Name of Unit	Lipid Metabolism/ Amino Acid Metabolism
Subject /Course name	Biochemistry
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Class: B.Pharm. Semester	II
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Learning Outcome of Module 03

LO	Learning Outcome	Course Outcome Code
LO1	To learn about Properties of Lipids	BP203.1
LO2	To gain knowledge about the biological roles of Lipids	BP203.1
LO3	To Learn about metabolism of Lipids	BP203.6
LO4	To learn about Properties of Amino acid	BP203.1
LO5	To gain knowledge about the biological roles of Amino acid	BP203.1
L06	To Learn about metabolism of Amino acid	BP203.6

Content Table

Topic
• β- oxidation of saturated fatty acid (Palmitic acid) • Formation and utilization of ketone bodies, ketoacidosis • De novo synthesis of fatty acid • Biological significance of cholesterol and conversion of cholesterol into bile acids, steroid hormone and vitamin D • Disorders of Lipid metabolism • General reactions of amino acid metabolism • Synthesis and significance of biological substances • Catabolism of Heme, hyperbilirubinemia and jaundice

LIPID METABOLISM

Lipids are a heterogeneous group of water-insoluble (hydrophobic) organic molecules that can be extracted from tissues by nonpolar solvents, because of their insolubility in aqueous solutions, body lipids are generally found compartmentalized, as in the case of membrane-associated lipids or droplets of triacylglycerol in adipocytes, or transported in plasma in association with protein, as in lipoprotein particles or on albumin. Lipids are a major source of energy for the body, and they provide the hydrophobic barrier. Lipids serve additional functions in the body, for example, some fat-soluble vitamins have regulatory or coenzyme functions, and the prostaglandins and steroid hormones play major roles in the control of the body's homeostasis.

Classification of lipids:

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.

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).

Saturated Fatty Acids may base on acetic acid (CH_3COOH) as the first member of the series in which **-CH_2-** isprogressively added between the terminals **-CH_3-** and **-COOH-** groups.

Saturated fatty acids.

Common Name	Number of C Atoms	
Acetic	2	Major end product of carbohydrate fermentation by rumen organisms[1]
Propionic	3	An end product of carbohydrate fermentation by rumen organisms[1]
Butyric	4	In certain fats in small amounts (especially butter). An end product of carbohydrate fermentation by rumen organisms[1]
Valeric	5	
Caproic	6	
Lauric	12	Spermaceti, cinnamon, palm kernel, coconut oils, laurels, butter
Myristic	14	Nutmeg, palm kernel, coconut oils, myrtles, butter
Palmitic	16	Common in all animal and plant fats
Stearic	18	

Unsaturated Fatty Acids contain one or more double bonds and it may be further subdivided as follows:

1) **Monounsaturated** (monoethenoid, monoenoic) acids, containing one double bond.
2) **Polyunsaturated** (polyethenoid, polyenoic) acids, containing two or more double bonds.
3) **Eicosanoids:** These compounds, derived from eicosa- (20-carbon) polyenoic fatty acids, comprise the **prostanoids, leukotrienes (LTs),** and **lipoxins (LXs).** Prostanoids include **prostaglandins (PGs), prostacyclins (PGIs),** and **thromboxanes (TXs).**

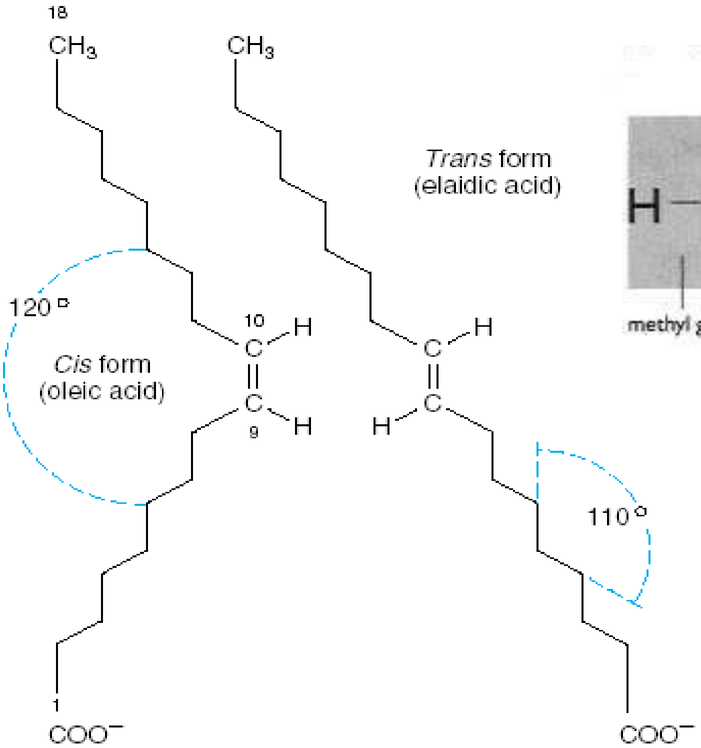
Unsaturated Fatty Acids

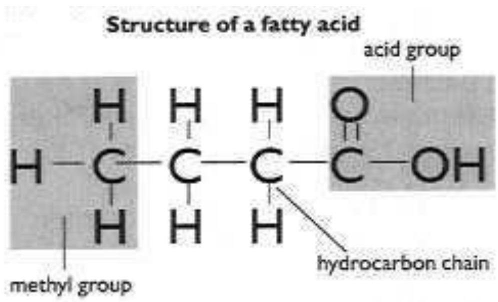
Number of C Atoms and Number and Position of Double Bonds	Common Name	Occurrence
		Monoenoic acids (one double bond)
16:1;9	Palmitoleic	In nearly all fats.
18:1;9	Oleic	Possibly the most common fatty acid in natural fats.
18:1;9	Elaidic	Hydrogenated and ruminant fats.
		Dienoic acids (two double bonds)
18:2;9,12	Linoleic	Corn, peanut, cottonseed, soybean, and many plant oils.
		Trienoic acids (three double bonds)
18:3;6,9,12	γ-Linolenic	Some plants, eg, oil of evening primrose, borage oil; minor fatty acid in animals.
18:3;9,12,15	α-Linolenic	Frequently found with linoleic acid but particularly in linseed oil.
		Tetraenoic acids (four double bonds)
20:4;5,8,11,14	Arachidonic	Found in animal fats and in peanut oil; important component of phospholipids in animals.

Chemistry of Fatty acids

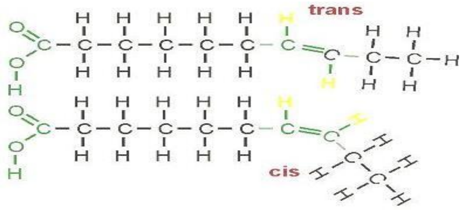
- The carbon chains of saturated fatty acids form a zigzag pattern when extended, as at low temperatures. At higher temperatures, some bonds rotate, causing chain shortening,
- A type of **geometric isomerism** occurs in unsaturated fatty acids, depending on the orientation of atoms or groups around 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 the ***cis*** configuration, the molecules being **“bent”** 120 degrees at the double bond. 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 like **arachidonic acid**, withfour ***cis*** double bonds, has **“kinks”** or a **U shape**.
- ***Trans*** double bonds alter these spatial relationships.

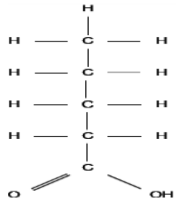
The melting points of even-numbered-carbon fatty acids increase with chain length and decrease according tounsaturation.

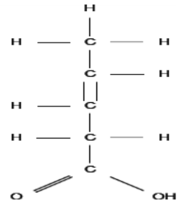




Geometric isomerism of fatty acids (oleic and elaidic acids)







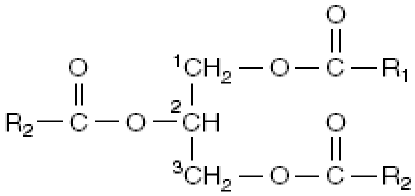
Trans and Cis- Fatty acid

Saturated Fatty acid Unsaturated Fatty acid

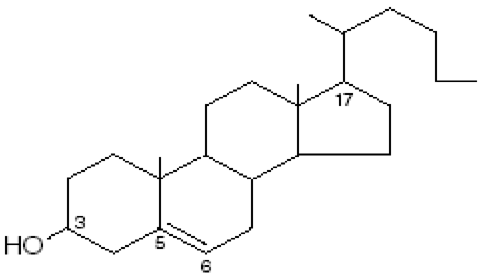
Structures of some common classes of lipids

$\overset{18}{C}H_3(CH_2)_7\overset{10}{C}H=\overset{9}{C}H(CH_2)_7\overset{1}{C}OOH$

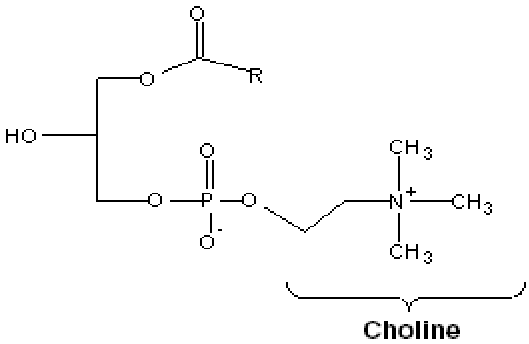
Oleic acid



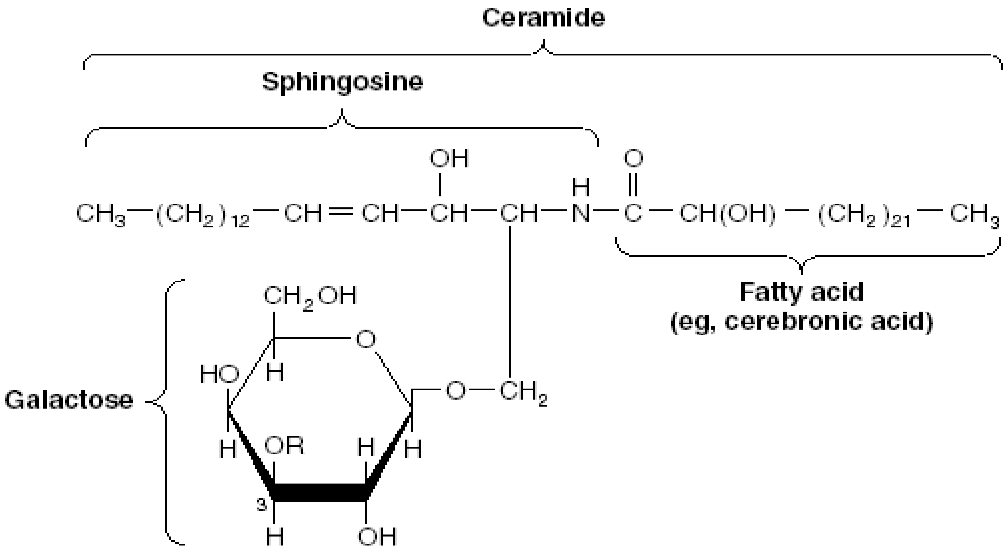
Triacylglycerol



Cholesterol



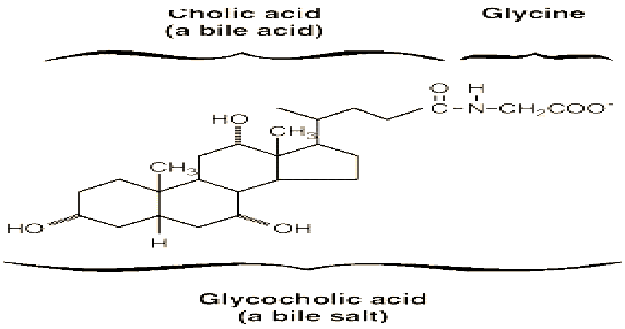
Phospholipid
[Lysophosphatidylcholine (lysolecithin)]



