स्वाध्याय स्वमन्थन स्वावलम्बन

उत्तर प्रदेश राजर्षि टण्डन मुक्त विश्वविद्यालय, प्रयागराज

उत्तर प्रदेश सरकार का एकमात्र मुक्त विश्वविद्यालय

।। सरस्वती नः सुभगा मयस्करत् ।।

PGZY-102 (N)

Physiology and Biochemistry

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संदेश

प्रयागराज की पवित्र भूमि पर भारत रत्न राजर्षि पुरुषोत्तम दास टण्डन के नाम पर वर्ष 1999 में स्थापित उत्तर प्रदेश राजर्षि टण्डन मुक्त विश्वविद्यालय, प्रयागराज उ0प्र0 का एकमात्र मुक्त विश्वविद्यालय है। यह विश्वविद्यालय उ0प्र0 जैसे विशाल जनसंख्या वाले राज्य में उच्च शिक्षा के प्रत्येक आकांक्षी तक गुणात्मक तथा रोजगारपरक उच्च शिक्षा के अवसर उपलब्ध कराने में निरन्तर अग्रसर एवं प्रयत्नशील है। तत्कालीन देश की सामाजिक एवं आर्थिक परिस्थितियों में एक वैकल्पिक व नवाचारी शिक्षा व्यवस्था के रूप में भारत में मुक्त एवं दूरस्थ शिक्षा प्रणाली का पदार्पण हुआ था, परन्तु वर्तमान परिस्थितियों तथा तकनीकी का सार्थक प्रयोग करते हुये मुक्त एवं दूरस्थ शिक्षा आज की सर्वोत्तम पूरक शिक्षा व्यवस्था के रूप में स्थापित हो चुकी है।

वर्तमान शिक्षा प्रणाली के सामने व्याप्त पाँच मुख्य चुनौतियों - (i) पहुँच (Access), (ii) समानता (Equity), (iii) गुणवत्ता (Quality), (iv) वहनीयता (Affordability) तथा (v) जवाबदेही (Accountability) को केन्द्र में रखकर घोषित देश की राष्ट्रीय शिक्षा नीति (NEP-2020) के प्रस्तावों को क्रियान्वित करने में उत्तर प्रदेश राजर्षि टण्डन मुक्त विश्वविद्यालय कृत संकल्पित है। उ0प्र0 की माननीय राज्यपाल एवं कुलाधिपति की सद्इच्छाओं के अनुरूप उत्तर प्रदेश राजर्षि टण्डन मुक्त विश्वविद्यालय, शैक्षिक दायित्वों के साथ-साथ सामाजिक दायित्वों के निर्वहन में भी लगातार नवप्रयास कर रहा है। चाहे वह गाँवों को गोद लेकर उनके समग्र विकास का प्रयास हो या ग्रामीण महिलाओं, ट्रान्सजेन्डर व सजायाफ्ता कैदियों को शुल्क में छूट प्रदान कर उनमें आत्मविश्वास जागृति व उच्च शिक्षा के प्रति अलख जगाने का प्रयास हो।

राष्ट्रीय विकास को बढ़ावा देने के लिए शिक्षा एक मूलभूत जरूरत है। ज्ञान-विज्ञान एवं तकनीकी के क्षेत्रों में हो रहे तीव्र परिवर्तनों व वैश्विक स्तर पर रोजगार की परिस्थितियों में आ रहे परिवर्तनों के कारण भारतीय युवाओं को विभिन्न क्षेत्रों में गुणवत्तापूर्ण शैक्षिक अवसर उपलब्ध कराने पर ही भारत का भविष्य निर्भर करेगा। इसीलिए विभिन्न क्षेत्रों में सफलता हेतु शिक्षा को सर्वसुलभ, समावेशी तथा गुणवत्तापरक बनाना समसामयिक अपरिहार्य आवश्यकता है। वर्तमान परिस्थितियों ने परम्परागत शिक्षा को और भी सीमित कर दिया है जिसके कारण मुक्त एवं दूरस्थ शिक्षा व्यवस्था ही एकमात्र पूरक एवं प्रभावी शिक्षा व्यवस्था के रूप में सार्थक सिद्ध हो चुकी है। ऐसी स्थिति में विश्वविद्यालय का दायित्व और भी बढ़ जाता है। इस दायित्व को एक चुनौती स्वीकार करते हुए विश्वविद्यालय ने प्राचीन तथा सनातन भारतीय ज्ञान, परम्परा तथा सांस्कृतिक दर्शन व मूल्यों की समृद्ध विरासत के आलोक में सभी के लिए समावेशी व समान गुणवत्तायुक्त शिक्षा सुनिश्चित करने तथा जीवन पर्यन्त शिक्षा के अवसरों को बढ़ावा देने के लिए अपने शैक्षिक कार्यक्रमों में जागरूकता में प्रमाणपत्र, डिप्लोमा, परास्नातक डिप्लोमा, स्नातक, परास्नातक तथा शोध उपाधि के समसामयिक शैक्षिक कार्यक्रमों की संख्या तथा गुणात्मकता में वृद्धि की है।

शैक्षिक कार्यक्रमों में संख्यात्मक वृद्धि, गुणात्मक वृद्धि तथा रोजगारपरक बनाने के साथ-साथ प्रत्येक उच्च शिक्षा आकांक्षी तक पहुँच सुनिश्चित करने के लिए अध्ययन केन्द्रों व क्षेत्रीय केन्द्रों के विस्तार के साथ-साथ प्रवेश परीक्षा, प्रशासन तथा परामर्श (शिक्षण) में आनलाइन व्यवस्थाओं को सुनिश्चित किया गया है। विश्वविद्यालय कार्यप्रणाली में पारदर्शिता तथा जवाबदेही सुनिश्चियन की दृष्टि से तकनीकी के प्रयोग को बढ़ाया गया है। 'चुनौती मूल्यांकन' की व्यवस्था सुनिश्चित करने का कार्य किया गया है, तो शिक्षार्थी सहायता सेवाओं में भी वृद्धि की जा रही है। शिक्षार्थियों की समस्याओं के त्वरित निस्तारण हेतु शिकायत निवारण प्रकोष्ठ को सुदृढ़ करने के साथ-साथ पुरातन छात्र परिषद को गतिशील किया गया है।

"गुरुकुल से छात्रकुल" के सूक्त वाक्य को आत्मसात करते हुए विश्वविद्यालय ने शिक्षार्थियों को विश्वविद्यालय द्वारा तैयार किये गये गुणवत्तापूर्ण स्वअध्ययन सामग्री उपलब्ध कराने के साथ-साथ विश्वविद्यालय की वेबसाइट पर भी उपलब्ध कराया गया है। छात्रहित को ध्यान में रखते हुए शिक्षकों द्वारा तैयार व्याख्यान को भी ऑनलाईन उपलब्ध कराया गया है।

शोध और नवाचार के क्षेत्र में अग्रसर होते हुए विश्वविद्यालय अनुदान आयोग (UGC) नई दिल्ली तथा माननीय राज्यपाल एवं कुलाधिपति, उ0प्र0 की अनुमति से विश्वविद्यालय में शोध कार्यक्रम पुनः प्रारम्भ किया गया है तथा वर्ष पर्यन्त समसामयिक विषयों पर व्याख्यान, सेमिनार, वेबिनार तथा आनलाइन संगोष्ठियों आदि की श्रृंखला भी प्रारम्भ की गयी है। विभिन्न क्षेत्रों में रिसर्च प्रोजेक्ट सम्पादन पर भी ध्यान केन्द्रित किया गया है। पुस्तकालय को अत्याधुनिक तथा सुदृढ़ बनाने हेतु कदम उठाये गये हैं। शिक्षकों व कर्मचारियों के स्वास्थ्य तथा कल्याण की योजनायें क्रियान्वित की गयी हैं।

प्रो0 सत्यकाम
कुलपति

U.P.Rajarshi Tandon Open University, Prayagraj

Master of Science

PGZY-102 (N)

Physiology and Biochemistry

COURSE INTRODUCTION

This course covers the Physiology and Biochemistry in three blocks. Block-1 Physiology, Block-2 Physiology and Biochemistry and Block -3 Biochemistry

Physiology is the science of life. At present physiology is the branch of science, which studied how the parts organs, organ system and the wholeness of healthy organisms, work and how these functions are regulated. The human body functions in health and diseases, and how the human body works, senses, reacts and defends itself. It considers how human bodies are supplied with energy, how they maintain their internal parameters, the ways in which they gather and process information or take action and the creation of new generations.

The biochemistry deals with the structures, functions and interactions of biological macromolecules, such as proteins, nucleic acids, carbohydrates and lipids, which provide the structure of cells and perform many of the functions associated with life.

U.P.Rajarshi Tandon Open University, Prayagraj

Master of Science

PGZY-102 (N)

Physiology and Biochemistry

1

Block

Physiology-I

Unit-1	**Digestion**
Unit-2	**Muscles and Nerve Fibers**
Unit-3	**Nervous System**
Unit-4	**Respiration**
Unit-5	**Excretion**
Unit-6	**Osmoregulation**

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BLOCK INTRODUCTION

Block-1

You will be introduced by physiology-I. This block of the study materials incorporates 6 units (unit 1 to 6) as under:

Unit-1 Begins with the digestion and absorption of proteins, Carbohydrates, lipids, Neural control, bile secretion and cholesterol, homeostasis, immune function of GI tract, physiology of gastrointestinal disorders.

Unit -2 Deals with types of mucles, mechanism of smooth muscle contraction, Cardiac muscle-structure and function.

Unit -3 deals with the Structure and function of nervous system

Unit -4 In this unit you will study about Respiratory pigments, oxygen and carbon-dioxide transport, mechanism and regulation of respiration.

Unit 5 It deals with the Kidney structure, tubular transpart mechanism, role of kidney in regulation of ionic, osmotic, acid and base balance of the body fluid, urine formation.

Unit-6 This unit also deals with the Osmoregulation in fresh water and marine fishes. Osmoregulation in migratory fishes. Homeostasis- neural and hormonal

Objectives:-

After studying this block you will be able to know:

- The digestion and absorption of carbohydrates, proteins and fats.
- The types and mechanism of muscle contraction
- Structure and function of nervous system
- The respiratory pigments and regulation of respiration
- The kidney structure and osmoregulation

UNIT-1 DIGESTION

1.1 INTRODUCTION

The digestive system includes the digestive tract and its accessory organs. The digestive tract, also called the alimentary canal or gastrointestinal tract. The gastrointestinal tract is essentially a tube that extends from the mouth to the anus. It has generally the same structure throughout. There is a hollow portion of the tube known as the lumen, a muscular layer in the middle, and a layer of epithelial cells. These layers are responsible for maintaining the mucosal integrity of the tract. There are three main functions of the gastrointestinal tract, including transportation, digestion, and absorption of food. The mucosal integrity of the gastrointestinal tract and the functioning of its accessory organs are vital in maintaining the health. The small intestine is composed of the duodenum, jejunum, and ileum. The large intestine extends from the terminal ileum at the ileocecal valve to the rectum.

The tongue and teeth are accessory structures located in the mouth. The salivary glands, liver, gall bladder and pancreas are major accessory organs that have a role in digestion. These organs secrete fluids into the digestive tract.

The gastrointestinal disorder is of condition that affects the digestive system. Symptoms are depending on the condition and underlying causes of disease. The most gastrointestinal symptoms are pain in the abdomen, diarrhoea, constipation, excess gas, bloating, and weight loss.

Objectives:-

After studying this unit you will be able to know:

- describe the digestion and absorption of carbohydrates, proteins and fats.
- describe the process of digestion and digestive enzymes.
- Neural Control of Gastrointestinal System
- Bile secretion and Cholesterol, homeostasis, immune function of GI tract

- Physiology of Gastrointestinal Disorders

1.2 GASTROINTESTINAL SYSTEM

The mucosal integrity of the gastrointestinal tract and the functioning of its accessory organs are vital in maintaining the health

The three main functions of the gastrointestinal tract, including

- Transportation,
- Digestion, and
- Absorption of food.

Gastrointestinal system included mouth, esophagus, stomach, small intestine, and large intestine and accessory organs include the liver, pancreas, and gallbladder.

The mouth functions to break down food into smaller parts and the esophagus are the tube like structure that allows the passage of the food bolus from the mouth to the stomach.

The stomach functions to store, churn, and puree food into a substance known as chime. The chemical digestion in stomach with the help of Gastric juices.

The small intestine includes duodenum, jejunum, and ileum which extend from the pylorus to the ileocecal junction. The primary function of the small intestine is the absorption of vitamins and nutrients, including electrolytes, iron, carbohydrates, proteins, and fats.

The large intestine extends from the ileocecal junction to the rectum, include the terminal ileum, the ascending colon, the transverse colon, then the descending colon. Following the descending colon is the sigmoid colon and the rectum. The main function of the large intestine is water absorption. That is about one and one-half liters of water per day.

The liver is a very large organ located in the upper right abdomen. Blood supply to the liver arises from both the portal vein and hepatic artery.

Gallbladder is accessory organ of gastrointestinal system a pear-shaped sac-like organ attached to the liver and works as a storage bile secreted from Liver. When a large or fatty meal is consumed, nerve and chemical signals (release of the enzyme CCK) cause the gallbladder to contract. This contraction releases bile into the Duodenum.

The pancreas is both an endocrine and exocrine gland. The exocrine function of the pancreas is digestive in nature and involves the secretion of pancreatic enzymes and bicarbonate.

Process of digestive ingestion involves-

- Placing the food into the mouth, Chewing the food into smaller pieces (mastication).
- Moistening the food with salivary secretion. Swallowing the food (deglutition).

Ingestion:-

- Chewing increases the surface area of the food. The mastication is a voluntary process in the man.

- **Swallowing (deglutition)** – The act of taking food of down in the oesophagus, from buccal cavity, through pharynx is called swallowing.
- **Peristalsis –** It is the reflex wave caused by the rhythmic movement of involuntary muscles of the gut wall. It pushes the food in forward direction.

Digestion:–

During digestion food is broken down into small particles by grinding action of the GIT and then degraded by digestive enzymes into usable nutrients.

- Starches are degraded by 'amylases' into monosaccharides.
- Proteins are degraded by proteases into dipeptides and amino acid.
- Fats are degraded by lipases and esterases into monoglycerides and free fatty acids.

Gastrointestinal Secretion

Process of digestion is accomplished with the help of gastro-intestinal juice. The digestive juices, secreted in the various parts of alimentary tract, are as follows –

- Salivary secretion
- Gastric secretion
- Pancreatic secretion
- Bile secretion

Salivary Secretion

Saliva contains –

(i) Water → up to 99.5% are found.

(ii) Inorganic components – are found 0.2% which includes Na, K, Ca, SO4, PO4 etc.

(iii) Organic matter – organic matter are found upto 0.3%, which include mucin, globulins, albumins, urea, uric acid etc.

(iv) Enzymes – Enzymes like ptyalin or salivary amylase.

Gastric Secretion

The semi-solids food after salivary digestion reaches in the stomach through oesophagus.

Gastric juice secreted by the inner lining of the stomach. It is colourless, highly acidic liquid containing water, some salt, hydrochloric acid and an enzyme called pepsin.

HCl is one of the most important constituent of gastric juice. It is secreted by parietal cells. The acid serves two functions –

(A) It kills any germs which may have entered along with the food.

(B) HCl converts inactive pepsinogen into active enzyme pepsin

Pepsinogen $\xrightarrow{HCl}$ Pepsin

(inactive) (active)

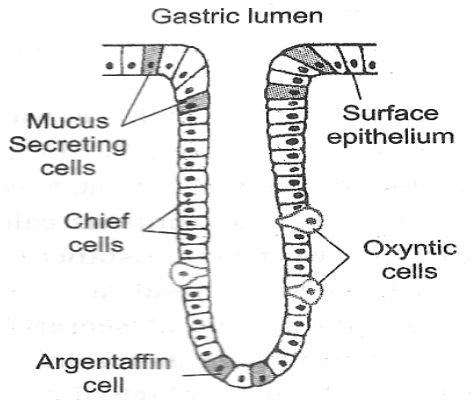


Fig 1.1. Gastric glands

Source: http://www.wikipedia.org

Pancreatic Secretion

Pancreas is a mixed gland. It has both exocrine activity as well as endocrine activity.

- The exocrine portion secretes pancreatic enzymes, useful in digestion.
- The endocrine portion secretes hormones like insulin, glucagon and somatostanin etc.
- The pancreas is connected to the duodenum through its main duct. This main duct of pancreas is called pancreatic duct.
- The exocrine portion of pancreas is of about 85%. It consists of many small lobules called acine. The acine synthesis pancreatic juice. The endocrine portion of pancreas is about 15%, it consists of small groups of cells called 'Islets of Langerhans'.
- These islets contain following types of cells –
  - **Alpha cells**:– These are about 25% of the total cells in an islet. These cells secrete glucagon hormone.
  - **Beta cells:–** These cells secrete insulin hormone.
  - **Delta cells:–**These cells secrete hormone called somatostanin (growth inhibitory factor).
  - **Fcells (PPcells):-** These cells secrete hormone called pancreatic polypeptide (PP).

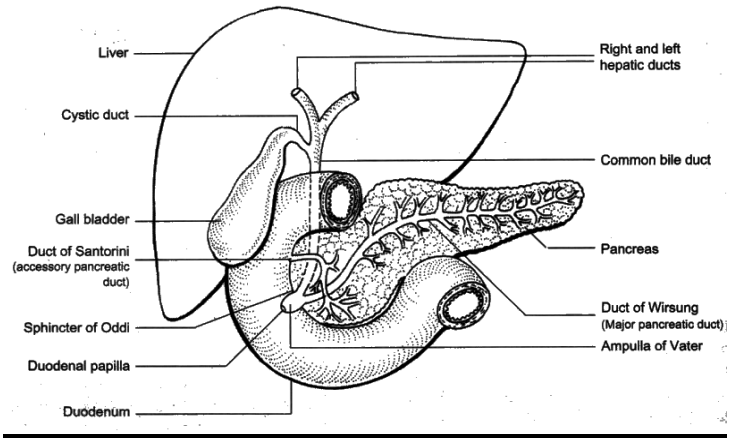


Fig 1.2. Structure of pancreas

Source: Human Physiology and Biochemistry by Prof. A.K.Jain

Bile Secretion

The secretion of liver is called bile juice. It is greenish yellow, watery liquid which is alkaline in reaction.

- Bile does not contain any digestive enzyme.
- Bile also contains bile pigments – bilirubin and biliverdin.

These pigments are the waste products of haemoglobin catabolism, (which are formed by the catabolism of haemoglobin).

Function of bile juice:-

Bile salts are necessary for the digestion and absorption of fat because –

- They emulsify fats
- Activate pancreatic lipase.
- Bile salts stimulate the secretion of more bile from the liver.
- Bile salts make the medium alkaline thus help in the functioning of amylases and proteolytic enzymes of pancreas and intestine (which function in alkaline medium only).

Digestive Enzymes, its regulation and control

The digestive process is not accomplished only by enzymes. Some peptide hormones are also needed during digestive process. These are called gastrointestinal hormones, because these are secreted by gastrointestinal wall. These hormones regulate and control the entire process by regulating secretions of digestive glands.

The three major classes of digestive enzyme are –

- **Proteases** – That hydrolyze peptide bonds in proteins.

- **Carbohydrases** – That hydrolyse glycosidic bonds in carbohydrates.
- **Lipases**- That hydrolyse ester bonds in fats.

Gastrointestinal secretion is largely under the control of gastrointestinal hormones secreted by endocrine glands of gastric and intestinal mucosa.

The three main mammalian gastrointestinal hormones are secretin, gastrin and cholecytokinin (CCK). Gastrin is secreted by gastric mucosa (stomach). Cholecystoknini and secretin are secreted by the mucosa of duodenum.

SAQ-1

1. The are three main functions of the gastrointestinal tract, including **.....** of food.
2. The small intestine is composed of the **.....**
3. The liver is a very large organ located in the **.....**

1.3 DIGESTION AND ABSORPTION OF CARBOHYDRATES

The different forms of carbohydrates are as follows-

(i) **Polysaccharides** – Starch, Dextrin, Glycogen and Cellulose

(ii) **Oligosaccharides** – Lactose, Maltose, Sucrose

(iii) **Monosaccharides** – Glucose and Fructose.

- Digestion of carbohydrates begins in the buccal cavity. Saliva contain the starch splitting enzyme ptyalin or salivary amylase, that act on the starch and converts its in maltose (disaccharides).
- Now the semidigested carbohydrate food is passed into stomach through pharynx and oesophagus, no digestive enzyme is secreted.
- When the food reached the stomach the pH changes the food becomes acidic, it is now called chyme.
- In the gastric juice does not possess any carbohydrates splitting enzyme, but gastric HCl can carry on some hydrolysis of sucrose.
- The pancreatic juice comes from the pancreas. The pancreatic juice contains two enzymes acting on carbohydrates.

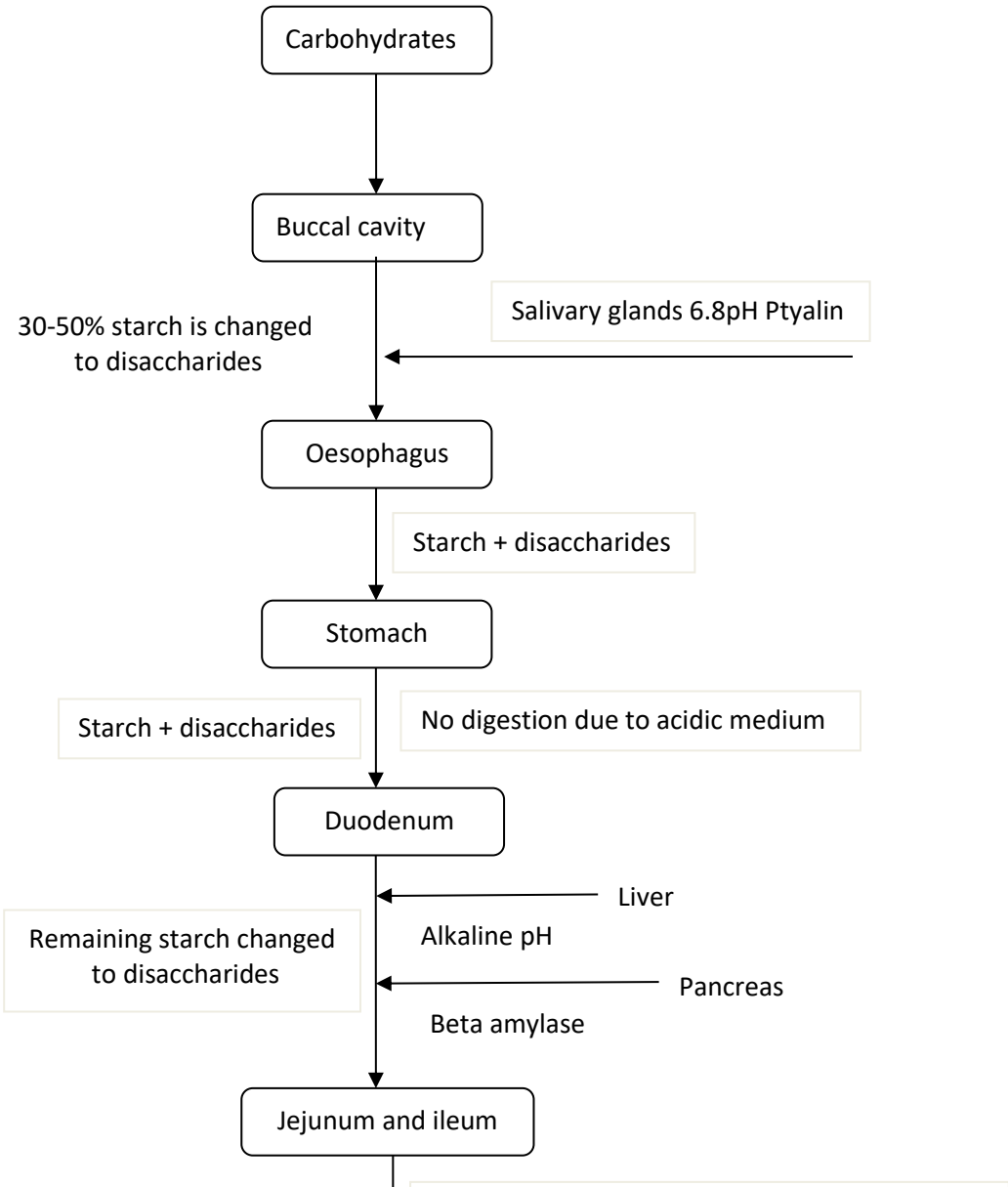
  A. Pancreatic amylase – Acting on starch and dextrin.

  B. Maltase – (in traces) acting on maltose.

1. Starch $\xrightarrow[pH\,6.8 to 7.0]{ptyalin}$ disaccharides
2. Starch $\xrightarrow[pH\,8.2 to 8.2]{pancreatic amylase}$ disaccharides
3. Starch, glycogen $\xrightarrow{-1,4\,glucosidose}$ maltose
4. Maltose $\xrightarrow{Maltase}$ glucose + glucose
5. Sucrose $\xrightarrow{Sucrase}$ glucose + fructose
6. Lactose $\xrightarrow{Lactase}$ glucose + galactose

Now food reaches ileum. In ileum various types of disaccharidases are present, such as sucrose, maltose and lactose etc. Thus the digestible carbohydrates are all converted into monosaccharides in which form they are absorbed.

Absorption is the process by which the end products of digestion pass through the intestinal epithelium and enter the blood stream.



Absorption of Carbohydrates

Most of the absorption occurs in small intestine, the mucosa of small intestine is provided with numerous finger like projection called villi. Villi and their brush border greatly increase the surface area for absorption of digested food.

There are two mechanism of absorption in the intestine (1) Diffusion (2) Active absorption.

- Fructose is transported by simple diffusion in response to a concentration gradient by the absorptive cells of the villi.
- Glucose and galactose are absorbed by active transport.
- This type of absorption (transport) requires metabolic energy.
- These monosaccharides are finally transported to the blood capillaries.

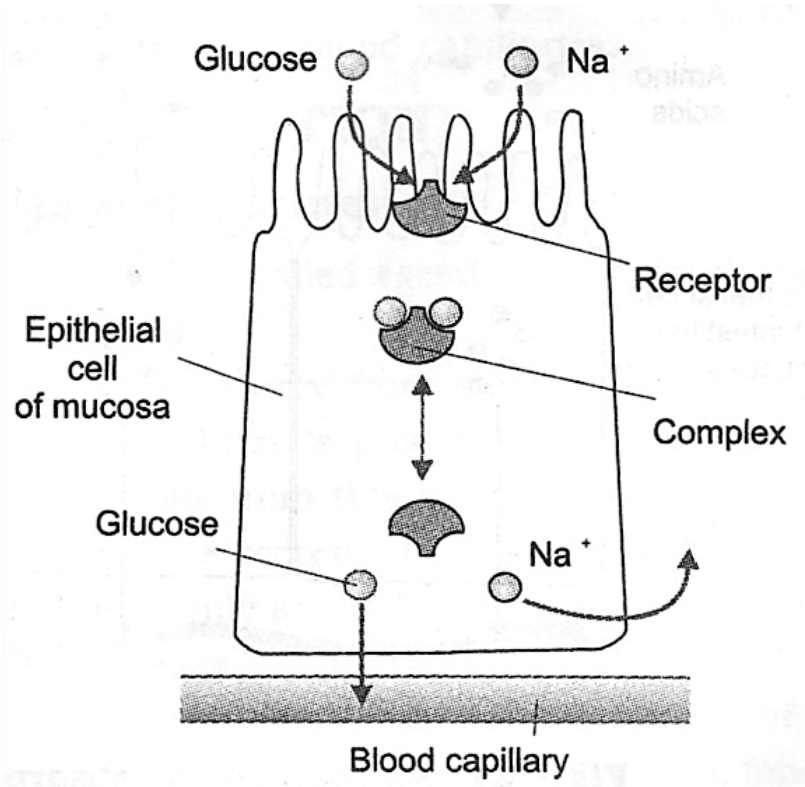


Fig.1.3: Absorption of glucose

Source: http://www.wikipedia.org

1.4 DIGESTION AND ABSORPTION OF PROTEIN

- Digestion of proteins starts in the stomach when food reaches the stomach, it gets mixed with HCl and becomes chyme (acidic).
- The food is passed to duodenum the medium becomes alkaline due to action of bile juice.

- In the gastric juice – pepsin is the proteolytic enzyme of gastric juice. It acts with the help of HCl and converts all digestible proteins up to peptone stage.

  Complex proteins $\xrightarrow{pepsin}$ Proteoses, peptones and large peptides.

Pepsin and its function

- Pepsin is protein in nature.
- It remains as pepsinogen in the peptic cells of stomach, HCl of gastric juice converts it into active pepsin.

Proteins

↓

(pepsin in gastric juice and trypsin in pancreatic juice)

Proteoses, peptides

(Proteases in pancreatic juice & peptidases in intestinal juice)

↓

Amino acid

Now the food reaches the jejenum and ileum, where many proteolytic enzyme are present. These enzymes finally convert the amino acid (which are end products of protein digestion)

Trypsinogen $\xrightarrow{enterokinase}$ Trypsin

Proteins, proteoses, peptone $\xrightarrow{trypsin}$ polypeptides, free amino acids

Chymotrypsins are secreted in their inactive forms known as chymotrypsinogens.

The conversion of chymotrypsinogens into active chymotrypsins is made by trypsin.

Chymotrypsinogens $\xrightarrow{trypsin}$ chymotrypsins

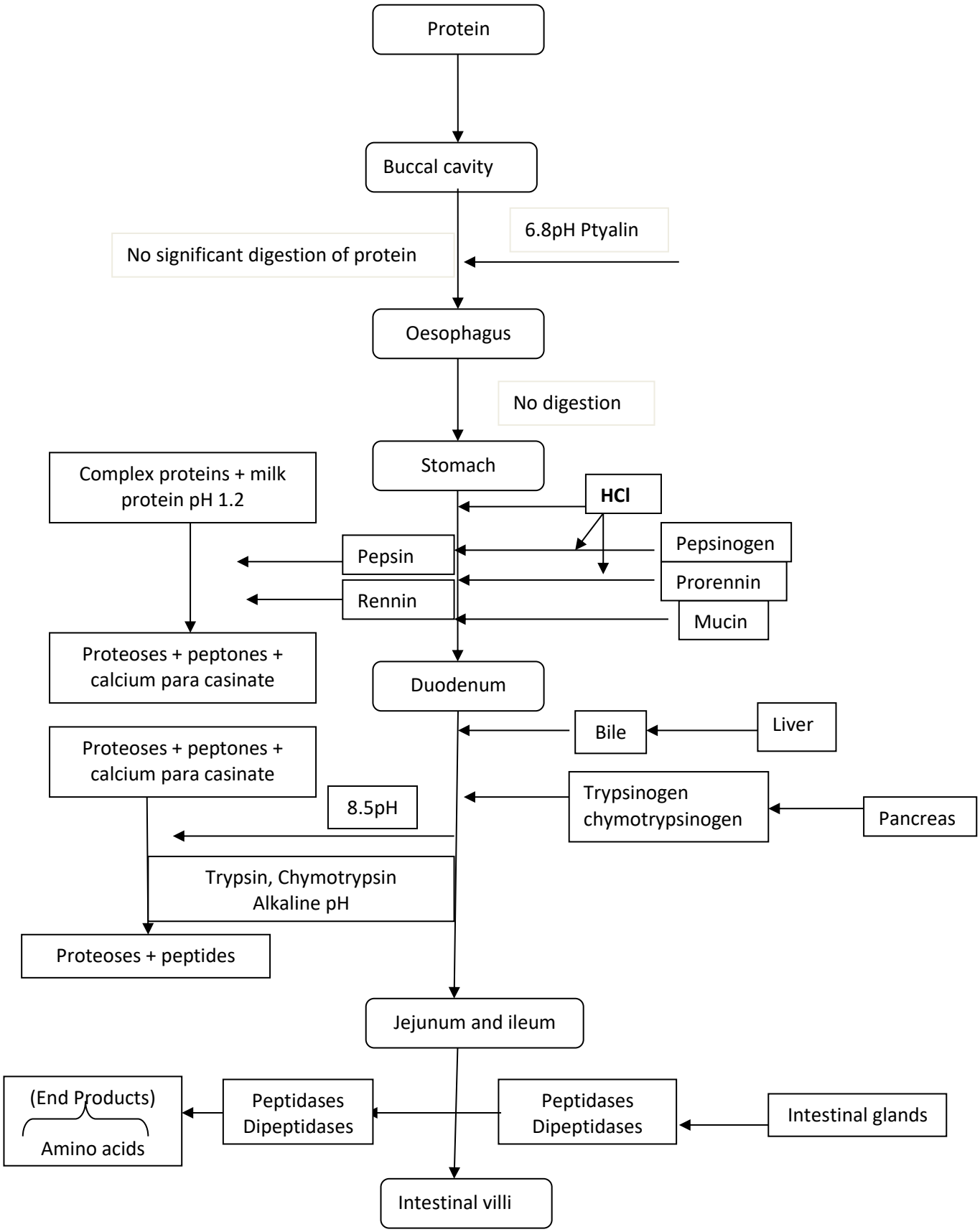

Protein
Buccal cavity
6.8pH Ptyalin
No significant digestion of protein
Oesophagus
No digestion
Stomach
Complex proteins + milk protein pH 1.2
HCl
Pepsinogen
Pepsin
Prorennin
Rennin
Mucin
Proteoses + peptones + calcium para casinate
Duodenum
Bile
Liver
Proteoses + peptones + calcium para casinate
8.5pH
Trypsinogen chymotrypsinogen
Pancreas
Trypsin, Chymotrypsin Alkaline pH
Proteoses + peptides
Jejunum and ileum
(End Products)
Amino acids
Peptidases Dipeptidases
Peptidases Dipeptidases
Intestinal glands
Intestinal villi

Fig.1.4: Digestion of proteins

Absorption of Proteins

Most of the proteins are converted to amino acids, a part is left in the form of small polypeptides. Some dipeptides are intracellularly digested, these enter the intestinal cells and of hydrolysed there. The free amino acids are absorbed both by diffusion and active transport. The active transport involves oxidative phosphorylation. The transport of neutral amino acid and sodium go together, but there are separate systems for basic and acidic amino acids.

Amino acids are mainly of two types D types and L type.

- D amino acid are absorbed solely by passive diffusion only. While L – amino acids are actively transported.
- L amino acids are absorbed more rapidly than D isomers.
- The absorbed amino acids are also transported to the underlying blood capillaries.

1.5 DIGESTION AND ABSORPTION OF FAT

Pancreatic juice also contains a number of lipolytic enzymes such as lipase, phospholipase and cholesterol esterase.

Lipase:-

It is an important enzyme in digestion. Neutral fats are digested into fatty acid and glycerol. Hydrolysis of fats takes place in different stages.

In the first stage there is formation of one molecule of fatty acid and a diglyceride. The diglyceride is broken down into another molecule of fatty acid and a monoglyceride. The monoglyceride is finally hydrolyzed into another molecule of fatty acid and glycerol. So the fat molecule after complete hydrolysis gives rise to 3 molecules of fatty acids and one molecule of glycerol. In human body bile juice is present to dissolve the fats. In duodenum, the bile juice is present (from liver) which emulsify the fats.

Lipase enzymes of pancreas and intestine can act only on emulsified fats. Once the fat is emulsified, the pancreatic lipase and then intestinal lipase play their roles.

Pancreatic lipase is the main enzyme for fat digestion. Both enzymes now convert the fat into fatty acids and glycerol. Which are the end products of fat digestion.

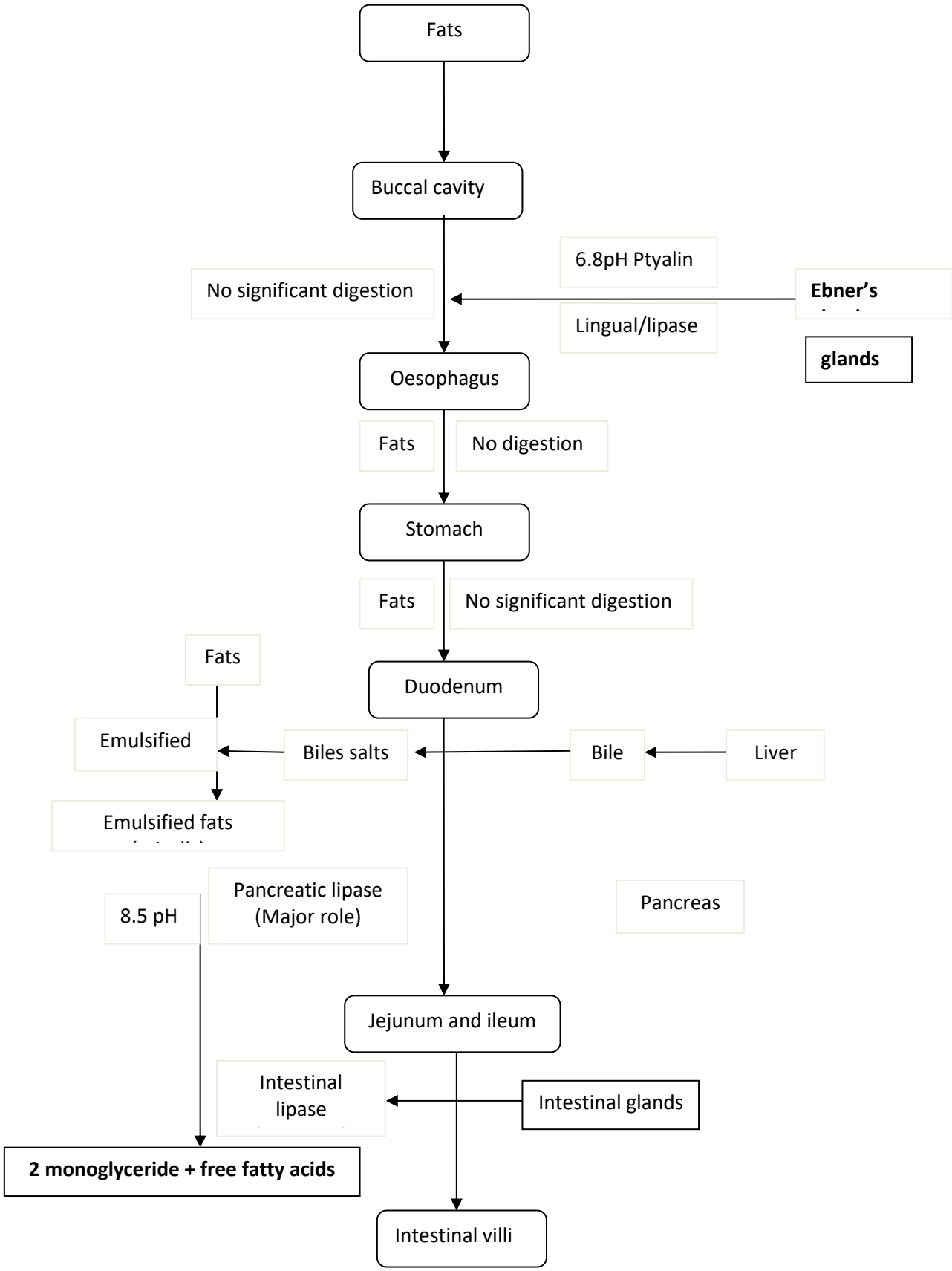

Fats
Buccal cavity
6.8pH Ptyalin
No significant digestion
Ebner's
Lingual/lipase
glands
Oesophagus
Fats
No digestion
Stomach
Fats
No significant digestion
Fats
Duodenum
Emulsified
Biles salts
Bile
Liver
Emulsified fats
8.5 pH
Pancreatic lipase
(Major role)
Pancreas
Jejunum and ileum
Intestinal
lipase
Intestinal glands
2 monoglyceride + free fatty acids
Intestinal villi

Fig.1.5: Digestion of fats

Fatty acids are insoluble in water, therefore they cannot reach the blood stream directly. They are first converted into small water soluble droplets called micelles.

1. **Lipolytic hypothesis:-**

   Fatty acids are insoluble in water, therefore they cannot reaches the blood stream directly. Triglycerides (fats) are absorbed mainly in the lymphatic vesseles after they have been resynthesised from fatty acid and glycerol in the mucosal epithelial cells.

   The main process of fat absorption are –

   - The short chain and water soluble long chain fatty acids are directly absorbed through the absorptive cells of the intestine into the portal blood system.
   - The unbroken fats, long chain fatty acids and glycerides of are in the form of micelles. These micelles can be absorbed into the intestinal cells by diffusion where they are resynthesized into very small fat molecules (droplets) called chylomicrons.
   - The chylomicrons are released from the intestinal cells into lymph present in the lymph capillaries known as lacteals.

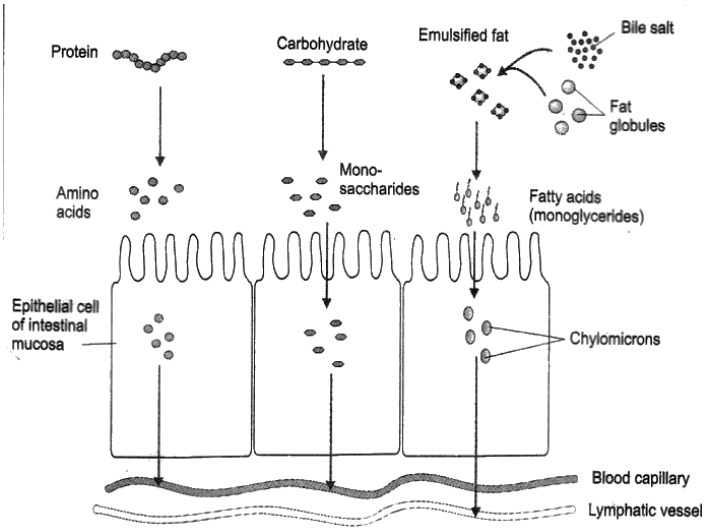


Fig.1.6: Absorption of different types of digested food particles

Source: http://www.wikipedia.org

Absorption of Water

The absorption of water from the small intestine is associated with the absorption of electrolytes and digested food.

Defecation

The elimination of undigested food material is called egestion (or defecation) it is the last step of entire digestive process.

Absorption of Salt:-

Stomach and large intestine absorb a little amount of salt, but small intestine is the main site for salt absorption. The chyme derived from the first food intake requires 36 hours for its solidification to be converted into solid residual matter known as faeces.

1.6 NEURAL CONTROL OF GASTROINTESTINAL SYSTEM

- The gastrointestinal tract has a nervous system all its own called the enteric nervous system. It lies entirely in the wall of the gut, beginning in the esophagus and extending all the way to the anus.
- This highly developed enteric nervous system is especially important in controlling gastrointestinal movements and secretion.

The enteric nervous system is composed mainly of two plexuses:

(a) An outer plexus lying between the longitudinal and circular muscle layers, called the ***myenteric plexus***,

The myenteric plexus controls mainly the gastrointestinal movements, and the submucosal plexus controls mainly gastrointestinal secretion and local blood flow. the extrinsic sympathetic and parasympathetic fibers that connect to both the myenteric and submucosal plexuses.

Sensory nerve endings that originate in the gastrointestinal epithelium (gut wall) and send afferent fibers to both plexuses of the enteric system,

- to the pre-vertebral ganglia of the sympathetic nervous system,
- to the spinal cord, and
- In the vagus nerves all the way to the brain stem.

These sensory nerves can elicit local reflexes within the gut wall itself and still other reflexes that are relayed to the gut from either the prevertebral ganglia or the basal regions of the brain.

Because the myenteric plexus lies between the longitudinal and circular layers of intestinal smooth muscle, it control muscle activity along the length of the gut.

The *myenteric plexus* neurons are act as excitatory as well as inhibitory *action on gastrointestinal tract*. The resulting inhibitory signals are especially useful for inhibiting some of the intestinal sphincter muscles such as the *pyloric sphincter*, which controls emptying of the stomach into the duodenum, and the *sphincter of the ileocecal junction*, which controls emptying from the small intestine into the cecum.

(b) An inner plexus, called the *submucosal plexus* or *Meissner's plexus* that lies in the submucosa. Which is mainly concerned with controlling function within the inner wall of each minute segment of the intestine. For instance, many sensory signals originate from the gastrointestinal epithelium and are then integrated in the submucosal plexus to help control local *intestinal secretion,* local *absorption,* and local *contraction of the submucosal muscle* that causes various degrees of infolding of the gastrointestinal mucosa.

Neurotransmitters Secreted by Enteric Neurons are two types

- Acetylcholine and nor-epinephrine and others are adenosine triphosphate, serotonin, dopamine, cholecystokinin, vasoactive intestinal polypeptide, somatostatin etc.
- Acetylcholine mostly excites gastrointestinal while Norepinephrine in hibits gastrointestinal activity. The other neurotransmitter substances are a mixture of excitatory and inhibitory in nature.

Autonomic Control of the Gastrointestinal Tract

A. Parasympathetic Innervations.

The parasympathetic supply to the gut is divided into

- *Cranial divisions* and
- *Sacral divisions*.

Except for a few parasympathetic fibers to the mouth and pharyngeal regions of the alimentary tract,

The *cranial parasympathetic* nerve fibers are almost entirely in the *vagus nerves* and provide extensive innervation to the esophagus, stomach, and pancreas and less to the intestines up to the first half of the large intestine.

The *sacral parasympathetic* nerve originate in the second, third, and fourth sacral segments of the spinal cord and pass through the *pelvic nerves* to the distal half of the large intestine and all the way to the anus.

The sigmoid, rectal, and anal regions are considerably better supplied with parasympathetic fibers than are the other intestinal areas.

These fibers function especially to execute the defecation reflexes. Stimulation of these parasympathetic nerves causes general increase in activity of the entire enteric nervous system.

B. Sympathetic Innervation.

Stimulation of the sympathetic nervous system inhibits activity of the gastrointestinal tract, causing many effects opposite to those of the parasympathetic system.

The sympathetic nerve endings secrete less amounts of *epinephrine* and mainly *norepinephrine* .

Sympathetic effects in two ways:

(a) The slight extent by direct effect of secreted norepinephrine to inhibit gastrointestinal tract smooth muscle (except the mucosal muscle, which it excites) and

(b) The major extent by an inhibitory effect of norepinephrine on the neurons of the entire enteric nervous system.

Afferent *Sensory* Nerve Fibers from the Gut

Afferent sensory nerves stimulated by

- Irritation of the gut mucosa,

- Excessive distention of the gut, or
- Presence of specific chemical substances in the gut.

Many afferent sensory nerve fibers innervate the gut. Some of them have their cell bodies in the enteric nervous system and some in the dorsal root ganglia of the spinal cord.

Signals transmitted through the fibers can then cause *excitation* or *inhibition* of intestinal movements or intestinal secretion.

Gastrointestinal Reflexes

There are three types of gastrointestinal reflexes of sympathetic and parasympathetic systems that are essential to control gastrointestinal function.

- **Reflexes** that are integrated entirely within the gut wall enteric nervous system. These include reflexes that control much gastrointestinal secretion, peristalsis, mixing contractions, local inhibitory effects.
- **Reflexes** from the gut to the prevertebral sympathetic ganglia and then back to the gastrointestinal tract. These reflexes transmit signals from the stomach to cause evacuation of the colon i.e. the gastrocolic reflex, signals from the colon and small intestine to inhibit stomach motility and stomach secretion i.e. the enterogastric reflexes, and reflexes from the colon to inhibit emptying of ileac contents into the colon i.e. the colonoileal reflex.
- **Reflexes** from the gut to the spinal cord or brain stem and then back to the gastrointestinal tract, these reflexes from
    1. The stomach and duodenum to the brain stem and back to the stomach by way of the vagus nerves to control gastric motor and secretary activity;
    2. Pain reflexes that cause general inhibition of the entire gastrointestinal tract; and
    3. Defecation reflexes that travel from the colon and rectum to the spinal cord and back again to produce the powerful colonic, rectal, and abdominal contractions required for defecation known as defecation reflexes.

The Gastrointestinal motility is controlled by neurogenic and myogenic mechanisms.

Neurogenic control is **at the level of central nervous system and transmitted by way of the extrinsic nerves of the sympathetic and parasympathetic nervous systems**.

1.7 BILE SECRETION AND CHOLESTEROL, HOMEOSTASIS, IMMUNE FUNCTION OF GI TRACT

The Synthesis of Bile acids from cholesterol takes place in Liver through the classic and alternate pathway. Bile acids work as digestive surfactant and promote absorption of lipids as well as fat-soluble vitamins that is the emulsification function of bile acids. Formation of bile acids are the primary pathway for cholesterol catabolism and account for ~50% of the daily turnover of cholesterol.

The synthesis of bile acids occurs exclusively in the liver in a series of enzymatic reactions in the hepatocyte that convert hydrophobic cholesterol into more water-soluble amphiphatic compounds.

The immediate products of the bile acid of synthetic pathways are primary bile acids i.e. Cholic acid and chenodeoxycholic acid are formed in humans. While the action of intestinal bacterial flora on primary bile acids results in the formation of secondary bile acids i.e. deoxycholic and lithocholic acids, derived from cholic acid and chenodeoxycholic acid consequently.

The liver is the organ that excrete significant amounts of cholesterol, either by converting it biosynthetically into bile salts or by secreting it as unesterified cholesterol into bile. From where cholesterol enters into small intestine and either reabsorbed or excreted via feces.

Homeostasis

Homeostasis is a self-regulating process that controls internal variables necessary to sustain life. In other words Homeostasis is self-regulating process by which an organism tends to maintain stability for its survival. If homeostasis is successful, a healthy life to continue; if unsuccessful, it results in a disaster or death of the organism.

Gastrointestinal homeostasis is a dynamic balance between the host, GI tract, nutrition and energy metabolism. Glucose is the main energy source in living cells. Two organs of the digestive system that work in unison are the pancreas and small intestine.

For digestive homeostasis liver, pancreas and small intestine are responsible of (other organs like the kidneys, and the brain (hypothalamus, the autonomic nervous system and the endocrine system) help to maintain homeostasis of body. The digestive system maintains homeostasis by ensuring that the stomach environment has the right pH balance.

Homeostasis is involved in **every organ system of the body**. Homeostasis is a mechanism that maintains a stable internal environment despite the changes present in the external environment by controlling body temperature, blood pH, blood glucose levels to fluid balance, sodium, potassium and calcium ion concentrations.

Regulation of Homeostasis

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

The regulation of homeostasis depends on three mechanisms:

1. Receptor,
2. Control Center and
3. Effector.

1. Receptor

The receptor is the sensing component responsible for monitoring and responding to changes in the external or internal environment.

2. Control Center

The control centre is also known as the integration centre. It receives and processes information from the receptor.

3. Effector

The effector responds to the commands of the control centre. It could either oppose or enhance the stimulus. The receptor receives information on the changing environment, and

the control centre processes the information received by the receptor. And the effector responds to the commands of the control centre by enhancing or opposing the stimulus.

The endocrine system and the nervous system are essential in maintaining the homeostasis of the body.

The digestive system liver plays a vital role in blood glucose homeostasis. When the blood glucose level rises after a meal, the liver removes glucose from the blood and stores it in the form of glycogen. When the blood glucose levels are low, it converts the stored glycogen back to glucose. In addition to the tube-like digestive pathway from the mouth to the anus, organs such as the liver, gallbladder, and pancreas are other parts of the digestive system with critical functions that help the body stay in equilibrium.

Providing Nutrients

The Human body requires proteins, carbohydrates, fats, vitamins, and minerals for all systems to work properly. The digestive system begin from mouth where bolus is formed from food and liquids. After being chewed and mixed with saliva and enzymes then the food passes through the osophagus and enters the stomach. In stomach it is churned and mixed with gastric juices. The stomach produces several hormones which regulate food ingestion and digestion. Food is propelled along slowly while being digested further by bacteria.

The small intestine absorbs nutrients from the proteins, fats and carbohydrates. Also absorbs water, minerals, and vitamins.

After, further breakdown and absorption of proteins, fats, carbohydrates and water, minerals, and vitamins also in the large intestine. The highly vascularized tissues in small and large intestine transport these nutrients throughout the body.

The waste that is leftover is moved toward the rectum and eliminated as feces.

To maintain homeostasis in the body (specially gastrointestinal tract) The bacterial flora in the intestines play very essential activities for homeostasis not only break down food for reabsorbed, they also produce vitamins like biotin and vitamin K and guard against harmful bacteria.

Immunity of gastrointestinal tract

The gastrointestinal tract continuously damage by viruses, bacteria, and parasites; ingested toxins and chemicals, including drugs and harmful food materials like additives.

The defense of the gastrointestinal tract is maintained by lymphoid tissue, which can be divided into three groups:-

1. The pharyngeal tonsils, the appendix, and The large nodules like structures known as Peyers patches located at intervals throughout the small intestine.
2. The second group includes the lymphocytes and plasma cells that populate the basement membrane i.e. lamina propria of the small intestine, the area of loose connective tissues above the supporting tissue of the mucosal lining extending into the villi.
3. The third group comprises lymphocytes that lie between the epithelial cells in the mucosa. The interaction between these cells of the lymphatic system and the threatening agent is the basis of defense in the gastrointestinal tract.

Lymphocytes are of two types, B and T, according to whether they originate in the bone marrow (B) or in the thymus gland (T), located in the chest. On leaving their tissue of origin, both types end up in the peripheral lymphoid structures. These include the peripheral lymph glands, the spleen, the lymph nodes in the mesentery of the intestine, the Peyers patches, and the spaces between the epithelial cells of the mucosa.

SAQ-2

1. The gastrointestinal movement in the digestive system is controlled by the **.....**
2. The intrinsic nervous system of the GI tract, containing a **.....** of neurons.
3. Bile acids are **.....**molecules synthesized from cholesterol in the liver.

SAQ-3

4. The regulation of homeostasis depends on three mechanisms:**....., ..., ...**
5. **.....**plays a vital role in blood glucose homeostasis.
6. The primary function of homeostasis is to maintain a balance within the body regarding its **.....**, food intake and pH levels.

1.8 PHYSIOLOGY OF GASTROINTESTINAL DISORDER

The gastrointestinal disorder is any condition that affects the digestive system. symptoms are depending on the condition and underlying causes of disease. The most gastrointestinal symptoms are pain in the abdomen, diarrhoea, constipation, excess gas, bloating, and weight loss.

Causes of gastrointestinal disorders are

1. **A low fiber diet**

   Fiber, a sort of carbohydrates found in plants that cannot be digested and It helps you feel full *and* aids in the digestion of certain foods. Everyone is talking about gut health, which in turn provide wide-ranging health benefits.

   The total daily recommended fiber intake is 25 grams for women and 38 grams for men under age 50. If you're older than 50, you will need to consume slightly less (around 21 grams for women and 30 grams for men). The good thing is that fiber is easily available in foods such as fruits (almost entirely in the skin, however), whole grains, legumes, beans, and vegetables.

   A diet low in fiber can be a **great way to help reduce bloating** and ease digestive problems, ranging from constipation, to abdominal pain, and even the onset of colon cancer.

2. **Being stressed**

Stress and anxiety can directly affect mental health as well as digestive health that is bi-directional communication - always sending messages to each other - which is why the gut has *more neurons than the whole spinal cord*.

Due to stress the digestive disorders:

- appetite loss,
- inflammation,
- bloating,
- cramping and
- changes in microbiota.

3. Not drinking enough water

Water require for easily break down food, absorb nutrients faster and more effectively in gastrointestinal tract to soften the stool, helping prevent constipation. Daily water intake not less than 8 glasses.

4. Eating a lot of dairy foods

Dairy is relatively new to the human diet - it was not really consumed for the first 200,000-plus years of mankind's existence. Milk and cheeses are usually loaded with fats and proteins that are difficult to digest, and according to some medical evidence have a *pro-inflammatory effect*. That's why consuming large amounts of dairy products can cause bloating, gas, constipation, and abdominal cramps.

5. Inactive lifestyle

Physical exercise is as important as food for overall digestion & health.

6. Aging

Aging can affect gut motility, reflux, and certain digestive conditions. The risk of developing cancers of digestive system also increases with age.

7. Genetic factors

Genetic and environmental factors can cause many immune and autoimmune gastrointestinal disorders like ulcerative colitis, Crohn's disease, celiac disease, cystic fibrosis, or hereditary pancreatitis and some liver conditions.

There are direct relation of gastrointestinal disorders with Lifestyle, side effects of medicines, laxatives, pregnancy, systemic diseases and inflammations.

The common gastrointestinal disorders are:

(A) Gastroesophageal Reflux Disease (GERD) and Peptic Ulcer Disease

(B) Liver Disease, Gallstones

(C) Acute and Chronic Pancreatitis

(D) Constipation and Chronic Diarrhea

(E) Irritable Bowel Syndrome (IBS):

- Celiac Disease,
- Crohn's Disease &
- Ulcerative Colitis

(F) Lactose Intolerance

(G) Diverticulitis

(A) Gastroesophageal Reflux Disease (GERD) and Peptic Ulcer Disease

Gastroesophageal Reflux Disease (GERD) – characterized by persistent bouts of acid reflux from the stomach up into the oesophagus causing a burning sensation and chest pain. GERD also known as acid regurgitation. If not treated acid reflux can damage the esophagus and lead to esophagitis, esophageal narrowing and other serious health complications including a precancerous lesion called Barrett's esophagus. Other features of GERD are dry cough, discomfort in the chest area, sore throat, swallowing difficulties, and sour taste in the back of the mouth.

Peptic ulcer disease –Peptic Ulcer Disease (PUD) is a gastrointestinal disorder, mostly caused by an infection by a microorganism called *Helicobacter pylori*, in which ulcers or open sores develop in the inner lining of the stomach and duodenum. Symptoms of Peptic Ulcers are loss of appetite, vomiting, chest pain, indigestion, weight loss, and bloody stools

(B) Liver Disease, Gallstones

Liver disease – Most common symptoms are pale stools, dark urine, jaundice (or yellowing of eyes and skin), loss of appetite, nausea, and vomiting. Liver diseases like liver cirrhosis, Chronic liver disease etc.

Gallstones- Gallbladder is a pear shaped small digestive organ located in the right upper abdomen and attached with Liver. Works as store and release bile, a yellowish-green fluid that aids in the digestion of fat. Causes of Gallstone formation is not well known, gallstones usually form when bile has a high concentration of bilirubin and cholesterol,these are small stone-like solids. they can cause no symptoms at all, gallstones may also cause pain in the upper abdomen.

(C) Acute and Chronic Pancreatitis

Acute and Chronic pancreatitis – Pancreas is an organ that produces digestive juices and hormones. Pancreatitis presented as abdominal pain, nausea, vomiting, weight loss. Acute Pancreatitis may be caused by acute infections, while chronic pancreatitis caused by

- Chronic infection and abdominal injury
- Alcoholism
- Smoking
- Obesity

The other causes are gallstones, cystic fibrosis and, hypertriglyceridemia (very high triglycerides), and some genetic disorders.

(D) Constipation and chronic Diarrhea

Constipation is a medical condition where the person experiences hard, dry and often painful bowel movements and occurring less frequently than normal (less than three bowel movements in a week). Constipation is caused by a low fiber diet, little or no physical activity, dehydration, certain medicines like sedatives and some antidepressants. Constipation may cause hemorrhoids and anal fissures due to strain.

Chronic diarrohea is a condition in which a person passes watery or loose stools more than three per day and this may cause dehydration and weakness. It may be caused by worm infestation (*Giardiasis*, *Clostridium difficile*, *Cryptosporidium*), chronic fungal and bacterial infections as well as IBS.

(E) Irritable Bowel Syndrome (IBS):

- Celiac Disease,
- Crohn's Disease &
- Ulcerative Colitis

Irritable Bowel Syndrome (IBS) is a group of gastrointestinal disorders presented with frequent abdominal pain, bloating and cramps associated with either diarrhea or constipation. Women are more susceptible to IBS than men. The cause is mostly unknown but symptoms are regurgitate by stressed.

Celiac disease is an autoimmune digestive disorder with unknown etiology, may be caused by gluten - proteins found in grains such as barley, rye, wheat, and their hybrids. Which destroys villi of the small bowel and the small intestine is unable to effectively absorb nutrients, vitamins, and minerals from food and cause malnutrition with many serious health problems e.g. infertility, permanent damage to the small bowel, and even the intestinal lymphoma.

Crohn's disease is a chronic inflammatory digestive disease affect any part of the GI tract, from the mouth to the anus. Commonly involves the ileum that becomes ulcerated and inflamed. It is also a medical condition of gastrointestinal disorders called inflammatory bowel syndrome (IBS).

Ulcerative colitis is another inflammatory bowel disease. In this condition the lining of the colon is affected by inflammation and open sores. Symptoms of Ulcerative colitis are abdominal pain, diarrhea, bloody stools, malnutrition and fever. Ulcerative colitis is one of the two most common inflammatory bowel syndrome (IBS), along Crohn's disease.

(F) Lactose Intolerance

Lactose intolerance is a disorder in which there is no proper digestion of lactose, a simple carbohydrate present in all mammals' milk and in its derivatives due to lack of lactase, an intestinal enzyme which normally digests lactose.

(G) Diverticulitis

Symptoms of Diverticulitis are constipation, diarrhea and bloating. Chronic diverticulitis can lead to rectal bleeding and other severe digestive complications. **In diverticulitis** there is formation of small pockets or pouches called diverticula (multiple in numbers, singular is divertculum) in the lower part of the inner lining of the colon of get inflamed with infection.

1.9 SUMMARY

- Digestion is a process that converts complex foodstuffs into simpler ones which can be readily absorbed by the gastrointestinal tract.
- Digestive tract starts at the mouth and ends at the anus.
- There are three main functions of the gastrointestinal tract, including transportation, digestion, and absorption of food.
- The stomach functions to store, churn, and puree food into a substance known as chime. Gastric juices are secreted by the cells of the stomach, contributing to chemical digestion.
- Stomach, duodenum and upper part of small intestine are the major sites of digestion.
- The small intestine is composed of the duodenum, jejunum, and ileum. The small intestine is the prime site for the absorption of digested foods.
- The large intestine extends from the terminal ileum at the ileocecal valve to the rectum. At the terminal ileum, the large intestine becomes the ascending colon, the transverse colon, and then the descending colon.
- The liver is a very large organ located in the upper right abdomen. Blood supply to the liver arises from both the portal vein and hepatic artery.
- The pancreas is both an endocrine and exocrine gland. The exocrine function of the pancreas is mainly digestive in nature and involves the secretion of pancreatic enzymes and bicarbonate.
- Digestion of carbohydrates is initiated in the mouth of salivary amylase and is completed in the small intestine by pancreatic amylase. Monosaccharides are the final absorbable products of carbohydrates digestion.
- Protein digestion begins in the stomach by pepsin which is aided by gastric HCl, pancreatic proteases (trypsin, chymotrypin) and intestinal amino peptidases and dipeptidases complete the degradation of proteins to amino acid and some dipeptides.
- Digestion of lipids occurs in the small intestine. Emulsification of lipids, brought about by bile salts.
- The gastrointestinal movement in the digestive system is controlled by the autonomic nervous system. The autonomic nervous system regulates the functions of gastro-intestinal tract.
- Bile acids are amphipathic molecules synthesized from cholesterol in the liver. Bile acid synthesis is a major pathway for hepatic cholesterol catabolism. Bile acid synthesis generates bile flow which is important for biliary secretion of free cholesterol, endogenous metabolites, and xenobiotics.

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

1.11 TERMINAL QUESTIONS

Q.1 Describe briefly digestion and absorption of carbohydrates.

.....

.....

.....

Q.2 Describe briefly digestion and absorption of proteins.

.....

.....

.....

Q.3 Describe briefly digestion and absorption of Fats.

.....

.....

.....

.....

Q.4 What is the primary function of homeostasis? How does the cell maintain homeostasis in the body?

.....

.....

.....

.....

Q.5 Describe in details about the gastrointestinal disorders?

.....

.....

.....

Q.6 Short notes on the following –

(1) What is the gastrointestinal tract?

.....

.....

(2) What are the functions of the gastrointestinal tract?

.....

.....

(3) State homeostasis definition.

.....

.....

(4) Which body systems help to maintain homeostasis?

.....

.....

(5) Gastrointestinal disorders.

.....

.....

(6) Discuss the term assimilation, Discuss the emulsification of fats.

.....

.....

1.9 ANSWERS

SAQ-1

1. transportation, digestion, and absorption
2. duodenum, jejunum, and ileum.
3. upper right abdomen

SAQ-2

1. autonomic nervous sytem.
2. mesh-like system
3. amphipathic

SAQ-3

1. Effector, Receptor & Control Center
2. Liver
3. temperature, salt concentration

References:

1 Human Physiology by C.C Chatterjee

2 Animal physiology and biochemistry by Dr. R.A. Agarwal and Dr. Anil kumar Srivastava

3 Regulatory mechanism in vertebrates by Pardey and Shukla

4 Anatomy, physiology and pathology by P.K. Agarwal

5 Biochemistry by Dr.U.Satyanarayana and Dr.U.Chakrapani

6 Human physiology and biochemistry by Prof. A.K.Jain

UNIT-2 MUSCLES AND NERVE FIBERS

Structure

2.1 INTRODUCTION

In the previous unit you have learnt about the digestion of vertebrates. In this unit you will learn briefly about the structure and functions of muscular system and nerve fibers. Muscles are an important part of the human body. Muscles help in managing the heartbeat, digestion, vision, breathing, and other important functions of the body. There are three types of muscles in a body- Cardiac muscles, smooth muscles and skeletal muscles. Smooth muscles can be traced inside the blood vessels and other organs of the body. Cardiac muscles are found only in the heart. In the heart, these muscles play coordinated contractions which help the heart in pumping blood via the circulatory system of the body. Skeletal muscles are attached to the bones throughout the body. These muscles help in the functioning of the body, as a whole.

The muscular system is composed of specialized cells called muscle fibres. The muscular system is responsible for functions such as maintenance of posture, locomotion, and control of various circulatory systems. The muscular system also plays a significant role in our Posture. This system in the body helps in keeping the body in a correct, definite, and aligned position. The muscular system also helps in protecting the internal organs of the body. The muscles in the body help in regulating the temperature of the body. It is found that the fluctuations in the temperature of the body are due to the contraction of muscles in the body.

Objectives:-

After studying this unit you should be able to:

- Describe the skeletal, cardiac and smooth muscles
- Know Different types of contractile filament

- UnderstandSarcotubular system of cardiac muscle
- Know Sliding filament theory of muscle contraction

2.2 TYPES OF MUSCLES

The body muscles are divided into three types -

1) Skeletal muscle
2) Cardiac muscle
3) Smooth muscle

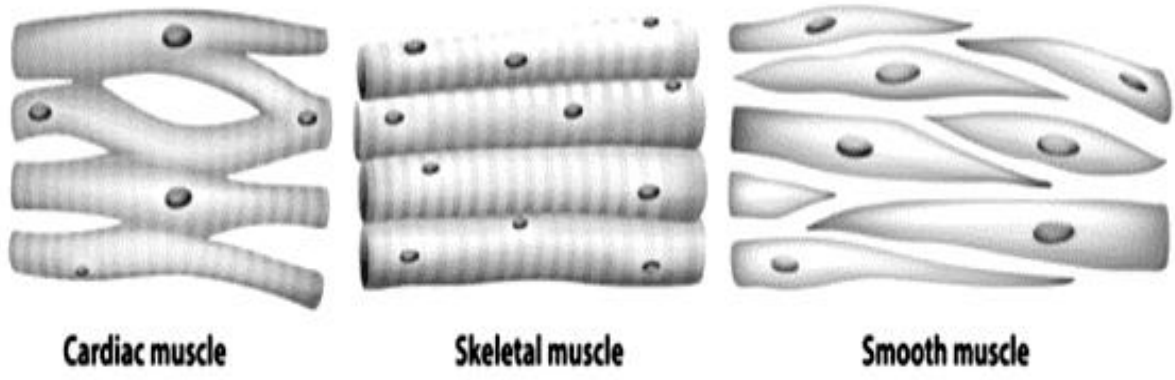


Fig.2.1: Types of Muscles

Source: http://www.wikipedia.org

1. Skeletal muscle

- Each skeletal muscle has three layers of connective tissue (called mysia) that enclose it, provide structure to the muscle, and compartmentalize the muscle fibers within the muscle.
- Each muscle is wrapped in a sheath of dense, irregular connective tissue called the **epimysium** or, which allows a muscle to contract and move powerfully, while maintaining its structural integrity.
- The epimysium also separates muscle from other tissues and organs in the area, allowing the muscle to move independently.
- The muscle fibre is enclosed in a sheath of connective tissue which is termed as **endomysium**. Such muscle fibres are arranged in bundles known as fascicule.
- The skeletal muscles are attached to the skeleton and form somatic musculature, also called the striated muscle. Generally under voluntary control.
- Sarcomeres is the basic functions unit of the muscle fibre.
- The term muscle fibre's is attributed to a muscles fiber. A single fibril is made up of many myofilaments and the myofibrils are collectively called the contractile elements of the muscle.
- Each muscles fibres are multinucleated cylindrical structure which tapers at both ends.

- The cell membrane of muscle fibre called sarcolemma and its cytoplasm called the sarcoplasm, contains numerous mitochondria are termed sacrosomes, smooth surface endoplasmic reticulum term as sarcoplasmic reticulum. The **sarcoplasmic reticulum (SR)**, stores, releases, and retrieves calcium ions (Ca^{++}).
- Each muscle fibres are made up of many fibrils called myofibrils; the myofibrils are composed of actine &myosine filaments.
- The filaments are chiefly made up of four contractile proteins – actin, myosin, tropomyosin and troponin.

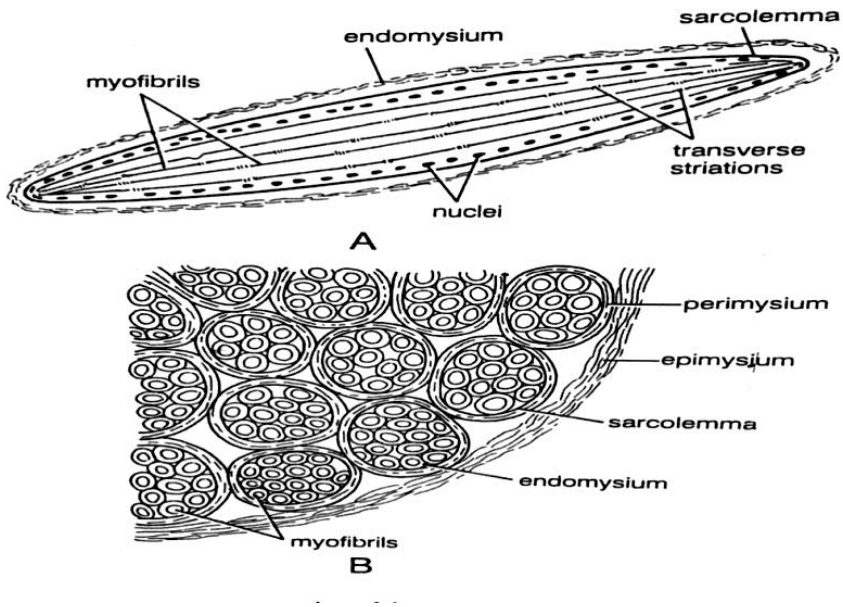


Fig. 2.2: Muscle Fibres

Source: http://www.wikipedia.org

Function of Skeletal muscle:-

- Skeletal muscles are attached to the bones throughout the body.Extensibility, Excitability, Contractibility, and Elasticity are a few of the properties of the Skeletal Muscles.
- These muscles are attached to the bones with the help of Tendons. Tendons are collagen fibres.
- Skeletal muscles include a bunch of muscle fibres- commonly known as the Fascicule. Each of these muscle fibres is lined by a plasma membrane.
- In skeletal muscles that work with tendons to pull on bones, the collagen in the three connective tissue layers intertwines with the collagen of a tendon. At the other end of the tendon, it fuses with the periosteum coating the bone.
- The tension created by contraction of the muscle fibers is then transferred though the connective tissue layers, to the tendon, and then to the periosteum to pull on the bone for movement of the skeleton. In other places, the mysia may fuse with a broad, tendon-like sheet called an **aponeurosis**, or to fascia, the connective tissue between skin and bones.

- The broad sheet of connective tissue in the lower back that the latissimus dorsi muscles (the "lats") fuse into is an example of an aponeurosis.
- Every skeletal muscle is also richly supplied by blood vessels for nourishment, oxygen delivery, and waste removal.
- Skeletal Muscles are of two types- Red and White. Red Muscles are tinier in diameter and the number of mitochondria in these muscles are huge. On the other type, white muscles are huge in diameter and have a small amount of myoglobin in them.

SAQ1.

(a). Each muscle is wrapped in a sheath of dense, irregular connective tissue called the **……..**

(b). There are three types of muscles in a body- ……..., ……. ……..

(c). Cardiac muscles are found only in the ……..

(d). ……. are attached to the bones throughout the body.

Sarcomere

The sarcomere is the smallest functional unit of skeletal muscle fibre and highly organised arrangement of contractile, regulatory and structural proteins.

- A sarcomere is defined as the region of a myofibril contained between two cytoskeletal structures called Z-discs (also called Z-lines or Z-bands), and the striated appearance of skeletal muscle fibers is due to the arrangement of the thick and thin myofilaments within each sarcomere.
- The dark striated **A band** is composed of the thick filaments containing myosin, which span the center of the sarcomere extending toward the Z-dics. The thick filaments are anchored at the middle of the sarcomere (the M-line) by a protein called myomesin.
- The lighter **I band** regions contain thin actin filaments anchored at the Z-discs by a protein called α-actinin. The thin filaments extend into the A band toward the M-line and overlap with regions of the thick filament.
- The A band is dark because of the thicker myosin filaments as well as overlap with the actin filaments.
- The **H zone** in the middle of the A band is a little lighter in color because it only contain the portion of the thick filaments that does not overlap with the thin filaments (i.e. the thin filaments do not extend into the H zone).

Because a sarcomere is defined by Z-discs, a single sarcomere contains one dark A band with half of the lighter I band on each end.

- During contraction the myofilaments themselves do not change length, but actually slide across each other so the distance between the Z-discs shortens resulting in the shortening of the sarcomere.

- The length of the A band does not change (the thick myosin filament remains a constant length), but the H zone and I band regions shrink. These regions represent areas where the filaments do not overlap, and as filament overlap increases during contraction these regions of no overlap decrease.
- The thin filaments are composed of two filamentous actin chains (F-actin) comprised of individual actin proteins. These thin filaments are anchored at the Z-disc and extend toward the center of the sarcomere. Within the filament, each globular actin monomer (G-actin) contains a myosin binding site and is also associated with the regulatory proteins, troponin and tropomyosin.
- The troponin protein complex consists of three polypeptides. Troponin I (TnI) binds to actin, troponin T (TnT) binds to tropomyosin, and troponin C (TnC) binds to calcium ions.
- Thick myofilaments are composed of myosin protein complexes, which are composed of six proteins: two myosin heavy chains and four light chain molecules.
- The heavy chains consist of a tail region, flexible hinge region, and globular head which contains an Actin-binding site and a binding site for the high energy molecule ATP.
- The light chains play a regulatory role at the hinge region, but the heavy chain head region interacts with actin and is the most important factor for generating force. Hundreds of myosin proteins are arranged into each thick filament with tails toward the M-line and heads extending toward the Z-discs.

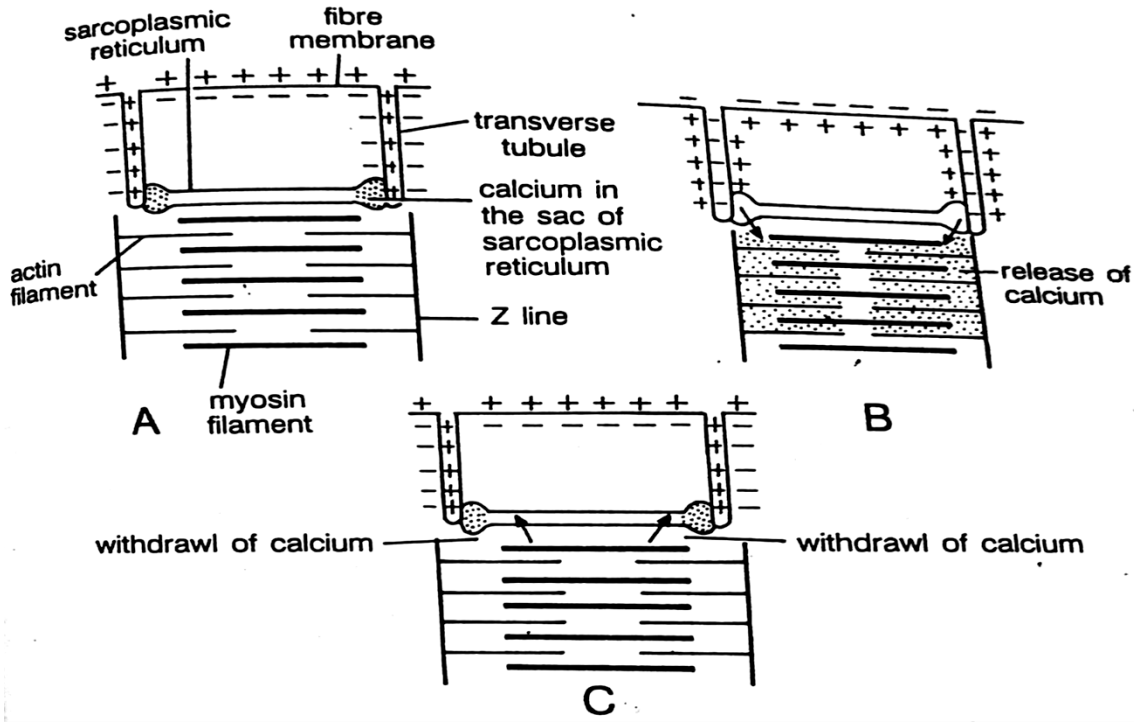


Fig. 2.3: electron microscopy appearance of the filament

Source: Human Physiology by C.C. Chaterjee

2. Cardiac Muscle:-

Striated involuntary muscle contracts rhythmically and automatically, present in the muscle layer of heart. Vertebrate cardiac muscles are composed of branched cells. In electron microscope studies that the heart muscles are made up of distinct individual cells, which appear like a syncytium because adjacent membranes are in very close contact with each other through special membranes, called the intercalated discs. The cardiac muscle fibres are smaller in size than the skeletal muscle fibres.

The functional properties of cardiac muscle differ from the skeletal muscle.

- The spontaneous nature of contraction and rhythmicity which is not subject to voluntary control.
- The fibres are not simple cylindrical but they bifurcate and come in contact with that of the neighbouring fibres and ultimately form a three dimensional network.
- The nucleus is single and placed deep in the sarcoplam more or less at the centre.

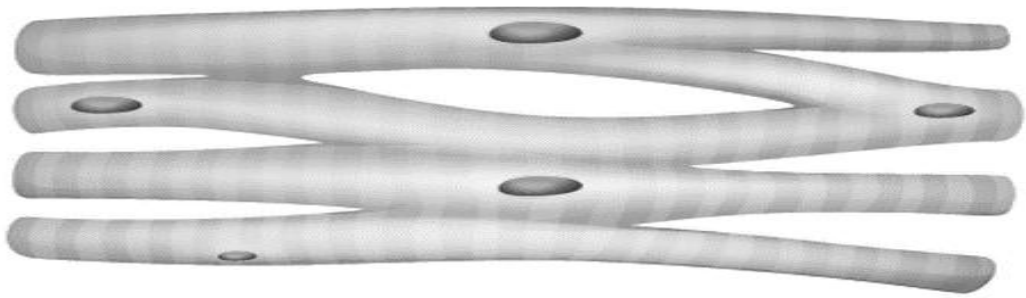


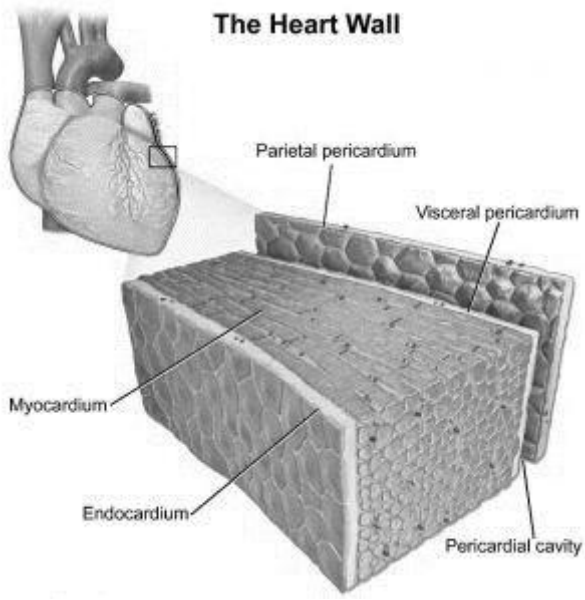
Fig.2.4: Cardiac Muscle

Source: http://www.wikipedia.org

Cardiac Muscle Structure

- These muscles are only found in the heart. In the heart, these muscles play coordinated contractions which help the heart in pumping blood via the circulatory system of the body.
- These muscles include involuntary movements- for keeping the heart pumping blood. The pacemaker cells help the Cardiac muscles in maintaining their functioning and the heart keeps beating throughout.
- Cardiac muscle, also known as heart muscle, is the layer of muscle tissue which lies between the *endocardium* and *epicardium*. It is a specialized form of muscle evolved to continuously and repeatedly contract, providing circulation of blood throughout the body. The heart is a relatively simple organ. Through all the twists and turns and various chambers, there are only three layers.
- The outer layer, known as the *epicardium* or *visceral pericardium*, surround the cardiac muscle on the exterior. This helps protect it from contact with other organs.
- The *parietal pericardium* attaches to this outer layer creates a fluid-filled layer which helps lubricate the heart.
- The inner layer, or *endocardium*, separates the muscle from the blood it is pumping within the chambers of the heart. In between these two sheets lies the cardiac muscle. Cardiac muscle is sometimes referred to as *myocardium*.

- At the microscopic level, cardiac muscle is organized much like skeletal muscle. Both muscle tissues are *striated*, meaning they show dark and light bands when viewed under a microscope. These band are created by the highly organized *sarcomeres*.
- A sarcomere is a bundle of protein fibers which respond to a signal and contract. In both skeletal and cardiac muscle, these sarcomeres are made of *actin* and *myosin* and are supported by the same proteins.
- *Tropomyosin* is a protein which wraps actin and stops myosin from binding to it. *Troponin* is a protein which holds tropomyosin in place until a signal to contract has been received. These proteins are the same in both skeletal and cardiac muscle.



