Notes

5

LIPIDS

5.1 INTRODUCTION

The lipids are a heterogeneous group of compounds, including fats, oils, steroids, waxes, and related compounds, which are related more by their physical than by their chemical properties. Lipids are a class of compounds distinguished by their insolubility in water and solubility in nonpolar solvents. Lipids are important in biological systems because they form the cell membrane, a mechanical barrier that divides a cell from the external environment. Lipids also provide energy for life and several essential vitamins are lipids. Lipids can be divided in two major classes, nonsaponifiable lipids and saponifiable lipids. A nonsaponifiable lipid cannot be broken up into smaller molecules by hydrolysis, which includes triglycerides, waxes, phospholipids, and sphingolipids. A saponifiable lipid contains one or more ester groups allowing it to undergo hydrolysis in the presence of an acid, base, or enzyme. Nonsaponifiable lipids include steroids, prostaglandins, and terpenes. Within these two major classes of lipids, there are several specific types of lipids important to life, including fatty acids, triglycerides, glycerophospholipids, sphingolipids, and steroids. Each of these categories can be further broken down. Nonpolar lipids, such as triglycerides, are used for energy storage and fuel. Polar lipids, which can form a barrier with an external water environment, are used in membranes. Polar lipids include glycerophospholipids and sphingolipids. Fatty acids are important components of all of these lipids.

OBJECTIVES

After reading this lesson, you will be able to:

- classify lipids
- describe fatty acids and classify them
- enlist functions of lipids
- describe cholesterol and its importance

5.2 BIOLOGICAL ROLES OF LIPID

Lipids have the common property of being relatively insoluble in water and soluble in nonpolar solvents such as ether and chloroform. They are important dietary constituents not only because of their high energy value but also because of the fat-soluble vitamins and the essential fatty acids contained in the fat of natural foods. Fat is stored in adipose tissue, where it also serves as a thermal insulator in the subcutaneous tissues and around certain organs. Nonpolar lipids act as electrical insulators, allowing rapid propagation of depolarization waves along myelinated nerves. Combinations of lipid and protein (lipoproteins) are important cellular constituents, occurring both in the cell membrane and in the mitochondria, and serving also as the means of transporting lipids in the blood. Knowledge of lipid biochemistry is necessary in understanding many important biomedical areas, e.g., obesity, diabetes mellitus, atherosclerosis, and the role of various polyunsaturated fatty acids in nutrition and health.

5.3 CLASSIFICATION OF LIPIDS

Lipids are classified as follows:

1. Simple lipids: Esters of fatty acids with various alcohols.
   - (a) Fats: Esters of fatty acids with glycerol. Oils are fats in the liquid state.
   - (b) Waxes: Esters of fatty acids with higher molecular weight monohydric alcohols.
2. Complex lipids: Esters of fatty acids containing groups in addition to an alcohol and a fatty acid.
   - (a) Phospholipids: Lipids containing, in addition to fatty acids and an alcohol, a phosphoric acid residue. They frequently have nitrogen containing bases and other substituents, eg, in glycerophospholipids the alcohol is glycerol and in sphingophospholipids the alcohol is sphingosine.
   - (b) Glycolipids (glycosphingolipids): Lipids containing a fatty acid, sphingosine, and carbohydrate.
   - (c) Other complex lipids: Lipids such as sulfolipids and aminolipids. Lipoproteins may also be placed in this category.
3. Precursor and derived lipids: These include fatty acids, glycerol, steroids, other alcohols, fatty aldehydes, and ketone bodies, hydrocarbons, lipid-soluble vitamins, and hormones. Because they are uncharged, acylglycerols (glycerides), cholesterol, and cholesteryl esters are termed neutral lipids.

5.3.1. Fatty Acids

A fatty acid is a molecule characterized by the presence of a carboxyl group attached to a long hydrocarbon chain. Therefore these are molecules with a formula R–COOH where R is a hydrocarbon chain. Fatty acids can be said to be carboxylic acids, and come in two major varieties.

- Saturated fatty acids do not have any double bonds. A fatty acid is saturated when every carbon atom in the hydrocarbon chain is bonded to as many hydrogen atoms as possible (the carbon atoms are saturated with hydrogen). Saturated fatty acids are solids at room temperature. Animal fats are a source of saturated fatty acids. In addition, fatty acids pack easily and form rigid structures (e.g., fatty acids are found in membranes).
- Unsaturated fatty acids can have one or more double bonds along its hydrocarbon chain. A fatty acid with one double bond is called monounsaturated. If it contains two or more double bonds, we say that the fatty acid is polyunsaturated. The melting point of a fatty acid is influenced by the number of double bonds that the molecule contains and by the length of the hydrocarbon tail. The more double bonds it contains, the lower the melting point. As the length of the tail increases, the melting point increases. Plants are the source of unsaturated fatty acids (Figure 5.1).

$$-CH = CH - CH = CH -$$

Unsaturated fatty acid chain

$$-CH - CH - CH -$$

Saturated fatty acid chain

Fig. 5.1: Aliphatic chain showing structure of unsaturated fatty acid chain with double bonds and saturated fatty acid chain with single bonds.