Glycolipids [galactosylceramide]

Emulsification of lipid in the small intestine

- The critical process of emulsification of lipids occurs in the duodenum. Emulsification is accomplished by the bile salts, and mechanical mixing due to peristalsis. Bile salts, made in the liver and stored in the gallbladder, are derivatives of cholesterol.
- Bile salts, produce in the liver and stored in the gallbladder, are derivatives of cholesterol. They consist of a sterol ring structure with a side chain to which a molecule of glycine or taurine is covalently attached by an amide linkage. These emulsifying agents interact with the dietary lipid particles and the aqueous duodenal contents, thereby stabilizing the particles as they become smaller, and preventing them from coalescing.



Use of dietary lipids by the tissues

- Triacylglycerol contained in chylomicrons is broken down primarily in the capillaries of skeletal muscle and adipose tissues, but also those of the heart, lung, kidney, and liver. Triacylglycerol in chylomicrons is degraded to free fatty acids and glycerol by *lipoprotein lipase*. Primarily adipocytes and muscle cells synthesize this enzyme. The free fatty acids derived from the hydrolysis of TAG be transported in the blood in association with serum albumin and they are taken up by cells where it oxidize fatty acids to produce energy.
- Glycerol that is released from TAG is used almost exclusively by the liver to produce glycerol 3-phosphate, which can enter either glycolysis or gluconeogenesis by oxidation to dihydroxyacetone phosphate.

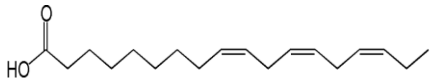
Note: ***Chylomicrons*** are large lipoprotein particles that transport dietary lipids from the intestines to other locations in the body. Chylomicrons are one of the 5 major groups of lipoproteins which enable fats and cholesterol to move within the water based solution of the blood stream. Chylomicrons transport exogenous lipids to liver, adipose, cardiac and skeletal muscle tissue.

Essential fatty acids

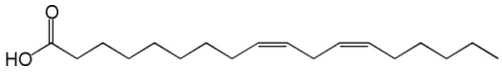
Two fatty acids are dietary essentials in humans

1. **Linoleic acid**, which is the precursor of arachidonic acid, the substrate for prostaglandin synthesis.
2. **α-linolenic** acid is the precursor for growth and development.

Essential fatty acid deficiency can result in a scaly dermatitis, as well as visual and neurologicabnormalities.



Linolenic acid



Linoleic acid

Fatty Acid and Triacylglycerol Metabolism

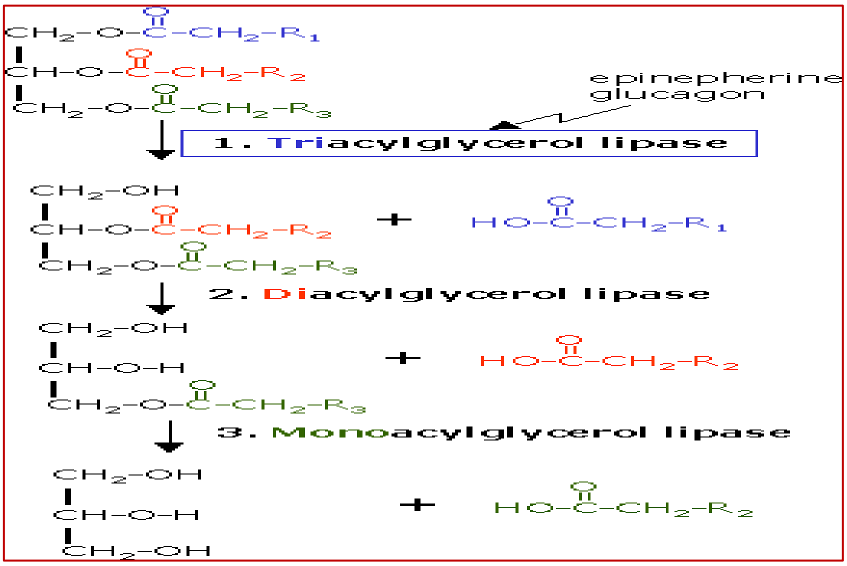
- Fatty acids exist "free" in the body and are found as fatty acyl esters in more complex molecules, such as triacylglycerols. Low levels of free fatty acids occur in all tissues, but substantial amounts can sometimes be found in the plasma, particularly during fasting.
- Free fatty acids can be oxidized by many tissues particularly liver and muscle to provide energy. Fatty acids are also structural components of membrane lipids, such as phospholipids and glycolipids.
- Fatty acids are also precursors of the hormone-like prostaglandins.
- Esterified fatty acids, in the form of triacylglycerols stored in adipose cells, serve as the major energy reserve of the body.
- Triglyceride breakdown is facilitated by three enzymes:

i. *Triacylglycerol lipase*

(Which is activated by epinephrine)

ii. *Diacyclglycerol lipase*

iii. *Monoacylglycerol lipase*



Release of fatty acids from TAG

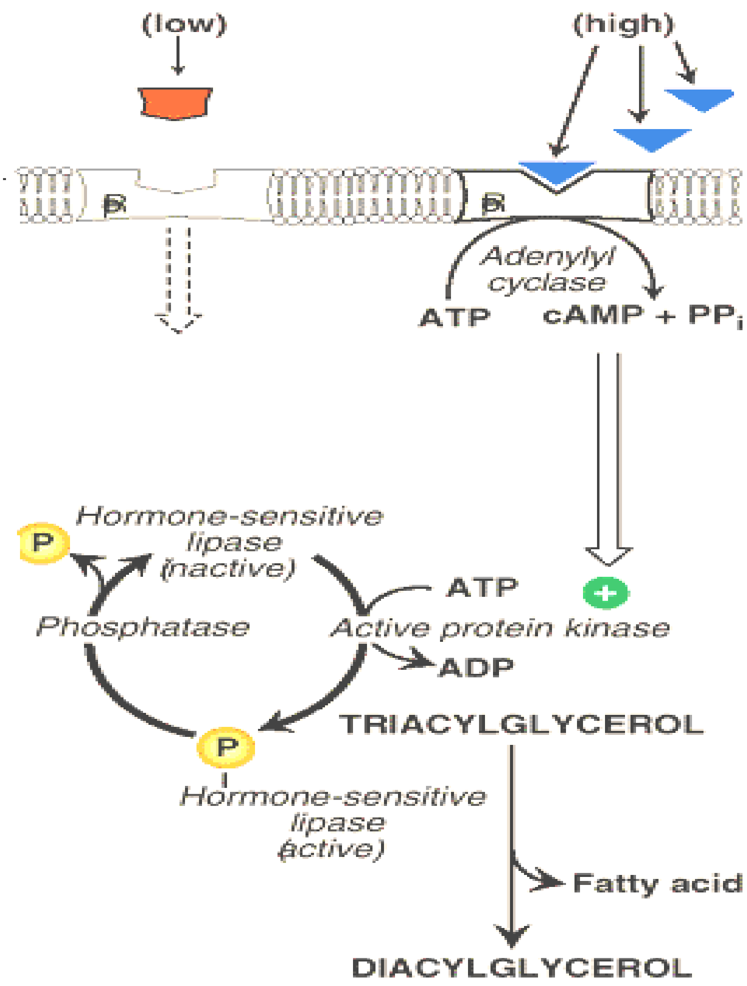
The mobilization of stored fat requires the hydrolytic release of fatty acids and glycerol from their TAG form. This process is initiated by hormone-sensitive lipase, which removes a fatty acid from carbon 1 and/or carbon 3 of the TAG. Additional lipases specific for diacylglycerol or monoacylglycerol remove the remaining fatty acids.

Hormonal control of lipolysis: The breakdown of triglycerides by lipases is under hormonal control. The main enzymes involved are epinephrine, glucagon and insulin. Epinephrine and glucagon promote the breakdown of fat (lipolysis) while insulin inhibits fat breakdown.