Function of Cardiac Muscle

- Skeletal muscle is controlled by the signal usually comes from the *somatic*, or voluntary, nervous system. Cardiac muscle is controlled by the *autonomous nervous system*.
- The *action potential*, or nerve impulse, on the surface of the cell stimulates a specialized organelle to release calcium ions (Ca^{2+}). This organelle is called the *sarcoplasmic reticulum*.
- The Ca^{2+} ions released into the cytoplasm affect the protein troponin, causing it to release tropomyosin. Tropomyosin shifts position and myosin is allowed to attach to actin.
- Myosin then used the energy stored in ATP molecules. When the impulse is transmit, the Ca^{2+} is reabsorbed quickly into the sarcoplasmic reticulum. Troponin reattaches to tropomyosin, and the cardiac muscle cells release. This general process happens every time your heart beats.

Differences between Cardiac Muscles and Skeletal Muscles

1. Cardiac muscles are found in the Heart and are involuntary muscles while skeletal muscles are attached to the bones and are voluntary in nature.
2. Cardiac muscles are only found in the heart wall of vertebrates while skeletal muscles can be found all over the body, attached with the help of Tendons.

3. Cardiac muscles have branched fibres while skeletal muscles have cylindrical fibres.
4. Cardiac muscles have only one centrally designated nucleus while skeletal muscles have several peripheral nuclei.
5. Cardiac muscles are shorter in size while skeletal muscles are longer, compared to cardiac muscles.
6. Cardiac muscles help in the pumping of blood from the heart while skeletal muscles help in the movement and functioning of the body.

Sarcotubular system (T system)

The T system is the tubular invagination of the sarcolemma of the cardiac muscle. Initation for contraction involving a system of tubules called sarcoplasmic reticulum.

T-system:-

This T-system is the tubular invagination of the sarcolemma of the cardiac muscle and is larger in diameter than that of the skeletal muscle. The T-tubules are present at the Z lines in the cardiac muscle fibres, but the same are at the A-I junction in case of the mammalian skeletal muscle.

These tubules also increase the surface for metabolic exchange in between the interior of the cardiac muscle fibres and the intercellular space.

Over and above they function for quick propagation of impulse from the cell surface to the interior.

Sarcoplasmic reticulum:-

The sarcoplasmic reticulum is identical with the endoplasmic reticulum of other cell type but with the difference that its membrane does not possess ribosomes.

They are consisted of longitudinal interconnected tubules which are expanded into small terminal sacs at the Z lines.

There are no well-developed transverse cisternae in the cardiac muscle.

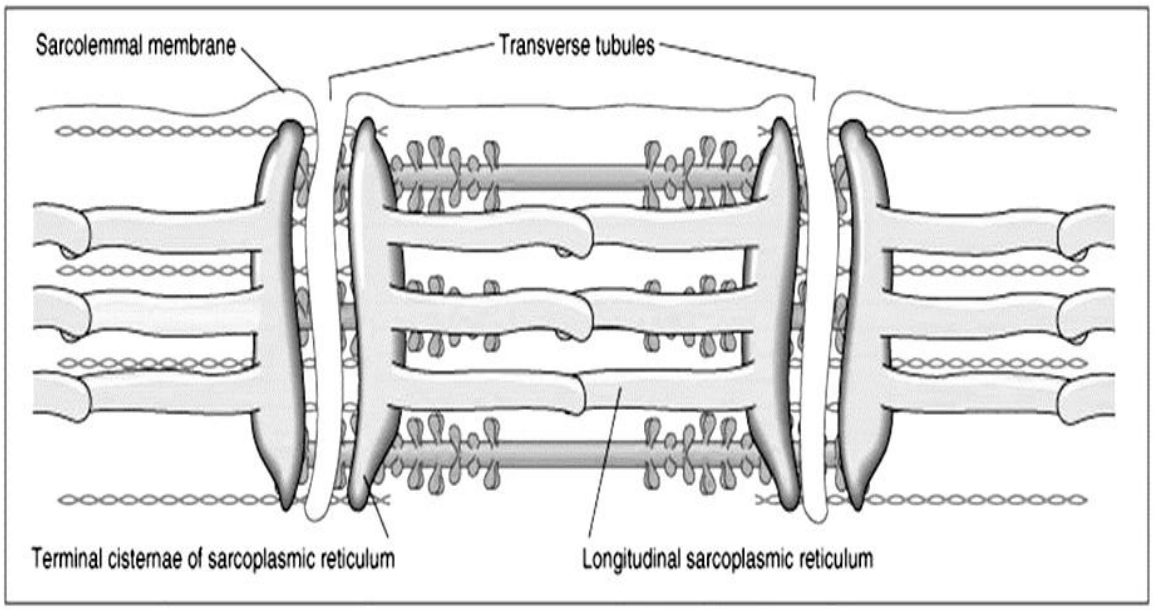


Fig.2.5:Sarcotubular System

Source: Physiology 3E www.studentconsult.com

SAQ 2

(a). **……..**sarcolemma of muscle fiber at the neuromuscular junction, with receptors for the neurotransmitter acetylcholine.

(b). **…….**long, cylindrical organelle that runs parallel within the muscle fiber and contains the sarcomeres.

(C). **……**protein that makes up most of the thick cylindrical myofilament within a sarcomere muscle fiber.

3. Smooth Muscle

Smooth muscle fibres are elongated and **spindle-shaped** cells which taper at both ends. This distinctive shape, along with the presence of a **single central nucleus**, helps to identify it histologically. These fibres are thousands of times shorter than skeletal muscle fibres.

Mostly in hollow viscera lacks cross- striations, therefore also called plain muscle. Involuntary in nature. Also called non-striated smooth involuntary muscle. Smooth muscles are small and spindle shaped, each muscle has a single nucleus. These muscles are present in all hollow viscera eg. gastro-intestinal tract, ducts of the glands, blood vessels, respiratory, urogenital and lymphatic system of the body .

These muscles are also present in the dermis, ciliary body and iris of the eye.

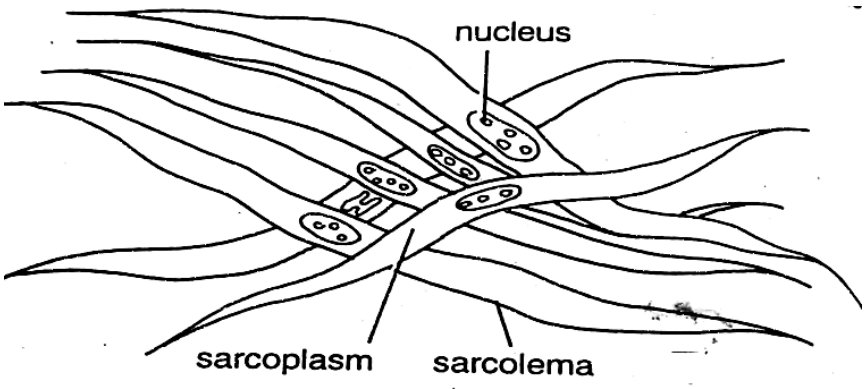


Fig.2.6:Smooth Muscle

Source: Animal Physiology by A.K.Berry

Smooth muscle differs from striated muscle in many ways. T-tubules, myofibrils and sarcomeres are all **absent**, in contrast to striated muscle. Actin and myosin contractile proteins are present, as are thick and thin filaments. However, these are arranged differently. Thin filaments are attached to a **dense body** (analogous to the Z-disc of skeletal and cardiac muscle).

Contraction of smooth muscle is not under conscious control, hence it is referred to as an **involuntary** muscle. Triggers for smooth muscle contraction include hormones, neuronal stimulation by the autonomic nervous system and other local factors.

Neurons of the autonomic nervous system do not form an organised neuromuscular junction with smooth muscle. Instead, swellings of axons filled with neurotransmitter known as **varicosities** lie in close contact with the sarcolemma.

SAQ 3,

(a). **……**outer layer of connective tissue around a skeletal muscle.

(b). **……..** sequence of events from motor neuron signaling to a skeletal muscle fiber to contraction of the fiber's sarcomeres.

(C). **……**bundle of muscle fibers within a skeletal muscle.

Control of Contraction

Smooth muscle is often **spontaneously active**, and can trigger action potentials without stimuli via the action of **pacemaker cells** in the walls of hollow organs. Its nerve supply acts to either stimulate or depress the activity of the fibre, depending on the neurotransmitter released.

In certain locations, muscle stretching can trigger its own contraction via the **stress-relaxation response**. In the stress-relaxation response, as the muscle stretches, the mechanical stress initiates muscle contraction, immediately followed by relaxation. This is especially important in **hollow organs** such as the stomach or urinary bladder, which continuously expand when they fill. This response allows smooth muscle surrounding these organs to maintain muscle tone when the organ empties and shrinks, preventing premature emptying and 'flabbiness' in the empty organ.

Function of Smooth Muscle

Smooth muscle is found in numerous body systems and has a variety of functions depending on its location.

- Cardiovascular system – vascular smooth muscle cells are present in all vascular segments in the **tunica media** layer, excluding capillaries. Smooth muscle contraction and dilation (**vasoconstriction** and **vasodilation** respectively) controls blood vessel diameter, thereby controlling the distribution of blood and determining blood pressure.
- Respiratory system – smooth muscle layers are present in the walls of the bronchi and bronchioles, helping to regulate air flow into the lungs.
- Gastrointestinal tract – extensive layers of smooth muscle are present to help move food down the GI tract via **peristalsis**, and eject bile into the digestive tract from the gallbladder.
- Urinary system – layers of smooth muscle are found in the ureter walls and bladder to aid movement of urine out of the body.
- Male reproductive tract – layers of smooth muscle are present in the **vas deferens** to help move sperm through the system, and also functions to cause ejection of glandular secretions from the prostate, seminal vesicle and bulbourethral glands.
- Female reproductive tract – the **myometrium** of the uterus mostly consists of smooth muscle, and is stimulated by oxytocin to contract during labour to aid in birthing of the foetus.
- Ophthalmic system – **ciliary muscle** contracts and dilates to change the size and shape of the lens, changing the amount of light entering the eye.
- Integumentary system – hair follicles in the skin are associated with **erector pili** muscles, which contact to elevate hairs in response to changes in temperature.

2.3 TRANSMISSION OF IMPULSE & MECHANISM OF CONTRACTION

The mechanism of contraction in the cardiac muscle is essentially same as that of the skeletal muscle. Impulse originated in the pace-maker area is transmitted through different conducting tissues and ultimately reaches the cardiac muscle fibres, and from which the impulse is transmitted

rapidly from cell to cell, through different surface. From the cell surface the impulse is transmitted to the contractile elements of the myofibrils through the sacroplasmic reticulum.

Following stimulation the impulse is transmitted to the myofibrils by the T-System and the depolarization causes the release of calcium from the sarcoplasmic reticulum, which in turn activates the myosin ATPase.

- This activated ATPase breaks the ATP to ADP and the ADP to AMP with the release of certain amount of energy which is required for the process of contraction.
- At the end of the contraction, the Ca^{++} ions returns to the sacroplasmic reticulum and relaxation occurs.
- Firstly myosin reacts with ATP to form myosin-ATP complex.
- Further, in the presence of k^{+} and F-actin, Actomyosin-ATP complex is formed.

$$Myosin + ATP \xrightarrow[F-actin]{K^{+}} \text{Actomyosin} - \text{ATP}$$

- This complex in the presence of Ca^{++} and ATPase splits the-ATP to inorganic phosphate and actomyosin ADP.

Thus, now it is known that the muscle contraction is turned on by the release of Ca^{++}ion and the hydrolysis of ATP of actomyosin – ATP complex provides the necessary energy.

- Relaxation of the muscles fibre results from the recovery of calcium ion back into the sarcoplasmic reticulum. This is done by an ATP dependent Ca^{++}ion pump. Decrease in the concentration of Ca^{++}ion dissociates Ca^{++}ion from troponin and then tropomyosin inhabits contraction.

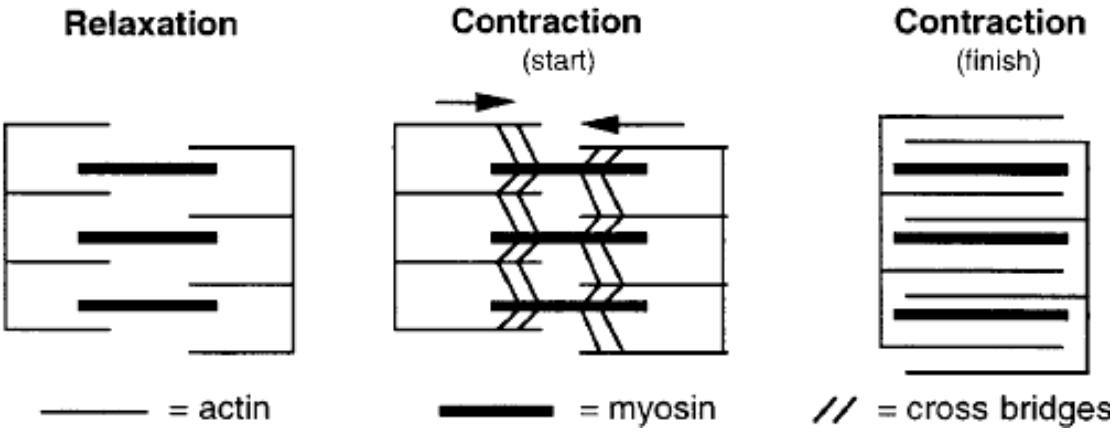


Fig. 2.7:Mechanism of Contraction

Source: Human Physiology C.C.Chatterjee

Sliding-filament theory of muscle construction:-

The sliding filament mechanism of muscle contraction was discovered by **Huxley**.

- The process by which the shortening of the muscle is brought about sliding of actin filament over the (thick) myosin filaments.

- When a muscle is in the resting state, it remains extended because actin and myosin components of the actomyosin-ATP complex.
- When a nerve impulse arrives at the junction between the nerve ending and the muscle, the **sarcolemma** of a muscle fibre is depolarized, Subsequently, the depolarization of sacrolemma is transmitted to the interior of the muscle fibre by a plexus of channels the **sarcoplasmic reticulum**.
- The action potential depolarizes the muscle membrane here, It causes the sarcoplasmic reticulum to release large quantities of Ca^{++}ion.
- Ca^{++}ion activates the contraction process.
- The released calcium binds to the TPC subunit of the troponin complex, producing conformational changes which are transmitted to tropomyosin and then to actin protein of the thin filament, so actin interact with myosin with resultant muscular contraction.
- Intact myosin has the activity of enzyme ATPase which hydrolyzes ATP and ADP, releasing the energy for activity.
- The thick and thin filaments interact by cross bridges.
- The sliding during muscle contraction is produced by breaking and reforming of cross bridge (cross linkage) between actin and myosin.
- The width of 'A' band is constant where as the Z lines move closer together when the muscle contracts and farther apart when it is stretched. As the muscle shortens filaments apparently overlap.

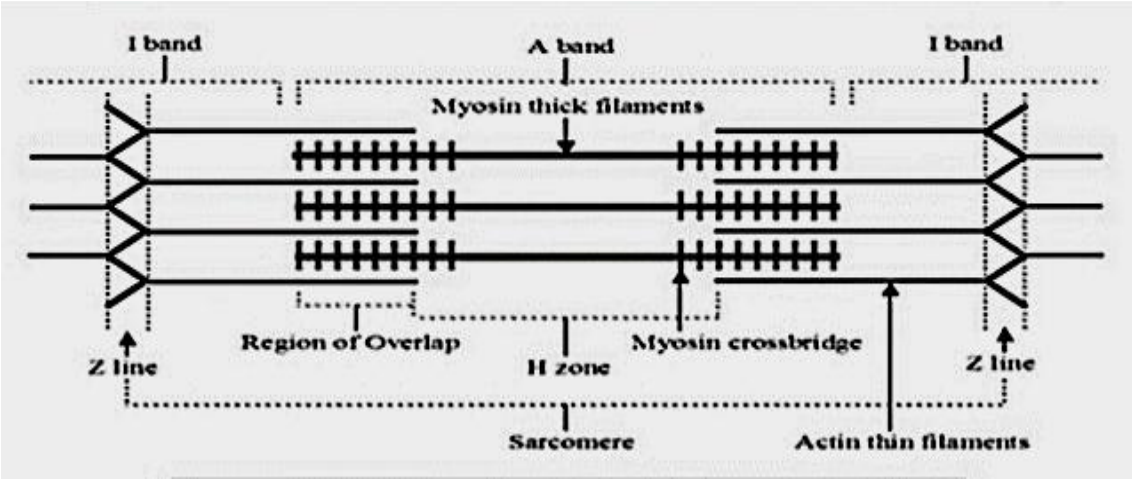


Fig.2.8: Sliding Filament Theory

Source: http://www.wikipedia.org

SAQ 4,

(a). **…….**neurotransmitter that binds at a motor end-plate to trigger depolarization.

(b). **……..**protein that makes up most of the thin myofilaments in a sarcomere muscle fiber.

(C). ……..change in voltage of a cell membrane in response to a stimulus that results in transmission of an electrical signal unique to neurons and muscle fibers.

(d). …….loose, and well-hydrated connective tissue covering each muscle fiber in a skeletal muscle.

2.4 NERVOUS CONTROL OF MUSCLES

Muscles are supplied both with sensory and motor fibres. The sensory nerves, sent information regarding the 'stage' of the muscle (pain, fatigue etc.) to the central nervous system. Motor nerves accordingly control the activity of the muscle. Special motor nerves which prevent muscles from contracting are called inhibitory nerves. Nerves which control the activity of automatically contracting muscles, like visceral and heart muscles are called regulatory nerves. Regulatory nerves can be both inhibitory and excitatory. The point at which the axon makes contact with the muscle is called myoneural junction or motor end plate.

- When a single axon divides into several terminals before supplying a muscle fibre it is termed mononeural multiterminal.
- When a muscle fibre receives stimuli from several axons it is called polyneuronal innervated by, it is called a motor unit. If a large number of motor units are present in a muscle, the muscle can contract in a finely graded manner.

2.5 PROTEINS IN MUSCLES (CONTRACTILE FILAMENT)

The filaments are chiefly made up of four contractile protein - **actin, myosin, tropomyosin and troposin**. A single fibril is made up of many myofilaments. Myofibrils and myofilaments are collectively called the contractile filaments of muscle.

Myosin:-

- Myosin binds to the polymerized form of actin, the major constituents of the thin filament. It is composed of about 200 myosin molecules, each having molecular weight of 4,80,000.
- Myosin is composed of six polypeptide chains (hexamer). It contains one pair of heavy chains and two pairs of light chains.
- The two heavy chains coil around each other to form a double helix.
- One end, of each of these chains, folded into a globular protein mass called head of the myosin, other end of helix is called the tail.
- The four light chains are also part of myosin heads, two to each head.
- These light chains aid to control the function of the head during the process of muscle contraction.
- The myosin molecule is composed of two parts : one part is called light meromyosin and the other part is called heavy meromyosin.
- The head fragment is globular in shape, this protein called the heavy meromyosin (HMM). Heavy meromyosin, contains the fibrous and globular proteins of myosin.
- The heavy meromyosin has two chemically different active sites.

- The tail fragments of myosin molecules are called light mermomyosin (LMM). It is a rod like structure consisting of two alpha helices coiled around each other like a two-stranded rope.
- The globular subunit of myosin has two active sites, one for actin and other for ATP.
- At one site binding to actin molecule and at the other hydrolysis of ATP occurs.
- In the cross bridging cycle, the globular head binds ATP and splits it to ADP + Pi in the presence of Mg^{2+}, but does not release the ADP and Pi.
- These energy released is stored in the myosin-ADP complex.
- This complex then binds actin, forming actin – myosin – ADP – Pi - complex.
- In the next step, ADP and Pi are released by myosin and the myosin head changes the conformation, pulling the attached actin towards the middle of the myosin filament.
- The myosin head then binds to a new ATP, triggering its release from actin subsequently, the new ATP is hydrolysed, blocking the myosin head in position to bind another actin molecule.
- Tropomyosin and Troponin are cross-linking proteins found in association with actin.

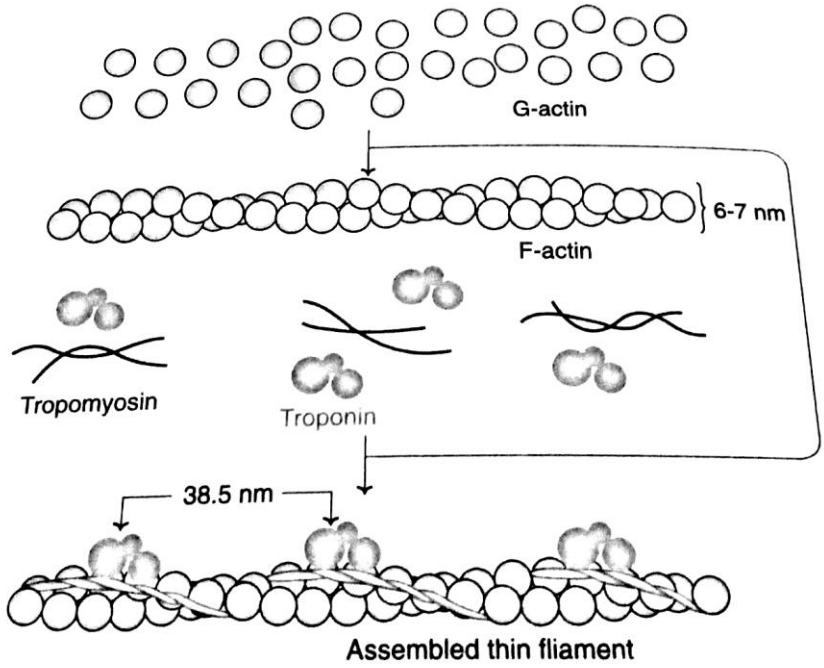


Fig Diagrammatic representation of the thin filament of a sarcomere

Source: Human Physiology and Biochemistry by Prof. A.K.Jain

<u>Tropomyosin</u>:-

- Tropomyosin is a long protein coiled along the groove between the chains of actin filament.
- Tropomyosin composed of two chains, attaches to F-actin in the grooves.

<u>Troponin:-</u>

- Troponin is also found on the actin filament.
- It is a protein molecule. It is attached to each tropomyosin molecule forming Troponin-Tropomyosin complex.
- Troponin has got a deep affinity for Ca^{++}. The calcium ions bind to troponin & bring about conformational changes in both troponin & tropomyosin molecules. This effects induces the movement of tropomyosin to uncover the binding sites & allow cross bridges of myosin to bind to actin filament. Thus calcium ion acts as the physiological regulation of muscle contraction.
- Troponin consist of three Polypeptide chains, according to its functions -
  - Troponin T (TPT binding to tropomyosin).
  - Troponin I (TPI, that inhibits F-actin myosin interaction)
  - Troponin C (TPC, calcium binding polypeptide)

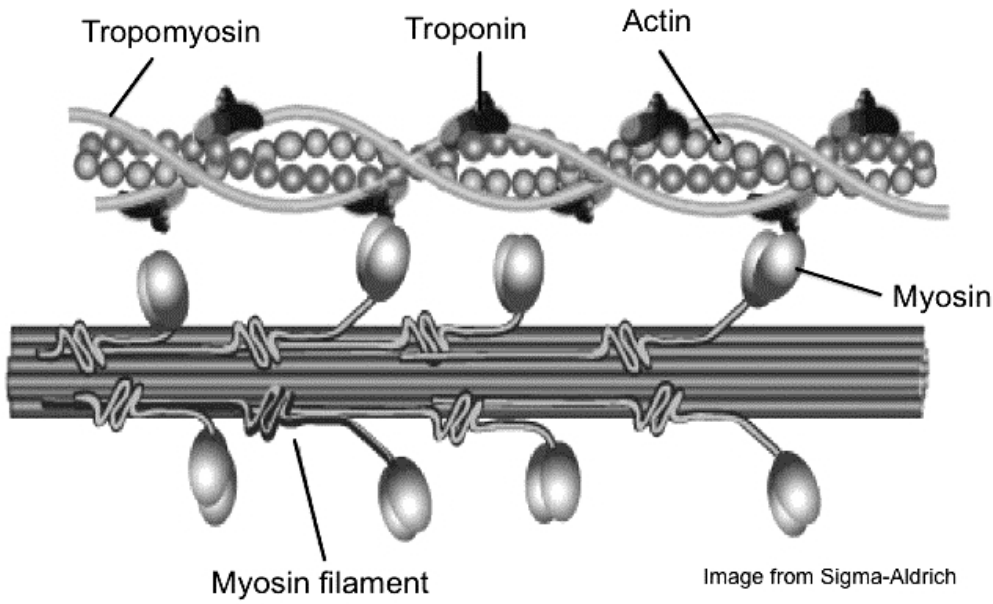


Fig. 2.9: Attachment of Tropomyosin, Troponin and Actin Filament

Source: Image from Sigma-Aldrich

Actin:-

Actin is a major constituents of thin filaments of sarcomere. It exists in two forms -

(a) Monomeric - G-actin (globular actin).

(b) Polymeric - F-actin (filament actin).

G-actin polymerizes to form an insoluble double helical F-actin.

- The backbone of actin filament is a double stranded helix of F-actin protein molecule.
- Each strand of F-actin is composed of polymerized G-actin molecule.
- To each one of G-actin molecule is attached one molecule of ADP.
- These ADP molecules are the active sites on the actin filaments with which the crossbridges of the myosin filaments interact to cause the muscle contraction.

2.6 SUMMARY

- Muscle is the single largest tissue of the human body 30-40% of the body weight). It is composed of fibre cells into which myofibrils are embedded.
- Each myofibril contains alternating A and I bands.
- Sarcomere is the functional unit of muscle.
- Actin, myosin, tropomyosin and troponin are the major contractile proteins found in the muscles. The muscle contraction and relaxation occur due to the active involvement of these proteins.
- ATP is the immediate source of energy for muscle contraction.
- Nerve impulse is transmitted via a motor nerve to motor end plate.
- Nerve impulse crosses the neuromuscular junction by causing release of Acetylcholine. Acetylcholin depolarizes sarcolemma.
- Impulse is conducted into T-tubules and to the sarcoplasmic reticulum.
- Sarcoplasmic reticulum releases large quantities of calcium ions into sarcoplasm. Calcium ions activate the contraction process.
- Calcium ions combine with troponin which pushes tropomysin away from actin receptor sites.
- Myosin crossbridges interact with actin receptor sites.
- As each sarcomere shortens, the whole muscle fibre contracts.
- Calcium ions are reabsorbed by the sarcoplasmic reticulum.
- **Neurotransmitter:** signaling chemical released by nerve terminals that bind to and activate receptors on target cells.
- **Perimysium:** connective tissue that bundles skeletal muscle fibers into fascicles within a skeletal muscle.
- **Sarcomere:** longitudinally, repeating functional unit of skeletal muscle, with all of the contractile and associated proteins involved in contraction.
- **Sarcolemma:** plasma membrane of a skeletal muscle fiber.
- **Sarcoplasm:** cytoplasm of a muscle cell.

- **Sarcoplasmic reticulum (SR) :** specialized smooth endoplasmic reticulum, which stores, releases, and retrieves Ca^{++}.
- **Synaptic cleft:** space between a nerve (axon) terminal and a motor end-plate.
- **T-tubule:** projection of the sarcolemma into the interior of the cell.
- **Thick filament:** the thick myosin strands and their multiple heads projecting from the center of the sarcomere toward, but not all to way to, the Z-discs.
- **Thin filament:** thin strands of actin and its troponin-tropomyosin complex projecting from the Z-discs toward the center of the sarcomere.
- **Triad:** the grouping of one T-tubule and two terminal cisternae.
- **Troponin:** regulatory protein that binds to actin, tropomyosin, and calcium.
- **Tropomyosin:** regulatory protein that covers myosin-binding sites to prevent actin from binding to myosin.

2.7 TERMINAL QUESTIONS

Q. 1: Give a detail account of various types of muscles.

Answer:……
……
……
…..……

Q. 2: Describe the role of myosin in muscle contraction.

Answer:……
……
……
…..……

Q. 3: Enumerate the important structural and functional differences between three types of muscles in a vertebrate

Answer:……
……
……
…..……

Q. 4: Explain the role of calcium in the regulation of muscle contraction.

Answer:……
….....
...……
……
…..……

Q. 5: Give a detail account of various types of muscles.

Answer:……
……

……
…..……...
.....

❖ **Short answer type questions:-**

1) Myosin filament
2) Actin filament
3) Skeletal muscles
4) Cardiac muscle
5) Visceral muscle

❖ **Describe the following in brief:-**

1) Sarcotubular system
2) Sources of energy for muscular contraction
3) Role of Ca^{++} in muscle contraction

OBJECTIVE QUESTIONS:-

❖ **(A) Multiple choice questions:-**

1) What is a given to the cytoplasm of the myofibril:

a) Ectoplasm
b) Endoplasm
c) Sarcoplasm
d) Sarcomere

2) Sliding filament theory of muscle contraction was given by:-

a) Huxley
b) Landsteiner
c) Cori
d) A.S. Gyorgi

3) One of the following element is essential for contraction of muscles:-

a) Na^{+}
b) Mn^{++}
c) K^{+}
d) Ca^{++}

4) Junction between muscle fibres and motor nerve is known as:-

a) Synapse
b) Neuromuscular junction
c) Axon
d) Neuromotor junction

5) Dark anisotropic band in muscle fibre is known as:-

a) M-band

b) H-band

c) Z-band

d) A-band

6) The sarcomere is the area between two:-

a) M-band

b) H-band

c) Z-band

d) A-band

7) Sarcolemma is the membrane which covers:-

a) Nerve fibre

b) Visceral fibre

c) Muscle fibre

d) Collagen fibre

8) Cardiac muscles have properties of:-

a) Straited muscles

b) Unstraited muscles

c) Both (a) and (b)

d) None of the above

9) Energy source for muscle contraction is:-

a) Actin-Tropomyosin

b) ATP

c) Lactic acid

d) Nicotinamide

10) End plate potential is characterized by:-

a) Hyperpolarization

b) Normal polarity

c) Depolarization

d) None of the above

❖ **(B) State whether True or False:**

1) Troponin has got a deep affinity for Ca^{++}.

2) Smooth muscles are present in all hollow viscera.

3) Sarcomere is the functional unit of muscle fibres.

4) The association of axon terminals with motor end plate forms neuromuscular junction.

5) Skeletal muscle doesn't exhibit a refractory period.

2.8 ANSWERS

❖ **(A)**

1)	(c)	6)	(b)
2)	(a)	7)	(c)
3)	(d)	8)	(c)
4)	(b)	9)	(b)
5)	(d)	10)	(c)

❖ **(B)**

(1) - True

(2) - True

(3) - True

(4) - True

(5) - False

SAQ1.

(a). Epimysium(b). Cardiac muscles, smooth muscles and skeletal muscles.

(c). heart. (d). Skeletal muscles

SAQ 2.

(a) motor end-plate (b) myofibril (C) myosin

SAQ 3.

(a) epimysium (b) excitation-contraction coupling (C) fascicle

SAQ 4.

(a) acetylcholine (ACh) (b) actin (C) action potential (d) endomysium

References:

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- Animal physiology and biochemistry by Dr. R.A. Agarwal and Dr. Anil kumar Srivastava
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UNIT-3 NERVOUS SYSTEM

Structure

3.1 INTRODUCTION

In mammals all body activities are either directly or indirectly under the control of the nervous system. Direct control is exercised by supplying nerves to the various organs and tissue, while indirect control is exercised through the endocrine glands and the circulatory system.

Brain, the most complex part of the body, communicates with each and every other body parts through a well-developed and essential electrical wiring known as nervous system which includes both the central nervous system (CNS) and the peripheral nervous system (PNS). The central nervous system is the main integration and command center of body and is made up of the brain and spinal cord where PNS connects the CNS to different effector organs of body and is divided into two subdivisions, somatic nervous system (SNS) and autonomic nervous system (ANS). Along with that recent researches also revealed the importance of enteric nervous system (ENS) or intrinsic nervous system as one of the major divisions of the nervous system. The neuron is the only functional unit of the nervous system. In most neurons, the axon is surrounded by a insulating sheath, known as myelin sheath. The white matter of central nervous system, cranial and spinal nerves consists largely of myelinated fibres.

Objectives:-

After studying this unit you should be able to –

- Describe the structure of nervous system & nerve cell.
- Classification of synapse.
- Transmission of nerve impulses & action potential.

- Degeneration and Regeneration of Nerve Fibers

3.2 STRUCTURE AND FUNCTION OF NERVE CELL

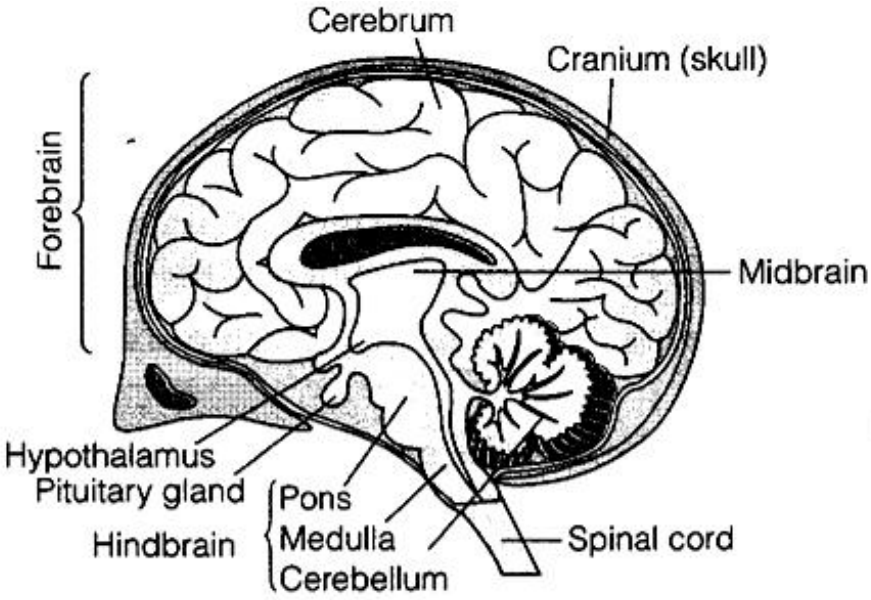
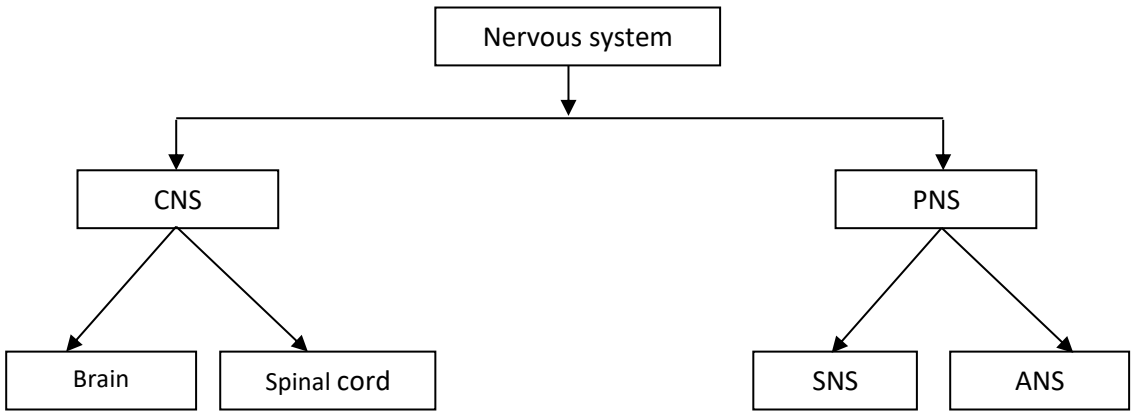


Fig. 3.1: Human Brain

Source: http://www.wikipedia.org

The cellular building blocks of the entire nervous system are nerve cells, called neurons, and supporting cells called glial cells. The human brain is composed of almost 100 billion of electrically excitable neurons and 10 times as many glial cells. Neurons are specialized for electrical and chemical signaling over long distances. Glial cells, in contrast to nerve cells, are not capable of transmission of electrical signaling; thereby the neuron is the only functional unit of the nervous system. Current evidences indicate that the supporting glial cells play an important role in modulation of neuronal activity and developmental processes.



Organisation of the Nervous System: CNS: Central Nervous system, PNS: Peripheral Nervous System, SNS: Sympathetic Nervous System, ANS: Autonomic Nervous System. Source: Self Drawn

The nerve cells have a cell body which encloses a cytoplasm containing a nucleus. The cell body gives off a number of processes. There is usually a single axon and a variable number of dendrites. The primary components of the neuron are the cell body. A typical cell body is rounded or polygonal

in shape. It contains a nucleus with large nucleolus. Special bodies called nissl granules are also present in this, these are composed of ribonucleoproteins.

Axon:-

The axon, a long slender protection that conducts electrical impulses away from the cell body.

Dendrites:-

Dendrite (tree like structure) that receive message from other neurons. They conduct nerve impulses to the cyton and synapses (specialized junction between neutrons).

- The flow of information moves in the following direction dendrite to cell body (soma) to axon to terminal button to synapse.
- It has all the organelles like other cell, only centrosome is absent because nerve cell have lost the ability to divide.

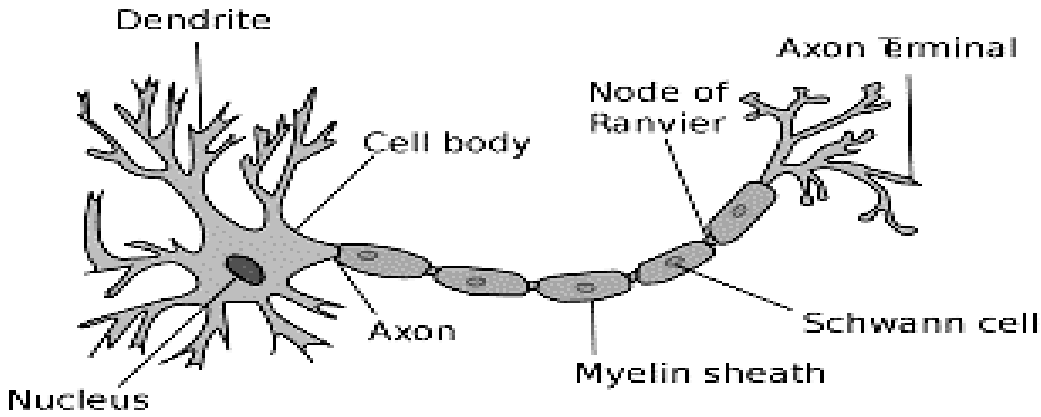


Fig.3.2: Nerve fibres

Source: http://www.wikipedia.org

An axon and its sheath are commonly called a nerve fibres.

Classification of nerve fibres –

(i) Myelinated nerve fibres.

(ii) Non-myelinated.

(1) Myelinated nerve fibres:-

Based on the presence or absence of myelin sheath, they are classified into myelinated or non-myelinated nerve fibers. In the peripheral nervous system, the Schwann cells are responsible for the formation of the myelin sheath.

In the central nervous system, the oligodendroglial cells are responsible for the formation of the myelin sheath. This sheath is broken at regular intervals known as the nodes of Ranvier.

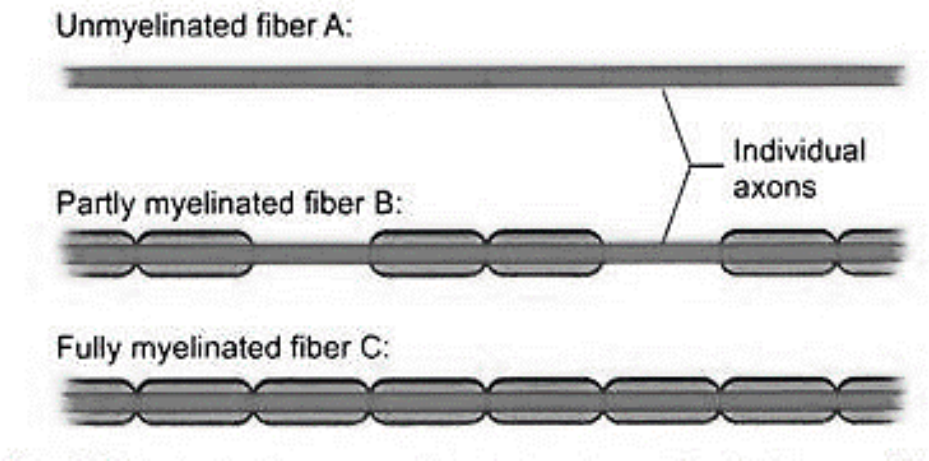


Fig.3.3: A typical non-myelinated and myelinated nerve fibre

- In most neurons, the axon is surrounded by a insulating sheath, known as myelin sheath. The white matter of central nervous system, cranial and spinal nerves consists largely of myelinated fibres.
- It has composed of three elements – axis cylinder, myelin sheath or medullary sheath and neurolemma.
- The axis cylinder in central and is the direct continuation of the protoplasm of the nerve cells. The unspecialized cytoplasm of an axon is called axoplasm.
- The surface membrane of the axoplasm is known as axolemma, which is directly concerned with the transmission of nerve impulse.
- The myelin sheath is composed of lipoprotein.
- The myelin sheath is surrounded by the cytoplasm of special types of cell called Schwann cells, which are always closely associated with nervous tissue.
- The myelin sheath provided both mechanical support and electrical insulation to the axon.
- The myelin sheath is broken at regular intervals along the lengths of the axon.
- The places where the myelin sheath is discontinuous are called nodes of Ranvier.
- The structure is very important in the conduction of impulses through myelinated nerve fibres.
- The axon is covered by a structure less membrane called neurilemma. The Schwann cells lie within this membrane (sheath of Schwann).
- The axon end is telodendrite, which terminate in minute knob known as synaptic knob.
- In myelinated nerve fiber, the wrapping of the axon by the myelin sheath provided by Schwann cell. Whereas in non-myelinated nerve fiber, the Schwann cell just covers the nerve fiber without wrapping. In myelinated nerve fibers, at certain places the myelin sheath is absent. These areas are called as nodes of Ranvier. The protoplasm present in the axon region is known as axoplasm.
- The transport of materials within the axoplasm can occur in either direction (from the cell body towards the axon and vice versa).

- When the substance is transported from the cell body towards the axon terminals, it is known as anterograde transport (fastest—400 mm/day). This type of movement of axoplasm helps for transport of neurotransmitter, proteins, etc. from the cell body to the end of the nerve terminals.
- When the transport of substance occurs in opposite direction (that is from the nerve terminals towards the cell body), it is known as retrograde transport (slowest—200 mm/day).
- Many of the viruses (rabies virus, polio), bacteria (tetanus), etc. reach the cell bodies in the nervous system because of the retrograde transport.

Functions of the Myelin Sheath:

- In myelinated nerve fibers, the velocity of impulse transmission is faster because the process of depolarization occurs only at the nodes of Ranveir and, therefore, it appears as if the impulses are jumping from one node to the successive node.
- This type of impulse transmission is known as saltatory or leaping type of conduction. Because of this type of impulse transmission, the energy required for conduction is markedly reduced.
- It acts as a protective sheath minimizing injury to the nerve fiber.
- It acts as an insulator and prevents cross transmission of impulses from one fiber to the other in a mixed nerve.

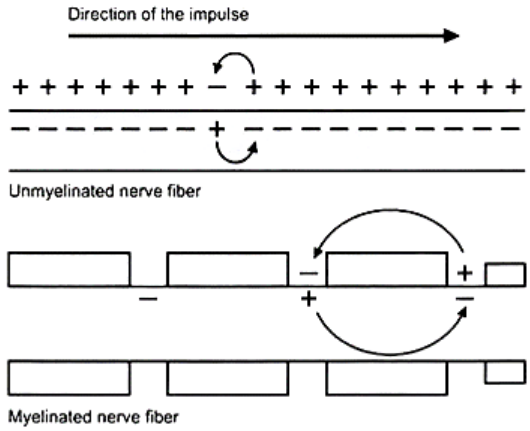


Fig.3.4: The process of impulse conduction in unmyelinated and myelinated nerve fibres. In myelinated nerve fiber, the impulse jumps from one node of Ranvier to the next

(2) <u>Non- myelinated fibres:-</u>

The post ganglionic fibres of the autonomic nervous system belong of this type.

These fibres are very much smaller and do not possess a myelin sheath.

1. Axons are simply buried (surrounded) in the Schwann cell without wrapping of myelin.

   For Examples: All post-ganglionic fibers of ANS, Nerve fibers in somatic nervous system less than 1 μm diameter.

2. Conduction of nerve impulse is slower because it is a continuous process.

Within the grey matter the axons are surround only by the plasma membrane, but upon leaving the grey substance they acquire myelin sheath is called *myelinated* (medullated) nerve fiber. When this fiber comes out of CNS it receives a second covering – the ***Neurolemma*** i.e. sheath of Schwann cell (glial like cell). While in *unmyelinated* (unmedullated) nerve fibers, when they emerge out of the grey substance, these fibers remain embedded in the Schwann cell.

Surrounding the 'neurolemma' of myelinated nerve fiber in peripheral nerve trunk is a thin layer of fine reticular fibers which form the ***Endoneurium or Sheath of Henle.*** Bundles (fascicles) of nerve fibers are enclosed in a connective tissue capsule called ***Perineurium.*** Number of fascicles are bounded together by connected tissue fibers, called ***Epineurium.***

SAQ-1

1. Neuron is the only functional unit of the **……..**
2. The axon, a long slender protection that conducts electrical impulses **……..** body.
3. Dendrite (tree like structure) that **……** message from other neurons.

3.3 CLASSIFICATION OF SYNAPSE AND SYNAPTIC TRANSMISSION

Classification of Synapse. Synapses are divided into four types -

- **Axodendritic synapse:-**

  Axodendritic synapse refers to the synapse between the axon terminal of presynaptic neuron and the dendrites of postsynaptic neuron. It is the most common type of synapse present in the nervous system. Axodendritic synapse is a kind of chemical synapse as the impulse is transmitted by chemical components named neurotransmitter.

- **Axosomatic synapse**:-

  Axosomatic synapse refers to the junction between axon terminal of presynaptic neuron and the cell body of postsynaptic neuron.

- **Dendrodendritic synapse:-**

  Dendrodendritic synapse refers to the junction between two different neurons. It is also one type of chemical synapse that receives depolarizing signal from incoming action potential and causes influx of calcium ions that intern leads to release of Neurotransmitter molecules to propagate the signal the post synaptic neuron. Signaling mechanism in this kind of synapse utilizes Na+ and Ca2+ pumps.

- **Axoaxonic synapse:-**

  Axoaxonic synapse refers to the synaptic junction of axon terminal of one neuron with either the initial axon segment or an axon terminal of another nerve cell.

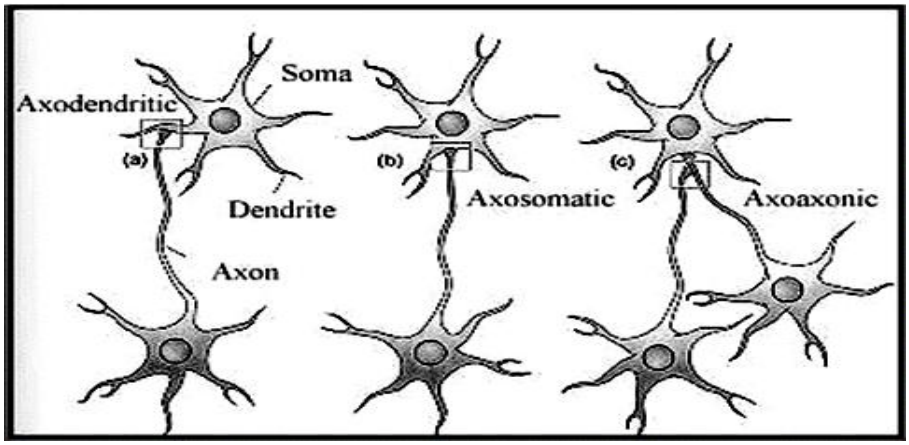


Fig.3.5: Anatomical Classification of Synapse

Source: http://www.wikipedia.org

Synaptic transmission:-

Synaptic transmission, using the example of acetylcholine: Synapses are junctional complexes between presynaptic membranes (synaptic knobs) and post synaptic membranes (effectors). So, presynaptic is the transmission side (synaptic knob) and post synaptic is the receiving side (dendrite, soma or effects).

Synaptic knob contain many membrane – bounded synaptic vesicle, synaptic vesicles contain the neurotransmitter. Synaptic knob also contains mitochondria, microtubules and other organelles. Neurotransmitter is released into the synaptic cleft by a process known as exocytosis. Neurotransmitter diffuses across the synaptic cleft and binds to nicotinic acetylcholine receptors on the postsynaptic membrane

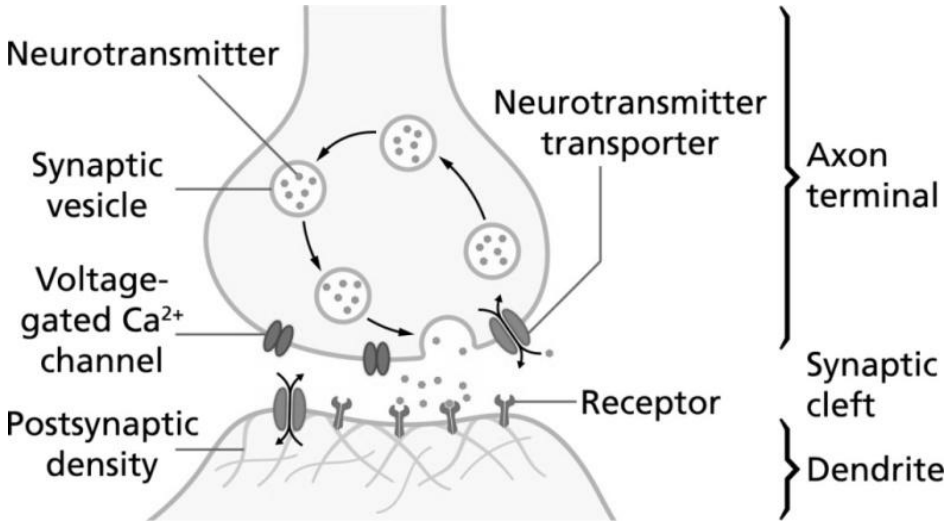


Fig.3.6: Synaptic Transmission

Source: http://www.wikipedia.org

Mechanism of synaptic transmission:-

Synapses are point of contact between one neuron and other. The synapses can be of two types- **Electrica**l and **Chemical transmission**.

Electrical transmission:-

Electrical synapse is defined as a gap junction-mediated connection between neighbouring neurons. It is found in all nervous systems, including human nervous system. Electrical synapse conduct nerve impulses at a much faster rate than that of chemical synapse

The electrical synapses pass on the electrical activity from one cell to another by passage of ions

The electrical synapse does not release neurotransmitters in the synaptic cleft instead there is a direct transfer of electrical signal from one cell to the other via opening of fluid channels that conduct electricity. Special tubular structures comprised of small proteins are formed called as gap junctions which connects the interior of one cell to the next allowing free movement of ions. An example of the electrical synapse is the way by which action potentials are transmitted between smooth muscle fibers.

Chemical transmission:-

Chemical synapse is defined as a specialized biological junction through which neurons signal to each other or to non-neuronal cell via secretion of chemical messenger. It is the most common type of synapse in the nervous system. Human nervous system is composed of a huge number of chemical synapses.

On the other hand, in the chemical synapse the message is passed on by transmission of neurotransmitters released by the **pre-synaptic membrane** which act on the **post,** the mechanism of neurotransmitter release across the chemical synapses. It is essential to note that the chemical synapses **are "unidirectional"**i.e. there is a one-way conduction of signals. That is from the *presynaptic neuron* from where the signal is generated and neurotransmitter is released to the *postsynaptic neuron* which has receptors to which the transmitter binds and executes its effect.

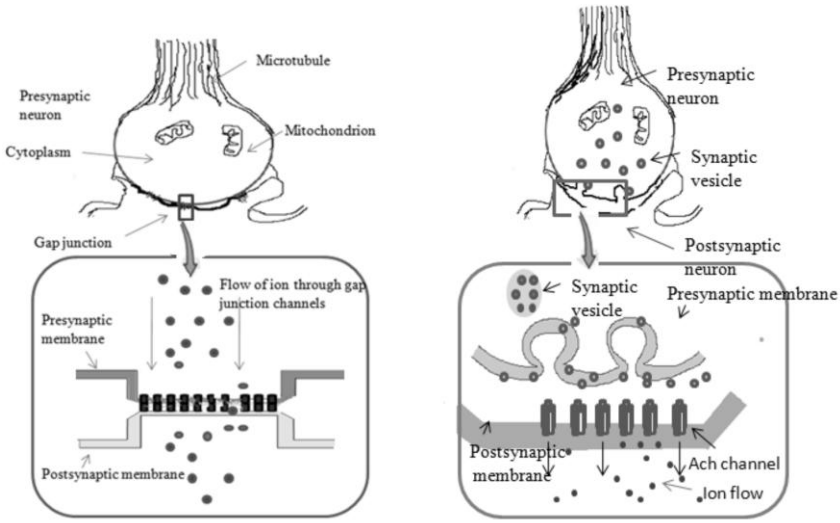


Fig.3.7: Electrical synapse&Chemical synapse

Source: http://www.wikipedia.org

3.4 NEUROTRANSMITTERS

Neurotransmitters are the chemicals released by the axonal end or terminal of a neuron to transmit the impulse to the next neuron called *neurotransmitters*. Presynaptic neurones release neurotransmitters which then diffuse across the synapse before binding to the receptor on the

postsynaptic neurone. This process is called *synaptic transmission*. Neurotransmitters divided into **excitatory** and **inhibitory**.

The first neurotransmitter to be discovered was a small molecule called acetylcholine. It plays a major role in the peripheral nervous system, where it is released by motor neurons and neurons of the autonomic nervous system. It also plays an important role in the central nervous system.

A neurotransmitter influences a neuron in one of different ways.

Excitatory, inhibitory.

Neuromodulators are a bit different, as they are not restricted to the synaptic cleft between two neurons, and so can affect large numbers of neurons at once.

- Synthesis of acetylcholine occurs in the presynaptic neurone. Acetylcholine is stored in vesicles within the presynaptic neurone.
- The influx of calcium ions following the depolarization of the presynaptic terminal initiates the fusion of vesicles with the presynaptic membrane. Neurotransmitter is released into the synaptic cleft by a process known as exocytosis.
- Neurotransmitter diffuses across the synaptic cleft and binds to nicotinic acetylcholine receptors on the postsynaptic membrane. Acetylcholine is broken down by acetylcholinesterase into choline and acetate. Choline is taken up by the presynaptic neuron for further production of acetylcholine.
    - At terminal nerve endings there are many mitochondria and minute vesicle (synaptic vesicles) which contain small packets of chemical transmitter, acetyl-choine (A-ch) responsible for synaptic transmission.
    - Nerve membrane which is in close with the muscle membrane, is known as presynaptic membrane, while the muscle membrane is called post synaptic membrane. The space between these two membrane is called synaptic cleft.
    - The nicotinic A-ch receptors are found on the post-synaptic membrane near the junction folds. They are so called because they are stimulated by both nicotine and A-ch, and inhibited by curare.
    - An enzyme specific acetyl-cholinesterase is found in high concentration in post synaptic clefts, which destroys (hydrolyzes) the A-ch.
- **Synthesis of A-ch:-**

  A-ch is synthesized within the mitochondria from choline in the presence of enzyme choline Acetyltransferase. In addition, it requires acetyl coenzyme A, ATP and glucose.

  A-ch once formed is temporarily stored in minute vesicles (synaptic vesicles).

  Nerve impulse causes fusion of vesicles with membrane of terminal nerve fibres by increasing permeability of Ca^{+}.

SAQ-2

1. The nervous system is the human organ system that coordinates all of the body's **……...**

2. The somatic system controls activities that are under …….. control.
3. The autonomic system controls activities that are …….. controls.
4. Signals sent by the nervous system are electrical signals called ……...

3.5 TRANSMISSION OF NERVE IMPULSES & ACTION POTENTIAL

The Na+-K+ pump transports three Na+ ions outside the cell for every two K+ ions in the cytosol. The unequal transport of these Na+ and K+ ions through Na-K pump separates the charges across the membrane, in which outside of the cell becomes relatively more positive and cytosol becomes relatively more negative. However, this active transport of Na+ and K+ ions only separates enough charges to generate a negligible membrane potential of -1 mV to -3 mV out of total -70 mV resting membrane potential in a typical neuron. The major membrane potential occurs due to the passive diffusion of Na+ and K+ down the concentration gradients. Therefore, Na+-K+ pump indirectly help in producing membrane potential, through its contribution to maintain the concentration gradients which is directly responsible for the ion movements that generate most of the potential.

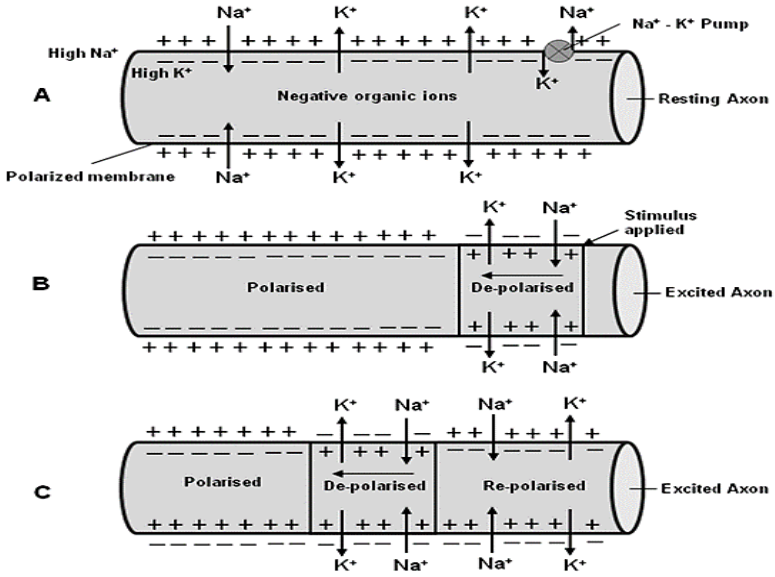


Fig.3.8: Transmission of Nerve impulses and Action Potential

Source: http://www.wikipedia.org

Temporary changes in the membrane potential from its resting potential generate electrical signals that are processed and transmitted by the nerve cells. These signals can be divided into two forms called as **graded potentials and action potentials**. The graded potential is important in transmitting the signaling over short distances, whereas action potentials are transmitted to the long-distance by nerve and muscle membranes. The direction of changes in the membrane potential from the resting potential is described by the terms depolarization, repolarization, and hyperpolarization The resting membrane potential is said to be polarized which denotes differences in the net charge between outside and inside of a cell. The membrane depolarization occurs when its potential is less negative or close to zero than the resting level. Overshoot describes a reversal of the membrane potential polarity. In other word, when cytosol of a cell becomes positive with respect to the outside of the cell, repolarization is returning of depolarized membrane towards the resting potential. The membrane is said to be hyperpolarized when the membrane potential becomes more negative than the resting potential.

1) Nerve impulse (action-potential) reaches presynaptic nerve ending.

2) As it reaches presynaptic membrane, it causes release of A-ch into the synapse (synaptic cleft).

3) A-ch after its release, diffuses within very short distance to the post synaptic membranes i.e. motor end plate.

4) A-ch attaches to nicotinic A-ch receptors on motor end plate surface and increases the permeability of motor end plate to Na^+ and other positive ions (Ca^{2+}).

5) Increased permeability of Na^+ causes depolarization at the post synaptic membrane, causing generation of local potential, called end plate potential.

6) Resting membrane potential (RMP) in skeletal muscle membrane is – 90 mv. When 30 – 40 mv, it depolarizes the surface membrane of the muscle and results in generation of action (spike) potential.

7) Spike potential thus sets up a propagated muscle action potential which can travel in both directions along the muscle membrane. Once it reaches the muscle cell (muscle fibre) then the muscle gives mechanical response by contraction.

- **Resting potential:-**

  During resting (polarised) state, the inside of nerve is negative and the outside of nerve is positive and the resting membrane potential in most of neurons is – 70 mv (extracellular fluid has a high concentration of Na+ and Cl^- and the intercellular fluid a high concentration of K^+)

- **Depolarization:-**

  During activation of the membrane depolarization means reduction in the membrane potential from its negative value towards zero. Na+ quickly moves in, this movement results in a positive charge on the inside of the cell as compared with the outside.

  This reverses of electric charges is called depolarization.

- **Repolarization:-**

  K^+ ion with their positive charge, now begin to flow out faster than the Na^+ flow in, when these positive charger are moved to the outside of the cell they initiate the process of repolarization (return to the resting state) and inside of the cell again becomes negative.

- **Metabolic pump:-**

  The active transports of Na+ out of the cell and at the same time also moves potassium back into the cell (inside) against concentration gradient called sodium potassium exchanges pump.

- **The action potential:-**

  As Na+ rushes into the fibre, the outside of the fibre briefly becomes negatively charged at that point. Adjacent to this point, a part of the fibre remains positively charged. This difference in potential between the two areas is called the Action Potential. Since opposite charges attract one another, positive charges move towards the negative chages on both sides of the membrane causes depolarization of the membrane.

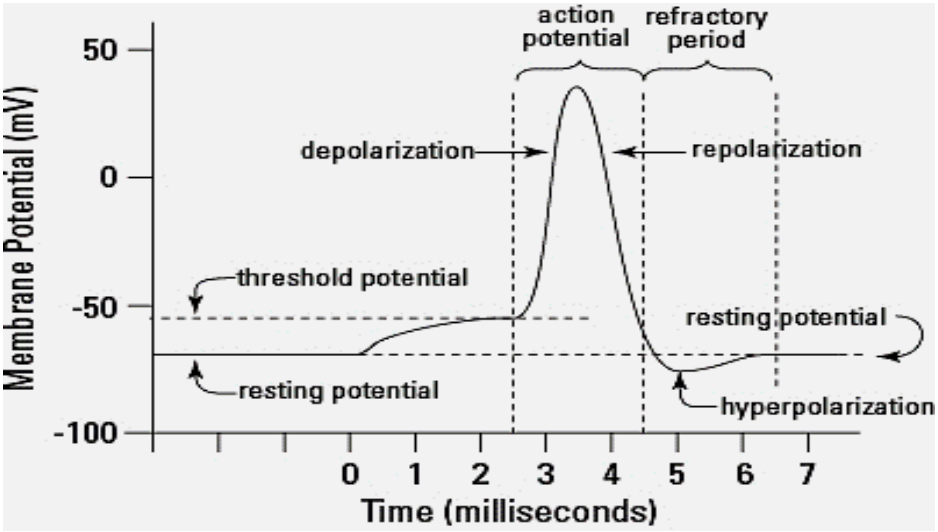


Fig.3.9: Action Potential

Source: http://www.wikipedia.org

This depolarization causes the membrane to become more permeable. As a result Na+ rushes into the cell. Thus action potential may be defined as a self propagating depolarization of nerve membrane.

The entire phenomenon of action potential can be summarized as follow-

1) Impulse is a beginning of depolarization of the membrane, after an initial 15 mv of depolarization, the rate of depolarization increases.
2) The point at which this change in rate occurs is called the firing level.
3) Thereafter, the tracing on the oscilloscope rapidly reaches and overshoot (spike) the isopotential (zeropotential) line to approximately +35 mv.
4) It then reverses and falls rapidly towards the resting level.
5) When repolarization is about 70% completed, the rate of repolarization decreased and the tracing approaches the resting level more slowly.
6) The sharp rise and rapid falls are the spike potential of the axon, and slower fall at the end of the process is the after depolarization.
7) After reaching the previous resting level the tracing overshoots slightly in the hyperpolarizing direction to form the small and prolonged after hyperpolarization.
8) The after depolarization is sometimes called the negative after – potential and the after hyperpolarization is called the positive after potential.
9) Inflamed fat the nerve has been conducting repetitively for a length of long time, the after hyperpolarization is usually quite large. These potential represent recovery process in the neuron rather than the events responsible for the spike portion of the action potential.

3.6 CONDUCTION OF NERVE IMPULSES AND REFLEX ARC

The propagation of action potential can be divided into two types:

1) **Continuous conduction:** This type of conduction involves step by step depolarization of membrane followed by repolarization of adjacent segment of the plasma membrane facilitated by different voltage-gated channels. The action potential propagation described so far in this module is called **continuous conduction**. It occurs in the unmyelinated axons of the neuron and also in muscle fibers.

2) **Saltatory conduction:** This type of conduction occurs along the myelinated axons of the nerve fiber. Myelin sheath acts as an insulator which prevents the flow of charges between intracellular and extracellular fluid compartments. There are only few voltage-gated channels present on the axolemma that is covered by myelin sheath. However, at the nodes of Ranvier, where myelin sheath is absent, axolemma bears large number of voltage-gated sodium and potassium channels that carried current across the membrane at the nodes. Therefore, instead of moving on the whole membrane, action potentials on myelinated fiber propagate through jumping from one node to another and for this reason such type of conduction is called **saltatory conduction**. The propagation of action potential through saltatory conduction is much faster as compared to continuous conduction on the axon of same diameter because only few charges are able to leak out through the myelinated sheath of the axon membrane.

Reflex is an involuntary response to a stimulus which depends on integrity (Completeness) of reflex pathway i.e. the reflex arc.

The Reflex Arc:-

- It forms the function unit of nervous system and consists of receptor, an afferent neuron, an efferent neuron and an effector organ.
- The number of synapses (connection between afferent and efferent neurons) varies from one to many hundred. These synapses are located in the brain or spinal cord.
- The afferent neurons enter via the dorsal roots are cranial nerves and have their cell bodies in the dorsal root ganglia. The efferent fibres leave via the ventral root are corresponding motor cranial nerves.
- Since the connection between afferent and efferent neurons is usually present in the CNS, therefore, activity in the reflex arc is modified by the multiple inputs converging on the efferent neurons.

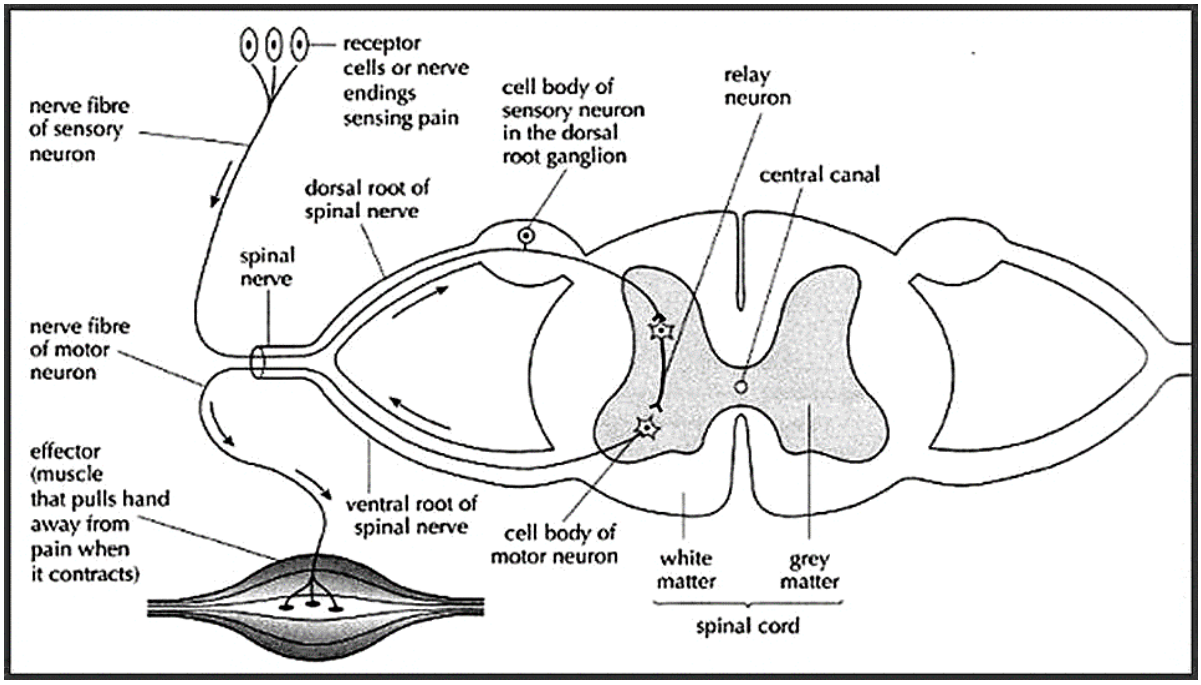


Fig.3.10: Reflex arc

Source: http://www.wikipedia.org

- **Unipolar neuron:** Unipolar neurons have a single axon but contain no Dendron. Unipolar neurons are commonly seen in insect's brain, where the cell body of the neuron is located at the peripheral region of brain and is inactive. Another is pseudounipolar type that contains an axon which has two branches. Pseudounipolar neurons are actually variations of bipolar neurons in that initially they have two processes which fuse during their development into one short common axon. Primary sensory neurons, located in the dorsal root ganglions of spinal nerves and the semilunar ganglions of the trigeminal nerves are the major examples of pseudounipolar neuron.
- **Bipolar neurons:** Bipolar neurons have an axon and a single dendrite. Bipolar cells mainly act as sensory neurons in the transmission of special senses like olfaction, taste and hearing.
- **Multipolar neuron**: Multipolar neurons contain several dendrites. It is the most common type of neurons present in CNS and includes inter-neurons and motor neurons. A special type of multipolar neuron, known as pyramidal neuron is found in some areas of brain including hippocampus, cerebral cortex and the amygdale. The main structural features of the neuron include conic shaped cell body, after which the neuron is named. Pyramidal neurons are majorly present in the corticospinal tract.

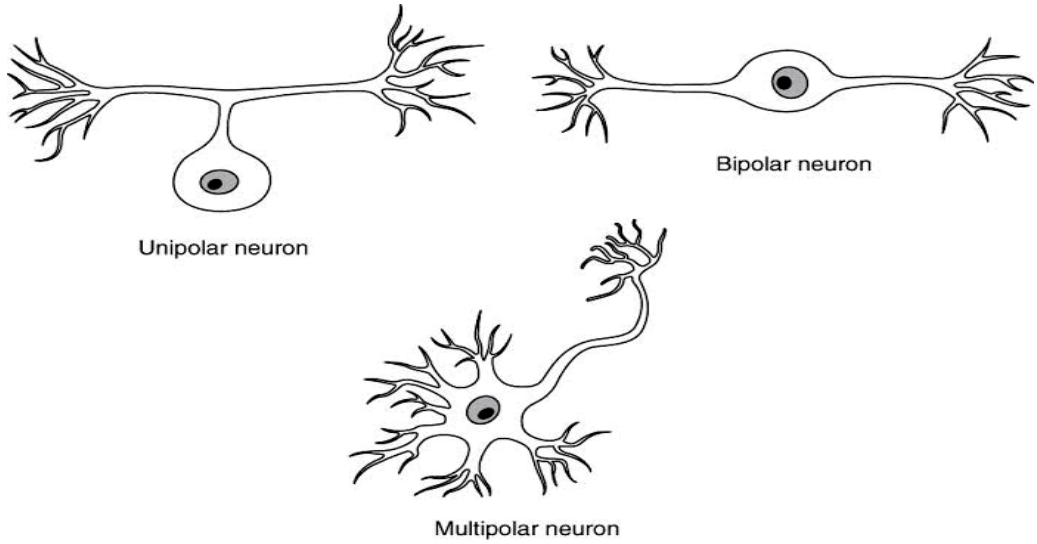


Fig. 3.11:Multipolar Neurons

Source: http://www.wikipedia.org

- **Sensory neuron or afferent neuron:** Sensory neurons are cells of nervous system responsible for converting external stimuli from the organism's environment into internal electrical impulses as sensory information e.g. the dorsal root ganglion cell. In response to a sensory input, peripheral sensory neuron (a first-order sensory neuron) conducts an electrical impulse that travels down the nerve fiber to the central nervous system. In sensory neurons an external stimulus may alters the permeability of cation channels present in the nerve endings, that in-turn generates a depolarizing current (receptor potential). Receptor potential if sufficient in magnitude, generates action potential in the sensory neuron. The axon diameter of a particular sensory neuron determines the conduction speed of action potential. A first order sensory neuron may activate a second- or third-order neuron or a motor neuron. The sensory division carries sensory information to the CNS that includes "special senses" of touch, smell, hearing, taste and sight. It also carries senses of pain, body position (proprioception) and a variety of other visceral sensory information. The neurotrophins family of polypeptide growth factors are very much important in regulation of development of sensory neurons GDNF promotes the survival of parasympathetic, sympathetic, proprioceptive, enteroceptive, and cutaneous sensory neurons.
- **Motor neuron or efferent neuron**: Motor neuron (or motoneuron) is the nerve cell along which electrical impulses pass from the brain or spinal cord to a gland, muscle or any other target area (for example neurons in the autonomic nervous system). Motor neurons are classified in three major types, somatic motor neurons (that send their axon to skeletal muscles), special visceral motor neurons (which innervate branchial muscles) and general visceral motor neurons (that innervate cardiac muscles and smooth muscles). According to position motor neurons are again classified into two

major group, upper motor neuron and lower motor neuron. Electrical impulse in the upper motor neuron travels from the cerebral cortex to the spinal cord. Nerve impulse then travels in the lower motor neuron that carries it from the spinal cord to the neuromuscular junction. Acetylcholine acts as a major neurotransmitter in motor neuron signaling.

- **Interneuron**: Interneurons are the neurons that connect various neurons within the brain and spinal cord and are very much important in neural circuits. Oscillatory activity of neuron and adult brain neurogenesis is dependent on interneurons present in the circuit.

3.7 DEGENERATION AND REGENERATION OF NERVE FIBERS

A. Degenerative Changes

Changes in the Nerve cell Body (Retrograde Changes)

Changes begin within 48 hours of the nerve section and reach to maximum by 15-20 days. After complete transaction of the nerve, the peripheral parts of the axons undergo certain degenerative changes which are often called Wallerian degeneration.

Degeneration takes place at three levels :

(a) In the nerve cell (b) In the proximal part of the cut fibre and (c) In the distal part of the cut fibre

Degeneration : Change occurring in the proximal part of the axons and also the cell bodies following section of an axon is known as retrograde degeneration. The changes in the cell bodies are :

1. Chromatolysis : Nissl granules disappear. *Chromatolysis:* Nissl's granules disintegrate (i.e. break up into a fine dust) and lose their staining rection after 15-20 days and cell becomes colourless. The process begins in the zone around the nucleus and spreads to the periphery of the cell. The dissolution of Nissl substance (RNA) occurs in order that the protein manufacturing process can be mobilized to help the neurons to survive.
2. Golgi apparatus, mitochondria and neurofibrils break up and disappear.
3. The cell draws in more fluid, swells up and becomes rounded.
4. The nucleus is pushed to the periphery. In severe cases it may be totally extruded, in which case, the nerve cell completely dies and disappears. The degree of damage and chromatolysis depend on : increases in size and displaced to the periphery and becomes oval. It may be completely thrown out of the cell. In which case the nucleus thrown out of the cell, the cell atrophies and finally dies off.

B. REGENERATIVE CHANGES

Regeneration : Regeneration takes place only outside the central nervous system where neurolemma is present. Presence of neurolemma is, therefore, essential for the process. Hence, in the central nervous system, neurolemma being absent, nerve fibre do not regenerate at all.

Changes in the nerve cell body

It begins in 20 days and completed in 80 days. Nissl granules and golgi apparatus gradually reappears, cell regains its normal size and nucleus returns to its normal size and nucleus returns to its central position. Repair of cell may even occur if the axon does not regenerate.

Changes in the distal stump and at the site of injury

- Axis Cylinder (Central Axon) from the proximal stump elongates and then grows out in all directions as rounded *pseudopod* like structures called *Fibrils* towards the distal stump.
- Each axon gives rise to 50-100 fibrils which are guided by the strands of Schwann cell into the distal ends of the endoneurial tubes.
- 2-3 weeks after the nerve section the distal endoneurial tube contains varying numbers of developing fibrils, some none, some as many as 20-30 fibrils.
- Eventally all the fibrils re-innervating one tube degenerate except one which thereupon progressively gets enlarged to fill the tube.
- To begin with, rate of growth is 0.25mm/day, but one it enters the distal stump, rate of growth becomes 3-4mm/ day. As it grows deeper down, the rate of growth further increases because mechanical conditions for regeneration are more suitable than those in a cut nerve end.
- In approx. 15 days, Schwann cell filling the endoneurial tube starts laying down myelin sheath round the successful fibril, which is completed by one year.
- Increase in fiber diameter takes place very slowly. Final diameter attained is 80-85% of normal. It is limited by diameter of the distal tube and the size of the parent nerve cell. Therefore functional recovery is not full which takes longer time and may be associated with different complications if does not reach its own cut stump. That is why, for a motor nerve, recovery may be complete but for a mixed nerve it is rarely so.

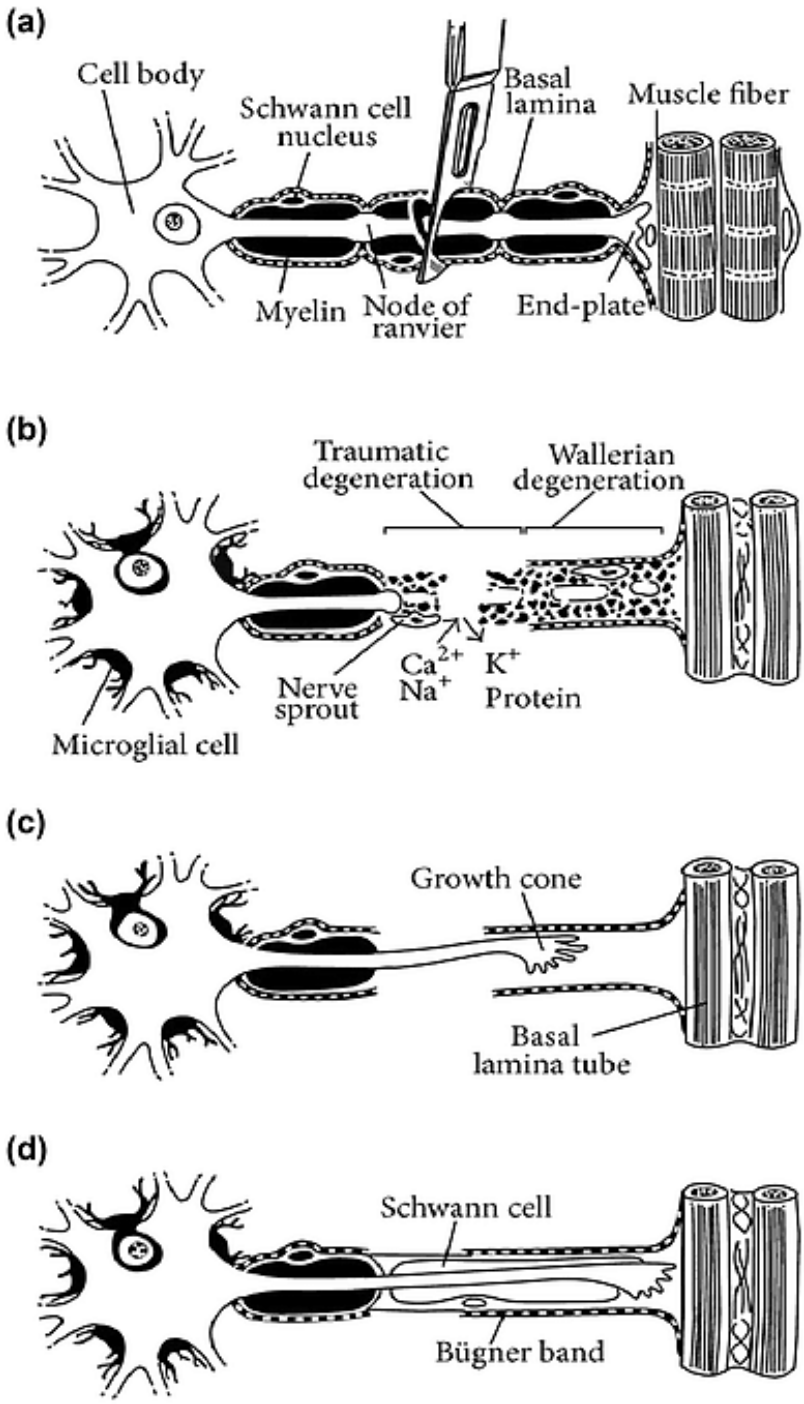


Fig.3.2: Degeneration and regeneration of nerve fiber

3.8 SUMMARY

- The nervous system is the human organ system that coordinates all of the body's voluntary and involuntary actions by transmitting signals to and from different parts of the body.
- The nervous system has two major divisions, called the central nervous system (CNS) and the peripheral nervous system (PNS).
- The CNS includes the brain and spinal cord, and the PNS consist mainly of nerves that connect the CNS with the rest of the body.

- The PNS also has two major divisions the somatic nervous system and the autonomic nervous system.
- The somatic system controls activities that are under voluntary control.
- The autonomic system controls activities that are not under voluntary controls.
- Signals sent by the nervous system are electrical signals called nerve impulses. They are transmitted by special nervous system cells called neurons or nerve cells. Nerve impulses can travel to specific target cells very rapidly.
- Dendrites of a neuron receive nerve impulse from other cells.
- **Excitatory neurotransmitters** increase the likelihood of postsynaptic neuron depolarization and generation of an action potential.
- **Inhibitory neurotransmitters** reduce the likelihood of postsynaptic neuron depolarization and generation of an action potential.
- The effects of an inhibitory neurotransmitter. **GABA** is the major inhibitory neurotransmitter in the mammalian nervous system. Similarly to glutamate, it acts via **ionotropic** receptors – $GABA_A$ receptors– as well as **metabotropic** receptors – $GABA_B$ receptors.

3.9 TERMINAL QUESTIONS

Q. 1: Describe in detail structure of nervous system.

Answer: ……

……

……

Q. 2: Describe in detail action potentials.

Answer: ……

……

……

Q. 3: Describe in detail structure & function of the neurons.

Answer: ……

……

……

Q. 4: Describe in detail classification of the synapse & synaptic transmission .

Answer: ……

……

……

Write Shorts Note On

Q. 5: Neurotransmitters.

Answer: ……

……

……

Q. 5: Neurotransmitters Substances.

Answer: ……

……

……

Q. 6: Neural Circuit

Answer: ……

……

……

Multiple choice questions:

(1) System of the body which co-ordinates and controls its activity is known as -

(a) Organ system

(b) It has to be changed.