5.4 CLASSIFICATION OF FATTY ACIDS

Naturally occurring fatty acids have cis bonds. Trans-fatty acids are created artificially using a process called hydrogenation. A trans-fatty acid has a trans configuration rather than cis configuration at each double bond. This causes the molecule to straighten. These two stereoisomers can be distinguished in the following way:

- In a cis stereoisomer, two similar groups attached to the carbon double bond are found on the same side.
- In a trans stereoisomer, two similar groups attached to the carbon double bond are found on opposite sides.

5.5 ESSENTIAL AND NONESSENTIAL FATTY ACIDS

If a fatty acid can only be obtained from the diet (for humans) then the fatty acid is an essential fatty acid. Two fatty acids cannot be synthesized in the human body and are therefore essential. These are linoleic and linolenic fatty acids, which are both unsaturated. Nonessential fatty acids can be made by the human body and so do not need to be obtained from diet alone. These are made from carbohydrates and proteins or from other fatty acids. Fatty acids are an important source of energy. While carbohydrates or proteins only provide 4 kcal/g of energy, fatty acids provide more than twice the energy per unit weight of 9 kcal/g. This is one reason why a high-fat diet can lead to obesity.

5.5.1 Fatty acids are aliphatic carboxylic acids

Fatty acids occur mainly as esters in natural fats and oils but do occur in the unesterified form as free fatty acids, a transport form found in the plasma. Fatty acids that occur in natural fats are usually straight-chain derivatives containing an even number of carbon atoms. The chain may be saturated (containing no double bonds) or unsaturated (containing one or more double bonds).

5.5.2 Most naturally occurring unsaturated fatty acids have cis double bonds

The carbon chains of saturated fatty acids form a zigzag pattern when extended, as at low temperatures. At higher temperatures, some bonds rotate, causing chain shortening, which explains why biomembranes become thinner with increases in temperature. A type of geometric isomerism occurs in unsaturated fatty acids, depending on the orientation of atoms or groups around the axes of double bonds, which do not allow rotation. If the acyl chains are on the same side of the bond, it is cis-, as in oleic acid; if on opposite sides, it is trans-, as in elaidic acid, the trans isomer of oleic acid.

Naturally occurring unsaturated long-chain fatty acids are nearly all of cis configuration. Thus, oleic acid has an L shape, whereas elaidic acid remains "straight." Increase in the number of cis double bonds in a fatty acid leads to a variety of possible spatial configurations of the molecule – e.g., arachidonic acid, with four cis double bonds, has "kinks" or a U shape. This has profound significance on molecular packing in membranes and on the positions occupied by fatty acids in more complex molecules such as phospholipids. Trans double bonds alter these spatial relationships. Trans fatty acids are present in certain foods, arising as a by-product of the saturation of fatty acids during hydrogenation, or "hardening," of natural oils in the manufacture of margarine. An additional small contribution comes from the ingestion of ruminant fat that contains trans fatty acids arising from the action of microorganisms in the rumen.

5.6 COMMON LIPIDS AND THEIR FUNCTIONS

5.6.1 Triglycerides

A triglyceride (often called triacylgycerol) is a fatty acid trimester of glycerol. Triglycerides are important for human health in that they provide most of the lipids in our diet. Glycerol has three hydroxyl groups. Fatty acids can be attached at these three sites forming a triglyceride. One important characteristic of a tryglycerol is its state at room temperature. The degree of saturation and the length of their chains attached to the glycerol backbone both determine their state at room temperature.

- Short-chain unsaturated triglycerides are liquid at room temperature.
- Long-chain saturated triglycerides are solid at room temperature.

Animal fats (lard) contain a high amount of saturated triglycerides while plant oils (vegetable oil) contain a high amount of unsaturated triglycerides. While neither is healthy when consumed in excess, vegetable oils are far healthier than lard.

5.6.2 Triglycerides are the main storage forms of fatty acids

The triglycerides are esters of the trihydric alcohol glycerol and fatty acids. Mono- and diacylglycerols wherein one or two fatty acids are esterified with glycerol are also found in the tissues. These are of particular significance in the synthesis and hydrolysis of triacylglycerols.

