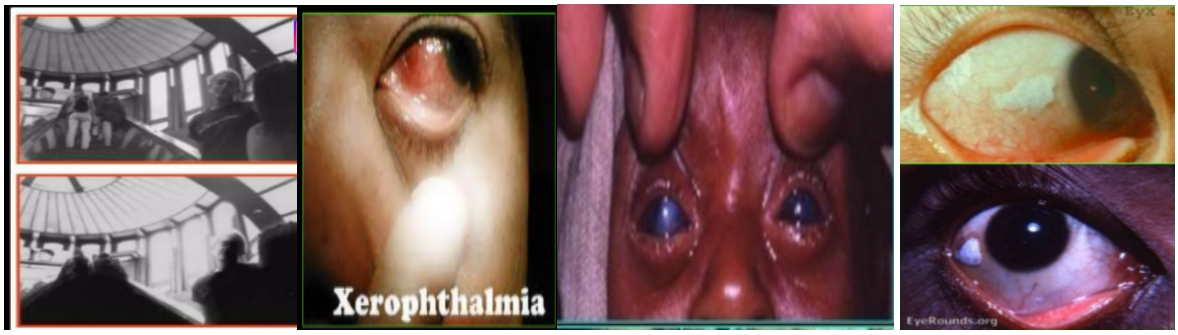

Fig. 13.8: Nightblindness Xeropthalmia Keratomalacia Bitots spots

13.2.5. FACTORS INFLUENCING BIOAVAILABILITY AND REQUIREMENTS

Dietary Factors

- Food Processing: Heating or pureeing helps release carotenoids (like β-carotene) from plant cell walls, enhancing absorption. Fruits generally allow better β-carotene absorption than vegetables due to weaker cell walls.
- Fat Intake: Since carotenoids are fat-soluble, even a small amount of fat in a meal is essential for forming micelles, which are needed for proper intestinal absorption. Fat substitutes and high fiber intake can hinder this process.
- Interference: Carotenoids can compete with each other (e.g., lutein can reduce β-carotene absorption). High doses of β-carotene supplements may also reduce its conversion to vitamin A.

Individual Factors

- Vitamin A Status: People with low vitamin A levels are more efficient at utilizing β-carotene-rich foods.
- Sex Differences: Women often show a greater increase in vitamin A levels from β-carotene than men, possibly due to differences in body composition.
- Health Conditions: Intestinal infections (like helminths) can impair the absorption of fats and fat-soluble vitamins, thus reducing carotenoid absorption.

Requirements (RDA):

Gender	Vitamin A µ/day
Men	1000
Women	840
Pregnant	900
Lactating	950
Infants and Children	350
Boys (10-18 yrs)	770-1000
Girls (10-18yrs)	790-860

Fig. 13.9: Source (ICMR, 2020)

13.3. VITAMIN D

Vitamin D is a fat-soluble vitamin structurally resembling sterols and functioning as a hormone. Historically recognized for preventing rickets, its antirachitic activity was linked to ultraviolet light by Hess (1924), and the vitamin was isolated and named calciferol by Angus (1931).

Vitamin D activity comes from two provitamins:

- Ergocalciferol (Vitamin D2): Formed from ergosterol and found in plants.
- Cholecalciferol (VitaminD3): Found in animals. It is synthesized in human skin from the intermediate 7-dehydrocholesterol (a cholesterol precursor) upon exposure to sunlight, earning it the nickname the "sunshine vitamin."

The synthesis of Vitamin is directly proportional to sunlight exposure. However, dark skin pigment (melanin) adversely influences this conversion process. Both are similar in structure, though ergocalciferol has an additional methyl group and a double bond.

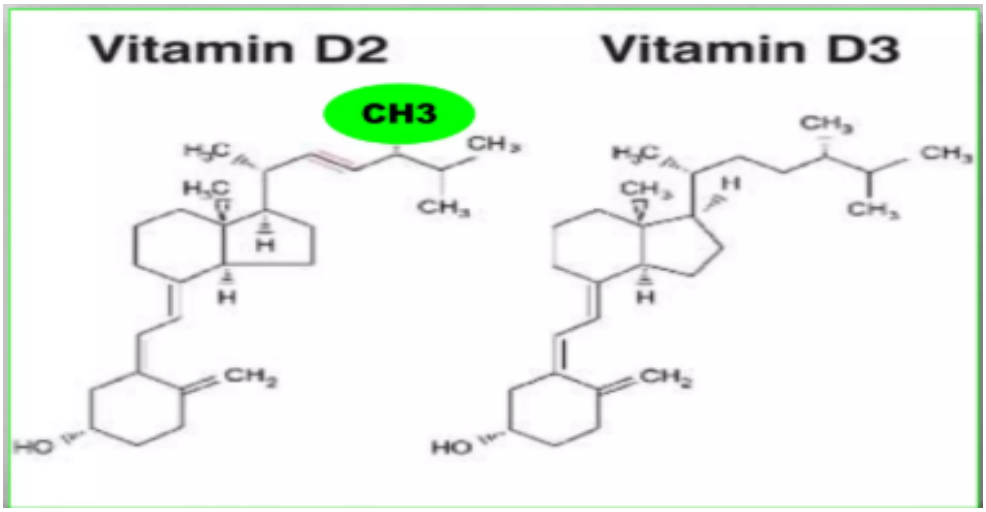

Fig. 13.10: Structure of Vitamin D2 and D3

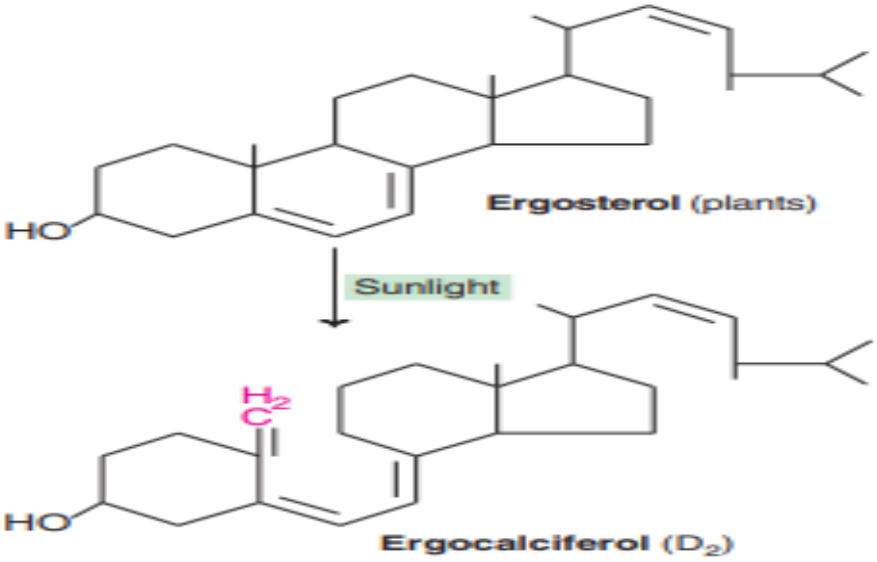

Fig. 13.11: Formation of ergocalciferol from ergosterol

13.3.1 SOURCES

Good sources of vitamin D include fatty fish, fish liver oils, egg yolk etc. Milk is not a good source of vitamin D. Vitamin D can be provided to the body in three ways: Exposure of skin to sunlight for synthesis of vitamin D; Consumption of natural foods; By irradiating foods (like yeast) that contain precursors of vitamin D and fortification of foods (milk, butter etc.).

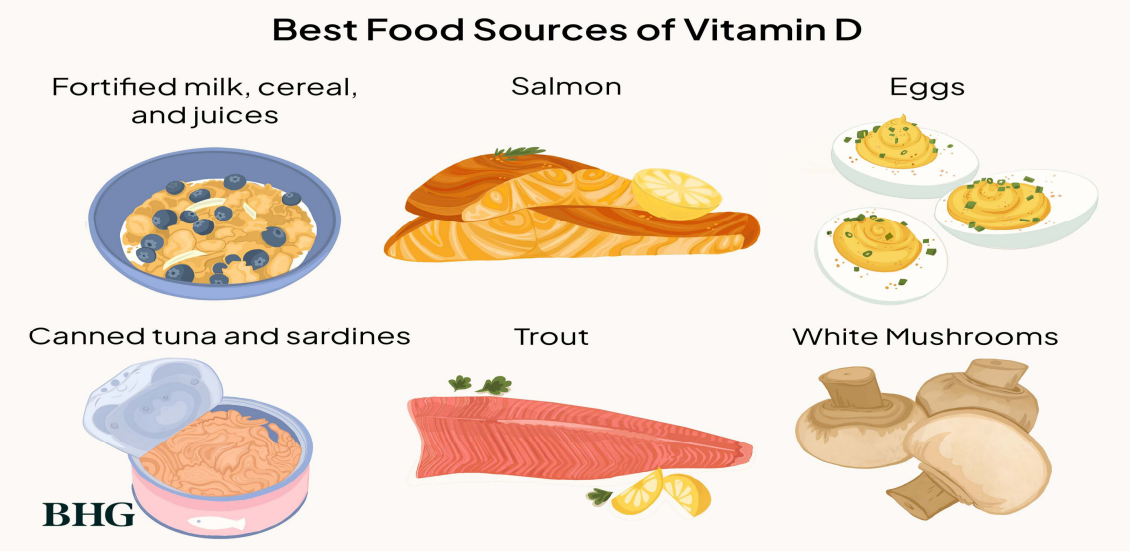

Fig. 13.12: Sources of Vitamin D

13.3.2. ABSORPTION AND TRANSPORT

Vitamin D is absorbed in the small intestine for which bile is essential. Through lymph, vitamin D enters the circulation bound to plasma D2-globulin and is distributed throughout the body. Liver and other tissues store small amounts of vitamin D.

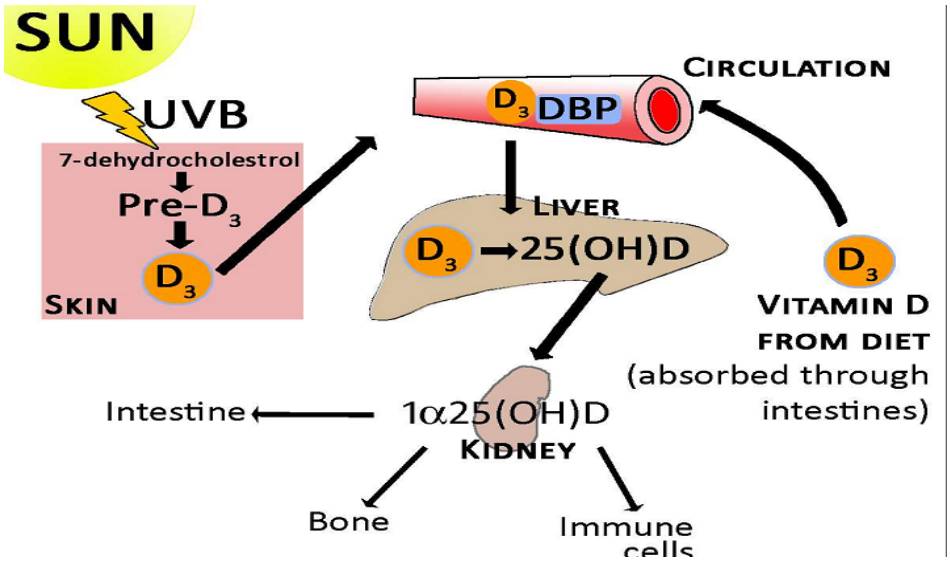

Fig. 13.13: Absorption and Transport of Vit D

13.3.3 FUNCTIONS

Calcitriol (-DHCC) is the biologically active form of Vitamin D, essential for regulating plasma calcium and phosphate levels to maintain a normal range. It achieves this balance by acting on three target tissues: the intestine, where it increases absorption of both minerals by inducing the synthesis of a calcium-binding protein (similar to steroid hormone action); the kidney, where it minimizes mineral loss by enhancing their reabsorption; and the bone, where it is necessary for formation (stimulating calcium uptake by osteoblasts) but also acts with parathyroid hormone (PTH) to increase the mobilization of calcium and phosphate into the plasma when needed. A related metabolite, -Dihydroxycholecalciferol (-DHCC), is synthesized by -hydroxylase in the kidney and is thought to be a less active compound produced when calcitriol levels are sufficient, contributing to overall calcium homeostasis.

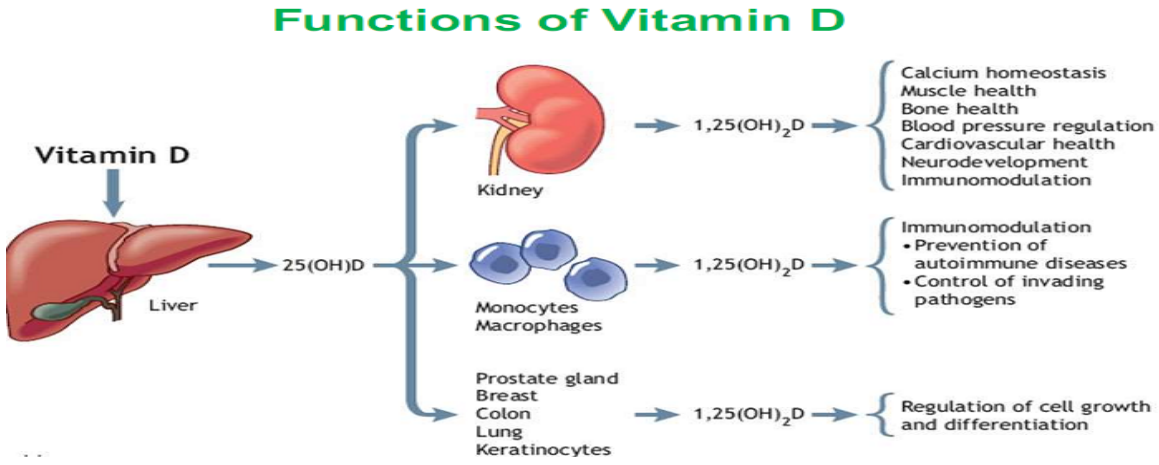

Fig. 13.14: Metabolism and Biochemical Functions of Vitamin D

13.3.4. DEFICIENCY STATE OF VITAMIN D

Though rare due to synthesis from sunlight exposure, vitamin D deficiency still occurs with poor diet or insufficient sun exposure, particularly in strict vegetarians, chronic alcoholics, those with fat malabsorption, and individuals with liver or kidney diseases (which

impair activation). Deficiency causes: Rickets in children, marked by soft, pliable bones and bow-legs due to incomplete mineralization and characterized by decreased calcitriol and high Alkaline Phosphatase (ALP); Osteomalacia (adult rickets), involving demineralization of bones that leads to fractures; and Renal Rickets in chronic renal failure patients due to decreased calcitriol synthesis, requiring exogenous calcitriol. Conversely, Hypervitaminosis D (toxicity), typically resulting from vast overdoses, is the most severe of any vitamin toxicity. It causes excessive intestinal calcium absorption and bone demineralization, leading to hypercalcemia (dangerously high plasma calcium). Sustained hypercalcemia results in the harmful deposition of calcium in soft tissues (like arteries and kidneys) and the formation of kidney stones (renal calculi), alongside general symptoms like loss of appetite, nausea, and weight loss.

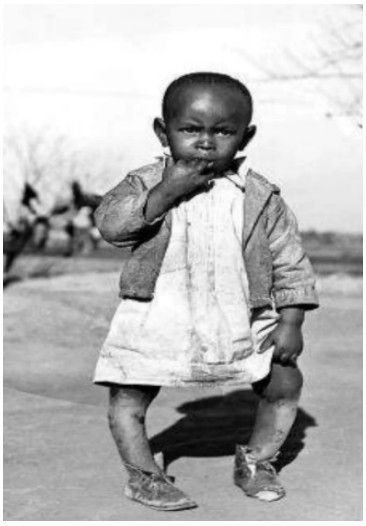

Fig. 13.15: Rickets in Children

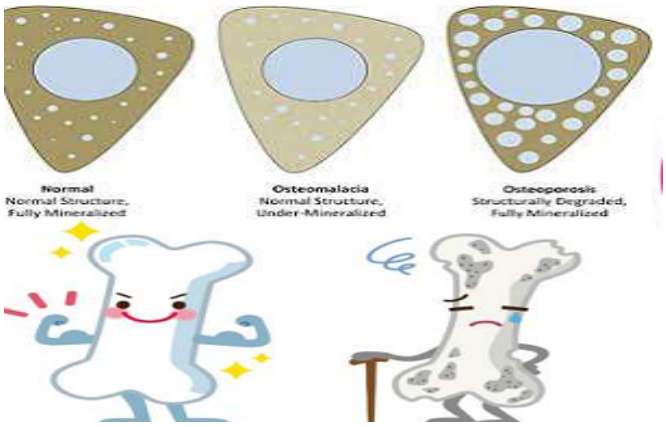

Fig. 13.16: Osteomalacia in Adults

13.3.5 Factors Influencing Vitamin D Bioavailability

Vitamin D has poor oral bioavailability, which can be improved by consuming it with dietary fat, as it's a fat-soluble vitamin that requires bile salts for emulsification and absorption via intestinal enterocytes. The bioavailability is significantly higher for the hydroxylated form, 25(OH)D, compared to vitamin D2 and D3, and is also increased by delivery in nanostructured systems like nanoemulsions. Factors like the presence of dietary fiber, lipid metabolism disorders, and the form of the supplement (oral solution vs. capsule) also influence absorption.

Factors Influencing Vitamin D Bioavailability

- **Dietary Fat:**

Vitamin D is fat-soluble, so its absorption is enhanced when consumed with dietary fat, as this helps with its emulsification by bile salts.

- **Bile Salts:**

Bile salts are necessary to emulsify dietary fat and vitamin D into mixed micelles, which are then absorbed by intestinal cells.

- **Food Matrix:**

The food matrix in which vitamin D is present can affect its absorption, with the presence of dietary fiber sometimes inhibiting micelle formation and absorption.

Requirements

Daily needs, varying by age, gender, and health, are 400 IU (10 mcg cholecalciferol), but only 200 IU (5 mcg) in sun-rich areas like India due to ample sunlight.

13.4. VIATAMIN E

Vitamin E (tocopherol) is a naturally occurring antioxidant, crucial for normal reproduction in many animals, thus often called the anti-sterility vitamin. It was named tocopherol by Evans (1936) (from Greek words meaning "to bear child-birth") after its isolation. Interestingly, it's often described as a 'vitamin in search of a disease' due to the lack of a specific human deficiency syndrome. Vitamin E collectively refers to a group of compounds, including eight main tocopherols and tocotrienols (vitamers). Tocopherol is the most biologically active form. Chemically, tocopherols are derivatives of the 6-hydroxy chromane (tocol) ring with an isoprenoid side chain, and their powerful antioxidant property stems directly from the hydroxyl group on this chromane ring.

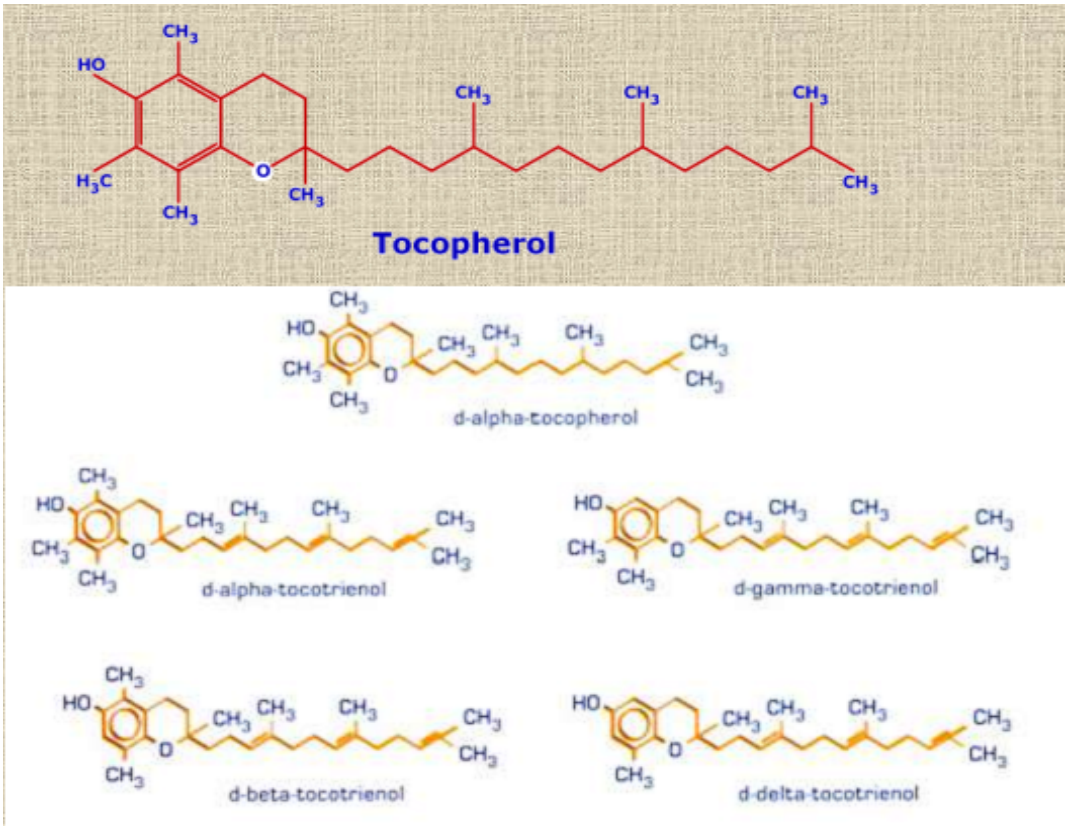

Fig. 13.17: Structures of D-tocopherol

13.4.1 SOURCES

Many vegetable oils are rich sources of vitamin E. Wheat germ oil, cotton seed oil, peanut oil, corn oil and sunflower oil are good sources of this vitamin. It is also present in meat, milk, butter and eggs.

Fig. 13.18: Sources of Vitamin E

13.4.2. ABSORPTION AND TRANSPORT

Vitamin E is absorbed along with fat in the small intestine. Bile salts are necessary for the absorption. In the liver, it is incorporated into lipoproteins (VLDL and LDL) and transported. Vitamin E is stored in adipose tissue, liver and muscle. The normal plasma level of tocopherol is less than 1 mg/dl.

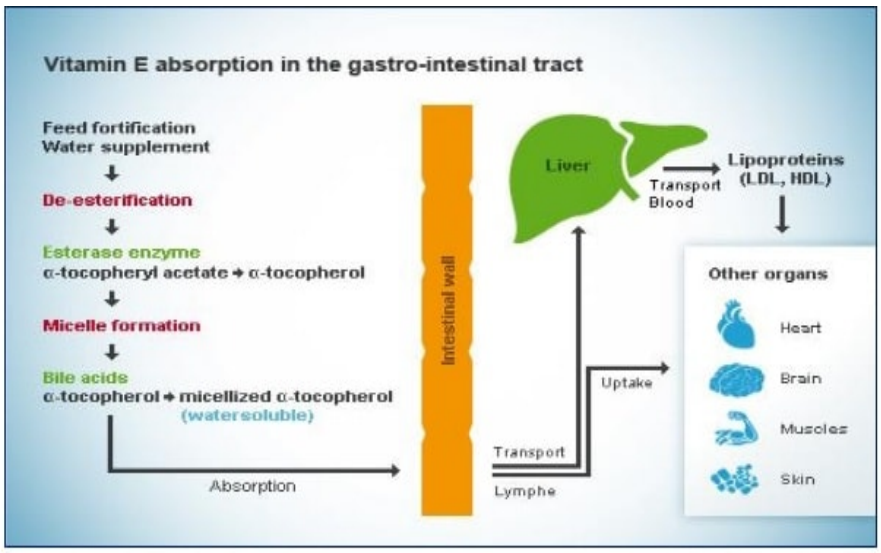

Fig. 13.19: Absorption and Transport of Vit E

13.4.3 FUNCTIONS

The central role of Vitamin E is as a lipophilic antioxidant. Being fat-soluble, it resides in cellular membranes and lipoproteins, essential for preserving their structure and integrity. Its primary mechanism is scavenging free radicals and molecular oxygen, preventing the nonenzymatic oxidation and subsequent peroxidation of polyunsaturated fatty

acids (PUFA); Vitamin E sacrifices itself (oxidizing to its quinone form) to protect PUFA, a process supported by selenium. Indirectly linked to this protective function, Vitamin E supports reproductive health (maintaining germinal epithelium), enhances heame synthesis, participates in cellular respiration (stabilizing coenzyme Q), protects other vitamins (A and carotenes), safeguards RBCs from hemolysis, and protects the liver from toxins. Although its use for preventing chronic diseases like heart disease (by inhibiting LDL oxidation) has been mostly discouraged by clinical trials, some clinicians still utilize it.

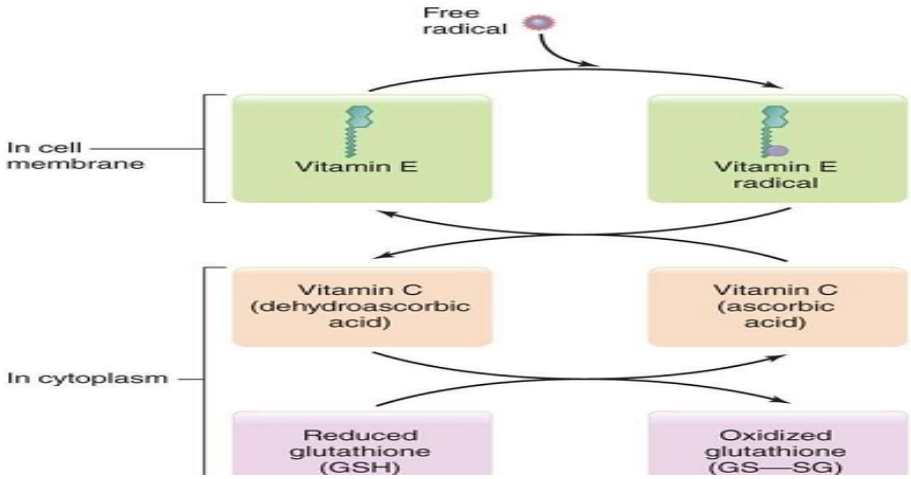

Fig. 13.20: Functions of Vit E

13.4.4. DEFICIENCY STATE OF VITAMIN E

The symptoms of vitamin E deficiency vary from one animal species to another. In many animals, the deficiency is associated with sterility, degenerative changes in muscle, megaloblastic anemia and changes in the central nervous system. Severe symptoms of vitamin E deficiency are not seen in humans except increased fragility of erythrocytes and minor neurological symptoms. Toxicity of vitamin E Among the fat soluble vitamins (A, D, E, K), vitamin E is the least toxic. No toxic effect has been reported even after ingestion of 300 mg/ day for 23 years.

Fig. 13.21: Deficiency symptoms of Vitamin E

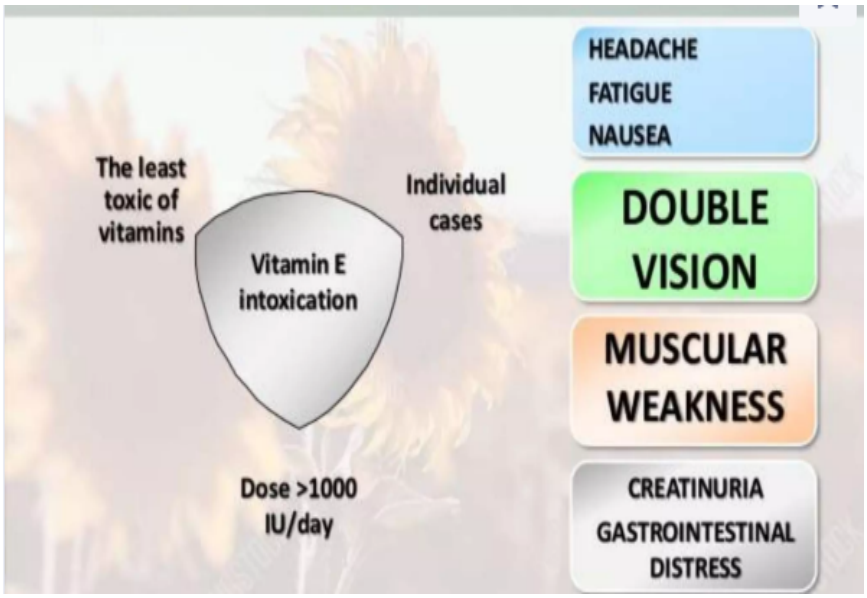

Fig. 13.22: Vitamin E Intoxication

13.4.5. FACTORS INFLUENCING BIOAVAILABILITY AND REQUIREMENTS

Vitamin E possesses high oral bioavailability, generally ranging between and, though this is subject to various factors. As a fat-soluble vitamin, its absorption is critically dependent on dietary fat; consuming it with meals containing fat (like nuts or butter) significantly enhances uptake, while absorption is minimal without it. Other dietary factors influencing bioavailability include the food matrix (the physical structure of the food) and the presence of other nutrients that may interfere with uptake. Additionally, host-related factors such as specific pathologies and individual genetic factors that affect the proteins involved in vitamin E processing can also alter its absorption efficiency.

Recommended intake is 10 mg (15 IU) for men and 8 mg (12 IU) for women (1 mg = 1.5 IU), with pregnant and breastfeeding women needing supplemented diets.

13.5. VIATAMIN K

Vitamin K is the only fat soluble vitamin with a specific coenzyme function. It is required for the production of blood clotting factors, essential for coagulation (in German– Koagulation; hence the name K for this vitamin). Chemistry Vitamin K exists in different forms. Vitamin K1 (phylloquinone) is present in plants. Vitamin K2 (menaquinone) is produced by the intestinal bacteria and also found in animals. Vitamin K3 (menadione) is a synthetic form. All the three vitamins (K1, K2, and K3) are naphthoquinone derivatives. Isoprenoid side chain is present in vitamins K1 and K2. The three vitamins are stable to heat. Their activity is, however, lost by oxidizing agents, irradiation, strong acids and alkalies.