(c) Muscular system

(d) Nervous system

(2) Which of the following is not the component of the PNS?

(a) Elastic connective tissue

(b) Cranial nerve

(c) Spinal nerve

(d) Ganglia

(3) Name the basic structural and functional unit of the nervous system.

(a) Neuroglia

(b) Glial cells

(c) Neurons

(d) Perikaryon

(4) Which of the following cells supports, nourishes, and protect the neurons ?

(a) Nissl bodies

(b) Perikaryon

(c) Ganglia

(d) Glial cells

(5) What are Nissl bodies.

(a) Golgibodies

(b) Lysosomes

(c) Cluster of rough ER

(d) Mitochondria

(6) Name the multipolar neuron which is located entirely within the central nervous system.

(a) Motor neuron

(b) Efferent neuron

(c) Afferent neuron

(d) Inter neuron

(7) Out of the following, which one does not affect the speed of conduction of nerve impulses.

(a) No. of ganglia

(b) Myelin sheath

(c) Axon diameter

(d) Temperature

(8) Chemicals which are released at the synaptic junction are called .

(a) Hormones

(b) Neurotransmitters

(c) Cerebrospinal fluid

(d) Lymph

3.10 ANSWERS

SAQ-1

1. **nervous system.**

2. **away from the cell**
3. **receive**

SAQ-2

1. **voluntary and involuntary.**
2. **voluntary**
3. **not under voluntary**
4. **nerve impulses.**

Multiple choice answers:

(1) d. (2) a (3) c (4) d (5) c (6) d (7) a (8) b

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UNIT-4 PHYSIOLOGY OF RESPIRATION

Structure

4.1 INTRODUCTION

All animals depend on oxidation of food materials for their energy requirements. They utilize oxygen and produce carbondioxide during the course of their metabolism. The respiratory system consists of the upper respiratory tract (nasal passages), the airway conduction system (larynx, trachea, bronchi, bronchioles) and the lower respiratory tract (alveolar ducts and alveoli).

The human respiratory system consists of specialized structures whose function is to take in oxygen from the surrounding environment and expel carbondioxide from the body. The primary organ involved in this process is the lung and each individual contains a right and a left lung. The lungs are found in the thoracic cavity of our body (chest region). Air passes into the nose and through the nasal cavity until it gets into the phaynx. From the pharynx, it travels into the larynx. The opening of the larynx contains a cartilaginous flap called the epiglottis. From the larynx, the air moves into the trachea (commonly known as the wind pipe) which connects to the left and right bronchi. The bronchi in each lung split into tiny airways called bronchioles. These bronchioles terminate at balloon like structures called alveoli. Below the lungs is a skeletal muscle called the diaphragm, which is involved in breathing.

Objective:-

After a careful study of this unit you will be able to –

- explain the need for respiration.
- describe the structural & functional differences between lungs & trachea.
- explain the process of gas transport between the blood & tissues in mammals.

- discuss the role of haemoglobin in transfer of oxygen & compare it to the transport of carbondioxide in blood.

4.2 STRUCTURAL ORGANIZATION OF LUNGS AND OTHER RESPIRATORY ORGANS

Respiratory Passages:-

The respiratory system consists of the respiratory passage, lungs and associated organs. It consists of air passage, of the nasal canals, pharynx, larynx, trachea, bronchi and bronchioles.

The nasal cavity is the first of the respiratory organs.

Air enters through the nostrils, which opens into internal nares, then open into pharynx.

Three changes thus takes place here -

- The dust particles and bacteria becomes caught up in the nasal mucus and are removed.
- The sense organ of smell being situated inside the nose. The organ of smell helps in selecting the air inspired.
- Thus purified air passes down the nasopharynx, larynx, trachea and enters the lungs and reaches the alveoli, where gaseous exchange takes place.

Larynx:-

Situated between the pharynx and the trachea, is a cartilaginous chamber, known as the larynx. It is associated with the production of sound. One of the cartilages of the larynx is called the epiglottis. The trachea is a tubular structure; trachea divides into two bronchi – one for the right lung, the other for the left lung . The trachea is provided with a series of 15-20 C-shaped cartilage rings incomplete dorsally, which prevent the trachea from collapse.

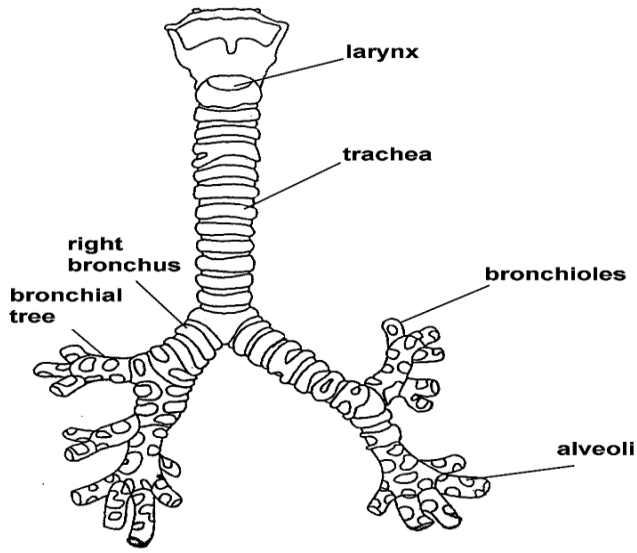


Fig.4.1: Structure of Trachea

Source: http://www.wikipedia.org

Lungs:-

The lungs are paired structures, the right lungs are divided into upper, middle and lower lobes by two deep clefts. Whereas the left one is divided into upper and lower lobes by one similar cleft. The bronchioles divide and subdivide and finally end up into blind sacs known as air sacs.

Each air sac looks like a cluster of grapes and consists of several (4-6) microscopic chambers or alveoli. The respiratory tract is lined by ciliated columnar epithelial cells.

The walls of the pulmonary or lung alveoli, on the other hand, are simply composed of a single layer of cuboidal non-ciliated epithelial cells. The alveoli are surrounded by a rich network of capillaries.

These capillaries receive the blood supply from the pulmonary artery which is returned through the pulmonary vein. The exchange of gases between the air and blood takes place in the alveoli. The alveolar wall is permeable only to gases, but not to plasma in the capillaries.

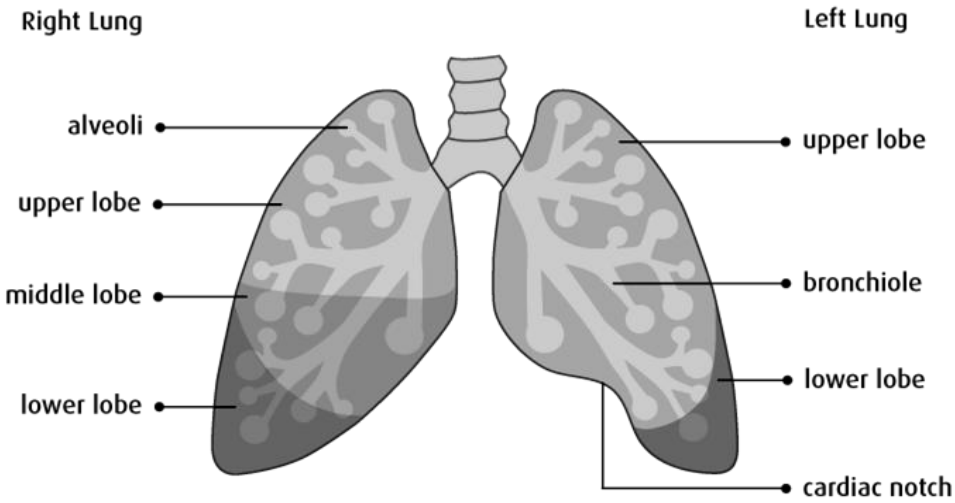


Fig.4.2: Structure of Lungs

Source: http://www.wikipedia.org

Associated organs: The thorax which contains the lungs is bounded by the rib cage on the lower side of the thorax, however, the lung is bounded by a dome -shaped sheet of skeletal muscle, the diaphragm within the thorax. The lungs are enclosed in the pleural cavities. The pleural cavity is a membranous double walled structure, the inner wall adjacent to the lungs is known as the visceral pleura, whereas the outer wall is called the parietal pleura. There is a thin layer of serous fluid between the two pleuras.

This prevents friction of the lungs during breathing movements.

4.3 TYPES AND MECHANISM OF RESPIRATION

Respiration can be classified into two types:

1. **Aerobic Respiration:**
   - It occurs in the presence of oxygen.
   - In **aerobic respiration**, the glucose is completely broken down with the help of oxygen to provide energy. Carbon dioxide and water are released as end products.
2. **Anaerobic Respiration:**
   - It occurs in the absence of oxygen.

- In this process, the glucose is incompletely oxidized into some carbonic compounds such as ethyl alcohol or lactic acid; relatively small amounts of energy are released along with the liberation of carbon dioxide.
- Yeast performs anaerobic respiration that is called **alcoholic fermentation**.
- During strenuous exercise, not enough oxygen reaches the muscles for aerobic respiration. Therefore, the muscle cells respire anaerobically to release energy. It is called **lactic acid fermentation**.

SAQ-1

(a) **……** occurs in the presence of oxygen.

(b) **……** occurs in the absence of oxygen

(c) Air enters through the nostrils, which opens into **……**, then open into **……**

- The mechanics of respiration in human beings takes place in two events: inspiration and expiration (inhale and exhale).
- The respiratory mechanism is the act of inhaling air into the lungs and is known as inspiration.
- Expiration is the process of removing air from the lungs. Amoeba and other unicellular organisms breathe through their skin.
- Inspiration is the active process, while expiration is passive.

Breathing movements are caused by the alternate expansion and contraction of the chest cavity.

- When the chest expands, its volume increases so that the pressure within the chest cavity falls below the atmospheric pressure.
- Air from outside enters the lung under pressure (inspiration).
- When the chest cavity contracts, its volume is reduced and the air is forced out (expiration).
- The change in volume of the chest cavity is brought about by the alternate contraction and relaxation of the diaphragm and external intercostals muscles present between the ribs.
- Enlargement of chest cavity is attained by the contraction of the dome-shaped diaphragm.
- Respiratory movements are primarily under the control of the autonomic nervous system.

Mechanism of Breathing

The entire Mechanism of breathing involves the following steps:

1. **Breathing (Pulmonary ventilation):**
    - The mechanism of breathing involves the **inspiration** and **expiration** of air with the movement of the diaphragm and intercostal muscles.

- During inhalation, external intercostal muscles contract. At the same time, the diaphragm contracts and flattens. These actions increase the volume of the thoracic (chest) cavity, and the air (oxygen) is forced into the lungs.
- On the contrary, exhalation occurs when the thoracic cavity is reduced, and the air (carbon dioxide) is expelled out.

2. External Respiration:

- It involves the diffusion of oxygen and carbon dioxide between the alveoli and the pulmonary capillaries due to the partial pressure difference.
- The solubility of oxygen in the blood is not high, hence there is a big difference in the partial pressure of oxygen in the alveoli versus in the blood of the pulmonary capillaries.
- The partial pressure of oxygen in the alveoli is about 104mmHg, and it is about 40mmHg in the capillary blood.
- The partial pressure of carbon dioxide between the alveolar air and the blood of the capillary is also different.
- The partial pressure of carbon dioxide in the capillary blood is about and, in the alveoli, it is about 40mmHg.It is because the solubility of carbon dioxide in the blood is much greater than that of oxygen.

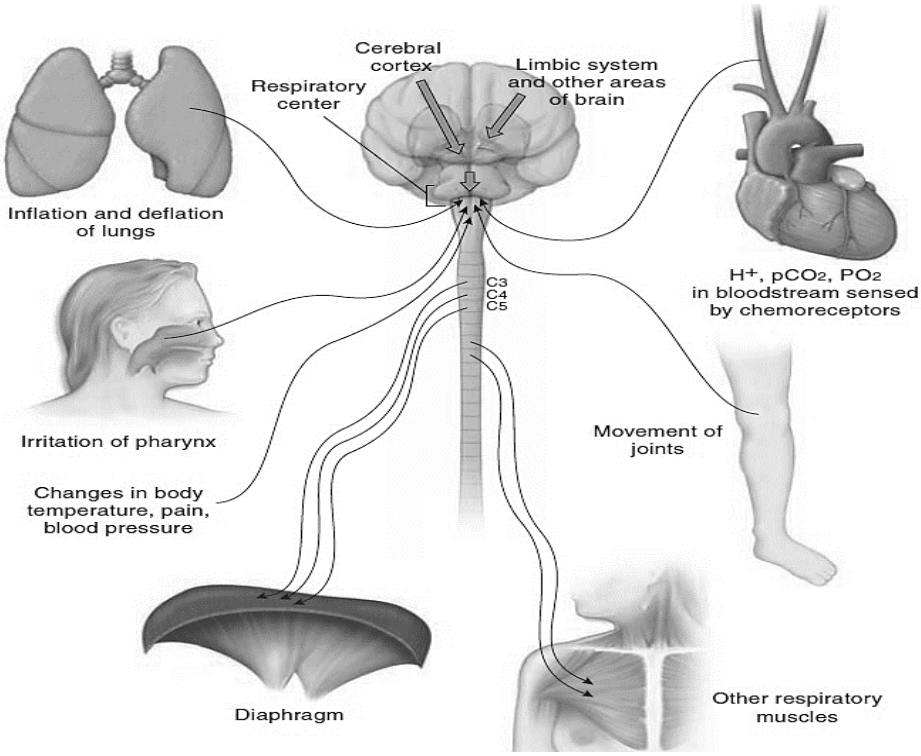


Fig.4.3: Regulation of respiration

3. Internal Respiration:

- The gaseous exchange process that takes place in the tissues is called internal respiration.
- The oxygen after dissociating from the haemoglobin reaches the tissues or cells. The oxygen causes the complete breakdown of the glucose molecules (food) into carbon, water, and energy.
- The energy remains stored in the form of ATP (Adenosine Triphosphate) and is further utilized to perform several living activities. This mechanism of internal respiration is also called Cellular Respiration.

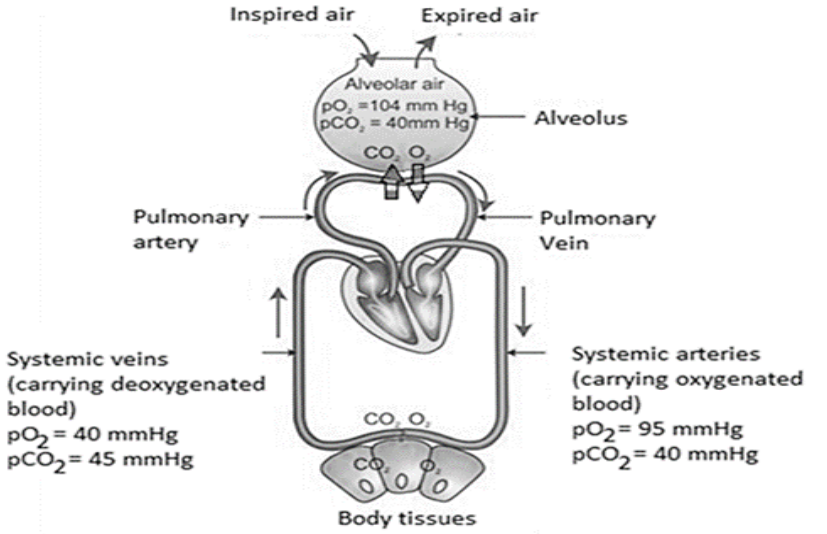


Fig.4.4 : Exchange of Gases between Alveolus and Body tissues

4.4 RESPIRATORY PIGMENTS

Haemoglobin is largely responsible for the transport of O_2 from lungs to tissues.

It is also helps to transport CO_2 from the tissues to the lungs. Haemoglobin is the best known O_2 carrying pigment .

Haemoglobin is the red pigment of blood. It is chromoprotein consisting of two parts -

- One part (96%) is a specific simple protein known as globin (histone). Globin is a protein built from 4 polypeptide chain two 'α' and two 'β' chains. Therefore, the normal adult haemoglobin (HbA) is written as HbA (α_2 β_2) of two α chains each contains 141 amino-acids. Each β-chain contains 146 amino-acids.
- When haemoglobin content of the blood is reduced, the result is anaemia. Haemoglobin is not only a carrier of O_2 and CO_2, but it is also one of the buffering agents in the blood.
- Myoglobin is found in striated muscle of vertebrates and combines with one molecule of oxygen.

- The haemoglobin can occur in two interchangeable forms, one is called T (tense) structure and the other is R (released) structure. T structure has relatively low affinity for oxygen and R structure has high affinity for oxygen.
- The uptake of oxygen by one subunit in T structure changes the whole complex to R structure, which then binds to oxygen one hundred times faster than the first haem group.
- One molecule of haemoglobin (with four hemes) can bind with four molecules of O_2. This is contrast to myoglobin (with one heme) which can bind with only one molecule of oxygen.
- Myoglobin is monomeric oxygen binding haemoprotein found in heart and skeletal muscle.

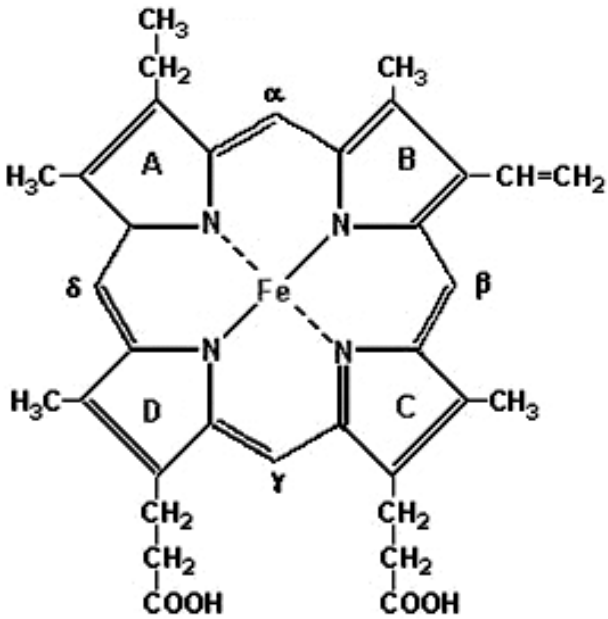


Fig.4.5: Heme Molecule

Source: http://www.wikipedia.org

Function of Haemoglobin:-

- It is essential for oxygen carriage.
- It plays an important part in CO_2 transport.
- It constitutes one of the important buffers of blood and helps to maintain its acid-base balance.
- Various pigments of bile, stool, urine etc, are formed from it.

Some important definition:-

1. **Oxyhaemoglobin:-**Haemoglobin reacts with oxygen to form oxyhaemoglobin and is represented as HbO_2.
2. **Carbamino-Haemoglobin:-**Carbon dioxide reacts with haemoglobin to form carbamino-haemoglobin.

3. **Reduced (Deoxygenated) Haemoglobin:-**Haemoglobin from which oxygen has been removed is called of deoxygenated haemoglobin and is represented as Hb.

Respiratory Centres

Three areas in the brainstem participate in the regulation of respiration. These centres are actually a network of neurons, with their cell bodies located in the medulla and pons.The medulla has the **respiratory rhythmic centre.** This centre has two groups of neurons.

- One group is situated dorsally the **dorsal respiratory group** and contains neurons that control the motor neurons that supply the diaphragm and the external inter-costal muscles. During quiet respiration, these neurons are active for about 2 seconds, stimulating the muscles and resulting in inspiration. Then they become inactive for about 3 seconds when the muscles relax and expiration occurs passively.
- Another group of neurons in the medulla, situated ventrally, the **ventral respiratory group,** is active during forced respiration. They communicate with the motor neurons that innervate the accessory respiratory muscles and stimulate the accessory muscles during inspiration and expiration. The neurons involved in inspiration and expiration are reciprocally innervated (i.e., when the inspiratory neurons are active, the expiratory neurons are inhibited simultaneously).
- The pons has collections of neurons known as the **pneumotaxic center** and **apneustic center.** Both adjust the output of the respiratory rhythmic centers of the medulla. They adjust the rate and depth of respiration in response to stimuli received from other parts of the brain and the rest of the body. For example, the pneumotaxic center reduces the duration of inspiration and facilitates the onset of expiration. The primary effect of this center is to stop inspiration before the lungs are over inflated. When this center is active, the respiratory rate is increased. The apneustic center has the opposite effect, increasing the duration of inspiration and inhibiting expiration.

Other Mechanisms That Control Respiration

Other than chemoreceptors, respiration is affected by stimulation of receptors in the airways and lungs. Impulses generated by these receptors are carried by the vagus nerve to the respiratory centers. These receptors respond to stretch and, when the lungs are over inflated, inhibit inspiration. This is considered a protective reflex that prevents overinflation of the lungs and is referred to as the **inflation reflex** (**Hering-Breuer reflex**).

Nerves from the hypothalamus and limbic system communicate with the respiratory centers, altering breathing when in pain or when emotional. For example, sudden severe pain can cause respiration to temporarily cease. Prolonged somatic pain can bring about an increase in respiratory rate.

Research shows that even active and passive movements of joints stimulate respiration. Proprioceptors that monitor movement of joints and muscle stimulate the respiratory centre even before changes in pH and oxygen and carbon dioxide levels are produced. Changes in blood pressure and state of the heart can affect respiration as well. A sudden rise in blood pressure decreases the rate of respiration through the influence of baroreceptors on the respiratory centre. Receptors from the mouth and pharynx also have an effect and are responsible for alterations vomiting, gagging, and swallowing .

During sleep, the control of respiration is less rigorous and sensitivity to changing levels of carbon dioxide is reduced; hence, brief periods of apnea may be observed.

In summary, the regulation of respiration is a complex process in which the activity of respiratory centers that generate rhythmic impulses to the respiratory muscles is altered by many stimuli, some stimulatory and some inhibitory arising from other parts of the brain and outside the nervous system.

Effect of Exercise on the Respiratory System

Many cardiovascular and respiratory mechanisms come into play to meet the oxygen needs of active tissue and to remove the extra carbon dioxide and heat produced during exercise.

Even before the start of exercise, respiratory rate and depth are altered as a result of the psychic stimuli on the respiratory centre. Soon after the onset of exercise, there is an abrupt increase in ventilation, probably a result of afferent stimuli from proprioceptors. When exercise is continued, there is a gradual increase in ventilation, presumably a result of changes in arterial pH, PCO_2 and PO_2.

The amount of oxygen entering the pulmonary capillaries is increased by many mechanisms. During exercise, the volume of blood in the pulmonary circulation is increased from 5 L/minute (1.3gal/min) at rest to as high as 20–35 litters/minute (5.3–9.2 gal). The gas exchange surface area is increased as more pulmonary capillaries open up and are better per-fused. In addition, the pressure gradient between alveoli air and blood is increased, speeding the rate of diffusion. This is because more oxygen is used by active tissue and the deoxygenated blood carried to the lungs has a lower partial pressure of oxygen. At the tissue level, the increase in carbon dioxide production, temperature increase, and lactic acid production all contribute to rapid unloading of oxygen from haemoglobin to the tissues.

If exercise is prolonged and strenuous, the respiratory and cardiovascular changes are not sufficient to keep up with oxygen use. As a result, energy is derived by anaerobic means, with accumulation of lactic acid (**oxygen debt**). After cessation of exercise, respiration reduces abruptly as a result of reduced neural stimulus. Respiration slows down further as arterial pH and PCO_2 return to normal. However, the respiration does not reach basal levels until the O_2 debt is repaid, which may take as long as 90 minutes.

SAQ-2

1. **……** are interconnected processes.
2. Respiration is an **……**process that is regulated by the medulla oblongata.
3. **……**is responsible for the transport of O_2 from lungs to the tissues.

4.5 TRANSPORT OF OXYGEN & CARBON DIOXIDE

1. **Transport of Oxygen:** Oxygen is carried through the blood from the respiratory organs to the different tissues. Oxygen can be carried in two forms:
   - Through plasma
   - Through Red Blood Cells (RBCs)

   Only about 3% is dissolved in plasma. Haemoglobin transports about 97% of the oxygen in the form of oxyhemoglobin.

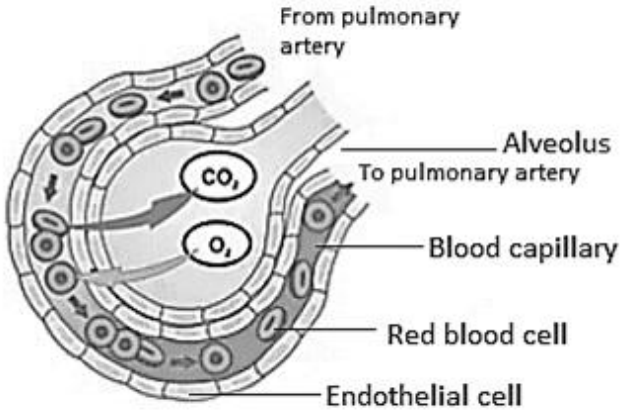


Fig 4.6: Exchange of Gases through Alveolus

2. **Transport of Carbon Dioxide:** Carbon dioxide is transported in the blood in the below-mentioned three ways:

Carbon dioxide transport in blood:-

In aerobic metabolism, for every molecule of O_2 utilized, one molecule of CO_2 is liberated. Haemoglobin actively participates in the transport of CO_2 from the tissues to the lungs.

Haemoglobin also helps in the transport of CO_2 as bicarbonate.

CO_2 transported through the blood in the following ways-

- A small amount (5%) of carbon dioxide is transported, being dissolved in the plasma of blood in the form of a simple solution in plasma and forms (H_2CO_3) carbonic acid. $CO_2 + HOH \rightarrow H_2CO_3$
- Increase in its concentration causes the dissociation of H_2CO_3 into H^+ion and a HCO_3^-ion. $H_2CO_3 \rightarrow H^+ + HCO_3^-$
- A major part (85%) as bicarbonate of sodium and potassium.
- About 10% in combination with haemoglobin in the form of carbaminohaemoglobin (combination of CO_2 with free amino group of Hb)
- $CO_2 + Hb.NH_2 \rightarrow Hb.NH.COOH$
- When the PCO_2 in the tissues is greater than the PCO_2 in the capillaries carbon dioxide diffuses into capillaries because of concentration gradient.

In physical solution:

A small part of the CO_2 dissolves in the plasma to form carbonic acid.

$$CO_2 + H_2O \rightarrow H_2CO_3$$

$$H_2CO_3 \rightarrow H^+ + HCO_3^-$$

- A major part of carbon dioxide from the plasma enters the red blood cells and combines with water. This reaction takes place in the presence of enzyme carbonic anhydrase which is associated with the haemoglobin in red cells and forms the H_2CO_3, which soon dissociates.

- The carbonic acid dissociates into bicarbonate and hydrogen ions.

$$H_2O + CO_2 \xrightarrow[anlydrase]{Carbonic} H_2CO_3 \rightarrow HCO_3^- + H^+$$

The hydrogen ions thus liberated are taken up by the protein molecules of the blood in exchange for metal ions (K^+ and Na^+)

- Diffusion of CO_2 from respiratory tissues into blood, therefore leads to the formation of bicarbonates of potassium and sodium.

$$KHb + H_2CO_3 \downarrow \xrightarrow{carbanic\ canhydrase} H.Hb + KHCO_3$$

Carbonic anhydrase also catalyses the splitting of the H_2CO_3 to H_2O and CO_2 in the lungs. This results in a rapid release of CO_2 during expiration.

- When the CO_2 concentration is high, some of the entering the erythrocytes from the tissues reacts with amino group ($-NH_2$) of haemoglobin to form carbaminohaemoglobin.

$$HbNH_2 + CO_2 \downarrow \underset{Law\ PCO2}{\overset{High\ PCO2}{\rightleftharpoons}} Hb\ NH\ COOH$$

The reaction is very rapid although no enzymes is required. Low CO_2 concentration leads to the dissociation of carbaminohaemoglobin to CO_2 and haemoglobin.

Chloride shift:

The plasma CO_2 diffuses into the RBC along the concentration gradient where it is combines with water to form H_2CO_3.

This reaction is catalyzed by carbonic anhydrase.

In the RBC, H_2CO_3 dissociates to produce H^+ and HCO_3^-.

The H^+ions are trapped and buffered by haemoglobin. As the concentration of HCO_3^- increases in the RBC, it diffuses into plasma along with the concentration gradient; the chloride in diffuses into the erythrocytes from the plasma in exchange for Cl^- ions, to maintain electrical neutrality. This phenomenon is known as chloride shift also known as Hamburgers phenomenon. All the reactions of chloride shift are reversible.

4.6 OXYGEN& CARBON DIOXIDE DISSOCIATION CURVE

The uptake of O_2 and the release of CO_2 by the blood of the alveolar capillaries can be explained by diffusion, i.e. the gases pass from the regions of high pressure to those of low pressure. The pressure of the gas refers to the partial pressure.

The tension of oxygen in the arterial blood is about 100 mm Hg. The oxygen tension in the tissue is less than 40 mm of Hg. Oxygen tension in the arterial blood falls.

Dissociation of oxyhaemoglobin in the blood depends upon -

- O_2 tension
- CO_2 tension
- H-ion concentration
- Electrolyte content

- Temperature

CO_2 tension and CO_2 content in the tissues are much higher than that of blood. Due to the difference of pressure CO_2 diffuses from the tissue cells to the blood capillaries. CO_2 tension in the blood rises which also favours dissociation of oxyhaemoglobin.

Lung alveolus	100 mm Hg O_2	40 mm Hg CO_2
	↓	↓
Lung capillary	40	46

When the venous blood passes through the pulmonary capillaries into the lungs, it has got the oxygen tension of about 40 mm Hg. oxygen tension in the alveoli is about 100 mm of Hg. Hence oxygen diffuses from the alveoli into the venous blood through the pulmonary and capillary endothelium. Oxygen tension rises and more oxyhaemoglobin is formed in the corpuscles.

Simultaneously, CO_2 is liberated from the venous blood of also diffuses through the pulmonary and capillary endothelium into the alveoli. CO_2 tension and H-ion concentration in the venous blood fall which favour entry of O_2 in the blood capillaries.

Oxygen dissociation curve:-

- The binding ability of hemoglobin with O_2 at different partial pressures of oxygen (PO_2) can be measured by a graphic representation known as O_2 dissociation Curve.

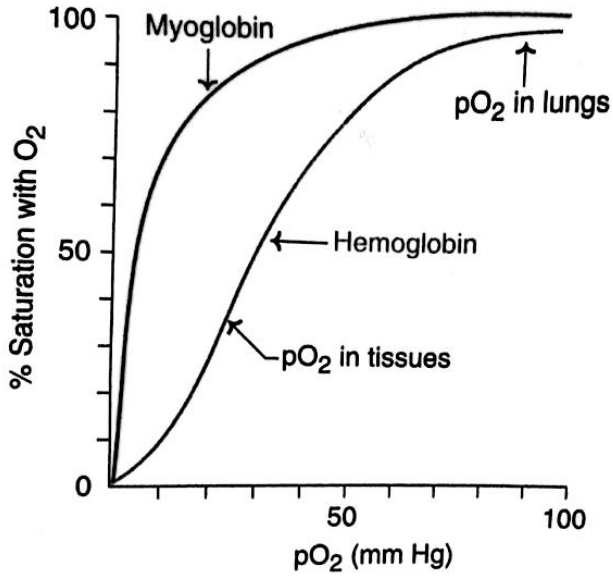


Fig.4.7: Oxygen dissociation curve of hemoglobin and myoglobin

Source: Biochemistry by Dr. U. Satyanarayana

It is evident from the graph that myoglobin has much higher affinity for O_2 than haemoglobin. Hence O_2 is bound more tightly with myoglobin than with haemoglobin.

- The (O_2) oxygen dissociation curve for hemoglobin is sigmoidal in shape. This indicates that the binding of oxygen to one heme increases the binding of oxygen to other hemes.
- Thus the affinity of Hb for the last O_2 is about 100 times greater than the binding of the first O_2 to Hb. This phenomenon is referred to as cooperative binding of O_2 to Hb or simply heme - heme interaction.
- At high O_2 pressure, the hemoglobin combines with O_2 to form oxyhaemoglobin. Each iron atom can bind one O_2 molecule, and when all sites are occupied, the hemoglobin cannot take on any more, since it is fully saturated.
- At low O_2 pressure, O_2 dissociates from its binding, and the hemoglobin will eventually give up all its O_2.
- The hemoglobin is completely oxygenated (approximately 98% saturation) by an oxygen tension of 100 mm Hg.
- When the oxygen tension falls below 60 mm Hg the oxyhaemoglobin dissociates rapidly. This is indicated by the steeper slope of the curve at low oxygen tensions.
- When the PO_2 is zero, oxyhaemoglobin loses all its oxygen.
- The haemoglobin gets completely oxygenated (98% saturation) in the alveoli of the lungs where the oxygen tension is 100 mm Hg and, later, donates the oxygen to the tissues where the oxygen tension is low and where oxygen is needed most. When PCO_2 is gradually increased, the O_2 carrying capacity of blood is also reduced and the O_2 dissociation curve move towards right side. This effect of CO_2 on O_2 carrying capacity of blood is Bohr effects.
- Any increase in protons / or lower PO_2 shifts the equilibrium to the right to produce deoxyhaemoglobin as happens in the tissues.
- On the other hand, any increase in PO_2 and / or a decrease in H^+shifts the equilibrium to the left, which occurs in lungs.

  Lungs (PO_2 = 100 mm Hg)

  $Hb + O_2 \rightarrow HbO_2$ (Oxyhaemoglobin)

  Tissues (PO_2 = 40 mm Hg)

  $HbO_2 \rightarrow Hb + O_2$

CO_2 dissociation curve:

Curve for oxygenated & deoxygenated blood differ somewhat.

This is because oxyhaemoglobin slightly more acidic then haemoglobin.

Hence, oxygenated blood will bind slightly less CO_2. This phenomenon is closely related to the Bohr Effect, an increase in the CO_2 shift the O_2 dissociation curve to the right, giving more O_2 from the blood to the tissue .

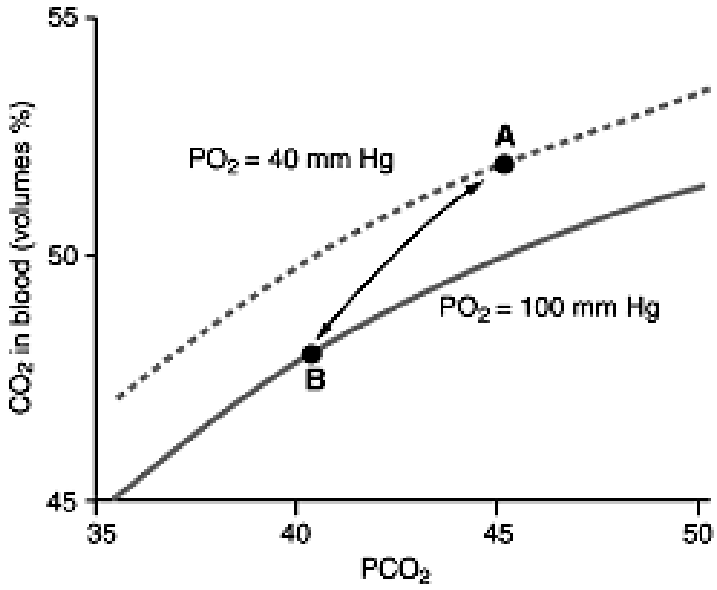


Fig.4.8: CO_2 dissociation curve

Source: http://www.wikipedia.org

When CO_2 is added to the blood, it pushed the equibrium between oxyhaemoglobin & haemoglobin in the direction of weaker acid (haemoglobin) Bohr Effect.

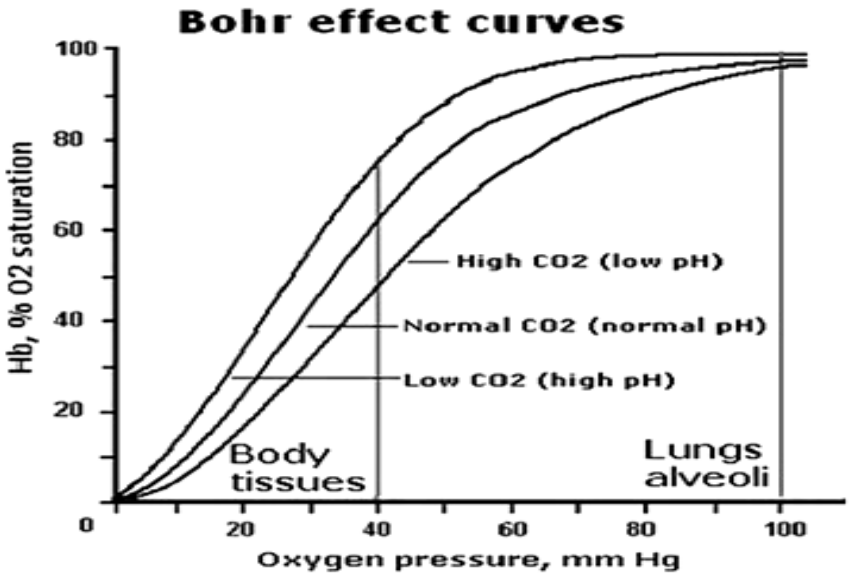


Fig.4.9: Bohr Effect on oxygen dissociation curve (Effect of pH)

Source: http://www.wikipedia.org

In the body the actual dissociation curve for CO_2 will be the fully drawn line A-V, in which the point A stands for the normal arterial blood and the point V for the mixed venous blood which is never completely deoxygenated and this curve therefore is said to be the functional curve or the physiological dissociation curve.

4.7 FUNCTION OF RESPIRATION

Metabolic function:- Oxygen is essential for maintenance of metabolism of tissue. Aerobic process of metabolism, cannot take place in absence of oxygen.

Excretion:-

It excretes volatile substances like ammonia, ketone bodies, essential oils, alcohol, water vapour etc.

Maintenance of acid base balance:-

This is done chiefly by adjusting the amount of CO_2 elimination.

Maintenance of temperature & pH balance:-

In the expired air, large quantity of heat is lost (the expired air is warmer than inspired air). The respiration plays an important role in the maintenance of pH of blood at normal levels.

Gaseous Exchange:-

Between the process of inspiration and expiration the interchange of respiratory gases occurs. This interchange takes place between the blood in the capillary network which surrounds the alveoli, and the air in the alveoli of the lungs. In external and internal respiration, gases always tend to diffuse from a high partial pressure to a lower partial pressure.

4.8 REGULATION OF RESPIRATION

The main important factors which are associated with the regulation of respiration-

- Nervous control.
- Chemical control.

Nervous Control:-

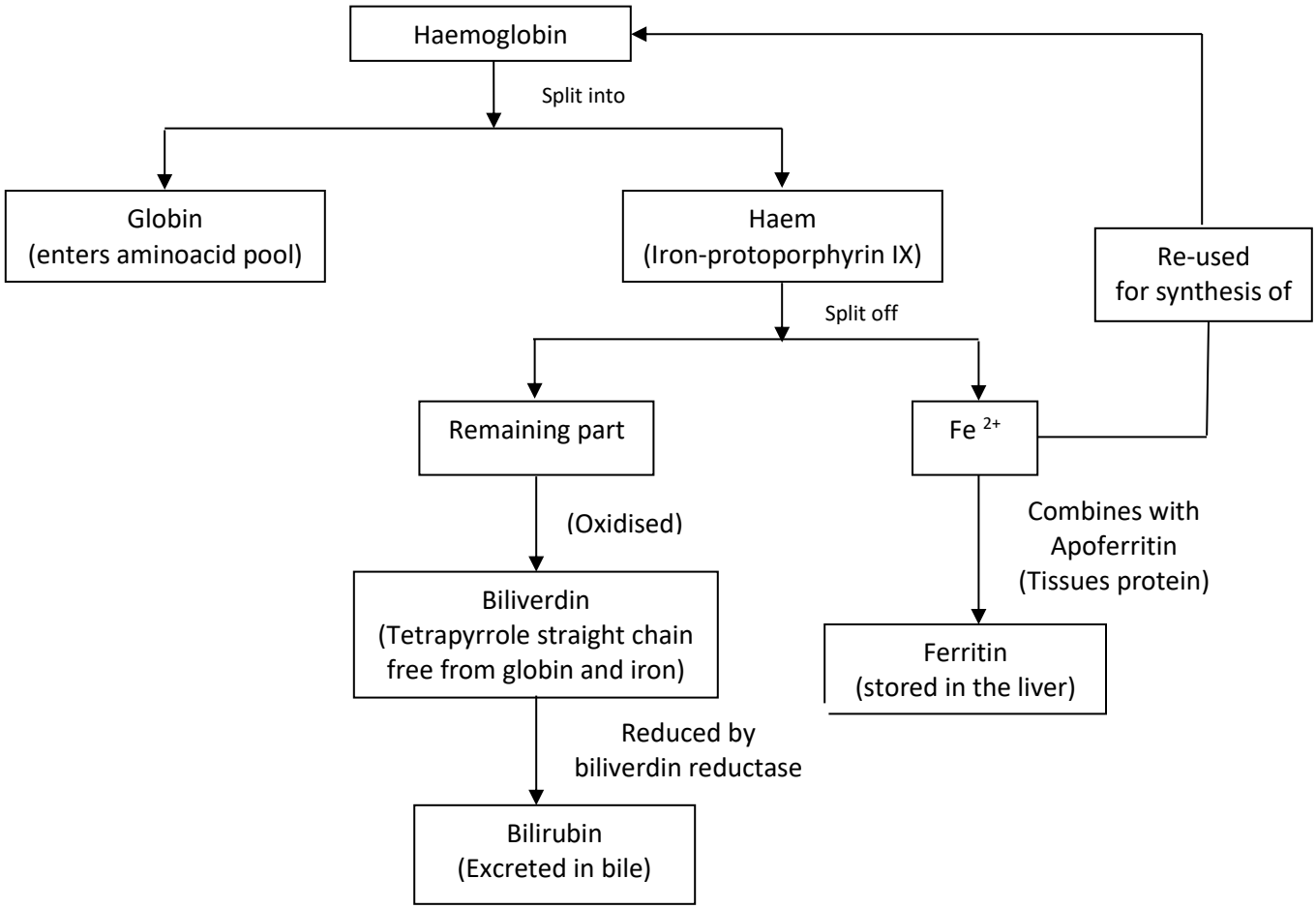
- Respiration is controlled by two separate neural mechanisms, one voluntary and other involuntary. Nerves from the cerebral cortex communicate with the motor neurons that directly innervate the diaphragm and the other respiratory muscles. This is responsible for the voluntary component. Other areas of the brain—classically referred to as the **respiratory centers**—located in the medulla and pons are responsible for the involuntary or automatic component. They, too, communicate with the motor neurons supplying the respiratory muscles. The final out-come or action depends on whether the motor nerves are inhibited or stimulated.
- Respiration can be regulated by chemical and neural factors. The process of breathing is essentially involuntary and automatic. However, it is influenced and controlled voluntarily within limits.
- Normally inspiration and expiration follow each other and both are basically muscular in action. The contraction and relaxation of the respiratory muscles (diaphragm and several chest muscles) depend on the arrival of nerve impulses originating from the group of neurons collectively forming the respiratory centre located in the medulla oblongata of the brain.

From this centre, nerve impulses pass out in the phrenic nerves to the diaphragm & intercostal muscles.

These impulses stimulate the muscles concerned to contract and increase the capacity of the thoracic cavity with the result that inspiration occurs.

Chemical control:

- The level of oxygen, carbon dioxide and hydrogen ions can alter respiration. This alteration is a result of special receptors that monitor the levels of these substances. These special sensors (chemoreceptors) are located near the aorta, carotid artery (peripheral chemoreceptors), and the medulla near the respira-tory center (central chemoreceptors).
- The chemoreceptors near the large blood vessels are known as aortic bodies and carotid bodies.
- The cells in the bodies are sensitive to the levels of dissolved oxygen in the plasma, increasing levels of carbon dioxide, and increase in hydrogen ions. When oxygen levels drop or carbon dioxide and hydrogen ion levels increase, the receptors are stimulated and take impulses to the respiratory center, which responds by increasing the rate and depth of respiration.
- The main chemical factors which influence the respiratory centre are the amount of carbon dioxide (carbonic acid) and oxygen in solution in the blood. In the carotid body, where the common carotid artery divides, and in the wall of the arch of the aorta there are cells which are sensitive to carbon dioxide excess and oxygen lack.
- When these cells are stimulated, impulses pass in branches of the vagus and glossopharyngeal nerves to the respiratory centre in the medulla oblongata.
- The accumulation of carbondioxide in solution in the blood is the most important stimulus to respiration. If the amount of carbondioxide rises in the blood, for example during muscular exercise, the respiratory centre is stimulated. It, therefore, sends out impulses to the respiratory muscles to produce deeper and quicker breathing, so that the carbon dioxide can be given out more rapidly by the lungs. In this way, the respiratory centre controls the rate and depth of breathing.



Fate of haemoglobin in the body

4.9 SUMMARY

- The human respiratory system is a series of organs responsible for taking in oxygen and expelling carbon dioxide. The primary organs of the respiratory system are lungs, which carry out this exchange of gases as we breathe.

  Respiration consists of two phases -

- The first phase consisting of gaseous exchange between the blood and the environment via the lungs, it referred to as external respiration.
- The second phase consisting of oxidative energy yielding reactions of the cells,is called as internal respiration.
- Haemoglobin is responsible for the transport of O_2 from lungs to the tissues.
- Each heme (of Hb) combined with one molecule of O_2 and this is facilitated by cooperative heme-heme interaction.
- Haemoglobin actively participates in the transport of CO_2 from tissues to lungs. Increased partial pressure of CO_2 (PCO_2) accompanied by elevated H^+ decreases the binding of O_2 Hb, a phenomenon known as Bohr effect.

- Gas exchange in lungs takes place in alveoli where partial pressure of oxygen is higher than that in blood hence O_2 diffuses from alveoli to blood.
- In body tissue the partial pressure of O_2 is low hence O_2 diffuses from blood into tissues.
- Respiration is regulated by levels of PCO_2 and by a respiratory centre in the brain which is sensitive to blood PCO_2.
- Respiratory gases are transported mainly by respiratory pigments in blood. The most wellknown pigment is haemoglobin which combines with O_2 to form oxyhaemoglobin.
- CO_2 is transported to lungs by formation of carbonic acid in red blood cells.
- This reaction is favoured by high PO_2 in tissues. Carbonic acid ionises into H^+ and HCO_3^-. Hydrogen ion is buffered by haemoglobin but anion balance is maintained by chloride shift.
- Respiration can be briefly described as an energy-releasing process involving the gaseous exchange. It is an essential life process that enables a person to perform life-sustaining activities. The main organ involved in the **mechanism of respiration** is a pair of lungs that consists of millions of air sacs that take part in the exchange of respiratory gases between the blood and lungs. In this article, learners will learn how respiratory gases are carried from the lungs to every cell of our body.
- Respiration and breathing are interconnected processes.
- Respiration is a biochemical process that involves the liberation of energy, while breathing is a physical process of gaseous exchange.
- Respiration is an involuntary process that is regulated by the medulla oblongata.
- Hemocyanin in molluscs and arthropods, hemerythrin in some annelids are the respiratory pigments similar to the haemoglobin found in human blood.
- Carbon monoxide is a toxic gas that has a great affinity with haemoglobin and forms carboxyhemoglobin, hence reducing the oxygen-carrying capacity of haemoglobin.

4.10 TERMINAL QUESTION

Q. 1: Describe in detail transport of carbondioxide. Add a note on the CO_2 dissociation curve.

Answer ……

……

……

Q. 2: Explain the transport of oxygen. Add a note on the oxygen haemoglobin dissociation curve.

Answer ……

……

……

Q. 3: Give detailed account of chemical control of respiration.

Answer: ……

……

……

Q. 4: Give detailed account of nervous control of respiration.

Answer: ……

……

……

Q. 5: Give the detailed account of respiratory pigment.

……

……

……

Write shorts notes on:

Q.1. What is the definition of respiration?

……

……

Q.2. What is the name of respiration that occurs in the presence of oxygen?

……

……

Q.3. What is the difference between breathing and respiration?

……

……

Q.4. What is the mechanism of internal respiration?

……

……

Q.5. What is the importance of respiration?

……

……

Short answer type question:-

(i) Chloride shift (b) Functions of respiration (c) Mechanism of respiration (d) Bohr effect

Multiple choice questions:-

1. **O_2 dissociation curve is**

   (a) Ball shaped (b) S-shaped (c) Normal curve type (d) Delta shaped

2. **CO_2 enters capillaries by**

   (a) Permeation (b) Osmosis (C) Diffusion (d) Active transport

3. **Hamburger shift is also called**

   (a) Hydrogen shift (b) HCO_3 shift (C) Chloride shift (d) No shift

4. **Gaseous exchange in lungs occurs by**

   (a) Osmosis (b) Simple diffusion (C) Active transport (d) Passive transport

5. **Chloride shift is essential for transport of**

   (a) O_2 and CO_2(b) N_2(c) CO_2(d)O_2

4.11 ANSWERS

Multiple choice answer:-

1 – (b), 2 – (c), 3 – (c) ,4 – (b),5 – (c)

SAQ-1

(a) aerobic respiration(b)**Anaerobic Respiration (**c) internal nares, pharynx

SAQ-2

1. Respiration and breathing 2. involuntary 3. Hemoglobin

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UNIT-5 EXCRETION

5.1 INTRODUCTION

Excretion is the removal of waste byproduct which is obtain after the metabolism of body. Animals routinely eliminate a variety of potentially deleterious waste products, including inorganic solutes for example Na^+, K^+, Cl^-, SO_4^{2-}, NH_4^+ and organic solutes e.g. urea, urate and other purines, benzoic acid. These wastes may be derived from the diet e.g. ions or may be end products of metabolic pathways. These various waste products must be excreted to avoid their accumulation to toxic level. Some are readily eliminated across the integument, for example aquatic animals can eliminate ammonia by diffusion across their skin or gills. However, many wastes are excreted in a solution that is formed by the animal specifically for the role of bulk elimination of water and/or solutes.

Mammalian nephrons are adopted for minimizing urinary water loss and excretion of ionic and nitrogenous solutes. The mammalian kidney has a complex structural organization of its nephrons, blood supply and the renal pelvis, there is a renal cortex and different zones of the medulla. The mammalian nephron has a glomerulus with afferent and efferent arterioles, bowman's capsule, proximal convoluted tubule, a loop of henle, a distal convoluted tubules and collected duct. The collecting duct drains into a renal pelvis that empties into the ureter.

Objective

After studying this unit you will be able to know:

- Structure of kidney specially nephrons.
- tubular function, tubular transport mechanism & transtubular potential.
- role of kidney in regulation of ionic, osmotic acid and base balance of the body fluid.
- understand to control of extracellular fluid volume.
- study about nitrogen excretory products and urine formation.

5.2 KIDNEY STRUCTURE

Each kidney is covered by a thin fibrous connective tissue layer called renal capsule. The kidney is a compact mass of about 10 to 12 lacs in man, of extremely fine and coiled tube like excretory tubules called uriniferous tubules or nephrons. The nephrons are packed together in connective tissue containing blood vessels, nerves and lymphatics. Because of a characteristic arrangement of nephrons and associated ducts, the mass of a kidney appears distinctly divided into an outer cortical (cortex) and inner medullary (medulla) regions. The middle part of medulla prominently projects towards, the hilus in the form of a conical renal papilla. About half a dozen narrow columns of cortical mass called renal columns of Bertini, extend into the peripheral zone of medulla, dividing it into many blunt lobes called pyramids. In most mammals, the renal columns of Bertini are more in number and extend up to the medial border of medulla dividing it into almost separate pyramids. Each such pyramids separately projects towards the hilus as a renal papilla. In human there are nearly a dozen pyramids appears.

The proximal part of a ureter, lying within the medial part of kidney, is expanded in the form of a wide funnel called pelvis or renal sinus. The pelvis is proximally divided into as many small cup shaped compartments called minor calyces, around individual renal papillas. The minor calyces in groups of two or more lead into a few major calyces which then empty into the undivided part of pelvis.

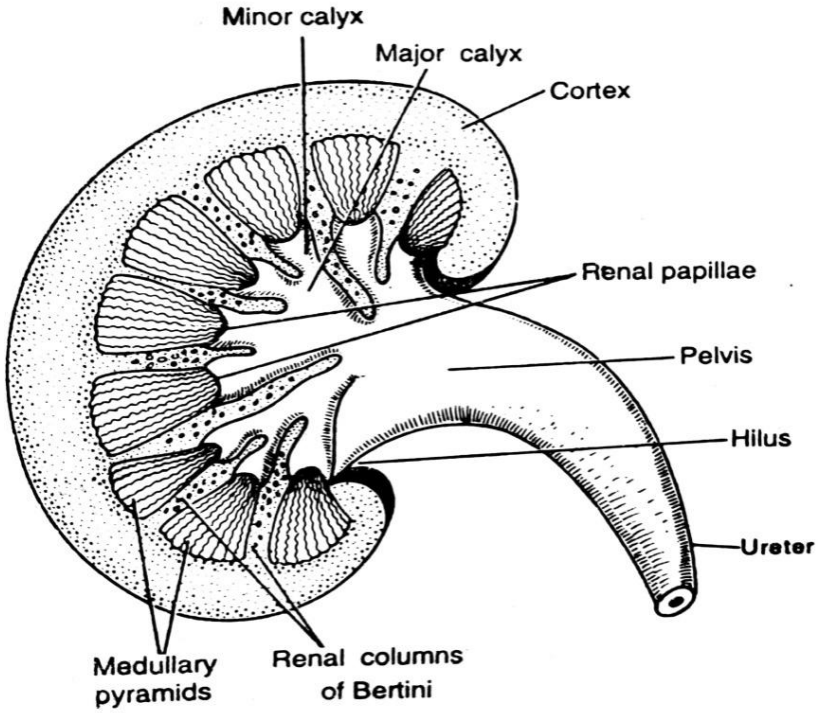


Fig 5.1: Diagram of LS of human kidney

Nephron –The nephron or uriniferous tubules consist of microscopic structure of Bowman's capsule, neck and secretory tubules. The Bowman's capsules of all tubules lie in the renal cortex. The Bowman's capsule contains a network of blood capillaries called glomerulus. The glomerulus connected with an afferent arteriole on one side and efferent arteriole on the other side. The Bowman capsule together with glomerulus is called renal or malpighian corpuscle. The outer wall of

Bowman's capsule is composed of flattened squamous cells. The inner invaginated wall that lines the concavity of the capsule, is composed of a special types of flattened cells called podocytes. These cells bear distinct finger like processes which interwine around capillaries of the glomerulus.

The Bowman's capsule is followed by a short and narrow "neck". The internal lining of neck is marked by ciliated cells of epithelium.

The secretory tubule can be distinguished into three parts are as follow –

(1) The proximal convoluted tubule lies behind the neck. It makes a few coils and is restricted to the cortical region of the kidney.

(2) The quite narrow and "U" shaped loop of Henle, having a descending limb that extends into the medulla and an ascending limb that extends back from the medulla into the cortex.

(3) The distal convoluted tubule which is thicker and coiled and situated in the cortex like the proximal tubules. The coils of both convoluted tubules are intermingled.

The distal convoluted tubules of a number of adjacent nephrons open into a common collecting duct or tubule. These collecting ducts are long tubules which traverse through the medulla in the pyramids. In the papilla of the medulla, several adjacent collecting tubules converge to open into a common short and thick duct of Bellini. All ducts of Bellini then open at the tip of the papilla into the pelvis. So the Malpighian corpuscles and proximal and distal convoluted tubules of the nephrons are constitute in renal cortex, where as the loops of Henle, collecting tubules and ducts of Bellini constitute the renal medulla.

The wall of a nephron consist of a simple epithelium with an external covering of a thin basal membrane .The epithelia cells are structurally and functionally variable in different parts of the nephrons. Those in the epithelium of proximal convoluted tubule are columnar, with a "brush border" of microvilli at free surface and interdigitating processes on the sides. Functionally, these are absorptive cells. The epithelium of descending limb of the loop of Henle is very thin and composed of squamous cells with few microvilli. The ascending limb of loop of Henle is distinguished into a proximal thin and a distal thicker portions. The epithelium of thinner portion is like that of the descending limb, but the thicker portion, distal convoluted tubule and collecting duct consist of interdigitating columnar cells with fewer microvilli than in the cells of proximal convoluted tubule

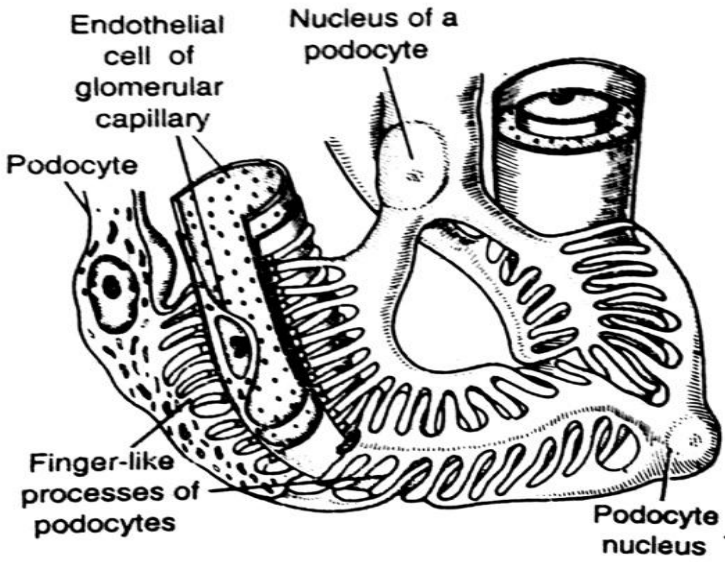


Fig: 5.2: A glomerular capillary entwined by processes of three podocytes

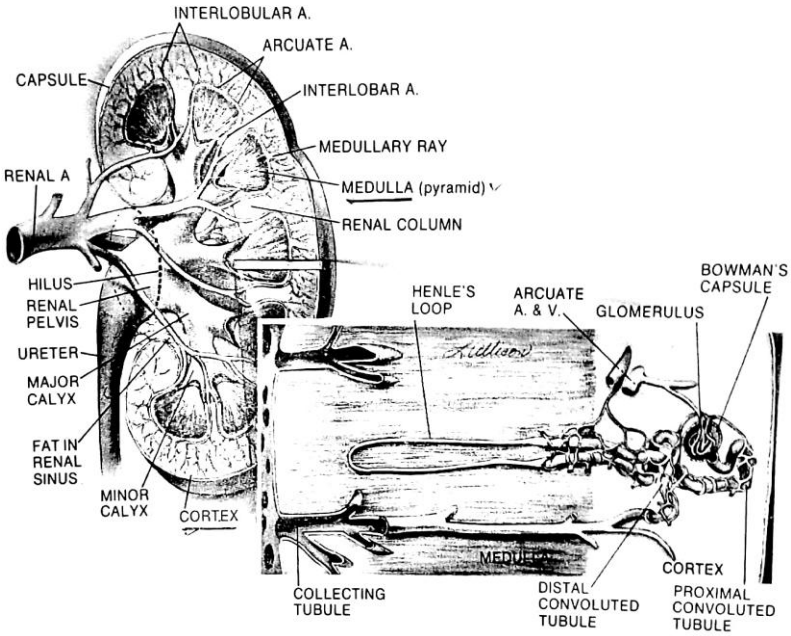


Fig 5.4: L.S of kidney showing Henle loop

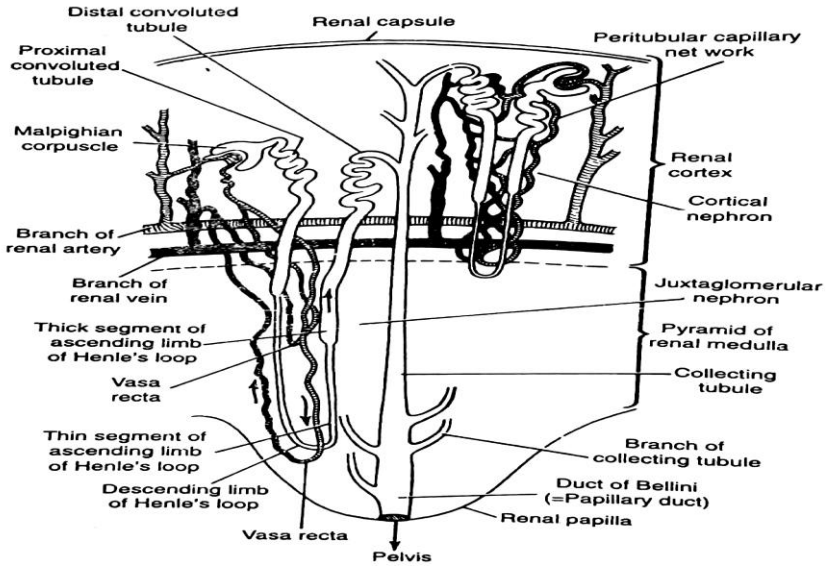


Fig.5.3: Position, structure & blood supply of cortical & juxtamedullary nephrons in a mammalian kidney

5.3 STUDY OF TUBULAR FUNCTION, TUBULAR TRANSPORT MECHANISM & TRANS TUBULAR POTENTIAL

Study of Tubular Function

After the filtration in nephron, the filtrate passes along the proximal tubule, most of its water and salts are reabsorbed into the blood of the network of capillaries around the tubules. The other substances, some are reabsorbed completely in different parts, because the portion of the nephron separates substances that must be retained in the body from those destined for excretion in the urine. The function of the proximal tubule is essentially re-absorption of filtrate in accordance with the needs of homeostasis (equilibrium), whereas the distal part of the nephron and collecting duct are mainly concerned with the regulation of water, electrolyte, and hydrogen-ion balance. All of these processes occur in the tubules through both chemical and physical means, and all are subject to hormonal regulation.

Re-absorption from the proximal tubule

Re-absorption in the proximal tubule of nephron affects all the glucose of the filtrate, up to 70 % of its water and sodium (the remainder is absorbed in the distal tubule), most of the potassium and chloride ions, some of the uric acid, 40 %of urea, and little or none of the sulfate. Out of total solids 75 % are reabsorbed in the proximal tubule. The first part of the tubule absorbs amino acids, glucose, lactate, and phosphate, while the whole convolution absorbs sodium, potassium, calcium, and chloride and by removing bicarbonate, acidifies the fluid slightly.

The tubule has only a certain capacity for re-absorption. Normally all the glucose arriving in the filtrate is absorbed, but if plasma glucose is increased to high levels, the glucose arrives at the tubule cells faster than it can be absorbed (diabetic condition). The rate of tubular re-absorption has an upper maximum value that is constant for any given substance. Consequently, if the plasma level rises sufficiently, all surplus of the substance will pass out in the urine, this is true even for glucose, which is totally reabsorbed under normal conditions. On the other hand, the upper maximum value is much lower for phosphate, so there is normally always some phosphate in the urine. The proximal tubular re-absorption of phosphate is also affected by the phosphate content of the filtrate and is

influenced by parathyroid hormone. Phosphate competes with glucose for re-absorption, and its re-absorption is reduced by parathyroid hormone and by vitamin D is increased. The amino acids also have their own maximum tubular reabsorption values, but these are high enough to ensure that they are entirely reabsorbed under normal conditions.

The re-absorption of about 70 % of the sodium ions in the filtrate means that a similar value of water in the filtrate must accompany these ions as a vehicle to prevent a rising osmotic gradient. The energy required for the re-absorption of sodium into the blood uses 80 %of the oxygen consumed by the kidney and represents one-eighth of the oxygen consumption of a person at rest. There is no evidence for active water transport, and the large volume of water re-absorption occurs passively in response to the movement of sodium..

The active re-absorption of sodium positive ion into the blood leaves the fluid remaining in the proximal tubule electronegative with respect to the peritubular fluids. This provides a driving force for the re-absorptive transport of negatively charged ions such as chloride, bicarbonate, and organic solutes. Re-absorption of neutral molecules such as urea into the blood is also driven by active sodium transport. Because the tubular epithelium is less permeable to urea and creatinine than it is to water or chloride, however, the free passive movement of water out of the tubular lumen leads to a rising luminal concentration of urea. As a result, a smaller proportion of filtered urea or creatinine than of sodium or water is reabsorbed into the blood, resulting in the elimination of a considerable amount in the urine.

Re-absorption from the loop of Henle

About one-third of the volume of the glomerular filtrate enters the descending limb of the loop of Henle. This fluid is isosmotic in nature with plasma. The re-absorptive characteristics of the descending thin limb and those of the bend of the loop differ greatly from those of the ascending thick limb. The thin epithelium lining the thin limb is permeable to water and solute and has no power of active transport. So the fluid entering the limb and the bend of the loop acquires the concentration of the fluid of the surrounding interstitial peritubular fluid. In comparison to the thick ascending limb lined by taller cells has low permeability to water and to urea but actively transports sodium and chloride into the peritubular fluid around both limbs. As a result this fluid in the medullary and deep cortical regions of the kidney becomes highly concentrated, reaching concentrations of up to four times that of the plasma is mainly due to the accumulation of sodium and chloride.

Re-absorption from the distal convoluted tubule

The active transport of sodium out of the ascending limb renders the fluid entering the distal convoluted tubule less concentrated than plasma. Active sodium re-absorption continues throughout the whole of the distal tubule, and this extends to the early part of the collecting duct. As this part of the nephron is relatively impermeable to water, a large concentration gradient of sodium and chloride between the luminal fluid and the plasma is maintained, the concentration of sodium in the tubule being kept well below that of the plasma. The luminal fluid here is also markedly electronegative to the surrounding tissues. The mechanism of sodium re-absorption appears to be directly linked to the secretion of potassium and of hydrogen ions into the tubule from the blood and is greatly influenced by the hormone aldosterone, which is secreted by the adrenal gland when the body's sodium level is deficient.

<u>Re-absorption & secretion at different site in nephron</u>

Proximal convoluted tubule

(i) Absorption : Water – 65%

Na^+ - 67%

K^+ - 65%

Glucose – 100%

Amino acid - 100%

Chloride - 55 - 60%

HCO_3 - 80 - 90 %

(ii) Secretion : H+ - Variable

NH_4 - Variable

Urea - Variable

Creatinine - Variable

At the end proximal convoluted tubule solutions has isotonic 500 mOsm/l.

Loop of Henle

(i) Absorption : Water – 15%

Na^+ - 25%

K^+ - 25 – 30%

Chloride - 35%

(ii) Secretion : Urea - Variable

Creatinine - Variable

At the end of loop of Henle fluid have isotonic 100 – 120 mOsm/l.

Distal convoluted tubule

(i) Absorption : Water – 5%

Na^+ - 5%

Cl^- - 5%

At the end of distal convoluted tubule fluid has isotonic 200 mOsm/l.

Collecting duct

(i) Absorption : Water – 15%

Na^+ - 3%

Urea - Variable

(ii) Secretion : K+ - Variable

H^+ - Variable

Urea - Variable

Tubular fluid coming out of collecting duct is normally hypotonic (up to 1200 mOsm/l)

Tubular secretion

The secretory mechanisms involve the addition of substances to the filtrate from the plasma in the peritubular capillaries. The small amount of secretion that does occur, except for the secretion of potassium and uric acid, takes place in the proximal tubule. Secretion occurs both passively and actively against an electrochemical gradient.

The secretion of potassium by the distal tubule is one of the most important events in the kidney as its control is fundamental to the maintenance of overall potassium balance. More than 75 % of the filtered potassium is reabsorbed in the proximal tubule and in the ascending limb of the loop of Henle, and this percentage remains virtually constant, irrespective of how much is filtered. The amount eliminated in the urine, which is ultimately determined by the dietary intake, is controlled by the distal convoluted tubule. In persons consuming a normal diet, probably about 50 % of the urinary potassium is secreted into the urine by the distal tubules. This amount can be adjusted according to body need. One of the several factors that influence potassium secretion is a hormone secreted by the cortex of the adrenal gland, aldosterone. In the absence of aldosterone and other mineralocorticoids, potassium secretion is impaired, and potentially dangerous amounts can accumulate in the blood. Excess aldosterone promotes potassium excretion.

The brush borders of the cells of the proximal tubules are rich in the enzyme carbonic anhydrase. This enzyme facilitates the formation of carbonic acid (H_2CO_3) from CO_2 and H_2O, which then ionizes to hydrogen ions (H+) and bicarbonate ions (HCO_3^-). The starting point for bicarbonate re-absorption is probably the active secretion of hydrogen ions into the tubular fluid. These ions may be formed under the influence of carbonic anhydrase from CO_2 liberated from oxidation of cell nutrients and H_2O already in the cells. The filtered base, bicarbonate, accepts the hydrogen ions to form carbonic acid, which is unstable and dissociates to form CO_2 and H_2O. The partial pressure of CO_2 in the filtrate rises and as CO_2 is highly diffusible, it passes readily from the tubular fluid into the tubular cells and the blood, and the water is either dealt with in the same way or is excreted. In the meantime the proximal tubular cells are actively reabsorbing filtered sodium, which is balanced by the HCO_3^- formed within the cells from the CO_2 generated by the hydrogen ions in the luminal fluid. Thus the bicarbonate actually reabsorbed is not that which was originally the filtrate, but the net effect is the same as if this were the case.

The other bases besides HCO_3^- may buffer the hydrogen ions secreted into the distal tubules, in addition, the ions may combine with ammonia also secreted by the tubules. The most important non-bicarbonate base present in the filtrate is dibasic phosphate (Na_2HPO_4), which accepts hydrogen ions to form monobasic phosphate (NaH_2PO_4).

In normal circumstances about two-thirds of the hydrogen ions to be secreted in the urine is in the form of ammonium salts (e.g., ammonium chloride). Ammonia (NH_3) is not present in plasma or filtrate but is generated in the distal tubular cells and passes into the lumen probably by passive diffusion down a concentration gradient. In the lumen the NH_3 combines with hydrogen ions secreted into the tubule to form ammonium ions (NH_4+), which are then trapped in the lumen because the lipid walls of the tubular cells are much less permeable to the charged than to the uncharged molecules.

So hydrogen ion secretion can be considered in three phases. The first occurs in the proximal tubule, where the net result is tubular re-absorption of filtered bicarbonate. The second and third phases take place in the distal tubule, where monobasic phosphate and ammonium salts are formed.

Tubular transport mechanism & Trans tubular potential

There are generally two modes of transport i.e. passive transport & active transport. The passive mode include solvent drag, osmosis, passive diffusion & facilitated diffusion. The active mode is primary and secondary active transport.

There are two ways of transport i.e. trans-cellular & para-cellular pathway. In trans-cellular pathway it occurs through the membrane and in para-cellular pathway it occurs between the cell junctions.

Passive Transport

Solvent drag : When bulk amount of water is re-absorbed and solute dissolved in water also transport for example potassium & calcium.

Osmosis : When considerable amount of osmotically active solute is transported, water is re-absorbed along with it to maintain osmotic balance. This is a major mechanism for re-absorption of water from tubular lumen. For example glycosuria in diabetes mellitus which produces osmotic diuresis due to holding of water by glucose molecule.

Passive diffusion : It involve diffusion from high concentration to low concentration and along the concentration gradient e.g. glucose & certain ions.

Facilitated diffusion : It has specific carrier protein e.g. re-absorption of glucose *via* glut & coupled transport is also coming under this. It is of two type sympod-2 & antipod-2. (Glucose transporter), In sympod-2 are more solute in same direction e.g. Na-amino acid, Na-glucose. Antipod-2 more solute in opposite direction e.g. Na^{-} H^{+} exchange

Active transport

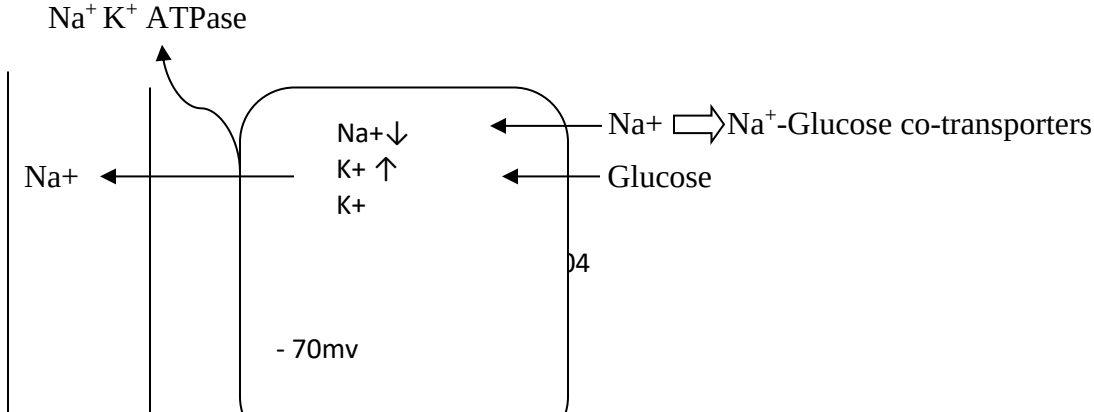
Primary active transport : In primary active transport energy is obtained directly from ATP. Example are

- Na^{+} K^{+} ATPase
- H^{+} ATPase
- H^{+} K^{+} ATPase
- C^{++} ATPase

Secondary active transport : In secondary active transport energy is obtained indirectly from ATP.

- Na-glucose co-transporter
- Na – Amino acid co-transporter
- Na – inorganic phosphate co-transporter
- Na^{+} H^{+} Exchange.

Near the proximal convoluted tubule (PCT) there are 3 site i.e. lumen of nephron, renal tubular proximal cell & peritubular capillary network. The lumen of nephron contains solute particles which has to be re-absorbed. There are various channels through which solutes substances are absorbed. The figure is as follow



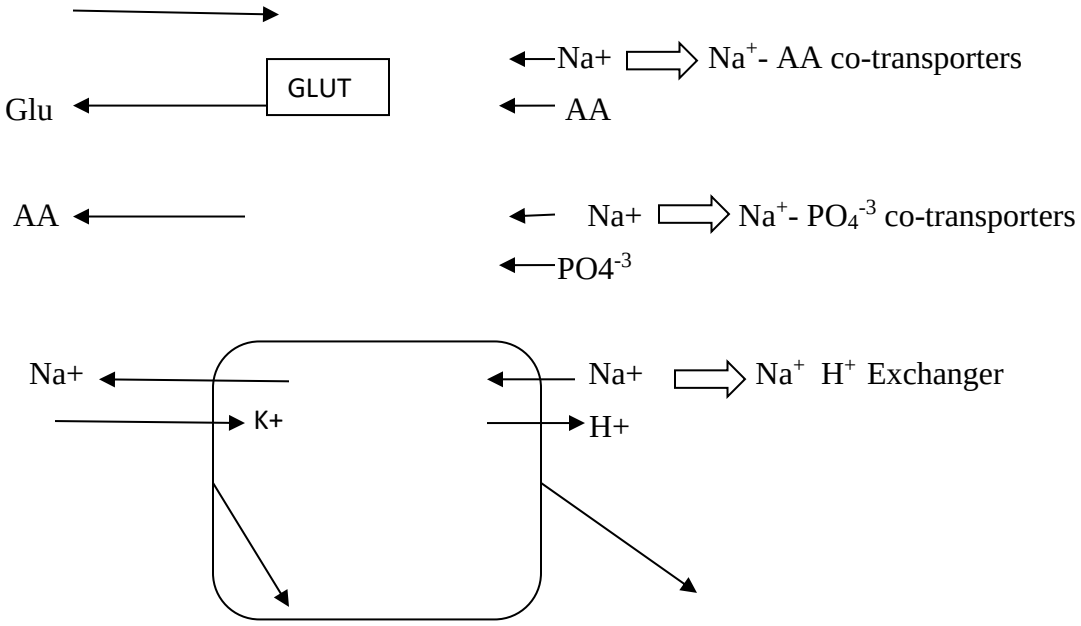


Fig. 5.4: Diagram shows the movement of solute particle through various channels

The wall of proximal cell has two face one toward the lumen which is called apical or lumial membrane and towards peritubular, it is called basolateral membrane. The baso lateral membrane contain sodium pump having $Na^+ K^+$ ATPase enzyme, which bring energy by disintegrating ATP. Toward the apical or lumen membrane contains 4 pump i.e. Na+-glucose co-transporter (SGLT), which is two types SGLT-1 & SGLT-2 (90% are of this type), Na^+- AA co-transporters, Na^+- PO_4^{-3} co-transporters, Na^+ H^+ Exchange.

The first step is by using sodium pump, sodium (Na^+) in pump into peritubular capillary & K^+ is influx in proximal cell. This is done by using $Na^+ K^+$ ATPase enzyme by breaking of ATP molecule. The above process is done due to low concentration of Na^+ in proximal cell so against concentration gradient $Na^+ K^+$ ATPase are used to pump Na^+ in peritubular capillary. Now there is decrease in amount of Na^+ in intracellular proximal cell and influx of K^+ increases brings about -70 mv charges on the cell.

In the lumen of nephron having large amount of Na^+ and less amount of Na^+ in intracellular proximal cells. So due to concentration gradient from high to low, Na^+ move from lumen into intracellular region and also due to negative charge of -70mv of intracellular cell help Na^+ in the influx of intracellular proximal cell. As sodium (Na^+) does not move alone from lumen into intracellular, it carried glucose along with it. It is also due to influx of Na^+ in intracellular (due to concentration gradient) cell, but glucose concentration is low in lumen and high in intracellular cell, so positive charge of Na^+ will help glucose to influx in intracellular from lumen. Now the glucose with the help of Glu receptor it enters into peritubular capillary. So by this way there is transfer of Na^+ take place. The reaction will be same for other secondary active transport like Na^+- AA co-transporters, Na^+- PO_4^{-3} co-transporters.

In Na^+ H^+ Exchanger same amount of Na^+ is released in proximal cell and H^+ released from intracellular cell to lumen to nephron. The reaction is same that due to concentration gradient Na^+ will influx in intracellular cell and high concentration of H^+ in intracellular help H^+ to move from intracellular to lumen or secrete outside.

In the first half of proximal convoluted tubule Na^+ is re-absorbed along with glucose, amino acid & PO_4^{-3} and Cl^- increases in the lumen of tubule. In second half of proximal convoluted tubule Na^+ is re-absorbed along with Cl^-.