5.6.3 The role of triglycerides in health

While fat may seem bad, triglycerides play many important roles in the body. For example, triglycerides can be used for energy storage in animals. This food reserve can be called upon during periods of starvation, with the high-calorie content of the fatty acids adding to the value of storing fat and providing much needed energy. In addition, triglycerides can provide insulation for animals in the form of body fat, which allows them to survive in colder temperatures. These two roles played by fat in the body, which arose over eons of evolution, are now deemed undesirable in modern industrialized society where humans no longer face starvation or have to deal directly with cold weather.

5.6.4 Phospholipids are the main lipid constituents of membranes

Phospholipids may be regarded as derivatives of phosphatidic acid, in which the phosphate is esterified with the OH of a suitable alcohol. Phosphatidic acid is important as an intermediate in the synthesis of triacylglycerols as well as phosphoglycerols but is not found in any great quantity in tissues. Amphipathic lipids self-orient at oil:water interfaces. They form Membranes, Micelles, Liposomes, & Emulsions (Figure 5.2). In general, lipids are insoluble in water since they contain a predominance of nonpolar (hydrocarbon) groups. However, fatty acids, phospholipids, sphingolipids, bile salts, and, to a lesser extent, cholesterol contain polar groups. Therefore, part of the molecule is hydrophobic, or water-insoluble; and part is hydrophilic, or water-soluble. Such molecules are described as amphipathic. They become oriented at oil:water interfaces with the polar group in the water phase and the nonpolar group in the oil phase.

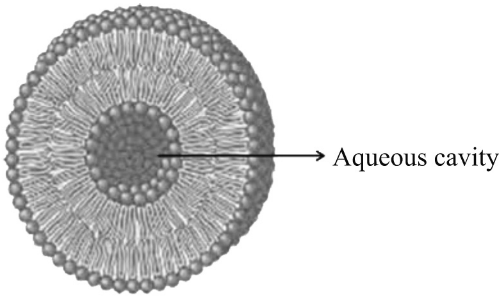

Fig. 5.2: Structure of liposome showing aqueous cavity at the centre of fatty acid bilayer.

A bilayer of such amphipathic lipids has been regarded as a basic structure in biologic membranes. When a critical concentration of these lipids is present in an aqueous medium, they form micelles. Aggregations of bile salts into micelles and liposomes and the formation of mixed micelles with the products of fat digestion are important in facilitating absorption of lipids from the intestine. Liposomes may be formed by sonicating an amphipathic lipid in an aqueous medium. They consist of spheres of lipid bilayers that enclose part of the aqueous medium. They are of potential clinical use – particularly when combined with tissue specific antibodies – as carriers of drugs in the circulation, targeted to specific organs, eg, in cancer therapy. In addition, they are being used for gene transfer into vascular cells and as carriers for topical and transdermal.

5.7 CHOLESTEROL AND ITS IMPORTANCE

Cholesterol is an important lipid found in the cell membrane. It is a sterol, which means that cholesterol is a combination of a steroid and an alcohol (Figure 5.3). It is an important component of cell membranes and is also the basis for the synthesis of other steroids, including the sex hormones estradiol and testosterone, as well as other steroids such as cortisone and vitamin D. In the cell membrane, the steroid ring structure of cholesterol provides a rigid hydrophobic structure that helps boost the rigidity of the cell membrane. Without cholesterol the cell membrane would be too fluid. In the human body, cholesterol is synthesized in the liver.

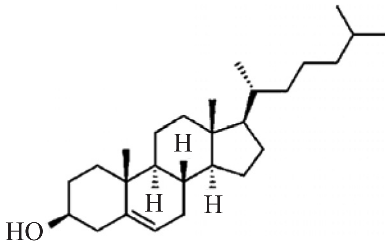

Fig. 5.3: Structure of cholesterol.

Cholesterol is insoluble in the blood, so when it is released into the blood stream it forms complexes with lipoproteins. Cholesterol can bind to two types of lipoprotein, called high-density lipoprotein (HDL) and low-density lipoprotein (LDL). A lipoprotein is a spherical molecule with water soluble proteins on the exterior. Therefore, when cholesterol is bound to a lipoprotein, it becomes blood soluble and can be transported throughout the body. HDL cholesterol is transported back to the liver. If HDL levels are low, then the blood level of cholesterol will increase.