FAT

Epinephrine (+)↓↑(+) Insulin

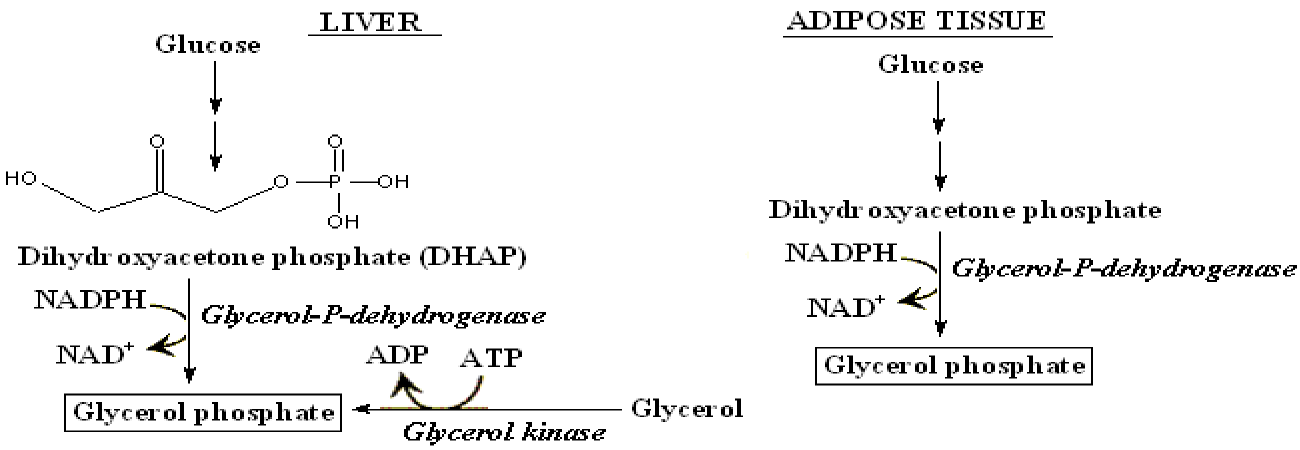
FATTY ACID

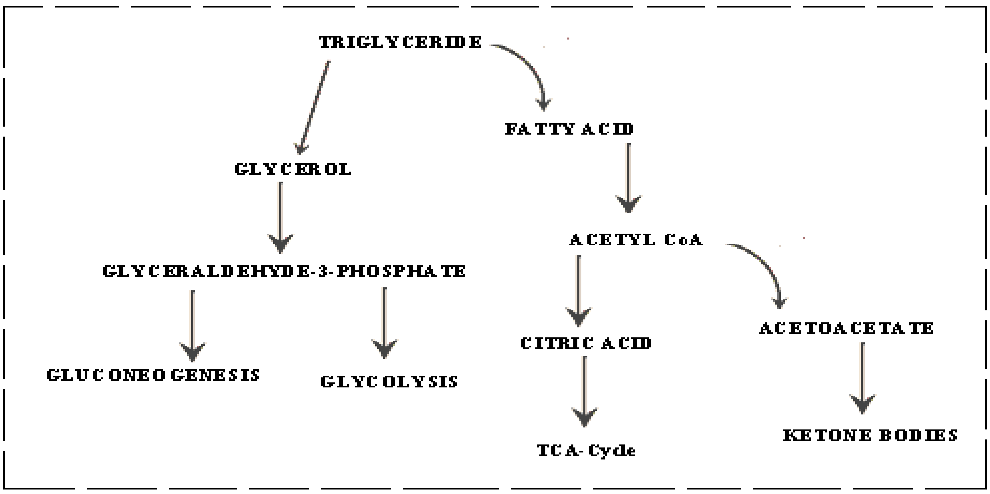


Hormonal regulation of triacylglycerol degradation

- Hormone-sensitive lipase (HSL) is activated when phosphorylated by a 3',5'-cyclic AMP(cAMP)–dependent protein kinase.
- 3',5'-Cyclic AMP is produced in the adipocyte by several hormones like as epinephrine or glucagon binds to receptors on the cell membrane, and activates *adenylyl cyclase*.
- Fatty acid synthesis is turned off when TAG degradation is turned on. In the presence of high plasma levels of insulin and glucose, HSL is dephosphorylated, and becomes inactive.
- The glycerol released during TAG degradation cannot be metabolized by adipocytes because they apparently lack *glycerol kinase*. Rather, glycerol is transported through the blood to the liver, where it can be phosphorylated. The resulting glycerol phosphate can be used to form **TAG** in the liver, or can be converted to **DHAP** by the *glycerol phosphate dehydrogenase*.

Various pathway generation during triacylglycerol degradation





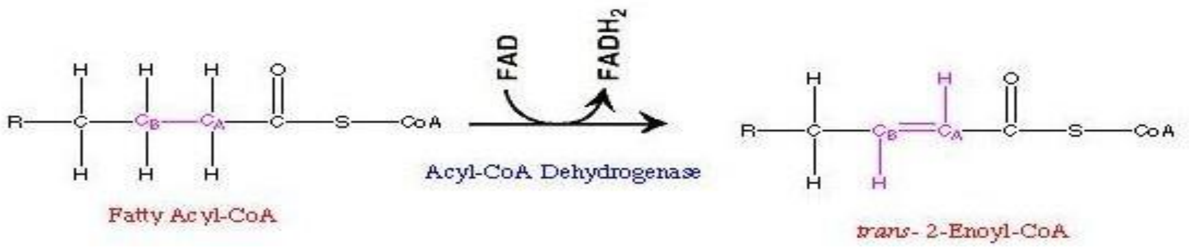
β- Oxidation of fatty acids

- The major pathway for catabolism of even-numbered saturated fatty acids is a mitochondrial pathway called β-oxidation. In which two-carbon fragments are successively removed from the carboxyl end of the fatty acyl Co A, producing acetyl CoA, NADH, and $FADH_2$.
- In β-oxidation, the fatty acid is broken down to release acetyl-CoA. The process involves 4 main steps:
  - **i.** Dehydrogenation
  - **ii.** Hydration
  - **iii.** Oxidation
  - **iv.** Thiolysis

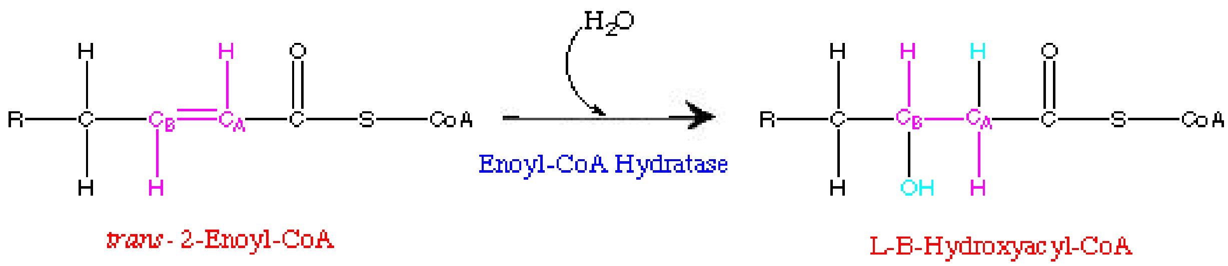
- Beta-oxidation of fatty acids takes place in the mitochondrial matrix for the most part. However, fatty acids have to be activated for degradation by ***coenzyme A*** by forming a **fatty acyl-CoA thioester**. For short and medium length fatty acids, they undergo this reaction in the mitochondria. The long chain fatty acids can't go through the membrane though, so this reaction occurs at the outer mitochondrial membrane.
- The final fatty acid products are **acetyl-CoA** for the even numbered fatty acids (without double bonds), and for those with an odd number of carbons, it is **3-carbon propionyl-CoA**.

A. Beta-Oxidation of Fatty Acids (even chain)

1. Dehydrogenation (Acyl-CoA Dehydrogenase): This first reaction is the oxidation of the **C_a-C_b** bond. It is catalyzed by *acyl-CoA dehydrogenases*. This catalyst is a family of three soluble matrix enzymes. These enzymes carry noncovalently bound FAD that is reduced during the oxidation of the fatty acid.

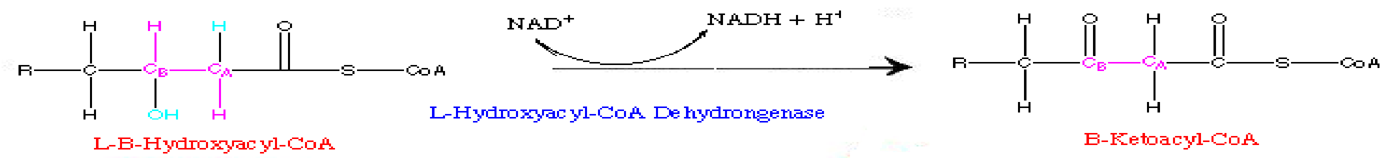


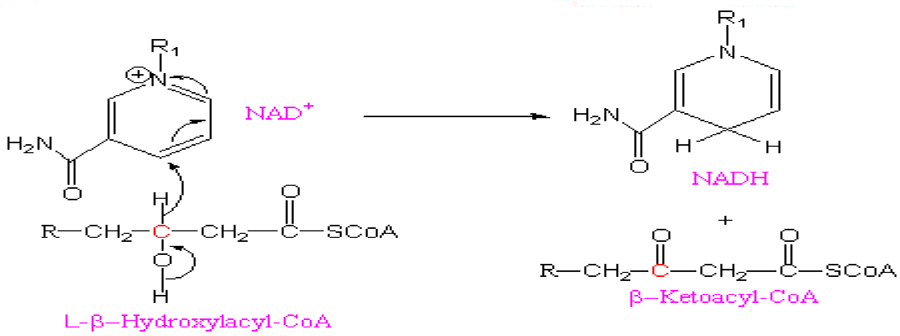
2. Hydration (Enoyl-CoA Hydratase): In this pathway is one in which water is added across the new double bond to make **hydroacyl-CoA**. The catalyst in this reaction is *Enoyl-CoA hydratase*. This is also called a *crotonase* and it converts **trans-enoyl-CoA** to **L-B-**



Hydroxyacyl-CoA. This reaction would be classified as a hydration reaction because you are adding water.

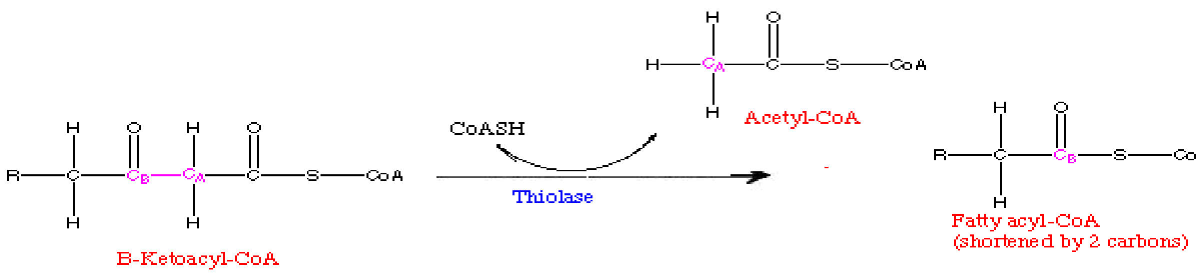
3. Oxidation (L-Hydroxyacyl-CoA Dehydrogenase): Here the oxidation of the hydroxyl group at the beta position which forms a **beta-ketoacyl-CoA** derivative and it is catalyzed by *L-Hydroxyacyl-CoA Dehydrogenase*. This enzyme needs to have **NAD**$^+$ as a coenzyme and the **NADH** produced represents metabolic energy because for every NADH produced, it drives the synthesis of 2.5 molecules of ATP in the electron transport pathway. So, this reaction is classified as an oxidation reaction.





Mechanism of L-Hydroxyacyl-CoA Dehydrogenase

Thiolysis: This is the final reaction of this pathway and *thiolase* catalyzed this reaction. This reaction cleaves the **β-ketoacyl-CoA**. The products of this reaction are an **acetyl-CoA** and a



fatty acid that has been shortened by two carbons. So, this reaction is classified as a **Cleavage Reaction**.

Repetition of the Beta Oxidation Cycle: The shortened fatty acyl-CoA that was the product of the last reaction now goes through another beta-oxidation cycle. This keeps happening until eventually you wind up with two molecules of acetyl-CoA in the final step. This acetyl-CoA is then available to be further metabolized in the TCA cycle, or it can be used as a substrate in amino acid biosynthesis. It cannot be used as a substrate for gluconeogenesis.