5.4 ROLE OF KIDNEY IN REGULATION OF IONIC, OSMOTIC, ACID AND BASE BALANCE OF THE BODY FLUID

Role of kidney in regulation of ionic, osmotic, acid and base balance of the body fluid

Kidney regulates ionic, osmotic and acid & base balance through 4 processes

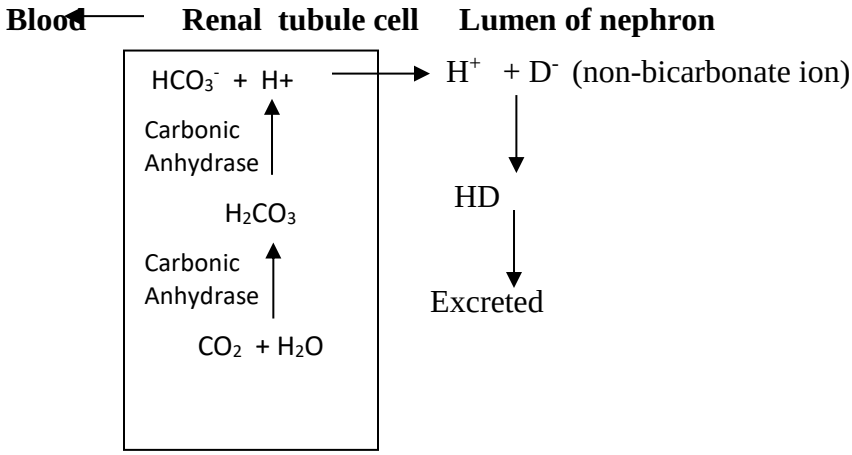
(i) Excretion of hydrogen ion

(ii) Absorption of bicarbonate

(iii) Excretion of titratable acid

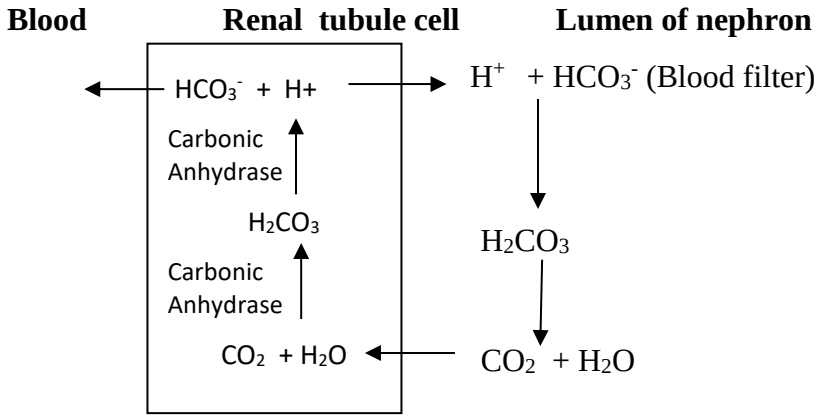
(iv) Excretion of Ammonium ion

(i) Excretion of hydrogen ion : Excretion of hydrogen ion (H^+) take place mainly in proximal convoluted tubule of nephrons. In the renal tubular cell H_2O & CO_2 react in the presence of carbonic anhydrase to form carbonic acid. Then carbonic acid break into bicarbonate (HCO_3^-) and hydrogen ion (H^+). The bicarbonate ion enters into the blood, while H^+ diffuse into the lumen of nephron and it react with non-bicarbonate ion and form compound which will excreted out with urine. The flow diagram is shown as

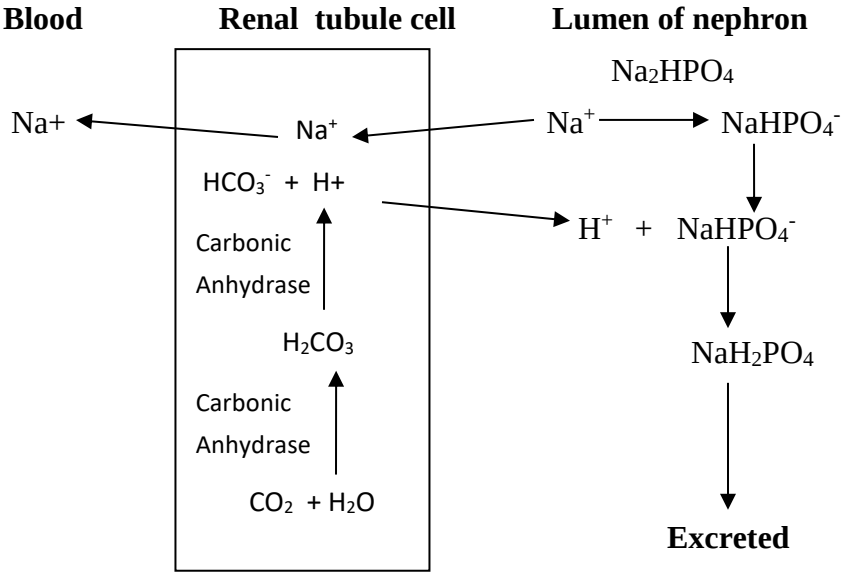


(ii) Absorption of bicarbonate : This case also takes place in the renal tubular cell where H_2O & CO_2 react in the presence of carbonic anhydrase to form carbonic acid. This carbonic acid break into bicarbonate (HCO_3^-) and hydrogen ion (H^+). The bicarbonate ion enters into the blood, while H^+ diffuse into the lumen of nephron and it react with bicarbonate ion (HCO_3^-) which is filtered out in urine (filter blood). This bicarbonate ion (HCO_3^-) which is filtered out in filtration must be re-absorbed by renal tubular cell otherwise it will diffuse out of body with urine and body will face deficiency of bicarbonate ion (HCO_3^-). Now the H^+ and bicarbonate ion (HCO_3^-) in the lumen of nephron react to form carbonic acid, which will again break into H_2O & CO_2. This H_2O & CO_2 diffuse into renal tubular cell. In this cell again it will break to form bicarbonate (HCO_3^-) and hydrogen ion (H^+). The H^+ will again diffuse into lumen and again react with next molecule of bicarbonate (HCO_3^-) to form

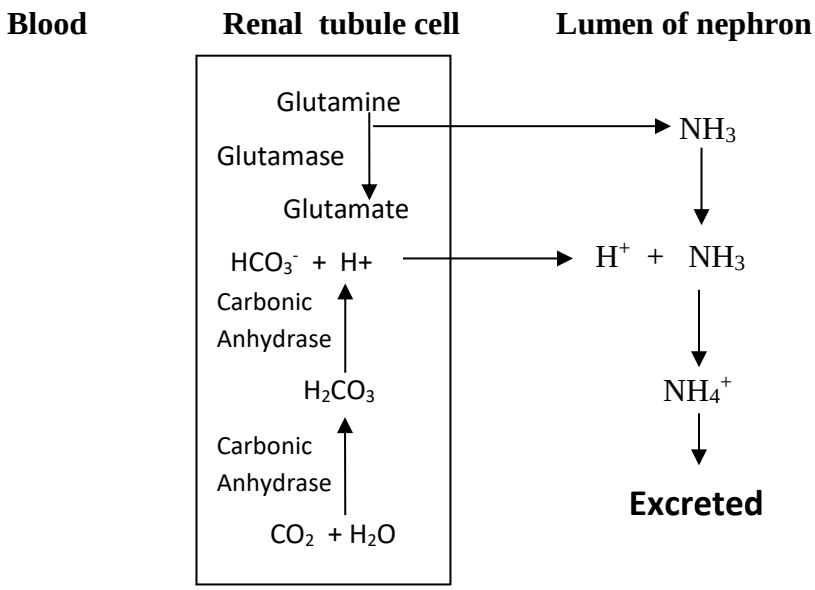
H_2CO_3. This cycle will repeat again and again till all bicarbonate (HCO_3^-) is absorbed. The flow diagram is shown as



(iii) Excretion of titratable acid : In the renal tubular cell H_2O & CO_2 react in the presence of carbonic anhydrase to form carbonic acid. Then carbonic acid break into bicarbonate (HCO_3^-) and hydrogen ion (H^+). The bicarbonate ion enters into the blood, while H^+ diffuse into the lumen of nephron and react with sodium hydrogen phosphate ($NaHPO_4$) to form sodium dihydrogen phosphate (NaH_2PO_4). The di sodium hydrogen phosphate (Na_2HPO_4) which is present in urine is break into Na^+ & $NaHPO_4$. The Na^+ will diffuse into renal and then into blood, while $NaHPO_4$ react to H^+ to form sodium dihydrogen phosphate (NaH_2PO_4) which will excreted out in urine. The flow diagram is shown as



(iv) Excretion of Ammonium ion : In the renal tubular cell glutamine in presence of glutamase enzyme it gives out NH_3 and glutamate. The ammonia enter into lumen of nephron. In the renal tubular cell H_2O & CO_2 react in the presence of carbonic anhydrase to form carbonic acid. Then carbonic acid break into bicarbonate (HCO_3^-) and hydrogen ion (H^+). The hydrogen ion (H^+) enters into lumen of nephron react to ammonia (NH_3) to form ammonium ion (NH_4^+). This ammonium ion (NH_4^+) is excreted out with urine. The flow diagram is shown as



***Osmosis* :**

Both blood and filtrate descending into their respective loops have low solute concentrations. Both flow beside upcoming columns having higher solute concentrations. As they move past one another, water from the down-flowing fluid columns will diffuse into the more concentrated up-flowing columns. However, only the up-flowing vasa recta is permeable to water meaning all is returned to the blood and none to the filtrate. This also insures that a high solute concentration will be maintained at the bottom of both loops. Urea passively diffuses among and between the lower portions of both the blood and the filtrate loops spanning this region. The result is that half the urea is excreted and half kept in the body.

5.5 CONTROL OF EXTRACELLULAR FLUID VOLUME, NITROGEN EXCRETORY PRODUCTS, URINE FORMATION

Control of Extracellular Fluid Volume

Body fluid consists of two parts, intracellular fluids (ICF) & extracellular fluids (ECF). The intracellular fluids are those which are found inside the cells and it constitute about 60% of total body water. It is rich in potassium, magnesium, protein & phosphate. The extracellular fluids (ECF) has two parts i.e. first interstitial fluid, which is ¾ part of extracellular fluid and it occupy the space between the cells. The second extracellular is intravascular fluid, which is ¼ part of ECF and is present in plasma and is rich with sodium, chloride & carbonate.

The control of body fluid volume involves two methods

(1) Water or H_2O balance

(2) Electrolytes balance

(1) Water or H_2O balance : It is a balance of the body fluid by water and it mainly brought about by kidney and achieved by balancing of input or output of water.

The input of water is done by 2 sources either by exogenous or by endogenous. In exogenous it is done by drinking of water & ingestion of water in the food. In endogenous it is done by water producing during tissue oxidation & account for 300 - 400 ml of water per day.

The output of water is done by occurring in form of urine, faeces, sweat & insensible form. About 1 - 1.5 litre of water is lost by urine and 200 ml of water is lost in faeces. The water is also lost through the sweat which is influenced by environmental factor (humidity) & by physical activity. The insensible loss of water is done by evaporation from skin & respiratory passage i.e. lung.

Factor responsible for influencing water balance

There are two factors responsible for influencing water balance are:

(i) Plasma osmolality

(ii) Blood volume

(i) Plasma osmolality : It is a particle present in our serum. It controls water balance by secreting stimulating thirst centre & antidiuretic hormone (ADH) secreted through osmo-receptors present in hypothalamus. It depends on the presence of osmoticallly active substance like NaCl, protein & glucose.

(ii) Blood volume : The change in the blood volume is detected by volume receptor present in atria. When blood volume is low, an impulse are send to hypothalamus & pituitary to secrete anti-diuretic hormone (ADH). It causes conservation of H_2O by kidney.

(2) Electrolytes balance : The chief electrolytes are Na^+ & K^+. The Na^+ is main electrolytes in extracellular fluid. It is responsible for maintenance of extracellular fluid (ECF) volume. It is responsible for producing axon potential. Na^+ is balance by maintaining like aldosterone, atrial natriuretic factor (ANF) or atrial natriuretic peptide and glomerular tubular balance.

The potassium (K^+) ion is main electrolytes of intracellular fluid (TCF). It is related to electrical activity of excitable tissue. Its balance is maintained by excretion rather than intake of K^+.

Nitrogen excretory products

There are large number of organic & inorganic nitrogen excretory products.

Organic nitrogen excretory products

- **Urea :** It is diamide of carbonic acid and is the most abundant substance of urine. The urea content depends on protein catabolism of an individual. Animals having low protein diet produce less urea, whereas in animals whose diet is rich in protein diet, urea content is high. It normally contains 60 – 90 % of total nitrogen.
- **Ammonia :** Fresh urine contains little ammonia. However, on standing ammonia is converted into urea which occurs mainly in the form of salts such as urates and chlorides.

- **Uric acid :** It is the most important end-product of purine metabolism in the body. In certain disease, like leukemia, liver disorders and gout, the uric acid output is increased.
- **Creatinine & Creatine :** The amount of creatinine contents of urine are fairly constant. The concentrations of creatinine are as : 20 – 26 mg/kg body weight/day in normal man, 14 – 22 mg/kg body weight/day in normal woman, creatine is also present in the urine of infants.
- **Amino acids :** Glycine, Histidine, Glutamine and Cystine are principal amino acids found in the urine. Other amino acids are also present, but very small quantities. About 200 mg of amino acids are expected /day in urine of a normal man.
- **Hippuric acid :** Hippuric acid are found in small quantity in the urine. It is formed by conversion of benzoic acid, which otherwise cannot be oxidized easily. Conversion is generally accomplished by the intestinal bacteria.
- **Allantoin :** This compound occurs in very small quantities in human urine. However, in other mammals its content is more where it is formed due to purine metabolism. This is derived from the partial oxidation of uric acid.

Inorganic nitrogen excretory products

- **Chloride :** It is the chief solid constituents of urine. Generally 6 – 9 gm/24 hour as chloride and 10 – 15gm as sodium chloride are excreted through the urine. Chlorides mainly excreted as sodium chloride.
- **Phosphate :** The amount of phosphate excreted through the urine varies widely and it depends largely upon the diet. It is normally excreted 0.8 – 1.3 gm/24 hours. Urine phosphates are combinations of Na^+ & K^+ phosphates as well as calcium and magnesium phosphates.
- **Sulphates :** Urinary sulphates are derived mainly from the metabolic degradation of sulphur containing amino-acids - methionine, cystine and cysteine. The quantity of excretion of sulphate depends upon the protein consumption and the breakdown of tissue protein.
- **Minerals :** The four cations - Na^+, K^+, Ca^{2+} and Mg^{2+} are present in the urine. The quantity of sodium is excreted through the urine normally ranges from 4 – 5gm/24hours. Urinary potassium is about 2.5 – 3.0 gm/day and rises when the intake is increased or in presence of excessive tissue catabolism. Calcium and magnesium are practically excreted through the faeces and very little amount is excreted through urine.

Urine formation

Urine formation is a mechanical process. It takes place in kidney. The unit of excretory system is uriniferous tubules or nephrons. Formation of urine takes place in 3 steps.

(a) Ultra filtration

(b) Selective absorption

(c) Tubular Secretion

(a) **Ultra filtration**: In ordinary filtration insoluble substances are separated from soluble substance but in ultra filtration both useful substance and harmful substance are soluble. So to separate soluble useful substance from soluble harmful substance is called ultra filtration. Ultra filtration takes place in bowman capsule. Ultra filtration is a mechanical process which is not control by nervous system or endocrine gland. From the renal artery afferent arteriole arise which goes in bowman capsule and form capillary network called glomerulus. From glomerulus efferent arteriole arise it from another network called peritubular capillary network around convoluted tubule. The blood comes from afferent arteriole into glomerulus with a pressure of 60- 70 mmHg. (*This is due to because diameter of afferent arteriole is double the diameter of efferent arteriole due to which a pressure is develop)*. This pressure is also called glomerular hydrostatic pressure, by which ultra filtration start but there are other two opposite pressures also lies

(i) Osmotic pressure due to colloidal protein = 25-30 mmHg

(Also called Colloidal hydrostatic pressure)

(ii) Capsular pressure =20mmHg

Total opposite pressure = 30 +20 = 50 mmHg

Resulting pressure of filtration = 70 – 50 = 20 mmHg

So the glomerular filtrate with 20 mmHg pressure. So this filtration is termed as ultra filtration and the substance which filtrate is termed glomerular filtrate. The glomerular filtrate contains both useful and harmful substance. The useful are glucose, mineral, water, amino acid, HCO_3^- , Po_4^-, and harmful substances are ammonia, urea, uric acid, creatine & urochrome.

(b) **Selective absorption :** The glomerular filtrate contains useful substance. These substance must be re absorbed otherwise it will go out along with urine and will make the deficiency for body. So to maintain the homeostasis of blood re-absorption must take place. The re-absorption takes place by the active transport process against concentration gradient and energy is used in this process is come from ATP. The re-absorption is also control by hormone. The glucose is re-absorbed by glucocorticoid of adrenal cortex, mineral absorbtion done by mineral corticoid or Aldosterone of the adrenal cortex. Water is absorbed by vasopressin or ADH of the posterior lobe of pituitary gland. It re-absorbs water makes the urine concentrated, deficiency of this hormone cause urine diluted, dehydrated and blood and caused thrust. This is called diabetes insipidus. After re-absorption of useful substance, concentrated urine is collected in collecting duct. The word Urine for the first time is used in collecting duct. In 1 minute 1.25 ml urine is formed.

The absorption of different substance takes place at different place of the tubule which causes the different osmotic pressure.

(i) Bowman’s capsule and the proximal part have Isosomatic.

(ii) Descending arm of Henle loop has more power for absorption.

(iii) Ascending arm of Henle loop has hypotonic.

(iv) Distal end of the tubule have hypertonic.

(c) Tubular Secretion : There are large no of solutes and water have been extracted from the nephric filtrate in the proximal convoluted part of the tubule and sodium having been exchanged with water in the loop of Henle, a dilute hypotonic fluid passes into distal convoluted tubule (DCT). There are some substances which are not undergoes to the ultra filtration in bowman capsule and goes to the peritubular capillary network. These substances such as **H^+, K^+, SO_3^- & uric acid** are taken from the peritubular capillary and secreted in the lumen of the tubule and ultimately more concentrated urine is formed in the collecting tubule.

Counter current multiplier Theory

The Counter current multiplier Theory operates in loop of Henle. It is now proven that the loop of Henle simply concentrates sodium chloride in the medulla of the kidney. *This then causes vigorous osmotic extraction of water from the distal convoluted tubule(DCT) and collecting tubules*, thereby concentrating the urine and making it hyperosmotic to blood. The sodium (K^+ and Cl^- also) is actively removed from the nephric filtrate as it passes up the ascending limb of the loop of Henle and deposited in the descending limb**.** For every Na^+ moving from the ascending limb into the descending, a molecule of water is exchanged i.e. passed on to the ascending limb. The sodium concentration is maximum at the U-bend of the loop which is quite deep into the medulla of the kidney. Sodium ions then diffuse out of the descending limb into the blood capillary paralleling the descending limb soon form NaCl with Cl- which are present in the blood. High concentration of NaCl in the medulla of kidney causes vigorous extracting of water from the fluid running down the distal convoluted tubule and collecting tubule. Water is thus returned to the blood of the peritubular capillaries, while highly concentrated urine reaches the collecting ducts and the ureter.

It is also noticed that active transfer of Na^+ takes place at all levels of the loop. At any level the effect of this transfer is to raise the sodium concentration in the descending limb very slightly above that in the ascending limb. The effect at any level is slight, but overall result is multiplied by the length of the hair pin bend formed by the loop of Henle.

The characteristic U-shap of loop of Henle provides a counter current system. The fluid in the descending and ascending limbs flows in opposite directions (i.e. counter currents are set up) concentrating Na^+ in the descending limb and decreasing Na^+ in the ascending limb. The flow of blood in the capillaries of the vasa recta is also opposite of the direction of the flow of fluid in the two limbs of the loop of Henle. The entire mechanism operating in the loop of Henle is known as hair pin counter current multiplier mechanism. This is so efficient that as much as 90% water of the nephric filtrate is re-absorbed by the kidney tubule and put back into the blood. If somehow kidney stops this vigorous absorption of water. The body of man will be dehydrated in three minutes.

Composition of Urine

The composition of human urine varies from day to day and from person to person. It also depends upon the diet and environmental conditions. The color of urine is dark yellow due to presence of

urochrome pigment. It is produced by the degradation of haemoglobin. Normally urine is slightly acidic pH – 6.8. Its specific gravity is 1.015 to 1.02. On standing it become cloudy and acquires ammonia odour due to formation of ammonium carbonate. Some important substances of urine are

(i) H_2O - 95%

(ii) Urea - 2.5 %

(iii) Salt - 2%

(iv) Uric acid -2 %

(v) Creatine & creatinine - very small quantity

(vi) NH_3 --Very little

(vii) Lippuric acid - Very little

(viii) Phosphate - 3.0 gm

(ix) Neutral sulphur - 0.12gm

(x) Phenol - 0.2 gm

SAQs 1.

Complete the following sentences by inserting appropriate words in the blanks.

(i) In mammals, the main excretory organ is ----------

(ii) Daily ---------ml of glomerular filtrate is produced by human kidneys

(iii) Re-absorption in kidney tubules is facilitated by ----------

(iv) The process of dilution of urine take place in ----------

5.6 SUMMARY

In this unit there is very large description about structure of kidney. There is also information about Tubular function, Tubular transport mechanism & Trans tubular potential in very detailed manner. This unit also contains role of kidney in regulation of ionic, osmotic, acid and base balance of the body fluid. There is also discussion about control of extracellular fluid volume, nitrogen excretory products, urine formation and composition of urine.

5.7 TERMINAL QUESTION

Q1 Describe the structure of nephron.

Q2 Describe the Re-absorption from the loop of Henle.

Q3 Describe the composition of urine.

5.8 ANSWERS

SAQ 1

(i) Kidney

(ii) 200

(iii) ADH

(iv) Proximal tubule

Terminal question

1. The nephron or uriniferous tubules consist of microscopic structure of Bowman's capsule, neck and secretory tubules. The Bowman's capsules of all tubules lie in the renal cortex. The Bowman's capsule contains a network of blood capillaries called glomerulus. The glomerulus connected with an afferent arteriole on one side and efferent arteriole on the other side. The Bowman capsule together with glomerulus is called renal or malpighian corpuscle. The outer wall of Bowman's capsule is composed of flattened squamous cells. The inner invaginated wall that lines the concavity of the capsule, is composed of a special types of flattened cells called podocytes. These cells bear distinct finger like processes which interwine around capillaries of the glomerulus.

The Bowman's capsule is followed by a short and narrow "neck". The internal lining of neck is marked by ciliated cells of epithelium.

The secretory tubule can be distinguished into three parts are as follow –

(1) The proximal convoluted tubule lies behind the neck. It makes a few coils and is restricted to the cortical region of the kidney.

(2) The quite narrow and "U" shaped loop of Henle, having a descending limb that extends into the medulla and an ascending limb that extends back from the medulla into the cortex.

(3) The distal convoluted tubule which is thicker and coiled and situated in the cortex like the proximal tubules. The coils of both convoluted tubules are intermingled.

2. About one-third of the volume of the glomerular filtrate enters the descending limb of the loop of Henle. This fluid is isosmotic in nature with plasma. The re-absorptive characteristics

of the descending thin limb and those of the bend of the loop differ greatly from those of the ascending thick limb. The thin epithelium lining the thin limb is permeable to water and solute and has no power of active transport. So the fluid entering the limb and the bend of the loop acquires the concentration of the fluid of the surrounding interstitial peritubular fluid. In comparison to the thick ascending limb lined by taller cells has low permeability to water and to urea but actively transports sodium and chloride into the peritubular fluid around both limbs. As a result this fluid in the medullary and deep cortical regions of the kidney becomes highly concentrated, reaching concentrations of up to four times that of the plasma is mainly due to the accumulation of sodium and chloride.

3. The composition of human urine varies from day to day and from person to person. It also depends upon the diet and environmental conditions. The color of urine is dark yellow color due to presence of urochrome pigment. It is produced by the degradation of haemoglobin. Normally urine is slightly acidic pH – 6.8. Its specific gravity is 1.015 to 1.02. On standing it become cloudy and acquires ammonia odour due to formation of ammonium carbonate. Some important substances of urine are

(i) H_2O - 95%

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(iii) Salt - 2%

(iv) Uric acid -2 %

(v) Creatine & creatinine - very small quantity

(vi) NH_3 --Very little

(vii) Lippuric acid - Very little

(viii) Phosphate - 3.0 gm

(ix) Neutral sulphur - 0.12gm

(x) Phenol - 0.2 gm

UNIT-6 OSMOREGULATION

6.1 INTRODUCTION

Osmoregulation is defined as the process by which organism regulates the water balance and maintains the homeostasis ion its body. In osmoregulation, it control excess of water loss or gain and maintaining the fluid balance and osmotic concentration of electrolytes such as Na^+, K^+, Ca^{++}, glucose, CO_2 & O_2 . It also ensures that the fluids in the body do not get too much diluted or concentrated. The osmoregulation is of two types.

(i) Osmoconformers : It includes most marine invertebrates whose internal salt and water concentration are equivalent to their external environment.

(ii) Osmoregulators : It includes many marine vertebrates such as fishes, whose internal salt concentrations is different from their external aquatic surroundings and must actively control their salt concentration.

Objective

After studying this unit you will be able to know:

- Definition of osmoregulation, know about osmoregulation in fresh water and marine water fishes.
- salt balance in aquatic medium and osmoregulation in migratory fishes.
- about the homeostasis.

6.2 OSMOREGULATION IN FRESH WATER AND MARINE FISHES

Fishes are surrounded by water, they may be either salt water or fresh water and they have a limited salt tolerance. Hence they are known as stenohaline. In fresh water fishes, the concentration of salt is more in the body than the outside water, so there is always entering of water into the body through the semi permeable membranes of the buccal cavity and gills. In marine water fishes, the concentration of salt in the marine water is more than in the body fluids of the fish, so that water tends to diffuse out of body. Hence marine fishes always tend to drink water to maintain salt balance. The kidney and gills play an important part in the excretion of nitrogenous wastes and in maintaining water salt balance.

According to habitat of fishes, it can be distinguished in the two type i.e. fresh water fishes and marine water fishes. The fresh water fishes and marine water fishes, osmo-regulates is different ways. Because it is due to the different nature of salinity of water in which they live, so their process of osmoregulation is also different.

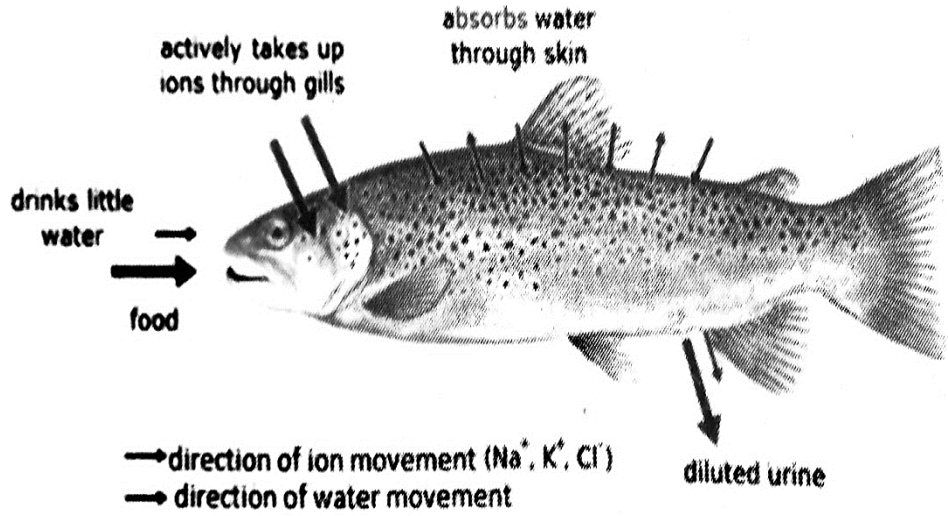

Fig: 6.1: Osmoregulation in fresh water fishes

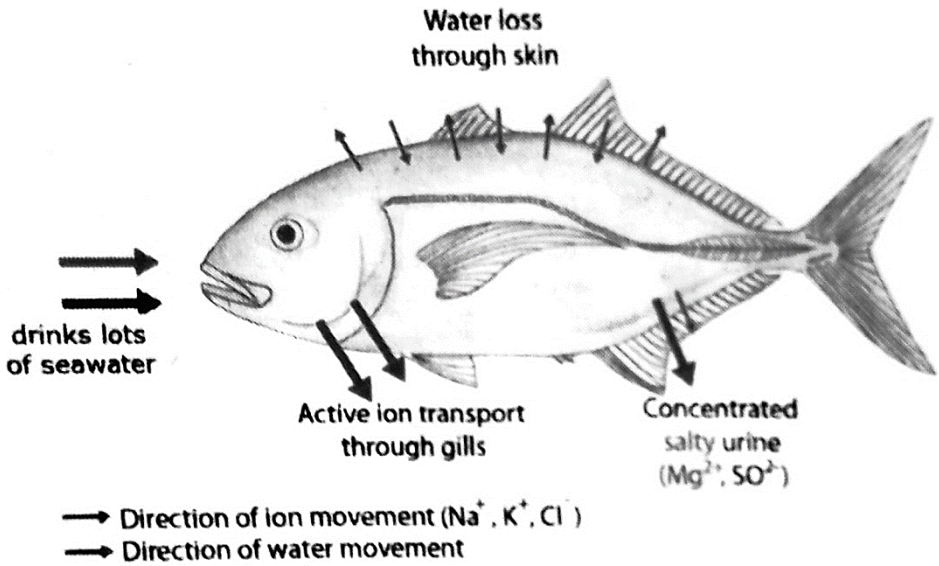

Fig. 6.2: Osmoregulation in Marine water fishes

Osmo-regulation Fresh water fishes

In fresh water fishes, the osmotic pressure of the body fluids is higher than that of the surrounding water, hence water diffuses into the animal body through gills, oral membranes and the intestinal

surface. Some water may also enter through the less permeable skin. Due to this steady inflow of water, fresh water fishes produce a large amount of dilute urine which is hypotonic with regard to the fish. It has been observed that the fresh water fishes have large no of functional glomeruli in kidney than those of a marine fishes kidney. The fresh water teleost fishes produce urine between 5 – 12% of the body weight per day. Due to large amount secretion of urine, many fresh water fishes have developed urinary bladder for storage.

Majority of the elasmobranchs fishes are marine, but some are also found in fresh water form like *Carcharhinus leucas*, *Potamotrygon* (Amazon sting ray). Their blood concentrations are lower than those of marine forms. The urea concentration is reduced to less than one third of the marine form. The problem of osmotic regulation is reduced due to the low level of solutes in the blood. The osmotic inflow of water is diminished because lower salt concentration is easier to maintain. The reduced osmotic inflow of water gives less water to be eliminated by the kidney.

Salt balance

The osmotic concentration of the body fluid in fresh water fishes is higher than that of the surrounding water, hence some salts especially the chlorides are lost into the water by diffusion through surface tissue, some salts are lost in the faeces and urine also. The quantity of salt lost per day varies in different species. However the loss of salts is kept at a minimum in all fresh water fishes by active re-absorption in the proximal segment of the renal tubule.

Salts are replaced partly through food and partly by active absorption of salt ions from the surrounding water. This take place mainly in the gills and the oral membrane. The important ions to be absorbed by these structures are Lithium (Li^+), sodium (Na^+), calcium (Ca^{++}), Chlorine (Cl^-), Bromine (Br^-), acid phosphate (HPO_4^-) and Sulphate (So_4^-). These ions are probably absorbed by the large acidophilic chloride cells at the base of the gill lamellae. Other cells of the oral membrane may also take part in the regulation of salt balance on the entire mechanism may be under the control of the endocrine glands. Fresh water fishes show considerable difference regarding their capacity for salt tolerance. Generally they are intolerant to large salinity changes and are called stenohaline fishes. Some species can survive in both fresh water as well as salt water (diadromous sps) can bear salinity changes. These are known as euryhaline species such as *Eel, Salmon, Hilsa* etc. The stenohaline fishes vary in their capacity to adjust to a higher than normal salt concentration. This depends on the histology of the gills, the areas of gill surface, rate of oxygen consumption the tolerance of the tissue for salts and control of permeability.

Marine Fishes

Marine fishes live in a medium having salt concentration much higher than that of the body fluid, so that they lose water by diffusion through semipermeable membrane and gain salts. Marine fishes, therefore drink sea water to make up the loss and this further increases the salt content of the body. Marine fishes are thus faced with the danger of dehydration which they counter act by drinking sea water but this increases the salts in the blood which must be eliminated. In order to conserve water, urine output is greatly reduced in marine fishes and the kidney tubules are modified for water retention.

The cartilaginous (elasmobranchs) fishes have a glomerular kidney as in fresh water fishes, but they maintain their blood at a slight higher concentration than that of the surrounding water, so that they are not in the danger of dehydration. In elasmobranch fishes urine is formed by filtration in the glomerulus but most of the urea contained in it is re-absorbed by special segments of the urinary tubules. The gills of elasmobranchs are almost impermeable to urea so that the urea is retained in the blood in large quantities, raising the osmotic concentration of the blood to a slightly higher level

than that of sea water. In addition to urea, trimethyl amine oxide (TMAO) also helps in maintaining the high osmotic pressure of the blood.

In marine teleosts lose water continuously through the gills and other permeable membranes because the concentration of the blood is lower than that of the sea water. These fishes drink sea water. Moreover the number and size of the glomeruli is reduced and water is re-absorbed in the kidney tubules. Large amount of water is not allowed to pass out through the glomeruli to form urine. In many species, the glomeruli become degenerate and nonfunctional. Marine teleosts drink large amount of sea water to prevent dehydration but this increases the quantity of salts in the body. The excess salts are excreted by the gills. A large number of salt secreting cells are present in the oral membrane, gill and on the inner surface of the operculum.

Osmo-regulation in marine fishes

The marine fishes can be categorized into different groups.

(i) Those whose osmotic concentration is same as, or slightly above sea water e.g. elasmobranch, *latimeria* etc. are called isosomatic fishes. This group of fishes has no major problem of water balance, because it's inside and outside concentrations are equal and there is no osmotic water flow.

(ii) Those whose osmotic concentrations are about one third of that of sea water e.g. teleosts, are called hyposomatic fishes. They live in constant danger of losing water to the osmotically more concentration medium.

In marine elasmobranch urea is a normal component of the body fluids, so in marine elasmobranch, the tissue cannot function normally in the absence of such high urea concentration. This urea is generally excreted through kidney but in shark actively re-absorb this urea. The use of urea for maintaining osmotic equilibrium helps these animals to keep salt concentration much lower those of sea water. But urea can pose problems in the body functioning. This problem is solved by converting into another compound trimethylamine-N-oxide (TMAO).

The elsamobranchs have solved the osmotic problem in sea by extensive ionic regulation. They have sodium concentration much lower than that of sea water. This means that sodium tends to diffuse from sea water into the body. Sodium enters into the body primarily through the thin epithelium of the gill and then through the ingested food. This enhances the sodium level in the body, which must have to be excreted or eliminated by the kidney, but major excretion of Na^+ is done by special rectal gland. The rectal gland open by a duct into the posterior part of intestine i.e. rectum. The glands secrete a fluid with high sodium and chloride concentration, which is higher than sea water concentration.

The elasmobranch blood is usually more concentrated than sea water. This higher concentration inside causes a slight osmotic inflow of water *via* the gill. In this way, the elasmobranch slowly gains water osmotically and this water is used for the formation of urine and for the secretion of rectal gland.

6.3 OSMOREGULATION IN MIGRATORY FISHES

There are certain fishes which migrate both from fresh water to sea water (Diadromous sps) or vice versa. Therefore they can tolerate a wide range of salinities. These are known as euryhaline species e.g. *Eel, Hilsa, Salmon*. These movements of fishes are associated with their life cycle such as breeding. But this change from one environment to the other environment requires profound changes in the osmoregulatory processes.

For example in case of anadromous *Salmon* which spend most of their life in ocean but for breeding purpose they move to the fresh water, river. After fertilization female lays eggs in fresh water. From these eggs young *Salmon* develop which start its life in a fresh water river, where it has to prepare for a life in a salty ocean. Now the young *Salmon* undergoes three important changes before it start migrating in sea. Firstly, it has to start drinking lots of water. Secondly, the kidneys must drop their urine production dramatically. Thirdly, the chloride cells in the gills (molecular pumps) shift to reverse i.e. pumping sodium out instead of in. If adult salmon migrate from sea to river the entire above three processes will reverse before entering into fresh water river. They stay a few days in the estuarial zone as these changes happen automatically.

There are also species living in estuaries, the environments, where freshwater meets the sea and salt concentration changes gradually. Some species of sharks can swim very far upwards the freshwater stream. Their osmoregulating process is quite different that the one of salmons. They are able to convert ammonia to urea and retain it in the blood to such an extent that the blood is slightly more concentrated than sea water. In this way, the loss of water *via* osmosis is prevented and animals do not need to drink sea water and excessive salt is excreted through the rectal gland. These switches are controlled in the brain and regulated by hormones. The cortisol and thyroid hormone are the main regulators of osmotic process, by influencing the rate and direction of ions pumped through the chloride cells.

6.4 HOMEOSTASIS – NEURAL AND HORMONAL

The endocrine gland is responsible for the regulating the amount of urine flow and salt balance. The hormones influence the filtering rate of the renal corpuscles by a change in the blood pressure and thus it control the amount of the urine output. The hormone is also responsible for the diffusion & absorption by the gills. The hormones produced by the adrenocortical, thyroid and supra renal bodies are responsible for osmoregulation & excretion in fishes.

Hormone	**Released**	**Function**
Epinephrine & Nor-epinephrine	Adrenal medulla	Can decrease kidney function temporarily by vasoconstruction
Renin	Kidney nephrons	Increases blood pressure by acting on angiotensinogen
Angiotensin	Liver	Angiotensin II affects multiple processes and increases blood pressure
Aldosterone	Adrenal cortex	Prevents loss of sodium and water
Anti-diuretic hormone (vasopressin)	Hypothalamus (stored in the posterior pituitary)	Prevents water loss
Artrial natriuretic peptide	Heart atrium	Decreases blood pressure by acting as a vasodilator

		and increasing glomerular filtration rate, decreases sodium reabsorption in kidneys

SAQs 1.

Complete the following sentences by inserting appropriate words in the blanks.

(i) The Osmoregulation that is active regulation of the ---------- to maintain the fluid balance and concentration of salts.

(ii) Osmoconformers include most marine invertebrates whose internal salt and water concentrations are ..... to their external environment.

(iii) In order to maintain a sufficient salt level, special cells in the gills ---------- take up ions from the water

(iv) Anadromous fishes migrate from sea to ----------

6.5 SUMMARY

In this unit there is very large description about osmoregulation in fishes. In this unit their is description about fresh water and marine water fishes and how they control water as well as salt balance in their body. In this unit there is also description about osmoregulation in fishes live in salt water and they migrate to fresh water for breeding purpose. There is also description about neural and hormonal control over osmoregulatory.

6.6 TERMINAL QUESTION

Q1 Describe Osmoregulation in fishes.

Q2 Describe the osmoregulation in fresh water fishes.

Q3 Describe the osmoregulation in marine water fishes.

6.7 ANSWERS

SAQ 1

(i) Osmotic pressure

(ii) Equivalent

(iii) Chloride cells

(iv) Fresh water

Terminal question

1. Osmoregulation is defined as the process by which organism regulates the water balance and maintains the homeostasis in its body. In osmoregulation, it control excess of water loss or gain and maintaining the fluid balance and osmotic concentration of electrolytes such as Na^+, K^+, Ca^{++}, glucose, CO_2 & O_2. It also ensures that the fluids in the body do not get too much diluted or concentrated. The osmoregulation is of two types.

(i) Osmoconformers : It includes most marine invertebrates whose internal salt and water concentration are equivalent to their external environment.

(ii) Osmoregulators : It includes many marine vertebrates such as fishes, whose internal salt concentrations is different from their external aquatic surroundings and must actively control their salt concentration.

2. In fresh water fishes, the osmotic pressure of the body fluids is higher than that of the surrounding water, hence water diffuses into the animal body through gills, oral membranes and the intestinal surface. Some water may also enter through the less permeable skin. Due to this steady inflow of water, fresh water fishes produce a large amount of dilute urine which is hypotonic with regard to the fish. It has been observed that the fresh water fishes have large no of functional glomeruli in kidney than those of a marine fishes kidney. The fresh water teleost fishes produce urine between 5 – 12% of the body weight per day. Due to large amount secretion of urine, many fresh water fishes have developed urinary bladder for storage.

3. Marine fishes live in a medium having salt concentration much higher than that of the body fluid, so that they lose water by diffusion through semipermeable membrane and gain salts. Marine fishes, therefore drink sea water to make up the loss and this further increases the salt content of the body. Marine fishes are thus faced with the danger of dehydration which they counter act by drinking sea water but this increases the salts in the blood which must be eliminated. In order to conserve water, urine output is greatly reduced in marine fishes and the kidney tubules are modified for water retention.

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Master of Science

PGZY-102 (N)

Physiology and Biochemistry

2

Block

Physiology-II and Bichemistry-I

BLOCK-2

In the previous block you have studied about the physiology 1. In this block you will be introduced by physiology-II and biochemistry-I. This block is divided into four units (unit 7 to 10) as under:

Unit 7 – It deals with the physiology of circulation and Endocrine regulation of implantations, Neuroendocrine system and neuro-secretions.

Unit 8 – In this unit you will study about Structure and biological importance of carbohydrates, proteins and lipids

Unit 9 - It deals with the Biosynthesis of amino acids (Phyenylalanine, Tryptophan, Aspartate, Proline, Threonine) deamination and transamination of amino acids.

Unit 10 - you will be study Biosynthesis of Palmitic acid, Ketogenesis

Objectives:-

After studying this block you will be able to know:

- The circulation and Endocrine system
- Structure and biological importance of carbohydrates, proteins and lipids
- Biosynthesis of Amino acids, Palmitic acid, Ketogenesis

UNIT-7 CIRCULATION AND ENDOCRINE SYSTEM

7.1 INTRODUCTION

The circulatory system, also called the cardio-vascular system or the vascular system is an organ system that permits blood to circulate and transport food materials (nutrients such as Amino Acids, glucose and electrolytes), O_2, CO_2, hormones and blood cells to and from the cells in the body. In other words the primary function of the circulatory system is to provide an adequate supply to all cells of the body of materials needed for their proper function and that carries away the waste products of their metabolism. The circulatory system is a well organized transport system of the body by which the blood being circulated within a closed system. Under different pressure gradient, created by the pumping mechanism where heart acts as the central pump.

The rhythmic series of changes in the sex organs that occurs about 28 days throughout the reproductive life of women i.e. from puberty to menopause is called menstrual cycle. The process of formation of placenta is called placentation, which is the site of exchanges of nutrients and wastes between mother and foetus.

Objective

After studying this unit you will be able to know:

- Open and closed type of circulation.
- Understand the types of heart.
- menstrual cycle and regulation of ovarian and testicular function.
- about endocrine regulation of implantation, hormonal regulation.
- About placenta in mammals, its classification.
- neuro-endocrine system and neuro-secretion.

7.2 CIRCULATION-TYPES OF CIRCULATION, PHYSIOLOGICAL CATEGORIES OF HEART

Circulation - Types of Circulation

There are two types of circulation observe in heart i.e. single circulation and double circulation:

(i) Single circulation : Such type of circulation is observed in 2 chambered or 3 chambered heart like fishes, Amphibian & reptilian. In 2 chambers heart like fishes it receives impure blood from different parts of the body and pump it into respiratory organ (gills) from where it gets oxygenated and this oxygenated blood is circulated to different parts of the body. So the blood passes single time from the heart.

In case of amphibian and reptiles where heart is of 3 chamber, the right side of heart i.e. right auricle receive deoxygenated blood from different parts of the body and left side i.e. left auricle receive oxygenated blood from the lungs and then both the deoxygenated & oxygenated blood from auricles enter into ventricle and from ventricle it is distributed to whole of the body i.e. blood pass single time from heart that is why it is called single circulation.

(ii) Double circulation : In 1628 William Harvey discovered the double circulation in heart. In mammals the blood circulates twice through the heart during one complete cycle. This is called double circulation. In mammals due to the complete separation of ventricle, the heart becomes four chambered. i.e., right auricle, left auricle, right ventricle & left ventricle. The right auricle of heart receive deoxygenated blood from whole of the body while left auricle receive oxygenated blood from lungs. The right ventricle receive deoxygenated blood from right auricle, while left ventricle receive oxygenated blood from left auricle.

The deoxygenated blood first enter into the right auricle and then right ventricle from right ventricle it pump into pulmonary artery for purification in respiratory organ. After purification the same blood return and enter into the left auricle then into left ventricle. From left ventricle it is force into the systemic aorta to distribute the pure blood throughout the body. So a single blood passes two times from the heart. Such type of circulation is called double circulation which is generally observed in warm blooded animals such as birds & mammals.

Mammalian heart maintains equal volume of blood round each circuit, in unit time, which is essential for double circulation. In man at rest, the blood requires about 86 second to complete this cycle.

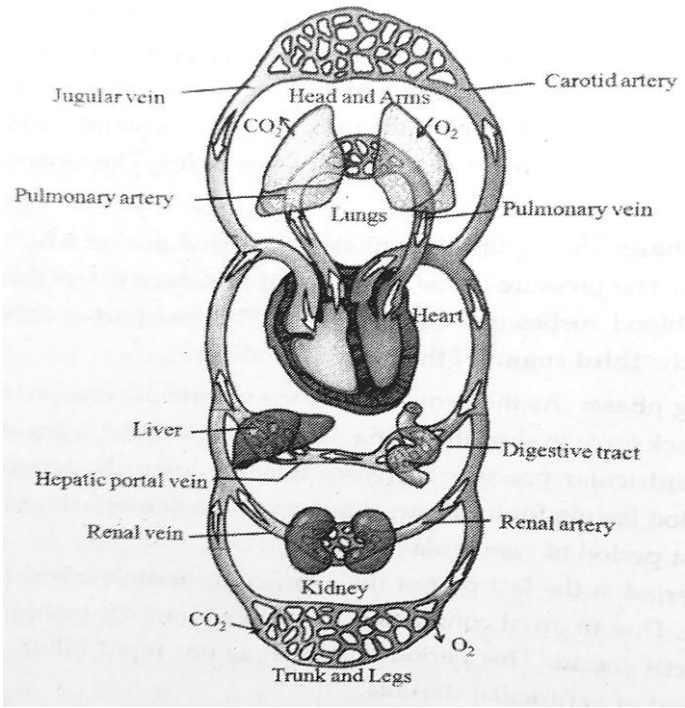


Fig 7.1 : Double circulation

Physiological Categories of Heart

Physiologically heart is of two types i.e. myogenic heart & neurogenic heart

(i) Myogenic heart : In such type of heart, the heart beat originate from its muscle i.e. a special node of modified or unmodified heart muscle, the sinus node or pace maker, which is present in the wall of right auricle. The pace maker produces rhythmic signals leading to contraction of the heart. When such heart is isolated and placed into an artificial nutrient medium, The heart may for a time contract and relax in a slow rhythms. In the body heart beat can be regulated by both amplitude (strength) and rate of control system, which are nervous, physical and chemical. Acetylcholine inhibits the heart beat of a myogenic heart. Such type of myogenic heart is seen in vertebrate and mollusca. In myogenic heart electrocardiogram shows waves which are large and slow with distinct P & QRS complex. Adrenaline acts as a transmitter of nerve impulse to smooth muscles, accelerates the myogenic pace makers.

(ii) Neurogenic heart : In such type of heart, the heart beat originate by nervous stimulation or neurogenically i.e. the contraction is initiated by the nervous ganglion stimulated in or close to the heart. The nerve cells acting as the pace maker, such as ganglion deliver rhythmic impulse to the heart muscle and removal of the ganglion stops the heart beat. Acetylcholine accelerates the heart beat of a neurogenic heart. Such types of heart seen in crustaceans, arachnids, insects etc. In neurogenic heart electrocardiogram shows waves that are oscillatory. Adrenaline has no effect on neurogenic pacemakers.

7.3 MENSTRUAL CYCLE, REGULATION OF OVARIAN AND TESTICULAR FUNCTIONS

Menstrual cycle

The rhythmic series of changes in the sex organs that occurs about 28 days throughout the reproductive life of women i.e. from puberty to menopause is called menstrual cycle. In one phase of

menstrual cycles uterine bleeding occur, which is referred as menstruation or menstrual period. The menstruation is also described as funeral of the unfertilized ovum or it is also called weeping of the uterus. The menstrual has duration of 3 to 5 days. Ovulation occurs about midway between the menstrual period i.e. somewhere between the 13^{th} to 17^{th} day following the commencement of the bleeding. The menstrual may also defined as the cyclical discharge of blood, mucus and certain other substances from the uterus in female at an average interval of 28 days (24 – 32 days). The menstrual blood contains stripped of endometrium, mucus, leucocytes and an unfertilized ovum. During each, menstrual cycle the uterine mucosa gradually hypertrophies. This is due to prepare suitable bed for the reception and implantation of fertilized ovum. If pregnancy occurs, the proliferated mucosa is converted into placenta. If pregnancy does not occurs the hypertrophied mucosa break down and is discharged as menstruation. The hormones involved in the menstrual cycle are progesterone, estrogen, luteinizing hormone (LH) and follicle stimulating hormone (FSH).

During the entire menstrual cycle, the endometrial tissue undergoes changes which have divided into four stages.

(i) **Menstrual or destructive phase :** This is also called menses. This phase mark the beginning of menstrual cycle and takes 3 to 5 days. It takes place when fertilization does not take place. In this phase there is destruction of endometrial lining of the uterus. If the ova is not fertilized, the corpus luteum under goes regression and causes deficiency of the ovarian hormone progesterone, so the endometrium is unable to maintain its nutrition and begins to regress and disintegrate. This results in bleeding of uterus. Blood with some uterine tissue and the unfertilized egg passes out through the vagina as menstrual flow.

(ii) **Follicular or Proliferative phase :** This phase take place between 6 – 14 days of menstrual cycle. It occurs between the end of menses and ovulation. During this phase, the egg matures within the follicles and lining of uterus prepares to receive the fertilized egg. The gonadotropin releasing factor (GRF) is released by hypothalamus, stimulate, the anterior pituitary gland to release gonadotropin hormone like follicle stimulating hormone (FSH) and Luteinizing hormone (LH).

During the 8 to 10 days, FSH stimulates about 10 – 20 primary follicles containing egg to grow in the ovary. It also stimulates the cells of the growing follicles to secrete estrogens mainly estradiol into the antrum of the follicle. Finally enough amount of estrogen accumulates in one follicle to make it independent of FSH for its continued growth and development. Only this follicle reaches to full maturation to the graafian follicle. The others are regress and finally die.

Estrogen causes changes in the endometrium lining of uterus. The endometrium undergoes a process of growth or proliferation. It becomes thicker and its blood supply also increases.

(iii) **Ovulatory or ovulation phase** : On the 14^{th} day ovulation of Graafian follicle takes place. At this time the level of estrogen in the blood reaches its peak. There is also a sudden increase in gonadotropin releasing factor (GRF) hormones. The anterior pituitary responds by a large surge in the release of LH and a lesser surge of FSH for a short time. The sudden surge of LH and FSH occurs on about the 14^{th} day. The high levels of LH, FSH and estrogen but especially LH, causes rupture of the Graafian follicle and release of the egg (Ovulation).

(iv) **Luteal or secretary phase :** This phase start immediately after ovulation and lasts till the end of the menstrual cycle. It lasts about 14 days i.e. 15 – 28 days. After the ovulation, there is an immediately decline in the production of released of estrogen. The cells of the ruptured

follicle are stimulated by LH to form corpus luteum. The corpus luteum secretes large amounts of progesterone and some estrogen. The corpus luteum is maintained by LH.

By the combined action of progesterone and estrogen, the endometrial begins its secretary phase. It continues to increase in size. Its glands become enlarged and coiled and undergo their maximal secretary activities. The uterus is ready for implantation, if fertilization occurs. If fertilization does not occur, the corpus luteum degenerates. This results in decrease in the amount of progesterone and estrogen. This causes the endometrial glands to stop secretion. The blood vessels of the endometrium involutes the tissues of the uterine wall begin to die. These constitute a premenstrual phase. But if fertilization occurs, the corpus luteum is maintained and continues to secrete progesterone and estrogen.

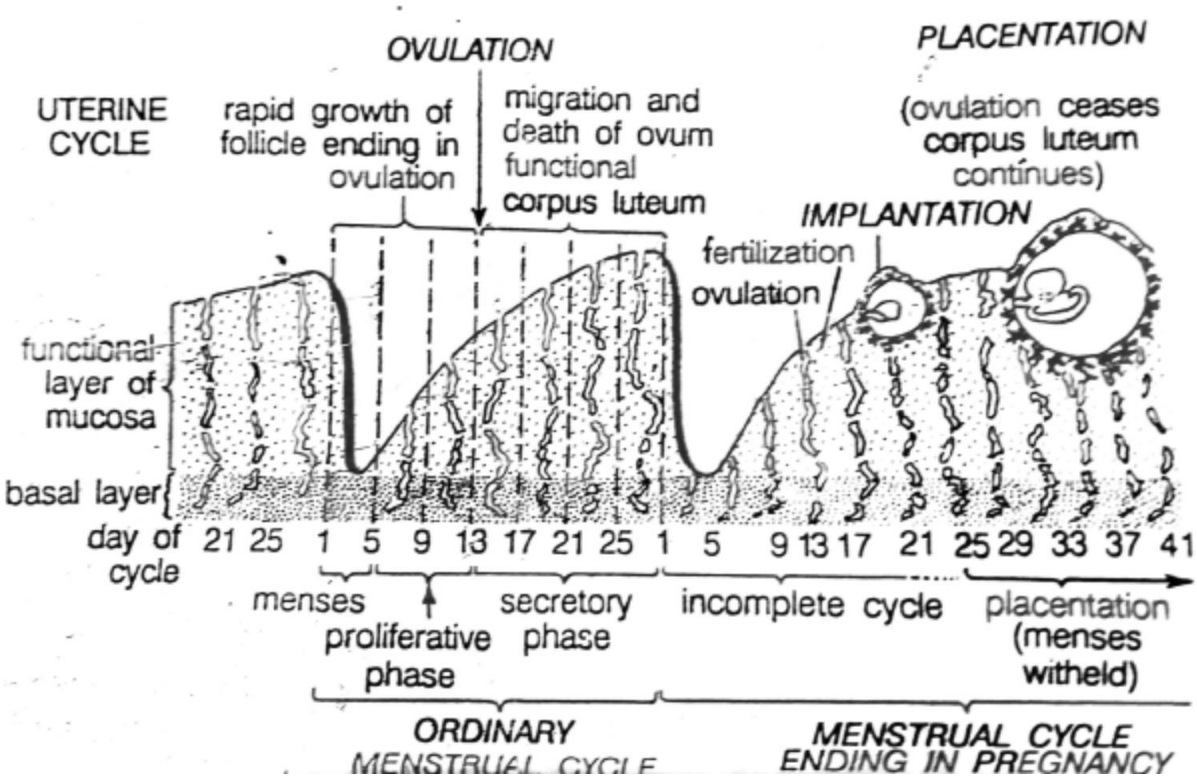


Fig 7.2: Menstrual cycle

Regulation of ovarian and testicular functions

Human body having sex hormones, which carry message between organs & cells. The hormones are secreted by endocrine glands that help the body to stay balanced and function normally. The main sex hormones found in female and male are estrogen, progesterone, inhibin, relaxin & testosterone.

(i) Estrogen : It is found in greater amount among women. It is produced by the ovarian follicle under the influence of follicle stimulating hormone (FSH) of pituitary gland. The oestrogen occurs in 3 different form estradiol, esterone and esteriol. The estradiol is considered as main role in physiological functions. The oestrogen is responsible for all the puberty changes such as growth of uterus, vagina, increased contractility, secretion and ciliary movement of the fallopian tube, development of breast, menstrual changes and appearance of secondary sexual characters. Oestrogen is also responsible for the development of female secondary sexual characters for e.g. formation of narrow shoulder, broad hips etc. Oestrogen is also responsible for the deposition of fat in subcutaneous tissue and also in other particular regions to make a typical feminine body. It also causes deposition of fat in breast,

development of hair in the pubic region. The oestrogen is also required for the preparation of endometrium for the implantation of embryo.

The deficiency of oestrogen causes several health concerns including decreased libido, fatigue, inflammation, hair loss, mood swings, wrinkles, brittle bone and dry skin. The excessive amount of oestrogen can causes bloating bleeding, breast tenderness and mood swings.

(ii) Progesterone : It is also produced under the influence of follicle stimulating hormone (FSH) of pituitary gland. The oestrogen and progesterone are required to prepare the endometrium for the implantation of embryo. Progesterone is responsible for the formation of placenta and it also causes growth of vagina. Progesterone is essential to the premenstrual cycle. It rises during the second part of the cycle to reduce premenstrual syndrome and prepares the uterus for implantation of a fertilized egg. Progesterone is also needed to support a healthy pregnancy as low levels can result in a miscarriage. It is also neuro-protective. An imbalance in the ratio of oestrogen to progesterone can lead to many problems like irritability, bloating, fluid retention, headaches and fibroids. Progesterone works with oestrogen to strengthen bones, sustain. Cholesterol levels and support libido. Excessive secretion of progesterone causes fatigue, dizziness and an increased appetite.

(iii) Inhibin : Inhibin is secreted by both male female sexes. The inhibin inhibits the follicle stimulating hormone (FSH) production, but it does not inhibit the releases of gonadotropin releasing hormone (GnRH) from the hypothalamus. Its mechanisms of action differ in both the sexes. In females inhibin is produced in the gonads pituitary gland, placenta, corpus luteum and other organs. The FSH stimulates the secretion of inhibin from the granulosa cells of the ovarian follicles in the ovaries. The inhibin also suppress FSH.

- Inhibin B reaches a peak in the early to mid follicular phase and a second peak at ovulation.
- Inhibin A reaches its peak in the mid luteal phase.

In males inhibin is secreted by the cell of sertoli of testes. Androgen stimulates inhibin production and this protein may also help to locally regulate spermatogenesis. It inhibits secretion of FSH from the anterior pituitary.

(iv) Relaxin : It is a polypeptide hormone and secreted by corpus luteum. Relaxin involves in the relaxation of pubic symphysis. It is believed that it softens the pubic symphysis and help in the relaxation of pelvic ligament at the time of child birth or parturition.

In female relaxin is produced by both pregnant and non-pregnant females. It rises to a peak within approximately 14 days of ovulation and then declines in the absence of pregnancy, resulting in menstruation. During the first trimester of pregnancy, level of relaxin rises and additional relaxin is produced by the decidua. The relaxin's peak is reached during the 14 weeks of the first trimester and at delivery. It is known to mediate the hemodynamic changes that occur during pregnancy such as increased cardiac output, increased renal blood flow and increased arterial compliance. It helps to delicate uterine cervix during labour and delivery. In male relaxin enhance motility of sperm in semen.

(v) Testosterone : The principle male sex hormone is testosterone. It is secreted principally by the interstitial cells which are located in between the seminiferous tubules in the testes. The testosterone and other chemicals like testosterone collectively are known androgens and render masculine characteristic.

Androgens produced in the male human foetus are important in the development of external genitalia. Androgen causes the enlargement of the penis, testes and also the prostrate, the seminal vesicles and other accessory organs. They also effect the growth of the larynx, muscle development, skeletal size and distribution of body hair. It is also responsible for the development of secondary sexual characters for e.g. growth of hair on the face, in the pubic region and also responsible for the sex urge and for the sexual behavior or affinity for a female partner. They stimulate the biosynthesis of proteins of muscle tissue and also the formation of red blood cells. They stimulate the apocrine sweat glands whose secretion attract bacteria and so produce body odour associated with sweat after puberty.

7.4 ENDOCRINE REGULATION OF IMPLANTATIONS, LACTATION AND ITS HORMONAL REGULATION

After the fertilizationthe ovum reaches the uterus and it become in morula stage. The morula is still surrounded by zona pellucida which prevents it from sticking to the wall of the uterine tube. The cell linings the surface of morula constitutes the trophoblast. The trophoblast has the property of attaching itself to and invading any tissue it comes in contact with. Once the zona pellucida disappears, the cells of trophoblast stick to the uterine endometrium. This is called implantation. It takes place after 6^{th} day of fertilization.

The trophoblast cells which are situated over the inner cell mass start penetrating the epithelium of the endometrium. This process of invading help by the proteolytic enzyme produced by the trophoblast cells. The blastocyst buried deeper and deeper into the uterine mucosa till the whole of it comes to lie within the thickness of the endometrium.

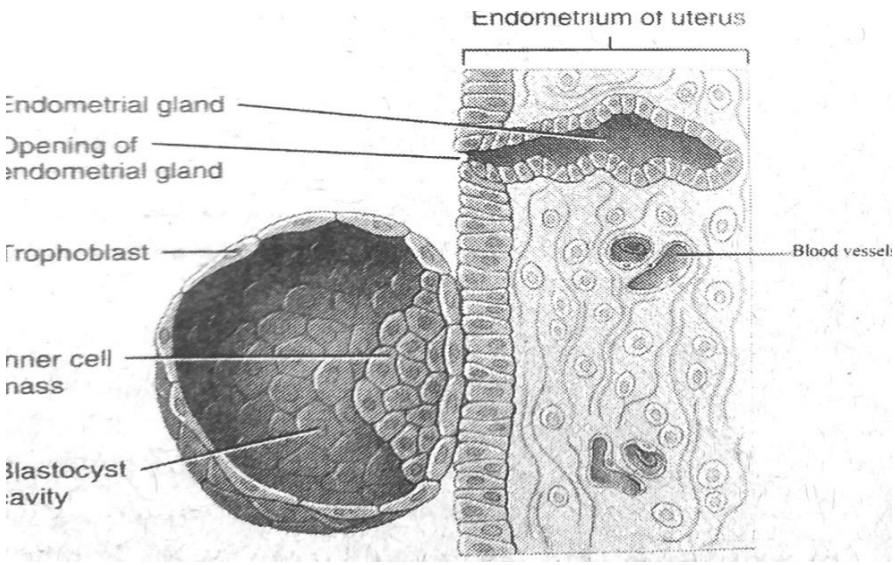


Fig 7.3: Implantation in Human

Endocrine Regulation of Implantations : There are certain endocrine hormone responsible for controlling implantation of embryo are as follows

(1) Role of Estrogen :

- There are group of steroid hormones mainly secreted by follicular epithelia cell of graafian follicle, though these are also produced by adrenal cortex & placenta.

- These include β-estradiol, estrone, estriol; etc. Most important estrogen is B-estradiol.
- Secretion of estrogens is stimulated by FSH of the anterior lobe of pituitary gland.
- These stimulate uterine endometrium epithelium to enlarge, become more vascular & more glandular.
- The uterine glands become tortuous and cork-screw shaped, so the endometrium prepare itself for implantation.
- This stimulation by the estrogen on the uterus generally occurs on 4^{th} days of pregnancy.
- Some of these proteins act as enzymes which activates the blastocyst for implantation which in turn, stimulates the uterine endometrium to undergo decidual cells reaction which is essential for implantation.

(2) Role of progesterone :

- It is also a steroid hormone which is secreted by corpus luteum, which is formed from empty graafian follicle during the pregnancy.
- It is small amount of progesterone is also secreted by the adrenal cortex and placenta.
- Secretion of progesterone is stimulated by LH of the anterior lobe of pituitary gland.
- Progesterone act on only those uterine cells which have been earlier stimulated by estrogens.
- Progesterone further stimulates the proliferation of endometrium of uterus and prepares it for implantation.
- It also helps in implantation, placenta formation and normal development of the foetus in the uterus.

Lactation and its hormonal Regulation

In human female feed its baby with milk, a few days after the birth, which is called breast feeding or nursing. This fed is done by the mother's mammary glands from constituents in the maternal blood and its formation is under control of prolactin and oxytocin hormones of the pituitary gland. The milk contains proteins, fat and carbohydrate which fulfill the requirement of baby for heat and energy as well as for growth and repair of tissue. The first milk which is produced by female is called colostrums. It contain high amounts of WBC and antibodies than mature milk and especially high in immunoglobin A (Ig-A), which coats, the lining of the baby's immature intestines and helps to prevent pathogens from invading the baby's system. Secretary Ig-A also helps prevents food allergies. Over the first two weeks after the birth, colostrums production slowly gives way to mature breast milk.

The human mammary glands consist of about 15 separate milk producing system which are arranged around the nipple. The milk is produced deep to the surface in the milk producing alveoli. These alveoli lead *via* series of branching ducts to a main milk duct which opens at the nipple. There are thus 15 openings at the nipple, each leading to its own producing alveoli. Then the main milk duct has dilation just below the surface and called lactiferous sinus in which some milk is stored. Baby can take milk from this sinus after taking the nipple and surrounding tissue into its mouth and using a sucking champing action.

However the suckling stimulates the sensory receptors present in the nipple and a nervous *via* hypothalamus releases oxytocin from the posterior pituitary gland. The oxytocin contracts the myoepithelium surrounding the alveoli and forces the milk towards the nipple. This process is termed milk ejection. Without an adequate level of circulating oxytocin, the breasts may be engorged with milk, but the baby cannot get an adequate milk supply.

7.5 PLACENTA IN MAMMALS

After the implantation of embryo, the uterine endometrium is called decidua (thick layer of modified mucous membrane which lines the uterus during pregnancy and is shed after birth). The different regions of the decidua are named based on their positions relative to the site of implantation. The portion of the decidua where the placenta is to be formed is called decidua basalis, it provides large amounts of glycogen and lipids for the developing embryo and foetus and later it becomes the maternal part of the placenta. The part of the decidua that separates the embryo from the uterine lumen is called decidua capsularis, while the part lining the rest of the uterine cavity is called the decidua parietalis. As the embryo and later the foetus enlarges the decidua capsularis bulges into the uterine cavity and fuses with the decidua parietalis causing obliterating the uterine cavity. After 27 week the decidua capsularis degenerate and disappears.

The process of formation of placenta is called placentation, which is the site of exchanges of nutrients and wastes between mother and foetus. The placenta is develop partially by mother and partially by foetus. The mother or maternal portion is formed by decidua basalis of endometrium and the foetal portion is formed by the chorionic villi of the chorion. The important part of placenta are very small finger like processes or villi. These villi are surrounded by maternal blood. In the substance of villi, there are capillaries through which the foetal blood circulates. The exchange of materials between the maternal and foetal circulation take place through the tissue forming the walls of the villi. The villi are formed as off shoots from the surface of the trophoblast. As the trophoblast, along with the underlying extra embryonic mesoderm constitutes the chorion, the villi arising from it are called chorionic villi.

The chorionic villi are first formed all over the trophoblast and grow into the surrounding decidua. Those villi related to the decidua capsularis are transitory and after sometime they degenerate and this part of the chorion become smooth and is called chorion laevae. The villi that grow into the decidua basalis undergo considerable development and form a disc shaped mass called placenta. The part of the chorion that helps to form the placenta is called chorion frondosum. There are 3 stages in the formation of chorionic villi are as

(i) Primary villi : It consist of a central core of cyto-trophoblast covered by a layer of syncytio-trophoblast. Adjoining villi are separated by an intervillous space.

(ii) Secondary villi : It shows three layers outer synctio-trophoblast, an intermediate layer of cyto-trophoblast and an inner layer of extra-embryonic mesoderm.

(iii) Tertiary villi : They are like secondary villi except that there are blood capillaries in the mesoderm.

In the later stages of foetus, the actual connection between the placenta & foetus is through the umbilical cord, which is develop from the connecting stalk. It is usually about 50 – 60 cm in length and 2 cm in diameter. The umbilical cord consist of two umbilical arteries that carry deoxygenated foetal blood to the placenta, one umbilical vein that carries oxygen and nutrients acquired from the mother's intervillous space into the foetus and supporting mucus connective tissue called Wharton's

jelly derived from the allantosis. A layer of amnion surrounds the entire umbilical cord and gives it a shiny appearance.

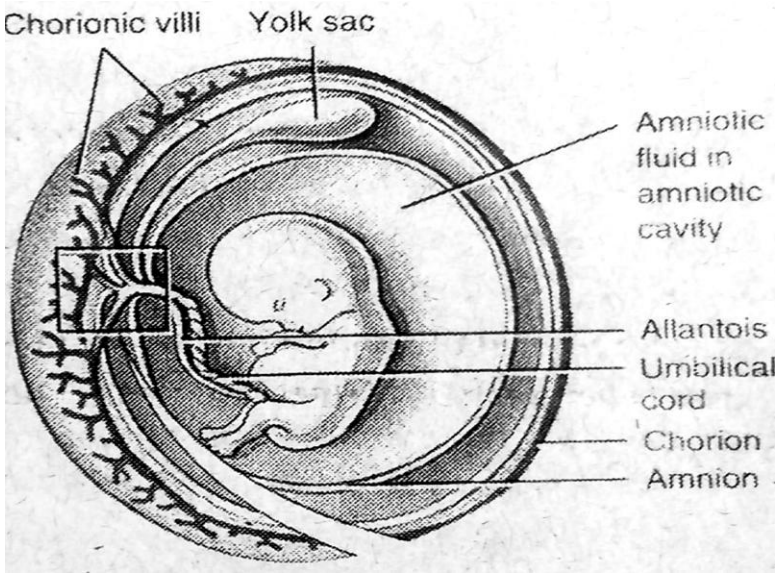


Fig 7.4: Formation of Placenta in Human

Classification of placenta

There are many variation observe in mammalian placenta. So they are classified on the basis into three types:

(i) Mode of origin or extra-embryonic membrane

(ii) Shape & distribution of villi

(iii) On the basis of histology

(i) Mode of origin or extra-embryonic membrane : These have been further classify into 3 types-

(a) Yolk sac placenta : These are observe in metatherian or marsupials such as kangaroo & opossum. In this type placenta is derived from yolk sac and chorion. The yolk sac developed from the lower part of blastocyst and is very large and nearly encloses the entire embryo and its amnion. The wall of yolk sac lies in direct contact with chorion which sends out finger like villi into uterine wall. Yolk sac wall also develops vitelline blood vessels for transporting secretions. Uterine milk absorbed from uterus to the developing embryo. Allantois remains poorly developed and never comes in contact with chorion.

The yolk sac placenta in metatherian is very weakly developed so that embryo born are very small & immature, so to compensate the intra-uterine development the young once are transferred to their abdominal pouch or marsupium and feed on the milk until fully formed.

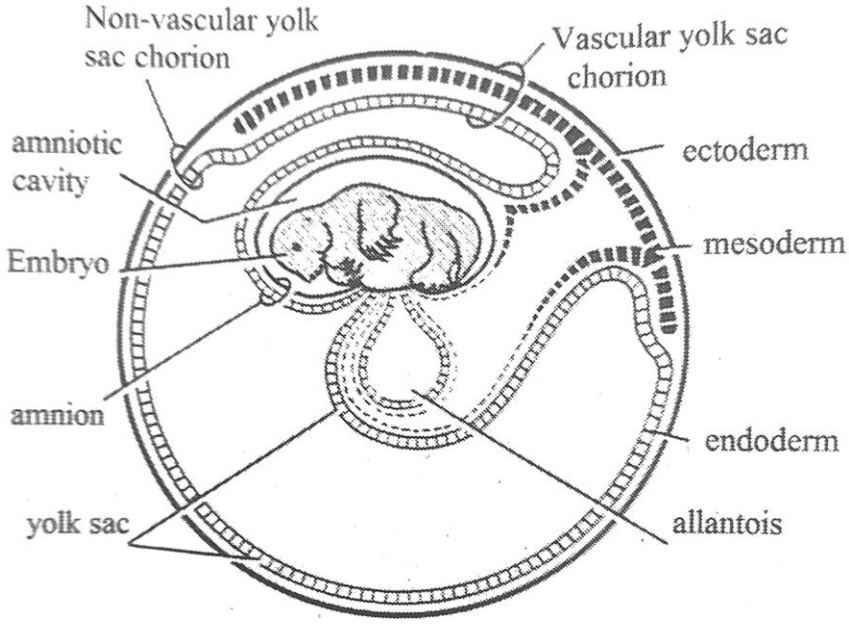


Fig 7.5: Yolk sac placenta of Opossum

(b) Allantoic placenta : These are observe in Eutheria. The allantois is a sac like out growth from the hind gut of embryo. It is lined internally by endoderm and externally by mesoderm. As allantois grows and spread in the extra-embryonic cavity its mesoderm fuses with that of chorion over a somewhat restricted region. The layer formed by the fusion of allantois & chorion is called allanto-chorion. It becomes richly vascular and thrown into small finger like processes, villi. The uterine wall forms corresponding depression, crypts, which are penetrated by foetal villi forming allantois placenta. The materials absorbed from maternal blood through allantoic placenta are carried to the foetus by allantoic blood vessels.

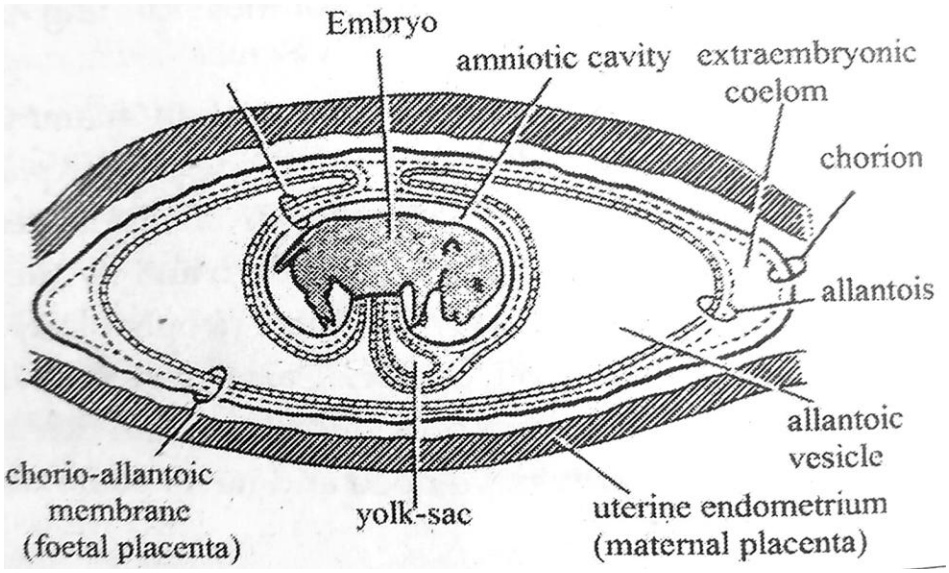


Fig 7.6: Allantoic placenta of Pig

(c) Chorionic placenta : These can be observe in man & apes. It is formed by chorion. Allantois remains small, burrows into body stalk or umbilical cord and does not reach chorion. The mesoderm and blood vessels grow up to chorion whose villi enter the uterine crypts forming chorionic placenta.

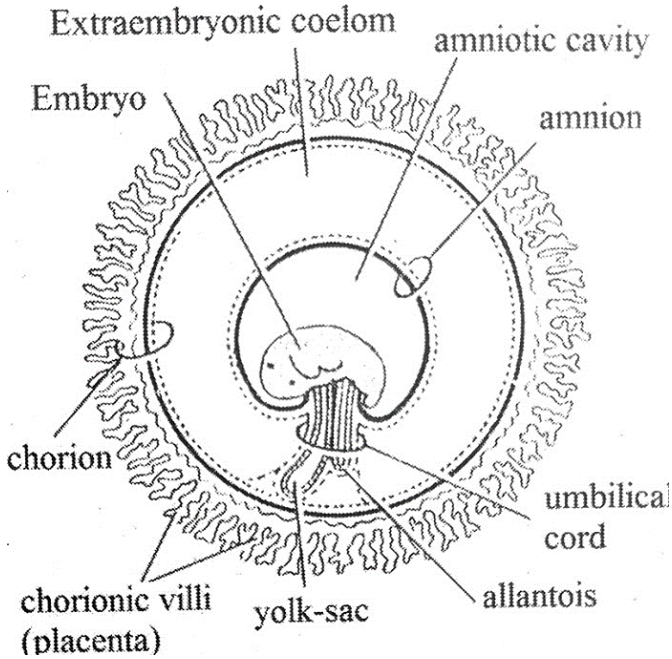


Fig 7.7: Chorionic placenta of man

(ii) Shape & distribution of villi : According to shape of placenta, manner or distribution of villi, degree of connection between foetal and maternal tissues and behavior of placenta at the time of birth can be divided and subdivided into various types.

(a) Non-deciduous placenta : In such type villi are simple, unbranched and merely apposed without intimate contact between foetus and uterine wall. At the time of birth villi are easily withdrawn from maternal crypts without causing any tissue damage. Thus no part of uterine tissues comes out and no bleeding occurs. According to manner of distribution of villi, it is of various types

- ***Diffuse placenta* :** The villi remain scattered all over the surface of allano-chorion e.g. pig, lemur & horse etc.
- ***Cotyledonary placenta* :** The villi are arranged in separate tuffs or patches called cotyledons e.g. deer, cow, goat.
- ***Intermediate placenta* :** The villi are arranged in cotyledons as well as scattered e.g. giraffe.

(b) Deciduous Placenta : The villi are complicated branched and intimately connected. At birth, a variable amount of maternal tissue is pulled out with the shedding of blood. It is also various types.

- ***Zonary Placenta* :** In carnivorous like dog, cat lion tiger etc. the villi are develop in the form of a belt around the middle of their blastocyst which is generally elliptical in shape.

- ***Discoidal Placenta* :** The villi are restricted to a circular disc or plate on the dorsal surface of blastocyst e.g. insectivores, bat, rabbit.
- ***Metadiscoidal placenta* :** The villi are at first scattered but latter become restricted to one or more disc . In man it is monodiscoidal and in monkey & apes it is bidiscoidal.

(c) Contra-deciduous placenta : In such type the foetal villi and uterine crypts are so intimately connected that even most of the foetal placenta is left behind at birth to be broken and absorbed by maternal leucocytes e.g. mole & Bandicoot.

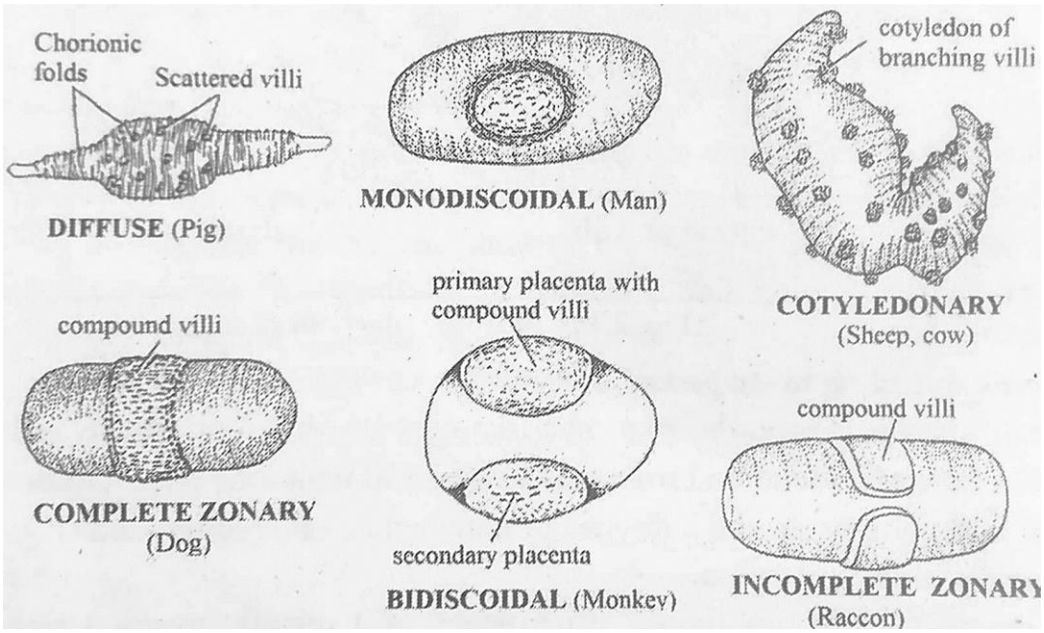


Fig 7.8: Types of placenta according to distribution of villi

(iii) On the basis of histology : On the basis of histology there are 6 membranes or tissue (barriers) lie between the foetal and maternal blood streams. These membranes are in order of their sequence from mother to foetus are endothelium of maternal blood vessel, endometrial connective of mother, uterine epithelium, chorionic epithelium, chorionic connective tissue of foetal & endothelium of foetal blood vessel. The presence or absence of these tissue placenta are of following 5 types.

(i) Epithelio-chorial placenta : It is most primitive type and found in marsupials, pig, horse, cattle, lemurs etc. In this type of placenta all 6 membranes are found. Because of the immediate contact of the two halves the placenta involves chorionic epithelium and uterine epithelium. This type of placenta is known as epithelio-chorial placenta. The villi of an epithelio-chorial placenta push in the wall of uterus and later lie in the pocket like depressions of the uterine wall.

(ii) Syndesmo-chorial placenta : In ruminants like cattle & sheep the foetal material is fused as result in destruction of uterine epithelium and bring chorion into contact with the connective tissue of the uterine mucosa. Only there are only 5 barriers are present except uterine epithelium.

(iii) Endothelio-chorial placenta : In carnivorous like dog, cat, bear etc. the uterine mucosa is reduced and chorionic epithelium comes in contact with endothelial wall of maternal

(uterine) blood vessels. So there are only four barriers between foetal & maternal blood vessel.

(iv) Haemo-chorial placenta : It is found in man, monkey, shrews etc. In this type there occur only 3 barriers i.e. endothelial wall of maternal blood vessel also disappears and chorionic epithelium is bathed directly in maternal blood flowing in sinuses.

(v) Haemo-endothelial placenta : It is found in higher rodents like rat, guinea pig, rabbit etc. The number of barriers between the maternal & foetal blood stream is reduced to two. In this chorionic epithelium and chorionic connective tissue also disappear, so allowing the foetal capillaries to come in direct contact with maternal blood.

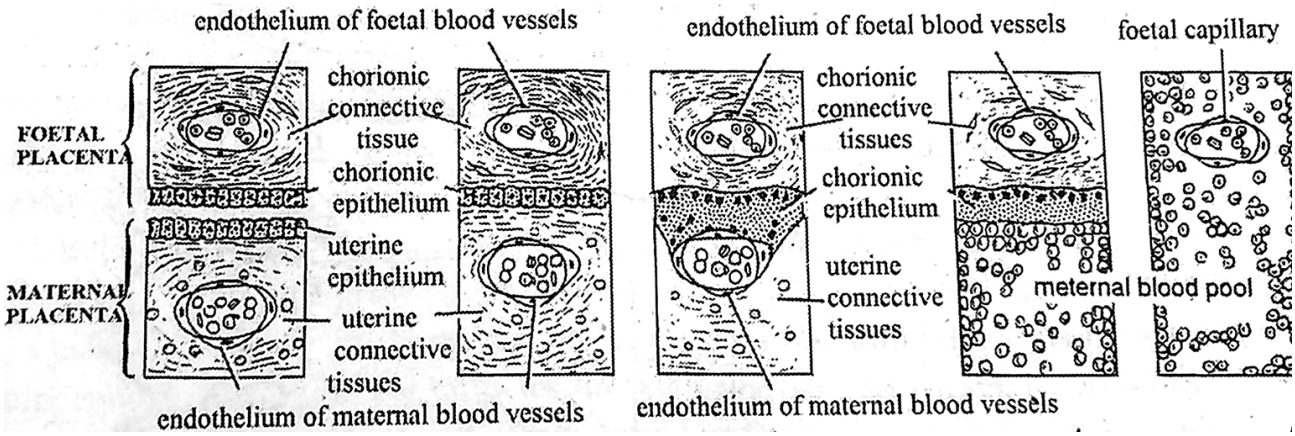


Fig 7.9: Histology of mammalian placenta (1) Epithelio-chorial, (2) Syndesmo-chorial, (3) Endothelio-chorial, (4) Haemo-chorial placenta, (5) Haemo-endothelial

Role of Placenta

(i) The placenta provides nourishment and oxygen to the embryo. Water, oxygen and small molecule substances such as monosaccharides, salts of sodium, potassium and magnesium diffuse through the placenta from the maternal blood into the foetal blood.

(ii) It serves as an excretory organ of the foetus. The foetal metabolic wastes like urea and carbon dioxide pass from foetal to maternal blood through placenta.

(iii) It anchorage the developing embryo with the uterine wall.

(iv) Placenta enables the transport of oxygen, water, electrolytes and nutrition from maternal to foetal blood. A full term foetus takes up about 25 ml of oxygen per minute from maternal blood.

(v) The placenta acts like a semipermeable membrane allowing some substances to pass through but keeping out others. It prevents the passage of harmful materials (blood proteins, sex hormones etc.) from the maternal blood into the foetal circulation.

(vi) Placenta acts as barrier against the transportation of microbes into the embryo but the viruses and antigen do pass through the placenta. However, most viruses (*viz*. poliomyelitis, measles and rubella) and some bacteria can pass across it.

(vii) Maternal antibodies (IgG) reaching the foetus through the placenta give the foetus immunity against some infections (e.g. diphtheria and measles).

(viii) The placenta functions as an endocrine gland. It secretes four important hormones in human female and most placental mammals. They are estradiol, progesterone, chorionic gonadotrophic hormone and placental lactogen. These hormones help in maintain pregnancy, abortion or premature birth.

7.6 NEURO-ENDOCRINE SYSTEM AND NEURO-SECRETIONS

The function of the body is coordinated by nervous system as well as endocrine system. The nervous system achieves functional co-ordination and integration for quick responses of the body by transmitting information in the form of nerve impulses or high speed communication take place in millisecond. The endocrine system achieves co-ordination and integration for slow and persistent responses of the body by transmitting information through chemical or hormonal messengers or low speed communication.

Harris (1955) explained that a number of physiological processes in the body are regulated jointly by nervous and endocrine systems and hypothalamus of the brain controls this coordination. So now it is called neuroendocrinology. In this system various endocrine are present in our body are thyroid gland, parathyroid gland, adrenal gland, pituitary gland, thymus & pancreas

Endocrine glands – These can be catagorised into two categories.