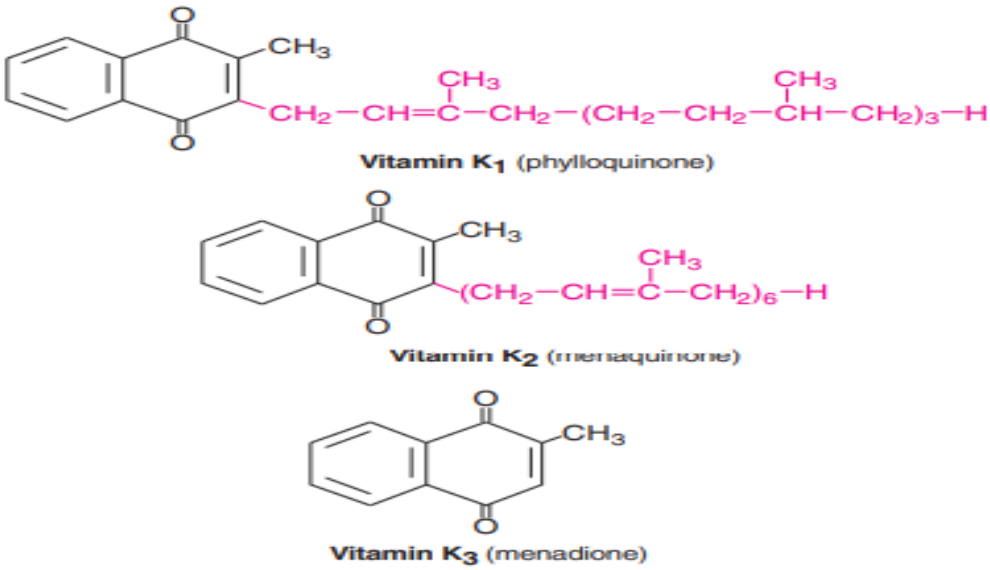

Fig. 13.23: Structures of vitamin K

13.5.1 SOURCES

Vitamin K is abundant in green vegetables such as cabbage, cauliflower, tomatoes, alfalfa, and spinach. It is also found in egg yolk, meat, liver, cheese, and other dairy products.

Fig. 13.24: Sources of vitamin K1 and K2

13.4.2. ABSORPTION AND TRANSPORT

Vitamin K is taken in the diet or synthesized by the intestinal bacteria. Its absorption takes place along with fat (chylomicrons) and is dependent on bile salts. Vitamin K is transported along with LDL and is stored mainly in liver and, to a lesser extent, in other tissues

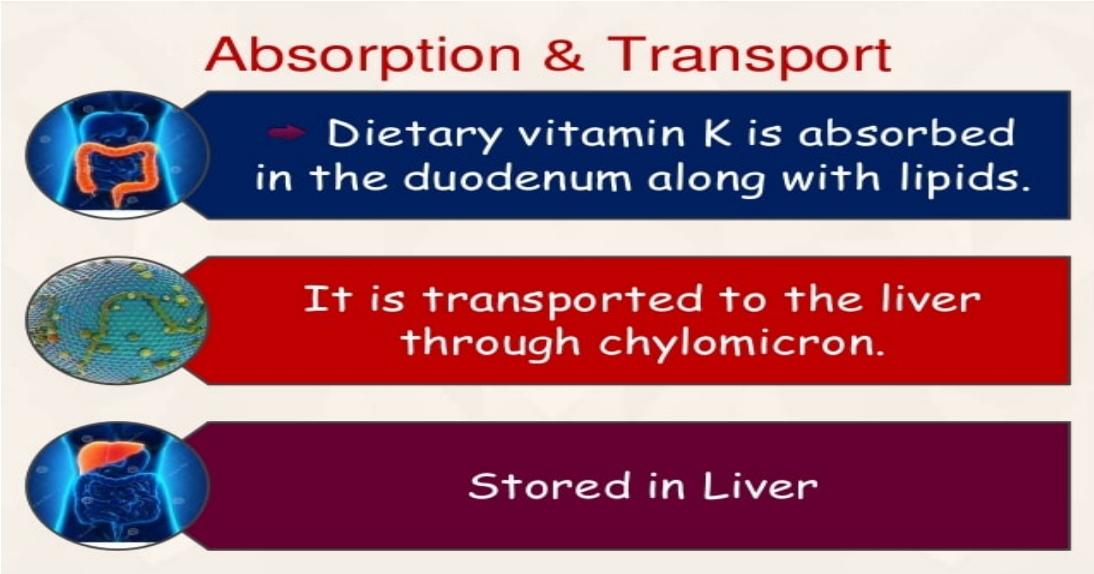

Fig. 13.25: Absorption and Transport of Vit K

13.5.3. FUNCTIONS

The primary function of Vitamin K is its critical role in the blood clotting cascade.

Vitamin K acts as a coenzyme for the essential post-translational modification of specific clotting factors namely Factors II (prothrombin), VII, IX, and X-which are synthesized as inactive precursors (zymogens) in the liver. This modification involves the microsomal carboxylation of multiple glutamic acid (Glu) residues within these proteins.

The resulting Gla residues possess two negative charges that enable them to strongly bind positively charged calcium ions. In the case of prothrombin, the prothrombin-complex then binds to phospholipids on the platelet surface, dramatically accelerating the conversion of prothrombin to the active enzyme, thrombin, thereby initiating effective coagulation.

Vitamin K action is inhibited by anticoagulants like dicumarol (found in spoiled sweet clover) and the synthetic analogue warfarin. These compounds work by blocking the reductase enzyme responsible for recycling an inactive intermediate, Vitamin K 2,3-epoxide, back into the active form of the vitamin. Beyond clotting, Vitamin K is also required for the carboxylation of osteocalcin, a calcium-binding protein vital for bone health.

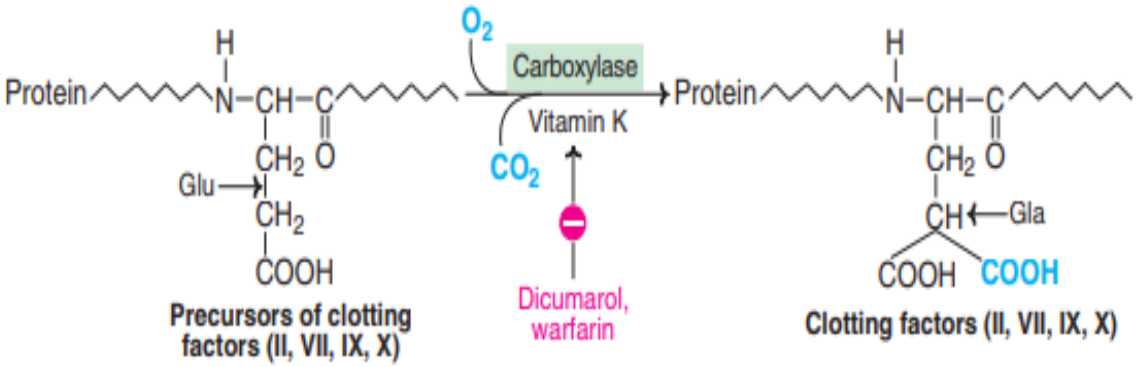

Fig. 13.26: Vitamin K dependent carboxylation of the precursors of clotting factors

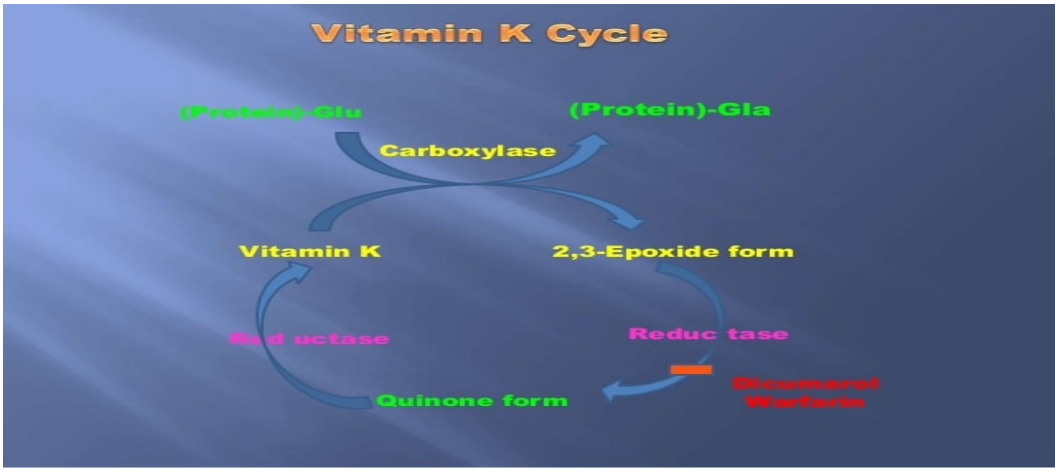

Fig. 13.27: Summary of vitamin K cycle in carboxylation reaction.

13.5.4. DEFICIENCY STATE OF VITAMIN K

Vitamin K deficiency is generally rare because it's available in the diet and is sufficiently synthesized by intestinal bacteria. However, deficiency can occur due to faulty absorption (e.g., lack of bile salts), excessive loss in feces (as in diarrheal diseases), or the long-term use of antibiotics (which kill the vitamin-producing intestinal flora). The resulting lack of active prothrombin and other clotting factors significantly impairs the blood coagulation process, leading to a prolonged clotting time and profuse bleeding even from minor injuries.

Conversely, Hypervitaminosis K (toxicity) is observed when large doses of Vitamin K are administered, particularly to infants. This can cause hemolytic anemia and jaundice due to an increased breakdown of Red Blood Cells (RBCs). Several compounds act as Vitamin K antagonists and are used clinically as anticoagulants; these include dicumarol, warfarin (a synthetic analogue of dicumarol), bishydroxycoumarin, and heparin.

Fig. 13.28: Deficiency symptoms of Vit K

13.5.5. FACTORS INFLUENCING BIOAVAILABILITY AND REQUIREMENTS

The bioavailability of Vitamin K varies significantly based on its form and the food matrix in which it is consumed. While free phylloquinone is highly absorbable, found in green vegetables is poorly absorbed because it is tightly bound within plant chloroplasts. This absorption is improved by consuming dietary fat, though it still remains much lower than absorption from oils or supplements. In contrast, menaquinones, particularly long-chain forms like MK-7, are absorbed more efficiently, leading to higher circulation levels and longer half-lives than phylloquinone. However, short-chain menaquinones like MK-4 do not significantly increase serum levels. Furthermore, it is sensitive to light and can degrade rapidly (up to loss after two days of fluorescent light exposure), necessitating storage of rich oils in dark containers.

RDA suggested that adults consume 55 µg/day, with about half obtained from diet and the rest from gut synthesis.

13.6 SUMMARY:

Fat-soluble vitamins A, D, E, and K are stored in the liver and fatty tissues, requiring dietary fat for absorption and posing a risk of toxicity if over consumed due to limited excretion. Vitamin A supports vision, immunity, and cell growth, with deficiency causing night blindness and xerophthalmia. Vitamin D, synthesized via sunlight, regulates calcium and phosphorus for bone health, with deficiency leading to rickets in children or osteomalacia in adults. Vitamin E, an antioxidant, protects cells and aids immunity, with deficiency potentially causing neurological issues. Vitamin K is crucial for blood clotting and bone health, with deficiency causing bleeding disorders, particularly in newborns or those with fat malabsorption.

13.7 TECHNICAL TERMS

Retinol, Beta-carotene, Rhodopsin, Xerophthalmia, Cholecalciferol, Ergocalciferol, Calcitriol, Rickets, Osteomalacia, Alpha-tocopherol, Antioxidant, Lipid peroxidation, Phylloquinone, Menaquinone, Coagulation factors, VKDB (Vitamin K Deficiency Bleeding), Osteocalcin, Bile salts, Micelle formation, Fat malabsorption

13.8 SELF-ASSESSMENT QUESTIONS

1) What are fat-soluble vitamins and how are they absorbed?
2) Mention the main biochemical functions of each fat-soluble vitamin.
3) Explain two health problems caused by Vitamin A, D, E and K deficiencies.
4) What is the role of Vitamin E in protecting body tissues?

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Dr. B. Babitha

LESSON-14

VITAMIN B1, B2, B3

14.0. OBJECTIVES:

After going through this lesson, students will understand:

- The role of vitamin B1 (Thiamine) in energy metabolism and nervous system function.
- The functions and food sources of vitamin B2 (Riboflavin).
- The importance of vitamin B3 (Niacin) in redox reactions and DNA repair.
- Discuss the Deficiency Symptoms and Clinical Manifestations of Vitamins B1, B2, and B3
- Understand the recommended dietary intakes and factors affecting the bioavailability of these vitamins.

STRUCTURE:

14.1 INTRODUCTION

B-complex vitamins are essential, water-soluble nutrients that play a critical role in maintaining health and supporting various physiological functions. Among them, Vitamin B1

(Thiamine), Vitamin B2 (Riboflavin) and Vitamin B3 (Niacin) are particularly important due to their involvement in energy metabolism, cellular function, and nervous system health.

Thiamine (B1) is essential for carbohydrate metabolism and the proper functioning of the nervous system. Its deficiency can lead to disorders such as beriberi and Wernicke-Korsakoff syndrome. Riboflavin **(**B2**)** acts as a precursor to the coenzymes FAD and FMN, which are involved in numerous oxidation-reduction reactions in the body. Niacin (B3) is crucial for the formation of NAD and NADP-coenzymes that support metabolic processes, DNA repair, and cellular communication.

14.2 VITAMIN B1

Thiamine (anti-beri-beri or antineuritic vitamin) is water soluble. It has a specific coenzyme, thiamine pyrophosphate (TPP) which is mostly associated with carbohydrate metabolism.

Chemistry:

Thiamine contains a pyrimidine ring and a thiazole ring held by a methylene bridge. Thiamine is the only natural compound with thiazole ring. The alcohol (OH) group of thiamine is esterfied with phosphate (2moles) to form the coenzyme, thiamine pyrophosphate (TPP or cocarboxylase). The pyrophosphate moiety is donated by ATP and the reaction is catalyzed by the enzyme thiamine pyrophosphate transferase.

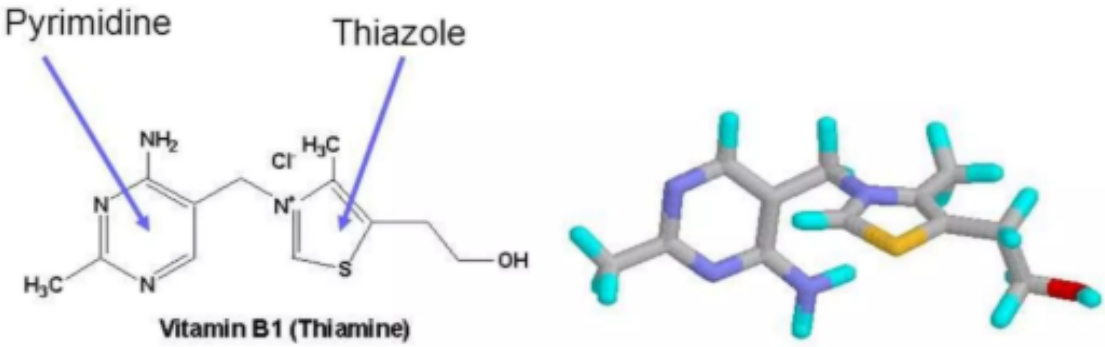

Fig. 14.1: Structure of Vitamin B1

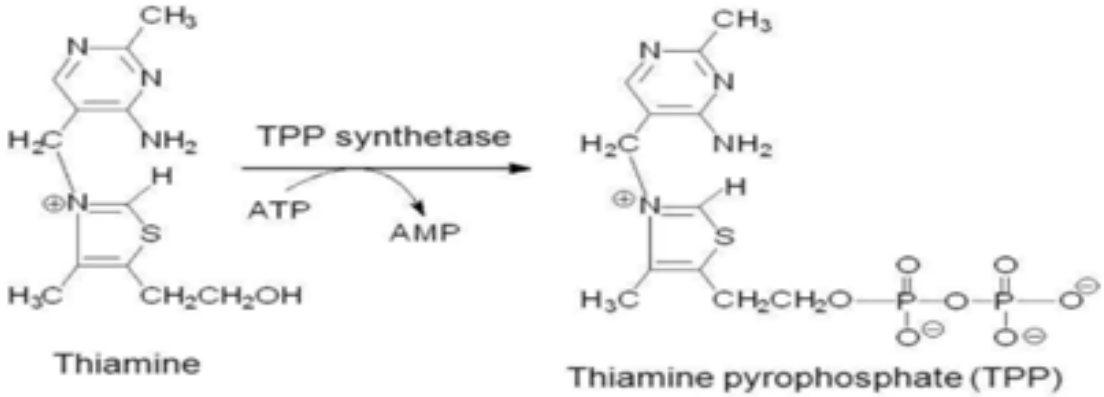

Fig. 14.2: Conversion of Thiamine into Coenzyme form (TPP)

14.2.1 DIETARY SOURCES

Cereals, pulses, oil seeds, nuts and yeast are good sources. Thiamine is mostly concentrated in the outer layer (bran) of cereals. Polishing of rice removes about 80% of thiamine. Vitamin B1 is also present in animal foods like pork, liver, heart, kidney, milk etc. In the parboiled (boiling of paddy with husk) and milled rice, thiamine is not lost in polishing. Since thiamine is a water-soluble vitamin, it is extracted into the water during cooking process. Such water should not be discarded.

14.2.2 FUNCTIONS

The coenzyme, thiamine pyrophosphate or cocarboxylase is intimately connected with the energy releasing reactions in the carbohydrate metabolism.

- The enzyme pyruvate dehydrogenase catalyses (oxidative decarboxylation) the irreversible conversion of pyruvate to acetyl CoA. This reaction is dependent on TPP, besides the other coenzymes (details given in carbohydrate metabolism).
- D-Ketoglutarate dehydrogenase is an enzyme of the citric acid cycle. This enzyme is comparable with pyruvate dehydrogenase and requires TPP.
- Transketolase is dependent on TPP. This is an enzyme of the hexose monophosphate shunt (HMP shunt).
- The branched chain D-keto acid dehydrogenase (decarboxylase) catalyses the oxidative decarboxylation of branched chain amino acids (valine, leucine and isoleucine) to the respective keto acids. This enzyme also requires TPP.
- TPP plays an important role in the transmission of nerve impulse. It is believed that TPP is required for acetylcholine synthesis and the ion translocation of neural tissue.

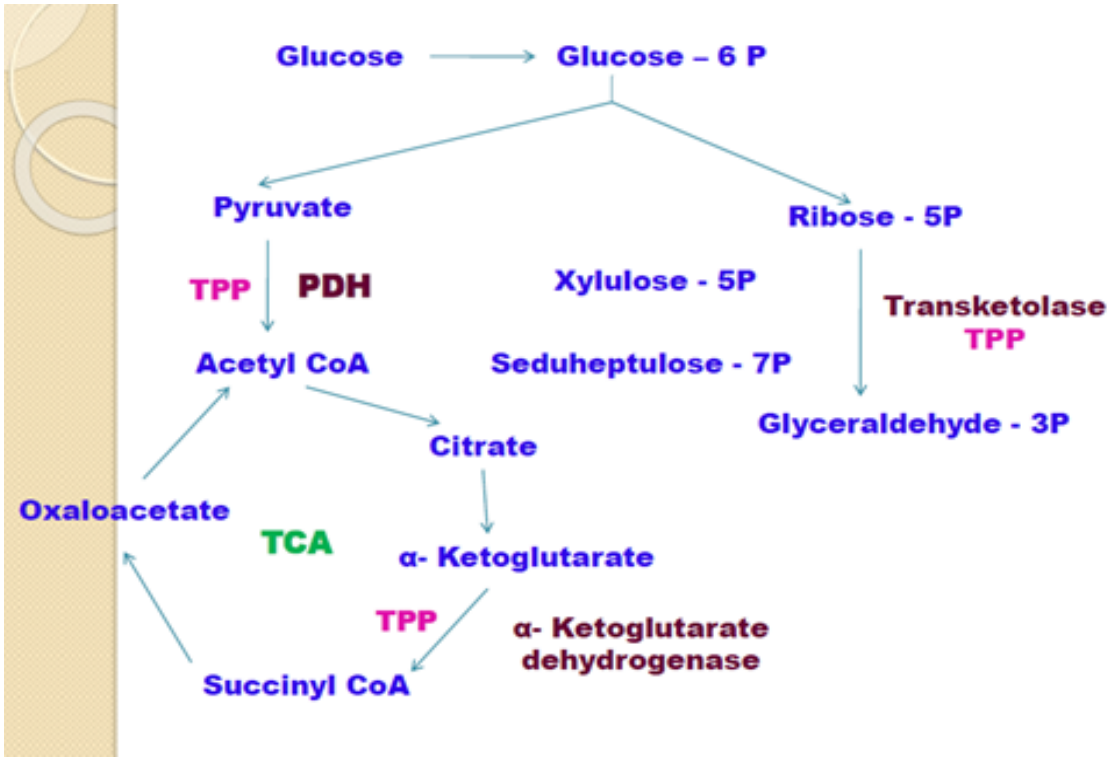

Fig. 14.3: Summary of the reactions dependent on thiamine pyrophosphate (TPP)

14.2.3 DEFICIENCY STATES

Vitamin B1 (thiamine) deficiency leads to a condition known as beri-beri, named from the Sinhalese phrase meaning "I cannot, I cannot." This reflects the profound weakness seen in affected individuals. The condition is common in populations whose diets rely heavily on polished rice, which is depleted of thiamine.

Clinical Features

Early symptoms of thiamine deficiency include loss of appetite, weakness, constipation, nausea, mental depression, irritability and peripheral neuropathy. Patients often complain of numbness and a tingling or pins and needles sensation, particularly in the legs.

Biochemical Changes

Thiamine is essential for carbohydrate metabolism as it functions as thiamine pyrophosphate (TPP), a coenzyme in several metabolic pathways. In its absence, pyruvate accumulates in tissues and plasma and is excreted in urine. Normally, pyruvate does not cross the blood brain barrier, but thiamine deficiency can alter this barrier, allowing pyruvate to enter the brain. This may disrupt neural metabolism and contribute to polyneuritis.

Thiamine deficiency also impairs nerve impulse transmission and reduces transketolase activity in red blood cells. Measuring this enzyme activity is a reliable diagnostic tool to assess thiamine status.

Types of Beri-Beri:

Wet Beri-Beri (Cardiovascular Form):
This type affects the cardiovascular system. It presents with edema in the legs, face, and trunk, along with breathlessness, palpitations, and mild calf muscle swelling. Systolic blood pressure increases while diastolic pressure falls. The pulse is rapid and forceful. If untreated, the heart may weaken, leading to heart failure and death.

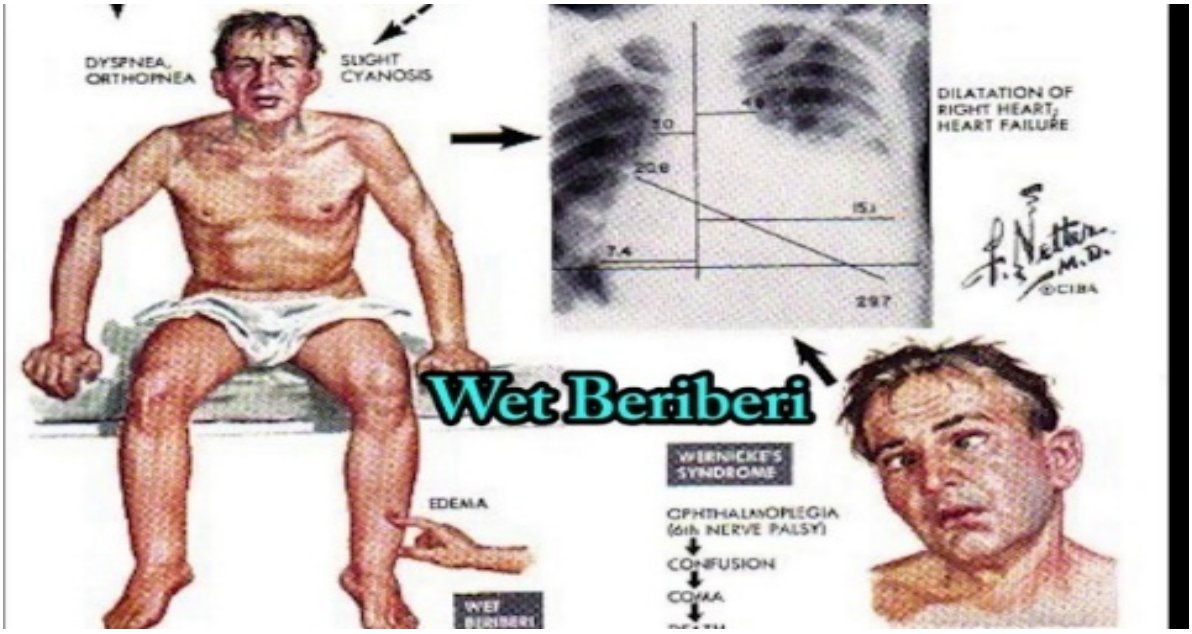

Fig. 14.4: Wet Beriberi

Dry Beri-Beri (Neurological Form):

This form is marked by progressive muscle weakness, difficulty walking, and peripheral nerve damage. Edema is typically absent. Patients may become unable to walk without support and eventually bedridden if untreated.

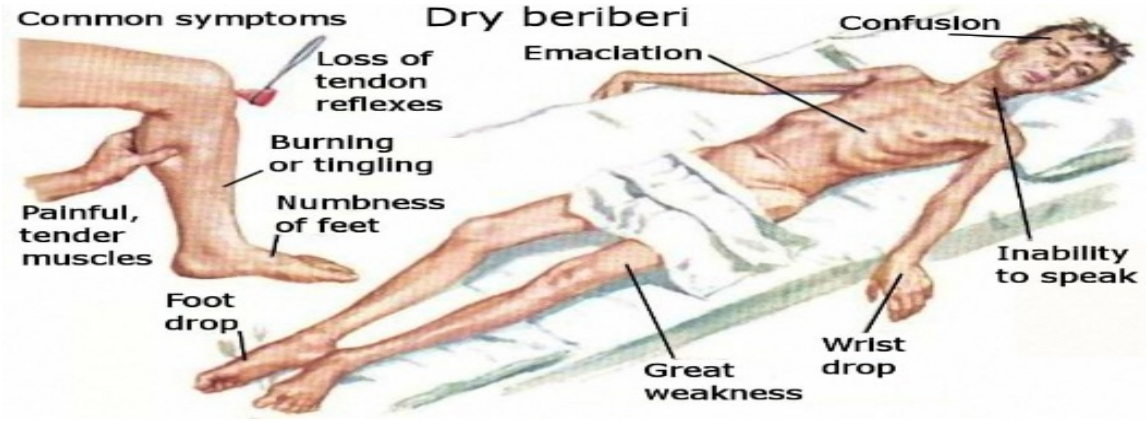

Fig. 14.5: Dry Beriberi

Mixed Beriberi:
This is a combination of cardiovascular and neurological symptoms.

Infantile Beri-Beri:
Occurs in infants breastfed by thiamine-deficient mothers. Their milk contains low thiamine levels. Affected infants show restlessness, insomnia, vomiting, convulsions, and episodes of screaming due to cardiac dilation.

Wernicke-Korsakoff Syndrome

Also called cerebral beri-beri, this syndrome is common in chronic alcoholics. Alcohol increases the body's thiamine requirement while also reducing absorption. Clinical features include memory loss, apathy, and nystagmus (involuntary eye movement). If untreated, it may lead to permanent brain damage.

Thiamine Antimetabolites

Pyrithiamine and oxythiamine are structural analogues of thiamine that block its action by interfering with normal metabolic pathways. Their presence in the diet or environment can worsen or mimic thiamine deficiency.

14.2.4 FACTORS INFLUENCING BIOAVAILABILITY AND REQUIREMENTS

Food matrix: The type of food can influence thiamine absorption. For example, the addition of UHT milk was found to enhance thiamine bio accessibility in baby biscuits.

Processing and cooking: High temperatures and neutral pH levels during food processing can significantly reduce thiamine content and bioavailability.

Degree of milling (DOM): For grains, a higher DOM (more refined) can decrease the bio accessibility of thiamine.

Other dietary factors: Dietary fiber and peptides in foods can also affect thiamine's bio accessibility.

Enzymes: Some foods like raw fish and shellfish contain thiaminases that deactivate thiamine, although deficiency from these foods is rare.

Gender	Vitamin B1 mg/day
Men	1.2 – 1.9
Women	1.1 – 1.8
Pregnant	1.6
Lactating	1.7
Infants	-
Children	0.6 – 1.0
Adolescents	1.2 – 1.9

Fig. 14.5: RDA

14.3 VITAMIN B2

Riboflavin through its coenzymes takes part in a variety of cellular oxidation-reduction reactions. Chemistry: Riboflavin contains 6,7-dimethyl isoalloxazine (a heterocyclic 3 ring structure) attached to D-ribitol by a nitrogen atom. Ribitol is an open chain form of sugar ribose with the aldehyde group (CHO) reduced to alcohol (CH2OH).

Riboflavin is stable to heat but sensitive to light. When exposed to ultra-violet rays of sunlight, it is converted to lumiflavin which exhibits yellow fluorescence. The substances namely lactoflavin (from milk), hepatoflavin (from liver) and ovoflavin (from eggs) which were originally thought to be different are structurally identical to riboflavin.

Coenzymes of Riboflavin: Flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD) are the two coenzyme forms of riboflavin. The ribitol (5carbon) is linked to a phosphate in FMN. FAD is formed from FMN by the transfer of an AMP moiety from ATP.

14.3.1 DIETARY SOURCES

Riboflavin is found in both animal and plant foods, with animal sources being more bioavailable. Key sources include milk, eggs, liver, kidney, fish, poultry, and lean meats. Plant sources include leafy vegetables, whole grains, legumes, nuts, seeds, and mushrooms. Fortified cereals, breads, and flours also add to intake. While riboflavin is stable during cooking, it is easily destroyed by sunlight exposure.

14.3.2 FUNCTIONS

The flavin coenzymes (mostly FAD and to a lesser extent FMN) participate in many redox reactions responsible for energy production. The functional unit of both the coenzymes is isoalloxazine ring which serves as an acceptor of two hydrogen atoms (with electrons). FMN or FAD undergoes identical reversible reactions accepting two hydrogen atoms forming FMNH2 or FADH2.

Enzymes that use flavin coenzymes (FMN or FAD) are called flavoproteins. The coenzymes (prosthetic groups) often bind rather tightly, to the protein (apoenzyme) either by non-covalent bonds (mostly) or covalent bonds in the holoenzyme. Many flavoproteins contain metal atoms (iron, molybdenum etc.) which are known as Metallo flavoproteins.

The coenzymes, FAD and FMN are associated with certain enzymes involved in carbohydrate, lipid, protein and purine metabolisms, besides the electron transport chain.