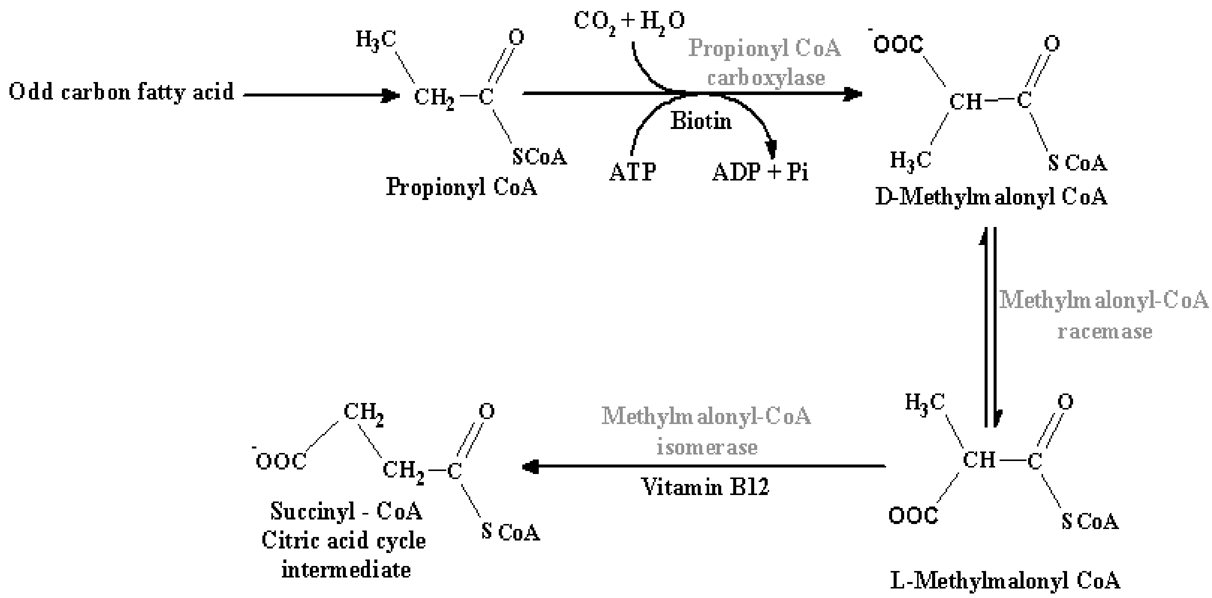
B. Beta oxidation of fatty acid with an odd number of carbons

Chains with an odd-number of carbons are oxidized in the same manner as even-numbered chains, but the final products are **propionyl CoA** and **acetyl CoA**.

Propionyl CoA is converted into **succinyl CoA** (which is an intermediate in the citric acid cycle) in a reaction that involves **Vitamin B_{12}**.

Succinyl CoA can then enter the citric acid cycle. Because it cannot be completely metabolized in the citric acid cycle, the products of its partial reaction must be removed in a process called **cataplerosis**. This allows regeneration of the citric acid cycle intermediates, possibly an important process in certain metabolic diseases.

Animals *cannot* make glucose from even carbon fatty acids. The only scope for glucose synthesis from **fatty acids** is from the ***propionyl CoA*** left behind after the beta-oxidation of odd carbon fatty acids.



Energy yield during β-oxidation of fatty acids

The ATP yield for every oxidation cycle is 14 ATP,

broken down as follows: 1 $FADH_2$ x 1.5 ATP = 1.5

ATP

1 NADH x 2.5 ATP = 2.5 ATP

1 acetyl CoA x 10 ATP = 10 ATP

For an even-numbered saturated fat **(C_{2n}), n - 1** oxidations are necessary and the final process yields an additional acetyl CoA. In addition, two equivalents of ATP are lost during the activation of the fatty acid. Therefore, the total ATP yield can be stated as:

(n - 1) * 14 + 10 – 2= No. of ATP

For instance, the ATP yield of

Palmitate (C_{16}, *n = 8*) is: (8 - 1)

* 14 + 10 – 2=**106 ATP**

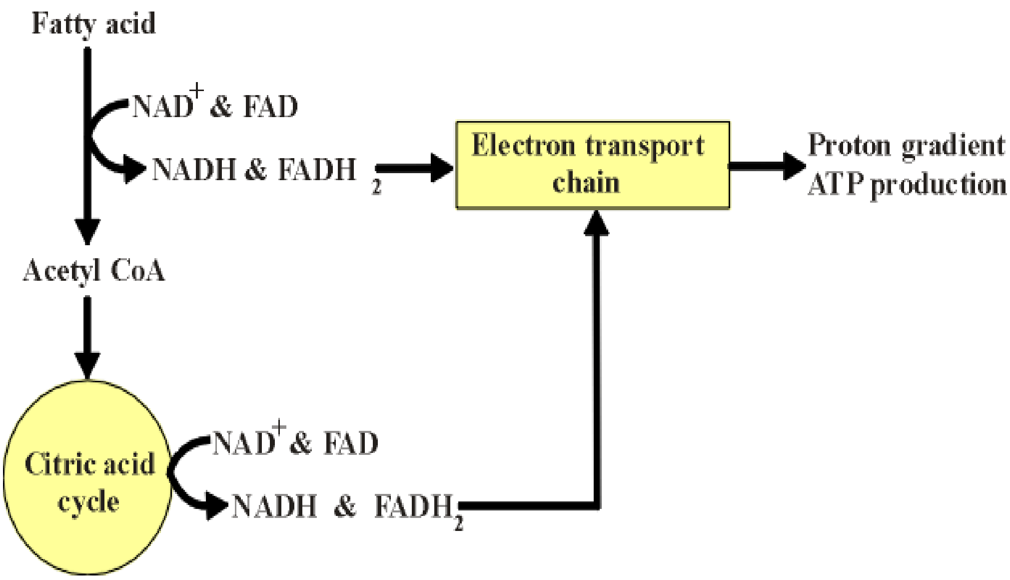
Or

7 $FADH_2$ x 1.5 ATP = 10.5 ATP

7 NADH x 2.5 ATP = 17.5 ATP

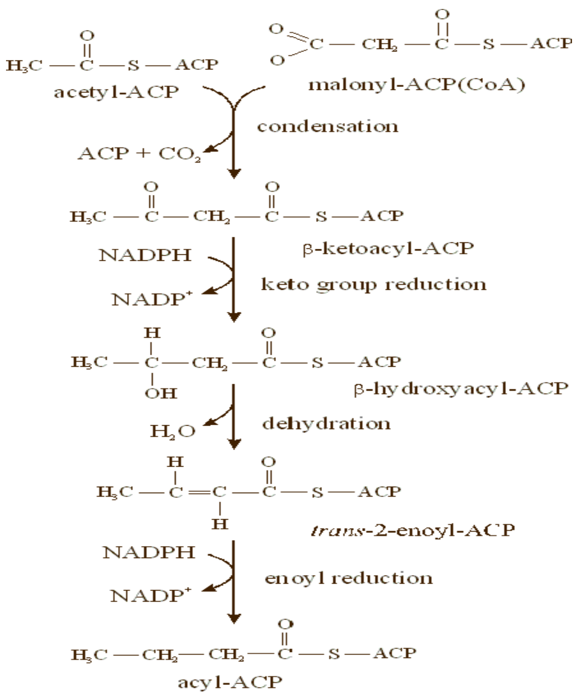
8 acetyl CoA x 10 ATP = 80 ATP

ATP equivalent used during activation = -2



BIOSYNTHESIS OF FATTY ACIDS

- **Fatty acid synthesis** is the creating of fatty acids from **acetyl-CoA** and **malonyl-CoA** precursors through action of enzymes called ***fatty acid synthases***. It is an important part of the lipogenesis process, which - together with **glycolysis** stands behind creating fats from blood sugar in living organisms.
- Synthesis takes place in the cytosol
- In humans, fatty acids are predominantly formed in the **liver** and **lactating mammary glands**, and, to a lesser extent, the **adipose tissue**.
- Most **acetyl-CoA** is formed from **pyruvate** by *pyruvate dehydrogenase* in the mitochondria. **Acetyl-CoA** produced in the mitochondria is condensed with **oxaloacetate** by *citrate synthase* to form **citrate**, which is then transported into the cytosol and broken down to yield **acetyl-CoA** and **oxaloacetate** by *ATP citrate lyase*. **Oxaloacetate** in the cytosol is reduced to **malate** by cytoplasmic *malate dehydrogenase*, and **malate** is transported back into the mitochondria to participate in the **Citric acid cycle**.
- The process involves 4 main steps: 1. Condensation, 2. Reduction, 3. Dehydration & 4. Reduction



***Acyl carrier protein* (ACP):** The acyl carrier protein (ACP) is an important component in both fatty acid andpolyketide biosynthesis

DIFFERENCES BETWEEN FATTY ACID DEGRADATION AND SYNTHESIS

Characteristic	***Degradation***	***Synthesis***
Location	Mitochondrial Matrix	Cytosol
Activated intermediates	Thioesters of CoA	Thioesters of ACP
Process	2-Carbon fragments removed as acetyl CoA	2-Carbon elongation using malonyl CoA
Direction	Starts at carboxyl end	Starts at methyl end
Redox reaction cofactors	FAD/FADH$_2$ and NAD$^+$/NADH	NADP+/NADPH
Major tissue site	Muscle and liver	Liver
Hormonal regulation	Low insulin / glucagon ratio	High insulin/glucagon ratio
Activator	FFA generated by hormone-sensitive lipase	Citrate
Inhibitor	Malonyl CoA (inhibits carnitine acyl transferase)	Fatty acyl CoA (inhibits acetyl CoAcarboxylase)

KETOGENESIS

- **Ketogenesis** is the process by which ketone bodies are produced as a result of fatty acid breakdown.
- Ketone bodies are produced mainly in the mitochondria of liver cells. Its synthesis occurs in response to low glucose levels in the blood, and after exhaustion of cellular carbohydrate stores, such as glycogen. The production of ketone bodies is then initiated to make available energy that is stored as fatty acids.
- Besides its role in the synthesis of ketone bodies, HMG-CoA is also an intermediate in the synthesis of cholesterol.
- The three ketone bodies are:
  - ✓ *Acetoacetate,* which, if not oxidized to form usable energy, is the source of the two other ketone bodies below

- ✓ *Acetone*, which is not used as an energy source, but is instead exhaled or excreted as waste
- ✓ *β-hydroxybutyrate,* which is not, in the technical sense, a ketone according to IUPAC nomenclature.