(A) Ductless gland - (a)Thyroid gland

(b)Parathyroid gland

(c)Adrenal gland

(d)Pituitary gland

(e)Thymus gland

(f) Pineal gland

(B) Mixed gland – (a) pancreas

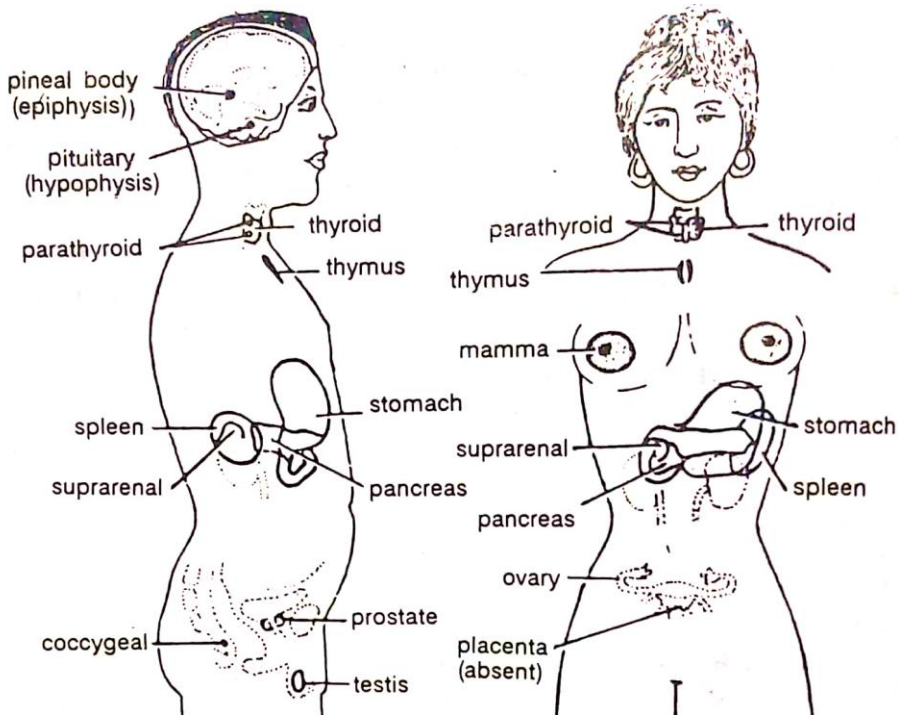


Fig 7.10: Diagrammatic representation of location of endocrine glands

Thyroid gland

Thyroid gland was described by Thomas Wharton. Thyroid gland is the largest endocrine gland. It is a dark brown and H-shaped bilobed gland. It is situated in the neck region near the trachea and anterior to larynx. It is endodermal in origin and arises in the embryo as a mid ventral processes from the floor of tongue in pharyngeal region between the first and second pharyngeal pouches. Later, the duct like connection or thyroglossal duct degenerate and the process get separated from tongue and become endocrine in function. Its weight is nearly 20- 40 gms. In female it is larger than male. It Disease of thyroid gland is more common in female than in male. size can be change during sexual cycle, pregnancy, lactation and menopause. The size of gland is also affected by seasonal variation.

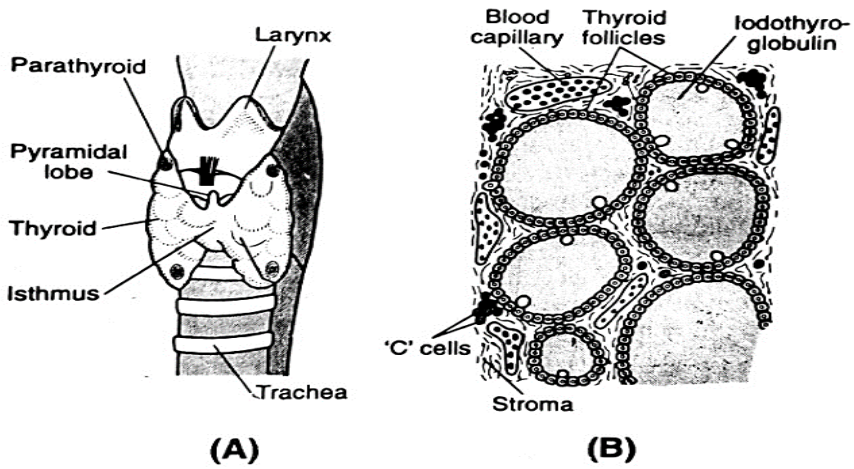


Fig. 1 A. Thyroid gland, B. Follicles suspended in stroma of a lobule

Thyroid gland consists of two lobes connected by a narrow band called isthmus. Each lobe is formed of numerous spherical masses called follicle. Each follicle is covered by a basement member. In the

centre each follicle contains a cavity filled with colloidal material. The cavity is lined by a layer of cuboidal epithelial cells. These consist of two types of cells, principal cells and parafollicular cells or C-cells. The principal cells are larger in number and contain lesser number of mitochondria and they secrete thyroxine hormones. The parafollicular cells are lesser in number but rich in mitochondria and they secrete thyrocalcitonin. Thyroid gland secretes 3 types of hormones.

(1) Thyroxine or tetraiodothyronin (T_4)

(2) Tri-iodothyronine (T_3)

(3) Calcitonin or Thyrocalcitonin

Thyroxine (T_4) and tri-iodothyronine (T_3) are iodinated amino-acids. They are stored in the colloidal material in the thyroid follicle & bounded with a protein thyroglobulin.

Thyroxine **–** It is iodine containing thyroid hormone. It is protein hormone and formed from iodinated tyrosine. T_3 is biologically more active agent then T_4. It has following function

(i) Metamorphosis in amphibian is bring about by thyroxin.

(ii) Moulting in reptiles bring about by thyroxine

(iii) Thyroxine improves growth in mammals. Thyroxine is essential for normal differentiation and maturation of foetal tissue.

(iv) Development of central nervous system during late embryonic and early postnatal development require adequate amount of thyroxin.

(v) T_4 & T_3 are necessary for the myelination of nerve fibre .

(vi) Thyroxin increases basal metabolic rate.

(vii) Thyroxin increases protein synthesis. It promotes the transfer of amino-acyl-t-RNA complex ribosome.

(viii) Thyroxin increases heat production by stimulation of sodium pump in cell membrane.

(ix) Thyroxin stimulates the rate of absorption of glucose and galactose through intestine. It stimulates break down of glycogen in liver. It also stimulate break down of insulin.

(x) T_4 & T_3 have a powerful lipolytic action on fat stores in tissue.

(xi) Thyroid hormones also influenced the absorption of vitamin B_{12}.

Disease:- *There are two types of disease occur, one may be hyposecretion and other is hypersecretion. The hyposecretion of thyroxine (hypothyroidism) produces cretinism in children and Myxodema in adults. The hypersecretion of thyroxine (hyperthyroidism) causes Grave's disease or Exophthalmic goiter.*

Parathyroid Gland

The parathyroid glands are situated in the thyroid gland in the form of four patches. Each parathyroid gland is surrounded by a connective tissue capsule. The parathyroid are yellowish brown, egg shaped bodies and their combined weight is approximately 0.06 – 0.3gm. The parathyroid gland secrete a hormone called parathormone or PTH. The parathormone was first isolated by J.D Collip in 1925. Rasmussen and Craig (1961) have purified parathormone and

established that it is a protein hormone and made up of one polypeptide chain consisting of 83 amino acids. It has several functions.

(i) It causes increas in serum calcium level by acting on osteoclasts (demineralization) of bones.

(ii) It increases renal tubular re-absorption of calcium.

(iii) It increases intestinal absorption of both calcium and phosphate.

(iv) It also increases the activity of phosphatase in serum.

(v) It increases glycolysis in bone.

(vi) PTH increases citrate and lactate accumulation in bone cells.

(vii) It reduces the secretion of Ca^{++} by the mammary gland.

Disease:

Hyposecretion - Parathormone is essential for life activity. If there is hyposecretion it causes tetany. It has following symptoms.

(i) Hyposecretion causes decrease in blood calcium level and it effects the motor pathway of central nervous system, which produces spontaneous and repetitive discharge of impulses. This will cause tetanic condition.

(ii) Locking of the jaws.

(iii) Twitching of the muscles.

(iv) Respiration becomes rapid and noisy.

(v) Heart rate increases.

(vi) It increases salivation and body temperature. The ultimate result is death due to asphyxia.

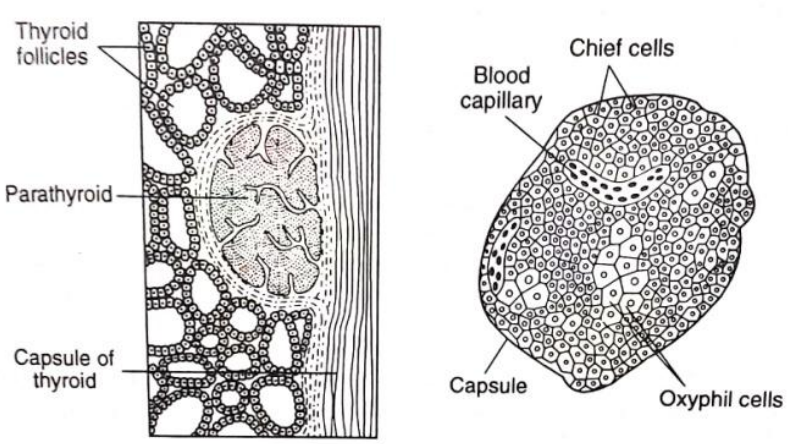
Hypersecretion – When there are excessive secretion of parathormone. It shows following symptoms.

(i) Hypersecretion causes increase in blood calcium level. It causes increase excretion of calcium through urine. Some time in glomerular filtration of calcium increases forming calcium rich cancaliculi or stone in kidney. Some time it is fatal.

(ii) It causes demineralization of bones and sometimes in the formation of bone cyst or giant cells bone pseudotumors.

(ii) Loss of muscular tone.

(iv) Weakness, vomiting, thirst, mental symptoms and polyurea.



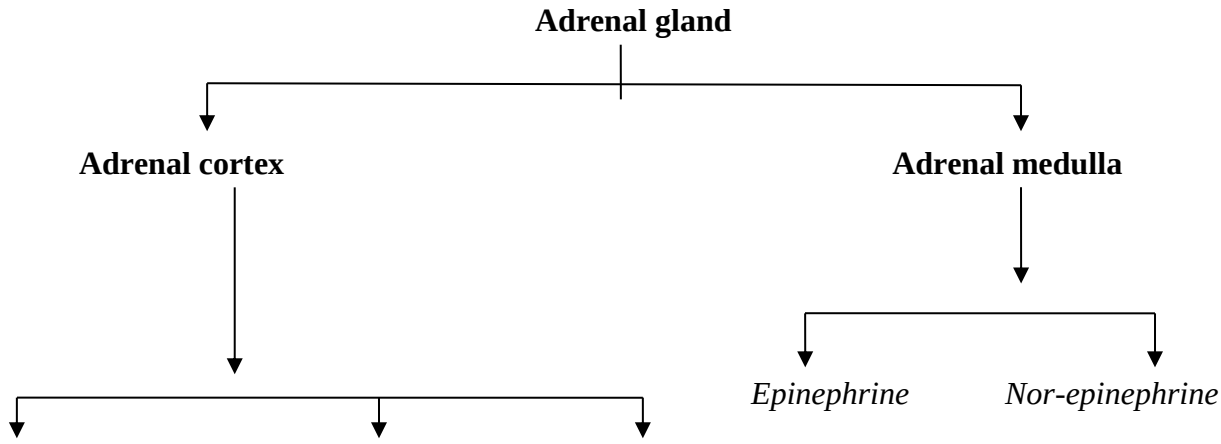
A B

Fig 7.11.: (A) parathyroid gland embedded in the surface of thyroid gland

(B)Ultra structure of a parathyroid gland

Adrenal Gland

Adrenal glands are located on the top of each kidney, Hence they are called supra renal gland (one on each kidney). It is small about 5cm long, 3cm broad and 1cm thick, triangular yellowish colored. Each gland is about 5 to 9 gms in the adult. But at birth the weight of the gland will be 16 to 20 times greater than in the adult. They gradually decrease in size as age increases. Each gland is enclosed by a capsule. It consists of two parts, the outer cortex, which is yellowish in color and inner medulla, which is brownish in color. The two parts are structurally, functionally and embryologically different.



Adrenal cortex- Adrenal cortex is the peripheral part of the adrenal gland. It is derived from mesodermal coelomic epithelium of the anterior part of the mesonephros. The adrenal cortex form about 70% to 75% part of the adrenal gland.

The adrenal cortex consists of fatty cholesterol-rich glandular cells. The different types of shapes and arrangements of these cells distinguish the cortex into three regions or zones.

(1) ***Zona glomerulosa*** **–** It form about 15% of the gland. It is thin outer layer with small polyhedral cells arranged in closely packed clusters over the cell columns beneath. They secrete Aldosterone, glucocorticoids and sex hormones.

(2) ***Zona fasciculata*** **–** It constitute about 50% of the gland. It is thick middle layer with large polyhedral or prismatic cells arranged in parallel cords or columns separated from each other by venous sinuses. These cells contain ascorbic acid (vitamin-C). They secrete glucocorticoid.

(3) ***Zona reticularis*** **–** It is the inner thin layer and constitutes about 7% of the gland. It is made up of an irregular network of row of cells. The meshes of the network are filled up with reticulo-endothelial cells. These cells contain ascorbic acid (vitamin-C). It secretes sex-hormones and glucocorticoids.

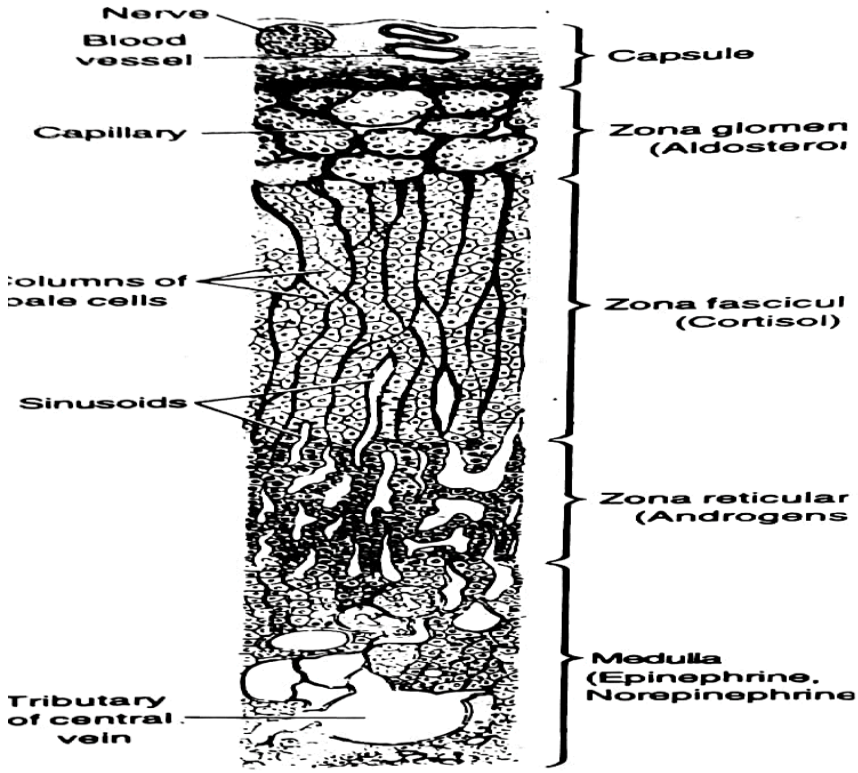


Fig. Vertical section of adrenal to sho ultrastructure of its different regions

Hormones of adrenal cortex- All the hormones secreted by the adrenal cortex are called corticosteroids. They are steroid and are derived from the cholesterol. It is of 3 types.

(a) Glucocorticoids

(b) Mineralocorticoids

(c) Sex steroid

(a) Glucocorticoids

(1) It consists of 21 carbon atom.

(2) It is of 4 types.

(i) Cortisol

(ii) Cortisone

(iii) 17-Hydroxy corticosterone

(iv) 11-Dehydroxy corticosterone

(3) The main role of glucocorticoid is involved in carbohydrate metabolism.

(4) The formation of glycogen in the liver through glycogenesis is stimulated by glucocorticoids.

(5) Gluconeogenesis is increased.

(6) It helps in the absorption of glucose from intestine and nephron.

(7) It increases the rate of deamination and breakdown of tissue proteins.

(8) It stimulates absorption of lipid from the intestine. Lipid is mobilized from fat depot and are broken to ketone bodies in the liver.

(9) They retain NaCl and H_2O, but excrete K and Po_4.

(10) Deficiency of cortisol produces hypoglycemia and increase sensitivity to insulin.

(11) Excess of cortisol causes osteoporosis due to decalcification and interference in formation of protein matrix.

(12) It also act as an anti-inflammatory compound.

(13) It inhibits the formation of antibodies.

(14) It also inhibits development of cartilage and interrupts growth in the children.

(B) Mineralocorticoids

(1) It consists of 19 carbon atom.

(2) It is of two types

(i) Deoxycorticosteroid

(a) 11-deoxycorticosterone

(b) 17-hydroxyl-11-deoxycorticosterone.

(ii) Aldosterone (Electrocortin)

(3) It is so called because it is involved in the metabolism of minerals.

(4) If a loss of adrenocortical section it causes death unless person receives salt therapy or mineralocorticoid therapy. Hence Mineralocorticoid are described as “life saving hormones”.

(5) It helps to re-absorb NaCl and H_2O from the renal tubules.

(6) It increases excretion of K.

(7) It provides resistance against stress condition.

(8) It enhance the absorption of Na by the intestine.

Diseases:- *There are two types of disease occur due to hyposecretion and hypersecretion. The hyposecretion causes Addison disease and hypersecretion causes cushing's syndrome disease.*

Addison disease - The deficiency of adrenocorticosteroid lead to a disease called Addison disease. It is due to the failure of the secretion of ACTH by the pituitary gland or tuberculosis of adrenal cortex. It has following symptoms.

(1) Its hyposecretion lead to the failure of re-absorption of Na and H_2O from the urine and hence Na^+, Cl^- and H_2O are largely lost and disturb electrolyte balance.

(2) There is melanin pigmentation on the mucous membrane of lips and on the thin skin of nipples. This caused by the effect of MSH & ACTH.

(3) Blood pressure becomes low.

(4) BMR is lowered.

(5) Subnormal body temperature

(6) Muscles become weak and fatigue due to the loss of NaCl.

(7) Vomiting occur frequently.

(8) Irritability of stomach

(9) Absorption and metabolism of glucose is upset.

(10) Restlessness, insomnia and lack of mental concentration also occur.

(11) Sexual desire are depressed.

Cushing's syndrome-

The hypersecretion of cortisol due to tumor in the adrenal cortex lead to a disease called Cushing syndrome. It is due to hyper secretion of ACTH by the pituitary gland. It has following symptom.

(1) In males there is excessive growth of hair, enlargement of penis and increased sexual desire in male.

(2) In female there is excessive growth of hair on face, chest and limbs. Breast become atrophy, voice become harsh and menstruation cycle may ceases. These effects make the female changes toward masculinity. This phenomenon is known as adrenal virilism (presence of male characters in female).

(3) There is an increased deposition of fat on the trunk, and face. But the limbs are free from fat deposition.

(4) There is a characteristic pad at the back of the neck and it looks like a buffalo hump.

(5) Osteoporosis of bones due to decalcification and loss of protein matrix.

(6) Na is retained and K is excreted in large amount.

Adrenal medulla

Adrenal medulla is the central part of adrenal gland. It constitutes about 25% to 30% part of the gland. It is derived from the neural crest cells. The adrenal medulla consists of rounded groups and short cords of relatively large and glandular cells. These cells are modified postganglionic cells of sympathetic nervous system, which have lost neural processes and have acquired a glandular function. These can be stained with chromic acid and hence they are called chromaffin cells. The

hormones of adrenal medulla secretes two types of hormones, which are chemically catecholamine. They are :

(a) Adrenaline or epinephrine

(b) Nor-adrenaline or non – epinephrine

Adrenal medulla contains 0.49mg epinephrine and 0.08mg nor-epinephrine per gram of the tissue. In plasma 0.06 μgm epinephrine and 0.03 μgm nor-epinephrine.

(a) Adrenalin or Epinephrine

(1) It is synthesized from phenylalanine in the liver tissue.

(2) The secretion of epinephrine from adrenal medulla is controlled by thoraco- lumber region of spinal cord.

(3) This hormone is produced under emergence conditions. Hence it is called **emergency hormone**. It is secreted in times of stress, emotion, threatened, danger, and hypoglycemia and hemorrhage, anesthetic and hypnotic drugs. Its secretion makes the individual ready for fight. Hence medulla is called the **gland of flight, fright and fight**.

(4) Adrenaline is a hyperglycemic hormone. It promotes glycogenolysis both in liver and muscle.

(5) Epinephrine increase mobilization of lipids from their stores. The level of non-esterified fatty acid (NEFA) in the blood is also increased.

(6) Lipolysis become active.

(7) Adrenaline also increases level of cholesterol in blood.

(8) It stimulates heart, heart rate, cardiac output and strength of contraction of heart.

(9) It brings about dilation of blood vessels of the skeletal muscles and constriction of arterioles of skin & mucus membrane.

(10) It increases blood pressure.

(11) It increases respiratory rate.

(12) It produces a sense of restlessness, anxiety and fatigue.

(13) Epinephrine contracts pyloric and ileocaecal sphincter but relaxes gastrointestinal tract musculature.

(b) Nor- adrenaline or Nor-epinephrine

(1) It is synthesized from phenylalanine in the liver tissue.

(2) Nor-adrenaline is also secreted under emergency condition hence it is also called emergency hormone.

(3) Nor-epinephrine increases mobilization of lipid from their stores. The level of non-esterified fatty acid (NEFA) is the blood in also increased.

(4) Lipolysis becomes active.

(5) Nor-epinephrine increases both systolic and diastolic blood pressure due to increased peripheral resistance.

(6) It has very little on cardiac output.

(7) It elicit a week influence on smooth muscles.

(8) Respiratory rate is increased.

(9) Metabolic rate increases.

(10) Blood sugar level is raised.

Function

The adrenaline and noradrenaline are known as emergency hormones released under conductions of "fright, fight, flight". It has following function.

(i) Epinephrine causes contraction of the blood vessels, which supply blood to those peripheral and abdominal organs (skin and organs of digestive, excretory and reproductive systems) that remain active while we are resting or sleeping.

(ii) It reduces the supply of blood causes a pale skin (pallor), but arrector pilli muscles of skin contract, causing gooseflesh.

(iii) Mouth becomes dry due to poor secretion of saliva.

(iv) Food digestion is retarded.

(v) In pregnant women, the muscles of uterus contract, increasing the possibility of abortion.

(vi) Epinephrine causes dilation of blood vessels which supply brain, skeletal muscles, heart, liver, adipose tissue, sensory organs etc.

(vii) Pupils dilate due to contraction of radial dilatory muscles of iris. Secretion of tear by lacrimal glands increases.

(viii) Contraction of cardiac muscle increases causes both rate and force of heart beat, pulse rate, arterial pressure and cardiac output.

(ix) Adrenaline produces restlessness, anxiety and fatigue.

Abnormality of Adrenal medulla - When the tumors are develop in medulla it produce hypersecretion of hormones which causes hypertension, coronary insufficiency, ventricular fibrillation or pulmonary edema take place.

Pituitary Gland

The pituitary gland is reddish, grey, oval structure about 10 mm in diameter. It lies between the roof of the mouth and floor of the brain in a depression (sella turcica) of the sphenoid bone of skull. It is connected, by a short infundibular stalk, to the ventral wall (hypothalamus) of diencephalon of the brain. That is why it is also called hypophysis cerebri. It is small rounded body about the size of a large pea weighing approximately 0.5 - 0.6 gm in man but it is usually become much larger in a pregnant women.

The pituitary gland is derived from embryonic ectoderm. It is formed of two embryonic structures one derived from the brain and other from the epithelium of the mouth. So it is formed by the fusion of these two structure namely infundibulum and Rathke's pocket respectively. The infundibulum develops as a ventral evagination of the diencephalon and it develops into the neurohypophysis (posterior lobe). It encloses a cavity called infundibular recess. This cavity is the continuation of the cavity of the diencephalon. Rathke's pocket is the dorsal evagination of the buccal cavity. It develops into a adenohypophysis (anterior lobe). The adenohypophysis consists of the large pars distalis (pars anterior), pars tuberalis and pars intermedia. The pars intermedia is separated from the

pars anterior by the interglandular cleft. The adenohypophysis encloses a cavity called hypophyseal recess. This cavity is the remnant of the lumen of the Rathke's pockets.

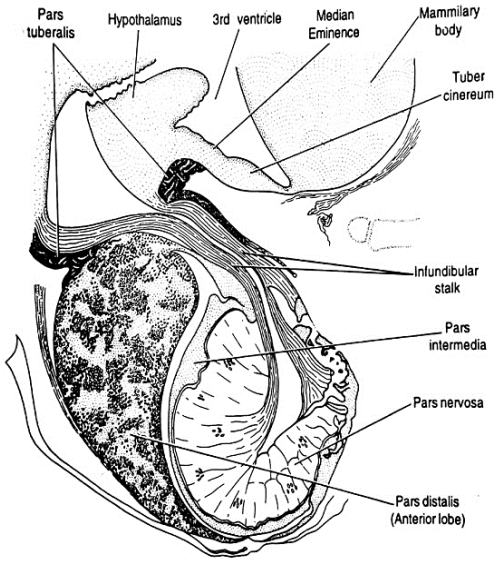


Fig. Gross structure of pituitary gland

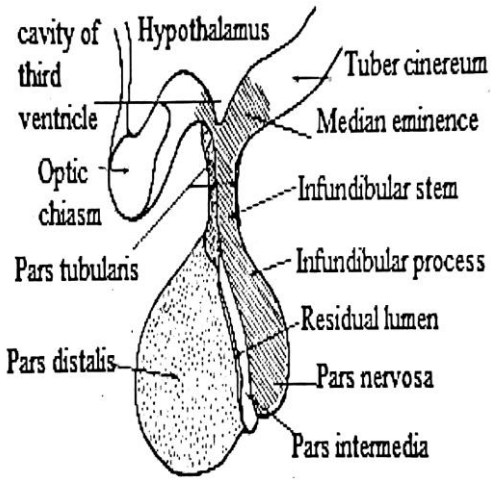


Fig. : Sagital section of Pituitary gland

Adenohypophysis or Anterior lobe – The adenohypophysis constitute about 75% part of the pituitary gland. In adult human, the adenophypophysis is distinguished into two main parts, the narrow proximal part called pars tuberalis or infundibularis which surround the infundibular stalk and second parts is large, globular and pinkish called pars distalis. A third narrow strip like part called intermediate lobe or pars intermedia which developer in embryo, but in adult it degenerate.

Adenohypophysis has a dual blood supply by means of a "circle of Willis". The superior hypophysial artery which brings blood into this circle bifurcates into two branches outside the lobe. One branch supplies the adenohypophysis and other supplies the hypothalamus. The veins that drain the blood from hypothalamus run into the pars distalis through pars tuberalis and divide into capillaries. Those vein are called portal hypophysial veins. These constitute a **hypothalamo – hypophysial portal system.**

The adenohypophysis consists of two types of epithelioid cells, chromophobes and chromophilis cells. The chromophobes cells are larger in number, non granular and cannot stained with any dyes. The chromophils are lesser in number, granular and can be stained with dyes. Hence they are of two types

(1) Acidophils- They are also called oxyphils or α- cells. There cytoplasm are granular and they are stained with acid dyes.

(2) Basophils – These are also called β-cells, cytoplasm are granular and can be stained with basic dyes.

The chromophils are most active and responsible for the hormone secretion while the chromophobes are most inactive. There are certain hormone secreted by anterior lobes and its functions are :

(1) ***Growth hormone or somatotrophin (STH)*** **–** The growth hormone is secreted by the acidophilic cells of adenohypophysis. It is a protein hormone and consists of linear polypeptide chain of 191 amino acids. It has following function

(i) It stimulates the growth of all the body cells including skeletal and muscular tissue.

(ii) It stimulates the multiplication of cells.

(iii) It stimulates the growth of thymus.

(iv) It increases the secretion of milk during lactation.

(v) It increases protein synthesis.

(vi) It promotes biosynthesis of messenger- RNA (m-RNA) and transfer – RNA (t-RNA).

(vii) It also increases transport of amino- acids into the cells across the membranes.

(viii) Ribosome becomes more active in presence of growth hormones.

(ix) Growth hormones inhibit the utilization and uptake of glucose by tissues.

(x) Growth hormone increases the release of fatty acids from the adipose tissue and therefore increases the fatty acids concentration in the body fluids. This will increase the use of fatty acids for supplying energy to the body.

(xi) It also stimulates the process of chondrogenesis and osteogensis. It promotes formation of chondroitin sulfate and bone matrix.

(xii) Growth hormone increases the size of kidney, rate of excretion through renal tubules and renal clearance.

(xiii) Growth hormone produces hyperglycaemia (high sugar level) and glycosuria. The high blood glucose level lead to over production of insulin by islet of Langerhans and finally to their exhaustion and atrophy, so the growth hormone is diabetagenic.

(ivx) It also increases intestinal absorption of calcium as well as its excretion. In addition to Ca, Na, K, Mg, Po_4 and chloride are also retained.

Disease:- *The hyposecretion of growth hormone for prolonged periods during growth phase results in* ***dwarfism,*** *whereas over secretion of the growth hormone prior to adult result in* ***gigantism.*** *Over secretion of the hormone after the attainment of full skeletal growth give rise to the condition called* ***acromegaly.***

(2) ***Thyroid Stimulating hormone (TSH)***

Thyroid stimulating hormone (TSH) is secreted by the basophil cells of the pituitary gland. It is a glycoprotein hormone and the carbohydrate portion is acetylglucosamine, acetylgalactosamine etc. TSH is released from pituitary gland under the influence of the thyroid releasing factor (TRF) secreted from hypothalamus. It has following function

(1) TSH increases the incorporation of inorganic iodine into thyroxine and other iodothyronines in the thyoid gland.

(2) The release of thyroxine and other iodothyroxine from the thyroid gland is increased by TSH.

(3) TSH also found to be increase pentose phosphate pathway *in vitro*.

(4) TSH promotes the release of free fatty acid from the adipose tissue.

(3) ***Adreno-corticotrophic hormone (ACTH)***

Adreno-corticotrophic hormone (ACTH) is secreted by basophil cells of anterior lobe of pituitary gland and it regulates the development and secretion of the adrenal cortex. It is a polypeptide hormone consists of 39 amino acids. The level of ACTH is found in normal healthy person is 10-60pg/ml. The diurnal variation have been reported for ACTH i.e. it's maximum level is found in the early morning and minimum level in the late evenings.

Function:-

(i) ACTH stimulates the activity of adrenal cortex for the secretion of glucocorticoids.

(ii) It stimulates the utilization of glucose and at the same time it promotes release of free fatty acid (FFA) from adipose tissue.

(iii) ACTH promotes insulin secretion from β – cells of pancreas.

(iv) The hyposecretion causes rheumatoid fever & Addision's disease.

(4) ***Gonadotropic hormones (GTH)***

The anterior lobe of pituitary gland secretes three gonadotropic hormones. These are follicle stimulating hormone (FSH), luteinizing hormone (LH) and lactogenic hormone (LTH).

Follicle stimulating hormone (FSH)

(i) It is a glycoprotein and it consists of polypeptide of 204 amino-acid. It is produced by the basophil cells of the pars distalis.

(ii) FSH contains sialic acid and if sialic acid is removed from FSH molecules, it looses its biological activity.

(iii) In human female it stimulates the development and maturation of ovarian follicle producing the egg cell and one of the female sex hormone, oestrogen.

(iv) In human males the FSH induces spermatogenesis by stimulating epithelium of seminiferous tubules in the testis.

(v) FSH increases the formation of C-AMP in target tissue.

(vi) FSH increases nucleic acid and protein synthesis formation.

Luteinizing hormone (LH)

(1) It is also called interstitial cell stimulating hormone (ICSH). It is produced by the pale basophil cells of the pars distalis.

(2) It is a glycoprotein and consists of polypeptide chain of 204 amino acid.

(3) In female, luteinizing hormone is involved in the further development of egg cell and it's release by rupturing of the ovarian follicle. It also stimulate the development of corpus. Luteum that in turn secrete progesterone. The oestrogen and progesterone are the two principal female sex hormone responsible for sexual drive and the development of secondary sexual characters (e.g. Mammary gland).

(4) In males, luteinizing hormones (LH) stimulates the secretion of the male sex hormones, testosterone by specialized interstitial cells in the testes.

(5) LH also promotes the development of accessory sex organs such as vas deferens, prostrate and seminal vesicle.

Lactogenic hormone (LTH) or Prolactin or Luteotropic Hormones

(i) It is a protein hormone with several disulphide bridges and is secreted by the red acidophil cells of the par distalis. It consists of polypeptide chain of 198 amino acid.

(ii) In mammal, this hormone induces the milk secretion (lactogenesis) in the mammary gland of the mother shortly after giving birth. That is why it is also called maternity

hormone. It is now clearly known that prolactin also function together with oestrogen in promoting the development of the mammary gland.

(iii) It also serve together with LH to maintain the corpus luteum which is also vital for the maintenance of pregnancy.

(iv) It is responsible for the maternal instincts of the mammals.

(v) In pigeon, it stimulates the epithelial cells of the crop in both males and females to secrete "pigeon milk" for nutrition of newly hatched infants.

(5) Melanocytes Stimulating Hormone (MSH)

The Melanocytes Stimulating Hormone (MSH) is secreted by the pars intermedia and it was also formerly known as inter-median hormone. It is found in two forms α-MSH consist of 13 amino acid while β-MSH consist of 22 amino acid. This hormone is responsible for stimulating the distribution and concentration of the melanin pigment granules in the epidermal cells. The action of MSH is interfere by epinephrine and norepinephrine. Glucocorticoid block the secretion of MSH. The effect of MSH in pigment depression has been well studied in lower vertebrates.

Neurohypophysis or Posterior Lobe

The posterior lobe of pituitary gland or neurohypophysis consists of pars nervosa, infundibulum and median eminence. The pars nervosa consist of ependymal cells, mostly neuroglial cells and pituicytes cells. The pituicytes are the chief cells and they are found in large number and are responsible for the secretion of hormones of neurohypophysis.

The hormones of neruohypophysis are formed in supra optic and par ventricular (tuber cinerials) nuclei of the hypothalamus are transported by non-medullated nerve fibre to the neurohypophysis. The neurohypophysis secretes two hormones vasopressin and oxytocin.

(1) Vasopressin

The vasopressin is secreted by the posterior lobe of pituitary gland. Chemically it is cyclic octapeptide and consists of eight amino acid residue with a disulphide (S-S) bond. Vasopressin is synthesized in the supra optic nucleus and it get bound with a protein called neurophysis and then it release from the cell body and pass down by the axon to the posterior lobe. When axon is stimulated it releases vasopressin from the nerve ending through the process of exocytosis. The secretion of vasopressin is stimulated by exocytosis. The secretion of vasopressin is stimulated by various ways such as pain, emotional state, hemorrhage, dehydration, excess salt intake, Acetylcholine and anesthetic drugs also stimulate secretion. The narcotics morphine, nicotine and barbiturates also increase. Epinephrine inhibits vasopressin secretion.

Function

(i) It constricts arterioles and capillaries, causing the raise of blood pressure.

(ii) The rate of heart beat reduces.

(iii) It reduces chloride absorption and thus chloride loss.

(iv) It causes the contraction of the plain muscles of urinary bladder, ureter, stomach and intestine. It cannot cause the contraction of the muscles of heart and uterus.

(v) It produces glycogenolysis, hyperglycaemia and glycosuria.

(vi) It stimulates the nephron to re-absorb water from the urine and thus it reduces the volume of urine formed. Hence this hormone is commonly called antidiuretic hormone.

(vii) Deficiency of this hormone produces large volume of urine. This defect is called diabetes insipidus.

(2) Oxytocin or Pitocin

The term oxytocin is derived from Greek word mean quick child birth. It is also secreted by the posterior lobe of pituitary gland. Chemically it is a cyclic octapeptide and consists of eight amino-acid residue with disulphide bond (S-S). Oxytocin is synthesized in par ventricular (tuber cinerials) nuclei of the hypothalamus and get bound with a protein neurophysin and then it release from the cell body and pass down by the nonmedullated nerve fibres to the posterior lobe of pituitary gland.

Function

(i) Oxytocin is very important for the ejection of milk from the mammary gland through nipple.

(ii) It plays a powerful stimulant in the contraction of pregnant uterus.

(iii) Oxytocin plays a very important role in parturition and expulsion of embryo from uterus.

(iv) Sexual stimulation of the female during intercourse increases the secretion of oxytocin and the increased oxytocin is responsible for uterine contractions that occur during the female orgasm.

(v) Oxytocin acts on uterine smooth muscle for contraction which will aid the transport of spermatozoa into the fallopian tube.

Thymus

Thymus is partly an endocrine gland and partly a lymphoid structure. It is a bilobed structure located in the upper part of the chest covering the lower end of trachea. The gland is conspicuous in infant weigh 10-12 gm and increases in childhood and during puberty maximum size is 20-30gms then it gradually undergoes involution and replaced by fat. By the time the person reaches maturity, the gland has atrophied.

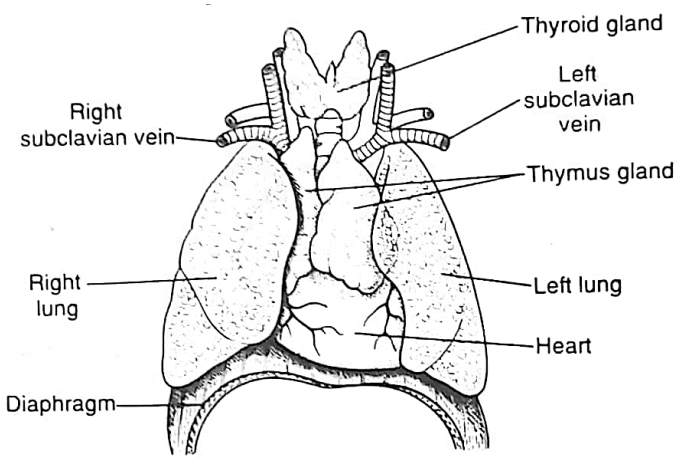


Fig 7.12: Thymus gland

The gland is covered by a connective tissue called capsule. It has a peripheral cortex and a central medulla. The gland is made up of numerous follicles. It secrete thymosin hormone. It is a protein hormone and mainly involve in the regulation of neuromuscular transmission. It has following function-

(1) It is the main source of lymphocytes.

(2) The rejection of graft is also brought about by thymus.

(3) It control immunologic phenomenon.

(4) It secretes Thymosin.

(5) It helps in the deposition of mineral salts on the bones.

(6) It helps in the development of sex gland.

Pineal Gland (Epiphysis)

Pineal gland is a situated below the corpus callosum. It is attached by a hollow stalk to the roof of diencephalon or it originate as a diverticulum from the root of diencephalon. It is flattened, cone-shaped, grey body measuring about 5 to 8 mm in length. The pineal body is formed of parenchyma cells and interstitial cells. The parenchyma cell consists of eosinophil cells and neuroglial cells.

The pineal body first appears at about 36 days of gestation. It attains its maximum development by about 7 years of age and then undergoes a very slow involution. This involution continues to about 14 years of age and in the adult it is made up largely of fibrous tissue.

Pineal body release a hormone called melatonin. The melatonin is synthesized from active substance serotonin. Melatonin is release in dark and as light is passed through the eye it inhibit the release of melatonin. Melatonin has antagonic effect to melanocyte stimulating hormone (MSH). MSH concentrates melanin pigments in the melanophores and known as darkening hormone while melatonin disperse melanin pigment from such cells and are known as lightening melanin hormone. Some of the other important role of melatonin is as-

(1) It regulates daily body rhythms i.e. day/night cycle (circadian rhythms).

(2) Melatonin slows the aging process (a defence against free radicals).

(3) It prevent jet lag.

(4) It implicates in seasonal affective dis-order, co-ordinates fertility and allows for deep restful sleep patterns.

(5) Melatonin plays a role in cancer inhibition by inhibiting the growth and metastasis of some tumors.

(6) Melatonin also decreases breast cancer.

(7) It also affect in sexual dysfunction, hypertension, epilepsy and Paget’s disease

(8) In children melatonin is believed to inhibit sexual development.

(9) In lower vertebrates it plays a major role in sexual development, hibernation in animals, metabolism and seasonal breding.

(10) In birds it is a center for navigation.

Pancreas

Pancreas is a flattened and pinkish mixed gland situated between the stomach and duodenum. It measures about 15 cm in length and 4 – 5cm in breath. It is formed by fusion of two bilateral endodermal processes of embryonic intestine. About 98% part of the gland is exocrine and formed of hollow pancreatic lobules embedded in a connective tissue stroma. In the stroma there are numerous small clusters of endocrine cells called Islets of Langerhans discovered by Paul Langerhans. There are 3 types of cells present in the islet of Langerhans.

(i) **α-cells –** These are granular cells and are also known as oxyphils. They secrete glucagon hormone. It constitutes about 20 %.

(ii) **β-cells** – These cells are present in major bulk of gland. They are granular and basophils and secrete insulin hormone. It constitutes about 70%.

(iii) **γ-cells** – They are non-granular cells and are precursors of α and β cells. It constitutes about 5%.

Insulin

Insulin is secreted by the **β** – cells of islet of langerhans. Chemically it is a polypeptide hormone. It consists of two peptide chains i.e. A and B chain. A chain having 21 amino acid and B chain having 30 amino acid and both the chains are joined by two disulphide bridges. The disulphide bridges are essential for the biological activity of the hormones.

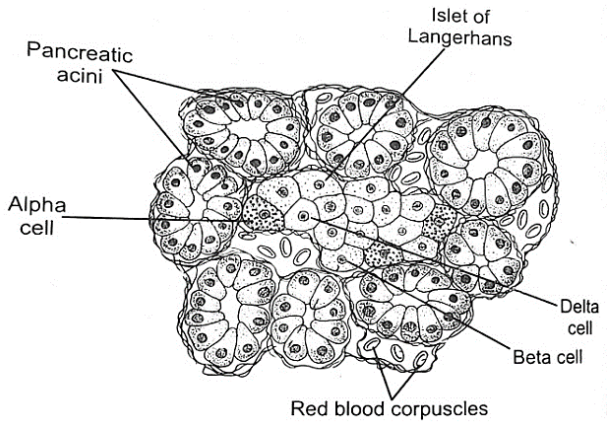


Fig. 7.13 A part of the section of pancreas to show an islet of langerhans

It has following function-

(1) The main function of insulin is to lower the blood sugar level. It bring down by

(a) By increasing the cells more permeable to glucose

(b) By enhancing glucose oxidation in the cells.

(c) It increases synthesis of glycogen from monosaccharide and lactates both in liver and muscle.

(d) It promotes the conversion of glucose into fat deposits.

(2) Insulin favour formation of m-RMA.

(3) Insulin increases the incorporation of amino acids into protein.

(4) It prevents formation of ketone bodies.

Deficiency – Secretion of insulin is controled by the blood sugar level. Its secretion increases when the blood sugar level rises and decreases when the blood sugar decreases. Deficiency of insulin or hyposecretion of insulin causes a disease called diabetes mellitus. It has following symptoms.

(a) Hyperglycaemia – Increase in blood sugar level

(b) Glycosuria- Increase of sugar in urine

(c) Polyuria – large volume of urine

(d) Frequent urination

(e) Ketonuria- Increased appearance of ketone bodies in the urine

(f) Ketonemia –Increased appearance of ketone bodies in the blood

(g) Depletion of glycogen depots of liver and muscle

(h) Lowering of respiratory quotient (RQ)

(i) Delayed healing of wounds.

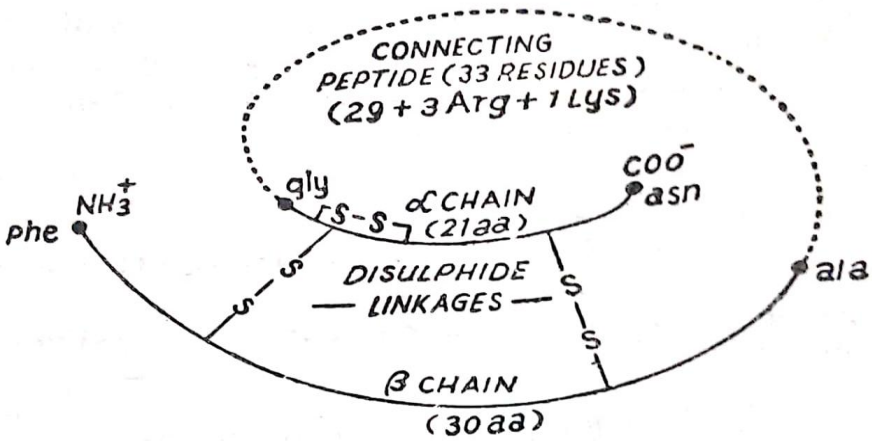


Fig 7.14: Structure of Insulin

Glucagon

Glucagon was first isolated by Kimball and Murlin in 1923 from the α-cells of Islet of langerhans of pancreas. It is a polypeptide hormone and is responsible for the increase of sugar level in blood. Hence it is also called hyperglycemic factor (HG- factor). It consists of 29 amino acid. Glucagon is a diabetogenic hormone and act as antagonistic to insulin i.e. has opposite effect to insulin. There is a proper balance between insulin and glucagon production is therefore necessary to maintain proper blood glucose concentrations.

It has following proportion.

(1) Glucagon promotes glycogenolysis i.e. break down of glycogen to glucose in liver and thus raise blood sugar.

(2) It stimulates hepatic gluconeogenesis.

(3) It activates adenyl cyclase.

(4) It inhibits biosynthesis of protein by inhibiting amino acid incorporation in the proteins.

(5) It also increases catabolism of amino acid which increases more urea.

(6) It modify the composition of chromatin in the liver tissue.

(7) It stimulates hepatic lipase which inhibit synthesis of triglycerides, phospholipids, long chain fatty acids and cholesterol.

(8) It increases synthesis of short chain fatty acid.

(9) It increase release of glycerol and free fatty acids from adipose tissue.

(10) It increases the rate of glomerular filtration and excretion of minerals such as Ca^{++}, Na^{+}, K^{+}, Cl^{-} and Po_2^{-}.

Deficiency

Deficiency of glucagon causes hypoglycemia and hyperglyceridemia.

SAQs 1.

Complete the following sentences by inserting appropriate words in the blanks.

(i) The foetal portion of placenta formed by the chorionic villi of the ----------

(ii) Haemo-chorial placenta is found in ----------

(iii) ---------- secreted by the placenta is essential for maintenance of pregnancy.

(iv) Prolactin hormone is concern with ----------

7.7 SUMMARY

In this chapter there is discussion of type of circulation i.e. single circulation & double circulation. There is also discussion of type of heart like myogenic heart and neurogenic heart. There is also given information about menstrual cycle and role of hormone play in this. There is also discussion about male & female sex hormones. Lactation and hormone involved in releasing milk. There is also given information about placenta and its various types. There is also information about neuro-endocrinology & hormone released by endocrine glands.

7.8 TERMINAL QUESTION

Q1. Describe the single circulation.

Q2. Describe the yolk sac placenta.

Q3. Describe function of oxytocin.

7.9 ANSWERS

SAQ 1

(i) Chorion

(ii) Monkey

(iii) Progesterone

(iv) Milk ejection

Terminal question

1. Such type of circulation is observed in 2 chamber or 3 chamber heart like fishes, Amphibian & reptilian. In 2 chambers heart like fishes it receives impure blood from different parts of body and pump it into respiratory organ (gills) from where it gets oxygenated and this oxygenated blood is circulated to different parts of the body. So the blood passes single time from the heart.

In case of amphibian and reptilies where heart is 3 chambered, the right side of heart i.e. right auricle receive deoxygenated blood from different parts of body and left side i.e. left auricle receive oxygenated blood from the lungs and then both the deoxygenated & oxygenated blood from auricles enter into ventricle and from ventricle it is distributed to whole of the body i.e. blood pass single time from heart that is why it is called single circuit.

2. Yolk sac placenta are observed in metatherian or marsupials such as kangaroo & opossum. In this type placenta is derived from yolk sac and chorion. The yolk sac developed from the lower part of blastocyst and is very large and nearly encloses the entire embryo and its amnion. The wall of yolk sac lies in direct contact with chorion which sends out finger like villi into uterine wall. Yolk sac wall also develops vitelline blood vessels for transporting secretions. Uterine milk absorbed from uterus to the developing embryo. Allantois remains poorly developed and never comes in contact with chorion.

The yolk sac placenta in metatherian is very weakly developed so that embryo born are very small & immature, so to compensate the intra-uterine development the young once are transferred to their abdominal pouch or marsupium and feed on the milk until fully formed.

3. Function of oxytocin are as follows

(i) Oxytocin is very important for the ejection of milk from the mammary gland through nipple.

(ii) It plays a powerful stimulant in the contraction of pregrant uterus.

(iii) Oxytocin plays a very important role in parturition and expulsion of embryo from uterus.

(iv) Sexual stimulation of the female during intercourse increases the secretion of oxytocin and the increased oxytocin is responsible for uterine contractions that occur during the female orgasm.

(v) Oxytocin acts on uterine smooth muscle for contraction which will aid the transport of spermatozoa into the fallopian tube.

UNIT-8 BIOCHEMISTRY OF CARBOHYDRATES, PROTEINS AND LIPIDS

8.1 INTRODUCTION

In animal cells carbohydrates are present in the form of glucose and glycogen which serve as an important source of energy for vital activities. Proteins are the nitrogen containing substances of immense important to the living beings. These are required by the living-beings for the formation of body tissue, enzymes, hormones, immunoglobulin and intracellular and extracellular proteins. Majority of the proteins are high molecular weight substance having very complex structures. Lipids are the organic substances insoluble in water, but soluble in organic solvents like chloroforms, ether and benzene. They are esters of fatty acids or substances capable of forming esters. They are utilize by the living organisms. Gluconeogenesis is the process of formation of glucose from non-carbohydrate precursor. The non-carbohydrate precursors are lactate, amino-acid, glycerol, pyruvate.

Objective

After studying this unit you will be able to know:

- About structure & biological importance of carbohydrate.
- classification of carbohydrate and its derivative.
- structure & biological importance of protein, its derivative.
- structure & biological importance of lipid, its derivative.
- metabolism of carbohydrate in which glycolysis cycle, citric acid cycle, gluconeogenesis, pentose phosphate pathway.

8.2 STRUCTURE AND BIOLOGICAL IMPORTANCE OF CARBOHYDRATES, PROTEINS AND LIPIDS

Carbohydrate

Carbohydrate consists of carbon, hydrogen and oxygen. The hydrogen and oxygen are found in 2:1 ratio. Carbohydrates are widely distributed both in plant and animal cells. In plants they are produced by the photosynthesis and are present in the form of cellulose in wood and starch in cereals, roots and tubers, cane-sugar and milk sugar. In animal cells carbohydrates are present in the form of glucose and glycogen which serve as an important source of energy for vital activities. Some carbohydrate have highly specific function e.g. galactose in certain lipids, ribose in the nucleo–

protein of the cell and the lactose of milk. Carbohydrates may be defined chemically as aldehyde or ketone derivative of the polyhydric alcohol or as compound that yields these derivatives on hydrolysis.

Classification of carbohydrate :

Carbohydrates have been classified into three major groups.

1- Monosaccharides

2- Oligosaccharides

3- Polysaccharides

(1) Monosaccharides – Monosaccharides are those compounds which cannot further hydrolyzed into simple sugar such as triose, tetroses, pentoses, hexoses and heptoses. Some monosaccharides contain aldehydric group and some others contain ketonic group. Based upon the presence of such groups, the monosaccharides have been further classified into aldosugars and ketosugars. The aldosugar are classified as aldotrioses, aldotetroses, aldopentoses, aldohexoses and the ketosugar are classified as ketotrioses, ketotetroses, ketopentoses and ketohexoses etc.

The simplest aldosugar is glyceraldehydes. The examples of higher aldosugars are erythrose, xylose, ribose, arabinose, glucose, galactose and mannose. The simplest ketosugar is dihydroxy-acetone. The examples of higher ketosugar are erythrulose, xylulose, ribulose, fructulose, and sedoheptulose.

In the crystalline form the monosaccharides containing 50 or more carbon atom exist in the tautomeric ring form. The free sugar mostly contain six- membered ring in which five members are carbon atoms and remaining one member is an atom of oxygen. The six member rings is known as pyranose ring. There is also a five member ring in the sugar in which four member of carbon atom and the remaining one member is an atom of oxygen. The five member ring is known as the furanose ring.

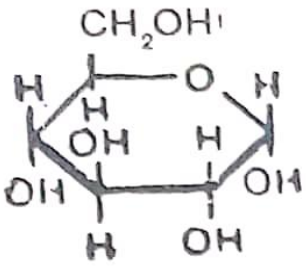


Fig 8.1: Glucopyranose

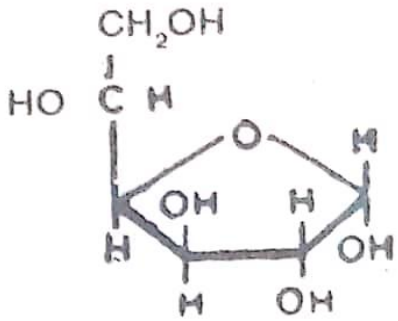
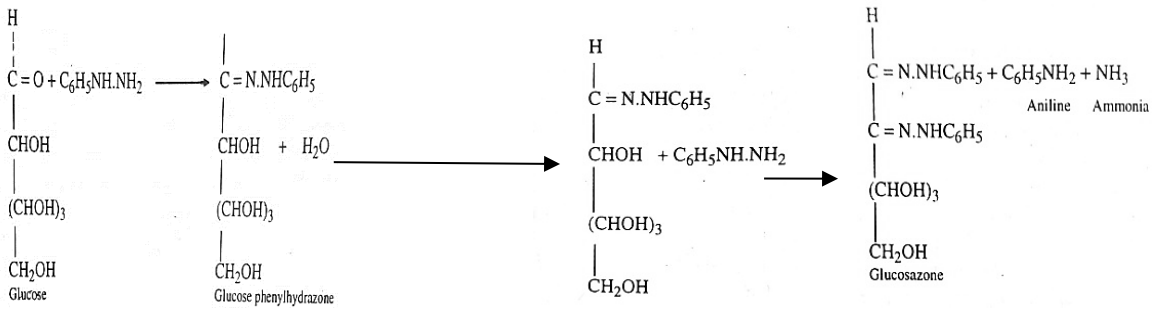


Fig 8.2: Glucofuranose

<u>Glucose</u> – Glucose is a white crystalline solid and easily soluble in water and is sweet in taste. It is the most commonly occurring monosaccharide which forms part of most of the polysaccharides such as starch, glycogen, cellulose and dextrin. This is also found in the plant saps and human blood and blood of all the animals.

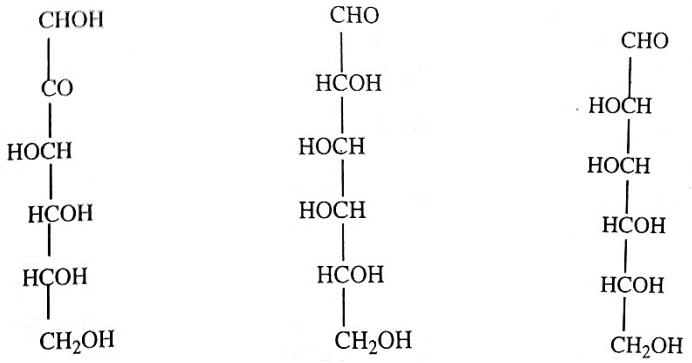
Glucose is an aldehyde, so it acts as reducing agent. It reduces cupric salt to cuprous salt. It also reacts with phenyl hydrazine to form an osazone called glucosazone, which shows different melting points and different crystalline forms of various sugars.



Fructose - Fructose is a laevorotatory ketose sugar. It is found in the free form in many plant products. It is found in honey and all sweet fruits. It is a constituent of sucrose. It is also found in the seminal fluid and is normally formed during glycolysis. It is the basic unit for the synthesis of the polysaccharide, insulin. It is soluble in hot absolute alcohol.

Galactose - Galactose is synthesized in the mammary glands from glucose and it forms the constituent of the milk sugar lactose, many glycol-proteins and galacto-lipids.

Mannose – Mannose does not occur freely in nature. It forms the constituents of some polysaccharides such as mannan in ivory nuts and in some glyco-proteins.



Fructose **Galactose** **Mannose**

Derivatives of monosaccharides

(A) Amino sugar – If there is removal of a hydroxyl group of sugar by amino group, it lead to the formation of amino-sugar. The two amino sugars are very important which exist in the biological system are glucosamine (chitosamine) and galactosamine (chondrosamine). Glucosamine is an important constituent of muco-polysaccharides and muco-proteins such as hyaluronic acid, heparin and blood group substance. It is also present in the cell walls of the fungi and the shells of crustacean as chitin. Galactosamine occurs in sulphated mucopolysaccharides like chondroproteins made up of chondiroitin sulphuric acid and protein existing in cartilage, bones, cornea, skin, tendons and heart valves.

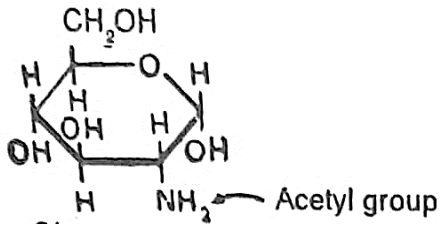


Fig 8.3: Glucosamine

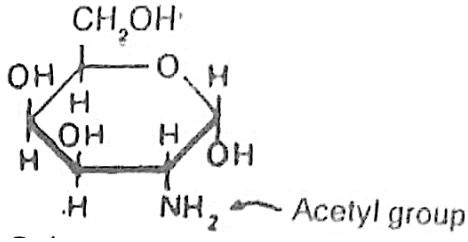


Fig 8.4: Galactosamine

Several antibiotics such as erythromycin and carbomycin contain amino-sugar. The erythromycin contains a dimethyl amino-sugar. Carbomycin contain the first known 3-amino sugar, 3-amino-β–ribose. The amino sugars are believed to be related to the antibiotic activity of these drugs.

(B) Uronic acid – If an aldose sugar is oxidized in such a way that primary alcoholic group is oxidized to carboxylic group, the resulting compound is known as uronic acid. Uronic acid of biochemical importance are glucouronic acid and galactouronic acid. Such acids are formed in the animal tissue during biosynthesis of mucopolysaccharide and detoxication processes.

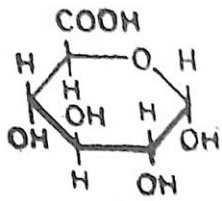


Fig 8.5: Glucouronic acid

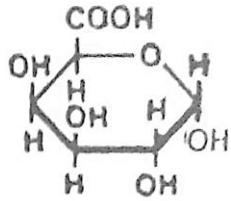


Fig 8.6: Galactouronic acid

(C) De-oxy-sugar – De-oxy-sugars are formed by removal of an oxygen atom from a hydroxyl group of sugar. The most important naturally occurring de-oxy-sugar is 2-de-oxy-D-ribose. De-oxy-ribose is found to be present in de-oxynucleotides and de-oxyribonucleic acid.

(2) Oligosaccharides – Oligosaccharides are those carbohydrates which on hydrolysis give rise to two to five simple monosaccharide molecules. These are mostly di or tri-saccharides.

The disaccharides are composed of two monosaccharide molecules. The disaccharides are of two types reducing and non-reducing. The reducing disaccharide includes maltose, lactose, cellobiose, and non-reducing disaccharide include sucrose and trehalose.

Maltose – This is made up of two α-D–glucose units joined by the 1,4-glycosidic linkage. One of the aldehyde group is remain free, so it exhibit all the properties of the aldehyde group such as formation of oxazone, reduction of cupric salt etc. It is obtained as a hydrolytic product by the action of amylase on starch.

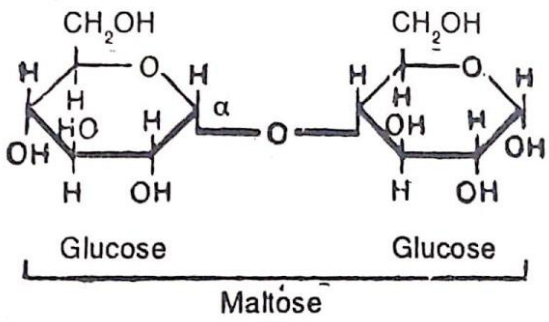


Fig 8.7: Structure of Maltose

Sucrose - Sucrose is a non-reducing disaccharide because its reducing groups both glucose and fructose are involved in the linkage and is not free. It is made up of one molecule of α-D-glucose and one molecule of β-D-fructose joined by 1,2-glycosidic linkage between the aldehyde and keto groups. Sucrose is dextrorotatory, but the mixture of glucose and fructose produced on hydrolysis is laevo-rotatory, because fructose is more laevorotatory than glucose is dextrorotatory. Hence the phenomenon by which the dextro-rotatory sucrose is converted into a laevo-rotatory mixture of glucose and fructose or the rotation changed from positive to negative during hydrolysis is known as inversion. So the sucrose is also called the invert sugar and the enzyme sucrase is also known as invertase. Sucrose is widely distributed in cane sugar, beet sugar and in many ripe fruits.

Lactose – This is made up of a molecule of α-D glucose joined by 1,4 glycosidic linkage to a molecule of β-D galactose. Lactose is a disaccharide consisting of glucose and galactose, which is synthesized in the mammary gland. Milk contains 5% lactose. It has same reducing properties as maltose. Upon hydrolysis it yields one molecule of glucose and one molecule of fructose.

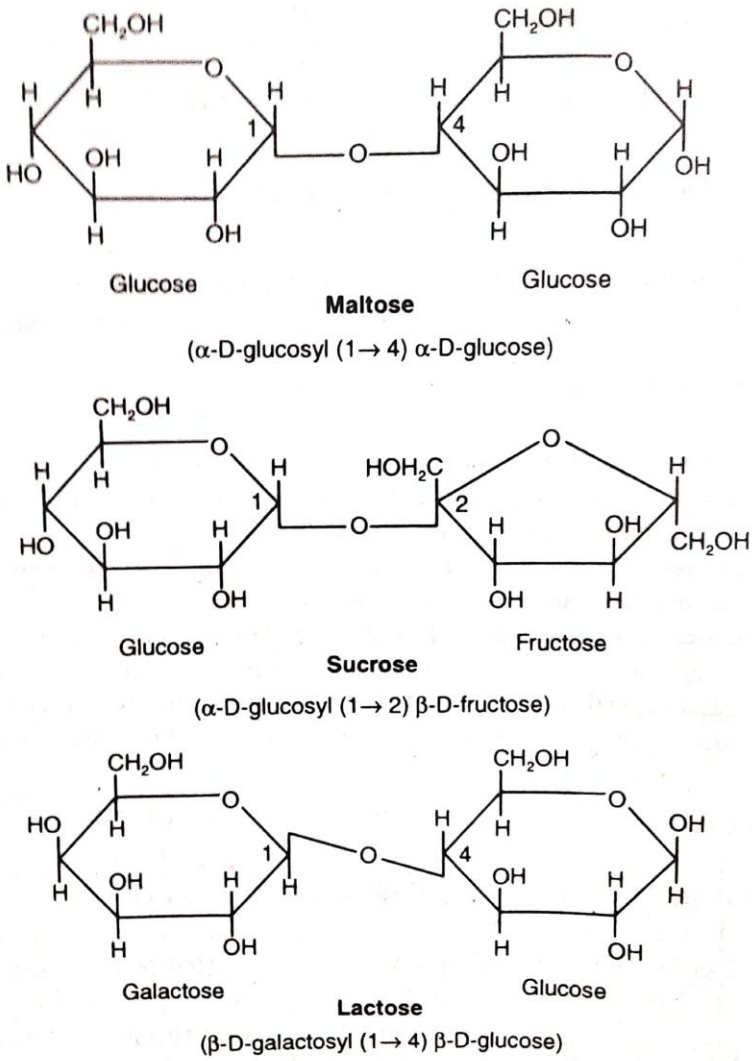


Fig 8.8: Structure of maltose, sucrose and lactose

Cellobiose – It is obtained by incomplete hydrolysis of cellulose. Cellobiose is composed of two molecule of glucose.

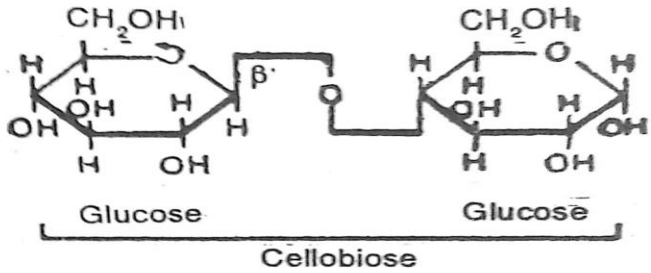


Fig 8.9 : Structure of cellobiose

Trehalose – It is made up of two glucose unit. It is found in the haemolymph of insects and in yeast and fungi.

Gentibiose – It is obtained from gentianose, a trisaccharide present in gentian roots. It is made up of two molecule of glucose and one molecule of fructose. It is hydrolyzed by weak acids. It split off fructose leaving the disaccharide glucose-glucose (gentibiose)

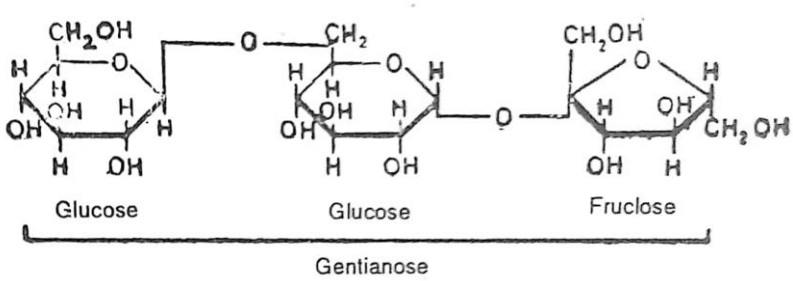


Fig 8.10 : Structure of gentianose

Melibiose - It is a disaccharide and it obtained by hydrolysis of raffinose, which is a trisaccharide, consisting of fructose–glucose-galactose. If this trisaccharide is treated with invertase, it will split off fructose and leave galactose glucose residue (melibiose).

(3) Polysaccharide – Polysaccharides are formed by the union of large number of monosaccharide, which are linked by glycosidic linkages. They may be in the form of linear chain or may by branched chain molecules. They are high molecular weight and are less soluble in water but if water is heated they formed colloidal solution. They are not sweetish and does not exhibit any properties of aldehyde or keto groups. The polysaccharide are of two types. If they are consist of only one type of monosaccharide they are called homopolysaccharides such as starch, glycogen, cellulose, chitin etc. If polysaccharide is consist of many types of monosaccharide molecules or a mixture of monosaccharide, it is called heteropolysaccharides e.g. Hyaluronic acid, chondroitin, heparin etc.

Cellulose – Cellulose form a substantial portion of the vegetable diet as it is the main constituent of the supporting tissue of the plant. It is made up of long chains of β–D-glucose molecule united by 1,4 linkage. There is no branching. It is insoluble in water and gives no colour with iodine. It can be hydrolyses by the enzyme cellulase. But this enzyme is present only in bacteria. Hence cellulose is not utilizable by human being but it serves the function of increasing the bulk of the food, thus giving the sense of satisfaction. Undigested cellulose also adds to the bulk of the faeces and helps in its movements. The herbivorous animals make use of cellulose as the bacteria and protozoans in the rumen and colon convert it to smaller fragments such as short chain fatty acid, carbon dioxide and methane.

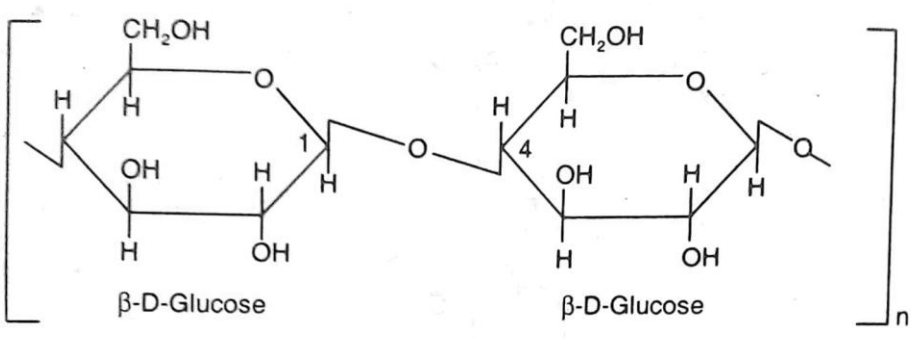


Fig 8.12: Structure of cellulose

Glycogen – Glycogen is made up of many molecules of glucose, which are joined by α-1,4 linkage in linear chain and at branching α-1,6 linkage occur. Glycogen is soluble in water and makes an opalescent solution. It react with iodine and gives reddish colour. Glycogen is also called animal starch and it is mainly stored in muscle and liver. It also occurs in some plant in which chlorophyll is not found such as yeast & fungi.

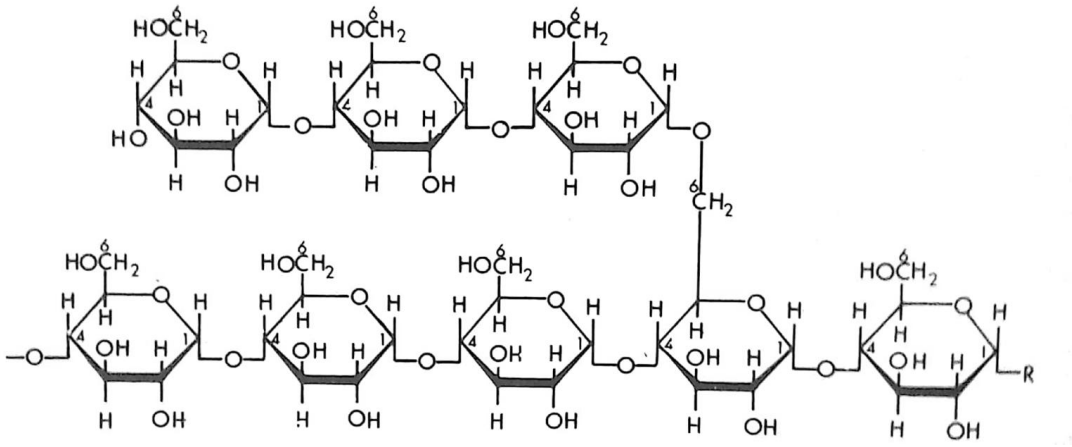
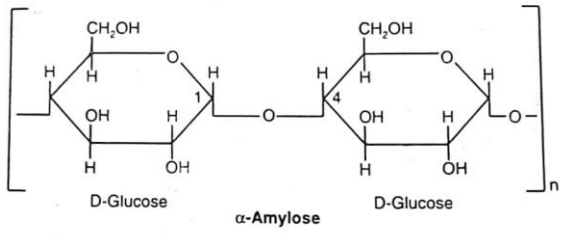


Fig.8.11: Structure of glycogen

Starch – Starch is a mixture of two polysaccharide amylose and amylopectin. About 20 % of the starch granule is composed of amylose unit and rest by the amylopectin. Amylose is soluble where as amylopection is insoluble in water. Amylopectin can absorb water and swell. Amylose is made up of glucose units joined by α-1,4 glycosidic linkage and is a straight chain polysaccharide. It contain 100 to 400 glucose unit. Amylopectin shows the presence of both α-1,4 and α-1,6 glycosidic linkage having linear and branch chain polysaccharide. Starch can be hydrolyse by enzyme amylase and pancreatic juice to yield called dextin, erythrodextrins and achrodextrins. Starch gives a bluish or violet colour with iodine while dextrin gives bluish or reddish colour with iodine in early stages of hydrolysis and at later stages it does not give any colour. Starch is tasteless and possesses no reducing properties. Starch is the chief form of storage product in plants and it the main constituent of food grain.



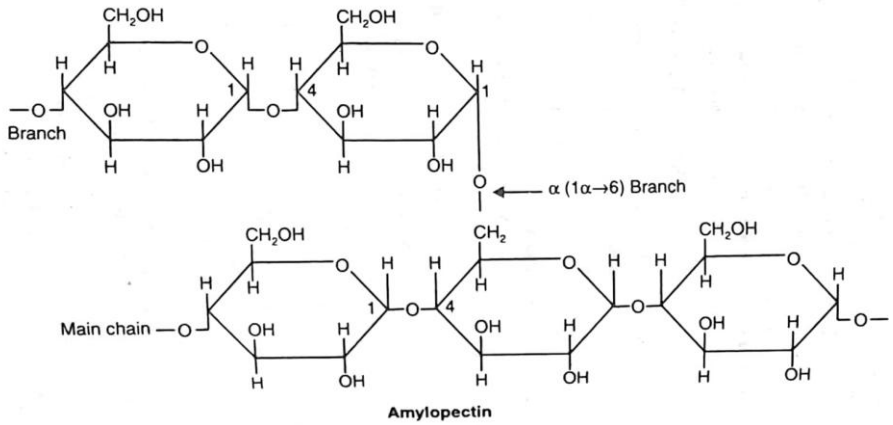


Fig.8.13: Structure of starch (α-Amylose & Amylopectin)

Mannan – Mannan is an important polysaccharide presents in yeast. It forms the cell wall of yeast. It is formed by the 1,2 and 1,6 linkage.

Xylan - Plants also contain another polysaccharide associated with cellulose known as xylan, which on hydrolysis yields D-glucose. These sugars are attached by β-1, 4 linkages.

Galacturonic acid – Many fruits such as apple, lemon and other fruits contain a polysaccharide of D-galacturonic acid unit, which are joined by α-1,4 linkage. This is known as pectic acid. These acids are found in pectins of the plants. They form gels with sugar solution.

Alginic acid – Alginic acid is a polysaccharide found in the brown marine algae. It is formed by α 1,4 linkages of the D-mannouronic acid.

Agar – It is made up of sulphated galactose unit. It is present in seaweeds. It dissolve in hot water and sets to a gel on cooling. It is used as a culture medium for bacteria. It is used in the treatment of constipation.

Chitin – Chitin is present in the endoskeleton of arthropods like crab, lobstar and insects. It is formed by the polymerization of N- acetylglucosamine by β-1, 4 linkages.

Insulin – Insulin is a polysaccharide made up of D–fructose units. It is found in tuber of chicory, dahlia, bulbs of onion and garlic. It is not utilized by human beings. It is used in assessing the glomerular filtration rate in the study of kidney function. It is a white crystalline powder and dissolves in hot water. It does not react with iodine.

Hyalouronic acid – Hyalouronic acid is a mucopolysaccharide and is present in the connective tissue. It acts as an intercellular cementing substance in tissues, capillary walls and forms a coating gel in ovum. It is abundantly present in the vitreous fluid of eye, umbilical cord and synovial fluid at the joint. It is a highly viscous substance and consists of N-acetyl glucosamine and glucouronic acid. The glycosidic linkage between N-acetylglucosamine and glucouronic acid are of β-1,4 linkage and between glucouronic acid and N-acetyl glucosamine are of β-1,3 type. The enzyme hyaluronidase is found in seminal fluid, which depolymerise the hyaluronic acid and help in the penetration of sperm in reaching the ovum for fertilization.

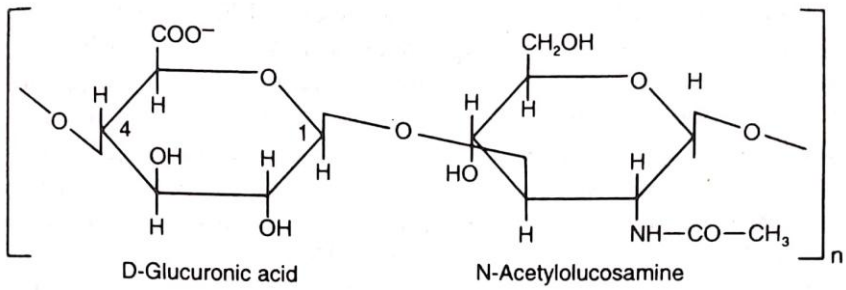


Fig .8.14: Structural pattern in hyaluronic acid

Chondroitin sulphate – Chondroitin sulphate is a mucopolysaccharide. It is present in cartilages, adult bones, cornea, skin, tendons and heart valves. It is made up of N-acetyl galactosamine and glucouronic acid. The galactosamine is esterified with sulphuric acid at position 4 and 6.

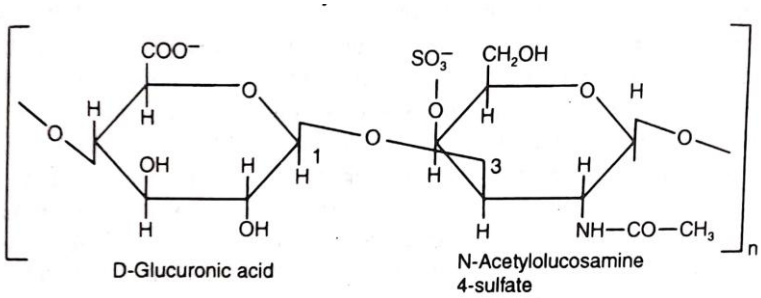


Fig.8.15: Structure of chondroitin-4 Sulphate

Heparin - Heparin is a mucopolyaccharide and consists of N-acetyl glucosamine glucouronic acid and sulphuric acid. It is a natural anticoagulant and found in liver, spleen, lung, kidney and intestine mucosa. It is produced by mast cells of the liver. It is purified and is used to prevent coagulation of blood.

Protein

Proteins are the nitrogen containing substances of immense important to the living beings. These are required by the living-beings for the formation of body tissue, enzymes, hormones, immunoglobulin and intracellular and extracellular proteins. Majority of the proteins are high molecular weight substance having very complex structures. On hydrolysis, protein yields amino acids and sometime certain non-protein residues in addition to the amino acids are also yields. Usually 20 different amino-acids are obtained on hydrolysis of protein. Thus amino acids are the building stones of the protein molecule. Amino acid in different protein molecules remain arranged in different but definite sequences which impart a specific type of property in these molecule. The important essential functions of protein molecule are as follows-

(1) Structural support – Proteins are a major structural component of bone, cartilage, feathers, fur and hair and a component of all biological membranes and chromosomes.

(2) Enzymatic catalysis – All enzymes are protein. They play a unique role in determining the pattern of all chemical transformation and thus of all growth and function.

(3) Movement – Muscle fibres are composed primarily of protein filaments. Muscle contraction is accomplished by the sliding motion of two major kinds of protein filaments actin & myosin.

(4) Immune protection – Immunoglobulin are a group of highly specific protein molecules that chemically "recognize" and combine with such potentially dangerous foreign invaders of the body as bacteria and viruses.

(5) Transport and storage – Specific proteins serves as carrier of many important small molecules and ions, some in trace amounts for e.g. iron atoms are carried in mammalian blood by the protein called transferrin and are stored in the liver as a complex with ferritin, another protein. Binding to proteins is a quick way of transporting storing molecules. It also increases metabolic efficiency by ensuring the delivery of substances only to the appropriate receptors of specific cells.

(6) Hormonal regulation of physiological activates - The physical activities of living are regulated and coordinated by hormones. Several hormones are protein.

(7) Sensory perception and integration of the nervous system – The responses of nerve cells to specific stimuli are often mediated by specific receptor proteins such as the light-sensitive, pigmented proteins in the retinal cells of the vertebrate eye.

Classification of protein

Protein can be classified into 3 groups on the basis of solubilities and other physical characters.

(1) Simple protein

(2) Conjugated protein

(3) Derived protein

(1) Simple protein – Simple protein are consist of only amino-acids or their derivatives. If it is hydrolyzed by acid, alkalies or enzymes, simple protein yields only amino-acids or their derivative. Simple proteins have been further classified into 7 groups.

(a) Albumins – These proteins are soluble in water and dilute salt solution and can be coagulated on heating. These proteins are found in all body cells and also in the blood stream for e.g. lacto-albumin found in milk and serum albumin found in blood, ovalbumin, myoalbumin.

(b) Globulin – These protein are insoluble in water and soluble in dilute salt solution but can be coagulated on heating for e.g. globulin are ovaglobulin (eggs), lactoglobulin (milk), fibrinogen, alpha, beta and gamma globulins (all in serum), myosin and tropomyosin (both in muscle).

(c) Globin – These are neutral type of histones which cannot be precipitated by adding ammonium hydroxide as histone can be precipitated. Such protein can easily combine with heme forming hemoglobin.

(d) Prolamines – Prolamines are water insoluble but soluble in 70% ethanol. These proteins are also insoluble in absolute alcohol and other neutral solvents. Such protein are found in the cereals e.g. gliadin (wheat protein), zein (corn protein) and hordein (barley protein).

(e) Histone – Histone are water soluble protein in which basic amino-acid are predominate. On heating these can be coagulated but this coagulum is soluble in very dilute acid. Since these protein are basic so they can easily combine with acidic substances. In eukaryotic DNA of the chromosome is associated with histones to form nucleoprotein. The histones are rich in arginine or lysine.

(f) Proto-amines – Proto-amine are water soluble basic polypeptide with a low molecular wt. They are rich in arginine amino-acids. The polypeptide chain consists of 28 amino-acid residues, which include 19 arginine and 8-9 non basic amino-acids. Proto-amine are found bound to DNA in spermatozoa of some fishes for e.g. proto-amine are salmine (salmon) and sturine (sturgeons).

(g) Albuminoid – These are insoluble in water and in all other neutral solvents. The albuminoid are keratins, elastins, collagens and keratohyaline. The keratins are present in the hairs, nails, horns, hoofs, and feathers. The outer most layer of skin is also formed by keratin. Keratohyaline is present in the lower layer of skin. These proteins are rich in arginine, lysine and histidine content. Collagen is found to exist in the connective tissues and in the bones and are insoluble in all the neutral solvents. Elastins are found to be present in the yellow elastic fibres of the connective tissues.

(2) Conjugated protein – These are those proteins which consist of simple proteins in combination with some non-protein organic substances called prosthetic group or a metal. These are of following 6 types.

(a) Glycoprotein (protein + carbohydrate) - These are those protein which have combination with carbohydrate. In most glycoproteins the linkage takes place between asparagine and N-acetyl-D-glucosamine. These include mucopolysaccharides and mucoproteins. The mucopolysaccharide contains more amount of carbohydrate and less protein, where as the mucoprotein contain more protein and less carbohydrate. The mucoproteins include ceruloplasmin which is a blue copper containing protein, transferrin which is an iron transferring protein, osseomuco-protein of bones, tendon mucoprotein which are found to be present in the cartilage and mucin which is found in digestive tract.