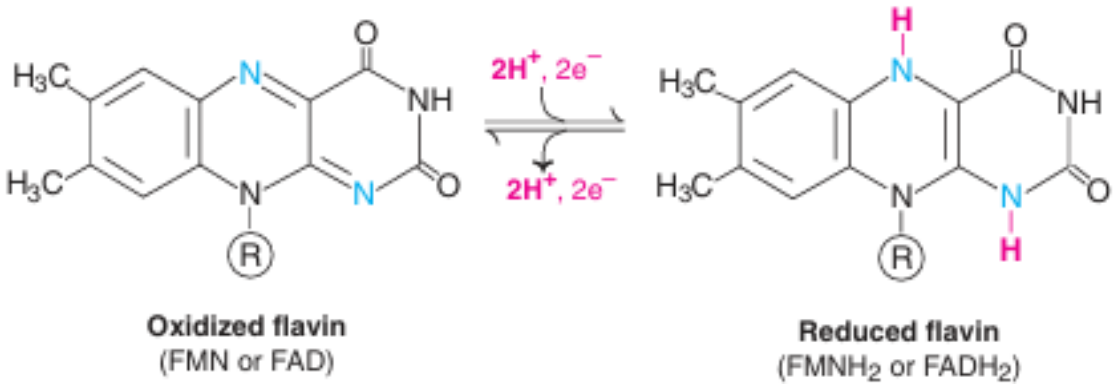

Fig. 14.6: Participation of FMN or FAD in oxidation-reduction reactions

14.3.3 DEFICIENCY STATES

Riboflavin deficiency symptoms include cheilosis (fissures at the corners of the mouth), glossitis (tongue smooth and purplish) and dermatitis. Riboflavin deficiency as such is uncommon. It is mostly seen along with other vitamin deficiencies. Chronic alcoholics are susceptible to B2 deficiency. Assay of the enzyme glutathione reductase in erythrocytes will be useful in assessing riboflavin deficiency.

Antimetabolite: Galactoflavin is an antimetabolite of riboflavin.

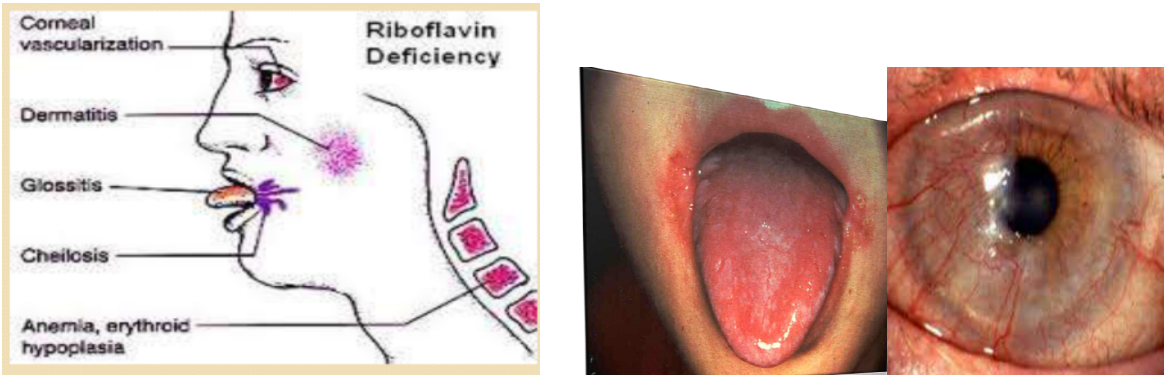

Fig. 14.7: Deficiency symptoms like Cheilosis, Glossitis and Corneal Vascularization

14.3.4 FACTORS INFLUENCING BIOAVAILABILITY

Riboflavin's bioavailability depends on several dietary and physiological factors. It is reduced by light exposure, as the vitamin is highly photosensitive and degrades under UV light, such as in transparent milk bottles. Alcohol consumption, malabsorption syndromes, and low intake of nutrients like iron or vitamin B6 can also impair its absorption and utilization. On the other hand, animal protein enhances absorption efficiency, while good

intestinal health with adequate bile and pancreatic enzyme secretion further supports uptake. Fortification and food enrichment practices also help improve riboflavin intake. The vitamin is generally heat-stable but light-labile, with most losses occurring from sunlight exposure rather than cooking.

Gender	Vitamin B2 mg/day
Men	1.6 – 2.7
Women	1.6 – 2.6
Pregnant	2.3
Lactating	2.5
Infants	-
Children	0.8 – 1.3
Adolescents	1.6 – 2.5

Fig. 14.8: RDA

14.4 VITAMIN B3

Niacin or nicotinic acid is also known as pellagra preventive (P.P.) factor of Goldberg. The coenzymes of niacin (NAD+ and NADP+) can be synthesized by the essential amino acid, tryptophan. The disease pellagra (Italian: rough skin) has been known for centuries. However, its relation to the deficiency of a dietary factor was first identified by Goldberger. Goldberger and his associates conducted an interesting experiment for this purpose. Twelve convicts were promised pardon if they consumed diet of pellagrous families for one year. The diet consisted of corn meal, corn starch, rice, sweet potato and pork fat. More than half of the subjects showed symptoms of pellagra in less than a year, while no such symptoms were observed in other prisoners on a regular diet. Administration of dried meat or liver to the patients cured pellagra (Goldberger, 1928).

Much before it was recognized as a vitamin, nicotinic acid was well known as a chemical compound, produced by the oxidation of nicotine (present in tobacco leaves). The term ‘niacin’ was coined and more commonly used for nicotinic acid. This was done to emphasize the role of niacin as a vitamin and avoid the impression that nicotinic acid is an oxidized form of nicotine. However, most of the authors use niacin and nicotinic acid synonymously.

Niacin is a pyridine derivative. Structurally, it is pyridine 3-carboxylic acid. The amide form of niacin is known as niacinamide or nicotinamide

Niacin functions mainly as a precursor for the coenzymes NAD^+ (nicotinamide adenine dinucleotide) and $NADP^+$ (nicotinamide adenine dinucleotide phosphate), which are essential for hundreds of enzymatic reactions across various metabolic systems.

14.4.1 DIETARY SOURCES

Niacin (Vitamin) is primarily sourced from liver, yeast, whole grains, and pulses, with moderate amounts in milk, fish, eggs, and vegetables. The essential amino acid tryptophan can act as a precursor for nicotinamide coenzyme synthesis, where is metabolically equivalent to (a conversion ratio). Tryptophan cannot fully replace dietary niacin due to its other critical roles, though it may account for up to of coenzyme synthesis. Both are necessary in the diet, with the conversion rate of tryptophan to niacin increasing under low-protein diets or starvation.

14.4.2 FUNCTIONS

The coenzymes NAD+ and NADP+ are involved in a variety of oxidation-reduction reactions. They accept hydride ion (hydrogen atom and one electron: H–) and undergo reduction in the pyridine ring. This results in the neutralization of positive charges. The nitrogen atom and the fourth carbon atom of nicotinamide ring participate in the reaction. While one atom of hydrogen (as hydride ion) from the substrate (AH2) is accepted by the coenzyme, the other hydrogen ion (H+) is released into the surrounding medium.

This reaction is reversed when NADH is oxidized to NAD+. NADP+ also functions like NAD+ in the oxidation-reduction reactions. A large number of enzymes (about 40) belonging to the class oxidoreductases aredependent on NAD+ or NADP+. The coenzymes are loosely bound to the enzymes and can be separated easily by dialysis. NAD+ and NADP+ participate in almost all the metabolisms (carbohydrate, lipid, protein etc.). Some enzymes are exclusively dependent on NAD+ whereas some require only NADP+. A few enzymes can use either NAD+ or NADP+.

NADH produced is oxidized in the electron transport chain to generate ATP. NADPH is also important for many biosynthetic reactions as it donates reducing equivalents.

14.4.3 DEFICIENCY STATES

Niacin deficiency results in a condition called pellagra (Italian: rough skin). This disease involves skin, gastrointestinal tract and central nervous system. The symptoms of pellagra are commonly referred to as three Ds. The disease also progresses in that order dermatitis, diarrhea, dementia, and if not treated may lead to death (4th D). Pellagra is frequently observed in Hartnup’s disease (See p-173).

Dermatitis (inflammation of skin) is usually found in the areas of the skin exposed to sunlight (neck, dorsal part of feet, ankle and parts of face). Diarrhea may be in the form of loose stools, often with blood and mucus. Prolonged diarrhea leads to weight loss. Dementia is associated with degeneration of nervous tissue. The symptoms of dementia include anxiety, irritability, poor memory, insomnia (sleeplessness) etc.

Pellagra is mostly seen among people whose staple diet is corn or maize. Niacin present in maize is unavailable to the body as it is in bound form, and tryptophan content is low in maize.

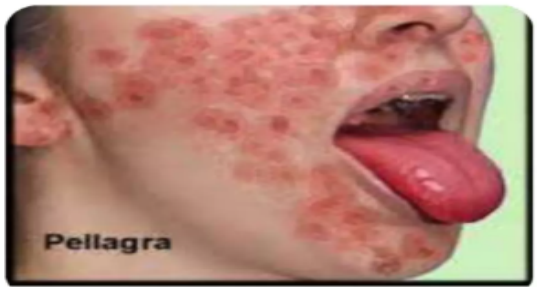

Fig. 14.9: Pellagra

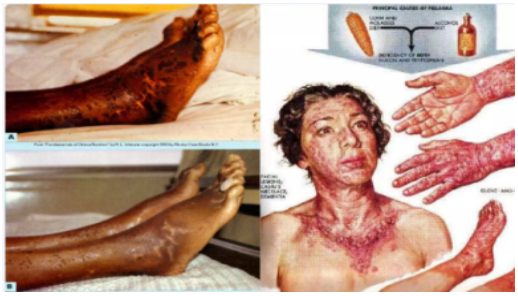

Fig. 14.10: Dermatits

14.4.4 FACTORS INFLUENCING BIOAVAILABILITY

Niacin absorption and utilization are influenced by diet, metabolism, and nutrient interactions. Its bioavailability is reduced when niacin is bound to carbohydrates in untreated corn (niacytin), in chronic gastrointestinal or liver disorders, and when tryptophan or its cofactors such as vitamin B6 and riboflavin are inadequate. Carcinoid syndrome also lowers availability, as tryptophan is diverted to serotonin synthesis. Bioavailability is enhanced through alkaline grain processing (e.g., nixtamalized maize), adequate protein intake to supply tryptophan, and sufficient co-nutrients like B6, iron, and riboflavin. Niacin is heat- and light-stable, making it highly resistant to losses during cooking and food processing.

Gender	Vitamin B3 mg/da
Men	12 – 19
Women	9 – 15
Pregnant	+2
Lactating	+4
Infants	-
Children	6 – 10
Adolescents	12 - 19

Fig. 14.11: RDA

14.5 SUMMARY

Vitamins B1, B2, and B3 are essential water-soluble members of the B-complex group, vital for metabolic functions. Vitamin B1 (Thiamine) acts as a coenzyme (TPP) in carbohydrate metabolism and neural activity, with deficiency leading to beriberi and Wernicke-Korsakoff syndrome. Vitamin B2 (Riboflavin) functions through FMN and FAD in redox reactions, supporting energy metabolism, tissue repair, and antioxidant defense; deficiency (ariboflavinosis) causes cracked lips, mouth inflammation, and sore throat. Vitamin B3 (Niacin) is required for NAD and NADP synthesis, key in energy production, DNA repair, and cellular signaling; deficiency causes pellagra, marked by dermatitis, diarrhea, and dementia. Together, these vitamins are critical for metabolic health, neurological function, and energy balance.

14.6 TECHNICAL TERMS

TPP (Thiamine Pyrophosphate), FAD (Flavin Adenine Dinucleotide), NAD (Nicotinamide Adenine Dinucleotide), Redox Reactions, Niacin Deficiency (Pellagra), Riboflavin Deficiency (Ariboflavinosis)

14.7 SELF ASSESSMENT QUESTIONS:

- What role does Vitamin B1 (Thiamine) play in carbohydrate metabolism, and what health issues arise from its deficiency?
- How does Vitamin B2 (Riboflavin) aid in energy production, and what are the common signs of riboflavin deficiency?
- What is pellagra, and how is it associated with a deficiency of Vitamin B3 (Niacin)?
- What are the main food sources of Vitamins B1, B2, and B3, and what factors can impact their absorption?
- How do the coenzymes TPP, FAD, and NAD facilitate metabolic reactions in the body, and how are they connected to B-complex vitamins?

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Dr. B. Babitha

LESSON-15

VITAMIN B5, B6, B7

15.0. OBJECTIVES:

After going through this lesson, students will understand:

- The significance of vitamin B5 in the synthesis of coenzyme A and its role in lipid metabolism, Identify the key functions and dietary sources of vitamin B6, particularly in protein metabolism and neurotransmitter production.
- Describe the role of Biotin (vitamin B7) in enzymatic carboxylation reactions and its contribution to gene expression.
- To recognize the clinical signs, consequences, RDA and factors affecting bioavailability of related to vitamin B5, B6, and B7.

STRUCTURE:

15.1 INTRODUCTION

Vitamins B5 (Pantothenic Acid), B6 (Pyridoxine), and B7 (Biotin) are essential water soluble B-complex vitamins that support key metabolic processes including energy

production, amino acid metabolism and coenzyme formation. Vitamin B5 is crucial for synthesizing coenzyme A which aids in carbohydrate, protein and fat metabolism as well as adrenal hormone production and tissue repair. Vitamin B6 is vital for amino acid metabolism, neurotransmitter synthesis and red blood cell formation with deficiency leading to neurological and hematological issues. Vitamin B7 acts as a coenzyme in carboxylation reactions, important for fat, protein and carbohydrate metabolism and also supports healthy skin, hair and nails. Deficiency in these vitamins can cause metabolic impairment, skin problems and neurological disturbances. This lesson explores their functions, sources, deficiency symptoms, and requirements to highlight their role in human nutrition.

15.2 VITAMIN B5

Pantothenic acid (Greek: pantos – everywhere) formerly known as chick anti-dermatitis factor (or filtrate factor) is widely distributed in nature. Its metabolic role as coenzyme A is also widespread. Chemistry and synthesis of coenzyme A Pantothenic acid consists of two components, pantoic acid and E-alanine held together by a peptide linkage. Synthesis of coenzyme A from pantothenate occurs in a series of reactions. Pantothenate is first phosphorylated to which cysteine is added. Decarboxylation followed by addition of AMP moiety and a phosphate (each from ATP) results in coenzyme A. The structure of coenzyme A consists of pantothenic acid joined to E-mercaptoethanolamine (thioethanolamine) at one end. On the other side, pantothenic acid is held by a phosphate bridge to adenylic acid. The adenylic acid is made up of adenine, and a phosphate linked to carbon-3 of ribose.

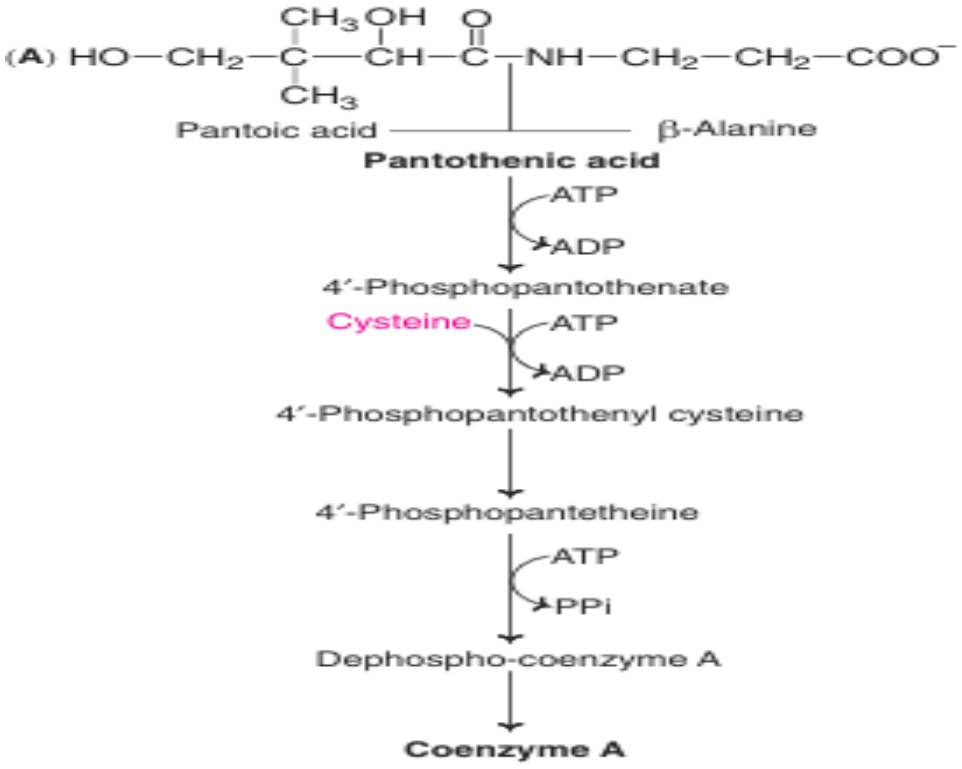


Fig. 15.1(A): Summary of the synthesis of coenzyme A from pantothenic acid

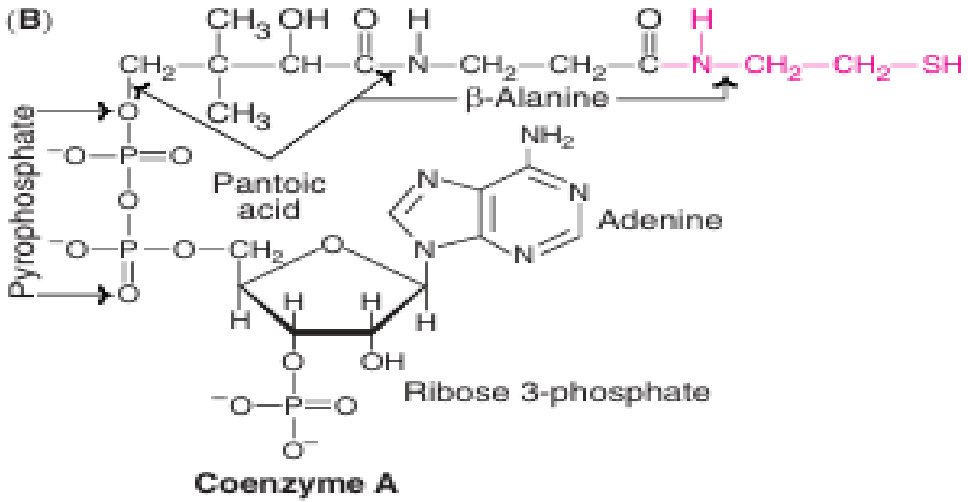


Fig. 15.1(B): Structure of Coenzyme A

15.2.1 DIETARY SOURCES

Pantothenic acid is one of the most widely distributed vitamins found in plants and animals. The rich sources are egg, liver, meat, yeast, milk etc.

Fig. 15.2: Sources of Vitamin B5

15.2.2 FUNCTIONS

The functions of pantothenic acid are exerted through coenzyme A or CoA (A for acetylation). Coenzyme A is a central molecule involved in all the metabolisms (carbohydrate, lipid and protein). It plays a unique role in integrating various metabolic pathways. More than 70 enzymes that depend on coenzyme A are known. Coenzyme A has a terminal thiol or sulfhydryl group (SH) which is the reactive site; hence CoA-SH is also used. Acyl groups (free fatty acids) are linked to coenzyme A by a thioester bond, to give acyl CoA. When bound to acetyl unit, it is called acetyl CoA. With succinate, succinyl CoA is formed. There are many other compounds bound to coenzyme A. Coenzyme A serves as a carrier of activated acetyl or acyl groups (as thiol esters). This is comparable with ATP which is a carrier of activated phosphoryl groups. A few examples of enzymes involved the participation of coenzyme A are given below.

- Pyruvate + CoA → Acetyl-CoA (via pyruvate dehydrogenase)
- α-Ketoglutarate + CoA → Succinyl-CoA (via α-ketoglutarate dehydrogenase)
- Fatty acid + CoA → Acyl-CoA (via thiokinase)
- Acetyl-CoA + Choline → Acetylcholine + CoA
- Acetyl-CoA + Oxaloacetate → Citrate + CoA
- Succinyl-CoA + Acetoacetate → Acetoacetyl-CoA + Succinate

Coenzyme A may be regarded as a coenzyme of metabolic integration, since acetyl CoA is a central molecule for a wide variety of biochemical reactions. Succinyl CoA is also involved in many reactions, including the synthesis of porphyrins of heme. Besides the various functions through coenzyme A, pantothenic acid itself is a component of fatty acid synthase complex and is involved in the formation of fatty acids.

15.2.3 DEFICIENCY STATES

It is a surprise to biochemists that despite theinvolvement of pantothenic acid (as coenzyme A) in a great number of metabolic reactions,its deficiency manifestations have not been reported in humans. This may be due to the widespread distribution of this vitamin or the symptoms of pantothenic acid may be similar to other vitamin deficiencies. Dr. Gopalan a world renowned nutritionist from India linked the burning feet syndrome (pain and numbness in the toes, sleeplessness, fatigue etc.) with pantothenic acid deficiency. Pantothenic acid deficiency in experimental animals results in anemia, fatty liver and decreased steroid synthesis etc.

Fig. 15.3: Burning Feet Syndrome, Sleeplessness

15.2.4 FACTORS INFLUENCING BIOAVAILABILITY

The bioavailability of pantothenic acid (vitamin B5) from food is estimated to be between 40% and 61%, with an average of about 50%. This estimation comes from studies comparing the amount absorbed from natural foods versus crystalline forms.

Factors Affecting Bioavailability

- Food processing: Refining grains, canning and freezing can cause significant losses of pantothenic acid (from 20% up to 80%).
- High doses: Absorption rates can decrease significantly if intake is very high as the transport system can become saturated.

- Supplement form: Supplements often contain calcium pantothenate which must also be converted to free pantothenic acid by intestinal enzymes before it can be absorbed.

REQUIREMENTS- RDA

The requirement of pantothenic acid for humans is not clearly known. A daily intake of about 5-10 mg is advised for adults.

15.3 VITAMIN B6

Vitamin B6 is used to collectively represent the three compounds namely pyridoxine, pyridoxal and pyridoxamine (the vitamers of B6).

Chemistry:

Vitamin B6 compounds are pyridine derivatives. They differ from each other in the structure of a functional group attached to 4th carbon in the pyridine ring. Pyridoxine is a primary alcohol; pyridoxal is an aldehyde form while pyridoxamine is an amine. Pyridoxamine is mostly present in plants while pyridoxal and pyridoxamine are found in animal foods. Pyridoxine can be converted to pyridoxal and pyridoxamine, but the latter two cannot form pyridoxine.

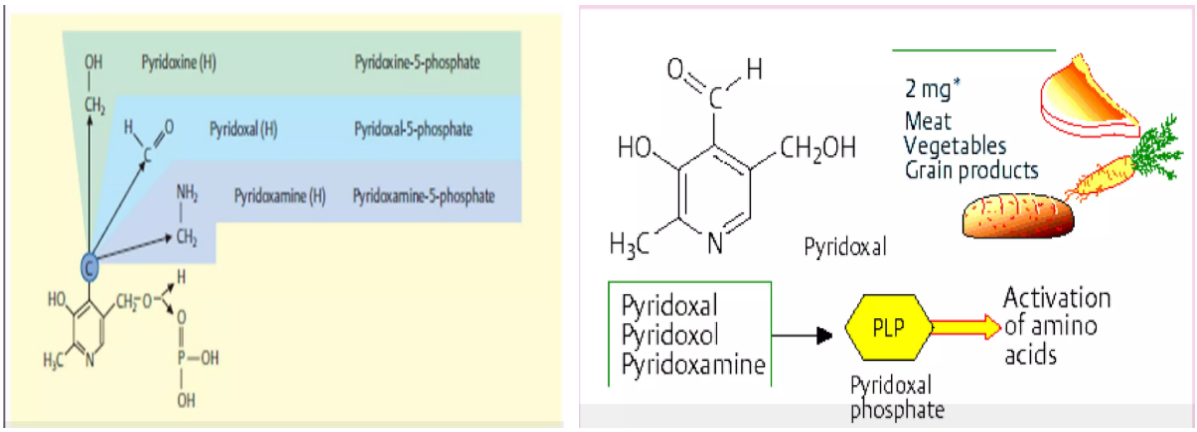


Fig. 15.4: Structure of Vitamin B6

15.3.1 DIETARY SOURCES

Animal sources such as egg yolk, fish, milk, meat are rich in B6. Wheat, corn, cabbage, roots and tubers are good vegetable sources.

15.3.2 FUNCTIONS

Pyridoxal phosphate (PLP), the active coenzyme form of vitamin B6, binds to the lysine amino group in enzymes and plays a critical role in amino acid metabolism and related processes. PLP is essential for synthesizing specialized compounds like serotonin, histamine and niacin coenzymes from amino acids and it facilitates reactions such as transamination, decarboxylation, deamination, transsulfuration and condensation. Below are its key functions:

- **Transamination**: PLP, via transaminases converts amino acids to keto acids, which enter the citric acid cycle for energy production linking carbohydrate and amino acid metabolism. PLP forms a Schiff base with an amino acid producing pyridoxamine phosphate and a keto acid.

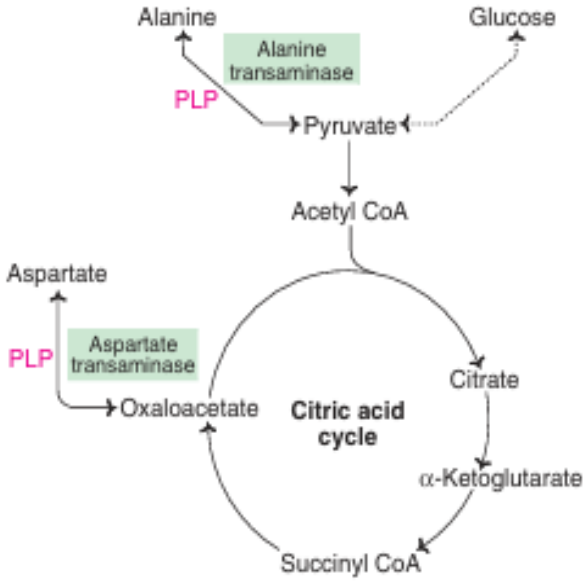


Fig. 15.5: Pyridoxal Phosphate (PLP) Integrates Amino Acid and Carbohydrate Metabolisms

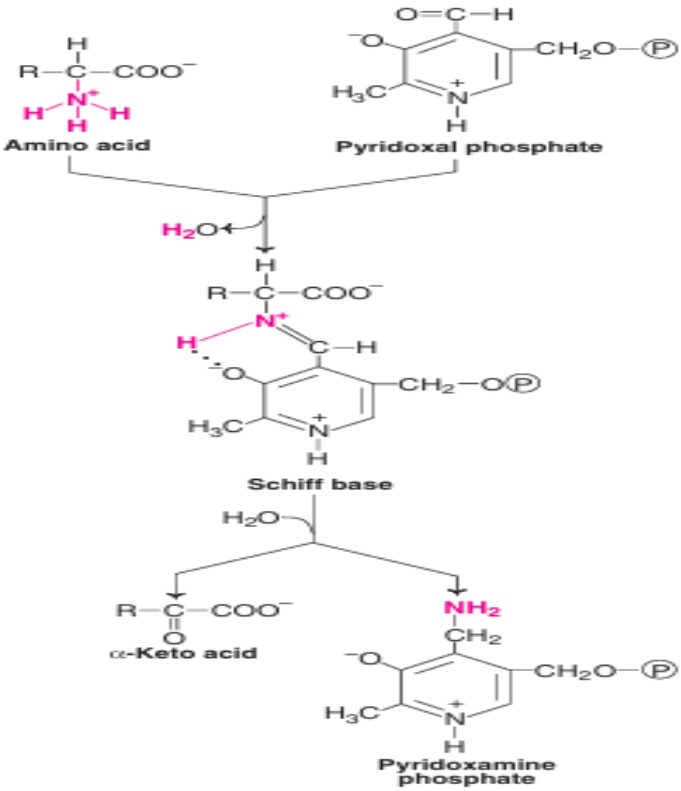


Fig. 15.6: Formation of Schiff base in transamination.

- **Decarboxylation**: PLP-dependent decarboxylases convert α-amino acids into bioactive amines:
  - **Serotonin**: Derived from tryptophan it regulates nerve transmission, sleep and blood pressure (Fig. 7.23).

  - **Histamine**: Formed from histidine it acts as a vasodilator, stimulates gastric acid secretion and mediates inflammation and allergies.
  - **GABA**: Produced from glutamate, it inhibits nerve transmission.
  - **Catecholamines**: PLP aids in synthesizing dopamine, norepinephrine and epinephrine from tyrosine for metabolic and nervous regulation.
- **Heme synthesis**: PLP is required for synthesizing δ-aminolaevulinic acid, a heme precursor via glycine and succinyl CoA.
- **Niacin synthesis**: PLP-dependent kynureninase converts tryptophan to niacin coenzymes (NAD+/NADP+). In B6 deficiency, xanthurenic acid accumulates, detectable in urine.
- **Sulfur amino acid metabolism**: PLP facilitates transsulfuration, transferring sulfur from homocysteine to serine to form cysteine. It also supports taurine production for bile acid conjugation.
- **Deamination**: PLP-dependent dehydratases convert hydroxyl-containing amino acids like serine and threonine to pyruvate or α-ketobutyrate and ammonia.
- **Serine synthesis**: PLP-dependent hydroxy methyltransferase synthesizes serine from glycine.
- **Glycogen breakdown**: PLP stabilizes glycogen phosphorylase, aiding the release of glucose 1-phosphate from glycogen.
- **Amino acid absorption**: PLP enhances intestinal absorption of amino acids.
- **Oxalate regulation**: Adequate B6 intake reduces hyperoxaluria, helping prevent urinary stone formation.

15.3.3 DEFICIENCY STATES

- **Neurological symptoms**: Pyridoxine deficiency causes depression, irritability, nervousness and mental confusion due to reduced synthesis of biogenic amines (serotonin, GABA, norepinephrine, epinephrine).
- **Severe deficiency effects**: Convulsions and peripheral neuropathy occur in severe cases; children may develop epilepsy from low GABA production.
- **Hematological impact**: Deficiency leads to hypochromic microcytic anemia due to impaired heme synthesis, reducing hemoglobin levels.
- **Niacin synthesis impairment**: Decreased production of niacin coenzymes (NAD+, NADP+) from tryptophan, with increased urinary xanthurenic acid as a deficiency marker (detectable via tryptophan load test).
- **Dietary deficiency**: Rare, but seen in women on oral contraceptives, alcoholics, and infants.
- **Drug-induced deficiency**:
  - **Isoniazid**: Used in tuberculosis treatment, binds pyridoxal phosphate, forming inactive hydrazones, causing peripheral neuropathy (treatable with B6 supplementation).
  - **Penicillamine**: Used for rheumatoid arthritis, Wilson’s disease and cystinuria, forms inactive thiazolidine with PLP, requiring B6 supplementation.