High levels of blood cholesterol are associated with plaque formation in the arteries, which can lead to heart disease and stroke. While most cholesterol in the body is synthesized in the liver, dietary cholesterol also adds to the total blood levels. Cholesterol intake from the diet enters the bloodstream in the LDL form. This helps explain why consumption of foods with high-cholesterol content can lead to increased blood levels of cholesterol which is bad for health. So reducing the cholesterol in the diet can lower the blood level of cholesterol. This can reduce the amount of plaque formation. Aerobic exercise also contributes to health by increasing HDL levels in the blood. Hence more cholesterol is returned to the liver leading to a lower blood level of cholesterol, and reduced plaque formation.

5.8 DIGESTION AND ABSORPTION OF LIPIDS

The major lipids in the diet are triacylglycerols and, to a lesser extent, phospholipids. These are hydrophobic molecules and must be hydrolyzed and emulsified to very small droplets (micelles) before they can be absorbed. The fat-soluble vitamins – A, D, E, and K – and a variety of other lipids (including cholesterol) are absorbed dissolved in the lipid micelles. Absorption of the fat-soluble vitamins is impaired on a very low fat diet. Hydrolysis of triacylglycerols is initiated by lingual and gastric lipases that attack the sn-3 ester bond, forming 1,2-diacylglycerols and free fatty acids, aiding emulsification. Pancreatic lipase is secreted into the small intestine and requires a further pancreatic protein, colipase, for activity. It is specific for the primary ester links – ie, positions 1 and 3 in triacylglycerols – resulting in 2-monoacylglycerols and free fatty acids as the major end-products of luminal triacylglycerol digestion. Monoacylglycerols are hydrolyzed with difficulty to glycerol and free fatty acids, so that less than 25% of ingested triacylglycerol is completely hydrolyzed to glycerol and fatty acids.

Bile salts, formed in the liver and secreted in the bile, enable emulsification of the products of lipid digestion into micelles and liposomes together with phospholipids and cholesterol from the bile. Because the micelles are soluble, they allow the products of digestion, including the fat soluble vitamins, to be transported through the aqueous environment of the intestinal lumen and permit close contact with the brush border of the mucosal cells, allowing uptake into the epithelium, mainly of the jejunum. The bile salts pass on to the ileum, where most are absorbed into the enterohepatic circulation. All long-chain fatty acids absorbed are converted to triacylglycerol in the mucosal cells and, together with the other products of lipid digestion, secreted as chylomicrons into the lymphatics, entering the blood stream via the thoracic duct. Free fatty acids are removed from the blood very rapidly and oxidized (fulfilling 25–50% of energy requirements in starvation) or esterified to form triacylglycerol in the tissues. In starvation, esterified lipids from the circulation or in the tissues are oxidized as well, particularly in heart and skeletal muscle cells, where considerable stores of lipid are to be found.

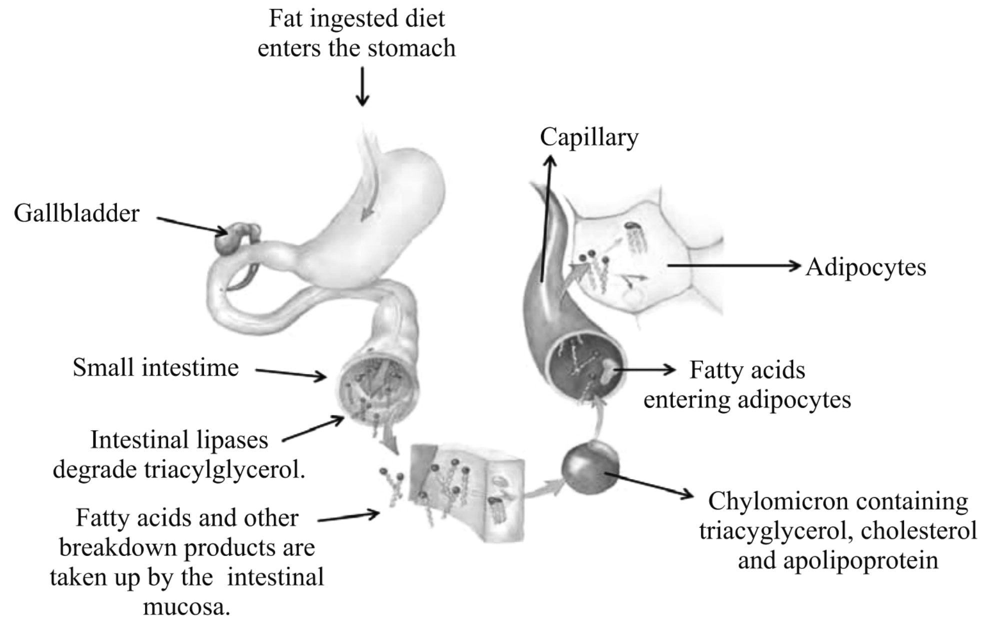

Fig. 5.4: Schematic representation of fat digestion at the intestinal region and absorption and transport of lipids in the form of triacylglycerol, fatty acids, cholesterol by chylomicrons. Fatty acids enter the blood circulation and stored in the adipose tissue.