(b) Nucleoprotein (protein + nucleic acid) – Nucleoprotein are protein in combination with nucleic acids. Such combinations occur both with ribonucleic acid (RNA) and deoxyribonucleic acid (DNA). The protein portion is usually a histone or a protamine. The other e.g. are chromosomal proteins, viral protein and some of the glandular proteins.

(c) lipoprotein – The lipoprotein are those when the protein conjugated with lipids. These are found to be soluble in the lipid solvent. There are four types of lipoproteins i.e. high density lipoprotein (HDL) or α-lipoprotein, low density lipoprotein (LDL) or β-lipoprotein, very low density lipoprotein (VLDL) or pre-β-lipoprotein and chylomicrons.

(d) Phospho-proteins – These proteins contain phosphoric acid in their molecular structure in addition to amino acids example are casein & vitellin. Casein is found to be present in the milk and vitellin is present in egg yolk.

(e) Chromo-proteins – These are proteins in combination with a prosthetic group that is a pigment. Examples are respiratory pigment hemoglobin and hemocyanin. Visual purple or rhodopsin found in the rods of the eye, flavoprotein and cytochromes.

(f) Metallo protein – Such protein contain metal alone which remains attached to the protein. for e.g. Ferritin (metal portion iron) and carbonic anhydrase (Zn).

(3) Derived protein – Derived proteins are the intermediate products formed from natural proteins when they are hydrolyzed by heat, acids, alkalies or enzyme. These are of two types.

(a) Denatured and coagulated protein – These are those protein which upon treatment with certain chemical agents or heat treatment the protein become insoluble on account of some sort of intra molecular rearrangement and it is said to have denatured and when it get separated in the form of precipitate, it is said to have undergone coagulation.

(b) Peptides – These include the various fragment of the protein which are broken off during hydrolysis of the big protein molecules either in the presence of acid or enzyme, the large fragment are called proteoses and smaller fragments as peptones.

Lipids

Lipids are the organic substances insoluble in water, but soluble in organic solvents like chloroforms, ether and benzene. They are esters of fatty acids or substances capable of forming esters. They are utilize by the living organisms. They form the dietary constituents on account of their higher calorific value. In the body they are present in the cytoplasm as well as in the cell wall and also some specialized area in the body as depots of fat. Nervous tissue also contain high amount of lipid which play a significant role in their function. The subcutaneous fat serves the role of insulation against atmospheric heat and cold. It also helps in shaping of the body.

Properties of lipid

(i) Physical properties – The lower fatty acids are liquid at ambient temperature and are soluble in water. The higher fatty acids are solid at room temperature and are insoluble in water but soluble in organic solvent except acetic acid all other fatty acids are lighter then water.

(ii) Biological properties –

(a) Lipids occur as component of some enzyme systems.

(b) Lipids are also component of some hormones for e.g. steroids.

(c) Lipids constitute important components of cell membranes for e.g. plasma membrane of eukaryotic cells.

(d) Lipid is present as a storage compounds for the reserve energy of the body. 1 gm of fat release 9 kcal of energy.

(e) Lipids are present in the myelin sheath of nerve fibre, which act as electrical insulators.

(f) Lecithin is the important phospholipid found in membranes as phospholipid and have both acidic and basic groups. Therefore it behaves as zwitterions.

(g) Waxes generally form protective covering in plants and animals. They protect living surface against bacteria and insect invasion.

(h) Fatty tissues around many vital organs protect against mechanical injury.

Classifications of lipids – Lipids are generally classified into three types. They are

(1) Simple lipids – Simple lipids are esters of fatty acids with alcohol. They are

(a) Neutral fat

(b) Waxes

(2) Compound lipids – Compound lipids on hydrolysis yields fatty acid, alcohol and other group. These are

(a) Phospholipid

(b) Glycolipid

(c) Lipoprotein

(3) Derived lipids – These are obtained on the hydrolysis of simple lipids and compound lipids. These are

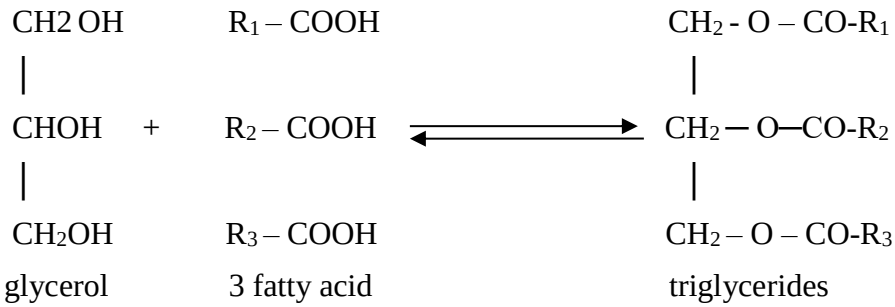
(a) Steroid

(b) Fatty acid

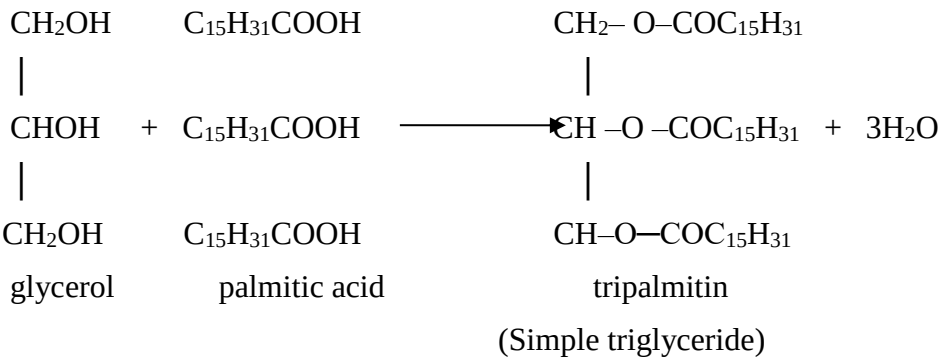
(c) Glycerol

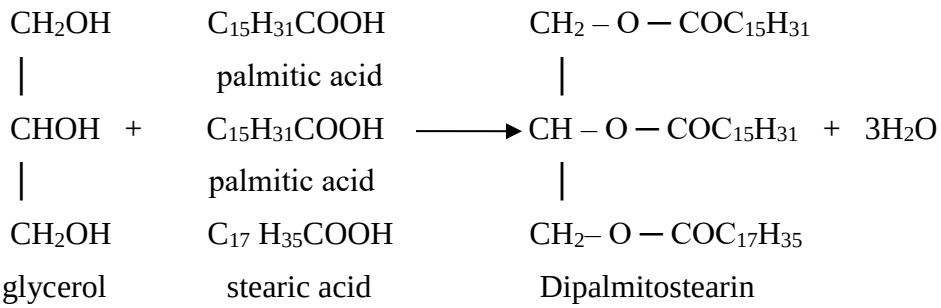
Neutral fats – These are the fatty acid ester of trihydroxyl alcohol glycerol. They are also known as triglycerides. Some are solid at ordinary room temperature while other are liquid. These are called oil. These are the main energy storing compounds in the body.

The triglyceride consists of trihydric alcohol i.e. glycerol are joined to three fatty acids by the ester linkage. Thus all the three hydroxyl groups of glycerol are esterified with fatty acids. If triglycerides are hydrolysis by lipase it yields fatty acids and glycerol.



If all the 3 fatty acids of triglycerides are identical then the fat is said simple triglycerides. If the fatty acids are different then the fat is said mixed triglyceride.



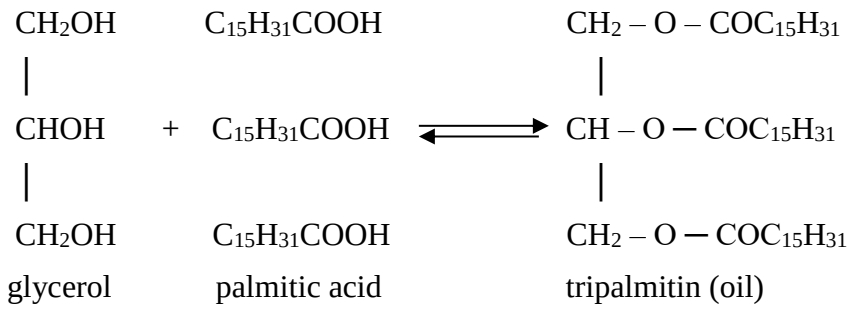


(Mixed triglyceride)

The fatty acids are of two types saturated fatty acid and unsaturated fatty acid. The saturated fatty acids have single bond for e.g. acetic acid, palmitic acid, stearic acid. The unsaturated fatty acid will have double bond for e.g. oleic acid, linoleic acid and Arachidonic acid. The unsaturated fats are more common in living organism then saturated fat.

Oils

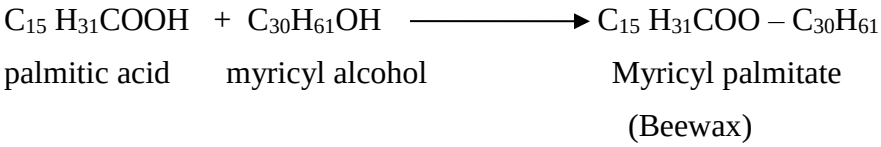
Oils are liquid fat. They are also esters of fatty acids and glycerol. They are remain liquid at room temperature. These are simple lipids.



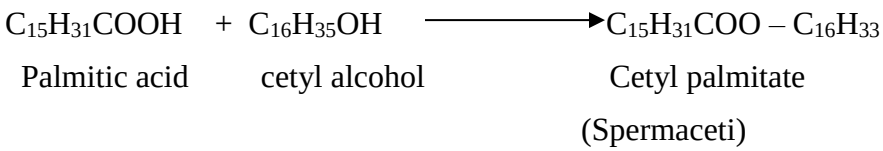
The fatty acids found in oil are mostly unsaturated have one or more double bonds. In oils if all the three fatty acids are similar, the oil is said simple oil, if the fatty acids are dissimilar, the oil is said mixed oil. The oil having low melting point. They are insoluble in water but soluble in organic solvents. Oils are found both in plants and animals. The oils found in plants are called vegetable oils for e.g. coconut oil, ground nut oil etc. The oils found in animals are called animal oils e.g. fish liver oils etc.

Waxes – Waxes are esters of fatty acid with higher monohydric alcohol for e.g. bee wax, spermaceti, lanoline etc.

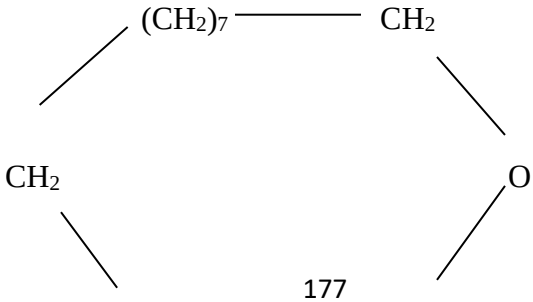
Bee wax



Spermaceti (sperm whale wax)



Ambretolide – It is composed of hydroxyl fatty acid and alcohol.



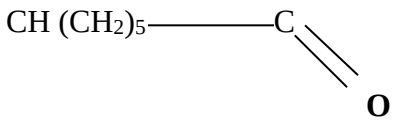


Fig 8.16: Ambretolide

***Lanoline* –** It is composed of palmitic, oleic or stearic acid ester of cholesterol.

Waxes have fully reduced hydrocarbon chain. They are insoluble in water and chemically inert. They have high melting point. They are not digested by enzyme but only split in hot alcoholic KOH. Waxes serves as water barriers in insects, birds and furred animals. Waxes also serve as protective coatings on fruits and leaves. Bee wax is used in sealing the honey comb cells to store the food for the winter season. Lanoline is useful in the manufacturing of cosmetic creams and ointments. Spermaceti are useful in the manufacturing of ointments, candles and polish.

Phospholipids

Phospholipids are formed by glycerol, phosphoric acid and fatty acid in which one of the fatty acid is replaced by phosphoric acid group. Due to the presence of phosphoric acid group they behave as polar lipids. They are hydrophilic in nature and are amphipathic. Phospholipids are present in brain and nervous tissues. It is present in varying amount of every living cell. They are present in cytoplasm and cell membranes. The important function is in both cell activity and cell permeability. It form important intermediate substance in the transport of lipids from intestine and then to liver. They are further divided into

(1) Lecithins

(2) Cephalins

(3) Plasmalogens

(4) Phosphoinositides

(5) Phosphospingosides

(1) ***Lecithins* –** It is esters of glycerol with fatty acids, in which two hydroxyl group of glycerol is esterified with two fatty acid and the third hydroxyl group of glycerol is esterified with phosphoric acid. The phosphoric group form ester with choline.

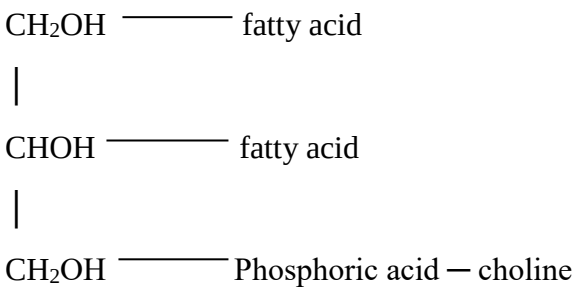


Fig 8.17: lecithin

Lecithins are widely distributed in cells and are the most abundant of animal tissue phospholipids. It is an important constituent of lipoprotein in chylomicrons. Dipalmaltoyl lecithin is an important of lecithin found in lungs. It prevents the adherence of the inner surface of the lungs due to surface.

(2) ***Cephalin*** **–** It consist of glycerol, fatty acid, phosphoric acid and ethanolamine. It is similar with lecithin but only differ that choline is replaced by ethanolamine.

CH_2OH — fatty acid
|
CHOH — fatty acid
|
CH_2OH phosphoric acid – $(NH_2CH_2CH_2OH)$
Ethanolamine

Fig 8.18: Structure of cephalin

(3) ***Plasmalogens*** **–** It has similar with lecithins and cephalins except that one of the fatty acid is replaced by a long chain aliphatic aldehyde or unsaturated ether.

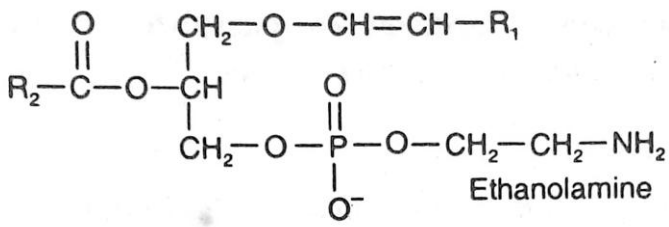


Fig 8.19: Structure of plasmologen

(4) ***Phosphoinositides*** **–** It is a cyclic hexahydroxy alcohol inositol is replaced by the base. In monophosphoinositide only one phosphate is attached to the alpha carbon atom while remaining two carbon atoms are attached to fatty acid. Diphosphoinositide has two phosphates attached to two alpha carbon atoms joined together by the inositol bridge. It is an important component of cell membranes. In this myoinositol is attached to phosphatidic acid. The phosphatidylinositol is break up into diacylglycerol and inositol triphosphate (Ip_3). This inositol triphosphate (Ip_3) act as second messenger in hormone action.

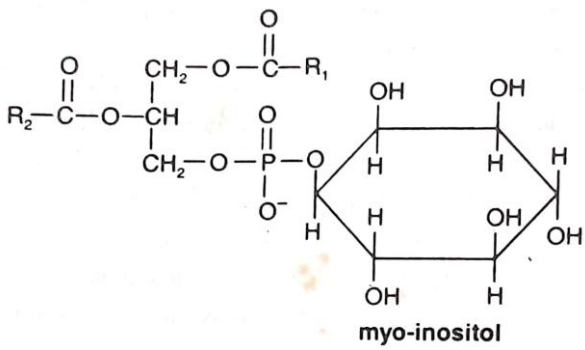


Fig 8.20: Structure of phosphatidylinositol

(5) ***Phosphospingosides or sphingomyelins*** – In phosphospingosides glycerol is replaced by an amino alcohol, "sphingosine". Sphingosine is attached by an amide linkage to a fatty acid to yield a substance known as ceramide. The alcoholic group of sphingosine is attached to phosphoryl choline to form sphingomyelin. Sphingomyelin are components of the myelin sheath and occur in abundance in brain and other nervous tissues.

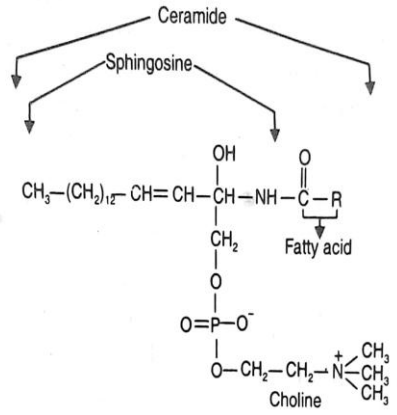


Fig 8.21: Structure of sphingomyelin

Glycolipids

Glycolipids are formed when sugar is attached to the high molecular weight fatty acids. They can be classified into two groups.

(1) **Cerebrodside –** These are formed by sphingosine, fatty acid and galactose sugar but no phosphoric acid or glycerol. The sphingosine is attached to the galactose by glycosidic linkage on its primary alcohol and fatty acid by an amide linkage on its primary amino group.

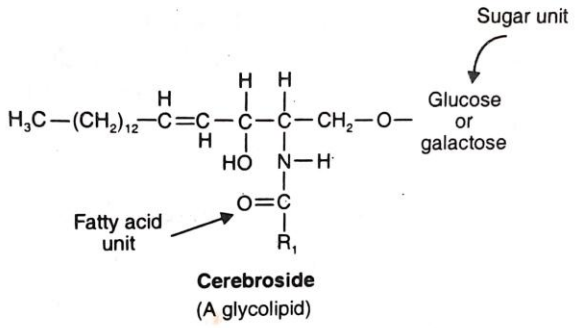


Fig 8.22: Structure of cerebroside

On the basis of length of fatty acid chain they are

(i) ***Oxynervon*** - It contain 24 carbon atom containing oxynervonic acid

(ii) ***Nervon*** - It contain nervonic acid

(iii) ***Kerasin*** - It contain lignoceric acid

(iv) ***Cerebron*** - It contains a 2-hydroxy derivative of lignoceric acid called cerebronic acid

(v) ***Behenon*** - It contain behenic acid

Cerebroside occurs in large amount in the white matter of the brain and in the myelin sheath of axons.

(2) Gangliosides - It consist of ceramide (an amide of sphingosine with fatty acid) carbohydrate and sialic acid. The carbohydrate is attached to ceramide by glycosidic bond to 2, 3, or 4 monosaccharide unit. In brain gangliosides contain N-acetylneuraminic acid as sialic acid. These compounds are more commonly occur in nerve ending and play a role in synaptic transmission. It is also responsible for blood group specificity and tissue and organ specificity.

Lipoprotein - Lipoprotein are complex of lipids joined to proteins. Lipoprotein acts as transport vehicles for lipid circulation. They are of five types

1. Chylomicrons
2. Very low density lipoproteins
3. Low density lipoproteins
4. High density lipoproteins
5. Free fatty acid albumin complexes.

Steroids – Steroids are a group of lipids having four fused ring structure called cyclopentano per hydrophenanthrene nucleus. The three will be 6-membered carbon ring and one will be five membered carbon ring. All the rings were fully saturated with hydrogen. Steroids do not contain fatty acids. The important steroids are cholesterol, ergosterol, testosterone, androsterone, oestrone, cortisol etc.

Cholesterol - Cholesterol are the animal origin fat such as egg yolk, meat, livers & brain. They are mainly occurs in bile, brain, spinal cord, skin and adrenal gland. It consists of 1,2 cyclopentanoperhydrophenanthrene nucleus. It has three 6 -membered carbon ring(hexagons) and one five membered carbon ring (pentagon). It has hydroxyl group at C_3 and double bond between C_5 and C_6. It has 8 carbon side chain attached to C_{17}. It has two methyl group (CH_3) at C_{10} and C_{13}.

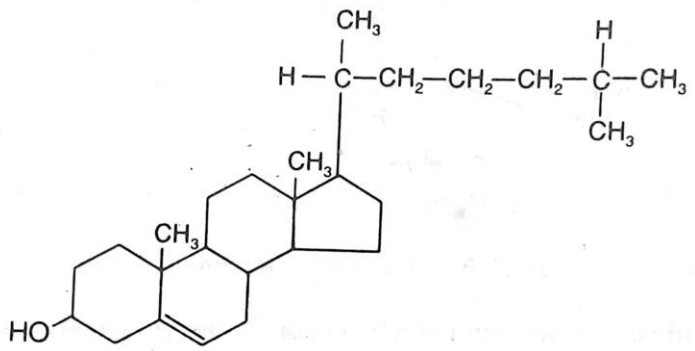


Fig.8.23 Structure of cholesterol

Cholesterol is present in tissues and in plasma lipoprotein either as free cholesterol or combined with a long chain fatty acid as cholesterol ester. The greater part of the cholesterol of the body arises by synthesis where as only about 0.3g/l is provided by the average diet. Cholesterol serves as an insulating covering over nerves during the transmission of nerve impulse as it is a poor conductor of heat and electricity. Cholesterol serves important function in cellular membrane structure and function, synthesis of bile acids, vitamin D. It is a precursor of 5 major steroid hormones for e.g.

testosterone, oestrone, progesterone, glucocorticoids and mineralocorticoid. It is synthesized in many tissues from acetyl co-A and is ultimately eliminated from the body in the bile as cholesterol bile salts.

SAQs 1.

Complete the following sentences by inserting appropriate words in the blanks.

(i) The Carbohydrates containing a functional aldehyde group are known as----------

(ii) Six carbon membered ring is called ----------

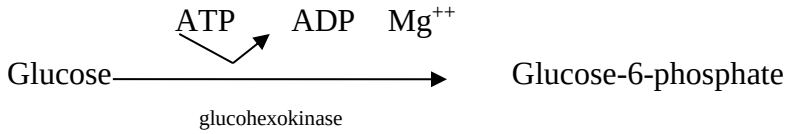
(iii) Functional proteins are ----------

(iv) Saturated fatty acids contain ----------

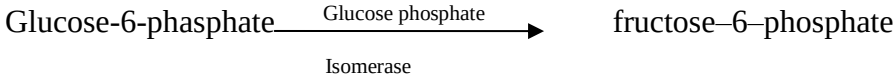
8.3 METABOLISM OF CARBOHYDRATES–GLYCOLYSIS AND CITRIC ACID CYCLE, GLUCONEOGENSIS, PENTOSE PHOSPHATE PATHWAY

Glycolysis – Glycolysis is a Greek word mean glyco = glucose and lysis = to break down. So the breakdown of glucose or carbohydrate is called glycolysis. The process takes place in absence or in presence of oxygen and inside the cytoplasm of cell. In this process a single molecule of glucose is broken down into two molecule of pyruvic acid. The entire biochemical reaction takes place in a series of sequential reaction which was worked out by three German scientists Embden, Mayerhoff and Parnas. Therefore it is also called EMP pathway. It takes place in following steps.

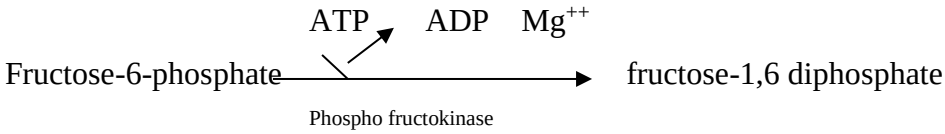
(i) In the first step glucose is phosphorylated by the ATP and Mg^{++} in the presence of enzyme glucohexokinase to form glucose–6–phosphate.



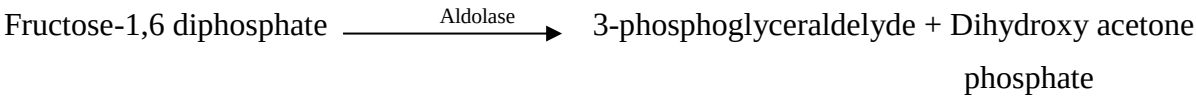
(ii) Glucose-6-phosphate is converted into fructose-6-phosphate by the enzyme glucose phosphate isomerase.



(iii) Fructose-6-phosphate is then phosphorylated by the ATP and Mg^{++} and in the presence of phosphofructokinase enzyme to form fructose 1,6diphosphate.

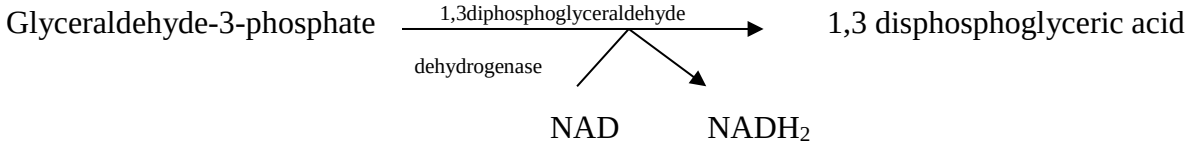


(iv) Fructose-1,6diphosphate is broken down into 3-phosphoglyceraldehylde and dihydroxy acetone phosphate by the enzyme aldolase. These two substances are interchangeable in the presence of triose phosphateisomerase.

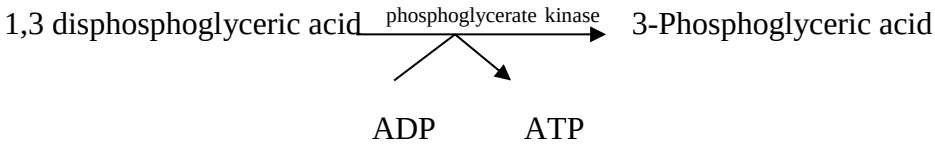


(v) The two molecule of 3–phospholyceraldehyde is phosphorylated by H_3PO_4 and in the presence of enzyme transphosphatase to form 1,3-diphosphoglyceraldehyde.

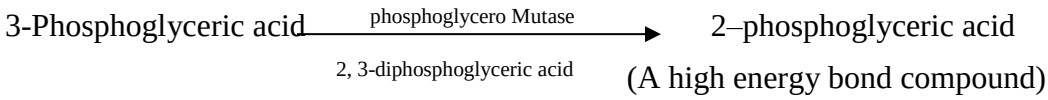
(vi) The 1,3-diphosphoglyceraldehyde in presence of nicotinamide adenine dinucleotide (NAD) as hydrogen acceptor and inorganic phosphate and in the presence of glyceraldehyde-3-phosphate dehydrogenase enzyme converted into 1,3 diphosphoglyceric acid.



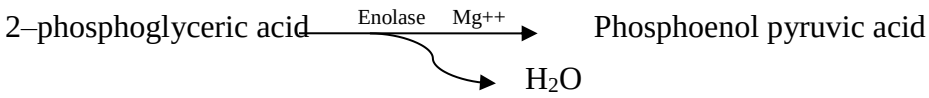
(vii) The 1,3 diphosphoglyceric acid is converted into 3 phosphoglyceric acid by the enzyme phosphoglycerate kinase and Mg^{++}



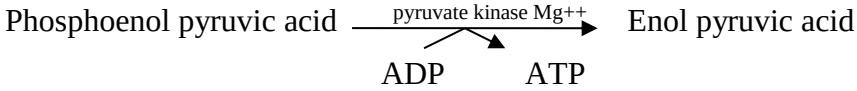
(viii) The 3-phosphoglyceric acid is converted into 2–phosphoglyceric acid in the presence of enzyme phosphoglycero mutase. This reaction requires 2, 3-diphosphoglyceric acid as co-factor



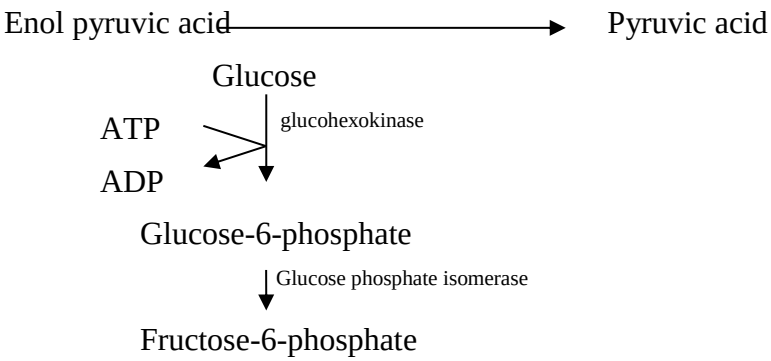
(ix) The 2-phosphoglyceric acid is converted into a high energy bond compound phosphoenol pyruvic acid in the presence of enzyme enolase and Mg^{++}. There are a removal of H_2O.



(x) The high energy bond in phosphoenol pyruvic acid is transfer its energy to ADP in the presence of enzyme pyruvate kinase and Mg^{++} to form enol pyruvic acid and ATP.



(xi) The enol pyruvic acid is automatically converted into pyruvic acid.



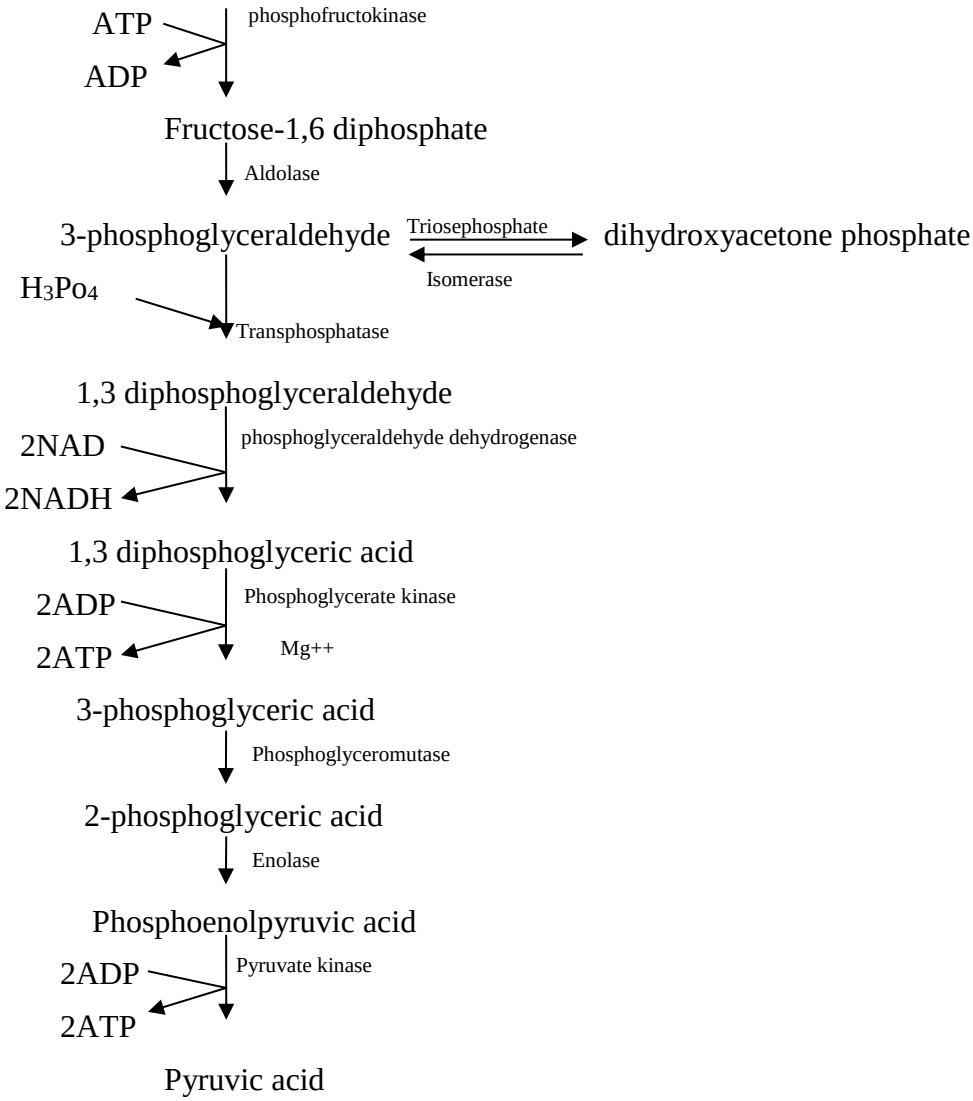
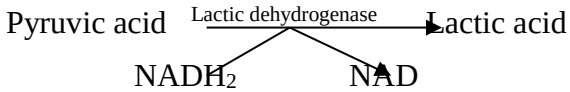


Fig 8.24: Pathway of glycolysis or EMP pathway

The pyruvic acid is the main end product of glycolysis in those cells or tissues in which oxygen are supplied in sufficient (aerobic condition) quantities. If oxygen supply are not in sufficient quantity (i.e. anaerobic condition) then pyruvic acid is reduced to lactic acid under the influence of enzyme lactic dehydrogenase.



Energetic of glycolysis – During glycolysis one molecule of glucose and 2 ATP are used of which one is used between glucose and glucose 6- phosphate and other between fructose-6-phosphate and fructose 1,6 diphosphate. There is synthesis of 4 ATP of which two ATP are synthesis between 1,3 diphosphoglyceric acid and 3-phospholyceric and between phosphoenol pyruvic acid and pyruvic acid. So the net gain will be only 2 ATP in anaerobic respirations. While in aerobic respiration 6 ATP is formed from $2NADH_2$. So 8 ATP is formed in aerobic respiration.

Citric acid cycle or **Kreb's cycle** – Kreb's cycle was first worked out by English biochemist Hans Krebs in pigeon breast muscle in 1937. Later Kreb's and Kornberg reported it in other plants and animals cells. In the honour of the discoverer this cycle was called Krebs cycle. However it is also

called citric acid cycle or tricarboxylic acid (TCA) cycle. It is called as citric acid cycle because citric acid is 1st stable product. It is called as tricarboxylic acid (TCA) because citric acid has three carboxylic group or there are three type of carboxylic compound such as six carbon compound citric acid, five carbon compound i.e. α- ketoglutaric acid and four carbon compound succinic acid, fumaric acid and malic acid are formed.

The Kreb cycle take place in the mitochondrial matrix. In the presences of oxygen pyruvic acid which is the end product of glycolysis 1st form Acetyl co-A by reacting with a sulphur containing co-enzyme A. This co-enzyme is catalyzed by enzyme complex pyruvic dehydrogenase. One molecule of Co_2 is given out.

$$\underset{\text{Pyruvic acid}}{CH_3COCOOH} + \underset{\text{Co-enzyme}}{H\text{-}S\text{–}Co\text{–}A} \xrightarrow{\text{Pyruvic dehydrogenase}} \underset{CO_2}{} \quad \underset{\text{Acetyl-co –A}}{CH_3CO - S - COA}$$

The Acetyl Co–A cross the outer and inner mitochondrial membrane and reaches to the mitochondrial matrix. In mitochondrial matrix acetyl Co-A react with a four carbon containing compound oxalo acetic acid to form citric acid. The acetyl Co-A is the substance which join the glycolysis to Kreb cycle. On entering into matrix it is completely oxidise to CO_2 and H_2O. So in Kreb cycle there is a production of ATP, CO_2 and H_2O.

In the Kreb cycle following steps take place are as follows –

(i) The Acetyl Co–A react with oxalo acetic acid to form a six carbon compound citric acid. This reaction is catalyzed by an enzyme citric synthetase. In this reaction oxalo acetic acid acts as catalyst.

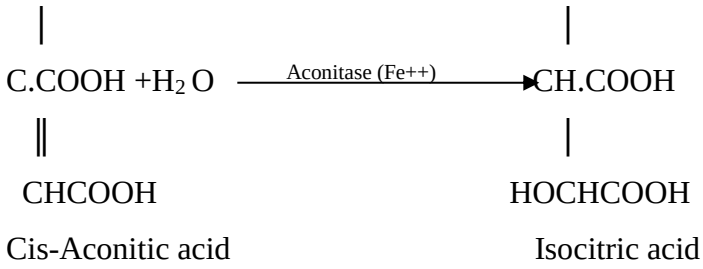
$$\underset{\text{Acetyl Co- A}}{CH_2\text{-}CO\text{-}S\text{–}CO\text{–}A} + \underset{\text{Oxalo acetic Acid}}{CH_2COOH\,(COCOOH)} \xrightarrow{\text{Citric synthetase}} \underset{\text{Citric acid}}{CH_2COOH\,(OH\text{-}C\text{-}COOH)\,CH_2COOH} + \text{Co-A–SH}$$

(ii) The citric acid undergoes dehydration in the presence of enzyme aconitase and Fe^{++} to form cis–Aconitic acid.

$$\underset{\text{Citric acid}}{CH_2COOH\,(OH\text{-}C\text{-}COOH)\,CH_2COOH} \xrightarrow{\text{Aconitase (Fe++)}} \underset{\text{Cis-Aconitic acid}}{CH_2COOH\,(C.COOH)\,CHCOOH} + H_2O$$

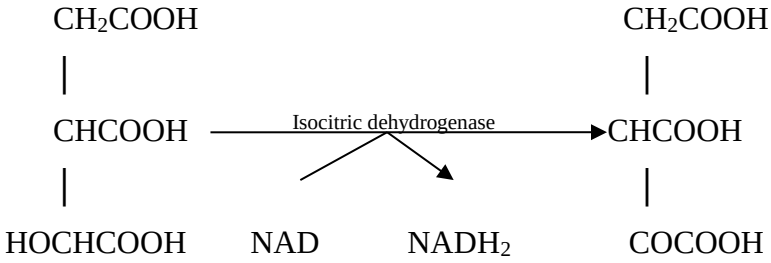
(iii) The cis-Aconitic acid under goes hydration to form isocitric acid in the presence of enzyme aconitase and Fe^{++} ions.

$$CH_2COOH \qquad CH_2COOH$$



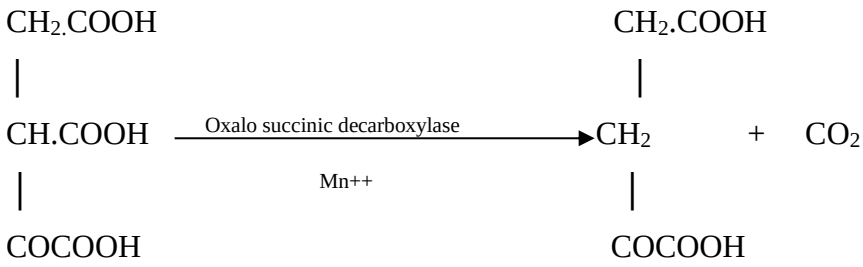
Cis-Aconitic acid Isocitric acid

(iv) The isocitric acid undergoes dehydrogenated to form oxalo succinic acid in the presence of isocitric dehydrogenase and NAD.



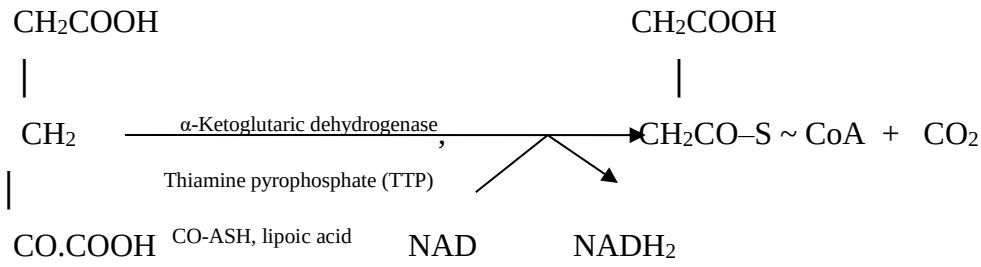
Isocitric acid Oxalo succinic acid

(v) The oxalo succinic acid is decarboxylated to form α-ketoglutaric acid in the presence of enzyme oxalo succinic decarboxylase and Mn^{++} ions.



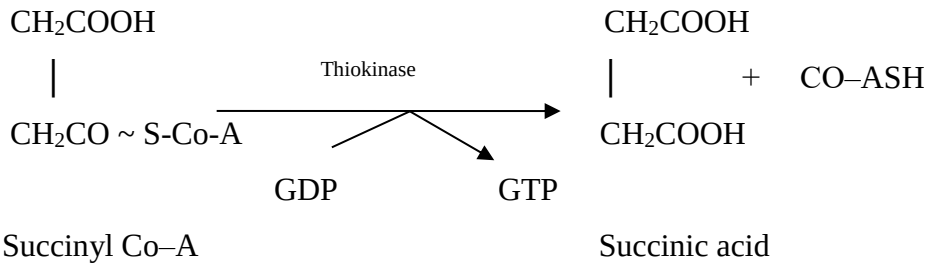
Oxalo succinic acid α- ketoglutaric acid

(vi) The α-ketoglutaric acid is oxidatively decarboxylated in the presence of an enzyme α-ketoglutaric dehydrogenase, thiamine pyrophosphate (TPP), Co-enzyme A, lipoic acid and NAD to form succinyl Co–A.



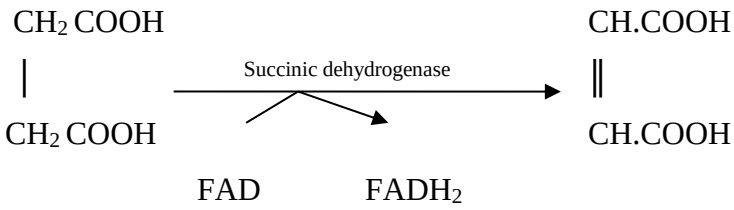
α-ketoglutaric acid Succinyl Co-A

(vii) The succinyl Co–A possesses high energy thiol group and in presence of thiokinase and guanosine diphosphate (GDP) and inorganic phosphate form guanosine triphosphate (GTP) and succinic acid.



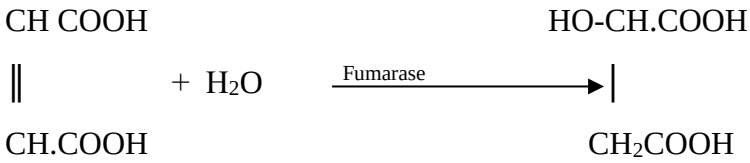
Succinyl Co–A Succinic acid

(viii) The succinic acid undergoes dehydrogenated by the enzyme succinic dehydrogenase to form fumaric acid. This dehydrogenation take place in presence of flavin adenine dinucleotide (FAD), which act as prosthetic group.



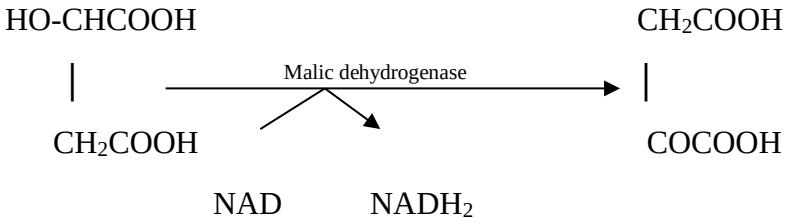
Succinic Acid Fumaric acid

(ix) The fumaric acid undergoes hydration to form malic acid in the presence of enzyme fumarase.



Fumaric Acid Malic acid

(x) The malic acid is dehydrogenated to form oxalo acetic acid in the presence of malate dehydrogenase and NAD.



Malic acid Oxalo acetic Acid

Energertics of Kreb cycle – In Krebs cycle energy is generated at six places are as follows.

(i) The first site is between conversions of pyruvic acid to acetyl co- A, where one molecule of NAD is used. This gives rise to 3 ATP molecules through electron transport system (ETS).

(ii) The second site is between isocitric acid and oxalo succinic acid, where also one molecule of NAD is used, which generate 3 ATP molecules.

(iii) The third site is between α- ketoglutaric acid and succinyl Co –A. One molecule of NAD is used, generate 3 ATP molecule.

(iv) The fourth site is between Succinyl Co–A and succinic acid. One molecule of GDP is used, which generate 1 ATP molecule.

(v) The fifth site is between succinic acid and fumaric acid. One molecule of FAD is used, generating 2 ATP molecules.

(vi) The six site is between malic acid and oxalo acetic acid. One molecule of NAD is used, generate 3 ATP molecule.

From one molecule of pyruvic acid 15 ATP are produced. As there are two molecule of pyruvic acid are formed during glycolysis which produced 30 ATP.

Under aerobic respiration which includes complete oxidation of one molecule of glucose through glycolysis and Krebs cycle which may produce 38 molecules of ATP.

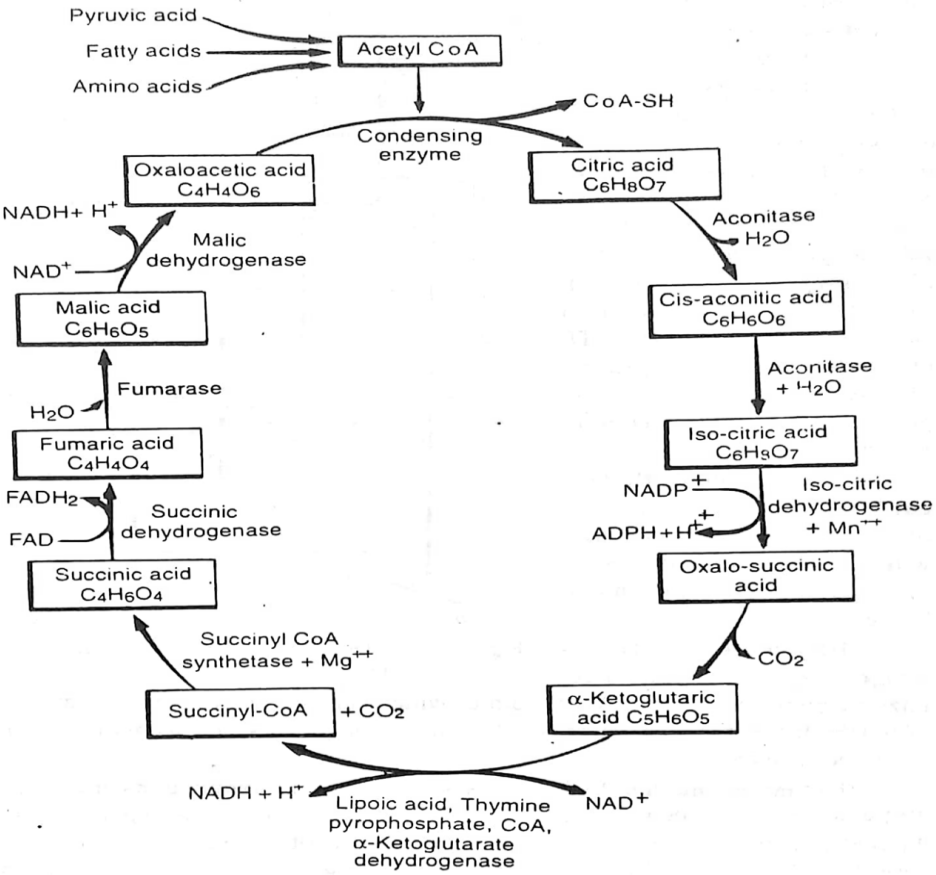


Fig .8.24: Krebs cycle or Tricarboxylic acid (TCA) cycle

Gluconeogenesis

Gluconeogenesis is the process of formation of glucose from non-carbohydrate precursor. The non-carbohydrate precursors are lactate, amino-acid, glycerol, pyruvate. The lactate is formed in the active muscle, when rate of glycolysis is more than metabolic rate of citric acid and respiratory chain. Amino-acid is formed from protein present in diet and during starvation from the breakdown

of protein in skeletal muscle. The hydrolysis of triacylglycerol in the fat cell to yield glycerol and fatty acid. The glycerol can be converted into glucose but the fatty acid cannot be converted into glucose in animal. This metabolic pathway is very important because certain tissue such as brain require high amount of glucose as a primary fuel. The daily requirement of glucose for brain in a typical adult is about 120 gm and for whole body glucose is required 160 gm. The 20 gm of glucose is present in body fluid and it readily available from the glycogen, a storage form of glucose is approximately 190gm. In longer period of starvation, glucose must be formed from non-carbohydrate sources for survival. Gluconeogenesis is also important during period of intense exercise.

The major site of gluconeogenesis takes place in liver. It also occurs in the cortex of the kidney. But the total amount of glucose formed in kidney is $1/_{10}$ (one tenth) of that formed in liver because of the kidney smaller mass. A very little amount of gluconeogenesis also takes place in the brain, skeletal muscle or heart muscle. The gluconeogenesis in the liver and kidney helps to maintain the glucose level in the blood so that brain and muscle can extract sufficient glucose from it to meet their metabolic demands. Gluconeogenesis is under the control of adrenal cortex hormone – cortisol or corticosterone.

Formation of glucose from pyruvate

(i) In the first steps the conversion of pyruvate into phospho-enol pyruvic acid which cannot occur by the presence of enzyme pyruvate kinase. So the phosphorylation of pyruvate is achieved by a no of reaction that takes place both in the cytoplasm and in mitochondria of the liver cell. The pyruvate will enter into the mitochondria and in the presence of pyruvate carboxylase enzyme which become active only in presence of acetyl-Co-A it will form oxalo acetic acid.

$$\text{Pyruvate} + CO_2 + ATP \xrightarrow[\text{Acetyl co A}]{\text{Pyruvate carboxylase}} \text{Oxalo acetic acid} + ADP + iP$$

(ii) The oxalo acetate in the presence of malate dehydrogenase and $NADH_2$ it will give to malate.

$$\text{Oxalo acetate} + NADH_2 \xrightarrow{\text{Malate dehydrogenase}} \text{Malate} + NAD$$

(iii) The malate leave the mitochondria and came into the cytoplasm where it is re-oxidizes by NAD and in the presence of malate dehydrogenase it will form extra-mitochondrial oxalo-acetate.

$$\text{Malate} + NAD \xrightarrow{\text{Malate dehydrogenase}} \text{Oxalo acetate} + NADH_2$$

(iv) The oxalo acetate in presence of phospho-enol pyruvate carboxy-kinase enzyme and GTP it will form phospho enol pyruvate.

$$\text{Oxalo acetate} + GTP \xrightarrow[\text{carboxy kinase}]{\text{Phospho-enol pyruvate}} \text{Phospho-enol pyruvate} + GDP + CO_2\uparrow$$

(v) The phospho-enol pyruvate in presence of Enolase and Mg^{++} it give rise to 2-phosphoglycerate.

$$\text{Phospho-enol pyruvate} \xrightarrow{\text{Enolase } Mg^{++}} \text{2-Phosphoglycerate}$$

(vi) The 2-phosphorglycerate in presence of phosphoglycerol mutase enzyme it will give rise to 3-Phosphoglycerate.

2-Phosphoglycerate $\xrightarrow{\text{phosphoglycerol mutase}}$ 3-Phosphorglycerate

(vii) The 3-phosphoglycerate in presence of phosphoglyceric kinase enzymes & ATP it will form 1, 3diphosphoglycerate.

3-Phosphorglycerate + ATP $\xrightarrow{\text{Phosphoglyceric kinase}}$ 1,3diphosphoglycerate

(viii) The 1,3diphosphoglycerate will convert into 3-phosphoglyceraldehydes in the presence of enzyme phosphoglyceraldehyde dehydrogenase and ADP and $NADH_2$.

1, 3 diphosphoglycerate $\xrightarrow[\text{dehydrogenase}]{\text{Phosphoglyceraldehyde}}$ 3-phosphoglyceraldehydes + ATP + NAD + ADP+$NADH_2$

(ix) The 3-phosphoglyceraldehydes in presence of enzyme aldolase it will form fructose 1,6diphosphate.

3-Phosphoglyceraldehyde $\xrightarrow{\text{Aldolase}}$ Fructose 1,6diphosphate

(x) The fructose 1,6diphosphate is converted into fructose-6-phosphate in the presence of enzyme fructose diphosphatase and Mg^{++}. This enzyme is strongly inhibited by negative modulator AMP but stimulated by the positive modulator ATP.

Fructose 1,6 disphosphate +H_2O $\xrightarrow[Mg^{++}]{\text{Fructose diphosphatase}}$ Fructose-6-phosphate + iP

(xi) The fructose-6-phosphate is changes into glucose-6-phosphate in the presence of enzyme phosphogluco isomerase.

Fructose-6-phosphate $\xrightarrow{\text{Phosphogluco isomerase}}$ Glucose-6-phosphate

(xii) The glucose-6-phosphate is converted into glucose in the presence of enzyme glucokinase.

Glucose-6-phosphate + H_2O $\xrightarrow{\text{Glucokinase}}$ Glucose + iP

So the formation of each molecule of glucose from pyruvate needs 4 ATP molecules and 2 GTP are used. Gluconeogenesis is regulated at two major points.

(i) The carboxylation of pyruvate by pyruvate carboxylase which is stimulated by the allosteric effect or Acetyl Co – A.

(ii) The diphosphorylation of fructose-1,6-diphosphate by fructose diphosphatase which is inhibited by AMP but stimulated by citrate.

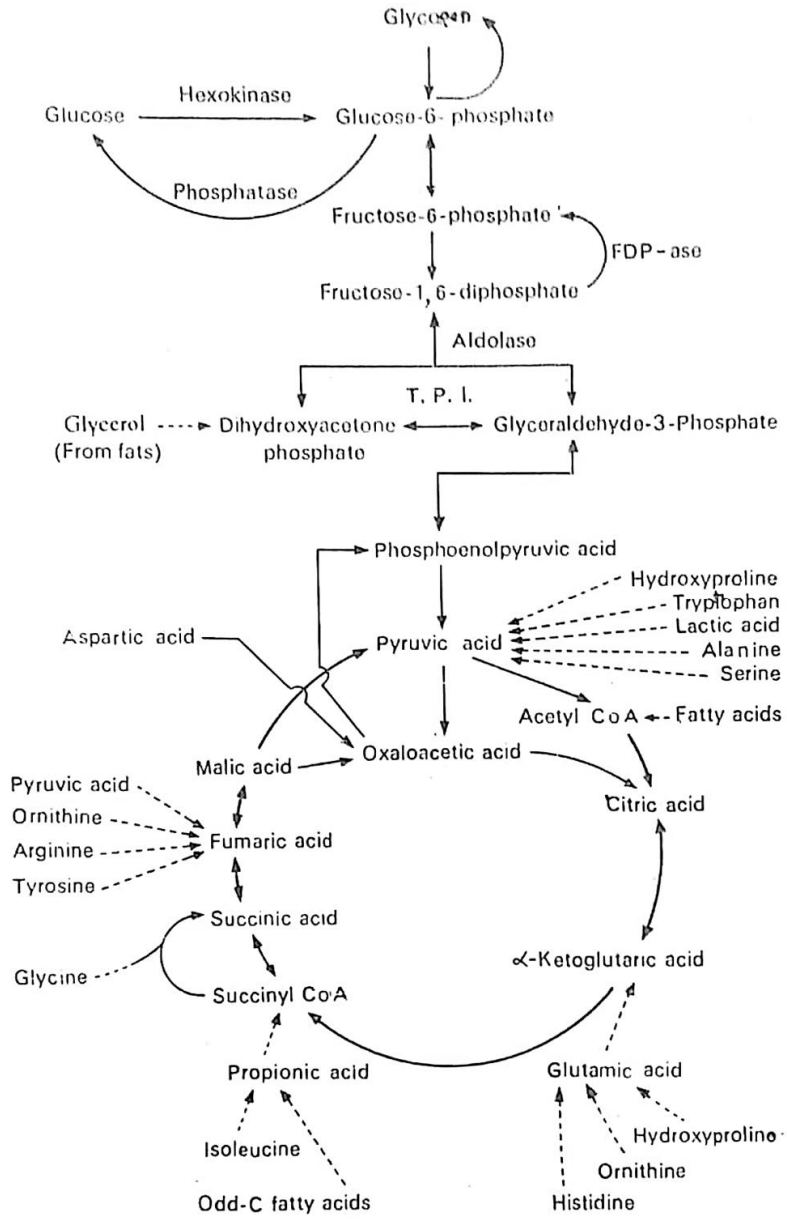


Fig 8.25: Pathway of gluconeogenesis

Glucose

ATP / ADP — glucohexokinase

Glucose-6-phosphate

Glucose phosphate isomerase

Fructose-6-phosphate

ATP / ADP — phosphofructokinase

Fructose-1,6 diphosphate

Aldolase

3-phosphoglyceraldehyde ⇄ (Triosephosphate) dihydroxyacetone phosphate

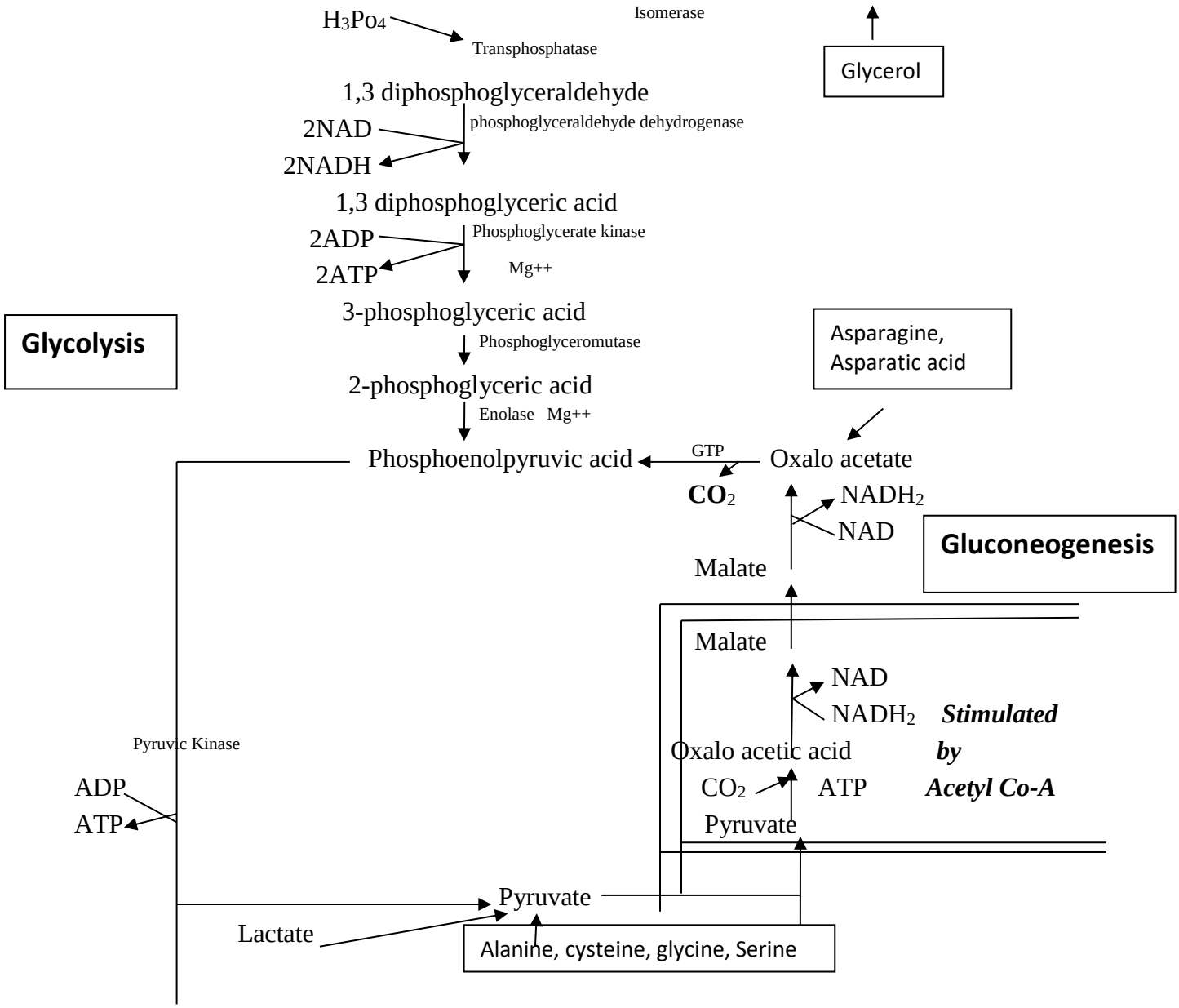


Fig. 8.26: Pathway of gluconeogenesis and showing entry of lactate, some amino acid and glycerol

Pentose Phosphate Pathway– This is an alternative pathway of glucose metabolism, which take place in liver, adrenal-cortex, adipose tissue, RBC and lactating mammary glands. This pathway occurs in the cytoplasm of cell. This alternative pathway forms the shorter route for complete oxidation of glucose as compared to combined pathway of glycolysis and citric acid cycle. The energy produced by this pathway is equal to the produced by the combined pathway of glycolysis and kreb cycle. In this alternative pathway glucose-6-phosphate is converted into CO_2 and ribulose-5-phosphate (a pentose). Hence the entire sequence is called a pentose phosphate pathway. Because the pathway is diverted from glucose-6-phosphate, it is also called hexose monophosphate shunt (HMS). The HMS pathway is widely distributed in plants, animals and bacteria and is responsible for some important metabolic function.

The HMP pathway starts from glucose. Glucose is activated by the ATP and enzyme glucokinase to form glucose-6-phosphate. Glucose-6-phosphate is dehydrogenated in the presence of enzyme glucose-6-phosphate dehydrogenase and NADP to form 6-phosphogluconolactone. The 6-phosphogluconolactone add a water molecule and in presence of enzyme lactonase to form 6-phosphogluconate. The 6-phosphogluconate in presence of enzyme 6-phosphogluconate dehydrogenase, NADP, Mg^{++}, Ca^{++} and Mn^{++} to form 3-keto-6-phosphogluconic acid. The 3-keto-6-phosphogluconoic acid is decarboxylated to form ribulose-5-phosphate. The ribulose-5-phosphate in the presence of enzyme ribose-5-phosphate isomerase and ribulose-5-phosphate epimerase is converted into ribose-5-phosphate and xylulose-5-phosphate respectively. The ribose-5-phosphate and xylulose-5-phosphate in presence of enzyme transketolase, Mg^{++} and thiamine pyrophosphate (TPP) to form glyceraldehyde-3-phosphate and sedoheptulose-7-phosphate. The glyceraldehydes-3-phosphate and sedoheptulose-7-phosphate is catalysed by enzyme transaldolase to form fructose-6-phosphate and erythrose-4-phosphate. The fructose-6-phosphate is converted into glucose-6-phosphate. The xylulose-5-phosphate and erythrose-4-phosphate in presence of enzyme transketolase & Mg^{++} to form glyceralelehyde-3-phosphate and fructose-6-phosphatase. The fructose-6-phosphate is converted into glucose-6-phosphate. The glyceraldehydes-3-phosphate is converted into dihydroxyacetone phosphate by the presence of triose–phosphate isomerase. The glyceraldehyae-3-phosphate and dehydroxyacetone in presence of enzyme aldolase to form fructose-1,6 diphosphate. The fructose 1,6 diphosphate is converted into fructose-6-phosphate. The fructose-6-phosphate is converted into glucose-6-phosphate.

Energertics of HMP pathway – The energy is generated at two sites.

(1) Between glucose-6-phosphate and 6-phosphogluconolactone, six NADP is used

(2) Between 6-phosphogluconate and 3-keto-6-phosphogluconic acid, six NADP is used.

If six molecule of glucose enter into the cycle, of which five molecules of glucose can be regenerated. Only one mole of glucose is oxidised and this will give to $12NADPH_2$. From Electron transport chain one NAD give rise 3ATP. So 12 NADP give raise 36 ATP. One ATP is used in initial hexokinase reaction. So the net gain will be 35 mole of ATP.

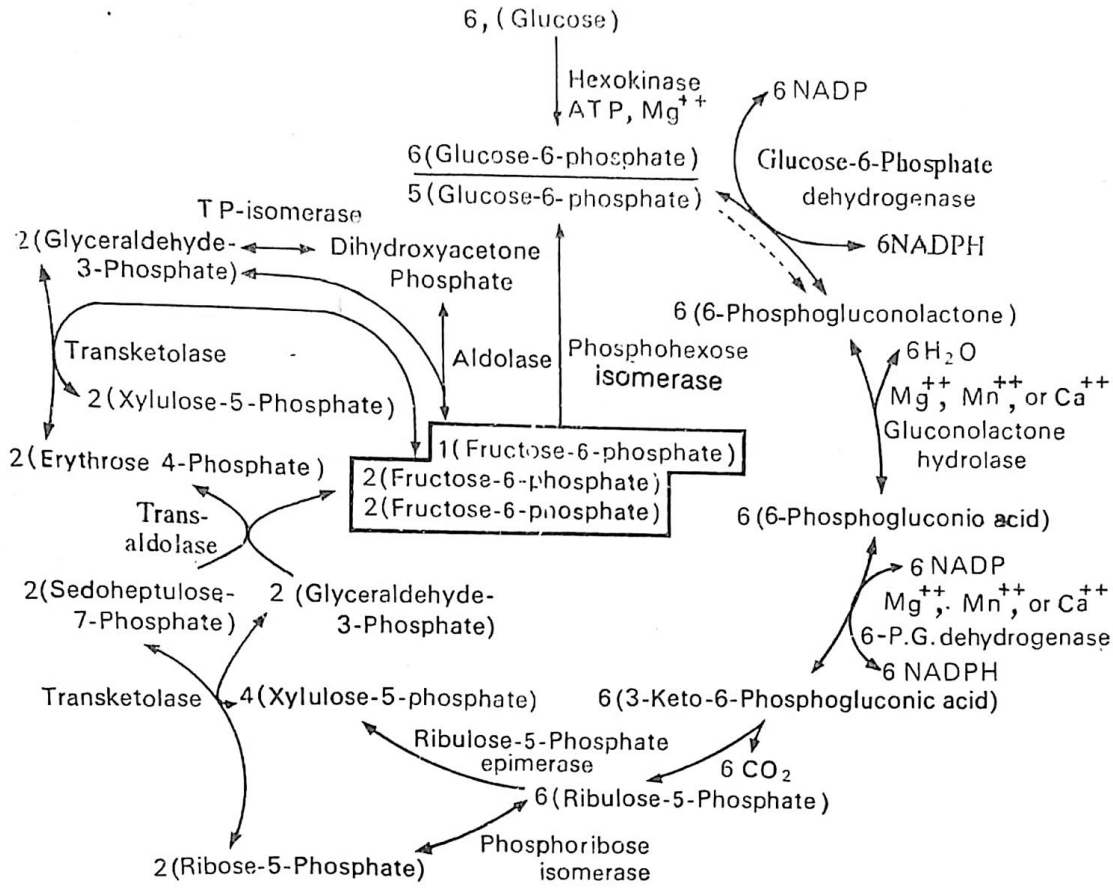


Fig 8.27: Reaction of Hexose monophosphate shunt

Significance of Pentose Phosphate Pathway or HMP pathway

(1) The HMP pathway produces $NADPH_2$. This is very useful for various synthetic pathways which require H_2.

(2) Ribose-5-phosphate produce building material utilized for various biological component e.g. DNA, RNA.

SAQs 2.

Complete the following sentences by inserting appropriate words in the blanks.

(i) Reverse process of glycogenesis is called ----------

(ii) Conversion of glucose into glycogen ----------

(iii) The process of deriving glucose from fat and proteins is known as ----------

(iv) Oxidative phosphorylation in a cell takes place in ----------

8.4 SUMMARY

In this unit there is description of structure and biological importance of carbohydrates, proteins and lipids in very detailed manner. In this unit there also classification of carbohydrate, protein, lipid.

This unit also contain metabolism of carbohydrate which includes glycolysis, citric acids cycle, gluconeogensis, pentose phosphate pathway in very detailed manner.

8.5 TERMINAL QUESTION

Q1 Explain carbohydrate and its distribution.

Q2 Explain citric acid cycle.

Q3 Explain Pentose Phosphate Pathway.

8.6 ANSWERS

SAQ 1

(i) Aldose

(ii) Pyranose

(iii) Enzyme

(iv) Single Bond

SAQ 2

(i) Glycogenolysis

(ii) Glycogenesis

(iii) Gluconeogenesis

(iv) Mitochondria

Terminal question

1. Carbohydrate consists of carbon, hydrogen and oxygen. The hydrogen and oxygen are found in 2:1 ratio. Carbohydrates are widely distributed both in plant and animal cells. In plants they are produced by the photosynthesis and are present in the form of cellulose in wood and starch in cereals, roots and tubers, cane-sugar and milk sugar. In animal cells carbohydrate are present in the form of glucose and glycogen which serve as an important source of energy

for vital activities. Some carbohydrate have highly specific function e.g. galactose in certain lipids, ribose in the nucleo–protein of the cell and the lactose of milk. Carbohydrates may be defined chemically as aldehyde or ketone derivative of the polyhydric alcohol or as compound that yields these derivatives on hydrolysis.

2. Kreb's cycle was first worked out by English biochemist Hans Kreb in pigeon breast muscle in 1937. Later Kreb's and Kornberg reported it in other plants and animals cells. In the honour of the discoverer this cycle was called Kreb cycle. However it is also called citric acid cycle or tricarboxylic acid (TCA) cycle. It is called as citric acid cycle because citric acid is 1st stable product. It is called as tricarboxylic acid (TCA) because citric acid has three carboxylic group or there are three type of carboxylic compound such as six carbon compound citric acid, five carbon compound i.e. α- ketoglutaric acid and four carbon compound succinic acid, fumaric acid and malic acid are formed.

The Kreb cycle take place in the mitochondrial matrix. In the presences of oxygen pyruvic acid which is the end product of glycolysis 1st form Acetyl co-A by reacting with a sulphur containing co-enzyme A. This co-enzyme is catalyzed by enzyme complex pyruvic dehydrogenase. One molecule of CO_2 is given out.

$$\underset{\text{Pyruvic acid}}{CH_3COCOOH} + \underset{\text{Co-enzyme}}{H\text{-}S\text{–}Co\text{–}A} \xrightarrow{\text{Pyruvic dehydrogenase}} \underset{\text{Acetyl-co –A}}{CH_3CO - S - COA} + \underset{}{CO_2}$$

The Acetyl Co–A cross the outer and inner mitochondrial membrane and reaches to the mitochondrial matrix. In mitochondrial matrix acetyl Co-A react with a four carbon containing compound oxalo acetic acid to form citric acid. The acetyl Co-A is the substance with join the glycolysis to Kreb cycle. On entering into matrix it is completely oxidise to CO_2 and H_2O. So in Kreb cycle there is a production of ATP, CO_2 and H_2O.

3.– This is an alternative pathway of glucose metabolism, which take place in liver, adrenal-cortex, adipose tissue, RBC and lactating mammary glands. This pathway occurs in the cytoplasm of cell. This alternative pathway forms the shorter route for complete oxidation of glucose as compared to combined pathway of glycolysis and citric acid cycle. The energy produced by this pathway is equal to the produced by the combined pathway of glycolysis and kreb cycle. In this alternative pathway glucose-6-phosphate is converted into CO_2 and ribulose-5-phosphate (a pentose). Hence the entire sequence is called a pentose phosphate pathway. Because the pathway is diverted from glucose-6-phosphate, it is also called hexose monophosphate shunt (HMS). The HMS pathway is widely distributed in plants, animals and bacteria and is responsible for some important for some important metabolic function.

UNIT-9 BIOSYNTHESIS OF AMINO ACIDS

9.1 INTRODUCTION

Amino acids are the molecule containing two functional groups i.e. amino group (NH_2) and a carboxylic group (COOH) and a side chain that are specific to each amino acid. The amino acids are the building block of different types of proteins. They are linked by covalent peptide bond. There are nearly 20 amino acids are found in living organisms. Now two more amino acids are also discovered are selenocysteine and pyrrolysine. So there are 22 amino acids an incorporated in synthesis of protein.

There are certain amino acids, which is required by the body and are not synthesized in the body. So they are supplied in the body from outside. Such types of amino acids are called **essential** or **indispensible amino acids**. There are also certain amino acids are required by the body for the formation of hormones, purines, enzymes, neurotransmitters and other compounds can be formed from metabolic intermediates by transamination, using the amino nitrogen from other amino acids by the body and are not needed to be present in diet are called **non-essential** or **dispensable amino acids**.

Essential amino acids	Non- Essential amino acids
Histidine	Alanine
Isoleucine	Arginine
Leucine	Asparagine
Methionine	Aspartate
Phenyalalanine	Cysteine
Threonine	Glutamine
Tryptophan	Glutamate
Valine	Glycine
Lysine	Proline

	Serine
	Tyrosine

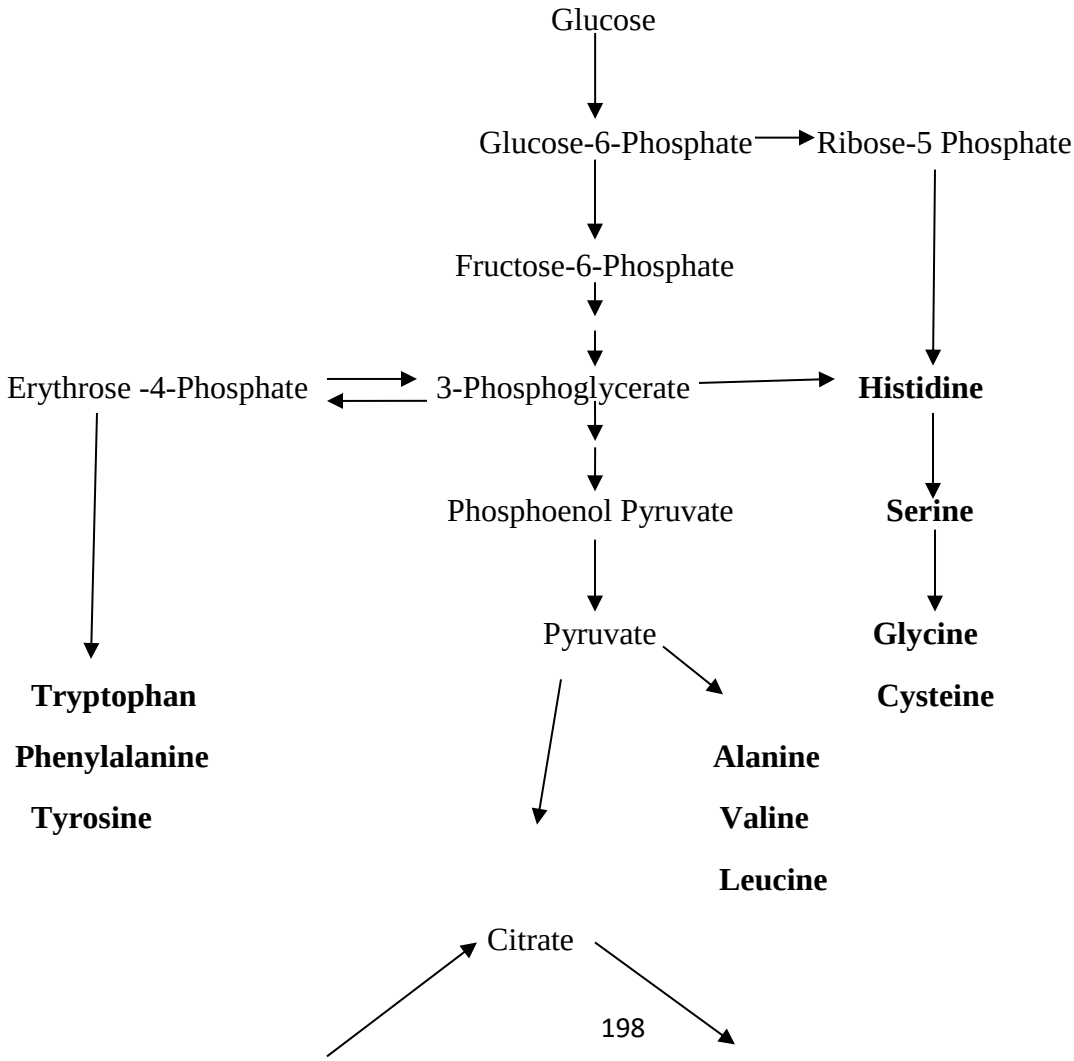
Objective

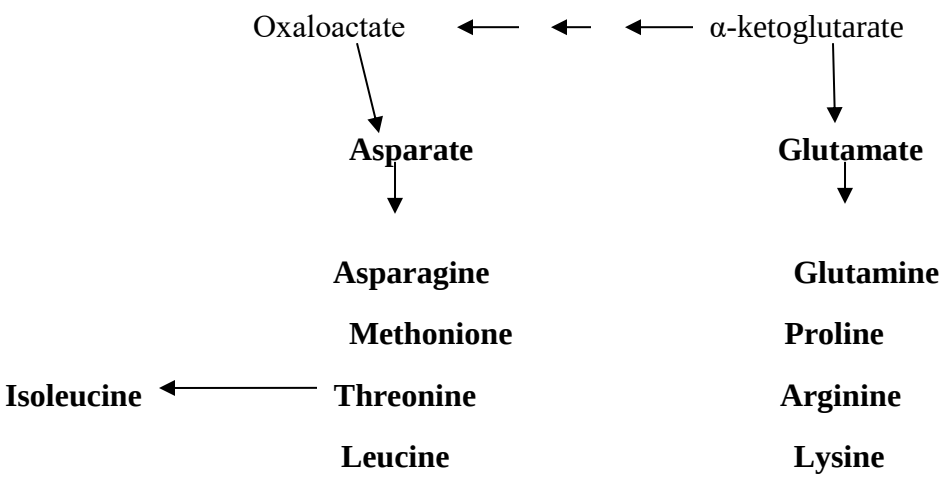
After studying this unit you will be able to know:

- essential and non-essential amino acids, biosynthesis of amino acid
- about deamination of amino acids.
- transamination of amino acids.

9.2 BIOSYNTHESIS OF AMINO ACIDS (PHENYLALANINE, TRYPTOPHAN, ASPARATE, PROLINE, THREONINE)

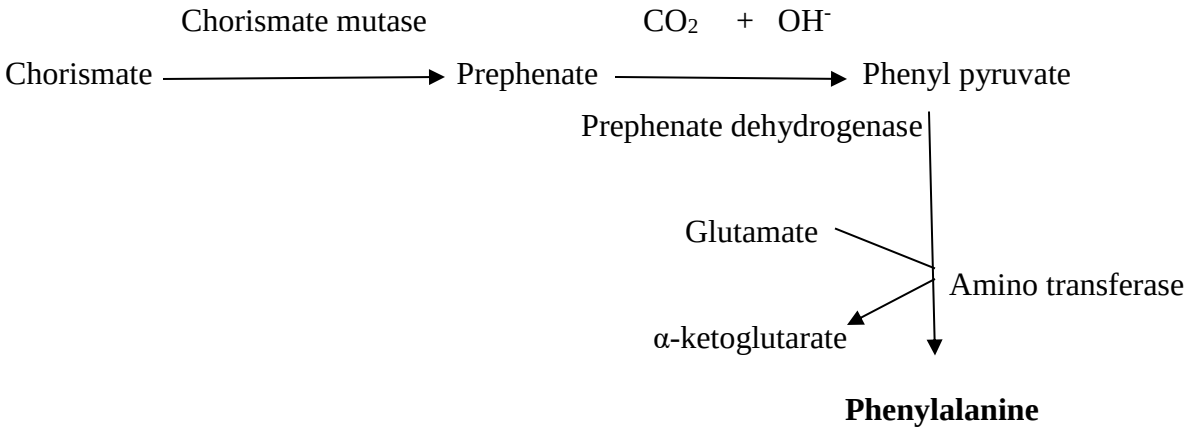
Biosynthesis of amino acid is multi-steps enzyme catalyzed process where substrates are converted into more complex product in living organism. In the biosynthesis of amino acids carbon is derived from three sources like glycolysis, citric acid cycle & pentose phosphate pathway. In amino acids biosynthesis, the key role played by the enzyme are glutamate dehydrogenase, glutamine synthetase and amino transferases. The combined effect of these three enzymes is to transform ammonium ion into the α-amino nitrogen of various amino acids. The entire process of synthesis of various amino acids are describe in figure below.





Biosynthesis of Phenylalanine

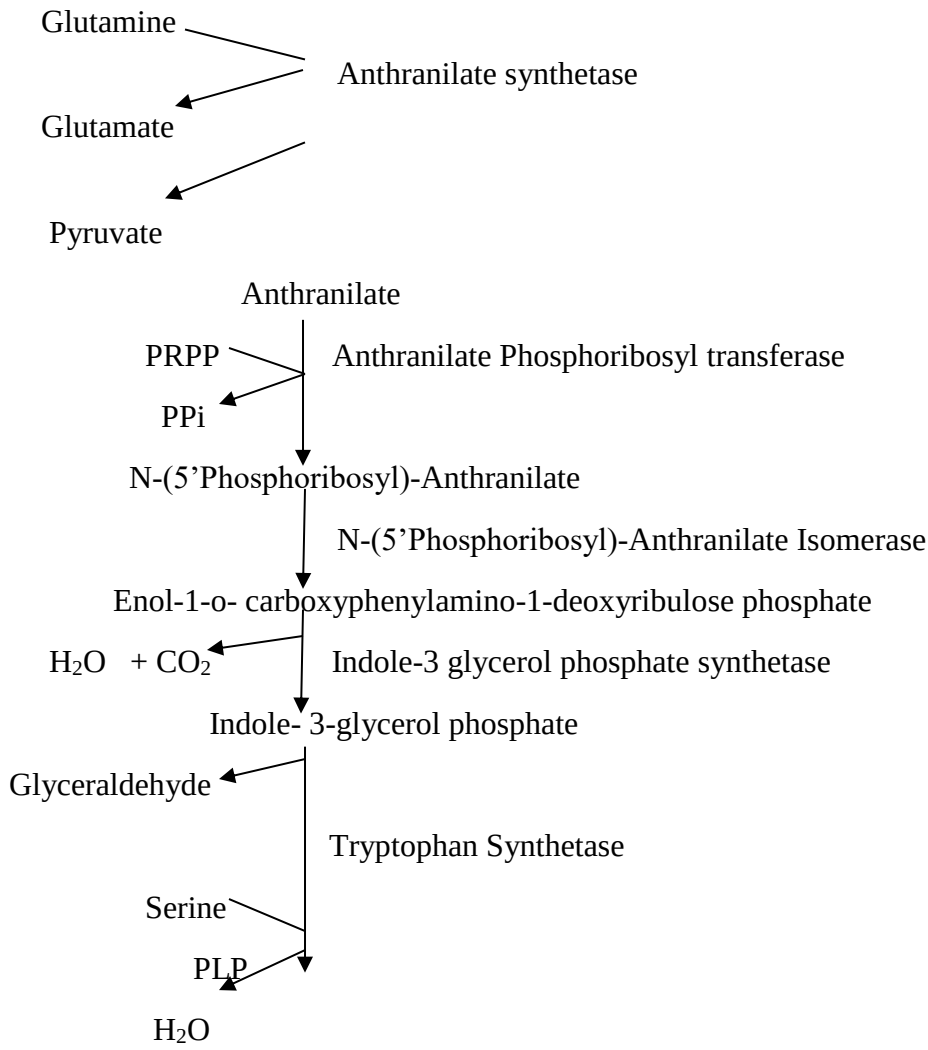
In the biosynthesis of phenylalanine amino acid, chorismate in the presence of chorismate mutase enzyme it is converted into prephenate, which get converted into phenyl pyruvate by the presence of enzyme prephenate dehydrogenase. Phenyl pyruvate reacts with glutamate and in presence of enzyme amino transferase it gives phenylalanine and α-ketoglutarate.