Regulation: Ketogenesis may or may not occur, depending on levels of available carbohydrates in the cell orbody. This is closely related to the paths of acetyl-CoA:

- When the body has ample carbohydrates available as energy source, glucose is completely oxidized to CO_2; acetyl-CoA is formed as an intermediate in this process, first entering the citric acid cycle followed by complete conversion of its chemical energy to ATP in oxidative phosporylation.
- When the body has excess carbohydrates available, some glucose is fully metabolized, and some of it is storedby using acetyl-CoA to create fatty acids. (CoA is also recycled here.)
- When the body has no free carbohydrates available, fat must be broken down into acetyl-CoA in order to get energy.

Pathology

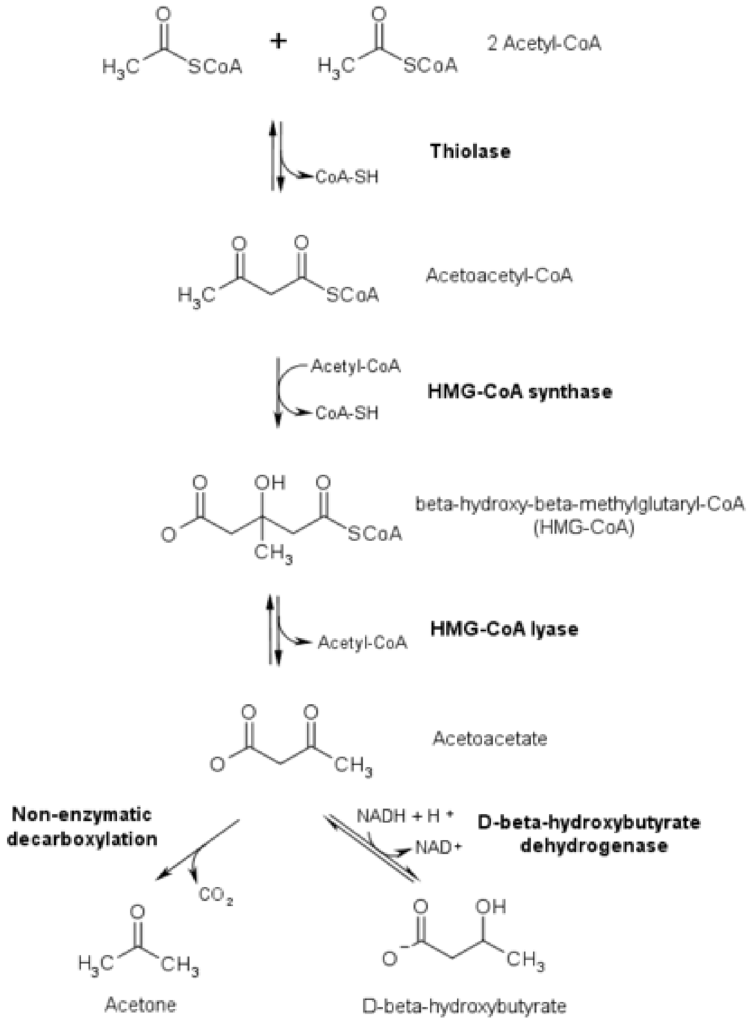
- Ketone bodies are created at moderate levels in everyone's bodies, such as during sleep and other times when nocarbohydrates are available.
- However, when ketogenesis is happening at higher-than-normal levels, the body is said to be in a state of ketosis.
- Both ***acetoacetate*** and ***beta-hydroxybutyrate*** are acidic, and, if levels of these ketone bodies are too high, the pHof the blood drops, resulting in ketoacidosis.
- ***Ketoacidosis*** is known to occur in untreated Type I diabetes (**diabetic ketoacidosis**) and in alcoholics after prolonged binge-drinking without intake of sufficient carbohydrates (**alcoholic ketoacidosis**).

KETOACIDOSIS

- ***Ketoacidosis*** is a metabolic state associated with high concentrations of ketone bodies, formed by the breakdown of fatty acids and the deamination of amino acids. The two common ketones produced in humans are acetoacetic acid and β-hydroxybutyrate.
- In ketoacidosis, the body fails to adequately regulate ketone production causing such a severe accumulation of keto acids that the pH of the blood is substantially decreased. In

extreme cases ketoacidosis can be fatal

- Ketoacidosis occurs when the body is producing large quantities of ketone bodies via the metabolism of fatty acids (ketosis) and the body is producing insufficient insulin to slow this production.

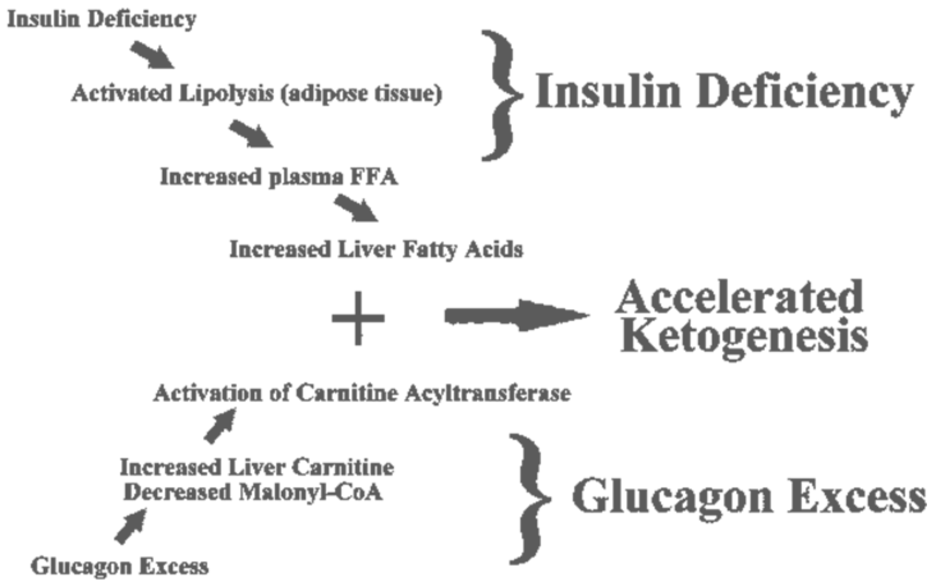


Ketogenesis Pathway

- The excess ketone bodies can significantly acidify the blood.
- There are two common types of **Ketoacidosis i.e.** diabetic and alcoholic ketoacidosis.

i. In diabetic patients, ketoacidosis is usually accompanied by insulin deficiency, hyperglycemia, and dehydration. Particularly in type 1 diabetics the lack of insulin in the bloodstream prevents glucose absorption and can cause unchecked ketone body production

ii. In alcoholic ketoacidosis, alcohol causes dehydration and blocks the first step of gluconeogenesis. The body is unable to synthesize enough glucose to meet its needs, thus creating an energy crisis resulting in fatty acid metabolism, and ketone body formation.



KETONE BODIES

- Ketone bodies are three water-soluble compounds that are produced as by-products when fatty acids are brokendown for energy in the liver and kidney.
- They are used as a source of energy in the heart and brain. In the brain, they are a vital source of energy duringfasting.
- The three endogenous ketone bodies are acetone, acetoacetic acid, and beta-hydroxybutyric acid, although beta- hydroxybutyric acid is not technically a ketone but a carboxylic acid.
- Ketone bodies can be used for energy. Ketone bodies are transported from the liver to other tissues, where acetoacetate and beta-hydroxybutyrate can be reconverted to acetyl-CoA to produce energy, via the citric acid cycle.
- Ketone bodies are produced from acetyl-CoA (ketogenesis) mainly in the mitochondrial matrix
- When even larger amounts of ketone bodies accumulate such that the blood's pH is lowered to dangerously acidiclevels, this state is called **ketoacidosis**.

KETONURIA

- Ketonuria is a medical condition in which ketone bodies are present in the urine.
- It is seen in conditions in which the body produces excess ketones as an alternative source of energy. It is seen during starvation or more commonly in type I diabetes mellitus.

Production of ketone bodies is a normal response to a shortage of glucose, meant to provide an alternate source of fuel from fatty acids.

Causes of ketosis and ketonuria

- Metabolic abnormalities such as diabetes, renal glycosuria, or glycogen storage disease
- Dietary conditions such as starvation, fasting, high protein, or low carbohydrate diets, prolonged vomiting, and anorexia
- Conditions in which metabolism is increased, such as hyperthyroidism, fever, pregnancy or lactation

In non-diabetic persons, ketonuria may occur during acute illness or severe stress. Approximately 15% of hospitalized patients may have ketonuria, even though they do not have diabetes.

In the non-diabetic patient, ketonuria reflects a reduced carbohydrate metabolism and an increased fat metabolism.

CHOLESTEROL SYNTHESIS, TRANSPORT & EXCRETION

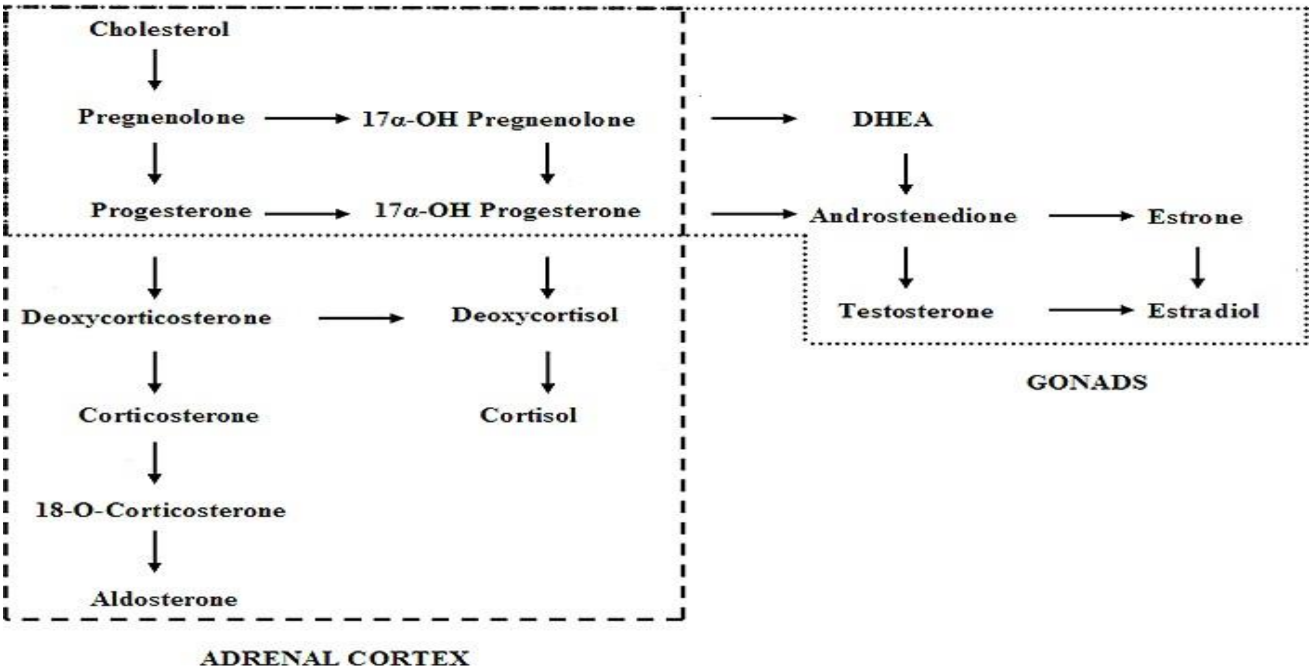
- Cholesterol is present in tissues and in plasma either as free cholesterol or as a storage form, combined with a long- chain fatty acid as cholesteryl ester.
- Cholesterol is an amphipathic lipid and as such is an essential structural component of membranes and of the outer layer of plasma lipoproteins.
- It is synthesized in many tissues from acetyl-CoA and is the precursor of all other steroids in the body such as corticosteroids, sex hormones, bile acids, and vitamin D.
- Plasma low-density lipoprotein (LDL) is the vehicle of uptake of cholesterol and cholesteryl ester into many tissues. Free cholesterol is removed from tissues by plasma high-density lipoprotein (HDL) and transported to the liver, where it is eliminated from the body either unchanged or after conversion to bile acids in the process known as **reverse cholesterol transport.**
- Cholesterol is a major constituent of **gallstones.** However, its chief role in pathologic processes is as a factor in the genesis of **atherosclerosis** of vital arteries, causing cerebrovascular, coronary and peripheral vascular disease.
- ***Biosynthesis of cholesterol*:** Cholesterol synthesis occurs in the cytoplasm and microsomes from the two-carbon acetate group of acetyl-CoA.