The free fatty acid uptake by tissues is related directly to the plasma free fatty acid concentration, which in turn is determined by the rate of lipolysis in adipose tissue. After dissociation of the fatty acid-albumin complex at the plasma membrane, fatty acids bind to a membrane fatty acid transport protein that acts as a transmembrane cotransporter with Na+. On entering the cytosol, free fatty acids are bound by intracellular fatty acid-binding proteins. The role of these proteins in intracellular transport is thought to be similar to that of serum albumin in extracellular transport of long chain fatty acids. Triacylglycerol is transported from the intestines in chylomicrons and from the liver in very low density lipoproteins. By definition, chylomicrons are found in chyle formed only by the lymphatic system draining the intestine. They are responsible for the transport of all dietary lipids into the circulation. Small quantities of VLDL are also to be found in chyle; however, most of the plasma VLDL is of hepatic origin. They are the vehicles of transport of triacylglycerol from the liver to the extrahepatic tissues (Figure 5.4).

5.9 CLASSIFICATION AND FUNCTIONS OF LIPOPROTEINS

Cholesterol and other lipids are carried on plasma lipoproteins. Cholesterol and cholesteryl esters, like triacylglycerols and phospholipids, are essentially insoluble in water, yet must be moved from the tissue of origin to the tissues in which they will be stored or consumed. They are carried in the blood plasma as plasma lipoproteins, macromolecular complexes of specific carrier proteins, apolipoproteins, with various combinations of phospholipids, cholesterol, cholesteryl esters, and triacylglycerols. Apolipoproteins ("apo" designates the protein in its lipid-free form) combine with lipids to form several classes of lipoprotein particles, spherical complexes with hydrophobic lipids in the core and hydrophilic amino acid side chains at the surface.

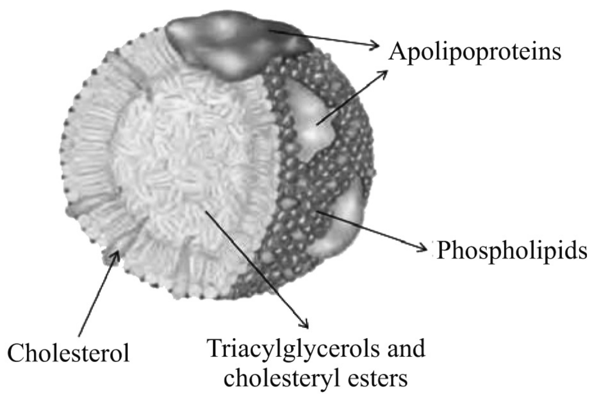

Fig. 5.5: Structure of chylomicron.

Different combinations of lipids and proteins produce particles of different densities, ranging from chylomicrons (Figure 5.5) to high-density lipoproteins. Each class of lipoprotein has a specific function, determined by its point of synthesis, lipid composition, and apolipoprotein content. At least nine different apolipoproteins are found in the lipoproteins of human plasma (Table), distinguishable by their size, their reactions with specific antibodies, and their characteristic distribution in the lipoprotein classes. These protein components act as signals, targeting lipoproteins to specific tissues or activating enzymes that act on the lipoproteins. Chylomicrons with the movement of dietary triacylglycerols from the intestine to other tissues are the largest of the lipoproteins and the least dense, containing a high proportion of triacylglycerols. Chylomicrons are synthesized in the ER of epithelial cells that line the small intestine, then move through the lymphatic system and enter the bloodstream via the left subclavian vein.

The apolipoproteins of chylomicrons include apoB-48 (unique to this class of lipoproteins), apoE, and apoC-II. ApoC-II activates lipoprotein lipase in the capillaries of adipose, heart, skeletal muscle, and lactating mammary tissues, allowing the release of free fatty acids to these tissues. Chylomicrons thus carry dietary fatty acids to tissues where they will be consumed or stored as fuel. The remnants of chylomicrons (depleted of most of their triacylglycerols but still containing cholesterol, apoE, and apoB-48) move through the bloodstream to the liver. Receptors in the liver bind to the apoE in the chylomicron remnants and mediate their uptake by endocytosis. In the liver, the remnants release their cholesterol and are degraded in lysosomes. When the diet contains more fatty acids than are needed immediately as fuel, they are converted to triacylglycerols in the liver and packaged with specific apolipoproteins into very-low-density lipoprotein (VLDL). Excess carbohydrate in the diet can also be converted to triacylglycerols in the liver and exported as VLDLs. In addition to triacylglycerols, VLDLs contain some cholesterol and cholesteryl esters, as well as apoB-100, apoC-I, apoC-II, apoC-III, and apo-E. These lipoproteins are transported in the blood from the liver to muscle and adipose tissue, where activation of lipoprotein lipase by apoC-II causes the release of free fatty acids from the VLDL triacylglycerols.