Biosynthesis of Tryptophan

Biosynthesis of tryptophan amino acids, started with chorismate react with glutamine, in presence of enzyme anthranilate synthetase form anthranilate, glutamate and pyruvate. The anthranilate treact with phosphoribosyl pyrophosphate (PRPP) in presence of enzyme anthranilate phosphoribosyl transferase it form N-(5'Phosphoribosyl)-anthranilate and PPi. The N-(5'Phosphoribosyl)-anthranilate in presence of enzyme N-(5'Phosphoribosyl)-anthranilate isomerase it form enol-1-o- carboxyphenylamino-1-deoxyribulose phosphate. The enol-1-o-carboxyphenylamino-1-deoxyribulose phosphate converted into indole- 3-glycerol phosphate in the presence of enzyme indole-3 glycerol phosphate synthetase. The indole - 3-glycerol phosphate react with serine and in presence of tryptophan synthetase it yield glyceraldehyde and tryptophan.

Biosynthesis of Tryptophan

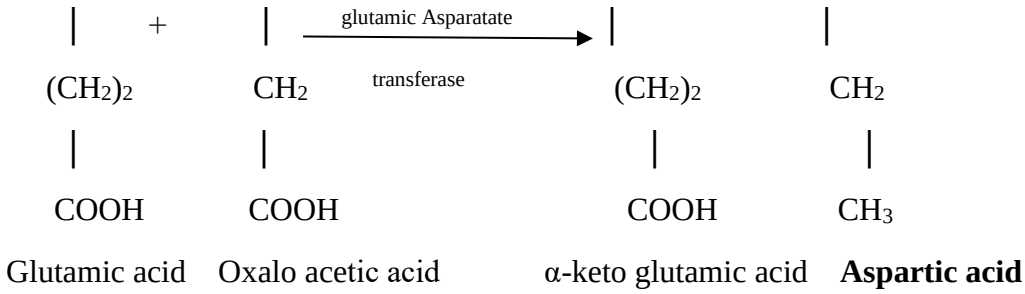


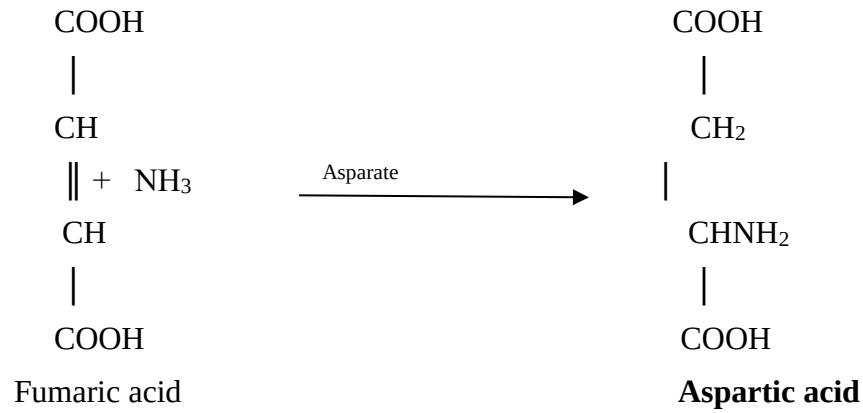
Tryptophan

Biosynthesis of Asparate

In many bacteria aspartic acid itself is produced by transamination of oxalo acetic acid on intermediate of TCA cycle. The amino donar being glutamic acid. Another possible route of asparatic acid formation is by animation of fumaric acid.

The amino group of glutamic acid is transfer to carbonyl group of oxalo acetic acid and the carbonyl group of oxalo acetic acid is transfer to amino group of glutamic acid. At the end of reaction the glutamic acid become α-keto glutamic acid and oxalo acetic acid become aspartic acid.

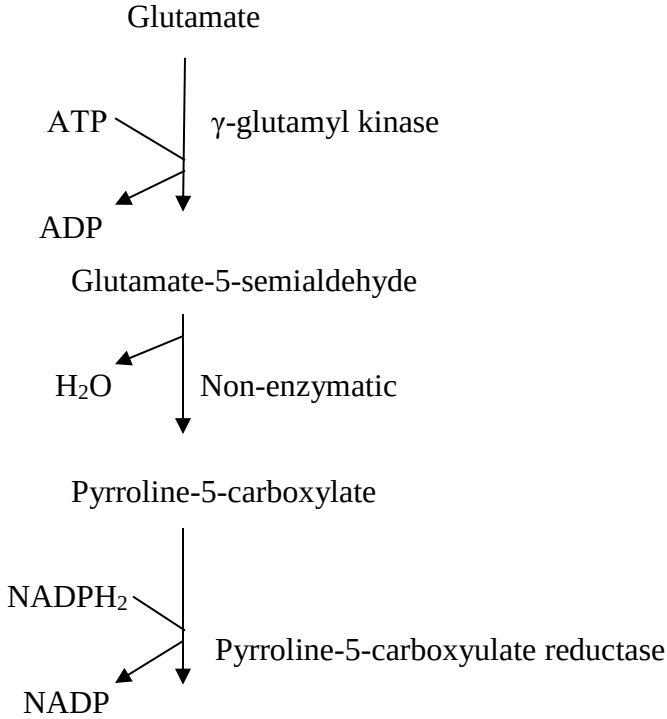




Biosynthesis of Proline

Proline is a heterocyclic amino acid. It is synthesized *via* the intermediate glutamic acid & semialdehyde and pyrroline 5'-carboxylic acid.

Glutamic acid is reduced by a $NADH_2$ linked dehydrogenase to glutamic acid –aldehyde will undergoes spontaneous cyclization to form pyrroline-5-carboxylic acid. The latter is reduced by an $NADPH_2$ linked dehydrogenase yielding Proline.

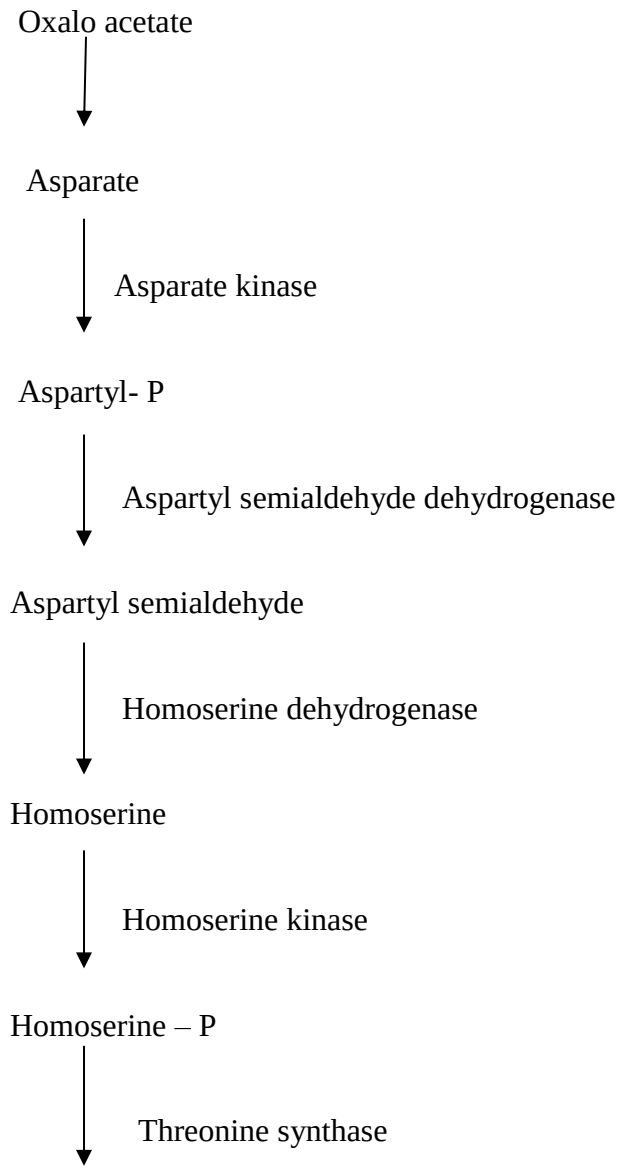


Proline

Biosynthesis of Threonine

Threonine is synthesized from homoserine *via* a intermediate, phosphomoserine. The conversion of homoserine to Threonine consists essentially of the transfer of the hydroxyl group from γ position to β- position.

The second step is catalyzed by threonine synthetase which requires pyridoxal phosphate as coenzyme. Inorganic phosphate is released from phosphomoserine



Threonine

9.3 DEAMINATION OF AMINO ACIDS

The removal of amino group from the amino acids is known as deamination. There are two types of deamination, non-oxidative and oxidative deamination.

(i) Non-oxidative deamination : The removal of amino group without oxidation is known as non-oxidative deamination. The enzyme is dehydrase, pyridoxal phosphate (PLP)' acts a cofactor. This occurs mainly on hydroxyl amino acids like serine and threonine.

Serine ⟶ pyruvate + NH_4^+

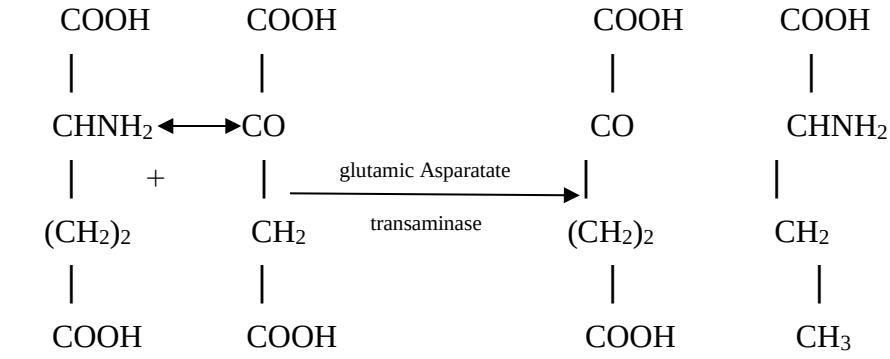
Threonine ⟶ alpha ketobutyrate + NH_4^+

(ii) Oxidative deamination : The removal of amino group following its oxidation is known as oxidative deamination. It takes place both in the liver and kidney. The coenzymes involved are FMN and FAD which are reduced to $FMNH_2$ and $FADH_2$. The enzyme is amino acid oxidase which is auto oxidizable i.e. the reduced $FMNH_2$ & $FADH_2$ are re-oxidised directly by oxygen without the involvement of electron transport chain. Hydrogen peroxide is formed here, which is converted to water by catalase.

Glutamate dehydrogenase, one among oxidative deaminases is an allosteric enzyme. ATP, GTP and NADH act as negative modulators where as ADP as a positive modulator. It converts glutamate to α-keto glutarate and ammonia.

9.4 TRANSAMINATION OF AMINO ACIDS

Transamination is a reaction in which the amino group from one amino acid transfer to a keto group of keto acid, at the end of the reaction the amino acid becomes the keto acid and the keto acid become the amino acid.



Glutamic acid Oxalo acetic acid α-keto glutamic acid Aspartic acid

The reaction is catalysed by the enzyme transminase. Coenzyme required is pyridoxal phosphate (PLP). It is a bi-substrate reaction. Schiff's base is formed as an intermediate. The mechanism is called ping-pong reaction.

Generally three keto acids participate in this reaction are (i) Pyruvate (ii) α-keto glutarate and (iii) Oxalo acetic acid. Transamination reaction mainly serves two roles in the amino acid metabolism (a) Inter conversion of amino acids and (b) To channel the amino group amino acids ultimately to glutamate and aspartate.

If these two amino acids are in excess than the requirement then the amino group is removed by deamination forming ammonium ion (NH_4^+) or urea which are excreted. All the amino nitrogen is ultimately concentrated on glutamate is only amino acid in mammalian tissue that undergoes oxidative deamination at an appreciable rate.

SAQs 1.

Complete the following sentences by inserting appropriate words in the blanks.

(i) The 3-phosphoglycerate is used to synthesize ----------

(ii) In non-oxidative deamination ---------- acts as co-factor.

(iii) Phenylalanine hydroxylase converts phenylalanine to ----------

(iv) Transamination of pyruvate leads to synthesis of ----------

9.5 SUMMARY

In this unit there is description of amino acid, essential and non essential amino acids and the biosynthesis of different types of amino acid in very detailed step wise manner. There is also description of deamination and transamination in very detailed manner with examples.

9.6 TERMINAL QUESTION

Q1 Describe the amino acid with essential and non essential amino acids.

Q2 Explain the biosynthesis of phenylalanine amino acid.

Q3 Explain of biosynthesis of tryptophan.

9.7 ANSWERS

SAQ 1

(i) Serine

(ii) Pyridoxal phosphate

(iii) Tyrosine

(iv) Alanine

Terminal question

1. Amino acids are the molecule containing two functional groups i.e. amino group (NH_2) and a carboxylic group (COOH) and a side chain that are specific to each amino acid. The amino acids are the building block of different types of proteins. They are linked by covalent peptide bond. There are nearly 20 amino acids are found in living organisms. Now two more

amino acids are also discovered are selenocysteine and pyrrolysine. So there are 22 amino acids an incorporated in synthesis of protein.

There are certain amino acids, which is required by the body and are not synthesized in the body. So they are supplied in the body from outside. Such types of amino acids are called **essential** or **indispensible amino acids**. There are also certain amino acids are required by the body for the formation of hormones, purines, enzymes, neurotransmitters and other compounds can be formed from metabolic intermediates by transamination, using the amino nitrogen from other amino acids by the body and are not needed to be present in diet are called **non-essential** or **dispensable amino acids**.

2. In the biosynthesis of phenylalanine amino acid, chorismate in the presence of chorismate mutase enzyme is converted into prephenate, which get converted into phenyl pyruvate by the presence of enzyme prephenate dehydrogenase. Phenyl pyruvate reacts with glutamate and in presence of enzyme amino transferase it gives phenylalanine and α-ketoglutarate.

3. Biosynthesis of tryptophan amino acids, started with chorismate react with glutamine, in presence of enzyme anthranilate synthetase form anthranilate, glutamate and pyruvate. The anthranilate treact with phosphoribosyl pyrophosphate (PRPP) in presence of enzyme anthranilate phosphoribosyl transferase it form N-(5'Phosphoribosyl)-anthranilate and PPi. The N-(5'Phosphoribosyl)-anthranilate in presence of enzyme N-(5'Phosphoribosyl)-anthranilate isomerase it form enol-1-o- carboxyphenylamino-1-deoxyribulose phosphate. The enol-1-o- carboxyphenylamino-1-deoxyribulose phosphate converted into indole- 3-glycerol phosphate in the presence of enzyme indole-3 glycerol phosphate synthetase. The indole - 3-glycerol phosphate react with serine and in presence of tryptophan synthetase it yield glyceraldehyde and tryptophan.

UNIT-10 LIPIDS-BIOSYNTHESIS OF PALMITIC ACID AND KETOGENESIS

10.1 INTRODUCTION

Lipids are the organic substances insoluble in water, but soluble in organic solvents like chloroforms, ether and benzene. They are esters of fatty acids or substances capable of forming esters. They are utilize by the living organisms. They form the dietary constituents on account of their higher calorific value. In the body they are present in the cytoplasm as well as in the cell wall and also some specialized area in the body as depots of fat. Nervous tissue also contain high amount of lipid which play a significant role in their function. The subcutaneous fat serves the role of insulation against atmospheric heat and cold. It also helps in shaping of the body.

Objective

After studying this unit you will be able to know:

- Definition and fatty acid synthesis.
- ketogenesis or formation of ketone bodies.
- triglyceride storage in adipocytes promoted by insulin.
- role of glucagon, epinephrine & insulin.

10.2 FATTY ACID SYNTHESIS & KETOGENESIS

Mechanism of synthesis of fatty acid

By the decarboxylation of pyruvate to yield acetyl Co-enzyme-A and CO_2. Since this reaction occur in mitochondria but the enzyme for synthesis of fatty acid occur in cytoplasm and also the acetyl-Co-A cannot across the mitochondrial membrane so it get converted into another compound and then across the membrane. The acetyl Co-A can react with oxalo-acetic acid to form citrate. This citrate can across the mitochondrial membrane and came into cytoplasm. In presence of cleaving enzyme it react with sulphur contain Co-enzyme A (Co-ASH) to form oxalo-acetic acid and acetyl Co-A or in mitochondria acetyl Co-A react with carnitine to form acetyl carnitine and Co-ASH. This acetyl carnitine across the membrane and change into carnitine and acetyl Co – A.

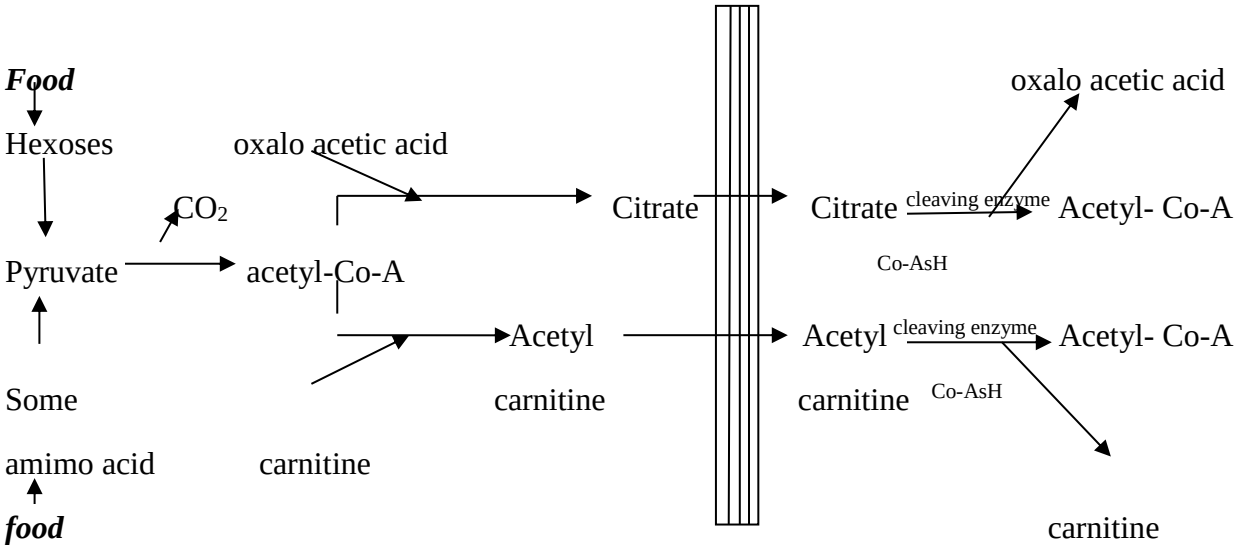


Fig 10.1: Showing of crossing of acetyl Co-A

In cytoplasm the acetyl-Co-A react with Co_2 in presence of ATP and enzyme biotin or acetyl-S-Co-A carboxylase to form malonyl-S-Co-A.

$$Co_2 + CH_3{-}\overset{\overset{O}{\|}}{C}{-}S{-}CO\text{-}A + ATP \xrightarrow[\text{carboxylase}]{\text{acetyl-S-Co-A}} CH_2COOH\sim S.CO\text{-}A$$

Malonly-CoA

Both acetyl Co-A and malonyl Co-A react with protein thio ester substance acyl carrier protein (ACP – SH). Then further reaction proceed

$$ACP{-}SH + CH_3{-}\overset{\overset{O}{\|}}{C}{-}S{-}CO\text{-}A \xrightarrow[\text{transacylase}]{\text{Acetyl}} ACP{-}S{-}COCH_3 + CO\text{-}ASH$$

Acetyl-S-ACP

$$ACP\text{-}SH + COOH{-}CH_2CO{-}S{-}COA \xrightarrow[\text{transacylase}]{\text{Malonyl}} ACP{-}S{-}CO{-}CH_2COOH + CO\text{-}ASH$$

Malonyl-S-ACP

Now the acetyl-S-ACP and malonyl-S-ACP in presence of β-ketoacyl-S-ACP synthatase to form aceto acetyl-S-ACP and CO_2.

$$CH_3CO\text{-}S\text{-}ACP + CH_2COCOOH\text{-}S\text{-}ACP \xrightarrow{\beta\text{-keto acyl-S-ACP synthatase}} \overset{\text{ACP-SH}}{CH_3COCH_2CO{-}S{-}ACP} + Co_2$$

(Acetoacetyl-S-ACP)

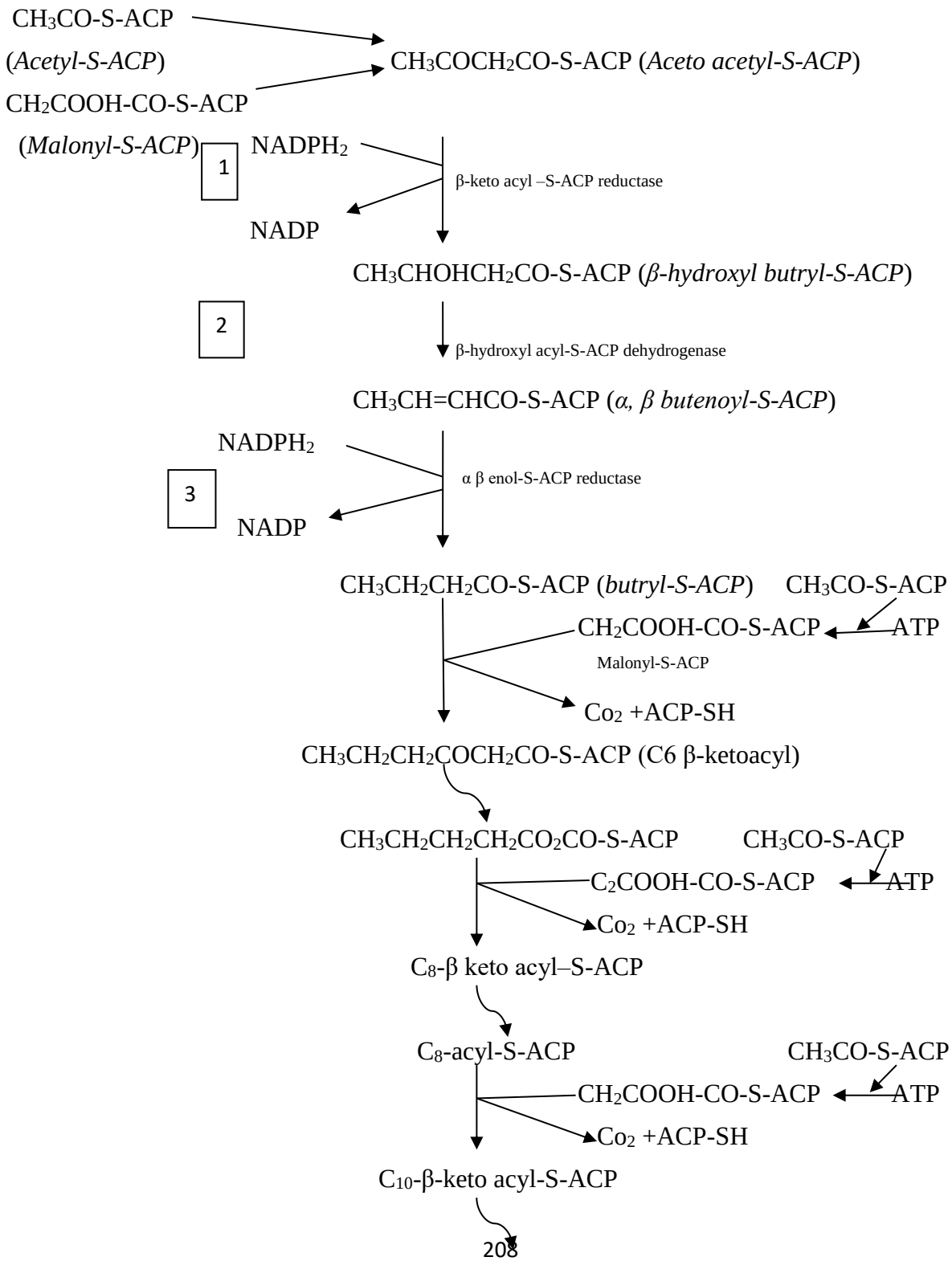
The aceto acetyl-S-ACP under goes 3 steps

(1) Reduced to a β-hydroxyl acyl group

(2) Dehydrate to an α, β enol group

(3) Reduced to a fully saturated acyl group

Ultimately it will give rise to butryl-S-ACP. This will again react with malonyl-S-ACP to for C_6β-keto-acyl-S-ACP. This will again undergo 3 steps and ultimately it will form C_{16}Acyl-S-ACP. This will hydrolyse to produce palmitate (fatty acid).



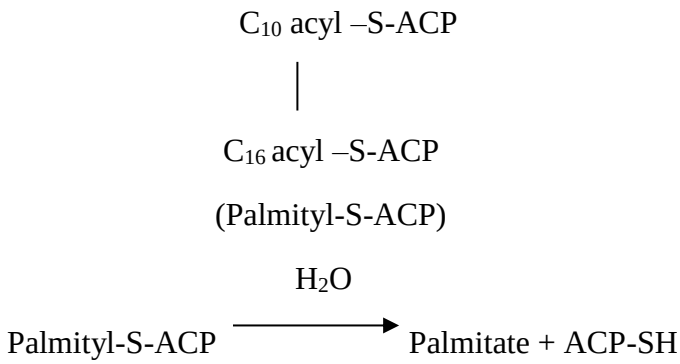


Fig 10.2: Summary of fatty acid anabolism *via* the malonyl-S-CoA-ACP pathway

KETOGENESIS

The formation of ketone bodies is called ketogenesis or ketogenesis is a metabolic pathway to produce ketone bodies, which provide an alternative form of energy for the body. The ketone bodies are aceto-acetic acid, β-hydroxy butyric acid and acetone. All these 3 things are produced in the normal course in the liver tissue during metabolism of fatty acid. The total amount of ketone bodies does not exceed 1mg/100 ml of blood. The body is constantly producing small amount of ketone bodies that can make 22 ATP each in normal circumstance and is regulated by insulin.

If due to certain reason the level of ketone bodies increases in blood is called ketonemia and if it appears in urine called ketonuria. The condition in which ketonemia & ketonuria occur called ketosis. The ketone body production is increased, when there is decreased or starvation of carbohydrate in diet or a diet is very rich in fatty acid. In pathological condition like uncontrolled diabetes mellitus, keto-acidosis can occur.

Formation of ketone bodies

The formation of ketone bodies or ketogenesis produce acetone, aceto-acetate and β-hydroxy butyrate molecule by the breakdown of fatty acid. Ketogenesis occurs primarily in the mitochondria of liver cells. The fatty acids are brought into the mitochondrial matrix by reacting with carnitine and enzyme.

After entering of fatty acid it undergoes β-oxidation to produce acetyl Co-A. Now two molecule of acetyl Co-A react in presence of enzyme thiolase or acetyl Co-enzyme-A transferase (ACAT) to form aceto-acetyl Co-A. The aceto-acetyl Co-A in presence of 3rd molecule of aceto acetyl Co-A and condensing enzyme HMG-Co-A synthatase it form β-hydroxy β-methyl glutaryl Co-A (HMG-Co-A). The HMG-Co-A is converted into aceto acetic acid in presence of enzyme HMG Co-A lyase (HMG Co-A cleavage enzyme). The aceto acetic acid undergoes decarboxylation to produce acetone. The aceto acetic acid in extra hepatic tissue converted into aceto acetyl co-enzyme-A. The aceto-acetyl Co-enzyme-A in presence of β-hydroxy butryl Co-A dehydrogenease

and NAD converted into β-hydroxy butryl Co-A. The β-hydroxy butryl Co-A in presence of enzyme deacylase it is converted into β-hydroxy butric acid.

The ketone bodies are oxidized in the extra hepatic tissue. The β-hydroxy butarate and aceto-acetate, when reaches the extra hepatic tissue, the β-hydroxy butarate is converted to aceto-acetate by the enzyme β-hydroxy butyrate dehydrogenease and aceto-acetate is converted into acetyl Co-A by the enzyme β-keto acyl Co-A transferease. The acetyl Co-A enter into the kreb cycle and oxidative phosphorylation it produce 22 ATP/molecule. The acetone does not converted back into acetyl Co-A, so it is excreted through urine or exhaled.

In condition like diabetes mellitus, alcoholism and starvation, the level of carbohydrate stores are significantly decreases or concentration of fatty acid increases. This lead to the formation of ketone bodies. If the amount of ketone bodies are higher in body its toxicity is due to their property of removing sodium ions resulting in keto-acidosis. Due to this rate of pulmonary ventilation is increased and the patient have fast breathing rate.

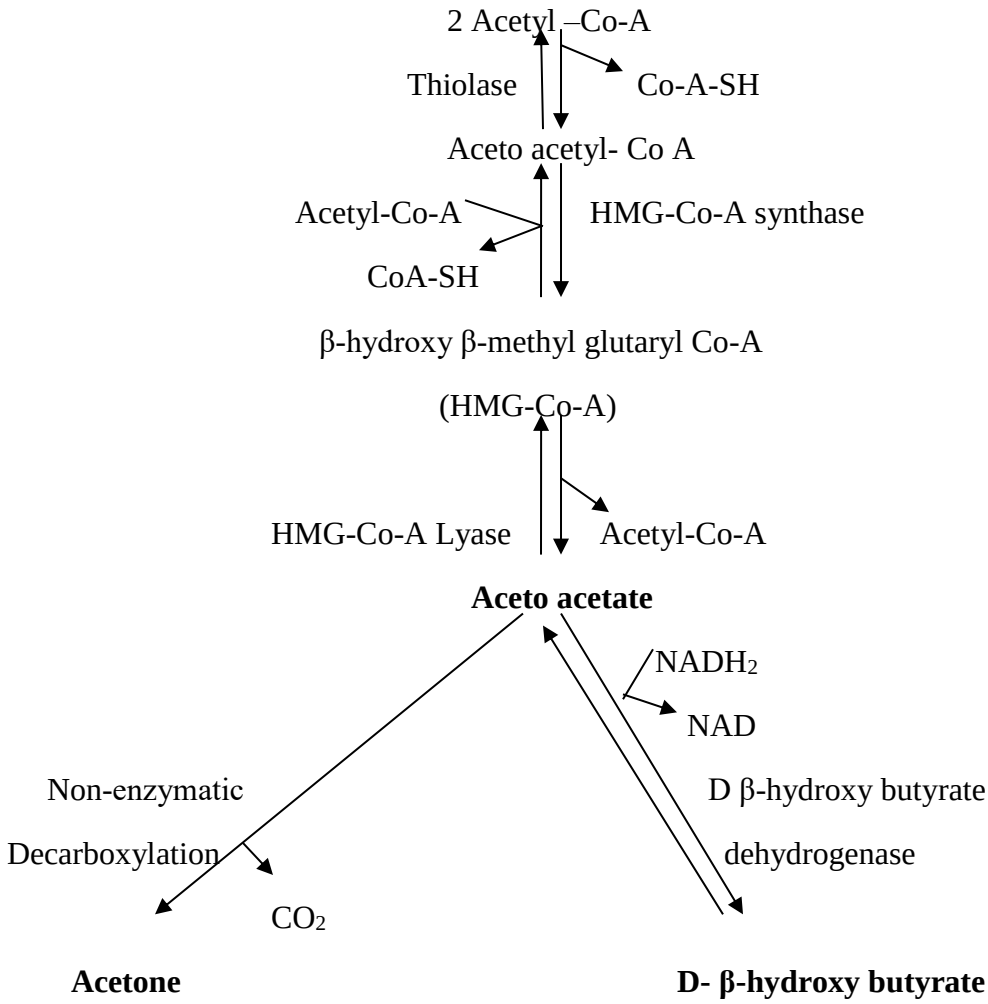


Fig 10.3: Formation of ketone bodies

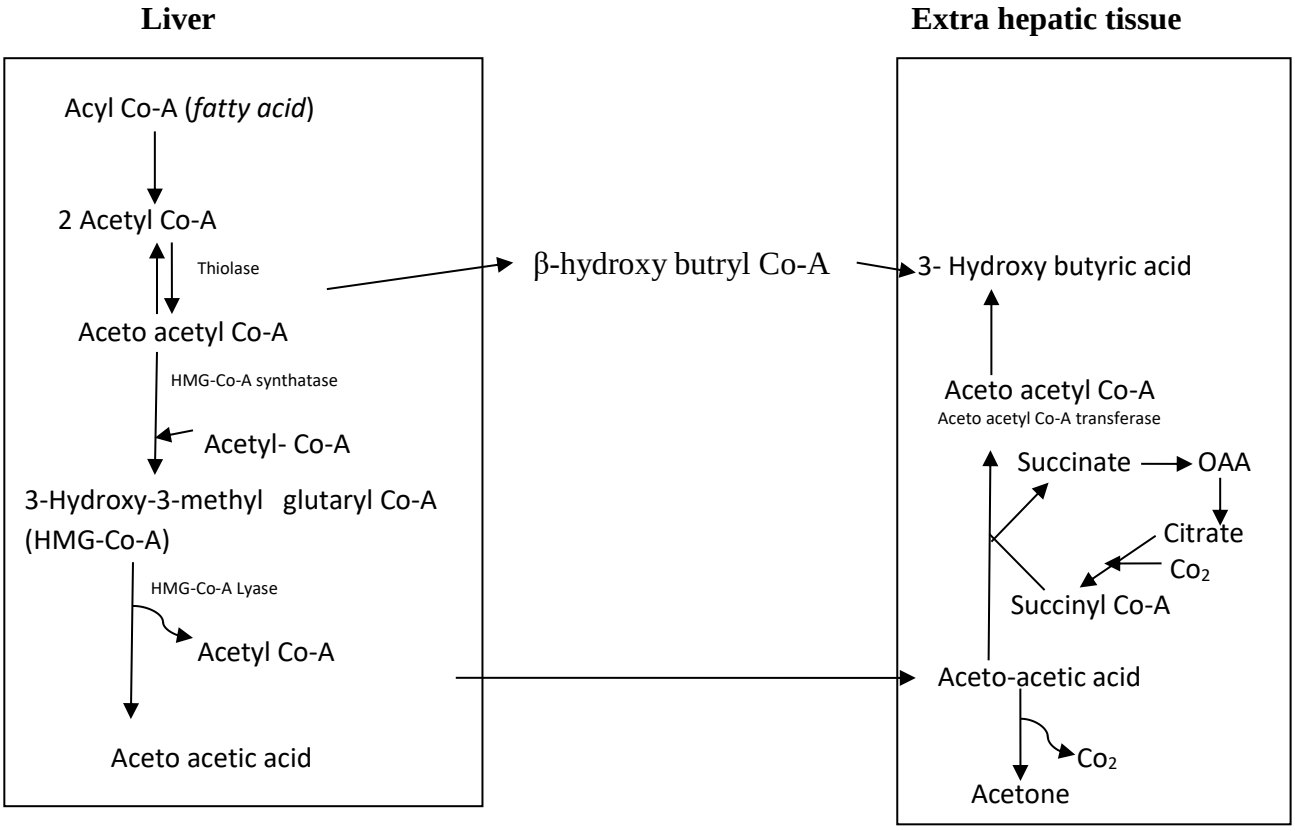


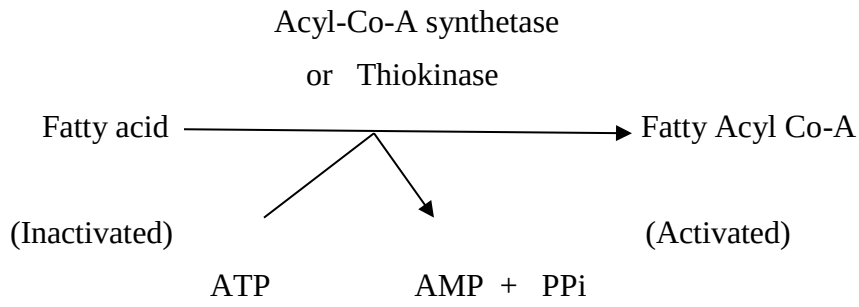
Fig 10.4: Pathway of ketone bodies formation

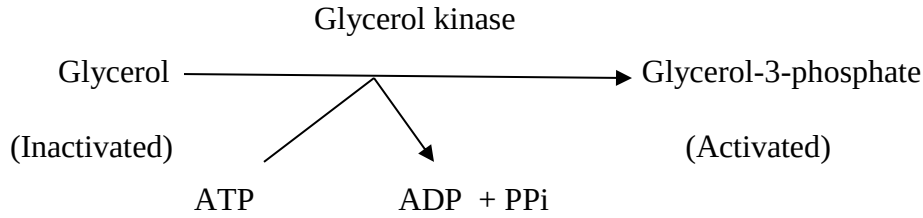
10.3 TRIGLYCERIDE STORAGE IN ADIPOCYTES PROMOTED BY INSULIN

After the digestion of carbohydrate, it forms glucose. This glucose enters into each and every cell of the body for energy generation. If there are more glucose in blood, it will convert into glycogen and stored in liver & muscles. If still there is glucose in blood, then the level of glucose in blood is maintained by insulin for its absorption by the liver cell again. This extra glucose is converted into triacylglycerol.

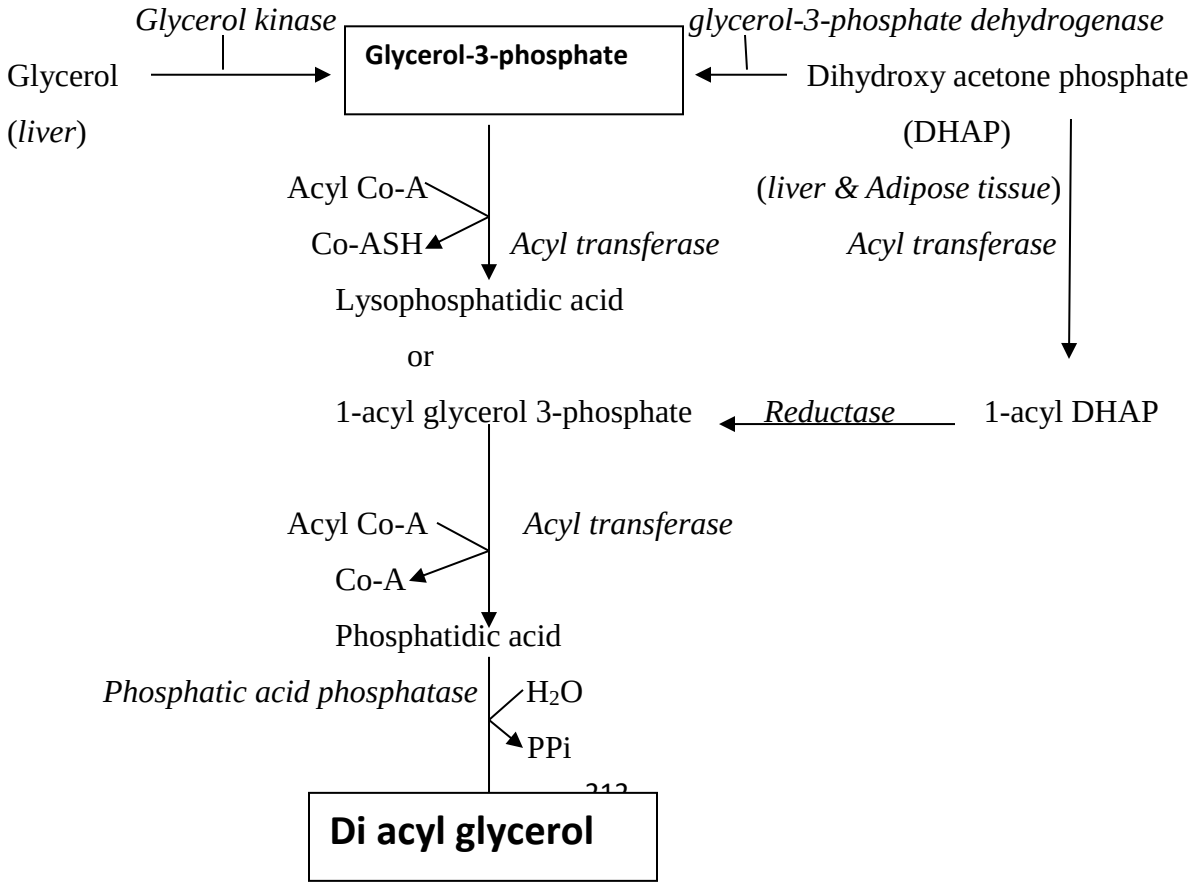
In liver and adipose tissue triacylglyceride (TAG) synthesis take place. The process of synthesis of triglyceride is called lipogenesis. In lipogenesis 3 molecules of fatty acid and glycerol react to form triacylglyceride (TAG). This reaction is favoured by insulin and the dephosporylation of enzyme.

The biosynthesis of triacylglyceride (TAG) occurs in smooth endoplasmic reticulum & adipose tissue. In adipose tissue glycerol is back bone of triacylglyceride (TAG) synthesis. The fatty acid & glycerol is activated by Acyl-Co-A synthetase and glycerol kinase respectively.





In liver glycerol is converted into glycerol-3-phosphate by the presence of enzyme glycerol kinase and ATP. In liver and adipose tissue dihydroxy acetone phosphate (DHAP) which formed by glycolysis, in the presence of glycerol-3-phosphate dehydrogenase is converted into glycerol-3-phosphate. This glycerol-3-phosphate in presence of activated 1st molecule of fatty acid and enzyme acyl transferase it will form lysophosphatidic acid or 1-acylglycerol-3-phosphate. The 1-acyl glycerol-3-phosphate can also derived from dihydroxy acetone phosphate, by converting into 1 acyl dihydroxy acetone phosphate which get reductase into 1-acyl glycerol-3-phosphate. This 1-acyl glycerol-3-phosphate reacts with 2nd molecule of Acyl Co-A and enzyme Acyl transferase to form phosphatidic acid. This phosphatidic acid in presence of phosphatidic acid phosphatase, it will form diacyl glycerol. The diacyl glycerol again react with 3rd molecule of activate Acyl Co-A and in presence of enzyme diacyl glycerol transferase it will form triacyl glycerol (TAG).



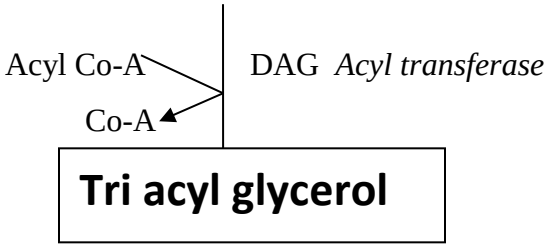


Fig 10.5: Pathway of Triacyl glyceride synthesis

Regulation of Triacyl glycerol

Insulin favour lipogenesis

- Insulin enhances the uptake of glucose by adipocytes by gluco-4 receptor present on adipose tissue. The glucose undergoes glycolysis to produce Dihydroxy acetone phosphate (DHAP) requires for synthesis of glycerol-3-phosphate. (later utilize for TAG synthesis)
- Insulin also increases the activity of

  (i) Pyruvate dehydrogenase

Pyruvate $\xrightarrow{\text{Pyruvate dehydrogenase}}$ Acetyl Co-A (↑) for (TAG)

(ii)Acetyl Co-A carboxylase $\longrightarrow$ **fatty acid synthesis (↑)**

- Insulin also depress hormone sensitive lipase $\longrightarrow$ dephosphoralation ↓ Inhibit lipolysis

Mechanism of hormone like glucagon, epinephrine & insulin

In fasting and starvation condition glucagon or epinephrine are released, they acted on G-protein coupled receptor and activate adenyl cyclase, which convert ATP into C-AMP. The cyclic –AMP further convert inactive protein kinase-A to active protein kinase-A. The activate protein kinase A acted on Hormone sensitive lipase or dephosphorylated (Inactive form) to activate into hormone sensitive lipase (Phosphoryated) (Active form). This is brought about by use of ATP. The activated hormone sensitive lipase causes lipolysis brings about lysis of TAG to DAG then MAG.

The other hormones like glucocorticoid, growth hormone, thyroid hormone also cause activation of Adenyl cyclase which similar convert ATP to C-AMP and ultimately bring about lipolysis.

If insulin is released, it activates protein phosphatase. This protein phosphatase causes hormone sensitive lipase or phosphorylate (Active) into hormone sensitive lipase (dephosphorylated) (inactive). Thus due to dephosphorylated enzyme be inactive and stop lipolysis. Insulin also converts C-AMP into 5'AMP by enzyme phosphodiesterase. Thus it decreases the concentration of C-AMP which less of phosphorylation which causes less lipolysis or more lipogenesis.

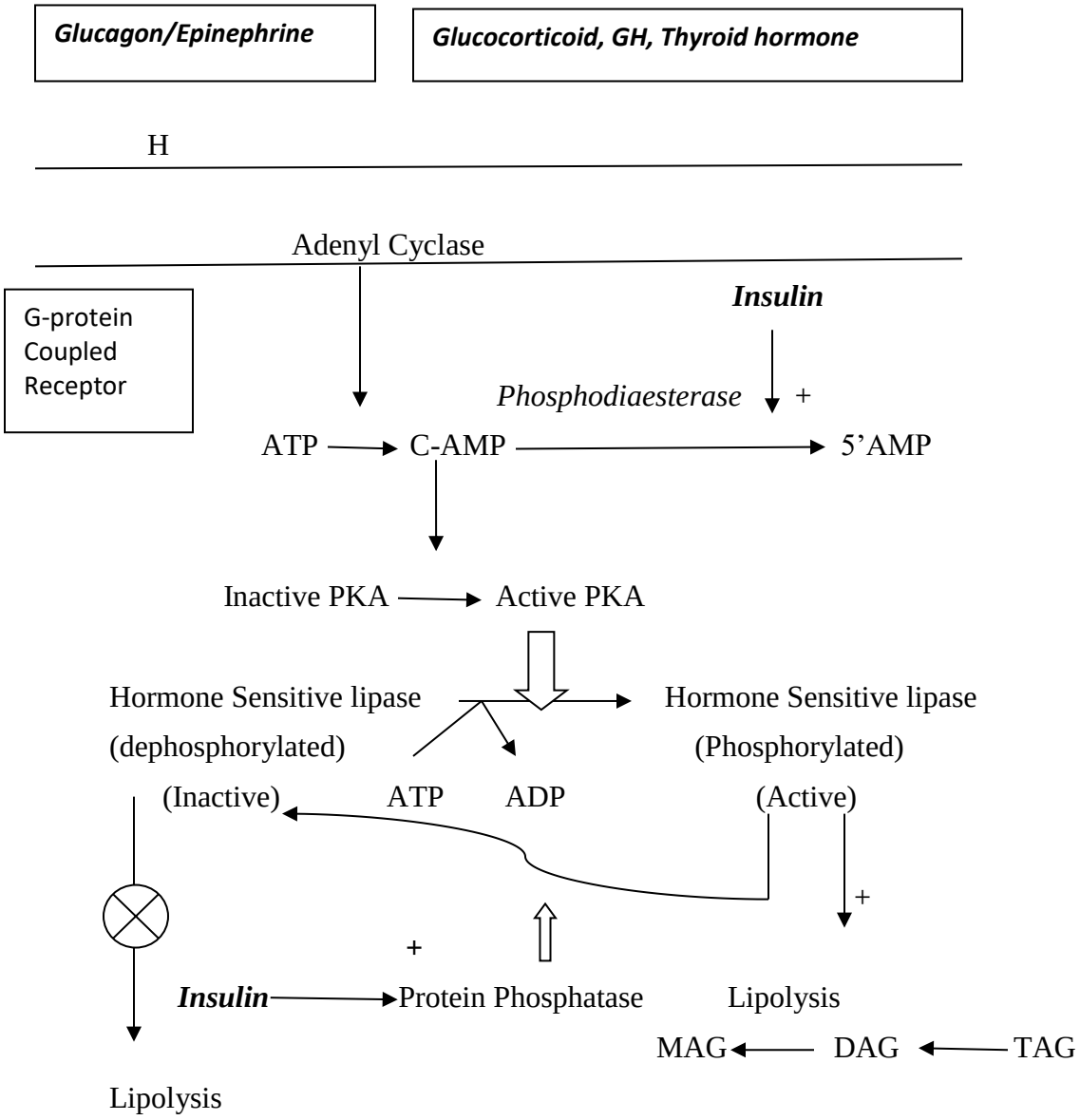
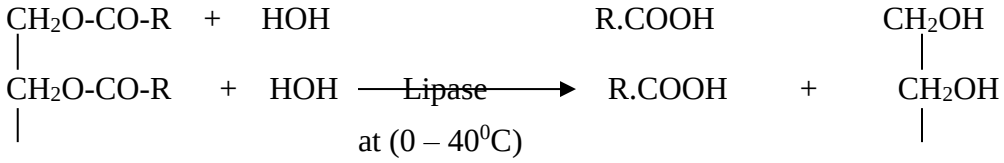


Fig 10.6: Mechanism of hormone like glucagon, epinephrine & insulin

10.4 TRIGLYCERIDE HYDROLYSIS AND FATTY ACID

Hydrolysis of glyceride gives rise to fatty side & glycerol. The hydrolysis can be brought about with the help of pancreatic enzyme lipase. Phospho-lipase act on the ester linkage in phospholipids.

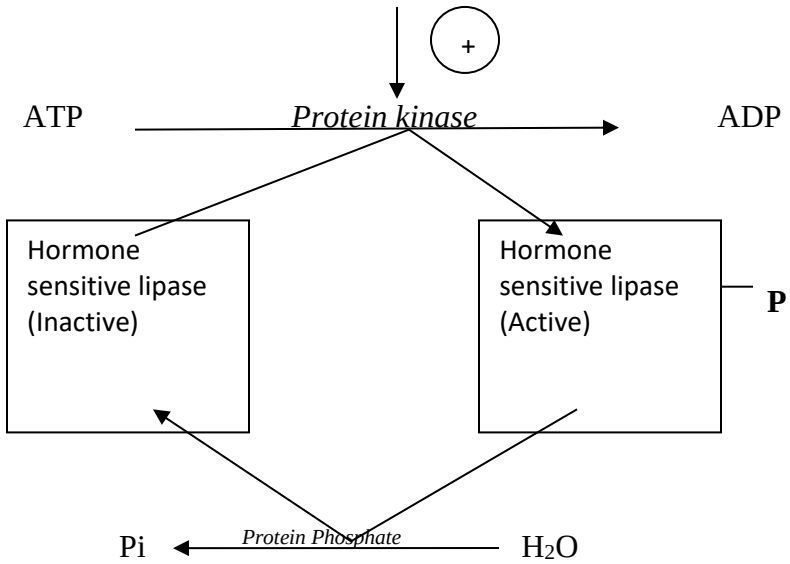


Triglyceride 3 fatty acid glycerol

The hydrolysis of triglyceride in adipose tissue is bring about by an hormone sensitive cellular lipase which catalysis the hydrolysis reaction of triglyceride to release free fatty acids & glycerol. The fatty acid is carried through the blood stream by being absorbed to serum albumin, while glycerol goes to the liver. In liver it enters into glycolytic pathway by the action of two enzyme glycerol kinase & glycerol-3-phosphate dehydrogenase. The glyceraldehyde-3-phopshate by back reaction of glycolysis form glucose or after forward reaction of glycolysis, it form phosphenol pyruvate, which enter into tricarboxylic acid cycle (TCA cycle) intermediate.

The hydrolysis of triglyceride is stimulated by many hormone, which increases the level of C-AMP in cells. There are two lipase that can hydrolyse the triglyceride are hormone-sensitive lipase and lipoprotein lipase. The hormone-sensitive lipase is present in tissue and lipoprotein lipase is present in plasma. The hormone sensitive lipase can undergo phosphorylation. The phosphorylation is an active while dephosphorylation is an inactive form. The activated protein kinase A converts the inactive form into the active form.

C-AMP



The protein kinase A is activated by the high level of concentration of C-AMP. Some hormone such as thyroxine, epinephrine, nor-epinephrine, and glucagon increases the C-AMP concentration in adipose tissue, which increase the hydrolysis of triglyceride or lipolysis. While certain other hormone like insulin lower the C-AMP level in adipose tissue causes decrease or inhibit hydrolysis of triglyceride or lipolysis. The lowering of C-AMP can be brought about by inhibition of adenylate cyclase or by stimulation of phosphodiesterase

Catabolism or oxidation of fatty acid – For the first time Knoop (1905) proposed the β-oxidation of fatty acid. According to him fatty acid undergo oxidation in step wise manner to produce new fatty acid having two less carbon atom and acetyl Co-A. This new fatty acid further

under goes step wise oxidation to produce new fatty acid which again contain two less carbon atom and acetyl Co-A and ultimately all fatty acid are converted in acetyl Co-A in step wise manner. Since this process is repeated it is also called fatty acid spiral. The whole process is described as follow

The fatty acid are synthesized in cytoplasm and it undergoes degradation in the mitochondrial matrix. The fatty acid are across the outer membrane of mitochondria but cannot across the inner mitochondrial membrane. So it reacts with carnitine which is present in intra-mitochondrial membranous space. In presence of enzyme carnitine acyl transferase, carnitine is converted into acyl-carnitine. The acyl-carnitine can across the inner membrane of mitochondria by the help of acyl carnitine translocase protein. Both carnitine acyl transferase and acyl carnitine translocase are present in inner mitochondrial membrane. The acyl carnitine in mitochondrial matrix convert into acyl-S-Co-A and free carnitine. The carnitine again move to intra mitochondrial membranous space to bring another molecule of fatty acid. In mitochondrial matrix acyl Co-A under goes β-oxidation in step wise manner as follows –

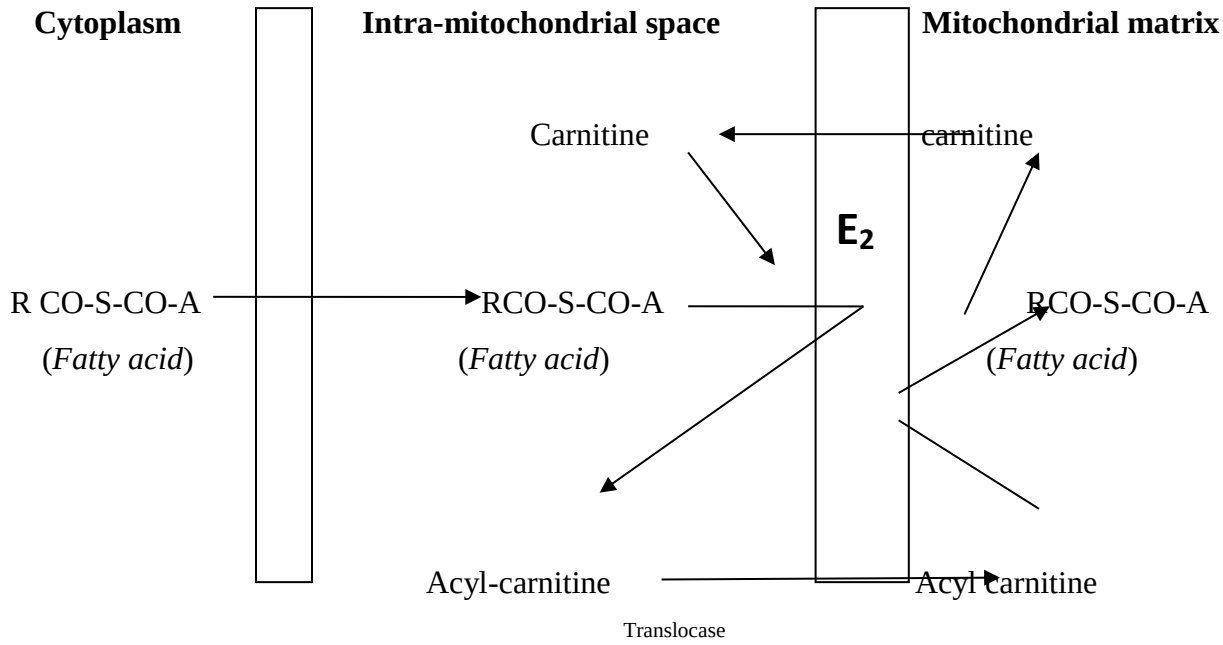


Fig 10.7: Showing of fatty acid movement from cytoplasm to mitochondrial matrix

(1) Activation

(2) Dehydrogenation I

(3) Hydration

(4) Dehydrogenation II

(5) Thiolytic cleavage

(1) Activation – The Ist step is activation of fatty acid. It take place in the presence of enzyme acyl-Co-A synthatase (thio kinase), Co-A and ATP to form acyl Co- A (activated fatty acid).

(2) Dehydrogenation -I – The activated fatty acid (acyl Co-A) undergo reduced to form α,β acyl Co-A. This reduction is brought about by an enzyme acyl Co-A dehydrogenase and FAD.

(3) Hydration – The reduced α,β acyl Co-A add water to form β-hydroxyl-acyl Co-A. This reaction is catalyse by enzyme enol hydrase.

(4) Dehydrogenation II – The β hydroxyl acyl Co-A further undergo dehydrogenation to form β-keto-acyl-S-Co-A. This is catalyse by enzyme β- keto-acyl-dehydrogenase and NAD.

(5) Thiolytic cleavage – The β-keto-acyl Co-A under goes thiolytic cleavage by enzyme β-keto-acyl thiolase to produce Acetyl Co-A and new fatty acid which have 2 less carbon atom.

The new fatty acid will further under goes 2, 3, 4 & 5 step and again form acetyl Co-A and new fatty acid with two less carbon atom. This will further undergoes same process until all the fatty acid molecule are converted into acetyl Co-A.

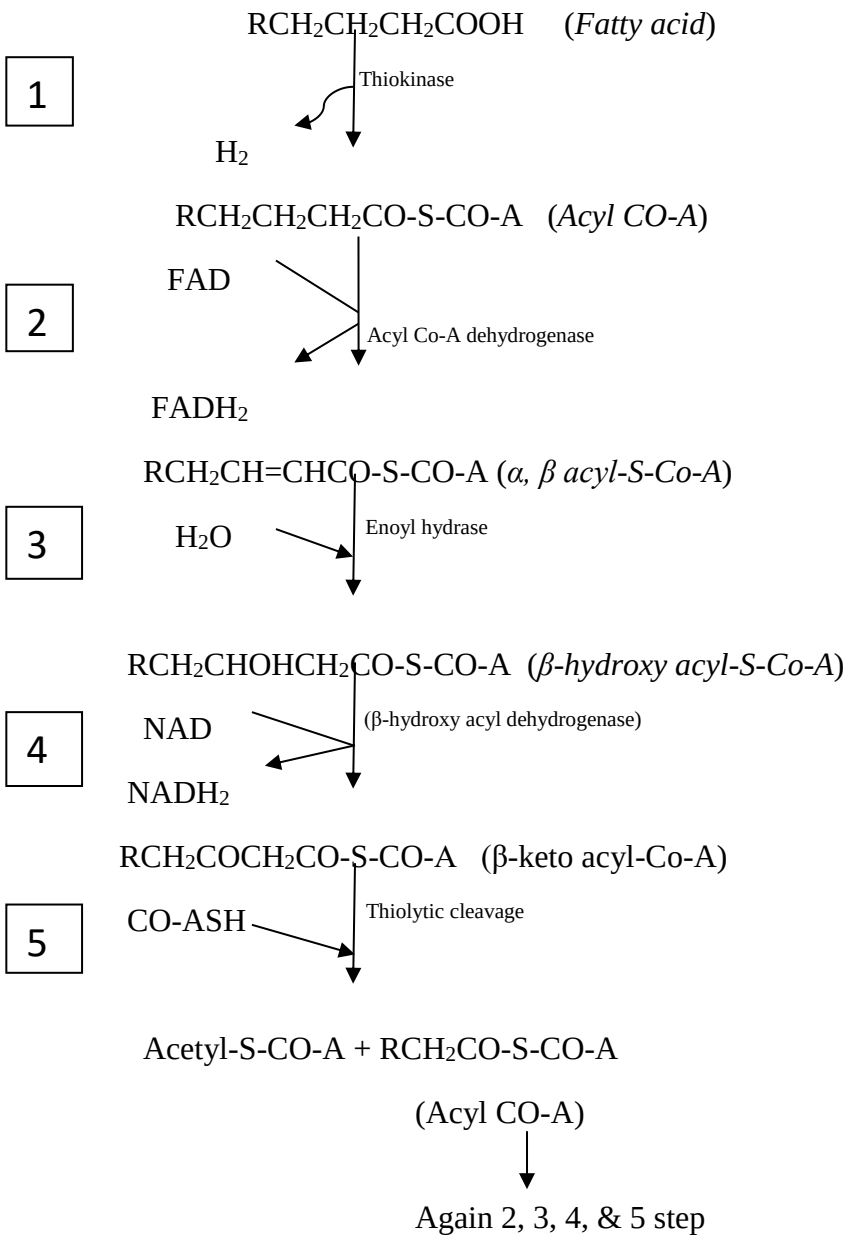


Fig: Summary of β- oxidation of fatty acid

SAQs 1.

Complete the following sentences by inserting appropriate words in the blanks.

(i) Fatty acids are synthesized in the ----------

(ii) In acetyl Co-A ---------- group is added to generate malonyl Co-A during biosynthesis of palmitic acid.

(iii) *De novo* lipogenesis is activated by ----------

(iv) Adipose triglyceride lipase is essential for ----------

10.5 SUMMARY

In this chapter the discussion about lipid is describe in very detailed manner. It has been discussed about fatty acid synthesis in detailed manner. There is also discussion about ketogenesis in very detail. The synthesis of triglyceride and the role of insulin are also discussed. There is also given information of hydrolysis of triglyceride. In this unit there is also discussion about fatty acid oxidation

10.6 TERMINAL QUESTION

Q1. Describe the Ketogenesis.

Q2. Describe the role of insulin in lipogenesis.

Q3. What is fatty acid spiral.

10.7 ANSWERS

SAQ 1

(i) Cytoplasm

(ii) Carboxyl

(iii) Insulin

(iv) Lipogenesis

Terminal question

1. The formation of ketone bodies is called ketogenesis or ketogenesis is a metabolic pathway to produce ketone bodies, which provide an alternative form of energy for the body. The ketone bodies are aceto acetic acid, β-hydroxy butaric acid and acetone. All these 3 things are produced in the normal course in the liver tissue during metabolism of fatty acid. The total amount of ketone bodies does not exceed 1mg/100 ml of blood. The body is constantly producing small amount of ketone bodies that can make 22 ATP each in normal circumstance and is regulated by insulin.

If due to certain reason the level of ketone bodies increases in blood is called ketonemia and if it appears in urine called ketonuria. The condition in which ketonemia & ketonuria occur called ketosis. The ketone body production is increased, when there is decreased or starvation of carbohydrate in diet or a diet is very rich in fatty acid. In pathological condition like uncontrolled diabetes mellitus, keto-acidosis can occur.

2. Insulin favour lipogenesis

- Insulin enhances the uptake of glucose by adipocytes by gluco-4 receptor present on adipose tissue. The glucose undergoes glycolysis to produce Dihydroxy acetone phosphate (DHAP) requires for synthesis of glycerol-3-phosphate. (later utilize for TAG synthesis)
- Insulin also increases the activity of

(i) Pyruvate dehydrogenase

Pyruvate $\xrightarrow{\text{Pyruvate dehydrogenase}}$ Acetyl Co-A (↑) for (TAG)

(ii) Acetyl Co-A carboxylase $\longrightarrow$ fatty acid synthesis (↑)

- Insulin also depress hormone sensitive lipase $\longrightarrow$ dephosphoralation

$\downarrow$

Inhibit lipolysis

3. For the first time Knoop (1905) proposed the β-oxidation of fatty acid. According to him fatty acid undergo oxidation in step wise manner to produce new fatty acid having two less carbon atom and acetyl Co-A. This new fatty acid further under goes step wise oxidation to produce new fatty acid which again contain two less carbon atom and acetyl Co-A and ultimately all fatty acid are converted in acetyl Co-A in step wise manner. Since this process is repeated it is also called fatty acid spiral.

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Master of Science

PGZY-102 (N)

Physiology and Biochemistry

3

Block

Bichemistry-II

Unit-11	**Enzymes**
Unit-12	**Vitamins**

BLOCK-3

In the previous block you have studied about the physiology-II and biochemistry-I. In this block you will be introduced by biochemistry-II. Enzymes and Vitamins. An enzyme is a substance that act as a catalyst in living organisms, regulating the rate at which chemical reactions proceed without itself being altered in the process. The vitamins are a group of complex organic compounds required in small quantities by the body for the maintenance of good health. This block is divided into two units (unit11 and 12) as under:

Unit-11 This unit deals with the Enzymes

Unit 12 In this we study about Vitamins

Objectives:-

After studying this block you will be able to know:

- The kinetics of enzyme reaction
- Fat and water soluble vitamins

UNIT-11 ENZYME

11.1 INTRODUCTION

Willy kuhne in 1864 for the first time coined the term enzyme from two Greek word "en" mean in and "zyme" mean yeast, as this substance is found in yeast. Later Edward Buchner (1892) was the first to isolate an enzyme from yeast extract which he named zymase. J.D. somner (1926) was the first to crystallize an enzyme which he named urease and established that enzymes are protein but all protein are not enzyme. Fedrich Sangar (1945) proposed the molecular structure of insulin $\mathbf{C_{254}\ H_{377}O_{75}N_{65}\ S_6}$**.**

Enzymes are complex organic nitrogenous substances and are produced by all living cell and its main function is to catalysis of the biochemical reaction without being used up in the reaction. The body of living organism having multitude of the biochemical reaction are going on. These reactions are not only catalyse by enzyme but also catalyse by vitamin and hormone. The vitamin and hormone differ from enzyme is that they are used up in the biochemical reaction.

Objective

After studying this unit you will be able to know:

- Definition of enzyme, kinetics of enzyme reaction.
- about order of enzyme reaction including zero, first, second & third order reaction.
- enzyme inhibition - competitive and non- competitive inhibitors.
- application of enzyme inhibition techniques in pest control
- allosteric enzyme.

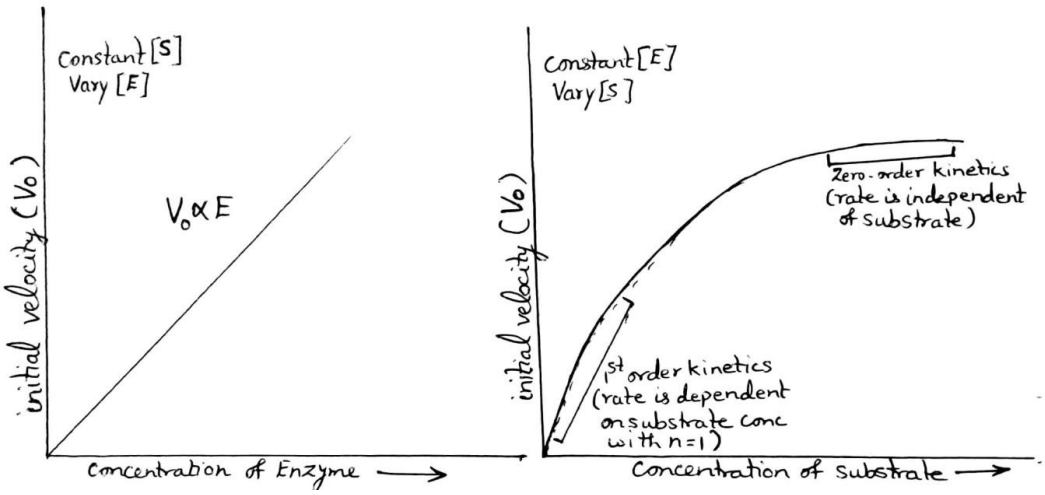
11.2 KINETICS OF ENZYME REACTION-KINETICS OF ENZYME CATALYZED

- The study of the rates of enzyme catalyzed biochemical reaction is called Enzyme kinetics.

- It refers to the relationship between the rate of a chemical reaction and the concentration of substrate.
- In enzyme kinetics, the rate of the reaction is measured and effects of changes of the reaction conditions are investigated.
- The rate of reaction is define as velocity of the reaction to convert the reactants into products.

Michaelis – Menten equation

Michaelis and Menten, while working with an extract of yeast rich invertase enzyme that catalyse the hydrolysis of carbohydrate sucrose. He collected the data by changing the initial velocity (V_o) in two separate experiments.



A B

In first (A) experiment when he kept the substrate [S] concentration constant and plot a graph between initial velocity and concentration of enzyme. He found that as the concentration of enzyme increases there is increase in initial velocity (V_o α E). In second experiment (B) he kept the concentration of enzyme constant and plot a graph between initial velocity and concentration of substrate he found that in early stage as the concentration of substrate increases, there is increase in initial velocity (1^{st} order reaction) but later when the concentration of substrate increases initial velocity V_o does not increases but slightly remain constant as in the hyperbolic curves.

In a simple model he proposed that when enzyme [E] combines with substrate [S] to form an enzyme-substrate complex [ES] complex with rate constant K_1. The ES has two possible fact that either it is dissociated in [E] and [S] with rate constant K_2 or it form [E] and [P] (product) with rate constant K_3.

$$E + S \underset{K_2}{\overset{K_1}{\rightleftharpoons}} ES \xrightarrow{K_3} E + P$$

(1) Rate of product formation $ES \xrightarrow{K_3} E + P$. In initial velocity will be equal to

$$V_o = K_3[ES] \quad \text{——————————} (1)$$

(2)As ES is an intermediate state is in steady state equilibrium. The rate of formation of ES is same as the rate of disappearances of ES. In other word there is no change in concentration of ES with time.

Rate of ES formation $= K_1 [E] [S]$

Rate of disappearance $= K_3 [ES] + K_2 [ES]$

$$[\, E + S \underset{}{\overset{K_2}{\longleftarrow}} E S \overset{K_3}{\longrightarrow} E + P\,]$$

The two event of ES decomposition

In equilibrium condition

Rate of formation = rate of ES disappearance

$$K_1 [E] [S] = K_3 [ES] + K_2 [ES] \quad \text{——————(2)}$$

$$K_1 [E] [S] = [K_2 + K_3] [ES] \quad \text{——————(3)}$$

$$[ES] = \frac{K_1 [E] [S]}{K_2 + K_3} \quad \text{——————(4)}$$

We put

$$\frac{K_2 + K_3}{K_1} = K_M \quad \text{——————(5)}$$

K_M is Michaelis menten constant

We put equation (5) into equation (4)

$$[ES] = \frac{K_1 [E] [S]}{K_2 + K_3}$$

$$[ES] = \frac{[E] [S]}{\frac{K_2 + K_3}{K_1}} = \frac{[E]\ [S]}{K_M}$$

$$ES = \frac{[E]\ [S]}{K_M} \quad \text{——————(6)}$$

(3) The concentration of total enzyme [ET] is the sum of the enzyme combined with substrate and the free enzyme [E]

$$[ET] = [ES] + [E]$$

$$E = [ET] - [ES] \quad \text{——————} \quad (7)$$

The value of E of equation (7) put in equation (6)

$$ES = \frac{\{[ET] - [ES]\}\ [S]}{K_M}$$

$$\frac{ES}{[S]} = \frac{[ET] - [ES]}{K_M}$$

$$\frac{ES}{[S]} + \frac{ES}{K_M} = \frac{[ET]}{K_M}$$

$$\frac{[ES]\ K_M + [ES]\ [S]}{[S]\ \cancel{K_M}} = \frac{[ET]}{\cancel{K_M}}$$

$$\frac{[ES]\ K_M + [S]}{[S]} = ET$$

$$[ES] = ET \frac{[S]}{K_M + [S]} \quad \text{——————} \quad (8)$$

If value of ES is put in equation (1)

$$V_o = K_3\ [ES] \quad \text{——————} \quad (1)$$

$$V_o = K_3\ ET \frac{[S]}{K_M + [S]} \quad \text{——————} \quad (9)$$

(4) The maximum initial velocity Vmax will be attained when all the enzyme will make complexed with substrate i.e. E = O. This condition is termed saturation of the enzyme with substrate. So

$$ET = ES \qquad \text{——————} \quad (10)$$

Put equation (10) in equation (1)

$$\mathbf{V_o = V_{max} = K_3\,[ES] = K_3\,[ET]}$$

$$V_{max} = K_3\,[ET] \qquad \text{——————} \quad (11)$$

$$[ET] = \frac{V_{max}}{K_3} \qquad \text{——————} \quad (12)$$

Equation (12) put in equation (9)

$$V_o = \frac{K_3 \times V_{max}}{K_3} \quad \frac{[S]}{[S] + K_M}$$

$$\boxed{V_o = V_{max}\,\frac{[S]}{[S] + K_M}} \qquad \text{——————} \quad (13)$$

This is **Michaelis - Menten equation**. This equation gives following data that

(a) If concentration of substrate is very low than K_M i.e. $S << K_M$ then

$$V = \frac{V_{max}\,[S]}{K_M}$$

Mean the rate is directly proportional to the substrate concentration

(b) If concentration of substrate is very high that K_M i.e. $S >> K_M$

$$V = V_{max}$$

Mean rate is maximum and independent of substrate concentration

(c) If $S = K_M$

$$V_O = V_{max}\,\frac{[S]}{[S] + [S]} = V_{max}\,\frac{S}{2[S]} = \frac{V_{max}}{2}$$

$$V_o = \frac{V_{max}}{2}$$

When K_M is equal to the substrate concentration at which the reaction rate is half of its maximum value.

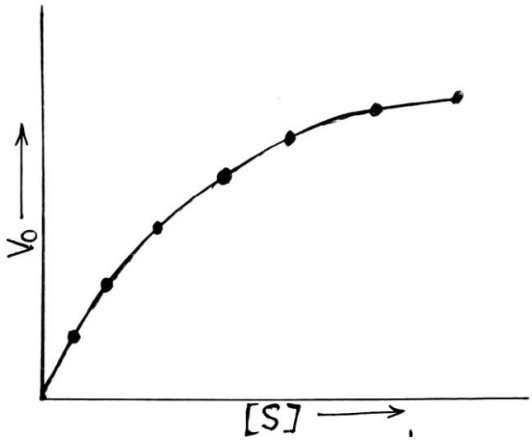


Fig 11.1: Graphical representation of Michaelis- Menten equation

11.3 ORDER OF ENZYME REACTION

The chemical reaction shows different reaction rates which depends on different ways on the concentration of reactant or substrates. The relationship between reaction rate & concentration of substrate is described as the **order of the reaction**. Order of reaction is the number of reacting species whose concentration determines the rate at which the reaction occurs.

Expression of the rate of the reaction

In order to determine the reaction order, the power law form of the rate equation is generally used

$$\text{Rate of reaction} = \frac{-d[S]}{dt} = K[S]^x [s']^y$$

K = rate constant

$[S]^x$ $[s']$ = concentration of the reactants

x & y = are exponents of the concentrations of the reactants are referred to as partial order of the reaction.

The sum all the partial order of the reaction yield the overall order of the reaction i.e. x + y.

Types of order

There are various types of order of reaction are as follows

(i) Zero order reaction : Break down rate is independent of the concentration of any of the reactants

$$V = \frac{-ds}{dt} = K[S]^0$$

(ii) First order reaction : Reaction rate is determine by the concentration of one reactant.

$$V = \frac{-ds}{dt} = K[S]^1$$

dt

(iii) Second order reaction : Reaction rate is determined by the concentration of two reacting species.

$$V = \frac{-ds}{dt} = K[S]^2$$

(iv) Third order reaction : Reaction rate is determined by the concentration of three or more reacting species.

$$V = \frac{-ds}{dt} = K[S]^{3 \text{ or above}}$$

Zero order of reaction

If the rate of reaction does not depends upon the concentration of reactants. These reactions are called zero order of reaction. In these reactions the velocity of reaction remains constant up to the completion of reaction. In these reactions, the concentration of reactant does not change with time. In zero order reaction, the velocity of reaction is proportional to zero power of initial concentration of reactant.

Let in a zero order reaction is A is reactant and B is product

$$A \longrightarrow B$$

$$-\frac{d[A]}{dt} \alpha [A]^0$$

$$-\frac{d[A]}{dt} = K_0 [A]^0$$

$$-\frac{d[A]}{dt} = K_0$$

If the concentration of product B is x then

$$\frac{dx}{dt} = K_0 \quad \text{——————} (1)$$

$$dx = K_0\, dt \quad \text{——————} (2)$$

On integrating equation (2)

$$\int dx = K_0 \int dt$$

$$X = K_0 t + C \quad \text{——————} (3)$$

Where C is integrating constant

If $t = 0$, $x = 0$ the $C = 0$

$$x = K_0 t \quad \text{——————} (4)$$

$$K_0 = \frac{x}{t} \quad \text{——————} (5)$$

This is zero order reaction

The examples of zero order reaction are

(i) $H_2 + Cl_2 \longrightarrow 2HCl$

(ii) $2HI \longrightarrow H_2 + I$

First order of reaction

First order reaction is one in which the rate of reaction is proportional to the concentration of the reactant.

Let in first order reaction, A is reactant and P product.

$$A \longrightarrow P$$

Initial concentration is A is 'a' gram mole/litre and after t - time, if x- gram mole react and only (a - x) gm mole concentration of

A (a - x)

After time t

$$-\frac{dx}{dt} \alpha (a - x) \quad \text{——————} (1)$$

$$\frac{dx}{dt} = K (a - x)$$

$$\frac{dx}{(a - x)} = K \cdot dt \quad \text{——————} (2)$$

Integrating the equation (2) we have

$$\int \frac{dx}{(a - x)} = \int K. dt$$

$$-\log (a - x) = Kt + C \quad \text{——————} (3)$$

where C is integration constant

For calculating the value of C in equation (3)

Put the value of t = 0 , x = 0

$$-\log a = C \quad \text{——————} (4)$$

On putting the value of C in equation (3)

$$-\log (a - x) = K t - \log a$$

$$\text{Log } a - \log (a - x) = Kt$$

$$\text{Log } \frac{a}{\quad} = Kt$$

$$(a - x)$$

$$K = \frac{1}{t} \log \frac{a}{(a - x)}$$

On changing the base of log, we get

$$K = \frac{2.303}{t} \log_{10} \frac{a}{(a - x)} \quad \text{(5)}$$

This is first order reaction. The equation is express for velocity constant K in first order reaction.

Unit of K

$$K = \frac{2.303}{t} \log \frac{a}{(a - x)}$$

$$K = \frac{1}{\text{time}} \log \frac{\text{conc}}{\text{conc}}$$

$$K = \frac{1}{\text{time}}$$

So unit of first order reaction is time $^{-1}$.

Example of first order reaction

(i) Inversion of cane sugar solution in presences of acid or alkali

$$C_{12}H_{22}O_{11} + H_2O \longrightarrow \underset{\text{Glucose}}{C_6H_{12}O_6} + \underset{\text{fructose}}{C_6H_{12}O_6}$$

In this reaction concentration is H_2O remain constant.

Second order of reaction

In second order reaction, the velocity of reaction depends upon 2 molecules of reactant. Second order reaction can be as

Two molecules of same reactant or two different molecules so

$$2A \longrightarrow P \quad \text{(same 2 molecules)}$$

$$A + B \longrightarrow P \quad \text{(2 different molecules)}$$

Let initial concentration for both reactant is a and after time t concentration is (a – x) remains.

According to law of mass action

$$\frac{dx}{dt} \alpha (a - x)(a - x)$$

$$\frac{dx}{dt} = K\ (a - x)^2$$

$$\frac{dx}{(a - x)^2} = K\ dt \qquad \text{——————————} (1)$$

Integrating equation (1)

$$\int \frac{dx}{(a - x)^2} = \int K.\ dt \qquad \text{——————} (2)$$

For integration of $\int \frac{dx}{(a - x)^2}$

Let $(a - x) = [P]$

On differentiation

$$O - dx = dp$$

In left hand side of equation (2)

$$\int \frac{dx}{P^2} = -\int P^2\ dp^{+1} = -\frac{P^{-2+1}}{-2+1} = -\frac{P^{-1}}{-1} = p^{-1} = (a - x)^{-1}$$

$$\int dx = \frac{1}{(a - x)^2} \quad \frac{}{(a - x)} \qquad \text{——————————} (3)$$

By equation (3) & (2)

$$\frac{1}{(a - x)} = Kt + C \qquad \text{————} (4)$$

Where C = integration constant

Where t= 0, x = 0

So $\frac{1}{(a - O)} = K \times O + C$

$$\frac{1}{a} = C$$

Put the value of C in equation (4)

$$\frac{1}{a-x} = Kt + \frac{1}{a}$$

$$\frac{1}{a-x} - \frac{1}{a} = Kt$$

$$\frac{a - (a-x)}{a(a-x)} = Kt$$

$$\frac{x}{a(a-x)} = Kt$$

$$K = \frac{1}{t} \cdot \frac{x}{a(a-x)} \qquad (5)$$

Equation (5) is expression for velocity constant in second order reaction

Unit of K

$$K = \frac{1}{t} \quad \frac{a}{a(a-x)}$$

$$K = \frac{1}{a.t} \quad \frac{a}{(a-x)}$$

$$= \frac{1}{\text{gm mole/litre x sec}} \quad X \quad \frac{\text{gm mole/litre}}{\text{gm mole/litre}}$$

$$= \text{litre (gm mole)}^{-1} \text{ second}^{-1}$$

Unit of velocity constant is litre/mole second

Example of second order reaction

(i)Hydrolysis of ester in presence of base

$$CH_3COOC_2H_5 + NaOH \longrightarrow CH_3COONa + C_2H_5OH$$

Third order of reaction

If the rate reaction is depend on concentration of three reactants. If the rate of reaction is A, B, & C and have same concentration then

$$A + B + C \longrightarrow P$$

At time t=0 — 0 0 0 — 0 — moles/dm^3

After some time — (a – x) (a – x) (a – x) — x — moles/ dm^3

$$\text{Rate equation} = -\frac{dx}{dt} = K\,(a-x)\,(a-x)\,(a-x) \qquad (1)$$

$$-\frac{dx}{dt} = K\,(a-x)^3 \qquad (2)$$

$$\frac{dx}{(a-x)^3} = K\,dt \qquad (3)$$

Integration of equation (3)

$$\int \frac{dx}{(a-x)^3} = K \int dt$$

$$\frac{1}{2(a-x)^3} = Kt + C \qquad (4)$$

$$\frac{1}{2a^2} = C$$

Now put C value in equation (4)

$$\frac{1}{2(a-x)^2} = Kt + \frac{1}{2a^2} \qquad (5)$$

$$y = mx + c$$

$$Kt = \frac{1}{2(a-x)^2} - \frac{1}{2a^2}$$

$$K = \frac{1}{t}\left\{\frac{1}{2(a-x)^2} - \frac{1}{2a^2}\right\}$$

This is 3rd order reaction.