Biosynthesis of cholesterol in the liver accounts for approximately 10%, and in the intestines approximately 15%, ofthe amount produced each day. The process has five major steps:

- Acetyl-CoAs are converted to 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA)
- HMG-CoA is converted to mevalonate
- Mevalonate is converted to the isoprene based molecule, isopentenyl pyrophosphate (IPP), with theconcomitant loss of CO_2
- IPP is converted to squalene and
- Then Squalene is converted to cholesterol.

Steroidogenesis

It is the process wherein desired forms of steroids are generated by transformation of other steroids. The pathwaysof human steroidogenesis are shown in the figure.

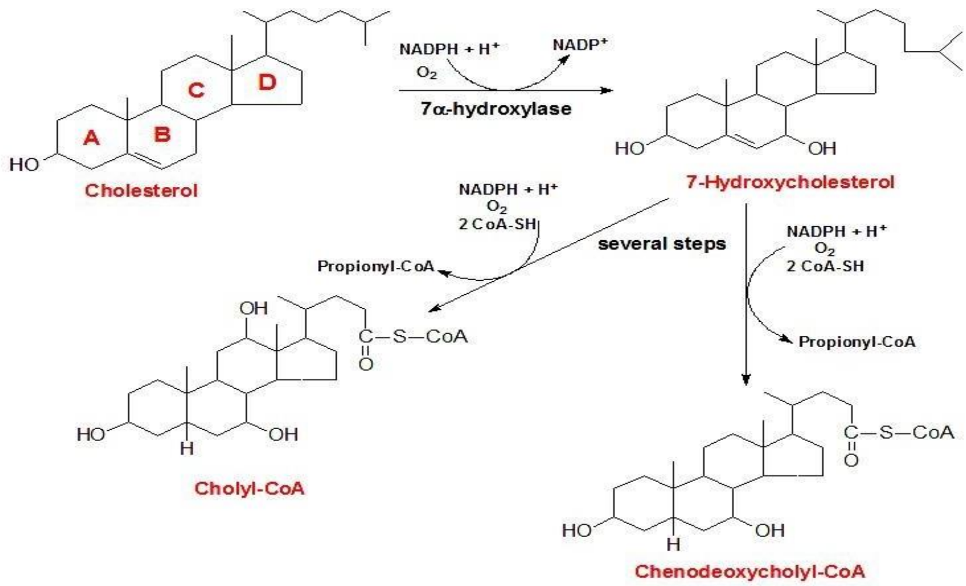


Products of steroidogenesis include:

- *androgens*
- *testosterone*
- *estrogens and progesterone*
- *corticoids*
- *cortisol*
- *aldosterone*

Elimination of Steroids:

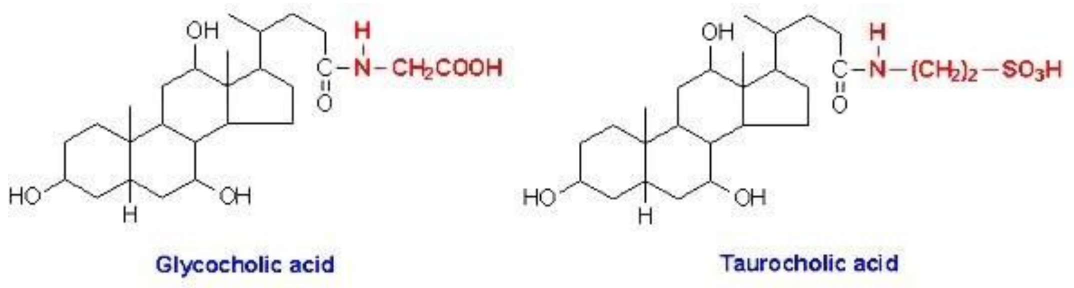
- Steroids are mainly oxidized by cytochrome P450 oxidase enzymes, such as CYP3A4. These reactions introduce oxygen into the steroid ring and allow the structure to be broken up by other enzymes, to form bile acids as final products. These bile acids can then be eliminated through secretion from the liver in the bile.
- The end products of cholesterol utilization are the bile acids, synthesized in the liver. Synthesis of bile acids is one of the predominant mechanisms for the excretion of



excess cholesterol. However, the excretion of cholesterol in the form of bile acids is insufficient to compensate for an excess dietary intake of cholesterol.

- The most abundant bile acids in human bile are chenodeoxycholic acid (45%) and cholic acid (31%). These are referred to as the primary bile acids. Within the intestines the primary bile acids are acted upon by bacteria and converted to the secondary bile acids, identified as deoxycholate (from cholate) and lithocholate (from chenodeoxycholate). Both primary and secondary bile acids are reabsorbed by the intestines and delivered back to the liver via the portal circulation.
- Within the liver the carboxyl group of primary and secondary bile acids is conjugated via an amide bond to either glycine or taurine before their being re-secreted into the bile canaliculi. These conjugation reactions yield glycoconjugates and tauroconjugates, respectively. The bile canaliculi join with the bile ductules, which then form the bile ducts. Bile acids are carried from the liver through these ducts to the gallbladder, where they are stored for future use. The ultimate fate of bile acids is secretion into the

intestine, where they aid in the emulsification of dietary lipids. In the gut the glycine and taurine residues are removed and the bile acids are either excreted (only a small percentage) or reabsorbed by the gut and returned to the liver. This process of secretion from the liver to the gallbladder, to the intestines and finally reabsorbtion is termed the enterohepatic circulation.



ATHEROSCLEROSIS

- Atherosclerosis is a disease in which plaque builds up on the insides of arteries.
- It is a syndrome affecting arterial blood vessels. It is a chronic inflammatory response in the walls of arteries, in large part due to the accumulation of macrophage white blood cells and promoted by low density (especially small particle) lipoproteins (plasma proteins that carry cholesterol and triglycerides) without adequate removal of fats and cholesterol from the macrophages by functional high density lipoproteins (HDL). It is commonly referred to as a "hardening" or "furring" of the arteries. It is caused by the formation of multiple plaques within the arteries.
- The **Atheromatous Plaque** is divided into three distinct components:
  a) The atheroma ("lump of porridge), which is the nodular accumulation of a soft, flaky, yellowish material at the center of large plaques, composed of macrophages nearest the lumen of the artery
  b) Underlying areas of cholesterol crystals
  c) Calcification at the outer base of older/more advanced lesions.
- Atherosclerosis can affect any artery in the body, including arteries in the heart, brain, arms, legs, and pelvis. As a result, different diseases may develop based on which arteries are affected.

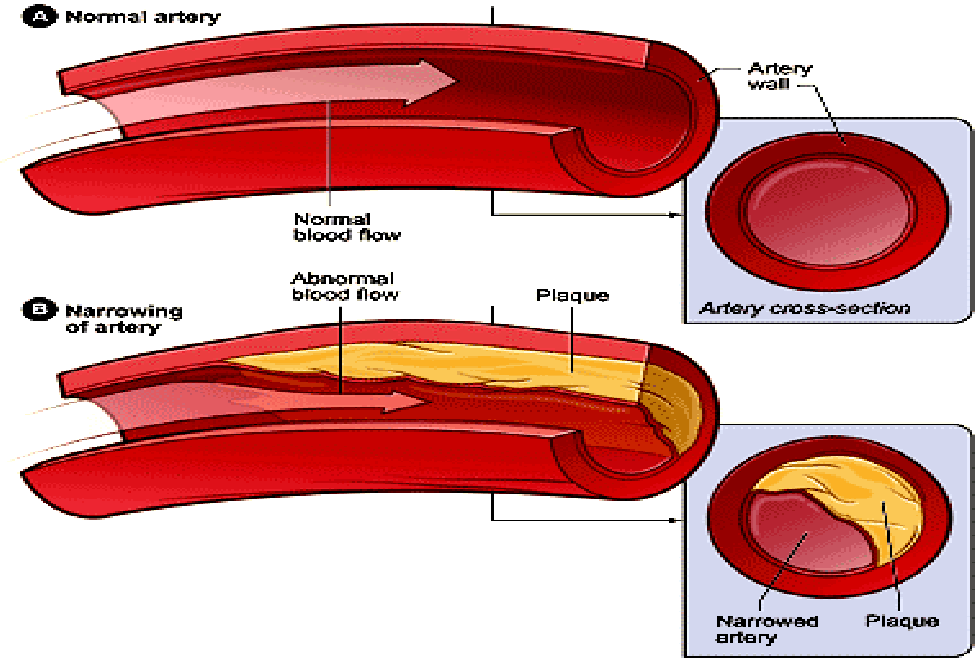
Coronary artery disease: (CAD). This is when plaque builds up in the coronary arteries. These arteries supply oxygen-rich blood to your heart. When blood flow to your heart is reduced or blocked, it can lead to chest pain and heart attack. CAD also is called heart disease, and it's the leading cause of death in the United States.

Carotid artery disease: This happens when plaque builds up in the carotid arteries. These arteries supply oxygen-rich blood to your brain. When blood flow to your brain is reduced or blocked, it can lead to stroke.