- **Pyridoxine antagonists**: Isoniazid, deoxypyridoxine and methoxypyridoxine inhibit B6 function.
- **Toxicity from overdose**: Excessive B6 intake (e.g., 2.5 g/day for premenstrual syndrome) causes sensory neuropathy; doses above 200 mg/day may lead to neurological damage.

15.3.4 FACTORS INFLUENCING BIOAVAILABILITY

The bioavailability of vitamin B6 from animal products is very high (close to 100%), while from plant foods it is generally lower, around 75% in a mixed diet. Factors that can reduce plant-based bioavailability include the presence of fiber which may decrease it by 5–10% and the form pyridoxine-5′-β-d-glucoside, which can lower bioavailability by 75–80%. Processing methods like heating can also decreases the amount of vitamin B6 in plant-based products.

REQUIREMENTS- RDA

Gender	Vitamin B6 mg/day
Men	1.9 – 3.1
Women	1.9 – 2.4
Pregnant	2.3
Lactating	+0.26
Infants	0.1 – 0.6
Children	0.9 – 1.5
Adolescents	1.9 – 3.0

Fig. 15.7: RDA

15.4 VITAMIN B7

Biotin (formerly known as anti-egg white injury factor, vitamin B7 or vitamin H) is a sulfur containing B-complex vitamin. It directly participates as a coenzyme in the carboxylation reactions. Boas (1927) observed that rats fed huge quantity of raw egg white developed dermatitis and nervous manifestations, besides retardation in growth. She however, found that feeding cooked egg did not produce any of these symptoms. It was later shown that the egg white injury in rats and chicks was due to the presence of an anti-vitamin in egg white. The egg-white injury factor was identified as glycoproteins. Hence, avidin and biotin was called as anti-egg white injury factor.

Chemistry:

Biotin is heterocyclic sulfur containing monocarboxylic acid. The structure is formed by fusion of imidazole and thiophene rings with a valeric acid side chain. Biotin is covalently bound to H-amino group of lysine to form biocytin in the enzymes. Biocytin may be regarded as the coenzyme of biotin.

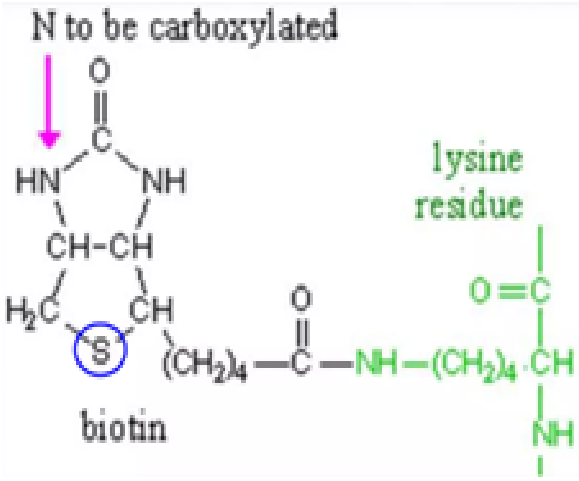


Fig. 15.8: Structure of Biotin with Binding Sites

15.4.1 SOURCES

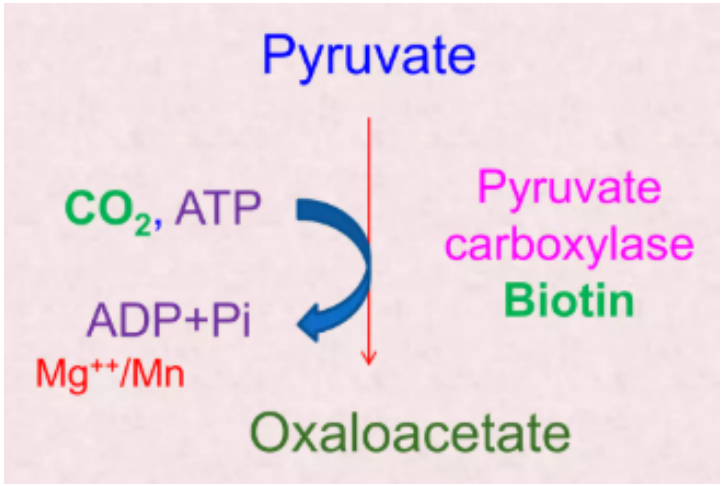
Biotin is widely distributed in both animal and plant foods. The rich sources are liver, kidney, egg yolk, milk, tomatoes, grains etc.

15.4.2 FUNCTIONS

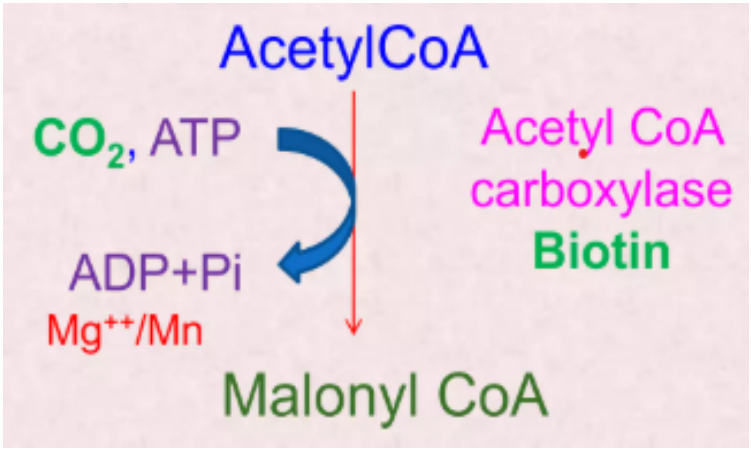
Biotin acts as a CO2 carrier in carboxylation reactions, notably in the pyruvate carboxylase reaction, which converts pyruvate to oxaloacetate. In this process, biotin is covalently bound to the apoenzyme via the lysine amino group, forming the active holoenzyme. The biotin-enzyme complex, powered by ATP, binds CO2 to form a carboxybiotin-enzyme complex, which transfers CO2 to pyruvate, producing oxaloacetate.

As a Coenzyme, Biotin is Critical for Several Metabolic Processes:

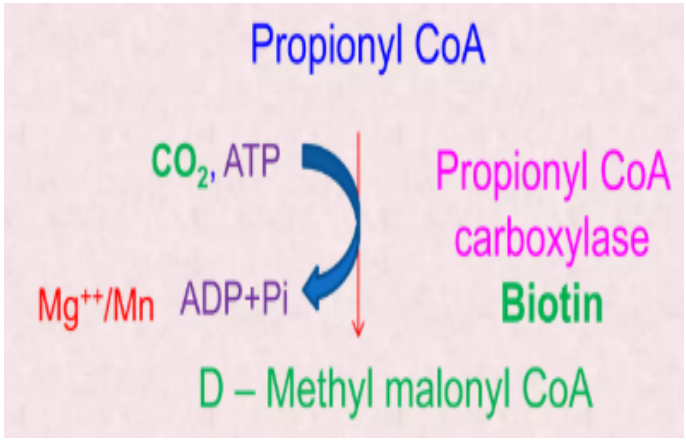
1) **Gluconeogenesis and Citric Acid Cycle:** Biotin-dependent pyruvate carboxylase converts pyruvate to oxaloacetate, essential for glucose synthesis from non-carbohydrate sources and for sustaining the citric acid cycle.



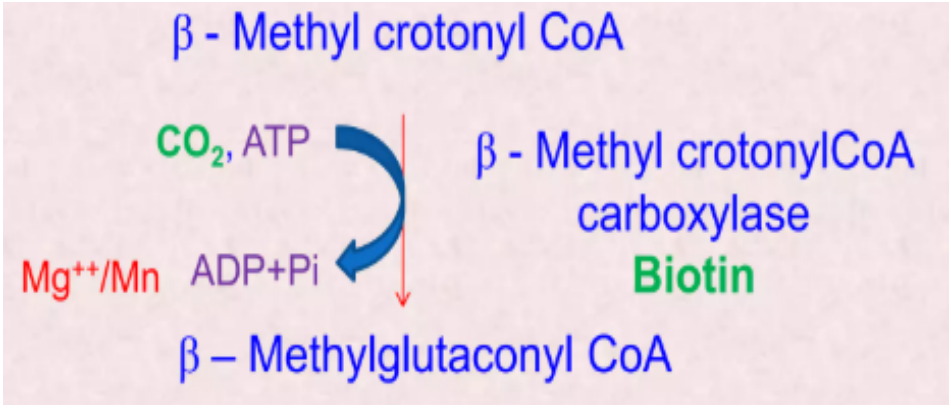
2) **Fatty acid Synthesis:** Biotin is required for the initial carboxylation step, where acetyl CoA carboxylase converts acetyl CoA to malonyl CoA a key precursor in fatty acid synthesis.



3) **Propionyl CoA Metabolism**: Biotin-dependent propionyl CoA carboxylase converts propionyl CoA (from certain amino acids and odd-chain fatty acid degradation) to methylmalonyl CoA.



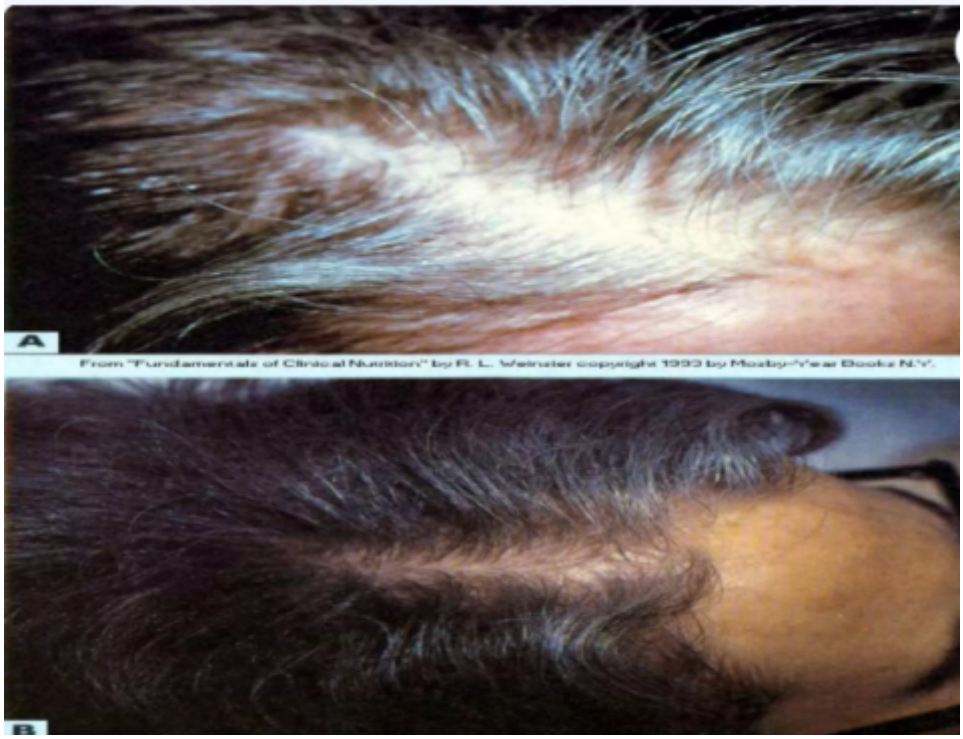
4) **Leucine Metabolism:** Biotin is involved in the carboxylation of methylcrotonyl CoA to methylglutaconyl CoA, catalyzed by methylcrotonyl CoA carboxylase.



15.4.3 DEFICIENCY STATES

The symptoms of biotin deficiency include anemia, loss of appetite, nausea, dermatitis, glossitis etc. Biotin deficiency may also result in depression, hallucinations, muscle pain and dermatitis. Biotin deficiency is uncommon, since it is well distributed in foods and also supplied by the intestinal bacteria. The deficiency may however, be associated with the following two causes.

1) Destruction of intestinal flora due to prolonged use of drugs such as sulfonamides.
2) High consumption of raw eggs. The raw egg white contains a glycoprotein, avidin which tightly binds with biotin and blocks its absorption from the intestine. An intake of about 20 raw eggs per day is needed to produce biotin deficiency symptoms in humans. Consumption of an occasional raw egg will not result in deficiency.



Antagonists: Desthiobiotin and biotin sulfonic acid act as biotin antagonists, interfering with its function.

15.4.4 FACTORS INFLUENCING BIOAVAILABILITY

In its free unbound form oral biotin is nearly 100% bioavailable and absorbed efficiently by the body. However, the bioavailability of biotin from food sources is more variable because it is often bound to proteins.

Factors that Influence Biotin Bioavailability

Dietary Factors

- Protein-binding: Much of the biotin found naturally in foods like meat and cereals is bound to protein. The bioavailability of this biotin varies depending on how easily it is released during digestion.
- Avidin from raw egg white: Raw egg white contains a protein called avidin, which binds tightly to biotin and prevents its absorption in the intestines. Cooking denatures the avidin eliminating its anti-biotin effect.

- Intestinal microflora: Bacteria in the large intestine can synthesize biotin. While the large intestine can absorb some of this biotin, its overall contribution to the body's biotin status is not fully understood.

RDA:

Adults are recommended to consume approximately 100–300 mg of biotin daily. While intestinal bacteria synthesize biotin, the extent to which this contributes to meeting the body's requirements remains unclear.

15.5 SUMMARY

Vitamins B5 (Pantothenic Acid), B6 (Pyridoxine) and B7 (Biotin) are essential water-soluble vitamins that play significant roles in various metabolic functions, including energy production, amino acid metabolism and the formation of key coenzymes.

Vitamin B5 (Pantothenic Acid) is crucial for the synthesis of coenzyme A, which facilitates the metabolism of fats, proteins and carbohydrates. It also supports adrenal function and promotes healing. Vitamin B6 (Pyridoxine) is involved in amino acid metabolism, neurotransmitter synthesis and red blood cell production. A deficiency in Vitamin B6 can lead to neurological and blood-related issues. Vitamin B7 (Biotin) functions as a coenzyme in carboxylation reactions, supporting the metabolism of fats, proteins and carbohydrates is essential for maintaining healthy skin, hair and nails.

Lack of these vitamins can result in various health problems, such as metabolic disturbances, skin disorders and neurological conditions. Adequate intake of Vitamins B5, B6 and B7 is necessary to ensure proper metabolic health. This lesson provides an overview of their functions, dietary sources, deficiency symptoms and recommended intakes highlighting their vital roles in maintaining overall well-being.

15.6 TECHNICAL TERMS

Coenzyme A synthesis, Amino acid catabolism, Synthesis of neurotransmitters, Carboxylation enzymatic reactions, Pyridoxal phosphate metabolism, Biotinidase enzyme activity

15.7 SELF ASSESSMENT QUESTIONS

- What is the function of Vitamin B5 (Pantothenic Acid) in the synthesis of coenzyme A and its role in energy metabolism?
- How does Vitamin B6 (Pyridoxine) aid in the metabolism of amino acids and the production of neurotransmitters? Explain.
- Discus about clinical manifestations and health issues caused by a deficiency of vitamin B5 and B6.
- In what ways does Biotin (Vitamin B7) contribute to the metabolism of fats, proteins and carbohydrates?
- Write about functions of B6 and B7.

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Dr. B. Babitha

LESSON-16

VITAMIN B9, B12, C

16.0. OBJECTIVES:

After going through this lesson, students will understand:

- Comprehend the essential functions of vitamin B9 (Folate), B12 (Cobalamin) and vitamin C (Ascorbic acid) in human health.
- Explain the biochemical roles of vitamin B9 in DNA synthesis and cellular growth.
- Describe how vitamin B12 supports red blood cell production and the proper functioning of the nervous system.
- Identify food sources and recommended intake levels for vitamins B9, B12 and C.
- Discuss the health effects of deficiencies in vitamins B9, B12 and C including conditions such as anemia and scurvy.

STRUCTURE:

16.1 INTRODUCTION

Vitamins B9 (Folate), B12 (Cobalamin) and C (Ascorbic Acid) are essential water-soluble nutrients that are integral to numerous physiological processes critical for good

health. These vitamins participate in a wide range of biochemical functions, including cellular maintenance, metabolic regulation and tissue regeneration.

Vitamin B9 (Folate) plays a key role in DNA synthesis and cell division, which is especially important during rapid periods of growth, such as pregnancy and infancy. It also supports cardiovascular health and helps prevent neural tube defects. Vitamin B12 (Cobalamin) is crucial for red blood cell production, nerve function and fatty acid metabolism. Insufficient levels of Vitamin B12 can lead to pernicious anemia and irreversible nerve damage. Vitamin C (Ascorbic Acid) is widely known for its antioxidant properties, its ability to enhance immune function and its role in collagen synthesis, which is vital for the health of skin, blood vessels and bones. This lesson will explore the biochemical roles, food sources, deficiency symptoms and recommended intake for these essential vitamins, offering a comprehensive understanding of their importance for maintaining health.

16.2 VITAMIN B9

Folic acid or folacin (Latin: folium-leaf) is abundantly found in green leafy vegetables. It is important for one carbon metabolism and is required for the synthesis of certain amino acids, purines and the pyrimidine-thymine.

Chemistry:

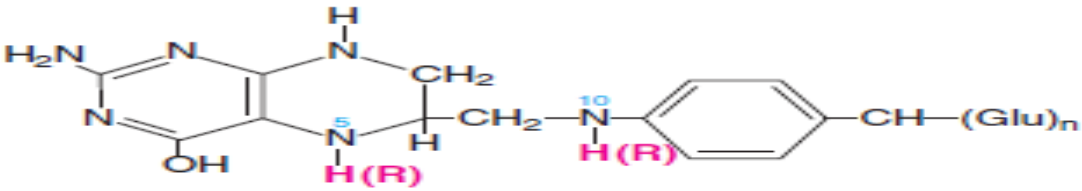
Folic acid consists of three components pteridine ring, p-amino benzoic acid (PABA) and glutamic acid (1 to 7 residues). Folic acid mostly has one glutamic acid residue and is known as pteroyl-glutamic acid (PGA). The active form of folic acid is tetrahydrofolate (THF or FH4). It is synthesized from folic acid by the enzyme dihydrofolate reductase. The reducing equivalents are provided by 2 moles of NADPH. The hydrogen atoms are present at positions 5, 6, 7 and 8 of THF.

16.2.1 SOURCES

Folic acid is widely distributed in nature. The rich sources are green leafy vegetables, whole grains, cereals, liver, kidney, yeast and eggs. Milk is rather a poor source of folic acid.

16.2.2 FUNCTIONS

Tetrahydrofolate (THF or FH_4), the coenzyme of folic acid, is actively involved in the one carbon metabolism. THF serves as an acceptor or donor of one carbon units (formyl, methyl etc.) in a variety of reactions involving amino acid and nucleotide metabolism. The one carbon units bind with THF at position N^5 or N^{10} or on both N^5 and N^{10} of pteroyl structure. The attachment of formyl (CHO) at position 5 of THF gives N^5-formyl tetrahydrofolate which is commonly known as folinic acid or citrovorum factor. The other commonly found one carbon moieties and their binding with THF are given below.



THF-1 carbon derivative	R group (one carbon unit)
N^5-Formyl THF	—CHO
N^{10}-Formyl THF	—CHO
N^5-Formimino THF	—CH═NH
N^5, N^{10}-Methenyl THF	≡CH
N^5, N^{10}-Methylene THF	═CH_2
N^5 – Methyl THF	—CH_3

Fig. 16.1

The essential functions of THF in one carbon metabolism are summarized in figure given below

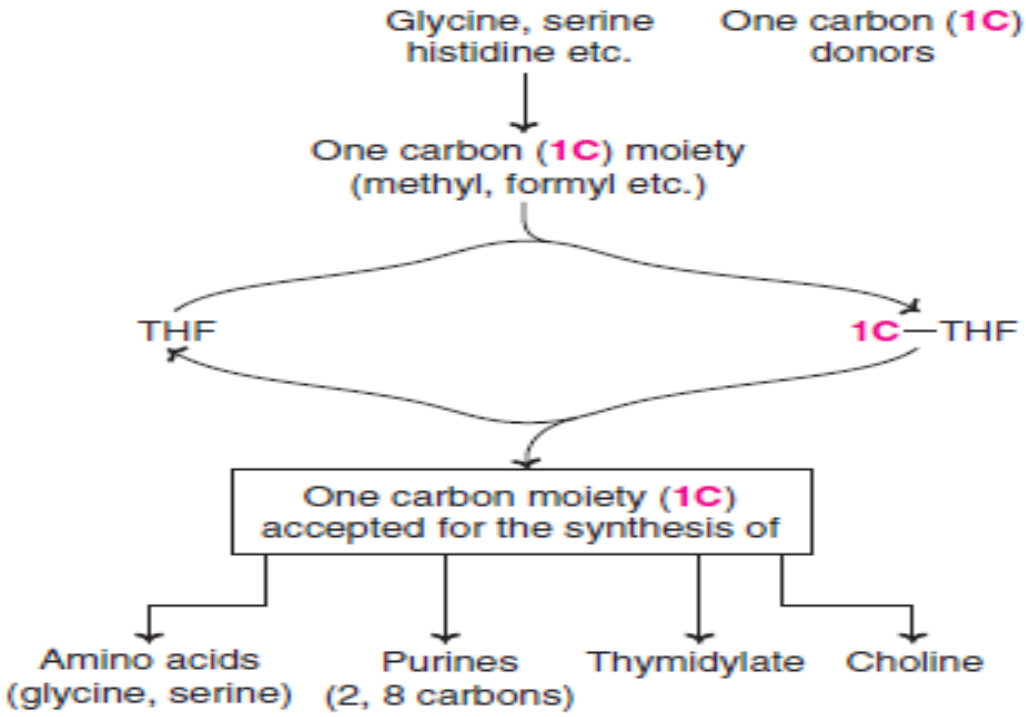


Fig. 16.2

Many important compounds are synthesized in one carbon metabolism.

1) Purines (carbon 2, 8) which are incorporated into DNA and RNA.
2) Pyrimidine nucleotide–deoxythymidylic acid (dTMP), involved in the synthesis of DNA.
3) Glycine, serine, ethanolamine and choline are produced.
4) N-Formylmethionine, the initiator of protein biosynthesis is formed.

16.2.3 DEFICIENCY STATES

Folic acid deficiency is the most common vitamin deficiency, often seen in pregnant and lactating women, alcoholics and those on oral contraceptives or anticonvulsant drugs. Causes include inadequate intake, defective absorption and increased demand.

Deficiency Effects

- **DNA synthesis impairment:** Deficiency causes decreased production of purines and dTMP, severely impairing DNA synthesis. This particularly affects rapidly dividing cells, like those in the bone marrow.
- **Macrocytic anemia:** The primary clinical feature is macrocytic anemia (abnormally large) with megaloblastic changes in the bone marrow caused by slowed erythrocyte maturation.
- **Neural defects:** Deficiency in pregnant women is linked to neural defects in the fetus, necessitating high-dose folic acid supplementation during pregnancy.
- **Histidine metabolism:** Folic acid is required to metabolize histidine, which produces Formiminoglutamate (FIGLU). In deficiency, accumulates and is excreted in urine, a principle used in the excretion test for assessment.

Folic Acid and Hyper Homocysteinemia

Elevated plasma homocysteine levels are associated with increased risk of cardiovascular diseases (atherosclerosis, thrombosis). This is often due to functional folate deficiency, which impairs the conversion of homocysteine to methionine by blocking the formation of methyl-tetrahydrofolate. Folic acid supplementation effectively reduces.

16.2.4 FACTORS INFLUENCING BIOAVAILABILITY

The bioavailability of vitamin B9 differs between food folate and synthetic folic acid. Dietary or "food" folate has about 50% bioavailability, while supplemental folic acid has nearly 100% bioavailability, especially when taken on an empty stomach. To account for this difference, the concept of dietary folate equivalents (DFEs) is used to express B9 needs in a way that reflects the higher bioavailability of folic acid.

Factors Influencing Bioavailability

- **Source**: As noted, the source of the B9 (food vs. supplement) is a primary factor.
- **Individual Status**: Bioavailability can vary based on individuals existing folate levels. It is higher in people with lower blood folate concentrations and the decline is less significant for the more bioavailable form of methylfolate compared to folic acid.
  Method of Consumption: The presence of food can slightly reduce the bioavailability of supplemental folic acid, from about 100% on an empty stomach to around 85% with food.

Age Group	Vitamin B9 (Folate) µg/day
Men	1000
Women	1000
Pregnant	1000
Lactating	1000
Infants	-
Children 1-9 yrs	300
Boys and Girls 10-18 yrs	600-800

Fig. 16.2: RDA

16.3 VITAMIN B12

Vitamin (Cyanocobalamin) is unique as it is synthesized only by microorganisms and not by animals or plants. Known as the anti-pernicious anemia vitamin, it was the last vitamin discovered.

Chemistry

Vitamin has the most complex structure of all vitamins centered on single cobalt (Co) atom.

- **Corrin Ring:** The structure features a corrin ring, similar to the porphyrin structure in heme and chlorophyll. This ring contains four pyrrole units, with two (A and D) linked directly and the others connected by methene bridges.
- **Cobalt Coordination:** The central cobalt atom is held in a six-coordinate state:
    - It is bonded to the four nitrogen atoms of the corrin ring.
    - It is linked (below the ring) to a nitrogen atom of dimethylbenzimidazole **(**DMB**)**, which is attached to ribose -phosphate and aminoisopropanol.
    - It possesses a sixth substituent group located abovethe corrin ring, which defines the vitamin form:
        1) **Cyanocobalamin (B12a):** Cyanide group (predominant form).
        2) **Hydroxycobalamin (B12b):** Hydroxyl group.

Coenzyme Forms

Vitamin functions biologically through two active coenzyme forms:

1) **Deoxyadenosyl cobalamin:** The cyanide is replaced by -deoxyadenosine, forming an unusual **carbon-cobalt bond**.
2) **Methylcobalamin:** The cyanide is replaced by a methylgroup.

16.3.1 SOURCES

Foods of animal origin are the only sources for vitamin B12. The rich sources are liver, kidney, milk, curd, eggs, fish, pork and chicken. Curd is a better source than milk due to the synthesis of B12 by Lactobacillus. Vitamin B12 is synthesized only by microorganisms (anaerobic bacteria). Plants cannot synthesize B12, hence it is never found in plant foods. Animals obtain B12 either by eating foods derived from other animals or from the intestinal bacterial synthesis.

16.3.2 FUNCTIONS

About ten enzymes requiring vitamin B12 have been identified. Most of them are found in bacteria (glutamate mutase, ribonucleotide reductase etc.). There are only two reactions in mammals that are dependent on vitamin B12.

- **Synthesis of Methionine from Homocysteine:** Vitamin B12 as methylcobalamin is used in this reaction. This is an important reaction involving N5-methyl tetrahydrofolate from which tetrahydrofolate is liberated (enzyme-homocysteine methyltransferase ormethionine synthase). This metabolic step signifies the interrelation between vitamin B12 and folic acid.
- **Isomerization of Methymalonyl CoA to Succinyl CoA:** The degradation of odd chain fatty acids, certain amino acids (valine, isoleucine etc.) and pyrimidines (thymine and uracil) produce directly or through the mediation of propionyl CoA, an important compound methylmalonyl CoA. This is converted by the enzyme methylmalonyl CoA mutase to succinyl CoA in the presence of B12 coenzyme, deoxyadenosyl cobalamin. This reaction involves hydrogen transfer and intramolecular rearrangement. In B12 deficiency methylmalonyl CoA accumulates and is excreted in urine as methylmalonic acid.

16.3.3 DEFICIENCY STATES

The most critical condition linked to vitamin deficiency is pernicious anemia characterized by low hemoglobin decreased and severe neurological manifestations.

Causes of Pernicious Anemia

Pernicious anemia is primarily a disease of the stomach rather than a simple dietary deficiency, often caused by:

1) Autoimmune destruction of gastric parietal cells, leading to a lack of Intrinsic Factor (IF), which is essential for absorption.
2) Gastrectomy (partial or total) or hereditary malabsorption.
3) Insufficient production of IF and/or gastric (common in older adults).
4) Strict dietary deficiency (seen mainly in strict vegetarians).

Neurological Effects

Deficiency leads to neuronal degeneration and demyelination of the nervous system resulting in symptoms like:

- **Paresthesia** (numbness/tingling in fingers and toes).
- In advanced stages: confusion, memory loss and psychosis.

These neurological symptoms are believed to stem from the accumulation of methylmalonyl which interferes with myelin sheath formation by two mechanisms:

1) It competitively inhibits malonyl impairing the synthesis of normal fatty acids required for myelin.

2) It substitutes for malonyl leading to the synthesis of abnormal branched-chain fatty acids that disrupt the normal membrane structure.

Deficiency is assessed by measuring serum levels and checking for elevated methylmalonic acid excretion in urine.

16.3.4 FACTORS INFLUENCING BIOAVAILABILITY

Vitamin B12 bioavailability is dose-dependent, decreasing as intake increases and varies based on the food source and the individuals gastrointestinal function. For healthy adults with normal gut function, the general estimate for vitamin B12 bioavailability from food is around 40-50%. However, it is generally higher from supplements and factors like intrinsic factor (IF) production, stomach acidity and intestinal health significantly influence the rate at which it is absorbed into the body.

Gender	Vitamin B12 µg/day
Men	2.2
Women	2.2
Pregnant	+0.25
Lactating	+1.0
Infants	1.2
Children	1.2 – 2.2
Adolescents	2.2

Fig. 16.3: RDA

16.4 VITAMIN C

Vitamin C is a water soluble versatile vitamin. It plays an important role in human health and disease. Vitamin C has become the most controversial vitamin in recent years. This is because of the claims and counter claims on the use of vitamin C in mega dose to cure everything from common cold to cancer. Scurvy has been known to man for centuries. It was the first disease found to be associated with diet. In the sixteenth century about 10,000 mariners died of a miraculous disease (scurvy) due to lack of fresh vegetables in their diet. James Lind a surgeon of the English Navy, in 1753 published ‘Treatise on Scurvy’. Based on Lind’s observations, the Royal Navy since 1795 used to supply lime or lemon juice to all the crews. The English Navy used to carry crates of lemons; hence they were popularly known as Limeys.

Chemistry:

Chemistry Ascorbic acid is a hexose (6carbon) derivative and closely resembles monosaccharides in structure. The acidic property of vitamin C is due to the enolic hydroxyl groups. It is a strong reducing agent. L-Ascorbic acid undergoes oxidation to form dehydroascorbic acid and this reaction is reversible. Both ascorbic acid and dehydroascorbic acid are biologically active. However, D-ascorbic acid is inactive. The plasma and tissues predominantly contain ascorbic acid in the reduced form. The ratio of ascorbic acid to dehydroascorbic acid in many tissues is 15:1.