Adipocytes take up these fatty acids, reconvert them to triacylglycerols, and store the products in intracellular lipid droplets; myocytes, in contrast, primarily oxidize the fatty acids to supply energy. Most VLDL remnants are removed from the circulation by hepatocytes. The uptake, like that for chylomicrons, is receptor-mediated and depends on the presence of apoE in the VLDL remnants. The loss of triacylglycerol converts some VLDL to VLDL remnants (also called intermediate density lipoprotein, IDL); further removal of triacylglycerol from VLDL produces low-density lipoprotein (LDL). Very rich in cholesterol and cholesteryl esters and containing apoB-100 as their major apolipoprotein, LDLs carry cholesterol to extrahepatic tissues that have specific plasma membrane receptors that recognize apoB-100 (Table 5.1).

The fourth major lipoprotein type, high-density lipoprotein (HDL), originates in the liver and small intestine as small, protein-rich particles that contain relatively little cholesterol and no cholesteryl esters. HDLs contain apoA-I, apoC-I, apoC-II, and other apolipoproteins, as well as the enzyme lecithin-cholesterol acyl transferase (LCAT), which catalyzes the formation of cholesteryl esters from lecithin (phosphatidylcholine) and cholesterol. LCAT on the surface of nascent (newly forming) HDL particles converts the cholesterol and phosphatidylcholine of chylomicron and VLDL remnants to cholesteryl esters, which begin to form a core, transforming the disk-shaped nascent HDL to a mature, spherical HDL particle. This cholesterol-rich lipoprotein then returns to the liver, where the cholesterol is unloaded; some of this cholesterol is converted to bile salts.

Table 5.1. Lipoproteins source and components and apolipoproteins.

Lipoprotein	Source	Main lipid components	Apolipoproteins
Chylomicrons	Intestine	Triacyglycerol	A-I, A-II, A-IV, B 48, C-I, C-II, C-III,E
Chylomicron remnants	Chylomicrons	Triacylglycerol, phospholipids, cholesterol	B-48, E
VLDL	Liver (intestine)	Triacylglycerol	B-100, C-I, C-II, C-III
IDL	VLDL	Triacylglycerol, cholesterol	B-100, E
LDL	VLDL	Cholesterol	B-100
HDL	Liver, intestine, VLDL, chylomicrons	Phospholipids, cholesterol	A-I, A-II, A-IV, C-I, C-II, C-III, D, E

5.10 KETONE BODY TYPES AND IMPORTANCE

Ketone bodies formed in liver to free up CoA for b-oxidation metabolized in other tissues, including brain, as an energy source. The formation of ketone bodies is a consequence of prolonged metabolism of fat. Their formation in the liver actually enables liver to metabolize even more fat by freeing up CoA that would otherwise be tied up as acetyl-CoA waiting to get into the TCA cycle. The liver exports the ketone bodies; and other tissues, particularly the brain, can adapt to use them. With increasing metabolism of fat through b-oxidation, much of the mitochondrial CoA pool may become tied up as acyl- or acetyl-CoA. In such cases, the supply of free CoA can be diminished, and this may limit the rate of b-oxidation. Upon prolonged fasting and heavy reliance on fat for energy, the liver induces the enzymes required for the formation of ketone bodies and brain induces enzymes required for their metabolism.