Peripheral arterial disease (PAD): This occurs when plaque builds up in the major arteries that supply oxygen-rich blood to the legs, arms, and pelvis. When blood flow to these parts of your body is reduced or blocked, it can lead to numbness, pain, and sometimes dangerous infections.

Symptoms of Atherosclerosis

1) Unfortunately, atherosclerosis produces no symptoms until the damage to the arteries is severe enough to restrictblood flow.
2) Restriction of blood flow to the heart muscle due to atherosclerosis can cause angina pectoris or a myocardialinfarction (a heart attack).
3) Restriction of blood flow to the muscles of the legs causes intermittent claudication (pains in the legs broughtabout by walking and relieved by rest).
4) Narrowing of the arteries supplying blood to the brain may cause transient ischemic attacks (symptoms and signs of a stroke lasting less than 24 hours) and episodes of dizziness, or ultimately, to a stroke itself.



Treatment of Atherosclerosis

- Medication is unsatisfactory for treating atherosclerosis, since the damage has already been done.
- Anticoagulant drugs have been used to try to minimize secondary clotting and embolus formation.
- Vasodilator drugs are helpful in providing symptom relief, but are of no curative value.
- Surgical treatment is available for those unresponsive to medical treatment or in certain high-risk situations.
- Balloon angioplasty can open up narrowed vessels and promote an improved blood supply.
- The blood supply to the heart can also be restored by coronary artery bypass surgery.

KETOLYSIS: The splitting up of ketone bodies.

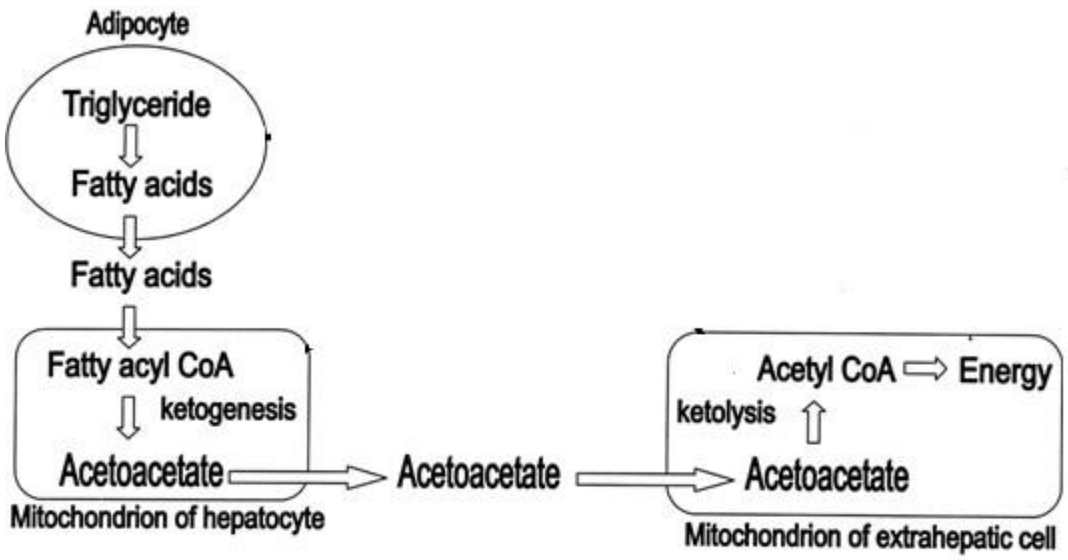


Diagram of ketone body metabolism

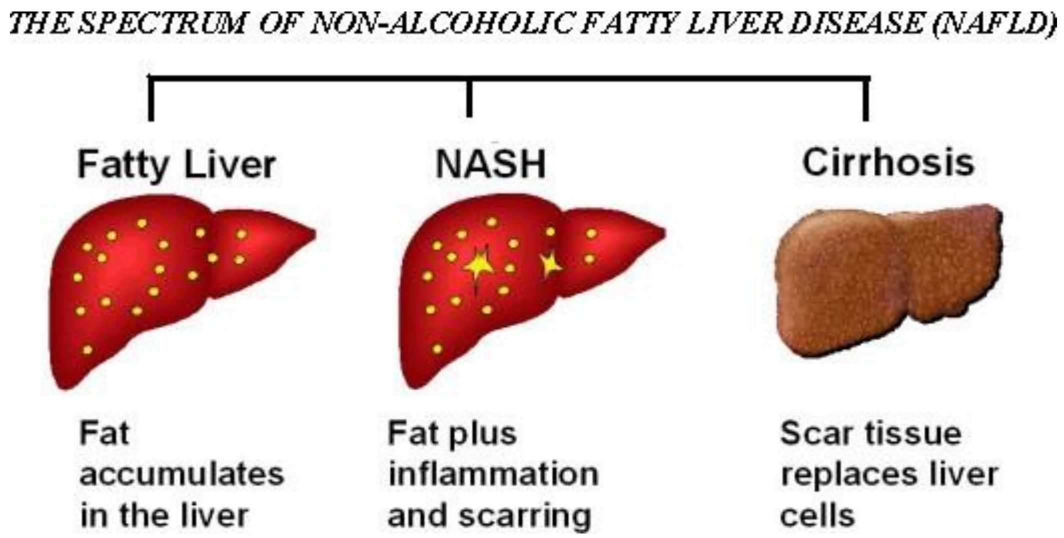
FATTY LIVER*:*

It is also known as ***fatty liver disease*** (**FLD**), is a reversible condition where large vacuoles of triglyceride fat accumulate in liver cells via the process of ***steatosis*** (i.e. abnormal retention of lipids within a cell).

Causes: Fatty liver is commonly associated with alcohol or metabolic syndrome (diabetes, hypertension, obesity anddyslipidemia)

Diagnosis of Fatty Liver*:* in routine blood screening or images of the liver obtained by an ultrasound test, **CT** (***computed tomography***) scan, or **MRI** (***magnetic resonance imaging***) may suggest the presence of a fatty liver or ***liver biopsy***, in which a small sample of liver tissue is obtained through the skin and analyzed under the microscope

The treatment of fatty liver is related to the cause. It is important to remember that simple fatty liver may not require treatment. The benefit of weight loss, dietary fat restriction, and exercise in obese patients is inconsistent. Reducing or eliminating alcohol use can improve fatty liver due to alcohol toxicity. Controlling blood sugar may reduce the severity of fatty liver in patients with diabetes.



HYPERCHOLESTEROLEMIA

- Hypercholesterolemia, or high cholesterol, occurs when there is too much cholesterol in the body.
- Cholesterol is a soft, waxy, fat-like substance that is a natural component of all the cells of the body.
- High cholesterol raises risk for heart disease, heart attack, and stroke. When there is too much cholesterol circulating in the blood, it can create sticky deposits (called plaque) along the artery walls. Plaque can eventually narrow or block the flow of blood to the brain, heart, and other organs. And blood cells that get caught on the plaque form clots, which can break loose and completely block blood flow through an artery, causing heart attack or stroke.
- There are two types of cholesterol -- HDL (high-density lipoproteins, or "good"

cholesterol) and LDL (low-density lipoproteins, or "bad" cholesterol).

- The amount of HDL relative to LDL is considered a more important indicator of heart disease risk.
- There is a third kind of fatty material, triglycerides, found in the blood. They also play a role (generally as triglyceride levels rise, "good" HDL cholesterol falls).
- The usual symptoms of high cholesterol, especially in early stages. The only way to determine cholesterol is high is through a blood test.

Treatment Approach: Lowering your cholesterol level reduces your risk of heart disease and stroke. Changes in lifestyle -- better diet, more exercise and specific cholesterol-lowering medications are often prescribed like, Lovastatin, Pravastatin, Rosuvastatin, Simvastatin, Atorvastatin or Fluvastatin, etc

Total cholesterol levels (mg/dL)**:**

- Desirable: Below 200
- Borderline high: 200 - 239
- High: Above 240

LDL cholesterol level (mg/dL)**:**

- Optimal for people with heart disease or who are at high risk: Below 70
- Optimal for people at risk of heart disease: Below 100
- Optimal: 100 - 129
- Borderline high: 130 - 159
- High: 160 - 189

HDL cholesterol level (mg/dL)**s:**

- Poor: Below 40
- Acceptable: 40 - 59
- Optimal: 60 or above

Triglyceride levels (mg/dL)**:**

- Optimal: Below 150
- Borderline high: 150 - 199

AMINO ACID METABOLISM

General reactions of amino acid metabolism: The breakdown method of proteins in amino acids is called proteolysis which occurs in gastrointestinal tract. This amino acid further degraded by the methods such as transamination, deamination and decarboxilation which occurs in the liver.

Transamination: It is the method through which α-amino group loses from amino acid by degradation i.e. transfer to an α-keto acid. Eg. Alanine convertes in Pyruvate in the presence of enzame Alanine aminotransferase

Alanine + α-ketoglutarate

Pyruvate + Glutamate

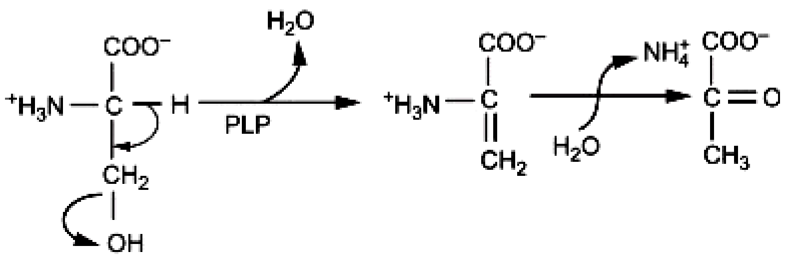
Significance:

1. it is an exchange of amno nitrogen between the molecule without a net loss.
2. It is important for formation of non-essential amino acids.

Deamination:

Deamination involves removal of amino group in the form of NH_3.

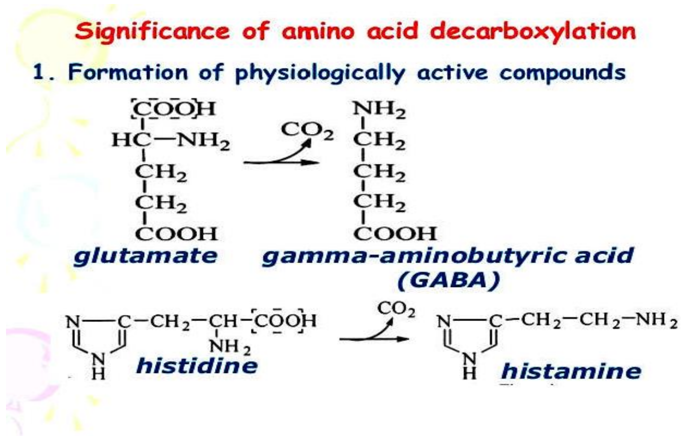
Libration of free ammonia from amino group of an amino acid coupled with oxidation takes place in oxidative deamination. The reaction occurs in the liver and kidney. e.g the conversions of glutamate to α- ketoglutarate occurs in the presence of enzymes glutamate dehydrogenase, e.g.