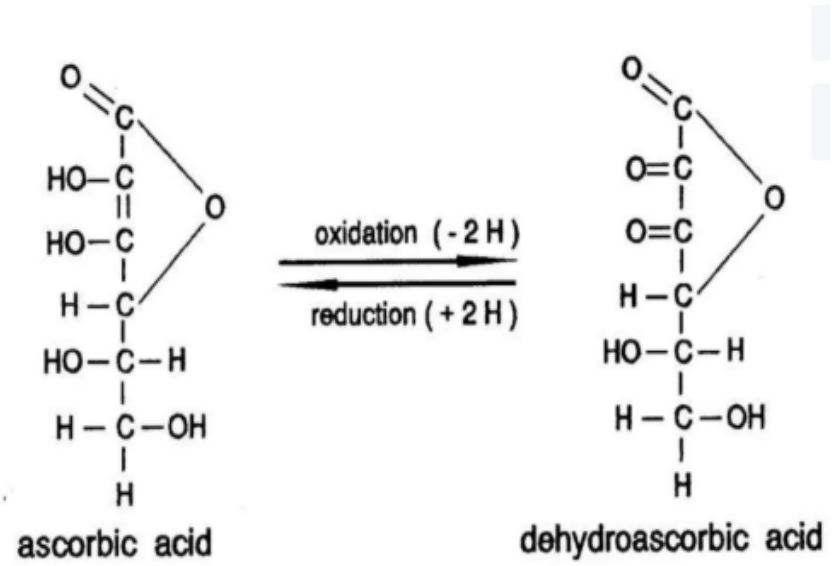


Fig. 16.4: Structure of Vitamin C

On hydration, dehydroascorbic acid is irreversibly converted to 2, 3- diketogulonic acid which is inactive. Hydration reaction is almost spontaneous, in alkaline or neutral solution. It is for this reason that oxidation of vitamin C is regarded as biological inactivation (formation of diketogulonic acid). Oxidation of ascorbic acid is rapid in the presence of copper. Hence vitamin C becomes inactive if the foods are prepared in copper vessels.

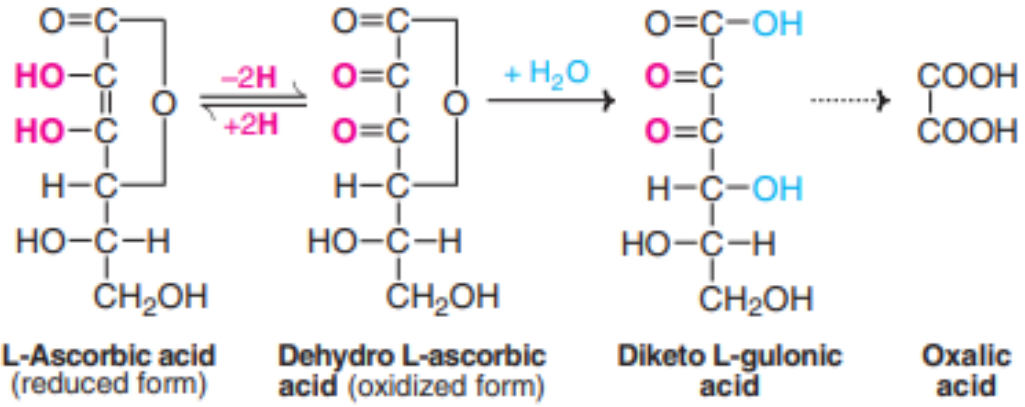


Fig. 16.5: Structures of vitamin C (ascorbic acid) and its related compounds.

16.4.1 SOURCES

Citrus fruits, gooseberry (amla), guava, green vegetables (cabbage, spinach), tomatoes, potatoes (particularly skin) are rich in ascorbic acid. High content of vitamin C is found in adrenal gland and gonads. Milk is a poor source of ascorbic acid.

16.4.2 FUNCTIONS

Most of the functions of vitamin C are related to its property to undergo reversible oxidation–reduction i.e., interconversion of ascorbic acid and dehydroascorbic acid.

Collagen formation: Vitamin C plays the role of a coenzyme in hydroxylation of proline and lysine while protocollagen is converted to collagen (i.e. post-translational modification). The hydroxylation reaction is catalysed by lysyl hydroxylase (for lysine) and prolyl hydroxylase (for proline). This reaction is dependent on vitamin C, molecular oxygen and D-ketoglutarate. Hydroxyproline and hydroxylysine are essential for the collagen cross-linking and the strength of the fiber. In this way, vitamin C is necessary for maintenance of normal connective tissue and wound healing process.

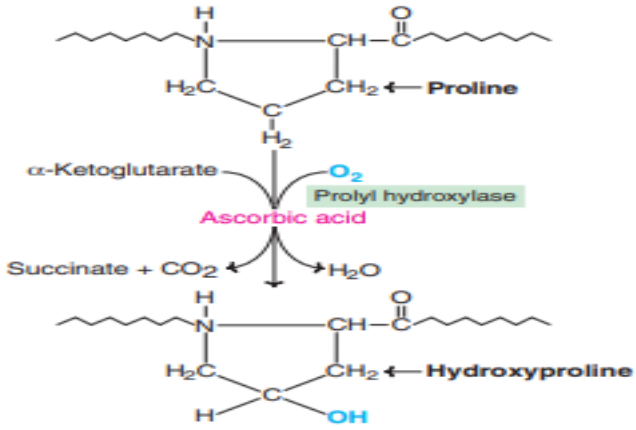


Fig. 16.6: Ascorbic acid dependent hydroxylation of proline of protocollagen.

- **Bone formation:** Bone tissues possess an organic matrix, collagen and the inorganic calcium, phosphate etc. Vitamin C is required for bone formation.
- **Iron and hemoglobin metabolism:** Ascorbic acid enhances iron absorption by keeping it in the ferrous form. This is due to the reducing property of vitamin C. It helps in the formation of ferritin (storage form of iron) and mobilization of iron from ferritin. Vitamin C is useful in the reconversion of methemoglobin to hemoglobin. The degradation of hemoglobin to bile pigments requires ascorbic acid.
- **Tryptophan metabolism:** Vitamin C is essential for the hydroxylation of tryptophan (enzyme-hydroxylase) to hydroxytryptophan in the synthesis of serotonin.
- **Tyrosine metabolism:** Ascorbic acid is required for the oxidation of p-hydroxy phenylpyruvate (enzyme hydroxylase) to homogentisic acid in tyrosine metabolism.
- **Folic acid metabolism:** The active form of the vitamin folic acid is tetrahydrofolate (FH4). Vitamin C is needed for the formation of FH4 (enzyme-folic acid reductase). Further, in association with FH4, ascorbic acid is involved in the maturation of erythrocytes.
- **Peptide hormone synthesis:** Many peptide hormones contain carboxyl terminal amide which is derived from terminal glycine. Hydroxylation of glycine is carried out by peptidyl glycine hydroxylase which requires vitamin C.
- **Synthesis of corticosteroid hormones:** Adrenal gland possesses high levels of ascorbic acid, particularly in periods of stress. It is believed that vitamin C is necessary for the hydroxylation reactions in the synthesis of corticosteroid hormones.

- **Sparing action of other vitamins:** Ascorbic acid is a strong antioxidant. It spares vitamin A, vitamin E and some B-complex vitamins from oxidation.
- **Immunological function:** Vitamin C enhances the synthesis of immunoglobulins (antibodies) and increases the phagocytic action of leucocytes.
- **Preventive action on cataract:** Vitamin C reduces the risk of cataract formation.
- **Preventive action on chronic diseases:** As an antioxidant, vitamin C reduces the risk of cancer, cataract and coronary heart diseases.

16.4.3 DEFICIENCY STATES

The deficiency of ascorbic acid results in scurvy. This disease is characterized by spongy and sore gums, loose teeth, anemia, swollen joints, fragile blood vessels, decreased immunocompetence, delayed wound healing, sluggish hormonal function of adrenal cortex and gonads, haemorrhage, osteoporosis etc. Most of these symptoms are related to impairment in the synthesis of collagen and/or the antioxidant property of vitamin C.

Megadoses of vitamin C and its controversy:

Linus Pauling (1970) first advocated the consumption of mega doses of ascorbic acid (even up to 18 g/day, 300 times the daily requirement) to prevent and cure common cold. He is remembered as a scientist who suggested 'keep vitamin C in gunny bags and eat in grams'. This generated a lot of controversy worldwide. It is now clear that mega dose of vitamin C does not prevent common cold. But the duration of cold and the severity of symptoms are reduced. It is believed that ascorbic acid promotes leukocyte function. Mega doses (1-4 g/day) of vitamin C are still continued in common cold, wound healing, trauma etc. As an antioxidant, ascorbic acid certainly provides some health benefits. Ascorbic acid, as such, has not been found to be toxic. But, dehydroascorbic acid (oxidized form of ascorbic acid) is toxic. Further, oxalate is a major metabolite of vitamin C. Oxalate has been implicated in the formation of kidney stones. However, there are controversial reports on the mega doses of vitamin C leading to urinary stones.

16.4.4 FACTORS INFLUENCINGBIOAVAILABILITY

The absorption and utilization of vitamin C are influenced by food preparation methods, dietary habits and physiological conditions.

Factors reducing bioavailability:

- **Food preparation**: Vitamin C is sensitive to heat, light and oxygen. Extended cooking, such as boiling or microwaving, significantly reduces its content in food.
- **Smoking**: Smokers have lower blood vitamin C levels due to increased oxidative stress which heightens the body demand for the vitamin to combat tobacco related damage.
- **Gastrointestinal conditions**: Disorders like Crohn's disease, celiac disease, or surgeries (e.g., gastric bypass) impair vitamin C absorption.
- **Alcohol consumption**: Chronic alcohol use reduces vitamin C absorption and its effective utilization in the body.

Factors Enhancing Bioavailability:

- **Fresh fruits and vegetables**: Eating raw or lightly cooked produce preserves vitamin C content and maximizes bioavailability.
- **Fortified foods**: Products like fortified juices and cereals provide additional vitamin C, especially beneficial for those with limited access to fresh produce.

To optimize vitamin C intake include a variety of raw or minimally processed fruits and vegetables in the diet.

Gender	Vitamin C mg/day
Men	80
Women	65
Pregnant	+15
Lactating	+50
Infants	20 – 30
Children	30 – 45
Adolescents	50 - 85

Fig. 16.7: RDA

16.5 SUMMARY:

Vitamins B9 (Folate), B12 (Cobalamin), and C (Ascorbic Acid) are essential water soluble vitamins that play significant roles in promoting good health. Vitamin B9 is vital for DNA synthesis and cell division. This is particularly important during periods of rapid growth such as pregnancy. It also helps prevent neural tube defects and supports heart health. Vitamin B12 is essential for the production of red blood cells, nerve function and fatty acid metabolism. A deficiency in B12 can result in pernicious anemia and neurological complications. Vitamin C is widely recognized for its antioxidant properties, immune system enhancement and its crucial role in collagen formation, which is necessary for the health of skin, blood vessels and bones.

These vitamins are obtained from various food sources and their deficiencies can lead to a range of health issues, including anemia, nerve damage and scurvy. Ensuring an adequate intake of Vitamins B9, B12 and C is critical for maintaining metabolic balance, immune health and proper tissue repair.

16.6 TECHNICAL TERMS:

Folate metabolism, Cobalamin absorption, Neurotransmitter synthesis, Erythropoiesis, Collagen synthesis, Antioxidant properties

16.7 SELF ASSESSMENT QUESTIONS:

- What are biochemical functions of B9 and B12 vitamins? Explain in Detail.
- What are the typical symptoms and health complications associated with a deficiency of Vitamin B9? Discus.
- In what ways does Vitamin C contribute to immune function and collagen formation?
- What are the primary food sources of Vitamin B12 andB9 its health issues arise from its deficiency?
- Describe about sources, function and deficiency states of Vitamin C intake?

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Dr. B. Babitha

LESSON-17

MINERALS SOURCES FUNCTIONS (ALSO THEIR ROLE AS COFACTORS IN METABOLISM) DEGICIENCY STATES, FACTORS INFLUENCING BIOAVAILABLITY AND REQUIREMENTS OF CALCIUM, PHOSHORUS, SODIUM, POTASSIUM

17.0. OBJECTIVES:

After going through this lesson, students will understand:

- To understand the concept of minerals in food and their essential role in body functions.
- To identify the primary dietary sources of essential minerals in food and their nutritional requirements.
- To recognize the effect of minerals deficiencies and consequences on health.

STRUCTURE:

17.1 INTRODUCTION

Calcium is a vital and abundant mineral that is essential for numerous physiological functions in the body. It is the most prevalent mineral in the human body, with about 99% of the body's calcium stored in the bones and teeth, contributing to their structure and strength. The remaining 1% of calcium is present in the blood and soft tissues, where it plays critical roles in various bodily processes, including muscle contraction, nerve signaling, blood clotting, and maintaining heart rhythm.

Potassium is an essential mineral and electrolyte that plays a fundamental role in various physiological functions, including maintaining fluid balance, transmitting nerve signals, and supporting muscle contractions. It is one of the most abundant minerals in the human body and is primarily stored within cells. Potassium is naturally present in a wide range of foods, making it easily accessible through a balanced diet.

Dietary potassium is crucial for maintaining normal blood pressure by counteracting the effects of sodium. It helps reduce the risk of hypertension, stroke, and cardiovascular diseases. Additionally, potassium supports kidney function by aiding in the excretion of excess sodium and fluid, which is essential for maintaining overall homeostasis.

Phosphorus is an essential mineral that plays a crucial role in various bodily functions, including bone health, energy production, and nerve function. It is the second most abundant mineral in the human body, with approximately 85% of it stored in bones and teeth.

17. 2 CALICIUM

17.2.1 SOURCES OF CALCIUM

Calcium can be sourced through both food and supplements. The best sources of calcium in the diet include:

1) **Dairy Products:** Milk, cheese, and yogurt are among the richest natural sources of calcium.
2) **Leafy Green Vegetables:** Greens like kale, bok choy, collard greens, and broccoli provide non-dairy sources of calcium.
3) **Fortified Foods:** Many products like fortified plant-based milk (soy, almond, oat milk), breakfast cereals, and juices are enriched with calcium.
4) **Fish with Edible Bones:** Fish like salmon, sardines, and mackerel are rich in calcium because of their soft, edible bones.
5) **Tofu and Soy Products:** Tofu, tempeh, and other soy-based products are excellent sources, especially when processed with calcium salts.
6) **Nuts and Seeds:** Almonds, sesame seeds, chia seeds, and flaxseeds are good sources of calcium.
7) **Legumes and Pulses:** Beans, chickpeas, and lentils contain moderate amounts of calcium.
8) **Other Sources:** Figs, seaweed, and fortified foods (like certain kinds of bread and pasta) can also contribute to calcium intake.

17.2.2 FUNCTIONS OF CALCIUM

Calcium is involved in many physiological functions, some of which are essential for life:

1) **Bone and Teeth Health:**

   Calcium is the primary mineral component of bones and teeth, contributing to their strength, rigidity, and structural integrity.

   Bone remodeling, a continuous process where old bone is replaced by new bone, requires adequate calcium intake for bone density and preventing diseases like osteoporosis.

2) **Muscle Function:**

Calcium is involved in muscle contraction. When a nerve stimulates a muscle, calcium ions are released inside the muscle cells, allowing the interaction of actin and myosin (muscle proteins) for contraction. A lack of calcium can result in muscle cramps or spasms.

3) **Nerve Transmission:**

Calcium ions play an essential role in neurotransmitter release at synaptic junctions. It helps transmit nerve impulses across the synapse, enabling communication between nerve cells, muscles, and organs.

4) **Blood Clotting:**

Calcium is a key component of the blood clotting cascade. It activates various proteins in the clotting process, ensuring proper healing after injury.

5) **Cardiac Function:**

Calcium helps regulate the heart's rhythm and is involved in the contraction of the heart muscle, ensuring normal cardiac function. Imbalance in calcium levels can lead to arrhythmias (irregular heartbeats).

6) **Hormonal Secretion and Enzyme Activation:**

Calcium is involved in the secretion of hormones, including insulin, and aids in activating certain enzymes that control various metabolic processes.

17.2.3 DEFICIENCY STATES OF CALCIUM

Calcium deficiency can lead to several health problems, many of which affect the bones and muscles. Common signs and conditions associated with calcium deficiency include:

1) **Osteoporosis:**

A condition characterized by weakened bones that are more susceptible to fractures. Osteoporosis is often a result of long-term calcium deficiency, especially in older adults.

2) **Rickets (in children):**

A skeletal disorder that causes bones to become soft and weak, leading to deformities. Rickets is often caused by inadequate calcium and vitamin D during childhood.

3) **Hypocalcaemia:**

Low calcium levels in the blood can lead to symptoms such as muscle cramps, tingling in the fingers and toes, and fatigue. In severe cases, hypocalcaemia can result in cardiac arrhythmias, seizures, or even death.

4) **Dental Problems:**

Insufficient calcium can contribute to weak teeth, increased risk of cavities, gum disease, and early tooth loss.

5) Tetany:

A condition marked by involuntary muscle contractions and spasms. It occurs due to extremely low calcium levels.

Fig. 17.1

17.2.4 FACTORS INFLUENCING BIOAVAILABILITY OF CALCIUM

Bioavailability refers to the degree to which calcium from food or supplements is absorbed and utilized by the body. Several factors affect how efficiently calcium is absorbed

- Vitamin D is essential for calcium absorption. It enhances the efficiency of calcium uptake in the intestines. A deficiency in vitamin D leads to reduced calcium absorption, increasing the risk of bone diseases such as rickets and osteomalacia.
- **Age and Life Stage:**

  Calcium absorption rates are highest during periods of growth (childhood and adolescence). In adults, the absorption rate declines with age, which is why older adults may require more calcium to maintain bone health.

  Pregnant and lactating women also require higher amounts of calcium to support fetal development and breastfeeding.
- **Phytates and Oxalates:**

  Phytates (found in whole grains and legumes) and oxalates (found in spinach, beet greens, and some nuts) can bind calcium, reducing its bioavailability. However, these compounds don't entirely block calcium absorption, and eating a varied diet can mitigate their effects.
- **Excessive Protein and Sodium:**

  High protein intake and excessive sodium can increase calcium excretion through urine, potentially leading to a decrease in calcium levels in the body. This is especially true in individuals with a high-protein diet or excessive salt intake.
- **Magnesium and Zinc:**

  High levels of magnesium or zinc may compete with calcium for absorption in the intestine, potentially reducing calcium absorption if consumed in large amounts.

- **Hormonal Influence:**

  Parathyroid hormone (PTH) and calcitonin regulate calcium levels in the body. PTH increases calcium levels in the blood when it is low, while calcitonin helps to lower calcium levels when they are too high.

17.2.5 REQUIREMENTS OF CALCIUM

The recommended dietary intake of calcium varies by age, sex, and life stage. These recommendations ensure proper bone health, nerve function, and muscle contraction:

- Infants (0-6 months): 200 mg/day
- Children (1-3 years): 700 mg/day
- Children (4-8 years): 1,000 mg/day
- Adolescents (9-18 years): 1,300 mg/day
- Adults (19-50 years): 1,000 mg/day
- Women (51+ years) and men (70+ years): 1,200 mg/day
- Pregnant and lactating women (under 19 years): 1,300 mg/day
- Pregnant and lactating women (19-50 years): 1,000 mg/day

It is crucial to meet calcium requirements through dietary sources, but supplements can be used if needed. It's important not to exceed the recommended intake as excessive calcium can lead to kidney stones or impaired absorption of other minerals.

17.3 PHOSPHORUS

17.3.1 SOURCES OF PHOSPHORUS

Phosphorus can be obtained from various dietary sources, including:

- Meat and poultry: Beef, chicken, turkey, and fish
- Dairy products: Milk, cheese, yogurt, and butter
- Legumes: Lentils, chickpeas, black beans, and kidney beans
- Nuts and seeds: Almonds, sunflower seeds, pumpkin seeds, and sesame seeds
- Whole grains: Brown rice, quinoa, whole wheat bread, and whole grain cereals

17.3.2 FUNCTIONS OF PHOSPHORUS

- Phosphorus performs several vital biological functions, including:
- Bone health: Phosphorus is essential for building and maintaining strong bones and teeth
- Energy production: Phosphorus is necessary for the production of ATP (adenosine triphosphate), the energy currency of the body
- Nerve function: Phosphorus is involved in the transmission of nerve impulses.

- Protein synthesis: Phosphorus is necessary for the synthesis of proteins, which are essential for various bodily functions
- Cell membrane structure: Phosphorus is a component of phospholipids, which are essential for the structure and function of cell membranes.

17.3.3 DEFICIENCY STATES OF PHOSPHORUS

Hypophosphatemia

Causes of Phosphorus Deficiency

Phosphorus deficiency (hypophosphatemia) is uncommon but can occur due to:

1) Poor Dietary Intake:

Malnutrition or prolonged fasting.Inadequate phosphorus intake from food sources.

2) Medical Conditions:

Chronic alcoholism (affects absorption and increases excretion).Diabetes (uncontrolled diabetes can lead to phosphorus loss in urine).Hyperparathyroidism (overactive parathyroid glands increase phosphorus excretion).Vitamin D deficiency (reduces phosphorus absorption).Kidney disorders (may lead to excess phosphorus loss).

3) Medications:

Long-term use of antacids containing aluminium or calcium.Diuretics and certain medications for diabetes.

Symptoms of Phosphorus Deficiency

Mild deficiency may not show symptoms, but severe cases can cause:

1. Musculoskeletal Symptoms

Bone pain and weakness (due to poor bone mineralization).Osteomalacia (soft bones) in adults, rickets in children.Muscle weakness and fatigue.

Fig. 17.2

2. Neurological Symptoms

Confusion, irritability, and memory issues.Numbness or tingling sensations.Seizures (in extreme cases).

3. Cardiovascular and Respiratory Symptoms

Irregular heartbeat (arrhythmia).Breathing difficulty (due to weak respiratory muscles).

Treatment

- Dietary adjustments: Increase phosphorus-rich foods such as dairy products, meat, fish, eggs, nuts, and whole grains.
- Phosphorus supplements (if severe deficiency is present).
- Treat underlying medical conditions (e.g., vitamin D supplementation for better phosphorus absorption).

Phosphorus deficiency is rare but can have serious consequences if left untreated. Maintaining a healthy diet and addressing underlying health conditions are key to preventing hypophosphatemia.

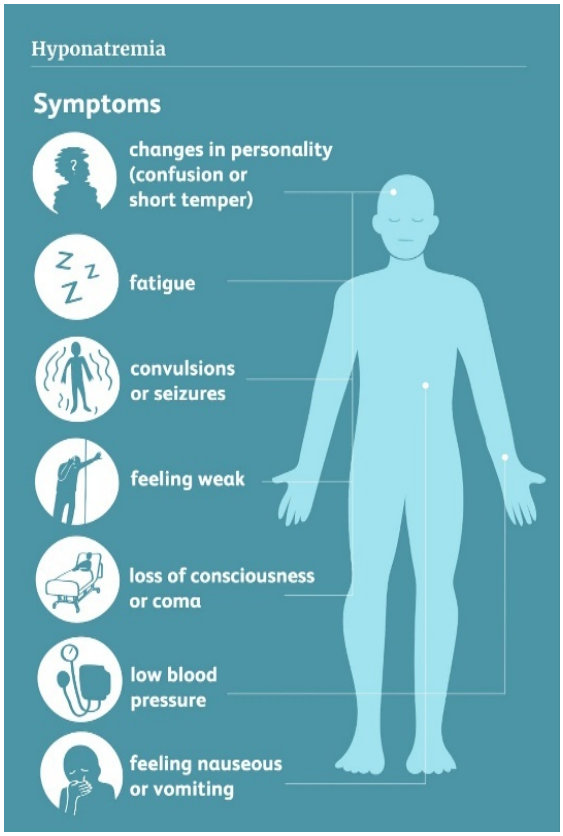

Fig. 17.3

17.3.4 FACTORS INFLUENCING BIOAVAILABILITY OF PHOSPHORUS

The bioavailability of phosphorus refers to the amount of phosphorus that is absorbed and utilized by the body. Several factors can influence phosphorus bioavailability, including:

1) Vitamin D: Vitamin D is essential for phosphorus absorption
2) Calcium: High levels of calcium can inhibit phosphorus absorption
3) Oxalic acid: High levels of oxalic acid in foods like spinach and beets can inhibit phosphorus absorption

4) Phytic acid: Phytic acid in foods like beans and grains can also inhibit phosphorus absorption
5) Age: Phosphorus absorption decreases with age
6) Kidney function: Impaired kidney function can lead to phosphorus deficiency

17.3.5 REQUIREMENTS OF PHOSPHORUS

Phosphorus is an essential mineral needed for bone health, energy production, and cellular functions. The requirement varies with age due to differences in growth rates, metabolic needs, and physiological changes.

1) Infants (0–12 Months)

0–6 months: 100 mg/day

7–12 months: 275 mg/day

2) Children (1–8 Years)

1–3 years: 460 mg/day

4–8 years: 500 mg/day

3) Adolescents (9–18 Years)

Both boys and girls: 1,250 mg/day

4) Adults (19+ Years)

700 mg/day

5) Pregnant & Lactating Women

≤18 years: 1,250 mg/day

≥19 years: 700 mg/day

17.4 SODIUM

17.4.1 SOURCES OF SODIUM

- The common salt (NaCl) used in the cooking medium is the major source of sodium
- Processed and Packaged Foods: Many foods like canned soups, fast food, snacks, and ready-to-eat meals are high in sodium.
- Natural Sources: Sodium is found in smaller amounts in meat, poultry, seafood, eggs, and dairy.
- Vegetables and Fruits: Some vegetables, such as celery, spinach, and beets, contain small amounts of sodium.
- Electrolyte Drinks: Sports drinks often contain added sodium to help replenish electrolytes after exercise
- The good sources of sodium include bread, whole grains, leafy vegetables, nuts, eggs and milk

17.4.2 FUNCTIONS OF SODIUM

Sodium plays several crucial biological roles in the human body. Here are its main functions:

1) **Regulation of Fluid Balance:** Sodium helps maintain the balance of fluids in and around cells by controlling osmotic pressure, which is essential for proper cell function.
2) **Nerve Impulse Transmission:** It is vital for generating and transmitting electrical signals in nerves and muscles. Sodium ions move across nerve cell membranes, creating action potentials that enable nerve impulses.
3) **Muscle Contraction:** Sodium is necessary for muscle contraction, including the contraction of heart muscles, by facilitating the exchange of sodium and potassium ions in muscle cells.
4) **Acid-Base Balance**: It helps regulate the body's pH by influencing acid-base balance, which is crucial for metabolic processes.
5) **Nutrient Absorption:** Sodium aids in the absorption of certain nutrients in the intestines, such as glucose and amino acids, through sodium-coupled transport mechanisms.
6) **Blood Pressure Regulation:** Sodium affects blood volume and pressure by influencing water retention in the kidneys, which plays a role in maintaining proper blood pressure levels.
7) **Enzyme Activation:** It serves as a cofactor for some enzymes, enhancing their activity in various metabolic pathways.

17.4.3 DEFICIENCY STATES OF SODIUM

1) **Hyponatremia:**

   This is a condition in which the serum sodium level falls below the normal. Hypernatremia may occur due to diarrhoea, vomiting, chronic renal diseases, adrenocortical insufficiency (Addison's disease). Administration of salt free fluids to patients may also cause hyponatremia. This is due to over hydration. Decreased serum sodium concentration is also observed in edema which occurs in cirrhosis or congestive heart failure. The manifestations of hyponatremia include reduced blood pressure and circulatory failure.

2) **Hypernatremia:**

   This condition is characterized by an elevation in the serum sodium level. The symptoms include increase in blood volume and blood pressure. It may occur due to hyperactivity of adrenal cortex (Cushing's syndrome), prolonged administration. of cortisone, ACTH and/or sex hormones. Loss of water from the body causing dehydration, as it occurs in diabetes insipidus, results in hypernatremia. Rapid administration of sodium salts also increases serum sodium concentration. It may be noted that in pregnancy, steroid and placental hormones cause sodium and water retention in the body, leading to edema. In edema, along with water, sodium concentration in the body is also elevated. Administration of diuretic drugs increases the urinary output of water along with sodium. In the patients of hypertension and congestive cardiac failure salt (Na) restriction is advocated.

17.4.4 FACTORS INFLUENCING BIOAVAILABILITY OF SODIUM

Factors influencing the bioavailability

1) Dietary Composition:

Presence of other nutrients: High intake of potassium, calcium, and magnesium can affect sodium absorption and balance.

2) Fibre content:

Dietary fibre may bind to sodium, reducing its absorption.

3) Form of Sodium:

Sodium in different chemical forms (e.g., sodium chloride, sodium bicarbonate) may have varying absorption rates.

4) Gastrointestinal Health:

Conditions like Crohn's disease, celiac disease, or irritable bowel syndrome can impair sodium absorption.

The integrity of the intestinal lining affects how well sodium is absorbed.

5) Fluid Intake:

Adequate water consumption enhances sodium absorption by maintaining proper osmotic balance.

6) Hormonal Regulation:

Aldosterone, a hormone, plays a critical role in sodium reabsorption in the kidneys, influencing overall sodium balance in the body.

7) Health Conditions:

Conditions like heart failure, liver disease, and adrenal gland disorders can influence how the body handles sodium.

8) Physical Activity:

Increased sweating during exercise leads to sodium loss, which may alter its bioavailability and the body's requirements

17.4.5 REQUIREMENTS OF SODIUM

Recommended Daily Intake:

Children: The recommended intake varies by age:

- 1-3 years: 1,000 mg/day
- 4-8 years: 1,200 mg/day
- 9-13 years: 1,500 mg/day
- 14-18 years: 1,500–1,800 mg/day

- Adults: The general recommendation is to consume less than 2,300 milligrams (mg) of sodium per day, which is about 1 teaspoon of salt.
- Ideal Limit: For most adults, an ideal limit is around 1,500 mg per day, especially for those with hypertension, diabetes, or cardiovascular diseases.

17.5 POTASSIUM

17.5.1 SOURCES OF POTASSIUM

Potassium is an essential mineral found in a wide range of foods, particularly in fruits, vegetables, dairy products, legumes, nuts, seeds, and animal-based foods. A diet rich in potassium helps regulate fluid balance, nerve function, and muscle contractions while reducing the risk of hypertension and cardiovascular diseases. Since the human body does not produce potassium, it is crucial to obtain it from dietary sources.