Ketone bodies are formed in the liver mitochondria by the condensation of three acetyl-CoA units. Two acetyl-CoAs are condensed to form acetoacetyl-CoA. The acetoacetyl-CoA is condensed with another acetyl-CoA to give hydroxymethylglutaryl-CoA (HMG-CoA). This is then split by HMG-CoA lyase to acetyl-CoA and acetoacetate. The hydroxybutyrate arises from acetoacetate by reduction. The overall sum of ketone body formation is the generation of acetoacetate (or hydroxybutyrate) and the freeing-up of the 2 CoAs that were trapped as acetyl-CoA. Ketone bodies are utilized in other tissues (but not the liver) by converting the acetoacetate to acetoacetyl-CoA and then converting the acetoacetyl-CoA to 2 acetyl-CoA, which are burned in the muscle mitochondria. Increased fatty acid oxidation is a characteristic of starvation and of diabetes mellitus, leading to ketone body production by the liver (ketosis). Ketone bodies are acidic and when produced in excess over long periods, as in diabetes, cause ketoacidosis, which is ultimately fatal. Because gluconeogenesis is dependent upon fatty acid oxidation, any impairment in fatty acid oxidation leads to hypoglycemia. This occurs in various states of carnitine deficiency or deficiency of essential enzymes in fatty acid oxidation, eg, carnitine palmitoyltransferase, or inhibition of fatty acid oxidation by poisons, eg, hypoglycin.

5.10.1 Ketogenesis occurs when there is a high rate of fatty acid oxidation in the liver

Under metabolic conditions associated with a high rate of fatty acid oxidation, the liver produces considerable quantities of acetoacetate and β-hydroxybutyrate. Acetoacetate continually undergoes spontaneous decarboxylation to yield acetone. These three substances are collectively known as the ketone bodies. Acetoacetate and 3-hydroxybutyrate are interconverted by the mitochondrial enzyme D(β)-3-hydroxybutyrate dehydrogenase; the equilibrium is controlled by the mitochondrial [NAD+]/ [NADH] ratio, ie, the redox state. The concentration of total ketone bodies in the blood of well-fed mammals does not normally exceed 0.2 mmol/L. Extrahepatic tissues utilize them as respiratory substrates. The net flow of ketone bodies from the liver to the extrahepatic tissues results from active hepatic synthesis coupled with very low utilization. The reverse situation occurs in extrahepatic tissues.

5.11 ATHEROSCLEROSIS

Unregulated cholesterol production can lead to serious human disease. When the sum of cholesterol synthesized and cholesterol obtained in the diet exceeds the amount required for the synthesis of membranes, bile salts, and steroids, pathological accumulations of cholesterol in blood vessels (atherosclerotic plaques) can develop, resulting in obstruction of blood vessels (atherosclerosis). Atherosclerosis is linked to high levels of cholesterol in the blood, and particularly to high levels of LDL-bound cholesterol; there is a negative correlation between HDL levels and arterial disease. In familial hypercholesterolemia, a human genetic disorder, blood levels of cholesterol are extremely high and severe atherosclerosis develops in childhood.

The metabolism of LDL and HDL intersects in the production and control of fatty streaks and potential plaques in blood vessels. Damage to the endothelium may be related to many factors, including normal turbulence of the blood, elevated LDL, especially modified or oxidized LDL, free radicals from cigarette smoking, homocystinemia, diabetes (glycation of LDL), and hypertension. The atherosclerotic lesion represents an inflammatory response sharing several characteristics with granuloma formation, and not simple deposition of cholesterol in the blood vessel.

Local inflammation recruits monocytes and macrophages with subsequent production of reactive oxygen species. LDL can become oxidized and then taken up, along with other inflammatory debris, by macrophages, which can become laden with cholesterol (foam cells). Initially the subendothelial accumulation of cholesterol-laden macrophages produces fatty streaks. As the fatty streak enlarges over time, necrotic tissue and free lipid accumulates, surrounded by epithelioid cells and eventually smooth muscle cells, an advanced plaque with a fibrous cap. The plaque eventually begins to occlude the blood vessel, causing ischemia and infarction in the heart, brain, or extremities. Eventually the fibrous cap may thin, and the plaque becomes unstable, leading to rupture and thrombosis.

HDL may be protective by picking up accumulating cholesterol before the advanced lesion forms. Apo-l activates LCAT, which in turn adds a fatty acid to cholesterol to produce a cholesterol ester that dissolves in the core of the HDL. The HDL may subsequently be picked up by the liver through the apoE receptor or deliver cholesterol through the scavenger receptor SR-Bl (reverse cholesterol transport from the periphery to the liver). The HDL may also transfer the cholesterol to an IDL reforming a normal, unoxidized LDL particle.