11.4 RATE OF REACTION, TWO SUBSTRATE REACTIONS, TEMPERATURE CO- EFFICIENT, ACTIVATION ENERGY

Rate of Reaction : Enzyme concentration affects the rate of a reaction. If the substrate concentration is increased the rate of enzyme reaction is also rises, beyond a certain point, however the enzyme become saturated with substrate molecule. Further increase in reaction velocity occurs only if the enzyme concentration is increased. For example during starvation the supply of the substrate glucose decreases and glycolysis is depressed conversely increase in glucose concentration accelerates the rate of reaction up to the point when enzyme is saturated with glucose.

Two Substrate Reactions

- The majority of enzymatic reactions involves two or m ore substrates with more than one product formation.
- It is based on number of substrates involved & products form, the reactions are termed as uni - uni, bi – bi, uni – bi, & bi – uni reaction.

Reaction	Name
$A \longrightarrow P$	Uni- Uni
$A + B \longrightarrow P$	Bi – Uni
$A + B \longrightarrow P_1 + P_2$	Bi – Bi
$A \longrightarrow P_1 + P_2$	Uni – Bi

- In two substrate reaction usually atom or functional group are transferred from one substrate to other for e.g.

$$C_2H_5OH + NAD^+ \rightleftharpoons CH3CHO + NADH + H^+$$

- In such reaction alcohol dehydrogenase binds both NAD+ and C_2H_5OH and oxidized into two products.

Mechanism of two substrate reaction

In an reaction, two substrate can bind to enzyme in different ways which can be categorized as

(i)Non-sequential or Ping-pong mechanism

(ii)Sequential mechanism

(i)Non-sequential or Ping-pong mechanism : In non sequential mechanism one substrate binds and one products is released and there after second substrate binds and a second product is released. Hence only one substrate is present on the enzyme at any one time which means only single binding site present on enzyme. No ternary complex

$$E + AX \leftrightarrow E.AX \leftrightarrow EX.A \rightleftharpoons EX \overset{B}{\rightleftharpoons} EX.B \leftrightarrow E.BX \leftrightarrow E + BX$$

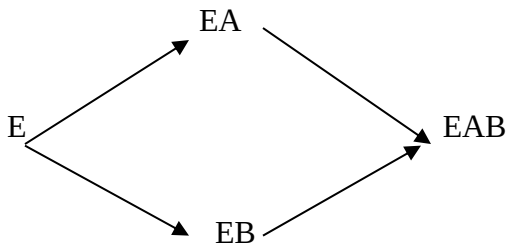
(A)

- AX binds to the enzyme (E) forms binary complex (E.AX).
- An intra – molecular re-arrangement take place in the binary complex (E.AX to EX.A).

- Thus first product (A) released before second substrate (B) binds. It only binds to the modified enzyme (EX).
- The best suitable example of non-sequential mechanism is action by chymotrypsin.

$$\text{Protein} + H_2O \xrightarrow{\text{chymotrypsin}} \text{Polypeptide} + \text{Polypeptide}$$

(ii)Sequential mechanism : In such reaction mechanism in both the substrate (A & B) binds to enzyme and form ternary complex (AEB) before products releases.



Temperature co-efficient

The enzymatic reaction occurs best at or around 37^0 C which is the average normal body temperature in homeotherms. The rate chemical reaction is increased by a rise in temperature but this is true only over a limited range of temperature. In most animals, enzymes rapidly denatured at temperature above 40^0C. The activity of enzymes is reduced at low temperature. The temperature at which enzymes show maximum activity is called Optimum temperature.

Activation Energy

Enzyme increases the speed of chemical reaction. They lower the energy of activation of a reaction thus enable it to occur at ordinary physiological temperatures, when reactions proceed from one direction to another they have to overcome an energy barrier called the activation energy. Normally only a small part of the total number of molecule in a compound contain enough energy to react. Application of heat enables a larger proportion of molecules to overcome the activation energy barrier. However living systems are relatively isothermal i.e. they do not have large temperature difference. They therefore employ enzymes to activate the molecules of the reacting compound. When the enzyme combines with the substrate to form the enzyme complex, the energy level of the substrate is raised and it reacts faster. Enzymes increases the speed of a chemical reaction thousands of times by bringing about mutual contact to reacting compounds. The coming together of these compounds is no longer a matter of chance, but become a certainty.

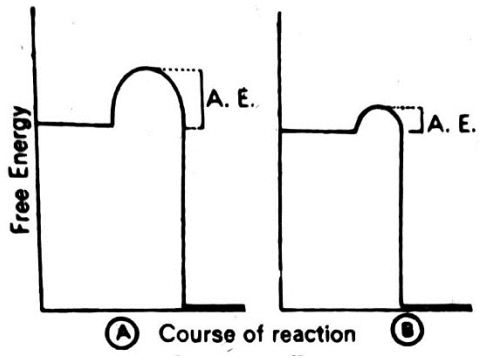


Fig 11.2 : change of activation energy A- Reaction without enzyme B- Reaction with enzyme

11.5 ENZYME INHIBITION-COMPETITIVE AND NON-COMPETITIVE INHIBITORS, APPLICATION OF ENZYME INHIBITION TECHNIQUES IN PEST CONTROL, ALLOSTERIC ENZYME

Enzyme Inhibition - Competitive and Non-Competitive Inhibitors

Enzyme can be inactivated by various inorganic and organic substances. Such substances are called enzyme inhibitors or negative modifier. Enzyme inhibitors are of the following 2 types -

(i) Competitive inhibitor

(ii) Non-competitive inhibitor

(i) Competitive inhibitor – The competitive inhibitors are those inhibitor which attached to the active site of the enzyme and thus renders it ineffective for e.g. malonic acid is a competitive inhibitor because it compete with succinic acid.

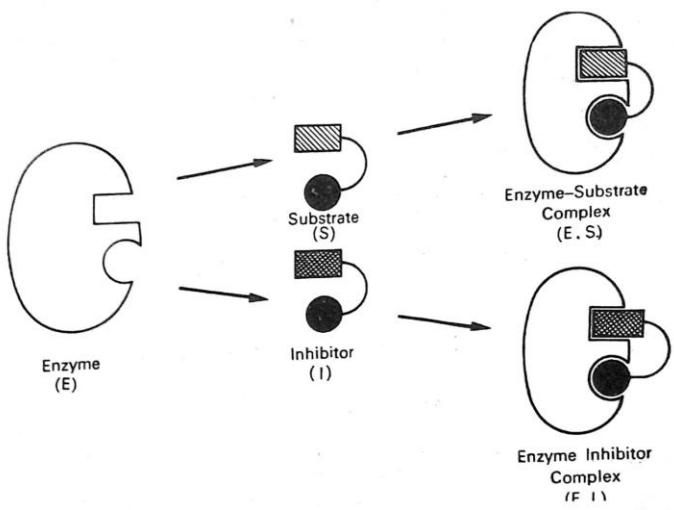


Fig: Competitive inhibition of an enzyme

In competitive inhibition both inhibitor and substrate molecule compete for binding the active site of enzyme to form enzyme-substrate complex (E.S.) or enzyme - inhibitor complex (E.I.).If the inhibitor is in sufficiently high concentration it will displace the substrate molecules and form enzyme-inhibitor complex (E.I.). If the substrate concentration is increases it will displace inhibitor and form enzyme substrate complex (E.S.). So competitive inhibition can be reversible by increasing the concentration of the substrate or inhibitor. Since the active site is directly involved, the K_m of the enzyme is altered.

(ii) Non competitive inhibitor – Non competitive inhibitors are those inhibitor which get attached to the surface of enzyme other than active site and thus render it ineffective for e.g. arsenate, chloride, fluorides etc. The inhibitor react with the various functional group of enzyme and result in death. The non-competitive inhibition cannot be reversed by increasing the concentration of the substrate. The amount of inhibition in this type of inhibition is related to (i) inhibitor-concentration (ii) Inhibitor affinity for the enzyme. The substrate concentration has no effect on this system and the K_m is not altered by the inhibitor because active site are not directly involved. The example of non- competitive inhibition is the reaction of iodoacetamide on triose phosphate dehydrogenase, a sulfhydryl enzyme.

$$\text{Enzyme} - SH + ICH_2CONH_2 \longrightarrow \text{Enzyme}–S\text{-}CH_2CONH_2 + H\,I$$

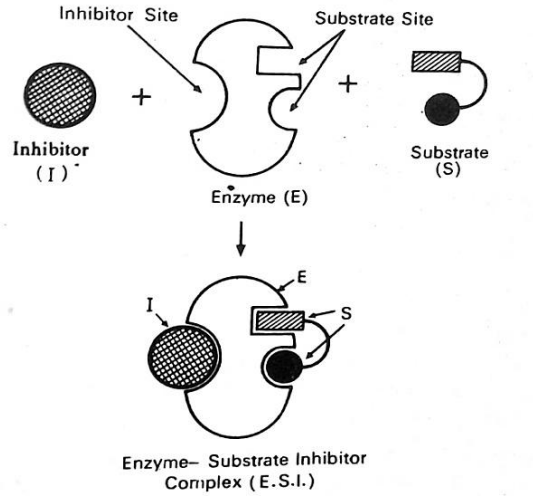


Fig 11.3: Non-competitive inhibition showing formation of enzyme-substrate-inhibitor complex

Application of enzyme inhibition techniques in pest control

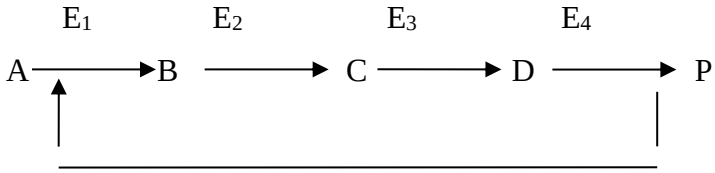
- Enzyme inhibitors are substances which bind to the enzyme resulting in loss of activity without damaging the enzyme's protein structure.
- In the gut of insect have proteoses enzyme which help in digestion of protein.
- Proteoses inhibitors are substances which inhibit the proteoses and effects digestion in insects.
- The inhibitor binds to the enzyme active site thus reduces the compatibility of substrate and enzyme and this lead to the inhibition of enzyme substrate complex formation and preventing the catalysis of reaction and decreasing the amount of product producing synthesis.
- It can be observe that as the concentration of enzyme inhibitors increases, the rate of enzyme activity decreases and thus the amount of product produce is inversely proportional to the concentration of inhibitor molecule.
- Due to blocking of an enzyme's activity can kill a pathogen or correct metabolism imbalance. Many drugs are enzyme inhibitors. They are also used in pesticides. Many pesticides are enzyme inhibitor.
- There are a variety of types of inhibitors including non-specific, irreversible, reversible, competitive and non competitive. Poisons and drugs are example of enzyme inhibitors. The most widely used type of insecticides are cholinesterase inhibitor, mainly organophosphorous compounds and carbamates.
- Acetylcholinesterase (AChE) is an enzyme which is found in animal from insect to human. This is essential to nerve cell function through the mechanism by breaking down the neurotransmitter substance acetylcholine (Ach) into acetate & choline.
- A large number of acetylcholine esterase inhibitor are used in both medicine & agriculture.
- The pesticide mostly exerts toxicity by inhibiting the enzyme Acetylcholinesterase.
- Organophosphates and carbamates are two of the most widely used classes of insecticides work by inhibiting a key enzyme acetylcholinesterase. The result is build up of the

neurotransmitter acetylcholine which then causes convulsions, paralysis and eventually death.

- PAGE analysis of the various preparations of the enzyme showed that the inhibition of the enzyme activity by DDT was associated with the presence of a selective protein band with an apparent molecular mass of 23kDa.
- The herbicide glyphosate is an inhibitor of 3-phospho-shikimate-1-carboxyvinyl transferease inhibits. The sulfenylurase inhibit the enzyme acetolactase synthetase. Both these enzyme are needed for plant to make branched chain amino acids.
- Many other enzymes inhibited by herbicide, inhibiting enzymes needed for the biosynthesis lipids and materials and the processes of photosynthesis and oxidative phosphorylation.

Allosteric enzyme

Allosteric Enzyme or Regulatory Enzyme - If a reaction is carried out in a number of steps, the last step govern the first step reaction or in other words if a product is formed after a series of enzyme reactions. The product formed influences the activity of the first enzyme in the reaction is called allosteric enzyme for e.g. A is converted into B, B is converted into C, C is converted into D, D is converted in product (P)



If the product P influences the activity of E_1. The E_1 is called allosteric enzyme or regulatory enzyme.

SAQs 1.

Complete the following sentences by inserting appropriate words in the blanks.

(i) Km constant is the substrate concentration to produce ---------- velocity in an enzyme catalyzed reaction

(ii) Sulfonamide has structural analogues with ---------- and acts as competitive inhibitor.

(iii) Which enzymes do not obey Km kinetics ----------

(iv) Which inactivates an enzyme by occupying the active site ----------

11.6 SUMMARY

In this chapter there is discussion about kinetics of enzyme reaction in which there is derivation of Michaelis – Menten equation in very detailed manner. It has been discussed about order of reaction of enzyme in which there is discussion about zero, first, second and third order reaction in detailed manner. There is also discussion about rate of reaction of enzyme, two substrate reactions, temperature co- efficient, activation energy in very detail. There is also given information of enzyme inhibition - competitive and non- competitive inhibitors, application of enzyme inhibition techniques in pest control, allosteric enzyme.

11.7 TERMINAL QUESTION

Q1. Describe the Activation Energy.

Q2. Describe the role of non competitive inhibitor.

Q3. Describe allosteric Enzyme.

11.8 ANSWERS

SAQ 1

(i) Half- maximum

(ii) P-aminobenzoic acid

(iii) Allosteric enzymes

(iv) Competitive inhibitor

Terminal question

1. Enzyme increases the speed of chemical reaction. They lower the energy of activation of a reaction thus enable it to occur at ordinary physiological temperatures, when reactions proceed from one direction to another they have to overcome an energy barrier called the activation energy. Normally only a small part of the total number of molecule in a compound contain enough energy to react. Application of heat enables a larger proportion of molecules to overcome the activation energy barrier. However living systems are relatively isothermal i.e. they do not have large temperature difference. They therefore employ enzymes to activate the molecules of the reacting compound. When the enzyme combines with the substrate to form the enzyme complex, the energy level of the substrate is raised and it reacts faster. Enzymes increases the speed of a chemical reaction thousands of times by bringing about mutual contact to reacting compounds. The coming together of these compounds is no longer a matter of chance, but become a certainty.

2. Non competitive inhibitor are those inhibitor which get attached to the surface of enzyme other than active site and thus render it ineffective for e.g. arsenate, chloride, fluorides etc. The inhibitor react with the various functional group of enzyme and result in death. The non-competitive inhibition cannot be reversed by increasing the concentration of the substrate. The amount of inhibition in this type of inhibition is related to (i) inhibitor-concentration. (ii) Inhibitor affinity for the enzyme. The substrate concentration has no effect on this system

and the K_m is not altered by the inhibitor because active site are not directly involved. The example of non- competitive inhibition is the reaction of iodoacetamide on triose phosphate dehydrogenase, a sulfhydryl enzyme.

$$\text{Enzyme} - SH + ICH_2CONH_2 \longrightarrow \text{Enzyme}–S\text{-}CH_2CONH_2 + H\,I$$

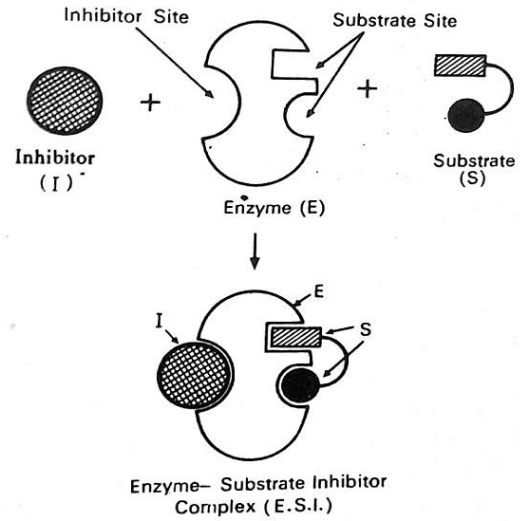
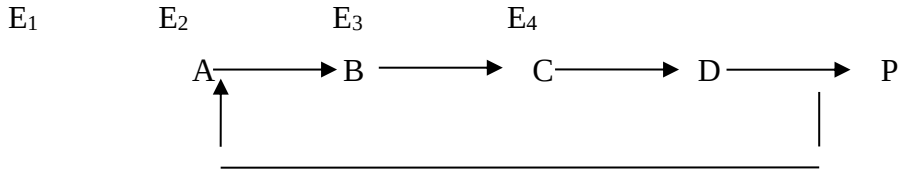


Fig: Non-competitive inhibition showing formation of enzyme-substrate-inhibitor complex

3. If a reaction is carried out in a number of steps, the last step govern the first step reaction or in other words if a product is formed after a series of enzyme reactions. The product formed influences the activity of the first enzyme in the reaction is called allosteric enzyme for e.g. A is converted into B, B is converted into C, C is converted into D, D is converted in product (P)



If the product P influences the activity of E_1. The E_1 is called allosteric enzyme or regulatory enzyme.

UNIT-12 VITAMINS

12.1 INTRODUCTION

Vitamins are the organic compounds which are required in small amount in diet as it is essential for variety of biochemical function for the normal maintenance of growth and metabolism of body. The vitamins cannot synthesize by body so it must be supplied in the diet. Funks (1911) for the first time isolated an active substance (amine) from rice polishing. He coined the term vitamine for this active substance essential for vitality. Later Sir J.C. Drummond (1920) modified the terms by removing 'e' and named it "Vitamins. There are large number of vitamins are known and some of them have been found to be amines but all have not amino compounds.

Objective

After studying this unit you will be able to know:

- Definition of vitamin, fat and water soluble vitamins.
- vitamins as co-enzymes.
- structure and function of vitamins and co-enzymes.

12.2 FAT AND WATER SOLUBLE VITAMINS

Vitamins are classified in two categories depending upon their solubility, they may fat soluble vitamins and water soluble vitamins. The fat soluble vitamins are vitamin A, D, E, K and lipoic acid and water soluble vitamins are different group of B–complex, vitamin C, Choline, Inositol, P- amino benzoic acid, bioflavonoids.

12.3 VITAMINS AS CO-ENZYMES

Vitamins are organic compounds that are essential in very small (trace) amounts for the maintenance of normal metabolism. They are generally cannot be synthesized at adequate level in the body, so they are obtained from the food.

Vitamins were found to function as components of the other coenzymes or of enzyme prosthetic groups. Coenzymes are catalytic in function and occur in very low concentration. Coenzyme is defined as when enzymes (apoenzyme) require the presence of certain additional organic substance in the reaction system for its activity. This organic substance is called as coenzyme. The vitamin act as coenzyme because they have group transfer agents, carrying electron and chemical group such as

acyl group, methyl group etc. depending on the coenzyme. All the water soluble vitamin and two fat soluble vitamin A & K act as coenzyme.

Vitamins B complex group acting as coenzymes	
Vitamin	**Active form (coenzymes)**
Vitamin B_1 or Thiamin	TPP (Thiamine pyrophosphate)
Vitamin B_2 or Riboflavin	FMN, FAD
Vitamin B_3 or Niacin	NAD, NADH
Vitamin B_5 or Pantothenic acid	Component of Coenzyme –A
Vitamin B_6	Pyridoxal phosphate (PALP)
Vitamin B_7 or Biotin	Biotin
Vitamin B_{12} or Cobalamin	Cobamide
Vitamin Bq or Foilc acid	THF (Tetra hydrofolate)
Vitamin A	Retinal
Vitamin K	

Vitamin B_1 or Thiamin : It is a derivative of substituted pyrimidine and a thiazole, linked by a methylene bridge. Its biologically active form is thiamin pyrophosphate (TPP). The TPP is formed in the brain & liver by the enzyme Thiamin diphosphotransferase. The thiamin pyrophosphate serve as a cofactor for the pyruvate and α-ketoglutarate dehydrogenase as well as the transketolase catalyzed reactions of the pentose phosphate pathway.

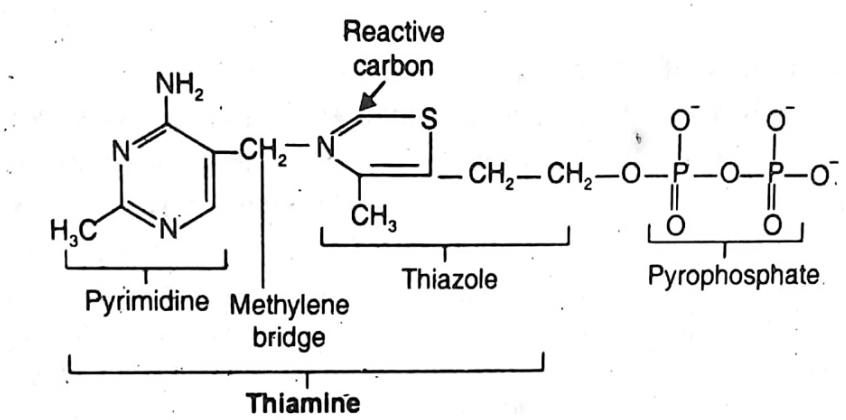


Fig 12.1: Structure of Vitamin B_1 or thiamine

Vitamin B_2 or Riboflavin : The coenzyme form of riboflavin are flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD). The enzymes that require FMN or FAD as cofactor are termed

flavoproteins. The flavoproteins are involved in a wide range of redox reaction like succinated dehydrogenease. The reduce form of FMN & FAD are $FMNH_2$ & $FADH_2$ respectively.

FAD & FMN act as intermediate hydrogen acceptors in the mitochondrial electron transport chain, accepting hydrogen derived from foods stuff and transferring electrons to the cytochrome system.

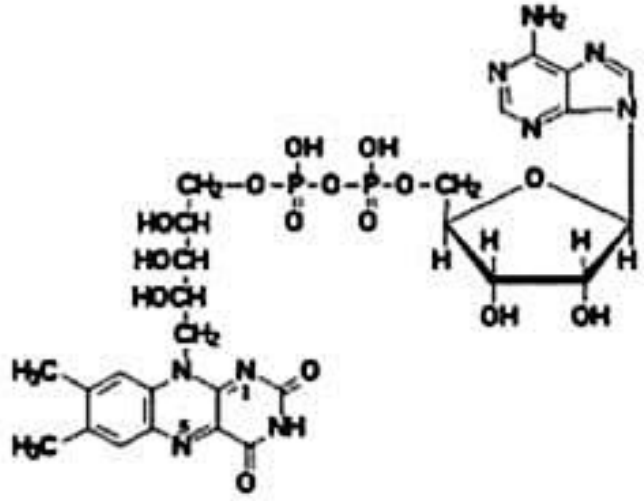


Fig 12.2: Structure of FAD

Vitamin B_3 or Niacin : The coenzyme forms of niacin are nicotinamide adenine dinucleotide (NAD^+) & nicotinamide adenine dinucleotide phosphate ($NADP^+$). Both NAD^+ & $NADP^+$ function as cofactor for numerous dehydrogenase e.g. lactate & malate dehydrogenase. In the oxidized form of NAD (NAD^+) the pyrimidine ring is positively charged due to the delocalization of the positive charge on the nitrogen atom. The coenzyme NAD^+ & $NADP^+$ are involved in a variety of oxidation-reduction reactions. They accept electrons in the form of hydride ion, H^+.

There are nearly 40 different oxido-reductase which use either NAD^+ or $NADP^+$ as cofactor. Some are specific to only NAD^+ or only $NADP^+$, while some use either one of them. These coenzymes are loosely bound to enzymes and can be separated from the enzyme by dialysis.

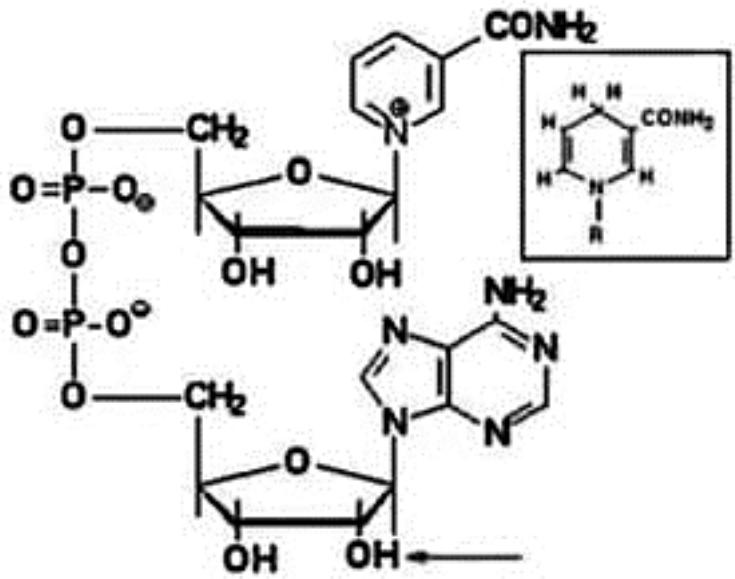


Fig 12.3: Structure of NAD^+

Vitamin B_5 or Pantothenic acid : The coenzyme form of Vitamin B_5 or Pantothenic acid is coenzyme-A. The coenzyme-A or Co-A has a terminal thiol group which is the reactive part of the coenzyme Acyl group (free fatty acids) are linked to Co-A by a thioester bond (-S-Co-A) to give acyl Co-A.

Acetate	form	Acetyl Co-A
CH_3COO^-		CH_3-CO-S-Co-A

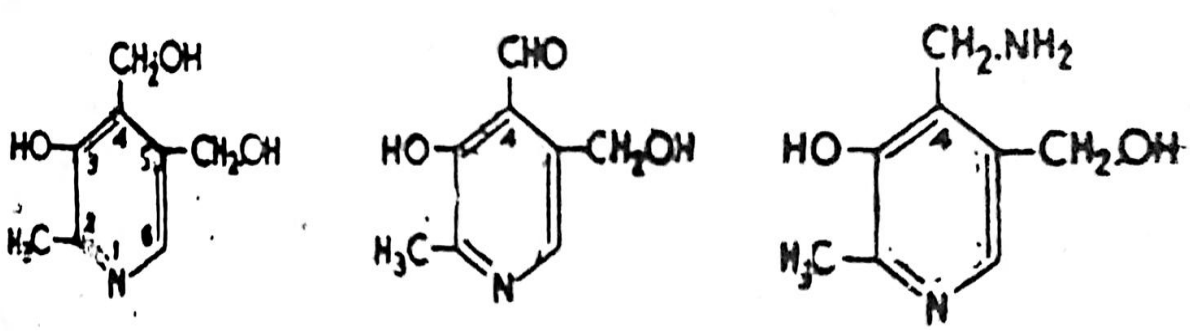
Coenzyme-A serve a carrier of activated acetyl or acyl groups a thiol esters.

Pyruvate $\xrightarrow[PDH]{CoASH}$ Acetyl Co-A

CH_3-CO-COO- CH_3-Co-S-CoA

Vitamin B_6 : Vitamin B_6 are pyridoxine, pyridoxal & Pyridoxamine. All the three compounds are efficiently converted in the body to coenzyme form of Vitamin B_6, pyridoxal phosphate (PALP). This is converted by an enzyme pyridoxal kinase.

Pyridoxal phosphate functions as cofactor for transamination, decarboxylation and racemase reactions.



Pyridoxin Pyridoxal Pyridoxamine

Fig 12.4: Structures of vitamin B_6

Vitamin B_7 or Biotin : Biotin is a prosthetic coenzyme that catalyzes carboxyl group transfer and ATP dependent carboxylation reactions. It is covalently linked to the active site of its host enzyme by a amide bond to the ε-amino group of a lysine residue.

Vitamin B_{12} or Cobalamin : The two coenzyme form of Vitamin B_{12} or Cobalamin is 5-deoxy adensyl cobalamin & methylcobalamin. The biochemical function of Vitamin B_{12} is a cofactor for two clinically significant reactions in the body.

In fatty acid synthesis, the enzyme methyl malonyl-Co-A mutase, require Vitamin B_{12} as a cofactor in the conversion methyl malonly-Co-A to succinyl-Co-A.

Vitamin B_{12} catalyzes the conversion of homocysteine to methionine and is catalyzed by methionine synthase.

Vitamin A : Vitamin A contains an alcohol group and is known as retinol. The retinol and retinoic acid forms are important regulators of gene expression, during development. The aldehyde form of retinol is the prosthetic group in the protein rhodopsin which captures photons in the eye.

Vitamin K : Vitamin K serve as a coenzyme in an important post translational modification of some blood coagulation proteins. In this reaction glutamate residue are carboxylated to their carboxy-glutamate form which bind calcium, the divalent cation serve as a bridge by which coagulation proteins are anchored to platelets, where clotting is needed. Vitamin K reversibly carries an electron in its quinone ring that is used in the carboxylation reaction.

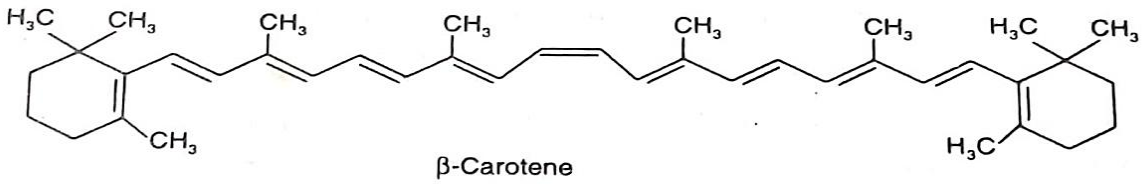
12.4 STRUCTURE AND FUNCTION OF VITAMINS AND CO-ENZYMES

Fat soluble vitamins

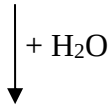
Vitamin A

History: Vitamin A was first time recognized by Elmer McCollum in 1915 and isolated from fish liver oil by Holmes in 1917. It play important role in the visual process, so it is also called "antixerophthalmic factor" or "bright eyes" vitamin. It was synthesized by Milas in 1946.

Structure: Vitamin A is found in two form vitamin A_1 and vitamin A_2. The carotenoid which gives rise to the vitamins A is called provitamin A_1. Provitamin A_1 consists of α, β. Carotenoid and cryptoxanthin. In which β-carotene is one of the most active form. β- caroteen is made up of eight 5-carbon isoprenoid unit linked to form a chain of 40 carbon unit with an ionone ring at each end. It is orange-red hydro-carbon and upon hydrolysis yield 2 moles vitamin-A. During hydrolysis a cleavage is occur at the midpoint of the β-carotene chain. This conversion occurs in liver of fishes and mammals. Vitamin A_1 is a complex primary alcohol called retinol, having the empirical formula $C_{20}H_{29}OH$. The terminal hydroxyl group is ordinarily esterified. It contains β-ionone ring. Vitamin A_2 is found in fresh water fishes. It differ from vitamin A_1 in possessing an additional conjugate double bond between carbon atom 3 and 4 of the ionone ring



β-Carotene



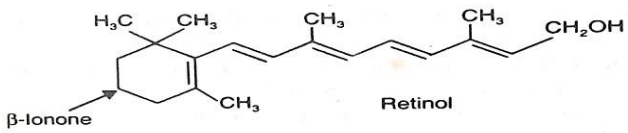


Fig 12.5: Structure of vitamin A_1 or Retinol or Axerophthol

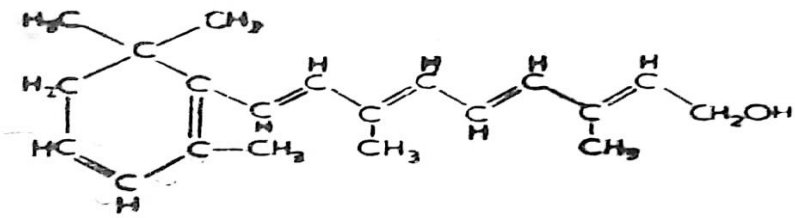


Fig 12.6: Structure of vitamin A_2 or 3-dehydro-retinol

Functions

(1) The main function of vitamin A is in the process of vision. The functional chemistry of vision is cyclic in nature. The retina contains two types of cells rods and cones. Rods are concerned with vision in dim light (night vision) while cones are concerned with bright light (day vision). Rods contain Rhodopsin, a photo sensitive pigment while cones contain iodopsin, pigments.

The first event of visual cycle is when exposed to light, the Rhodopsin (11-cis-retinal-opsin) is converted into all-trans-retinal. This all-trans-retinal is converted into 11-cis-retinal by the help of enzyme retinal isomerase. The 11-cis-retinal combines with opsin and regenerates rhodopsin and completes the visual cycle.

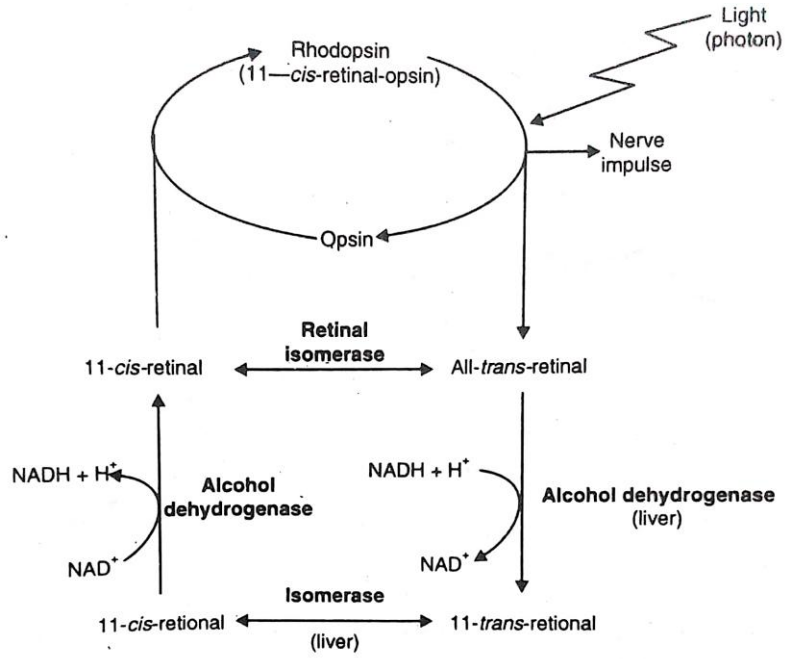


Fig 12.7: Structure of visual cycle

The cones are responsible for colour perception. The cones contain the colour sensitive pigments porphyropsin (red), iodopsin (green) and cyanopsin (blue). When light strikes the retina, it bleaches one or more of these pigments based upon the quality of light. The

pigments are converted to all–trans–retinene and protein opsin. This reaction produces the nerve impulse which is read as blue, green or red based on the pigment affected,

(2) The vitamins A is responsible for the maintenance of the integrity of epithelial tissue. In its absence, normal secretry epithelium is replaced by a dry, keratinized epithelium. This is due to retinol and retinoic acid are required to prevent keratin synthesis. The retinyl phosphate helps to maintain moist surface of the epithelial cells by forming mucopolysaccharides.

(3) Vitamins A help in the prevention of infection.

(4) Vitamins A are essential to cell growth and differentiation.

(5) Retinol and retinoic acid are essential for the synthesis of transferrin, the iron transporting protein.

(6) Cholesterol synthesis requires vitamin A.

Vitamin–D

History – In 1922 Elmer Mc Collum, first demonstrate the existence of Vitamin D. He found that cod liver oil was effective in preventing rickets. Due to its preventive action on rickets, vitamin D is called as antirachitic factor. It is also called as sun shine vitamin as its provitamin form present in human skin is easily converted to the active form by irradiation with ultra- violet light. Vitamin D was isolated in crystalline form by August, windows and other in 1931 who named it calciferol.

Structure – Vitamin D is present in two form mainly ergocalciferol (vitamin D_2) and cholecalciferol (vitamin D_3) The ergocalciferol (vit. D_2) is present in plant and formed from ergosterol . The cholecalciferol (vit. D_3) is present in animal and is formed by irradiating the animal sterol, 7-dehydrocholesterol. The vitamin D_2 is formed from ergosterol in following series of reaction

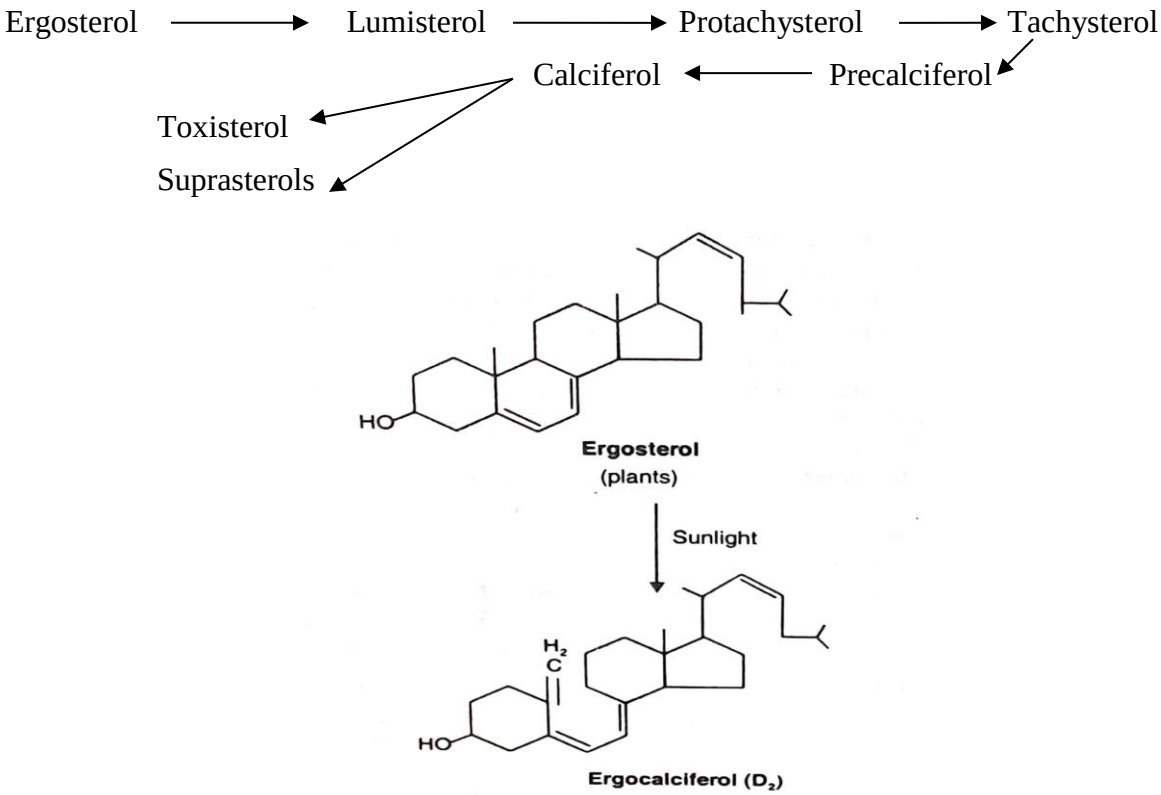


Fig 12.8: Formation of ergosterol (provitamin D_2) to ergocalciferol (vitamin D_2)

The vitamin D_3 (cholecalciferol) is formed from 7-dehydrocholesterol in following series of reaction

7-dehydrocholesterol ⟶ lumisterol$_3$ ⟶ Tachysterol$_3$ ⟶ Precalciferol$_3$

↓

Cholecalciferol

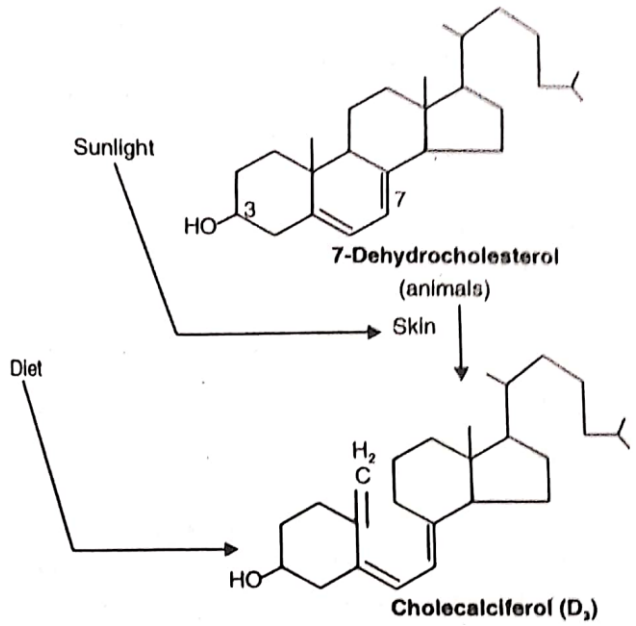


Fig 12.9: Formation of 7-dehydrocholesterol (provitamin D_3) to Cholecalciferol (vitamin D_3)

Function - The active form of vitamin D is calcitriol. It acts

(i) Calcitriol stimulates the calcium uptake by osteoblasts of bone for deposition as calcium phosphate. Thus it is essential for bone formation, hence it promotes growth.

(ii) Calcitriol helps in minimizing the excretion of calcium and phosphate.

(iii) Calcitriol helps the absorption of calcium and phosphate by the intestine. In the intestinal cells, calcitriol binds with a cytosolic receptor to form a calcitriol-receptor complex. This will interact with specific DNA leading to the synthesis of calcium binding protein. This protein participates in the active transport of calcium across the small intestinal mucosa.

(iv) Vitamin D increases citrate content of bone, blood and other tissues.

(v) Vitamin D exerts an anti-rachitic effect.

Vitamin E

History – Vitamin E was first discovered by Evans and Matill independently in 1920 from vegetable oils. Later in 1936 Evans and Emerson isolated vitamin E from wheat germ oil and named it tocopherol. Vitamin E is also called as anti-sterility factor because in absence of this vitamin makes the animal sterile.

Structure – Vitamin E or tocopherol exhibit in different form α, β, γ, δ, Є, etc. Of these α-tocopherol ($C_{29}H_{50}O_2$) has the widest distribution and most active form. It has a chromane ring system containing four methyl groups, one phenolic group and a phytyl side chain.

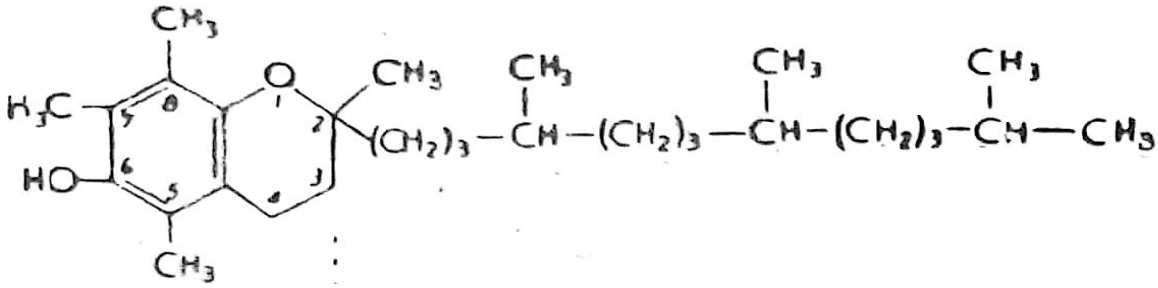


Fig 12.10: Structure of α- tocopherol (5,7,8 – trimethyl tocol)

Functions – Vitamin E is act as antioxidant. It has following function.

(i)Vitamin E preserves and maintains germinal epithelium of gonads for proper reproductive function.

(ii)It prevents the oxidation of vitamin A and carotenoids.

(iii)It protects liver from toxic compounds such as carbon tetrachloride.

(iv)Vitamin E maintains the structural integrity of muscles and peripheral muscular system in the animals.

(v)It also has been observed that vitamin E protects against the development.

Vitamin K

History – Vitamin K (German word mean koagulation) is responsible for blood clotting and hence it is called antihemorrhagic factor or coagulation vitamin. It is the only fat-soluble vitamin with a specific co-enzyme function. Dam (1929) observed that a specific factor presents in natural diet which protect against hemorrhagic disease is called vitamin K. Vitamin K occur in two form vitamin K_1 & vitamin K_2. The vitamin K_1 was first isolated by Dam *et.al.* from alfa-alfa in 1939 and vitamin K_2 from fish meal by Doisy *et.al.* in 1939 .

Structure – Chemically vitamin K is derivatives of quinones and it exist in two forms K_1 & K_2. The vitamin k_1 ($C_{31}H_{46}O_2$) is a phytol radical and vitamin k_2 ($C_{41}H_{56}O_2$) is a difarnesyl radical.

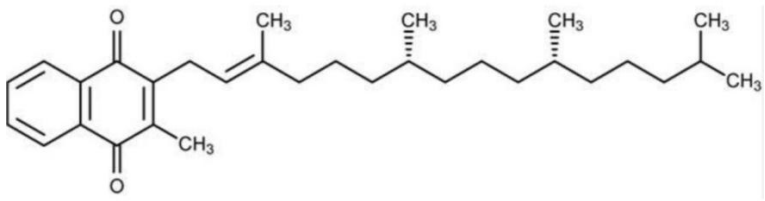


Fig 12.11: Structure of vitamin K_1 (2-methyl- 3-phytye-1, 4 naphthoqunione)

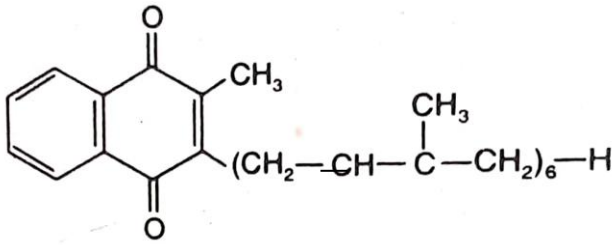


Fig 12.12 : Structure of vitamin K_2 (2-methyl- 3difarnesyl-1, 4 naphthoqunione)

There is also vitamin K_3 which is a synthetic product and also known as menadione.

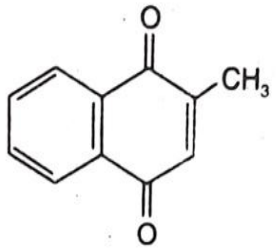


Fig 12.13: Structure of vitamin K_3 (2-methyl-1, 4 naphthoqunione)

Vitamin k_1 is a yellow viscoid oil but vitamin k_2 is a yellowish crystalline solid. It is sensitive to light and hence it is kept on dark bottles. It is destroyed by irradiation, strong acids, alkalis and oxidizing agents.

Function-

(i) Vitamin K promotes the biosynthesis of prothrombin in liver tissue.

(ii) Vitamins K are absorbed only in the presence of bile. The absorption occurs in the upper portion of the small intestine where bile salts are presents.

Water soluble vitamins

Vitamin B complex: The vitamin B complex includes a group of different vitamins which are structurally and functionally different from each other. The only common property exhibited by these vitamins is that they form co-enzyme or prosthetic group of different enzymes. Thus vitamin B helps in the metabolism of carbohydrates, lipids, proteins, nucleic acids, minerals and numerous other substances. Generally these vitamins are synthesized by the intestinal flora of micro-organisms. The groups of vitamin B are as follows:

(1) Vitamin B_1 or Thiamine

(2) Vitamin B_2 or Riboflavin

(3) Vitamin B_3 or Niacin

(4) Vitamin B_5 or Pantothenic acid

(5) Vitamin B_6 or Pyridoxine

(6) Vitamin B_7 or Biotin

(7) Vitamin B_9 or Folic acid

(8) Vitamin B_{12} or Cyano-cobalamine

Vitamin B_1 or Thiamine

History- Vitamin B_1 or Thiamine was the first member of the vitamin B group. Thiamine was first isolated by Jansen (1926) in Holland and Windows in Germany from the rice polishing. However it's structure was described in 1936 by Williams, Clarks and co-workers and they synthesized it in laboratory. It is also called anti beri-beri or anti-neuretic factor vitamin.

Structure -Thiamine ($C_{12}H_{17}N_4OS$) is 2,5-dimethyl, 6-amino pyrimidine + 4-methyl, 5-hydroxy ethyl thiazole. Thiamine possesses a pyrimidine ring attached to a thiazole nucleus.

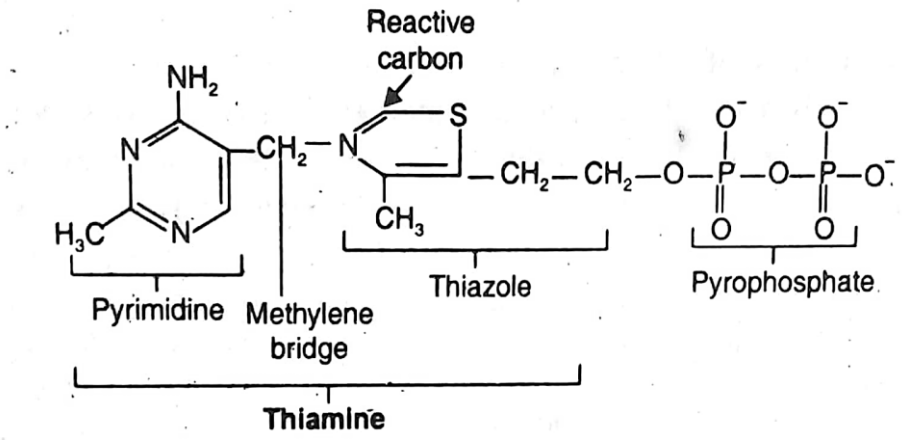


Fig 12.14 : Structure of Vitamin B_1 or thiamine

Function: Thiamine act as a co-enzyme in the carbohydrate metabolism especially in glycolytic pathway and kreb cycle. The reaction of enzyme pyruvate dehydrogenase, which catalyzes the irreversible conversion of pyruvate to acetyl Co-A, is dependent on Thiamine pyrophosphate (TPP). The α-ketoglutarate dehydrogenase of kreb's cycle requires TPP. The enzyme transketolase of hexose monophosphate shunt (HMP shunt) is dependent on TPP. The thiamine pyrophosphate also 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 nerve impulse.

It has also been reported that thiamine is necessary for normal uptake of oxygen by the brain tissue. In polyneuritic pigeons having severe deficiency of Thiamine.

Vitamin B_2 or Rioflavin

History – Vitamins B_2 or riboflavin was first isolates in 1879 from milk whey, which is an essential dietary factor for rats. Since it was first isolated from milk, vitamin B_2 is also known as lactoflavin. It was synthesized by Kuhn and Karrer. Riboflavin was the first B complex vitamin that was isolated in pure form. It is popularly called as the "yellow enzyme" because of its color.

Structure: Riboflavin is chemically 6,7 dimethyl-9-D–1-ribityl-isoalloxazine. It contains a sugar alcohol, ribitol, which is derived from ribose sugar. Riboflavin is stable to heat but sensitive to light. when exposed to UV light, it is converted to lumiflavin which exhibits yellow fluorescence.

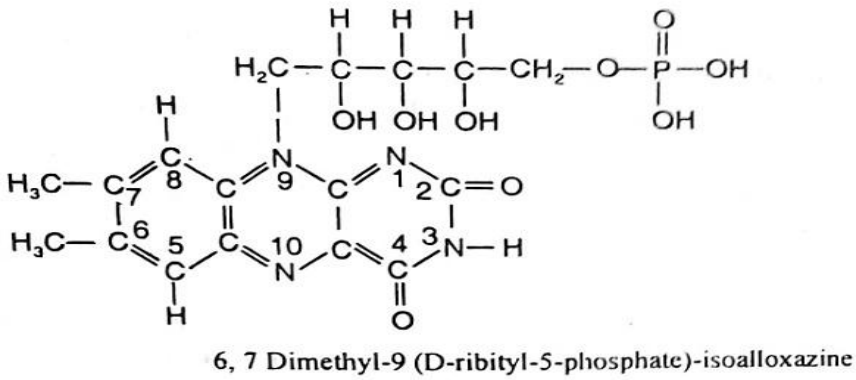


Fig 12.15: Structure of vitamin B_2 or Rioflavin

Function – Vitamin B_2 or riboflavin is involved in the metabolism of proteins, fats, carbohydrates and nucleic acids by forming part of the flavo-proteins. Flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD) are two co-enzyme forms of riboflavin. The important enzymes such as L-amino acid oxidase, D-amino acid oxidase, succinic dehydrogenase, xanthin oxidase, cytochrome C-reductase all contain riboflavin in their molecular structure. The main function of this vitamin is concerned with oxidation reductions.

Vitamin B

History – Vitamin B_3 or pantothenic acid was 1st isolated by Roger Williams in 1938 from yeast and liver concentrates. On its wide distribution it is also called as pantothenic acid (panto = everywhere). This vitamin is sometime also called as filtrate factor or yeast factor.

Structure – Pantothenic acid ($C_9H_{17}NO_5$) is an amide of pantoic acid (α, γ - dihydroxy –β, β – dimethyl butyric acid) and β-alanine.

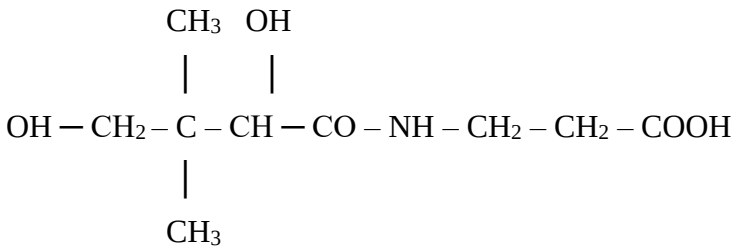


Fig 12.16 : Structure of vitamin B_5 or Pantothenic acid

Function – The metabolic fate of this vitamin is its participation in the formation of the biologically important co-enzyme – A. It functions as a thio-ester of carboxylic acids.

Vitamin B_3

History – Vitamin B_3 or nicotinic acid or niacin was first isolated by funk in 1911. Goldberg 1928 was first identified its relation to the deficiency of a dietary factor. Elvehjem and his co –worker 1938 isolate nicotinic acid from liver and used for curing action against black tongue disease in dog and hence called anti-black tongue factor. It is also used in curing pellagra disease therefore it is also called pellagra - preventive (pp) factor.

Structure – Niacin or nicotinic acid ($C_6H_5O_2N$) is a pyridine derivative.

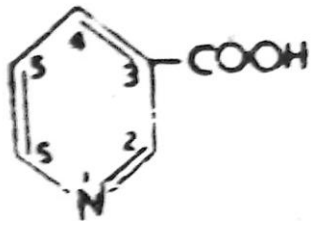


Fig 12.17: Structure of vitamin B_3 or Niacin

Function – Vitamins B_3 forms two co-enzyme NAD & NADP which carry out two important functions in the tissues.

(a) Oxidation of alcohols, aldehydes, amino-acids and hydroxyl carboxylic acids.

(b) Reduction of the flavin co-enzymes.

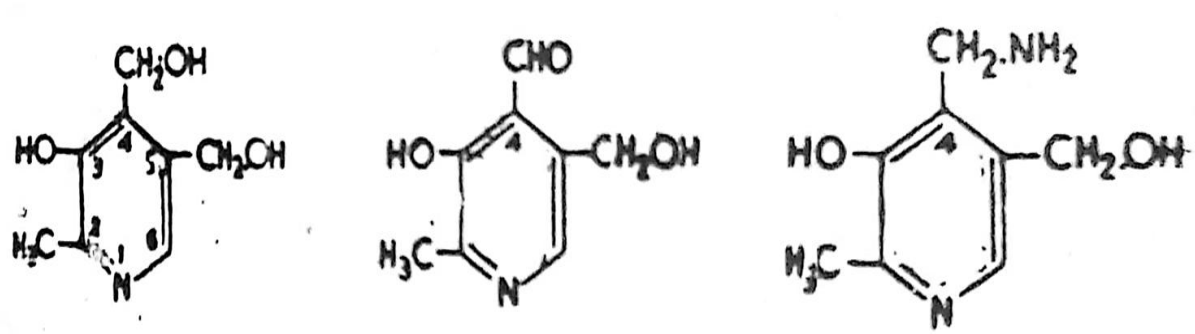
It is also involved in the oxidation of carbohydrates, lipids, deamination of amino acids and metabolisms of α-keto-acid. It in the form of NAD forms the normal component of electron transport chain

Vitamin B_3 produces marked vasodilation and a sense of warmth in the face, neck and arms due to increased blood flow. The plasma lipid level falls. Therefore, it is used in the treatment of hyperglycemia.

Vitamin B_6

History – Vitamin B_6 are used in curing dermatitis in rats. So it is also called adermin or antidermatitis factor. Vitamin B_6 includes 3 compound pyridoxine, pyridoxal and pyridoxamine. Pyridoxine was first isolated in 1938 from yeast and liver. The Snell (1942) isolate pyridoxal and pyridoxamine.

Structure – Vitamin B_6 are pyridine derivatives, C_5H_5N. They differ from each other in the structure of functional group attached to 4th carbon in the pyridine ring. Pyridoxine is a primary alcohol, pyridoxal is an aldehyde and pyridoxamine is an amine. Pyridoxine is 2-methyl 3-hydroxy 4, 5 di hydroxy methyl pyridine. All the 3 forms are readily inter convertible biologically.



Pyridoxin Pyridoxal Pyridoxamine

Fig 12.18: structures of vitamin B_6

Function – The active form of vitamin B_6 is the co-enzyme pyridoxal phosphate. It is essential for the metabolism of amino acids. Pyridoxine is responsible for the synthesis of some important products such as serotonin, histamine and niacin. Pyridoxal phosphate is also important for some functions.

(i) Deamination – It is involved in the deamination of hydroxyl group containing amino acids.

$$\text{Threonine} \xrightarrow[\text{Pyridoxal phosphate}]{\text{Dehydratase}} \alpha\text{ - ketobutyrate} + NH_3$$

(ii) Decarboxylation – Pyridoxal phosphate is also involved in decarboxylation of some α – amino acids.

$$\text{Glutamate} \xrightarrow{\text{Pyridoxal phosphate}} \text{Gamma amino butyric acid} + CO_2$$

Pyridoxal phosphate

Tyrosine ⟶ Tyramine + CO_2

(iii) Pyridoxal phosphate is responsible for the synthesis of NAD and NADP from amino acid tryptophan.

(iv) Pyridoxal phosphate is required for the synthesis of sphingosine from serine, arahidonic acid and linoleic acid.

(v) The formation of co-enzyme from pantothenic acid requires pyridoxal phosphate.

(vi) Pyridoxal phosphate play an important role in the metabolism of sulphur containing amino acid i.e. cysteine.

(vii) Pyridoxal pyrophosphate is involved in the transamination reaction converting amino acid to keto acids. The keto acids formed enter the citric acid cycle and gets oxidized to generate energy.

(viii) Pyridoxine is also considered to be essential for metabolism of unsaturated fatty acids.

(ix) Pyridoxine has been found to be associated with the active transport of amino acid into the cells.

(x) The effect of B_6 is antagonized by isonicotinic acid hydrazide (INH) which is used in the treatment of tuberculosis.

(xi) It has also been reported to promote transport of potassium across the membranes from exterior to interior.

Vitamin B $_7$

History - It was 1st isolated by fritz kogl (1935) from 250 kg of dried egg yolks about 1mg of a "bios" factor (growth promoting factor) necessary for yeast and named it as "biotin". It is also called "anti egg white injury factor" which is also responsible for the curing of egg white injury induced in rats and other animal by feeding them with raw egg white. It is also called co- enzyme R because it is a growth factor for the N_2 fixing bacterium *Rhizobium*.

Structure - The structure of biotin ($C_{10}H_{16}O_3N_2S$) was worked out by du Vigneaud in 1942. The Biotin has an unusual structure and consists of a fused imidazole and thiophene ring with a fatty acid side chain.

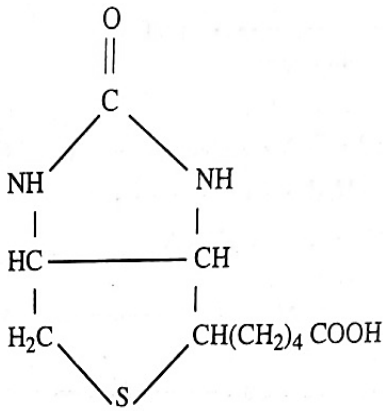
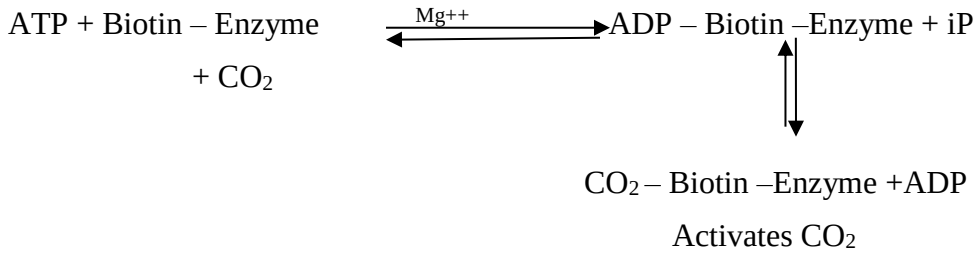


Fig 12.19: Structure of Vitamin B $_7$ or Biotin

Function - Biotin is involved in the carboxylation reactions. It is involved in the activation of CO_2 in the following manner.



This CO_2 can be fixed with other compounds such as pyruvic acid, propionic acid and acetyl co-enzyme. Active CO_2 is also involved in the synthesis of carbonyl phosphate. Fatty acid synthesis is significantly reduced in biotin deficiency.

Vitamin B_9

History – Vitamin B_9 or folic acid was 1st suggested by Day as a nutritional requirement for curing cytopenia, a disease induced in monkey. The potent factor was obtained from spinach leaf and hence it is called as folic acid. This folic acid is known as folacin. This is also known as liver lactobacillus casei factor as it was isolated from liver and was shown as necessary for the growth of lactic acid bacteria. Hogan called vitamin B_9 as vitamin B_c. There are several other compound which have been obtained from different sources having almost similiar biological properties as folic acid. These are *Streptococcus lactis* R (SLR) factor, factor U, vitamin M and Citrivorum. Factor (CF). The folic acid was obtained in pure crystalline form in the Lederle laboratories in USA.

Structure – Angier and his co- worker established the structure of folic acid in 1946 and synthesized it chemically. Folic acid is made up of glutamic acid, P-amino benzoic acid (PABA) and pteridine ring. The active form of folic acid is tetrahydrofoliate.

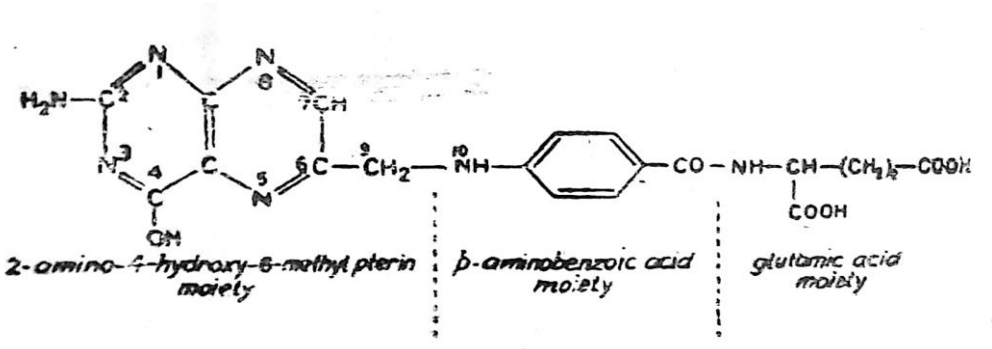


Fig 12.20: structure of vitamin B_9 or folic acid

Function –

(i) The tetra-hydrofoliate (THF), co-enzyme of folic acid is actively involved in single carbon metabolism. It serves as an acceptor or donor in a variety of reaction involving amino acid and nucleotide metabolism. Many important compounds are synthesized in single carbon metabolism. Purines which are incorporated into DNA are synthesized. N- Formyl methionine, the initiator protein synthesis is formed.

(ii) Folic acid taken part in the formation and maturation of blood cells.

(iii) The bacteria which require PABA for growth also utilize folic acid with almost equal ease.

(iv) Folic acid is essential for lactation in rats and hatchability of eggs in chicks, turkeys and guinea pigs.

(v) Rats, dogs, and probably man do not need folic acid because the intestinal bacteria synthesize sufficient quantity of this vitamin.

Vitamin B_{12}

History – Shorb for the first time identified vitamin B_{12} is essential for growth factor for *lactobacillus lactis*. In 1926 George Minot and George William Murphy discovered that the person suffering from pernicious anaemia can be cured by feeding with raw liver. Hence is called anti-pernicious anaemia factor (APA factor). It was isolated and crystallized in 1948 independently by E. Lestersmith in England, Edward Rickes and Karl folkers of USA. It has cobalt, cyanide and amino group in its molecular structure and hence it is also known as cyano-cobalamin. The co-enzyme of this vitamin has been called a "biologic Grignard reagent".

Structure – Vitamin B_{12} has a complex structure. Its structural formula is $C_{63}H_{90}N_{14}O_{14}PCO$. Cyano-cobalamin is a compound containing one atom of cobalt bound by co-ordinate linkages to the four nitrogen atoms of a partially hydrogenated tetrapyrrole, a cyanide group and to a nucleotide 5,6-dimethyl-1-(D-ribofuranosyl)–benzimidazole – 3phosphate.

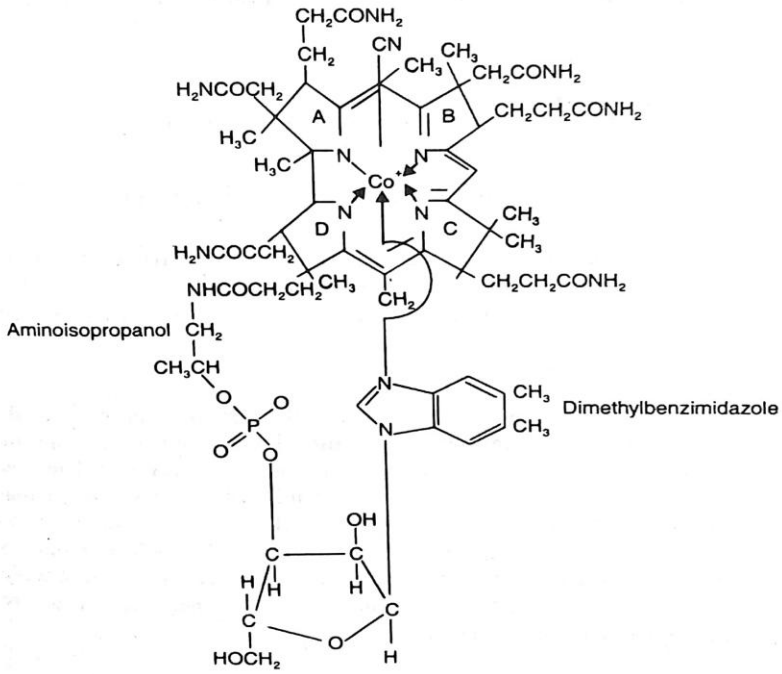


Fig 12.21: Structure of Vitamin B_{12} or Cyanocobalamin

Vitamin B_{12} is of 3 types B_{12}a, B_{12}b and B_{12}c. In vitamin B_{12}a cobalt is bound to cyanide, vit B_{12}b is bound to hydroxyl group and vit B_{12}c is bound to nitrite group. Hence vit B_{12} a is known as cyano-cobalamin, B_{12}c is known as nitrito-cobalamin.

Function

(i) Vitamin B_{12} is essentially required for normal hematopoiesis (formation of blood) and erythrocyte maturation.

(ii) Vitamin B_{12} as a growth promoting effect in young children.

(iii) Vitamin B_{12} is innovated in biosynthesis of nucleic acids.

(iv) It is involved in the metabolism of glycine, serine, methionone, choline and methyl group.

(v) It is also involved in the enzyme conversion of methyl malonyl co-A to succinyl co -A.

(vi) Vitamin B_{12} is clinically used in cases of megaloblastic anaemia and to treat neurological disturbance.

(vii) Vitamin B_{12} is also required for the formation of myelin sheath in the nerve.

Vitamin C

History – In 1928 Albert-Szent-Gyorgi isolated vitamin C from the paprika plant and named it hexuronic acid. In 1932 king and Waugh of USA isolate this vitamin from lemon juice. It was synthesized by Reichstein in 1933. It is also called cevitamin. It has a curing action against scurvy and hence popularly called as antiscorbutic factor.

Structure – Haworth established the structure of ascorbic acid ($C_6H_8O_6$). It is a derivative of a hexose called L-glucose. Chemically it is 1-threo-2,4,5,6-pentoxyhexen-2-carboxylic acid lactones.

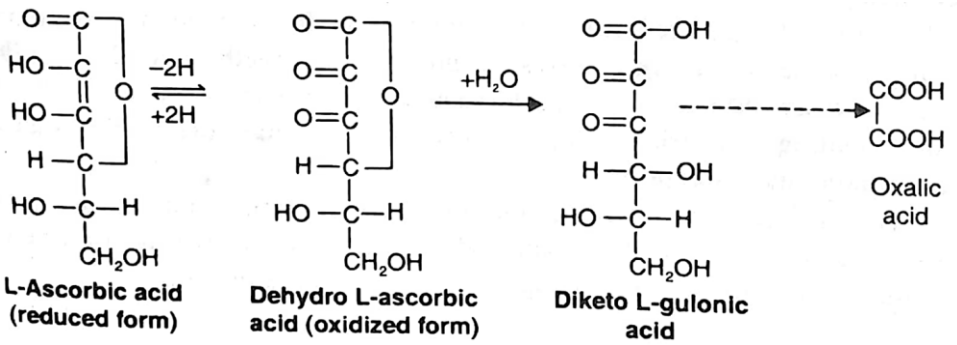


Fig 12.22: Structure of vitamin C and related compounds

In animals liver and adrenal cortex are the main sites of synthesis. The biosynthesis of ascorbic acid in animal take place in following ways.

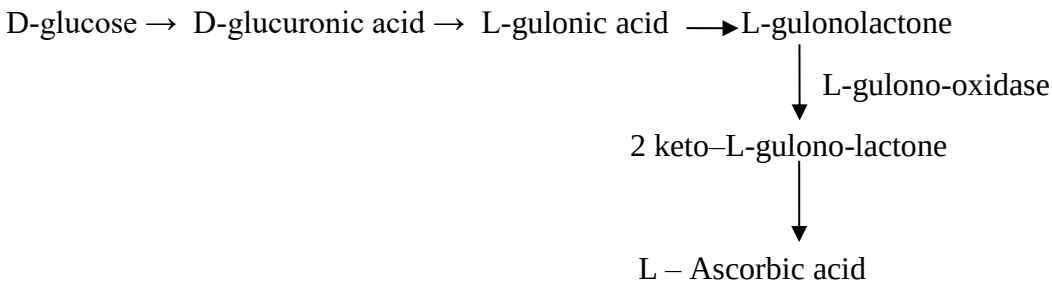


Fig 12.23: Biosynthesis of Vitamin C

In man L-gulono-oxidase enzyme does not found and hence incapable of synthesizing ascorbic acid.

Function

(i) Vitamin C is involved in the electron transports in the microsomal fraction.

(ii) Vitamin C enhances the synthesis of immunoglobulin and increases the phagocytic action of the leucocytes.

(iii) In adrenal cortex, high concentration of ascorbic acid is found. It is believed that the vitamin is necessary for hydroxylation reaction in the synthesis of corticosteroid hormones.

(iv) Ascorbic acid enhanced the synthesis of bile acid from cholesterol.

(v) Vitamin C is essential for the formation of active form of vitamin folic acid (tetrahydrofolate).

(vi) Vitamin C helps in tryptophan metabolism.

(vii) Vitamin C is required in the formation of bone.

(viii) Ascorbic acid is required for the oxidation of P-hydroxy-phenylpyruvate to homogentesic acid in tyrosine metabolism.

(ix) Vitamin C plays the role of a co-enzyme for the hydroxylation of proline and lysine.

(x) Vitamin C provides resistance against common cold.

(xi) It also plays an important role in wound healing and activates metabolism.

(xii) Its presences enhance the absorption of iron from vegetables, cereals and fruits.

(xiii) Vitamin C act as an anti-ageing agent.

(xiv) Vitamin C plays an important role in leprosy treatment.

Inositol

History – Woolley (1940) discovered that when mice feed on a synthetic diet containing all the known vitamins even failed to grow and their hair growth are also arrested. It cans be cure by addition of phytin (obtained from cereal) or inositol (from liver) and hence it is called mouse antialopecia factor. It is also known as muscle sugar.

Structure – Chemically it is carboxylic hexahydric alcohol. The formula is $C_6H_{12}O_6$ or $C_6H_6(OH)_6$. It has 9 stereoisomers, of which only one myo-inositol, found in muscle, is biologically active and most important factor.

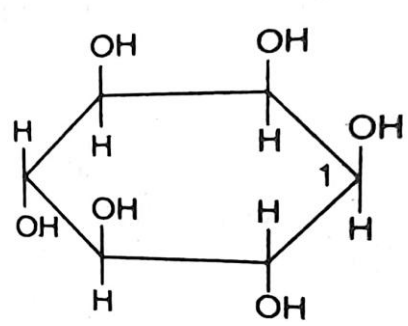


Fig 13.24: Structure of inositol

Function -

(i) Phospho inositol help in transport processes in cells.

(ii) It stimulates the growth of many micro-organisms such as *Saccharomyces cerevisiae* and *Neurospora*.

(iii) Inositol act as lipotropic factor and prevents the formation of fatty liver.

(iv) It acts as second messenger for some hormones.

(v) It is an intermediate between carbohydrate and aromatic substances.

(vi) Inositol, as hexaphosphate form phytin in plant prevents the absorption of iron and calcium from the intestine.

Deficiency – Its deficiency results in retard growth and a peculiar hairlessness in mice, lack of inositol also causes insufficient lactation in experimental animals.

Choline

History – For the 1st time Best and Huntsman (1934) found that choline prevents the development of fatty livers in depancreatized dogs. Hence choline is an important metabolites of the diet of animals and is therefore usually include among the vitamins.

Structure – Choline ($C_5H_{15}O_2N$) is a chemically trimethyl hydroxyl ethyl ammonium hydroxide.

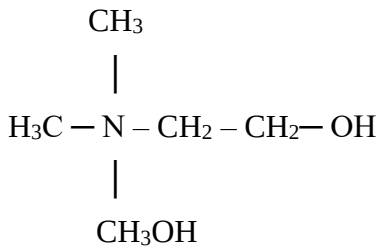


Fig 12.25: structure of choline

Function

(i) It undergoes esterification with acetyl Co-A to form acetylcholine. Acetylcholine is responsible for the transmission of nerve impulses in the central nervous system.

(ii) It is an important lipotropic agent and prevents the accumulation of fat in liver.

(iii) It is constituent of phospholipid and hence is involved in membrane structure and lipid transport.

Deficiency – Deficiency of choline causes development of fatty liver. In puppies growth is retarded and there occurs severe anorexia (loss of appetite). In rat, normal lactation does not occur. In hens, laying of eggs is stopped. Liver cirrhosis is observed in the rats.

Para – amino benzoic Acid

History– For the first time Ansbacher demonstrated that depigmentation of the hair (achromotrichia) in mouse could be cured by adding P-amino benzoic acid (PABA) in their diet.

Structure –

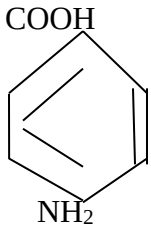


Fig 12.26: structure of P-amino benzoic acid

Function –

(i) It act as antagonist of sulfanilamide.

(ii) It blocks the bacteriostatic properties of sulfanilamide.

(iii) It is also believe that PABA has a catalytic property only when it forms the structural part of folic acid.

Carnitine

History – Carnitine has been shown as an essential food factor of certain insects such as yellow med worm *Tenebrio molitor* and hence from this its vitamins nature has established. It was first isolated from muscle.

Structure - Carnitin (β-hydroxy-ϒ-butyrobetaine) is a betaine.

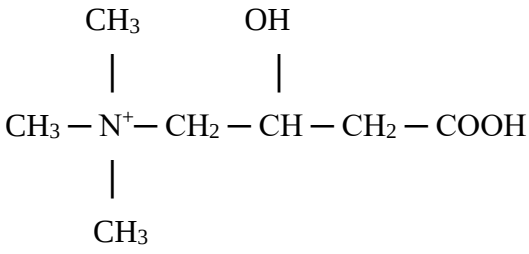


Fig 12.27: Carnitine

Function – Carnitine is the carrier molecule for the transport of fatty acids across the mitochondrial membranes which are otherwise impermeable for activated fatty acid. Carnitine enables the fatty acids to get oxidized within the mitochondria. It also facilitates exist of acetyl Co-A and aceto-acetyl Co-A from mitochondria to the non-mitochondrial fraction of the cells which subsequently used for long chain fatty acid biosynthesis.

Alpha – lipoic Acid

History – Reed isolate α-lipoic acid factor from the insoluble residue of liver. It is important for the growth of a number of bacteria and protozoa. It is called as pyruvate oxidation factor (POF) or acetate replacement factor or protogen.

Structure – Chemically α-lipoic acid ($C_8H_{14}O_2S_2$) is a cyclic disulfide (6,8-dimercapto – n – caprylic acid).

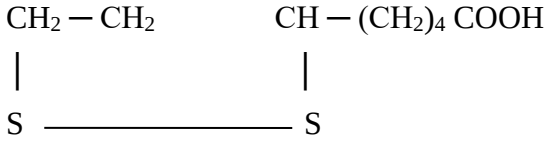


Fig 12.28 Fig: 6.1: Osmoregulation in fresh water fishes

: Structure of α-Lipoic acid

Function –

It act as a catalytic agent for the oxidative decarboxylation of pyruvic acid and α-ketoglutaric acid by certain micro-organism. It is a co-enzyme called lipothiamide pyrophosphate (LTPP) for this reaction.

Deficiency - Its deficiency usually does not occur in man as it is synthesized by most animals. Hence it is sometimes called a pseudo-vitamin.

Bioflavonoids

History – In 1936 Albert-Szent-Gyorgyi and his co-worker reported the bioflavonoids compound are present is lemon peel and named it citrin. It is a mixture of flavonoids and it maintain normal capillary permeability and fragility. The active compound in citrin was hesperidin. It was also called vitamin P (for permeability).

Structure – Hesperidin is 5', 3' dihydroxy-4'-methoxy-7-rhamnoglucosido flavanone.

Source and requirement – These are always of plant origin. The rich sources are juice, peel and pulp of citrus fruits, tobacco leaves, buck wheat, grapes and other fruits and vegetable. The daily requirement is still not known.

Function – The bioflavonoids act as antioxidants and protect ascorbic acid from oxidative destruction. The effect is indirect due to the chelation of heavy metal ion (Cu^{++}) that catalyzes oxidative degradation of ascorbic acid. Bioflavonoids thus decrease oxidative losses of ascorbic acid from during storage or in intestinal tract.

Deficiency – The deficiency of bioflavonoid in animals result in a syndrome characterized by increased capillary permeability.

SAQs 1.

Complete the following sentences by inserting appropriate words in the blanks.

(i) The vitamin involved in coagulation of blood is ----------

(ii) Scurvy is produced due to the deficiency of ----------

(iii) Calcium deficiency occurs due to the deficiency of ----------

(iv) Pernicious anemia is caused due to the deficiency of ----------

12.5 SUMMARY

In this unit vitamins are dercribe in very detailed manner. Vitamins are organic compounds that are essential in very small (trace) amounts for the maintenance of normal metabolism. They are generally cannot be synthesized at adequate level in the body, so they are obtained from the food.

Vitamins are classified in two categories depending upon their solubility, they may fat soluble vitamins and water soluble vitamins. The fat soluble vitamins are vitamin A, D, E, K and lippolic acid and water soluble vitamins are different group of B–complex, vitamin C, Choline, Inositol, P-amino benzoic acid, bioflavonoids.

12.6 TERMINAL QUESTION

Q1 Describe the function of Vitamin B_1.

Q2 Describe the structure of Vitamin A.

Q3 Describe the function of vitamin C.

12.7 ANSWERS

SAQ 1

(i) Vitamin K

(ii) Vitamin C

(iii) Vitamin D

(iv) Vitamin B_{12}

Terminal question

1. Thiamine act as a co-enzyme in the carbohydrate metabolism especially in glycolytic pathway and kreb cycle. The reaction of enzyme pyruvate dehydrogenase, which catalyzes the irreversible conversion of pyruvate to acetyl Co-A, is dependent on Thiamine pyrophosphate (TPP). The α-ketoglutarate dehydrogenase of kreb's cycle requires TPP. The enzyme transketolase of hexose monophosphate shunt (HMP shunt) is dependent on TPP. The thiamine pyrophosphate also 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 nerve impulse.

2. Vitamin A is found in two form vitamin A_1 and vitamin A_2. The carotenoid which gives rise to the vitamins A is called provitamin A_1. Provitamin A_1 consists of α, β and carotenoid and cryptoxanthin. In which β-carotene is one of the most active form. β- carotein is made up of eight 5-carbon isoprenoid unit linked to form a chain of 40 carbon unit with an ionone ring at each end. It is orange red hydro-carbon and upon hydrolysis yield 2 moles vitamin-A. During hydrolysis a cleavage is occur at the midpoint of the β-carotene chain. This conversion occurs in liver of fishes and mammals. Vitamin A_1 is a complex primary alcohol called retinol, having the empirical formula $C_{20}H_{29}OH$. The terminal hydroxyl group is ordinarily esterified. It contains β-ionone ring. Vitamins A_2 is found in fresh water fishes. It differ from vitamin A_1 in possessing an additional conjugate double bond between carbon atom 3 and 4 of the ionone ring

3. (i) Vitamin C is involved in the electron transports in the microsomal fraction.

(ii) Vitamin C enhances the synthesis of immunoglobulin and increases the phagocytic action of the leucocytes.

(iii) In adrenal cortex, high concentration of ascorbic acid is found. It is believed that the vitamin is necessary for hydroxylation reaction in the synthesis of corticosteroid hormones.

(iv) Ascorbic acid enhanced the synthesis of bile acid from cholesterol.

(v) Vitamin C is essential for the formation of active form of vitamin folic acid (tetrahydrofolate).

(vi) Vitamin C helps in tryptophan metabolism.

(vii) Vitamin C is required in the formation of bone.

(viii) Ascorbic acid is required for the oxidation of P-hydroxy-phenylpyruvate to homogentesic acid in tyrosine metabolism.

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