1) **Fruits**

   Bananas, Oranges and Orange Juice, Mangoes, Melons (Cantaloupe, Honeydew, Watermelon),Avocados,Papayas and Kiwi

2) **Vegetables**

   Spinach, Potatoes (with skin), Tomatoes and Tomato Products, Sweet Potatoes, Mushrooms, Broccoli, and Beet Greens

3) **Legumes and Pulses**

   Lentils, Kidney Beans, Black Beans, and Chickpeas, Soybeans and Edamame

4) **Dairy Products**

   Milk, Yogurt, Cheese

5) **Nuts and Seeds**

   Almonds and Cashews, Sunflower Seeds and Flaxseeds

6) **Meat and Seafood**

   Salmon and Tuna, Chicken and Beef, Pork

17.5.2 FUNCTIONS OF POTASSIUM

Potassium is an essential mineral and electrolyte that plays a vital role in maintaining overall health. It is involved in various physiological processes that support normal body functions. The key functions of potassium include:

1) **Regulating Fluid and Electrolyte Balance**

   Potassium helps maintain the body's fluid balance by working alongside sodium. It ensures that cells retain the necessary amount of water, preventing dehydration and maintaining proper cellular function.

2) Supporting Nerve Function

As an electrolyte, potassium plays a crucial role in transmitting nerve impulses throughout the body. It helps nerves communicate with muscles, allowing for proper movement and reflexes.

3) Aiding Muscle Contraction

Potassium is essential for muscle function, including the contraction and relaxation of muscles. It helps prevent muscle cramps, weakness, and fatigue, ensuring smooth voluntary and involuntary muscle movements.

4) Maintaining Heart Health

Potassium supports heart function by regulating heartbeat and preventing irregular heart rhythms (arrhythmias). It counteracts the effects of sodium, helping to lower blood pressure and reduce the risk of cardiovascular diseases.

5) Controlling Blood Pressure

Potassium helps lower high blood pressure by balancing sodium levels and relaxing blood vessel walls. This reduces strain on the cardiovascular system, decreasing the risk of hypertension, stroke, and heart disease

6) Supporting Kidney Function

The kidneys rely on potassium to regulate fluid balance and excrete excess sodium through urine. Adequate potassium intake helps prevent kidney stones and supports overall renal health.

7) Enhancing Metabolism and Energy Production

Potassium is necessary for the activation of enzymes involved in metabolism. It supports the breakdown of carbohydrates and proteins to produce energy for the body.

8) Promoting Bone Health

Potassium helps reduce calcium loss from bones, supporting bone density and reducing the risk of osteoporosis. It works alongside calcium and magnesium to strengthen the skeletal system.

9) Reducing the Risk of Stroke

Studies have shown that a diet rich in potassium can lower the risk of stroke by reducing blood pressure and improving overall cardiovascular function.

10) Supporting Digestive Health

Potassium plays a role in muscle contractions in the digestive tract, aiding smooth bowel movements and preventing constipation.

17.5.3 DEFICIENCY STATES OF POTASSIUM

Hypokalaemia

Potassium deficiency, known as hypokalaemia, occurs when potassium levels in the blood drop below the normal range of 3.5–5.0 mmol/L. Since potassium is essential for maintaining nerve function, muscle contractions, and heart rhythm, its deficiency can lead to severe health complications.

Causes of Potassium Deficiency

Several factors contribute to potassium deficiency, including dietary habits, medical conditions, and lifestyle factors.

1) **Inadequate Dietary Intake**

   A diet low in potassium-rich foods, such as fruits, vegetables, dairy, and legumes, can lead to insufficient potassium levels.

2) **Excessive Potassium Loss**

   Potassium is lost through urine, sweat, and the digestive system. Certain conditions can cause excessive potassium loss like Prolonged Vomiting and Diarrhea, Excessive Sweating, Chronic Kidney Disease, Hormonal Imbalances

3) **Medication-Induced Deficiency**

   Certain medications contribute to potassium loss, including: Diuretics (Water Pills), Laxatives, Corticosteroids, Some Antibiotics

4) **High Alcohol or Caffeine Consumption**

   Excessive alcohol intake leads to dehydration and increased potassium excretion.

   High caffeine intake may act as a mild diuretic, promoting potassium loss through urine.

5) **Metabolic and Endocrine Disorders**

   Diabetic Ketoacidosis (DKA) – A complication of diabetes that causes excessive potassium loss.

   Cushing's syndrome – High cortisol levels increase potassium excretion.

   Magnesium Deficiency – Low magnesium levels can disrupt potassium balance.

Symptoms of Potassium Deficiency:

Potassium deficiency symptoms vary based on severity. Mild cases may be asymptomatic, but moderate to severe deficiency can cause:

1) **Muscle-Related Symptoms**

   - Muscle Weakness and Fatigue – Potassium is crucial for muscle contractions, and low levels cause weakness.
   - Muscle Cramps and Spasms – Potassium imbalance can lead to involuntary muscle contractions.
   - Paralysis (in severe cases) – Extreme hypokalaemia can lead to muscle paralysis, affecting mobility.

2) **Nervous System Effects**

   - Tingling and Numbness (Paraesthesia) – Low potassium disrupts nerve signals, causing numbness or tingling sensations.
   - Mental Fatigue and Confusion – Potassium plays a role in cognitive function, and deficiency can cause mental sluggishness.

3) Heart and Circulatory Effects

- Irregular Heartbeat (Arrhythmia) – Potassium regulates heart function, and low levels can cause palpitations or serious heart conditions.
- High Blood Pressure (Hypertension) – Potassium helps balance sodium; deficiency can contribute to high blood pressure.
- Increased Risk of Stroke – Due to hypertension and cardiovascular strain.

4) Digestive Issues

- Constipation and Bloating – Potassium is essential for smooth muscle contractions in the digestive system.
- Slow Digestion and Poor Absorption – Low potassium affects gut motility.

5) Kidney and Urinary Symptoms

- Frequent Urination and Increased Thirst – Due to potassium's role in kidney function and fluid balance.
- Higher Risk of Kidney Stones – Chronic deficiency may contribute to kidney stone formation.

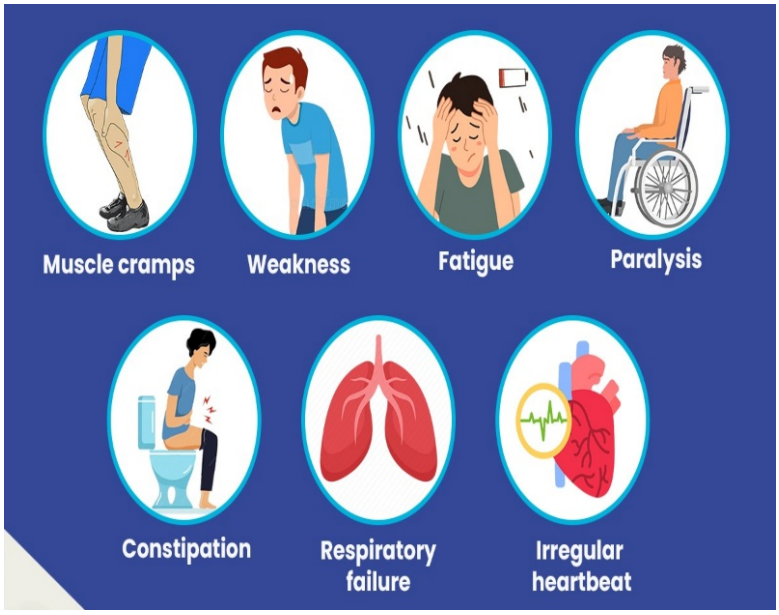

Fig. 17.4

Prevention and Treatment:

- Eating a potassium-rich diet is the best way to prevent and correct deficiency. Foods high in potassium include: Bananas, oranges, avocados, melons, Spinach, potatoes, tomatoes, Beans, lentils, almonds, Milk, yogurt, fish, chicken.
- In cases of moderate to severe deficiency, oral potassium supplements may be prescribed.
- Intravenous (IV) potassium may be needed for critically low levels.

- Treating chronic kidney disease, diabetes, or gastrointestinal disorders can help prevent potassium loss.
- Reducing diuretic or laxative overuse if medically appropriate.
- Limiting Alcohol and Caffeine Intake – Helps reduce excessive potassium loss.
- Maintaining Hydration – Ensures proper electrolyte balance.

17.5.4 FACTORS INFLUENCING BIOAVAILABILITY OF POTASSIUM

Potassium bioavailability is influenced by several factors, including dietary sources, food processing, interactions with other nutrients, and physiological conditions.

1) Dietary Sources

- Potassium from plant-based foods (fruits, vegetables, legumes) is generally more bioavailable.
- Animal-based sources (meat, dairy) also provide potassium but may have varying absorption rates due to differences in food matrices.
- Potassium supplements (potassium chloride, potassium citrate) can enhance bioavailability, but their absorption varies.

2) Food Processing and Cooking

- Boiling can lead to potassium loss as it leaches into water.
- Processed foods may contain potassium additives (e.g., potassium phosphate), which have different absorption rates compared to natural potassium.

3) Nutrient Interactions

- High sodium intake can reduce potassium retention by increasing its excretion through urine.
- High fibre diets (particularly insoluble fibre) may slightly reduce potassium absorption by trapping it in plant cell walls.
- Magnesium deficiency can negatively impact potassium retention, as these minerals work together in muscle and nerve function.

4) Physiological and Health Conditions

- Kidney function: Healthy kidneys regulate potassium balance, but kidney disease can lead to potassium retention.
- Acid-base balance: Metabolic acidosis increases potassium excretion, whereas alkalosis can lead to retention.
- Hormonal influences: Aldosterone promotes potassium excretion; insulin helps drive potassium into cells.

5) Age and Absorptive Efficiency

- Infants and young children absorb potassium efficiently.
- Elderly individuals may experience altered potassium homeostasis due to declining kidney function.

17.5.5 REQUIREMENTS OF POTASSIUM

The daily potassium requirement varies based on age, sex, physiological conditions, and specific health needs. The Recommended Dietary Allowance (RDA) or Adequate Intake (AI) for potassium is generally expressed in milligrams (mg) per day.

According to the National Academies of Sciences, Engineering, and Medicine (NASEM, 2019) and WHO guidelines, the recommended potassium intake is:

- Infants require around 400–700 mg/day, with needs increasing as they grow.
- Children between 1–8 years need 2,000–2,300 mg/day
- Adolescent boys require 2,500–3,000 mg/day
- Adolescent girls need about 2,300 mg/day
- For adults, the recommended intake is 3,400 mg/day for males and 2,600 mg/day for females. Pregnant women are advised to consume 2,900 mg/day
- While lactating women need approximately 2,800 mg/day.

17.6 SUMMARY

Minerals play a crucial role in maintaining overall health, with key minerals including calcium, potassium, phosphorus, and sodium. Calcium is essential for bone and teeth health, muscle function, nerve signaling, and blood clotting, with rich sources including dairy, leafy greens, fortified foods, and nuts. Potassium regulates fluid balance, supports nerve transmission, and helps maintain normal blood pressure, found abundantly in fruits, vegetables, dairy, and legumes. Phosphorus is vital for bone structure, energy production, and cellular functions, sourced from dairy, meat, legumes, and whole grains. Sodium is critical for fluid balance, nerve function, and muscle contraction, mainly obtained from table salt, processed foods, and natural sources like dairy and vegetables. Deficiencies in these minerals can lead to conditions such as osteoporosis, muscle cramps, nerve dysfunction, and cardiovascular issues, while excessive intake may pose health risks such as hypertension or kidney stones. The bioavailability of these minerals depends on factors like vitamin D levels, dietary composition, and age. Maintaining a balanced diet with adequate mineral intake is essential for optimal health and physiological functions.

17.6 TECHNICAL TERMS

Osteoporosis, osteoarthritis, hypokalaemia

17.7 SELF ASSESSMENT QUESTIONS

1) What is the difference between macro minerals and trace minerals? Give examples of each.
2) Why are minerals important for the human body? Name at least three functions they support.
3) How does a deficiency in iron affect the body?
4) How do calcium and vitamin D work together in bone health?

17.8 REFERENCE BOOKS:

1) Ross, A. C., Caballero, B., Cousins, R. J., Tucker, K. L., & Ziegler, T. R. (2020). Modern Nutrition in Health and Disease (12th ed.). Wolters Kluwer.
2) Mahan, L. K., Raymond, J. L., & Escott-Stump, S. (2020). *Krause's Food & the Nutrition Care Process* (15th ed.). Elsevier.

Dr. Ch. Manjula

LESSON-18

IRON, IODINE, ZINC

18.0. OBJECTIVES:

After going through this lesson, students will understand:

- To understand minerals in food and their essential functions in the human body this objective aims to provide knowledge about the roles of iron, iodine, and zinc as vital micronutrients.
- It includes understanding how these minerals contribute to bodily functions such as iron's role in oxygen transport and energy production, iodine's importance in thyroid hormone synthesis, and zinc's involvement in immune function and wound healing.
- A clear understanding of these roles is crucial for promoting general health and preventing deficiency-related disorders.
- To identify food sources rich in iron, iodine, and zinc for a balanced diet this involves recognizing both plant-based and animal-based dietary sources of these minerals.

STRUCTURE:

18.1 INTRODUCTION

Iodine is an essential trace element vital for human health, primarily known for its role in thyroid hormone production. It is a non-metallic chemical element with the symbol I and atomic number 53, belonging to the halogen group on the periodic table. Iodine naturally occurs in the earth's crust, seawater, and certain foods.

The human body requires iodine to produce thyroxin (T4) and triiodothyronine (T3)hormones that regulate metabolism, growth, development, and energy production. Without adequate iodine, the thyroid gland cannot function properly, leading to health issues such as goitre and hypothyroidism.

Iodine deficiency remains a major public health concern in many regions, particularly in areas were soil lacks iodine. To prevent deficiency, many countries fortify table salt with iodine, a simple and effective public health intervention.

Beyond human health, iodine is used in various industries, including medical imaging, antiseptics, and chemical synthesis. Its unique properties, such as forming purple vapours when heated, make it both scientifically and industrially significant.

Zinc is an essential trace mineral that plays a crucial role in various biological functions, including immune support, enzyme activation, wound healing, DNA synthesis, and cell growth. It is required for proper growth, development, and maintenance of the body. Since the body does not store zinc, it must be obtained regularly through diet or supplements.

Zinc is naturally found in foods such as meat, seafood, dairy, nuts, seeds, and whole grains. It is also available in fortified foods and supplements.

18.2 IRON

18.2.1 SOURCES OF IRON

Iron is an essential mineral needed for producing haemoglobin and maintaining overall health. There are two types of dietary iron:

1. Heme Iron (Easily Absorbed)

- Found in animal-based foods:
- Red meat (beef, lamb, pork)
- Poultry (chicken, turkey)
- Seafood (oysters, clams, mussels, tuna, salmon)
- Organ meats (liver, kidney, heart)

2. Non-Heme Iron (Plant-Based, Less Easily Absorbed)

- Found in plant-based and fortified foods:
- Legumes (lentils, chickpeas, beans)
- Dark leafy greens (spinach, kale, Swiss chard)
- Tofu & soy products
- Whole grains (quinoa, fortified cereals, oatmeal)
- Nuts & seeds (pumpkin seeds, sesame seeds, cashews)
- Dried fruits (raisins, apricots, prunes)

18.2.2 FUNCTIONS OF IRON

- Iron is an essential element for the growth and development.
- Transport and Storage of Oxygen

- Each gram of haemoglobin contains about 3.34 mg of iron. Iron within the metalloproteinase haemoglobin and myoglobin can bind to oxygen molecules and transport them through the blood or store them within muscles. The iron in a haeme group itself is bound to the protein chain.
- Myoglobin is found only in muscle, where it serves as a reservoir of oxygen. The oxygen is needed to combine with nutrient molecules to release the energy to power muscle contraction.
- Co-factor of Enzymes and other Proteins
- The iron containing haeme group is also a part of several proteins involved in the release of energy during the oxidation of nutrients and the trapping of that energy within adenosine triphosphate (ATP). Also iron on its own is a co-factor bound to several non-haeme enzymes required for the proper functioning of cells. Iron along with copper is a metal co-factor for cytochrome oxidase. Some of the other processes that depend on the activities of iron containing enzymes are the following: Conversion of ß-carotene to the active form of vitamin A.
- Synthesis of purines, which form an integral part of deoxyribonucleic acid and ribonucleic acid.
- Synthesis of carnitine, a vitamin like substance needed for the transport of fatty acids
- Synthesis of collagen, one of the proteins of the body
- Detoxification of drugs and other toxic compounds in the liver and intestine.
- Synthesis of the neurotransmitter dopamine, serotonin and norepinephrine.
- Essential for catecholamine metabolism.
- Formation of Red Blood Cells

Bone marrow produces immature cells known as erythroblasts. As erythroblasts mature in the bone marrow, they synthesise the iron containing haeme group in a process requiring the help of vitamin B, and copper. The haeme group becomes bound to globin molecules, also synthesised by the erythroblasts, to form completed haemoglobin molecules. The haemoglobin containing cells are known as reticulocytes and are released from the bone marrow into the blood. Within 24 to 36 hours after their release the nuclei of the reticulocytes disintegrate and the cells become mature erythrocytes ready to begin the transport of oxygen to the tissues and that of carbon dioxide away from the tissues.

Red blood cell has no nucleus, hence it cannot produce the enzyme and proteins necessary for long-term survival. The life of RBC is 120 days. When red blood cells die, they are removed from the blood by cells of the liver, bone marrow and spleen which are part of the reticuloendothelial system. In the spleen, the iron and amino acids derived from haemoglobin are salvaged and recycled. The iron is stored as haemosiderin and ferritin in the liver and spleen or is returned to the bone marrow for incorporation into new haemoglobin molecules. In this way, iron is effectively conserved and reused. The amino acids are released

to the blood, where they are available to all cells for the synthesis of new proteins or for the oxidative release of energy. The remaining portion of haemoglobin molecule, its haeme group are converted to bilirubin, which is transported to the liver and then excreted in bile.

18.2.3 DEFICIENCY STATES OF IRON

Iron deficiency can manifest in several stages, progressing from mild depletion to severe anaemia.

1. Iron Depletion (Pre-latent Iron Deficiency)

Body's iron stores (ferritin) are low, but haemoglobin levels remain normal.

No significant symptoms, though fatigue and reduced exercise tolerance may begin.

2. Iron-deficient Erythropoiesis (Latent Iron Deficiency)

Iron stores are nearly exhausted, and serum iron levels drop.

Haemoglobin production starts to decline, leading to mild symptoms like weakness, headaches, and reduced cognitive function.

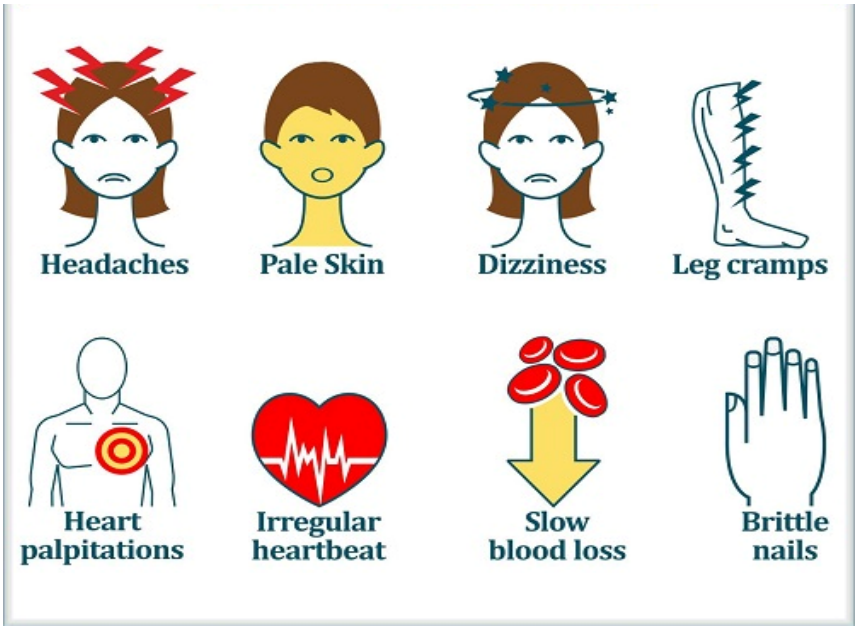

Fig. 18.1

3. Iron Deficiency Anaemia (IDA)

Haemoglobin and red blood cell production are significantly impaired.

Symptoms include:

- Fatigue and weakness
- Pale skin and brittle nails
- Shortness of breath
- Dizziness and headaches
- Cravings for non-nutritive substances (pica), like ice, dirt, or clay

If untreated, iron deficiency can lead to severe complications, including heart problems and developmental delays in children. Treatment typically involves dietary changes, iron supplements, or addressing underlying causes like blood loss.

18.2.4 FACTORS INFLUENCING BIOAVAILABILITY OF IRON

The bioavailability of iron refers to the proportion of dietary iron that is absorbed and utilized by the body. Several factors influence this process, including dietary composition, physiological conditions, and interactions with other nutrients.

1. Dietary Factors

Heme iron (from animal sources like meat, poultry, and fish) is more bioavailable (15–35%) than non-heme iron (from plant sources, 2–20%).Non-heme iron requires conversion from ferric (Fe^{3+}) to ferrous (Fe^{2+}) form for better absorption.Vitamin C (Ascorbic Acid): Strongly enhances non-heme iron absorption by reducing Fe^{3+} to Fe^{2+}. Found in citrus fruits, tomatoes, and bell peppers.Meat, Fish, and Poultry (MFP Factor): Animal proteins enhance non-heme iron absorption.

Inhibitors of Iron Absorption

Phytates (in grains, legumes, nuts, and seeds): Bind iron and reduce absorption. Soaking, fermenting, or sprouting foods can reduce phytate levels.Polyphenols (in tea, coffee, red wine, and some vegetables): Form complexes with iron, inhibiting absorption.Calcium (in dairy products and supplements): Competes with iron for absorption sites.Oxalates (in spinach, rhubarb, and some nuts): Form insoluble complexes with iron, reducing availability.

2. Physiological Factors

- Iron Status of the Individual:People with low iron stores absorb more iron, while those with sufficient stores absorb less.
- Gastrointestinal Health:Conditions like celiac disease, inflammatory bowel disease, and gastric surgery reduce iron absorption.
- Age and Life Stage:Infants, children, and pregnant women have higher iron needs and absorb iron more efficiently.
- Menstruation and Blood Loss:Women with heavy periods or frequent blood donation need more iron.

3. Genetic and Metabolic Factors

- Hepcidin Regulation:Hepcidin, a liver hormone, controls iron absorption.High levels (due to inflammation or infection) decrease absorption.
- Genetic Disorders:Hemochromatosis leads to excessive iron absorption.Iron-refractory iron deficiency anaemia (IRIDA) impairs iron absorption.

4. Interaction with Other Nutrients

- Zinc and Copper: Compete with iron for absorption.
- Folic Acid and Vitamin B12: Support red blood cell production, influencing iron utilization.

18.2.5 REQUIREMENTS OF IRON

Iron requirements vary based on age, sex, and physiological conditions such as pregnancy or menstruation. The recommended dietary allowance (RDA) for iron is measured in milligrams (mg) per day.

1. Infants and Children

- 0–6 months: 0.27 mg (Adequate Intake, AI from breast milk)
- 7–12 months: 11 mg
- 1–3 years: 7 mg
- 4–8 years: 10 mg

2. Adolescents and Adults

- Boys 9–13 years: 8 mg
- Boys 14–18 years: 11 mg
- Girls 9–13 years: 8 mg
- Girls 14–18 years: 15 mg (higher due to menstruation)
- Men 19+ years: 8 mg
- Women 19–50 years: 18 mg (higher due to menstrual blood loss)
- Women 51+ years (postmenopausal): 8 mg

3. Pregnancy and Lactation

- Pregnant women: 27 mg (due to increased blood volume and fetal development)
- Lactating women (0–6 months): 9 mg
- Lactating women (7–12 months): 9 mg

18.3 IODINE

18.3.1 SOURCES OF IODINE

Iodine is naturally found in certain foods and is also added to others to prevent deficiency. The primary sources of iodine include:

1. Natural Food Sources

Fish (cod, tuna, salmon), shellfish (shrimp, crab, oysters), and seaweed (kelp, nori, wakame), Milk, yogurt, and cheese, Eggs, potatoes, prunes, and bananas

2. Fortified and Processed Sources

- Iodized Salt: A major source of iodine in many countries, where iodine is added to table salt to prevent deficiency.
- Processed Foods: Some bakery products, cereals, and bread may contain iodine if fortified.

3. Supplements

- Iodine Supplements: Often recommended for individuals at risk of deficiency, such as pregnant women or those living in iodine-deficient regions.
- Multivitamins with Iodine: Some multivitamin formulations contain iodine to help meet daily requirements.

18.3.2 FUNCTIONS OF IODINE

Iodine is a crucial trace element primarily involved in the production and regulation of thyroid hormones. Its biological functions include:

1. Synthesis of Thyroid Hormones

- Iodine is essential for the production of thyroxin (T4) and triiodothyronine (T3) in the thyroid gland.
- These hormones regulate metabolism, growth, and energy production in the body.

2. Regulation of Metabolism

- Thyroid hormones, which contain iodine, control the body's basal metabolic rate (BMR), influencing how energy is produced and utilized.
- They help regulate protein synthesis, carbohydrate metabolism, and fat breakdown.

3. Growth and Development

- Iodine is crucial for fetal brain development and growth in children.
- Deficiency during pregnancy can lead to cretinism, a severe condition causing intellectual disabilities and stunted growth.

4. Nervous System Function

- Iodine helps in the proper development and function of the central nervous system (CNS).
- It plays a role in maintaining cognitive abilities, memory, and mental alertness.

5. Regulation of Body Temperature

- By influencing metabolism, iodine helps in maintaining body temperature and heat production

6. Immune System Support

- Iodine has antimicrobial properties and helps protect against infections.
- It also plays a role in the detoxification of harmful substances in the body.

18.3.3 DEFICIENCY STATES OF IODINE

Iodine deficiency occurs when the body does not receive enough iodine, leading to impaired thyroid function and various health complications. Since iodine is essential for the production of thyroid hormones, a deficiency can affect metabolism, growth, and brain development.

Causes of Iodine Deficiency

- Insufficient Dietary Intake: Lack of iodine-rich foods like seafood, dairy, and iodized salt.
- Iodine-Poor Soil: Some regions, especially inland or mountainous areas, have low iodine levels in the soil, leading to iodine-deficient crops.
- Pregnancy and Lactation: Increased iodine demands can lead to deficiency in mothers and infants.
- Goitrogens in Diet: Foods like cabbage, broccoli, and soy can interfere with iodine absorption when consumed in excess.

Health Effects of Iodine Deficiency

1. Goitre (Thyroid Gland Enlargement)

The thyroid gland enlarges in an attempt to trap more iodine from the bloodstream.

Visible swelling in the neck can occur.

2. Hypothyroidism

- Low levels of thyroid hormones cause symptoms such as:
- Fatigue and weakness
- Weight gain
- Cold intolerance
- Dry skin and hair loss
- Slow heart rate

3. Cognitive Impairment and Cretinism

- In infants and children: Severe iodine deficiency during pregnancy can cause cretinism, leading to irreversible brain damage, intellectual disability, and stunted growth.
- In adults: Deficiency can result in decreased cognitive function, poor concentration, and memory problems.

4. Developmental Issues in Children

- Stunted growth and delayed brain development.
- Reduced school performance due to lower IQ levels.

5. Increased Risk of Pregnancy Complications

- Miscarriages and stillbirths.
- Congenital abnormalities in newborns.

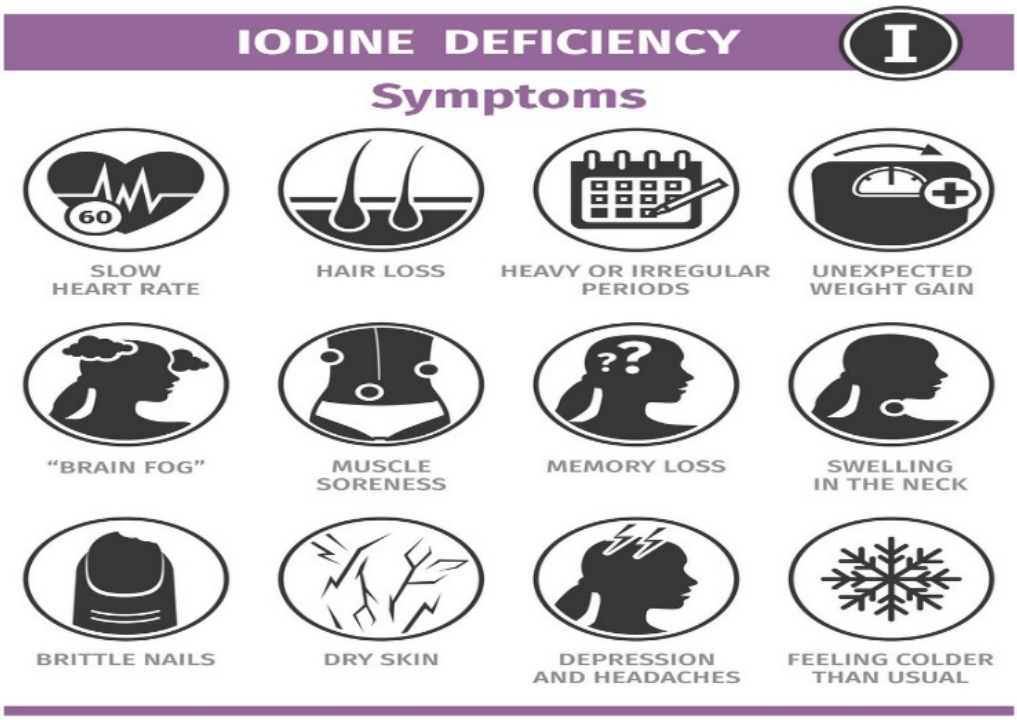

Fig. 18.2

Prevention and Treatment

- Iodized Salt: A primary strategy in many countries to prevent deficiency.
- Dietary Intake: Consuming iodine-rich foods such as seafood, dairy, eggs, and fortified products.
- Supplements: Iodine supplements may be recommended for pregnant and lactating women or those in iodine-deficient areas.

18.3.4 FACTORS INFLUENCING BIOAVAILABILITY OF IODINE

Several factors affect iodine levels in the body, influencing its absorption, utilization, and overall impact on health. These factors include:

1. Dietary Intake

- Iodine-Rich Foods: Seafood, dairy, eggs, and iodized salt provide sufficient iodine.
- Iodine-Poor Diet: A lack of iodine-containing foods can lead to deficiency.
- Vegetarian and Vegan Diets: Plant-based diets may lack adequate iodine if not supplemented properly.