INTEXT QUESTIONS 5.1

I. Choose the best answer

1. Lipid stored in the form of energy in the body adipose tissue is

   (a) Steroid (b) Fatty acid

   (c) Sphingolipid (d) Phospholipid

2. Combination of lipid and protein serving as the means of transporting lipids in the blood is
   (a) Glycoprotein (b) Phosphoprotein
   (c) Lipoprotein (d) None
3. The enzyme which catalyzes the formation of cholesteryl esters from lecithin and cholesterol.
   (a) Lecithin-cholesterol acyl transferase
   (b) D(b)-3-hydroxybutyrate dehydrogenase
   (c) Lipoprotein lipase
   (d) Carnitine palmitoyltransferase
4. A human genetic disorder in which the extremely high levels of blood cholesterol develops atherosclerosis is
   (a) Familial hypercholesterolemia
   (b) Obesity
   (c) Apolipoproteinemia
   (d) None
5. The molecule acting as both hydrophobic and hydrophilic is termed as
   (a) Amphipathic (b) Aliphatic
   (c) Polar (d) Nonpolar

II. Fill in the blanks

1. .... act as electrical insulators, allowing rapid propagation of depolarization waves along myelinated nerves.
2. Vegetable oil contains high amount of .... triglycerides.
3. Aggregation of bile salts into .... facilitates the absorption of lipids from the intestine.
4. A lipoprotein is a spherical molecule with water soluble .... on the exterior.
5. Triglyceride is hydrolysed to .... and ....

III. Match the following

1. Cholestrol	(a) Phospholipid
2. Liposome	(b) Diabetes mellitus
3. Linoleic	(c) Steroid
4. Glycerophospholipid	(d) Unsaturated fatty acid
5. Ketoacidosis	(e) Amphipathic molecule

WHAT HAVE YOU LEARNT

- Lipids are a heterogeneous group of compounds, including fats, oils, steroids, waxes, and related compounds and can be divided in two major classes as nonsaponifiable and saponifiable lipids.
- Saturated fatty acids do not have any double bonds. Animal fats are a source of saturated fatty acids. Unsaturated fatty acids can have one or more double bonds along its hydrocarbon chain. Plants are the source of unsaturated fatty acids.
- Fatty acid that cannot be synthesized by the body is an essential fatty acid. Linoleic and linolenic are the two essential fatty acids (both are unsaturated). Nonessential fatty acids can be made by the human body and so do not need to be obtained from diet alone.
- Animal fats (lard) contain a high amount of saturated triglycerides while plant oils (vegetable oil) contain a high amount of unsaturated triglycerides. While neither is healthy when consumed in excess, vegetable oils are far healthier than lard.
- Phospholipids are amphipathic lipids seen as a bilayer and form the structure in biologic membranes.
- Cholesterol is a sterol and an important component of cell membranes. It is also the basis for the synthesis of other steroids, including the sex hormones estradiol and testosterone, as well as other steroids such as cortisone and vitamin D.
- Cholesterol is insoluble in the blood, so when it is released into the blood stream it forms complexes with lipoproteins. Cholesterol can bind to two types of lipoprotein, called high-density lipoprotein (HDL) and low-density lipoprotein (LDL).
- High levels of blood cholesterol are associated with plaque formation in the arteries, which can lead to heart disease and stroke.
- The major lipids in the diet are triacylglycerols and, to a lesser extent, phospholipids. These are hydrophobic molecules and must be hydrolyzed and emulsified to very small droplets (micelles) before they can be absorbed.
- The fat-soluble vitamins – A, D, E, and K – and a variety of other lipids (including cholesterol) are absorbed dissolved in the lipid micelles.
- Bile salts, formed in the liver and secreted in the bile, enable emulsification of the products of lipid digestion into micelles and liposomes together with phospholipids and cholesterol from the bile. Because the micelles are soluble, they allow the products of digestion absorbed at the intestinal region.

- Low density lipoprotein (LDL), high density lipoprotein (HDL), very low density lipoprotein (VLDL), and intermediate density lipoprotein (IDL) are the types of lipoprotein.
- Ketogenesis occurs when there is a high rate of fatty acid oxidation in the liver. Acetoacetate, β-hydroxybutyrate and acetone are the products of fatty acid oxidation.
- Atherosclerosis is linked to high levels of cholesterol in the blood, and particularly to high levels of LDL-bound cholesterol; there is a negative correlation between HDL levels and arterial disease. LDL-cholesterol is called as bad cholesterol and HDL-cholesterol is called as good cholesterol.

TERMINAL QUESTIONS

1. Classify lipids with suitable examples.
2. What are essential and nonessential fatty acids.
3. Write short on importance of cholesterol.
4. Write short note on digestion and absorption of lipids.

ANSWERS TO INTEXT QUESTIONS

5.1

I. 1. (b) 2. (c) 3. (a) 4. (a) 5. (a)

II.
1. Nonpolar lipids
2. Unsaturated
3. Micelles
4. Proteins
5. Glycerol and free fatty acid

III. 11. (c) 12. (e) 13. (d) 14. (a) 15. (b)