2. Iodine Content in Soil and Water

- Geographical Variations: Iodine levels in soil and water vary, with mountainous, inland, and flood-prone areas often having low iodine levels.
- Agricultural Practices: Crops grown in iodine-poor soil may lack sufficient iodine content.

3. Presence of Goitrogens (Iodine Absorption Inhibitors)

Certain foods contain goitrogens, which interfere with iodine absorption and thyroid function, including:

- Cruciferous vegetables (cabbage, broccoli, cauliflower, kale)
- Soy products (tofu, soybeans)
- Cassava and millet
- Cooking these foods reduces their goitrogenic effects.

4. Physiological Conditions

- Pregnancy and Lactation: Increased iodine demand for fetal brain development and milk production.
- Growth and Development: Children and adolescents require adequate iodine for proper growth.
- Aging: Older adults may have altered iodine metabolism due to declining thyroid function.

5. Thyroid Health and Hormonal Regulation

- The thyroid gland's ability to absorb and utilize iodine affects iodine levels.
- Thyroid disorders (e.g., hypothyroidism, hyperthyroidism) can impact iodine metabolism.

6. Iodine Supplementation and Fortification Programs

- Iodized Salt: Many countries implement salt iodization to prevent deficiency.
- Supplements: Used in high-risk populations, such as pregnant women or those in iodine-deficient regions.

7. Environmental Factors

- Water Contamination: Certain chemicals, such as perchlorate, can block iodine uptake by the thyroid.
- Radiation Exposure: Can affect thyroid function and iodine metabolism.

8. Health Conditions and Medications

- Certain Medications: Lithium and amiodarone can interfere with iodine uptake by the thyroid.
- Kidney and Liver Diseases: Can impact iodine metabolism and excretion.

18.3.5 REQUIREMENTS OF IODINE

Iodine is an essential trace element required for thyroid function and overall health. Here are its key requirements:

The recommended dietary allowance (RDA) varies by age and condition:

- Infants (0-6 months): 110 mcg/day
- Infants (7-12 months): 130 mcg/day
- Children (1-8 years): 90 mcg/day
- Children (9-13 years): 120 mcg/day
- Adolescents & Adults (14+ years): 150 mcg/day
- Pregnant women: 220 mcg/day
- Breastfeeding women: 290 mcg/day

18.4 ZINC

18.4.1 SOURCES OF ZINC

Animal-Based Sources (Highly Absorbable):

Oysters, Beef, Lamb, Pork, Chicken, Fish (Salmon, sardines), Eggs, Dairy (Cheese and milk)

Plant-Based Sources (Lower Absorption Due to Phytates)

Lentils, chickpeas, black beans, and kidney beans, Pumpkin seeds, hemp seeds, sesame seeds, and cashews, Quinoa, oatmeal, brown rice, and whole wheat, Mushrooms, spinach, kale, and potatoes, Tofu & Tempeh

If you're on a plant-based diet, pairing zinc-rich foods with vitamin C can enhance absorption. Also, soaking, sprouting, and fermenting legumes and grains can help reduce phytates and improve zinc availability.

18.4.2 FUNCTIONS OF ZINC

Zinc is an essential mineral that plays a vital role in numerous physiological functions in the body. Here are its key functions:

1) Immune System Support

Helps the body fight infections by supporting white blood cell function.Plays a role in wound healing and reducing inflammation.

2) Growth & Development

Essential for proper growth, especially in infants, children, and teenagers.Supports cell division and tissue repair.

3) Enzyme Activation & Metabolism

Involved in over 300 enzymatic reactions, including digestion and energy metabolism.Helps with the breakdown of carbohydrates, proteins, and fats.

4) Skin Health & Wound Healing

Supports collagen synthesis and tissue repair.Used in acne treatments and helps with skin conditions like eczema.

5) Antioxidant & Anti-Inflammatory Properties

Helps neutralize free radicals, reducing oxidative stress.May lower the risk of chronic diseases.

6) Brain Function & Mental Health

Plays a role in neurotransmitter function and brain signalling.Supports memory, learning, and mood regulation (linked to depression and anxiety).

7) Reproductive Health

Crucial for sperm production and testosterone levels in men.Supports ovulation and fertility in women.

8) Taste & Smell

Essential for proper function of taste and smell receptors.Zinc deficiency can lead to a reduced sense of taste and smell.

9) DNA & Protein Synthesis

Necessary for building and repairing DNA, which is crucial for cell growth.

10) Eye Health

Helps prevent age-related macular degeneration (AMD) by protecting retinal cells.

Since the body does not store zinc, it must be consumed regularly through diet or supplements.

18.4.3 DEFICIENCY STATES OF ZINC

1. Causes of Zinc Deficiency

- Inadequate Dietary Intake – Common in vegetarians, vegans, and people with poor diets.
- Malabsorption Disorders – Conditions like Crohn's disease, celiac disease, and chronic diarrhoea reduce zinc absorption.
- Increased Demand – Pregnant and breastfeeding women, growing children, and athletes need more zinc.
- Chronic Illnesses – Diabetes, liver disease, and kidney disease can increase the risk.
- Excessive Alcohol Consumption – Reduces zinc absorption and increases loss through urine.
- Phytates in Plant-Based Foods – Whole grains, legumes, and nuts contain phytates that inhibit zinc absorption.

2. Symptoms of Zinc Deficiency

- Weakened Immune System – Frequent infections, slow wound healing.
- Hair Loss – Thinning or shedding of hair.

- Skin Issues – Dryness, acne, eczema, rashes, and delayed wound healing.
- Loss of Taste & Smell – Reduced sensitivity to flavors and scents.
- Delayed Growth & Development – Stunted growth in children.
- Loss of Appetite – Can lead to unintentional weight loss.
- Cognitive Issues – Brain fog, difficulty concentrating, and memory problems.
- Mood Disorders – Increased risk of depression and anxiety.
- Diarrhea – Chronic digestive issues and loose stools.
- Vision Problems – Increased risk of night blindness and macular degeneration.
- Reproductive Issues – Low testosterone, poor sperm quality, and menstrual irregularities.

3. Treatment & Prevention

- Increase Zinc-Rich Foods – Oysters, beef, chicken, fish, dairy, nuts, seeds, and legumes.
- Zinc Supplements – May be necessary for those at risk
- Avoid Excessive Iron & Calcium Intake – These minerals compete with zinc for absorption.

Fig. 18.3

18.4.4 FACTORS INFLUENCING BIOAVAILABILITY OF ZINC

Several factors affect how well the body absorbs and uses zinc, including diet, health conditions, and interactions with other nutrients.

1. Dietary Factors

- Animal vs. Plant-Based Sources – Zinc from animal foods (meat, seafood, dairy) is more bioavailable than plant-based sources due to the absence of inhibitors like phytates.

- Phytates (Antinutrients) – Found in whole grains, legumes, nuts, and seeds, phytates bind zinc and reduce absorption. Soaking, sprouting, or fermenting these foods can help.
- High-Fiber Diets – Excess fibre (common in vegetarian and vegan diets) may decrease zinc absorption.
- Protein Intake – Animal proteins enhance zinc absorption, while excessive plant proteins (like soy) may inhibit it.

2. Nutrient Interactions

- Iron & Calcium – High doses of iron and calcium can compete with zinc for absorption, potentially leading to deficiencies.
- Copper – Zinc and copper share the same absorption pathway, so excessive zinc intake can reduce copper levels.
- Vitamin C – Enhances zinc absorption and supports immune function.
- Folic Acid – In high amounts, it may interfere with zinc absorption.

3. Health Conditions Affecting Zinc Levels

- Digestive Disorders – Conditions like Crohn's disease, celiac disease, and chronic diarrhea impair zinc absorption.
- Liver & Kidney Diseases – Can lead to increased zinc loss and poor absorption.
- Diabetes – Higher urinary zinc excretion can contribute to deficiency.
- Alcoholism – Increases zinc loss through urine and reduces absorption.

4. Physiological Factors

- Age & Growth – Children, teenagers, and pregnant women require more zinc due to rapid growth and development.
- Stress & Infections – Increase the body's zinc demand, potentially leading to depletion.
- Hormonal Changes – Pregnancy, lactation, and testosterone production require higher zinc intake.

5. Supplementation & Medications

- Zinc Supplement Form – Zinc citrate, gluconate, and picolinate are better absorbed than zinc oxide.
- Medications – Diuretics, antibiotics, and proton pump inhibitors (for acid reflux) can reduce zinc levels.
- To optimize zinc absorption, consuming a balanced diet with animal-based sources or properly prepared plant foods, along with adequate vitamin C, can help.

18.4.5 REQUIREMENTS OF ZINC

- Infants (0-6 months): 2 mg (Adequate Intake)
- Infants (7-12 months): 3 mg
- Children (1-3 years): 3 mg
- Children (4-8 years): 5 mg
- Children (9-13 years): 8 mg
- Teen Boys (14-18 years): 11 mg
- Teen Girls (14-18 years): 9 mg
- Men (19+ years): 11 mg
- Women (19+ years): 8 mg
- Pregnant Teens (14-18 years): 12 mg
- Pregnant Women (19+ years): 11 mg
- Breastfeeding Teens (14-18 years): 13 mg
- Breastfeeding Women (19+ years): 12 mg

18.5. SUMMARY:

Iodine is an essential element crucial for thyroid function, metabolism regulation, and brain development, especially during pregnancy and childhood. Deficiency can lead to goiter, hypothyroidism, and cognitive impairments. To prevent deficiency, many countries implement iodized salt programs, and consuming iodine-rich foods like seafood and dairy is recommended.

Iron is vital for oxygen transport, energy production, and overall cellular function. It is found in heme sources (meat, poultry, fish) with high bioavailability and non-heme sources (legumes, leafy greens) with lower absorption. Iron deficiency can cause anemia, fatigue, and impaired cognitive function, particularly in children and pregnant women. Proper dietary intake and absorption enhancers like vitamin C help maintain adequate iron levels.

Zinc supports immune function, wound healing, growth, enzyme activation, and reproductive health. Since the body does not store zinc, regular intake from sources like meat, seafood, dairy, legumes, and nuts is essential. Deficiency can weaken immunity, slow growth, and cause cognitive issues. While vegetarians and pregnant women may require higher intake, excessive zinc consumption can also be harmful. Maintaining a balanced intake ensures overall health and well-being.

18.6. TECHNICAL TERMS:

Eczema, macular degeneration,

18.7. SELF ASSESSMENT QUESTIONS:

1) What are factors influencing bioavailability and requirements of iron, iodine, zinc?
2) What is the primary function of iron in the human body?
3) What are the common symptoms of iron deficiency anaemia?
4) What role does iodine play in thyroid function?
5) What are the key functions of zinc in the body?
6) Why is zinc important for immune function and wound healing?
7) What are the symptoms of zinc deficiency?

18.8. REFERENCE BOOKS:

1) Iron Disorders Institute Guide to Hemochromatosis – Cheryl Garrison
2) Nutritional Anaemia – Klaus Kraemer, Michael Zimmermann
3) Zinc Biochemistry, Physiology, and Homeostasis – W. Maret, H. Sies
4) Handbook of Nutritionally Essential Mineral Elements – Robert A. Goyer, C. Nordberg, M. F. Hughes (Covers multiple minerals, including zinc
5) Iodine Deficiency in Europe: A Continuing Concern – F. Delange, John Dunn, David V. Laurberg

Dr. Ch. Manjula

LESSON-19

CHLORIDE AND FLOURINE

19.0. OBJECTIVES:

After going through this lesson, students will understand:

- To understand minerals in food and their physiological roles, particularly the functions of chloride and fluorine in maintaining human health.
- This objective focuses on exploring the essential roles these minerals play in the body.
- To evaluate the dietary sources and recommended intake levels of chloride and fluorine in various food items.

STRUCTURE:

19.1 INTRODUCTION:

Chloride is a chemical element that plays a vital role in both environmental and biological systems. Commonly found in the form of chloride ions (Cl^-), it is an essential electrolyte that helps regulate fluid balance, blood pressure, and the function of nerves and muscles in the human body. Chloride is most widely recognized as a component of table salt, or sodium chloride (NaCl), which is a major source of dietary chloride. In nature, it is present

in seawater and many minerals. Its importance extends to industrial uses as well, where it is involved in the production of chemicals, plastics, and disinfectants.

Fluorine is a highly reactive, pale-yellow gas and the most electronegative element on the periodic table. As a member of the halogen group, it readily forms compounds with many other elements. In nature, fluorine is rarely found in its pure form due to its high reactivity, but it commonly exists as fluoride (F^-) in minerals and water. Fluoride is well known for its benefits to dental health, as it helps prevent tooth decay by strengthening enamel. Fluorine is also important in industrial applications, including the production of Teflon, refrigerants, and various pharmaceuticals. Despite its usefulness, fluorine must be handled with care due to its toxic and corrosive nature.

19.2 CHLORIDE

19.2.1 SOURCES OF CHLORIDE

Chloride is an essential mineral primarily found in salt and various foods. The main dietary sources of chloride include:

- Table Salt (Sodium Chloride) – The most common source, often added to processed and homemade foods.
- Seafood – Fish, shrimp, seaweed, and other marine foods naturally contain chloride.
- Dairy Products – Cheese, milk, and yogurt provide chloride along with calcium and protein.
- Meat and Poultry – Beef, pork, chicken, and turkey contain chloride naturally.
- Eggs – A good source of chloride, particularly in the yolk.
- Vegetables – Tomatoes, lettuce, celery, and seaweed contain natural chloride.
- Processed Foods – Canned soups, sauces, processed meats, and fast foods often have high chloride content due to added salt.
- Beverages – Sports drinks and electrolyte-enhanced waters contain chloride to help maintain hydration.

19.2.2 FUNCTIONS OF CHLORIDE

Chloride is an essential mineral that plays several important roles in the body, including:

1) Maintaining Fluid Balance: Works with sodium and potassium to regulate fluid levels inside and outside cells.
2) Aiding Digestion: A key component of hydrochloric acid (HCl) in the stomach, which helps break down food and kill harmful bacteria.
3) Supporting Nerve Function: Helps maintain proper nerve signal transmission and muscle contraction.

4) Regulating Acid-Base Balance (pH): Helps maintain the body's pH balance, preventing excessive acidity or alkalinity.
5) Transporting Nutrients and Waste: Assists in the movement of fluids and nutrients across cell membranes.
6) Supporting Blood Pressure Regulation: Works alongside sodium to maintain proper blood pressure and hydration levels.

19.2.3 DEFICIENCY STATES OF CHLORIDE

Hypochloremia:

A deficiency of chloride in the body can lead to various health issues. Since chloride is an essential electrolyte, its deficiency disrupts fluid balance, acid-base regulation, and nerve function.

Causes of Chloride Deficiency:

1) Excessive Vomiting – Loss of stomach acid (HCl) reduces chloride levels.
2) Diarrhoea – Severe diarrhoea leads to dehydration and electrolyte imbalance.
3) Diuretic Medications – Some drugs used for blood pressure and kidney conditions cause excessive chloride loss.
4) Chronic Kidney Disease – Impaired kidney function affects chloride retention.
5) Excess Water Intake – Dilutes chloride levels in the blood.

Symptoms of Chloride Deficiency:

- Fatigue and weakness
- Dehydration
- Muscle cramps
- Low blood pressure
- Confusion or difficulty concentrating
- Respiratory issues due to acid-base imbalance

Fig. 19.1

Effects of Severe Deficiency:

Metabolic Alkalosis: A condition where blood pH becomes too high, leading to muscle twitching, irritability, and irregular heartbeats.

Electrolyte Imbalance: Disrupts sodium and potassium levels, affecting nerve and muscle function.

Treatment & Prevention:

- Increasing chloride intake through diet (salt, dairy, seafood, processed foods).
- Correcting dehydration with electrolyte solutions.
- Treating underlying conditions causing chloride loss.

19.2.4 FACTORS INFLUENCING BIOAVAILABILITY OF CHLORIDE

Several factors influence chloride levels in the body, environment, and industrial processes:

- Dietary Intake: Chloride is mainly obtained from salt (NaCl) in food. A low-sodium diet can reduce chloride levels.
- Fluid Balance: Excessive sweating, dehydration, or water retention can affect chloride concentration.
- Kidney Function: The kidneys regulate chloride levels by excreting excess amounts or retaining it when needed.
- Acid-Base Balance: Chloride helps maintain pH levels; imbalances (e.g., metabolic alkalosis) can affect its levels.
- Medications: Diuretics, corticosteroids, and certain drugs can alter chloride balance.
- Diseases: Conditions like kidney disease, cystic fibrosis, and gastrointestinal disorders influence chloride absorption and excretion.

19.2.5 REQUIREMENTS OF CHLORIDE

The body's need for chloride varies based on age, health status, and activity level. Chloride is primarily obtained from dietary sources, mainly salt (sodium chloride).

According to the National Academies of Sciences, Engineering, and Medicine (NASEM):

- Infants (0–6 months): 0.18 g/day
- Infants (7–12 months): 0.57 g/day
- Children (1–3 years): 1.5 g/day
- Children (4–8 years): 1.9 g/day
- Adolescents (9–13 years): 2.3 g/day
- Teens & Adults (14+ years): 2.3 g/day

- Pregnant Women: 2.3 g/day
- Lactating Women: 2.3 g/day

Factors Affecting Chloride Requirements

- Physical Activity: Athletes or individuals sweating heavily may need more chloride.
- Climate: Hot environments increase chloride loss through sweat.
- Health Conditions: Kidney disease, diarrhea, vomiting, or diuretic use can increase chloride needs.

19.3. FLOURINE

19.3.1 SOURCES OF FLOURINE

Fluorine is found in various foods primarily due to its presence in water, soil, and certain plants and animals. Dietary sources of fluoride:

1. Water & Beverages:

Fluoridated drinking water, Tea, Wine & beer

2. Seafood:

Fish with bones (e.g., canned sardines, salmon), Shellfish (e.g., shrimp, crab), Seaweed (absorbs fluoride from seawater)

3. Dairy Products:

Milk, Cheese

4. Fruits & Vegetables:

Potatoes, Spinach & kale, Grapes & raisins

5. Grains & Processed Foods:

Rice & wheat products, Fluoridated salt,Processed foods

6. Meat & Poultry:

Organ meats, Chicken

19.3.2 FUNCTIONS OF FLOURINE

Fluorine, primarily in the form of fluoride (F^-), is an essential trace element in the human body. It plays a key role in maintaining dental and skeletal health, influencing enzymatic activity, and interacting with metabolic processes.

1. Dental Health

- **Strengthening Tooth Enamel**
  - Fluoride integrates into the mineral structure of teeth, forming fluorapatite ($Ca_5(PO_4)_3F$) instead of hydroxyapatite ($Ca_5(PO_4)_3OH$).
  - Fluorapatite is more resistant to acid dissolution, making teeth less prone to decay.

- **Cavity (Dental Caries) Prevention**
    - Fluoride reduces the solubility of enamel, protecting it from bacterial acids.
    - It inhibits demineralization and promotes remineralization, helping repair early tooth decay.
    - Fluoride reduces bacterial activity in the mouth by inhibiting glycolysis (the process that produces acid in bacteria like Streptococcus mutans).

2. Bone Health

- **Bone Mineralization**
    - Fluoride stimulates osteoblast activity, enhancing bone formation.
    - It increases the deposition of calcium and phosphate in bones, contributing to their strength.
- **Bone Density and Fracture Prevention**
    - Fluoride can increase bone mass and density, particularly in conditions like osteoporosis.
    - However, excessive fluoride intake can cause skeletal fluorosis, leading to joint stiffness, bone deformities, and increased fracture risk due to brittle bones.

3. Enzymatic and Metabolic Functions

- **Enzyme Activation and Inhibition**
    - Fluoride interacts with enzymes, sometimes enhancing or inhibiting their function.
    - It inhibits enolase, a key enzyme in glycolysis, reducing bacterial acid production in the mouth.
    - Fluoride can also affect phosphatases, proteases, and ATPases, influencing cellular metabolism.
- **Impact on Hormonal Regulation**

Some studies suggest fluoride can affect the endocrine system, including the thyroid gland, by interfering with iodine metabolism, potentially leading to hypothyroidism.

4. Nervous System Effects

- **Neurotransmission**
    - Fluoride may influence neurotransmitter activity, affecting brain function.
    - Some studies have linked excessive fluoride exposure to cognitive effects, though this remains debated.

- **Potential Neurotoxicity**
    - High fluoride exposure in developing brains has been associated with reduced IQ levels in some epidemiological studies.
    - However, normal dietary fluoride intake from water and toothpaste is generally considered safe.

5. Other Biological Roles

- **Antibacterial Properties**
    - Fluoride disrupts bacterial metabolism by inhibiting enzymes essential for their survival.
    - This is why fluoride is commonly used in water fluoridation and toothpaste to prevent oral infections.
- **Interaction with Other Minerals**
    - Fluoride interacts with calcium, phosphorus, and magnesium, playing a role in maintaining skeletal integrity.
    - Excess fluoride can bind to calcium, leading to hypocalcaemia in severe cases.

19.3.3 DEFICIENCY STATES OF FLOURINE

Fluorine (mainly as fluoride) is not classified as an essential nutrient, but inadequate fluoride intake can lead to dental and skeletal problems.

1. Causes of Fluoride Deficiency

- Lack of Fluoridated Water (in areas where water is not fluoridated)
- Poor Dental Hygiene (not using fluoride toothpaste or mouthwash)
- Low Fluoride in Diet (minimal consumption of fluoridated foods like tea, seafood, or dairy)
- Malabsorption Issues (conditions that affect mineral absorption, though rare for fluoride)

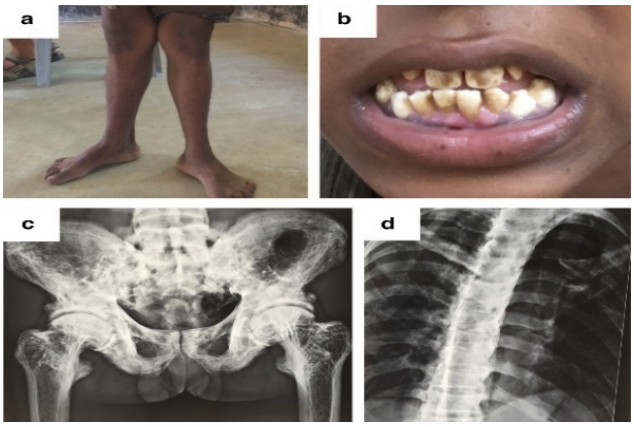

Fig. 19.2

2. Effects of Fluoride Deficiency

- Dental Issues
- Increased risk of tooth decay (cavities).
- Weak enamel, leading to sensitivity and erosion.
- Higher susceptibility to plaque and bacterial infections.
- Bone Problems
- Reduced bone mineralization, leading to weaker bones.
- Higher risk of fractures, especially in older adults.
- Possible link to osteoporosis (though excessive fluoride intake can also harm bones).

3. Prevention

- Use Fluoridated Toothpaste & Mouthwash (daily brushing with fluoride toothpaste).
- Drink Fluoridated Water (many public water supplies are fluoridated).
- Consume Natural Sources
- Dental Treatments (fluoride varnishes and supplements for children in low-fluoride areas).

19.3.4 FACTORS INFLUENCING BIOAVAILABILITY OF FLOURINE

Fluoride bioavailability refers to how much fluoride is absorbed, distributed, and utilized by the body. Several factors affect its absorption and effectiveness, including dietary components, physiological conditions, and the source of fluoride.

1. Dietary Factors

- **pH and Solubility**
  - Fluoride absorption is highest in the stomach and small intestine.
  - Acidic conditions (low pH) enhance fluoride solubility and absorption.
  - Alkaline conditions (high pH) may reduce fluoride absorption by causing it to precipitate.
- **Calcium and Other Minerals**
  - High calcium intake (e.g., from dairy products) can reduce fluoride absorption by forming calcium fluoride (CaF_2), which is poorly absorbed.
  - Magnesium and aluminium (from antacids or food) also bind fluoride, decreasing its bioavailability.
  - Phosphates and sulphates may interfere with fluoride absorption similarly.
- **Presence of Food**
  - Fluoride is better absorbed when consumed on an empty stomach.
  - If taken with food, absorption decreases but retention in bones and teeth may improve.

2. Source and Form of Fluoride

- **Natural vs. Synthetic Fluoride**
  - Naturally occurring fluoride (from water, seafood, and tea) is absorbed efficiently.
  - Fluoride from dental products (toothpaste, mouthwash) has limited absorption as it is mostly spit out.
- **Chemical Form**
  - Sodium fluoride (NaF) in water or supplements is highly bioavailable (80-100% absorption).
  - Calcium fluoride (CaF_2) found in groundwater has lower absorption.
  - Fluorosilicates used in water fluoridation are well absorbed but depend on ph.

3. Physiological Factors

- Age and Developmental Stage
  - Infants and young children absorb more fluoride (up to 80%) due to higher metabolic activity.
  - Adults absorb around 50-60% of ingested fluoride.
- Renal Function
  - Kidneys excrete excess fluoride, so individuals with kidney disease may retain more fluoride, increasing toxicity risk.
  - Dehydration or impaired kidney function reduces fluoride elimination.
- Bone Health and Metabolism
  - Fluoride accumulates in bones, and its uptake depends on bone turnover rate.
  - Growing bones absorb more fluoride than mature bones.

4. Fluoride Interaction with Other Substances

- Aluminium and Magnesium Compounds
  - Found in antacids and certain foods, these reduce fluoride absorption by forming insoluble complexes.
- High Fluoride Exposure
  - Chronic high intake reduces fluoride bioavailability due to self-regulation mechanisms in bones and teeth.
  - Fluoride retention increases in areas with high fluoride water levels, leading to fluorosis.

19.3.5 REQUIREMENTS OF FLOURINE

The adequate intake (AI) levels for fluoride vary by age and physiological status, as recommended by health authorities like the U.S. National Academy of Medicine and the World Health Organization (WHO).

The recommended daily intake (Adequate Intake, AI) for fluoride varies by age and gender:

- 0–6 months: 0.01 mg/day
- 7–12 months: 0.5 mg/day
- 1–3 years: 0.7 mg/day
- 4–8 years: 1.0 mg/day
- 9–13 years: 2.0 mg/day
- 14–18 years: 3.0 mg/day
- Adult men (19+ years): 4.0 mg/day
- Adult women (19+ years): 3.0 mg/day
- Pregnancy: 3.0 mg/day
- Lactation: 3.0 mg/day

19.4 SUMMARY

Chloride is an essential element in both biological and environmental systems, primarily found as the chloride ion (Cl^-). It plays a crucial role in maintaining fluid balance, nerve transmission, and muscle function in the human body. Most commonly consumed through table salt (sodium chloride), chloride is also present in seawater and various minerals. Beyond its biological importance, chloride is widely used in industrial applications, such as in the production of cleaning agents, plastics, and chemicals.

Fluorine, the most reactive and electronegative element, is typically found in nature as fluoride (F^-). It is best known for its role in dental care, helping to prevent tooth decay by strengthening tooth enamel. Fluorine also has many industrial uses, including in the manufacturing of Teflon, refrigerants, and certain pharmaceuticals. While beneficial in controlled amounts, fluoride can be harmful if overused, making proper management important in both health and industrial contexts.

19.5. TECHNICAL TERMS:

Aiding digestion, hyochlorimia, hypocalcaemia

19.6. SELF ASSESSMENT QUESTIONS:

1) What is the role of chloride ions in the human body?
2) How does chloride help maintain fluid balance in the body?
3) How does fluoride help in maintaining dental health?
4) Why fluorine is considered highly reactive?
5) What are the potential risks of excessive fluoride exposure?

19.7. REFERENCE BOOKS:

1) "Chlorine and Chlorine Compounds" by Joseph R. Meehan (Kirk-Othmer 5. "Fluorine and the Environment: Atmospheric Chemistry, Emissions, & Lithosphere" edited by Alain Tressaud Encyclopaedia of Chemical Technology).
2) "Fluorine and the Environment: Atmospheric Chemistry, Emissions, & Lithosphere" edited by Alain Tressaud.

Dr. Ch. Manjula

LESSON-20

METABOLISM OF CALCIUM AND PHOSPHORUS

20.0. OBJECTIVES:

After going through this lesson, students will understand:

- To understand minerals in food and their biological significance this objective aims to provide foundational knowledge about essential minerals, particularly calcium and phosphorus, found in various food sources.
- To examine the absorption, transport, and regulation of calcium and phosphorus in the human body:
- This objective focuses on identifying foods rich in calcium and phosphorus (such as dairy, leafy greens, nuts, and fish), understanding daily intake requirements based on age and health status, and recognizing the symptoms and health consequences of imbalances—like osteoporosis, rickets, or kidney stones.

STRUCTURE:

20.1 INTRODUCTION

Calcium is a vital mineral in the human body, best known for its role in building and maintaining strong bones and teeth. It is also crucial for proper functioning of the heart, muscles, and nerves. Found naturally in dairy products, leafy greens, and fortified foods, calcium is the most abundant mineral in the body. Beyond its biological functions, calcium plays important roles in chemical processes and industrial applications, including cement production and water treatment.

Phosphorus is another essential mineral that works closely with calcium to support bone health and energy production. It is a key component of DNA, RNA, and ATP—the molecule that stores and transfers energy in cells. Phosphorus is mainly obtained through protein-rich foods like meat, dairy, and legumes. In addition to its biological importance, phosphorus is widely used in agriculture as a component of fertilizers, supporting plant growth and crop production.

20.2 CALCIUM METABOLISM

1. Dietary Intake and Absorption

- Calcium is obtained primarily through dietary sources such as dairy products, leafy green vegetables, and fortified foods.
- Absorption occurs mainly in the small intestine, facilitated by vitamin D.

2. Regulatory Hormones

- Calcium levels in the body are tightly regulated by three main hormones:
- Parathyroid Hormone (PTH): Increases blood calcium by stimulating bone resorption, enhancing intestinal absorption, and promoting kidney reabsorption.
- Vitamin D (Calcitriol): Enhances calcium absorption in the intestine and supports bone mineralization.
- Calcitonin: Lowers blood calcium levels by inhibiting bone resorption and promoting calcium excretion in the kidneys.

3. Calcium Storage and Bone Remodelling

- The skeleton serves as the primary reservoir of calcium, with about 99% of total body calcium stored in bones and teeth.
- Osteoblasts and osteoclasts regulate bone remodeling, ensuring a balance between bone formation and resorption.

4. Excretion and Homeostasis

- Calcium is excreted primarily through the kidneys, with small amounts lost in sweat and feces.
- The body maintains a tightly controlled serum calcium level (8.5–10.5 mg/dL) to support normal physiological functions.

20.2.1 ABSORPTION OF CALCIUM

Calcium absorption is a crucial process that ensures adequate calcium levels for various physiological functions such as bone health, muscle contraction, and nerve signalling. This process primarily occurs in the small intestine and is influenced by several factors, including vitamin D, dietary intake, and overall calcium balance in the body.

Sites of Calcium Absorption

- Duodenum and Jejunum: The main sites of active calcium absorption, facilitated by vitamin D.
- Ileum: Contributes to passive calcium absorption.
- Colon: Minor absorption occurs here, primarily from calcium bound to fiber.

20.2.2 MECHANISMS OF CALCIUM ABSORPTION

There are two main pathways through which calcium is absorbed in the intestine:

1. Active Transport (Transcellular Absorption)

- Occurs in the duodenum when dietary calcium intake is low or moderate.
- Vitamin D (Calcitriol) enhances this process by increasing the expression of calcium-binding proteins such as calbindin.

Steps involved:

1) Calcium enters the intestinal cells through calcium channels (TRPV6).
2) Binding to calbindin helps transport calcium across the cell.
3) Calcium exits the cell via ATP-dependent calcium pumps (PMCA) or sodium-calcium exchangers (NCX1) into the bloodstream.

2. Passive Diffusion (Paracellular Absorption

- Occurs in the jejunum and ileum, especially when dietary calcium intake is high.
- Calcium moves between intestinal cells following its concentration gradient.
- This process does not require vitamin D.

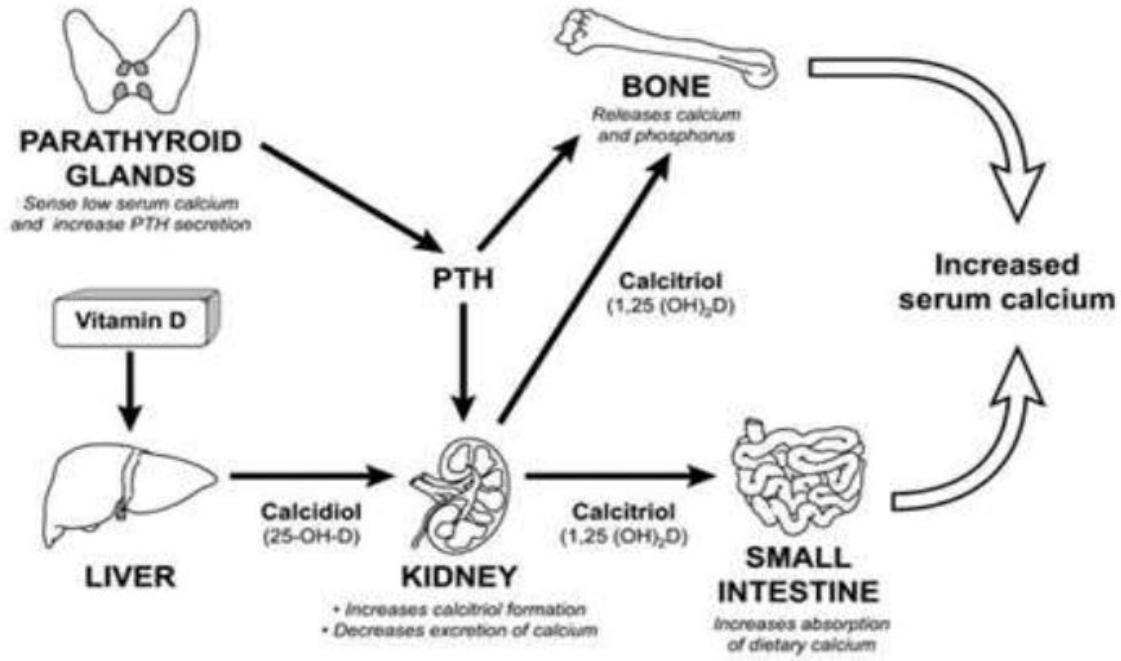

Fig. 20.1

20.2.3 FACTORS AFFECTING CALCIUM ABSORPTION

1. Enhancers of Calcium Absorption:

- Vitamin D (Calcitriol) – stimulates active calcium transport.
- Acidic pH – improves solubility and absorption.
- Lactose – enhances calcium uptake.
- Amino acids (e.g., lysine, arginine) – promote absorption.

2. Inhibitors of Calcium Absorption:

- Oxalates (found in spinach, rhubarb) – bind calcium and reduce absorption.
- Phytates (found in whole grains, legumes) – form insoluble complexes with calcium.
- High dietary fibre – may interfere with calcium absorption.
- Excess phosphorus – competes with calcium for absorption.

20.2.4 CALCIUM BIOAVAILABILITY FROM DIFFERENT SOURCES

- Dairy products (milk, cheese, yogurt): High bioavailability (~30-35%).
- Green leafy vegetables (kale, broccoli): Moderate bioavailability (~40-50%), but oxalates can reduce absorption.
- Fortified foods (orange juice, cereals): Well-absorbed depending on the form of calcium used.
- Supplements (calcium carbonate vs. calcium citrate): Citrate is better absorbed, especially in individuals with low stomach acid.

20.2.5 TRANSPORT OF CALCIUM IN BLOOD

Once absorbed from the intestine, calcium is transported in the bloodstream to various tissues, where it plays a vital role in muscle contraction, nerve function, and bone mineralization. Blood calcium levels are tightly regulated within the normal range of 8.5–10.5 mg/dL to prevent imbalances that can lead to health complications.

Forms of Calcium in Blood

Calcium exists in the blood in three main forms:

1. Ionized (Free) Calcium (~50%)

- The biologically active form that is crucial for cellular functions.
- Plays a role in muscle contraction, nerve conduction, blood clotting, and enzyme activation.
- Regulated by hormones such as parathyroid hormone (PTH), calcitonin, and vitamin D.

2. Protein-Bound Calcium (~40%)

- Mostly bound to albumin, with a smaller portion attached to globulins.
- This form is not freely available for physiological functions.
- Blood pH affects protein-bound calcium:
- Acidosis (low pH) reduces binding, increasing ionized calcium levels.
- Alkalosis (high pH) increases binding, reducing free calcium levels.

3. Complexed Calcium (~10%)

- Bound to anions such as bicarbonate, phosphate, citrate, and lactate.
- This form is diffusible but not ionized, meaning it does not directly participate in cellular functions.

Calcium Transport in Bloodstream

- Calcium enters the bloodstream after intestinal absorption or bone resorption.
- It is transported to various tissues via the circulatory system.
- Hormonal regulation maintains calcium homeostasis
- PTH increases blood calcium by stimulating bone resorption and enhancing kidney reabsorption.
- Calcitonin lowers blood calcium by inhibiting bone resorption.
- Vitamin D (Calcitriol) increases calcium absorption in the intestine and supports bone mineralization.

Role of the Kidneys in Calcium Transport

- The kidneys filter calcium, with most of it being reabsorbed to prevent excessive loss.

- PTH enhances calcium reabsorption in the kidneys, reducing urinary excretion.
- Excess calcium is excreted through urine to maintain balance.

20.2.6 STORAGE AND UTILIZATION OF CALCIUM

Calcium is the most abundant mineral in the human body, primarily stored in bones and teeth, with a small fraction circulating in the blood. It plays a crucial role in numerous physiological processes, including muscle contraction, nerve transmission, blood clotting, and enzymatic activity.

1. Storage of Calcium

Approximately 99% of the body's calcium is stored in bones and teeth, while the remaining 1% is found in extracellular fluids and soft tissues.

- Calcium in Bones and Teeth

Bones serve as the primary reservoir of calcium, helping maintain calcium homeostasis.

The stored calcium is in two forms:

1) Stable Calcium: Incorporated into the hydroxyapatite crystals in bone, providing structural strength.
2) Exchangeable Calcium: A small, readily available pool that can be released into the bloodstream when needed.

Teeth also store calcium, primarily in the enamel and dentin, providing strength and durability.

- Role of Bone Remodelling

Bone continuously undergoes remodelling, balancing calcium deposition and resorption:

- Osteoblasts (Bone-forming cells): Deposit calcium to strengthen bones.
- Osteoclasts (Bone-resorbing cells): Break down bone tissue to release calcium into the blood when needed.
- This process is regulated by parathyroid hormone (PTH), vitamin D, and calcitonin.

2. Utilization of Calcium

The 1% of calcium found in extracellular fluid and soft tissues is essential for various biological functions:

- Physiological Functions of Calcium

1) Bone and Teeth Health

- Supports bone mineralization and growth.
- Maintains bone density, preventing osteoporosis.

2) Muscle Contraction

- Calcium binds to troponin, triggering muscle contraction.
- Plays a role in both skeletal and cardiac muscle function.

3) Nerve Transmission

- Essential for neurotransmitter release at synapses.
- Facilitates communication between nerve cells.

4) Blood Clotting (Coagulation)

- Calcium is a cofactor in the clotting cascade, necessary for blood clot formation.

5) Enzyme Activation

- Activates various enzymes, including those involved in digestion and metabolism.

6) Hormone Secretion

- Calcium regulates the secretion of hormones such as insulin and parathyroid hormone (PTH).

7) Cell Signaling

- Functions as a second messenger in various cellular processes, including cell division and apoptosis.

3. Regulation of Calcium Storage and Utilization

The balance between calcium storage and utilization is controlled by:

- Parathyroid Hormone (PTH): Increases blood calcium by stimulating bone resorption, kidney reabsorption, and intestinal absorption.
- Vitamin D (Calcitriol): Enhances intestinal calcium absorption and bone mineralization.
- Calcitonin: Lowers blood calcium by inhibiting bone resorption.
- Hormonal Regulation of Calcium
- Calcium homeostasis is tightly regulated by hormones to maintain blood calcium levels within the normal range of 8.5–10.5 mg/dL.

20.2.7 EXCRETION OF CALCIUM

Calcium excretion is the process of eliminating excess calcium from the body to maintain proper calcium balance and prevent toxicity. The kidneys, intestines, and skin play essential roles in calcium excretion.

1. Routes of Calcium Excretion

A. Renal (Kidney) Excretion (Primary Route) – ~80%

- The kidneys filter calcium from the blood, and most of it is reabsorbed to prevent excessive loss.

- Parathyroid Hormone (PTH): Increases calcium reabsorption in the renal tubules, reducing urinary calcium loss.
- Calcitonin: Promotes calcium excretion in urine when blood calcium levels are high.
- Vitamin D (Calcitriol): Enhances calcium reabsorption, reducing excretion.

Factors affecting renal calcium excretion:

- High sodium intake → Increases calcium loss.
- High protein intake → Can lead to increased calcium excretion.
- Acidic pH → Increases calcium excretion, while alkalosis reduces it.

B. Faecal (Intestinal) Excretion – ~20%

- Unabsorbed dietary calcium is excreted in the feces.
- Some calcium is secreted into the intestine via bile and pancreatic secretions.
- Vitamin D deficiency reduces calcium absorption, leading to increased faecal calcium loss.

C. Sweat and Skin Loss – <5%

- A small amount of calcium is lost through sweat and skin shedding.
- Heavy sweating (e.g., during intense exercise) can increase calcium loss.

2. Regulation of Calcium Excretion

- Low blood calcium:

PTH reduces renal calcium excretion and enhances intestinal absorption.

- High blood calcium:

Calcitonin increases calcium excretion via urine and reduces bone resorption.

20.2.8 CALCIUM IMBALANCES

Calcium imbalances occur when blood calcium levels deviate from the normal range (8.5–10.5 mg/dL). These imbalances can lead to serious health issues affecting the bones, muscles, nerves, and cardiovascular system. The two main types of calcium imbalances are:

1. Hypocalcaemia (Low Blood Calcium Levels)

Blood calcium levels fall below 8.5 mg/dL.

Causes of Hypocalcaemia:

- Vitamin D deficiency → Reduced intestinal calcium absorption.
- Parathyroid hormone (PTH) deficiency (Hyperparathyroidism) → Decreased calcium release from bones.
- Kidney disease → Impaired vitamin D activation and calcium reabsorption.
- Malabsorption syndromes (e.g., celiac disease) → Poor calcium absorption in the gut.

- Hypomagnesaemia → Affects PTH secretion and function.
- Acute pancreatitis → Calcium binds with fatty acids, reducing blood levels.
- High phosphate levels (e.g., in chronic kidney disease) → Calcium binds with phosphate, reducing free calcium.

Symptoms of Hypocalcaemia:

- Muscle cramps, spasms, or twitching (tetany).
- Chvostek's sign (facial muscle twitching when tapping the cheek).
- Trousseau's sign (carpal spasm when inflating a blood pressure cuff).
- Numbness and tingling (especially in hands, feet, and around the mouth).
- Seizures in severe cases.
- Weak heartbeat, arrhythmias.
- Prolonged QT interval on ECG.
- Osteomalacia (soft bones) in adults.
- Rickets in children.

Treatment of Hypocalcaemia:

- Oral calcium supplements (e.g., calcium carbonate, calcium citrate).
- Vitamin D supplementation to enhance absorption.
- Intravenous calcium gluconate in severe cases.
- Magnesium supplementation if low magnesium is contributing.

2. Hypercalcemia (High Blood Calcium Levels)

Blood calcium levels exceed 10.5 mg/dL.

Causes of Hypercalcemia:

- Hyperparathyroidism → Excess PTH increases calcium release from bones.
- Malignancies (cancer) → Bone metastases or PTH-related protein (PTHrP) secretion.
- Excessive vitamin D intake → Increased intestinal calcium absorption.
- Prolonged immobilization → Bone resorption increases calcium release.
- Thiazide diuretics → Reduce renal calcium excretion.
- Sarcoidosis and tuberculosis → Granulomas produce excess vitamin D.

Symptoms of Hypercalcemia:

- Muscle weakness, fatigue, sluggish reflexes.
- Confusion, depression, memory issues.
- Nausea, vomiting, constipation.

- Kidney stones (nephrolithiasis), frequent urination, and dehydration.
- Hypertension, short QT interval, arrhythmias.

Treatment of Hypercalcemia:

- Hydration with IV fluids to promote calcium excretion.
- Loop diuretics (e.g., furosemide) to increase calcium excretion.
- Bisphosphonates (e.g., alendronate, zoledronic acid) to inhibit bone resorption.
- Calcitonin to lower blood calcium levels.
- Dialysis in severe cases with kidney failure.

20.3 PHOSPHORUS METABOLISM

Phosphorus is an essential mineral in the human body, playing a crucial role in various physiological processes. It is a key component of nucleic acids (DNA and RNA), ATP (adenosine triphosphate), phospholipids, and bone mineralization. The metabolism of phosphorus involves its absorption, transport, utilization, and excretion, maintaining a delicate balance to support cellular functions and skeletal integrity.

The body regulates phosphorus levels through dietary intake, intestinal absorption, renal excretion, and hormonal control by parathyroid hormone (PTH), vitamin D, and fibroblast growth factor 23 (FGF-23). These mechanisms ensure adequate phosphorus availability while preventing imbalances that could lead to disorders such as hypophosphatemia or hypophosphatemia.

20.3.1 ABSORPTION OF PHOSPHORUS

Phosphorus is primarily absorbed in the small intestine, mainly in the duodenum and jejunum, through two mechanisms:

1) Passive Diffusion – The main mode of absorption, occurring when dietary phosphorus levels are high. It follows a concentration gradient, requiring no energy.
2) Active Transport – When phosphorus intake is low, sodium-phosphate cotransporters help absorb phosphorus actively, which requires energy.

Factors Influencing Phosphorus Absorption

Several factors regulate phosphorus absorption:

- Dietary Intake – Organic phosphorus from plant sources (e.g., phytates in grains) is less bioavailable, while inorganic phosphorus (e.g., in animal products and processed foods) is easily absorbed.
- Vitamin D (Calcitriol) – Enhances active phosphorus absorption by stimulating phosphate transporters in the intestine.
- Parathyroid Hormone (PTH) – Indirectly increases phosphorus absorption by stimulating vitamin D production.

- Calcium Levels – High dietary calcium can reduce phosphorus absorption due to the formation of insoluble calcium-phosphate complexes.
- pH Levels – Alkaline conditions enhance phosphorus absorption, while acidic conditions may reduce it.
- Once absorbed, phosphorus enters the bloodstream and is distributed to various tissues, particularly bones and teeth, where it plays a vital role in mineralization and cellular metabolism.

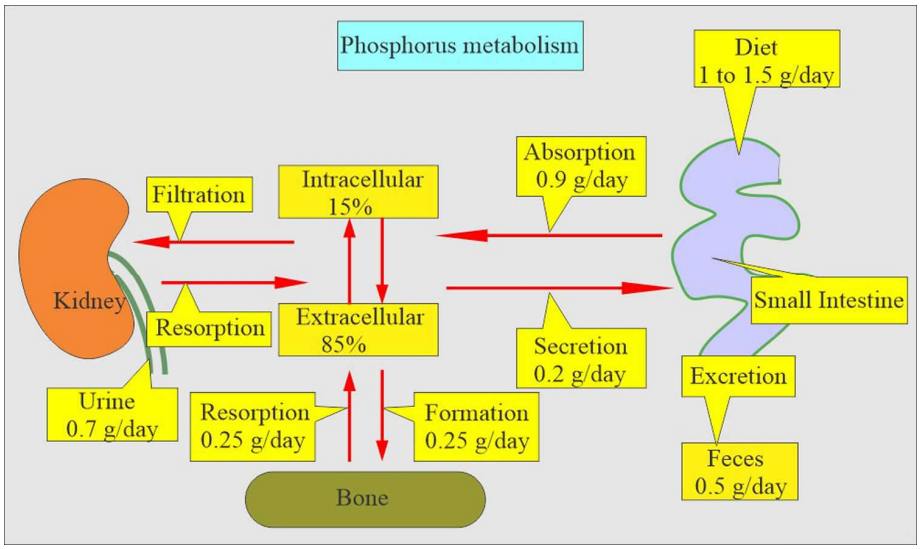

Fig. 20.2

20.3.2 TRANSPORT OF PHOSPHORUS IN BLOOD

After absorption in the intestine, phosphorus enters the bloodstream in the form of inorganic phosphate (Pi). The normal serum phosphorus concentration in adults ranges between 2.5–4.5 mg/dL.

Forms of Phosphorus in Blood

Phosphorus circulates in the blood in three main forms:

1) Free (Ionized) Phosphate (55%) – The biologically active form involved in metabolic processes.
2) Protein-Bound Phosphate (10%) – Primarily bound to albumin.
3) Complexed Phosphate (35%) – Bound to cations like calcium, magnesium, and sodium.

Regulation of Phosphorus Transport

- Phosphorus levels in the blood are tightly regulated by:
- Parathyroid Hormone (PTH) – Increases renal excretion of phosphorus and decreases its reabsorption, lowering blood phosphate levels.
- Vitamin D (Calcitriol) – Enhances intestinal phosphorus absorption and promotes bone mineralization, increasing blood phosphate levels.

- Fibroblast Growth Factor 23 (FGF-23) – Inhibits phosphorus reabsorption in the kidneys and suppresses vitamin D activation, reducing blood phosphate levels.
- Insulin and Growth Hormone – Stimulate phosphate uptake into cells, particularly in bones and muscles.

Tissue Distribution

- Once in the bloodstream, phosphorus is distributed to various tissues:
- Bones and Teeth (85%) – Stored as hydroxyapatite for structural strength.
- Soft Tissues and Muscles (14%) – Used in energy metabolism (ATP) and cellular functions.
- Extracellular Fluid (1%) – Maintains phosphate balance for physiological processes like buffering and enzyme activity.
- Efficient transport and regulation of phosphorus are essential for maintaining bone health, energy production, and cellular signaling.

20.2.3 STORAGE AND UTILIZATION OF PHOSPHORUS

Storage of Phosphorus

Phosphorus is primarily stored in the body in two major locations:

1) Bones and Teeth (85%) – The majority of phosphorus is stored in bones and teeth as hydroxyapatite crystals ($Ca_{10}(PO_4)_6(OH)_2$), providing structural integrity. This phosphorus reserve can be mobilized when needed for metabolic functions.
2) Soft Tissues and Muscles (14%) – A smaller portion is stored in muscle cells, red blood cells, and various tissues, where it plays a role in cellular metabolism.
3) Extracellular Fluid (1%) – A minor fraction circulates in the blood as inorganic phosphate (Pi), which is crucial for physiological processes.

Utilization of Phosphorus

Phosphorus plays a vital role in numerous biological processes, including:

1. Energy Metabolism

- Phosphorus is a key component of ATP (adenosine triphosphate), the primary energy carrier in cells.
- It is involved in the formation of creatine phosphate, which provides energy for muscle contraction.

2. Bone and Teeth Mineralization

- Phosphorus, along with calcium, is essential for maintaining strong bones and teeth.
- It plays a role in bone remodeling and repair.

3. Nucleic Acid Synthesis

Phosphorus is a fundamental component of DNA and RNA, necessary for genetic information storage and protein synthesis.

4. Cell Membrane Structure

Phosphorus is part of phospholipids, which form the structural framework of cell membranes, regulating permeability and cellular communication.

5. Enzyme Activation

- Many enzymes require phosphorylation (attachment of phosphate groups) for activation and proper function.
- Examples include kinases and phosphatases that regulate metabolic pathways.

6. Acid-Base Balance (Buffering System)

Phosphates act as buffers in blood and cells, helping to maintain pH homeostasis and prevent acidosis or alkalosis.

7. Intracellular Signalling

Phosphorylation of proteins is essential for intracellular signal transduction pathways, regulating cell growth, metabolism, and apoptosis.

20.2.4 REGULATION OF PHOSPHORUS

Phosphorus metabolism is tightly regulated to balance storage and utilization, ensuring adequate availability for essential physiological processes.

Hormonal Regulation of Phosphorus

Phosphorus levels in the body are tightly regulated by several hormones that control its absorption, storage, and excretion. The key hormones involved in phosphorus homeostasis include:

1. Parathyroid Hormone (PTH)

Source: Secreted by the parathyroid glands in response to low blood calcium or high phosphorus levels.

Effects on Phosphorus:

- Increases renal excretion of phosphorus by inhibiting its reabsorption in the proximal tubules.
- Stimulates bone resorption, releasing both calcium and phosphorus into the bloodstream.
- Enhances vitamin D activation, which increases intestinal phosphorus absorption.
- Lowers serum phosphorus levels by promoting excretion.

2. Vitamin D (Calcitriol or 1,25-dihydroxyvitamin D_3)

Source: Activated in the kidneys from dietary or sunlight-derived precursors.

Effects on Phosphorus:

- Increases intestinal absorption of phosphorus by up regulating phosphate transporters.
- Enhances phosphorus reabsorption in the kidneys.
- Promotes bone mineralization, incorporating phosphorus into bones.
- Increases serum phosphorus levels.

3. Fibroblast Growth Factor 23 (FGF-23)

Source: Secreted by osteocytes and osteoblasts in response to high phosphorus levels.

Effects on Phosphorus:

- Inhibits renal phosphorus reabsorption, increasing its excretion.
- Suppresses vitamin D activation, reducing intestinal phosphorus absorption.
- Lowers serum phosphorus levels.

4. Insulin

Source: Secreted by the pancreas in response to high blood glucose.

Effects on Phosphorus:

- Promotes phosphorus uptake into cells, particularly muscle and liver cells.
- Enhances glucose metabolism by increasing phosphorylation reactions.
- Lowers extracellular phosphorus levels but supports cellular metabolism.

5. Growth Hormone (GH) and Insulin-like Growth Factor-1 (IGF-1)

Source: GH is secreted by the pituitary gland, stimulating IGF-1 release from the liver.

Effects on Phosphorus:

- Increases intestinal phosphorus absorption.
- Enhances renal phosphorus reabsorption.
- Promotes bone growth, increasing phosphorus demand.
- Increases serum phosphorus levels.

6. Thyroid Hormones (T3 and T4)

Source: Secreted by the thyroid gland.

Effects on Phosphorus:

- Increases bone turnover, releasing phosphorus into the bloodstream.
- Enhances renal excretion of phosphorus.
- Can either increase or decrease phosphorus levels depending on bone metabolism activity.

7. Calcitonin

Source: Secreted by the thyroid gland in response to high calcium levels.

Effects on Phosphorus:

- Inhibits bone resorption, reducing phosphorus release into the blood.
- Increases phosphorus excretion through the kidneys.
- Lowers serum phosphorus levels.

Phosphorus homeostasis is a dynamic process controlled by these hormones to ensure proper bone health, energy metabolism, and cellular function.

20.3.5 EXCRETION OF PHOSPHORUS

Phosphorus is primarily excreted by the kidneys, with a smaller amount lost through the feces and sweat. The body tightly regulates phosphorus excretion to maintain balance and prevent disorders like hypophosphatemia or hypophosphatemia.

1. Renal (Kidney) Excretion

- The kidneys are the main site of phosphorus excretion, filtering about 7–10 g/day of phosphate, with 80–90% being reabsorbed in the renal tubules.
- The remaining 10–20% is excreted in urine, depending on dietary intake and hormonal regulation.

Regulation of Renal Phosphorus Excretion:

- Parathyroid Hormone (PTH) → Increases phosphorus excretion by inhibiting reabsorption in the proximal tubules.
- Fibroblast Growth Factor 23 (FGF-23) → Increases phosphorus excretion by reducing phosphate transporters in the kidney.
- Vitamin D (Calcitriol) → Decreases phosphorus excretion by enhancing reabsorption.
- Dietary Intake → High phosphorus intake increases excretion, while low intake reduces it.

2. Intestinal (Fecal) Excretion

- Some phosphorus is excreted through the feces, especially unabsorbed dietary phosphorus (e.g., from plant-based phytates that are poorly absorbed).
- Biliary excretion contributes to fecal phosphorus loss.

3. Sweat and Minor Losses

- A small amount of phosphorus is lost through sweat, but this is not a major route of excretion.
- Losses may increase with heavy exercise or prolonged sweating.

Efficient phosphorus excretion is essential for preventing imbalances, particularly in individuals with kidney disease, where reduced excretion can lead to hypophosphatemia and complications like vascular calcification.

20.3.6 PHOSPHORUS IMBALANCES

Phosphorus imbalances occur when there is too much (hypophosphatemia) or too little (hypophosphatemia) phosphorus in the blood. Since phosphorus plays a key role in bone health, energy metabolism, and cellular function, imbalances can lead to serious health complications.

1. Hypophosphatemia (Low Blood Phosphorus Levels)

Serum phosphorus level < 2.5 mg/dL

Causes of Hypophosphatemia

- Inadequate Intake – Malnutrition, chronic alcoholism, or low-phosphate diets.
- Malabsorption – Conditions like celiac disease, Crohn's disease, or prolonged diarrhea.
- Increased Excretion – Hyperparathyroidism (excess PTH increases phosphate excretion), renal tubular defects.
- Intracellular Shifts – Insulin therapy (e.g., after diabetic ketoacidosis), refeeding syndrome, respiratory alkalosis.
- Vitamin D Deficiency – Reduced intestinal phosphate absorption.

Symptoms of Hypophosphatemia

- Muscle Weakness – Due to impaired ATP production.
- Bone Pain & Fractures – Reduced mineralization.
- Neurological Symptoms – Confusion, irritability, seizures, coma.
- Respiratory & Cardiac Issues – Difficulty breathing, arrhythmias, heart failure.

Treatment of Hypophosphatemia

- Mild Cases: Increase dietary phosphorus intake (dairy, nuts, meat).
- Moderate to Severe Cases: Oral or intravenous phosphate supplementation.
- Treat Underlying Cause: Correct vitamin D deficiency, adjust insulin therapy, manage hyperparathyroidism.

2. Hypophosphatemia (High Blood Phosphorus Levels)

Serum phosphorus level > 4.5 mg/dL

Causes of Hypophosphatemia

- Kidney Disease (Most Common Cause) – Reduced phosphorus excretion.
- Excess Intake – High-phosphate diet, phosphate-containing laxatives.
- Cellular Breakdown – Tumor lysis syndrome, rhabdomyolysis, hemolysis.
- Hypoparathyroidism – Low PTH reduces phosphate excretion.
- Vitamin D Excess – Increased phosphate absorption from the intestine.

Symptoms of Hyperphosphatemia

- Calcification of Soft Tissues – Excess phosphate binds with calcium, leading to deposits in organs (kidneys, arteries, joints).
- Muscle Cramps & Weakness – Due to calcium-phosphate imbalance.
- Bone & Joint Pain – Secondary to chronic kidney disease (CKD) complications.
- Neurological Symptoms – Tingling, numbness, confusion.

Treatment of Hyperphosphatemia

- Reduce Dietary Phosphorus Intake – Limit processed foods, dairy, nuts, and meats.
- Phosphate Binders – Medications (e.g., calcium acetate, sevelamer) reduce intestinal phosphate absorption.
- Dialysis – In severe kidney disease, dialysis helps remove excess phosphorus.
- Manage Underlying Conditions – Treat CKD, adjust vitamin D or PTH levels.

20.4 SUMMARY

Calcium is a crucial mineral for the human body, primarily responsible for building and maintaining strong bones and teeth. It also plays key roles in muscle function, nerve transmission, blood clotting, and heart health. The body tightly regulates calcium levels in the blood to ensure these functions operate properly. Dietary sources such as milk, cheese, yogurt, leafy greens, and fortified foods are important for meeting daily calcium needs and preventing conditions like osteoporosis or muscle cramps.

Phosphorus is another essential mineral that works closely with calcium, especially in bone formation and maintenance. It is a key component of DNA, RNA, and ATP, which are necessary for energy storage and genetic function in all living cells. Phosphorus also helps maintain the body's acid-base balance and supports cell repair and growth. Found in protein-rich foods like meat, dairy, nuts, and legumes, phosphorus is widely available in the diet. Together, calcium and phosphorus contribute significantly to overall health, especially in growth, energy metabolism, and skeletal strength.

20.5 TECHNICAL TERMS

Homeostasis, calcitonin, seizures, chvostek, trousseau

20.6 SELF ASSESSMENT QUESTIONS

1) What are the main functions of calcium in the human body?
2) How does calcium contribute to bone and dental health?
3) What are some symptoms of calcium deficiency?

4) Why is calcium important for muscle and nerve function?

5) How does phosphorus support energy production in cells?

6) How does phosphorus work with calcium in bone development?

20.7 REFERENCE BOOKS:

1) "Calcium and Bone Disorders in Children and Adolescents" By J. Allgrove and N.J. Shaw

2) Calcium in Human Health Edited by Connie M. Weaver and Robert P. Heaney

3) "Calcium and Phosphate Metabolism Management in Chronic Renal Disease"

4) "Phosphorus and Bone Health" Editors: Elsevier Health Sciences

Dr. Ch. Manjula