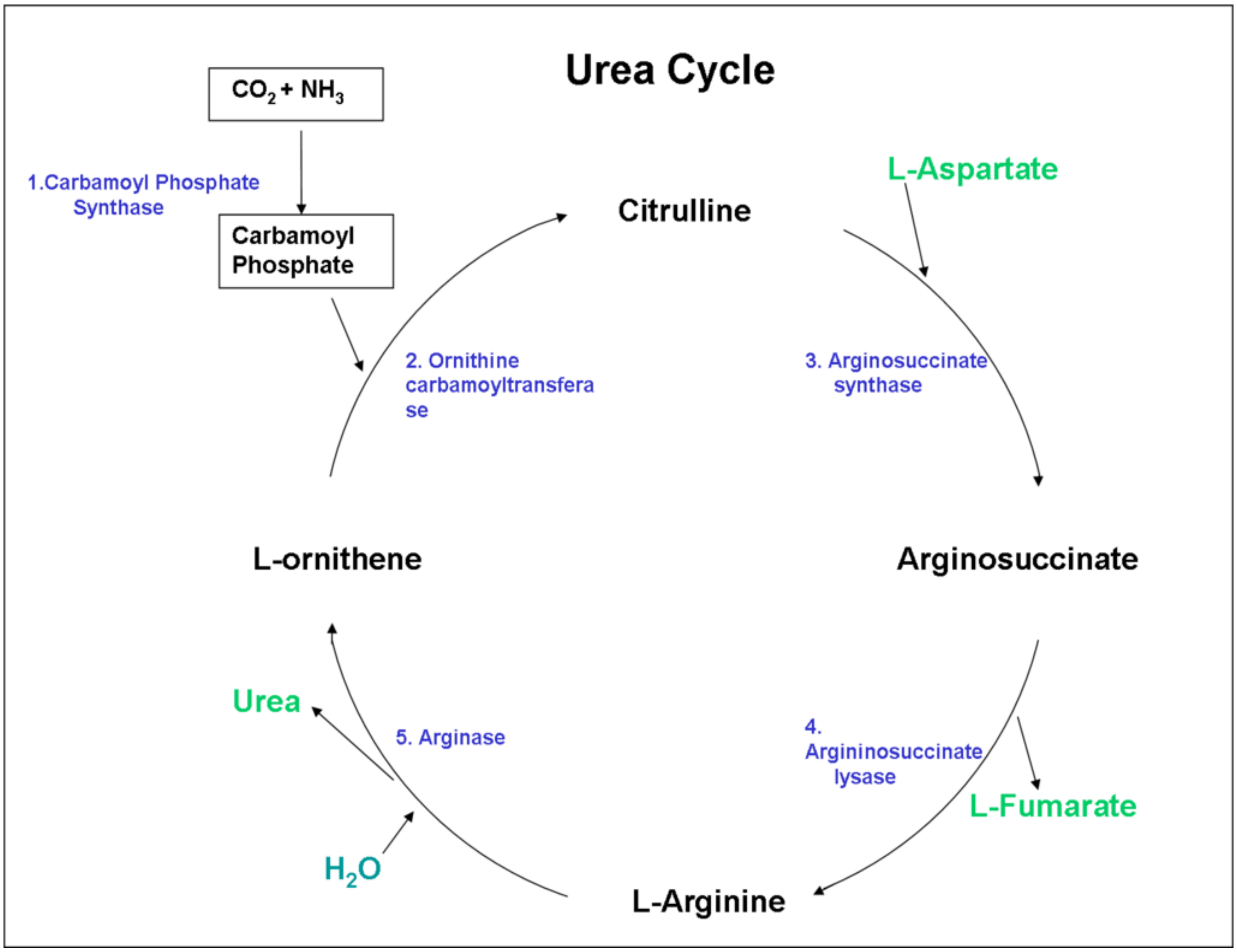
L-Serine Aminoacrylate Pyruvate

Non-oxidative deamination takes place by reduction, hydrolytic or intra molecular reactions.

Decarboxylation: It is the process by which carboxylic group is removed from the amino acid and biogenic amines are formed.



Urea cycle and its disorders: The urea cycle is a biochemical reaction by which highly toxic ammonia is converted into urea and excreted from the body through urine. This cycle is also known as **ornithine cycle**. The urea is absorbed first into the blood stream then filtered by kidney and then excreted through urine. Various steps of urea cycle are shown in figure.



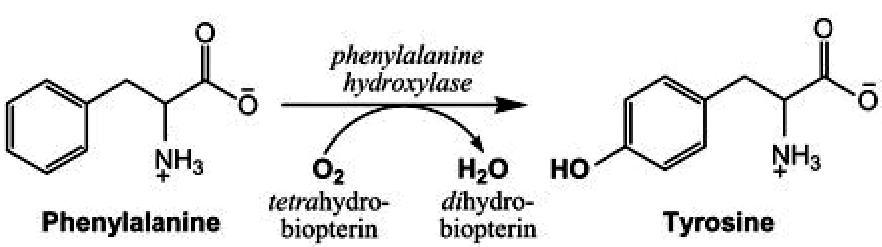
Significance of urea cycle:

- Urea cycle is the first elucidated metabolic pathway.
- The cycle is also known as **Krebs-Henseleit urea cycle**
- Ornithin is the first member of the reaction and hence known as ornithin cycle.
- Toxic ammonia is converted into non-toxic urea.
- The excess nitrogen forms urea
- It removes CO_2 and NH_3.
- It recycles TCA cycle intermediate.
- It recycles amino acids and keto acids.
- Urea production takes place in liver, transported to kidney and excreted through urine.

Energetic of Urea cycle: Urea cycle utilized overall 1,5 ATP.

Metabolic disorder of urea cycle:

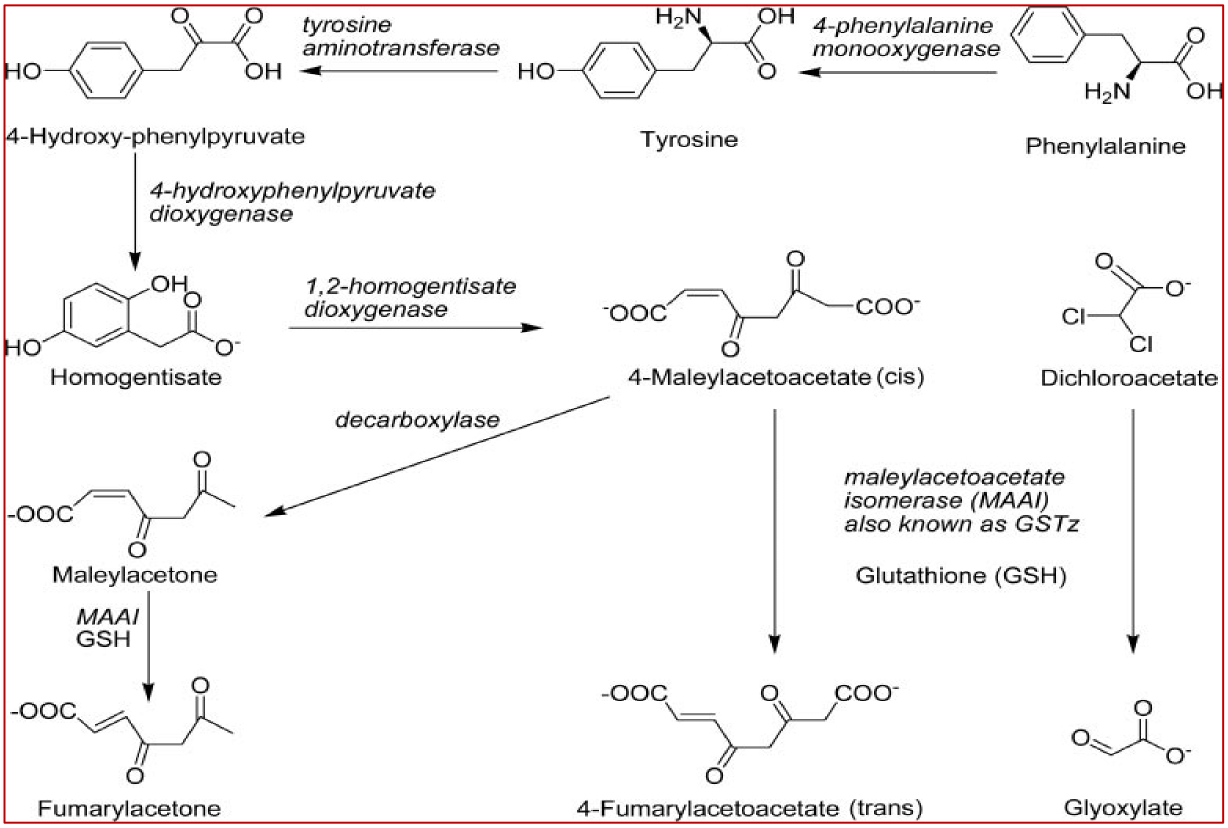
Deficiency	Disorder
N-Acetylglutamate synthase	Hyperammonemia that may be accompanied by high plasma concentrations of alanine and glutamine
Carbamoyl phosphate synthetase	Hyperammonemia; citrullinemia; respiratory alkalosis
Ornithine transcarbamylase	Hyperammonemia; respiratory alkalosis; elevated orotic acid in urine
Arginosuccinate synthetase	Citrullinemia
Arginosuccinate lyase	Elevated arginosuccinic acid in urine
Arginase	Markedly elevated plasma arginine, lactate, and CSF glutamine, and modestly elevated blood ammonia



Catabolism of phenylalanine and tyrosine:

1) Phenylalanine is an essential amino acid, however tyrosine is non-essential. Both of them are aromatic amino acids having similarity in their structures. Phenylalanine is converted in Tyrosine catalyzed by enzyme phenylalanine hydroxylase.
2) The metabolism of phenylalanine and tyrosine is considered together.
3) During catabolism, phenylalanine and tyrosine are converted in fumerate (an intermediate of TCA cycle and gluconeogenesis) and acetate (a ketone body from which fats can be synthesized).

Various step of metabolism of phenylalanine and tyrosine are as follow:



Metabolic disorders of phenylalanine and tyrosine (Phenyketonuria, Albinism, alkaptonuria, tyrosinemia):

Various common disorders are as follow:

Phenyketonuria: Phenylketonuria (PKU) is an inborn error of metabolism that results in decreased metabolism of the amino acid phenylalanine. Untreated, PKU can lead to intellectual disability, seizures, behavioral problems and mental disorders. It may also result in a musty smell and lighter skin.

Other names: Phenylalanine hydroxylase deficiency.

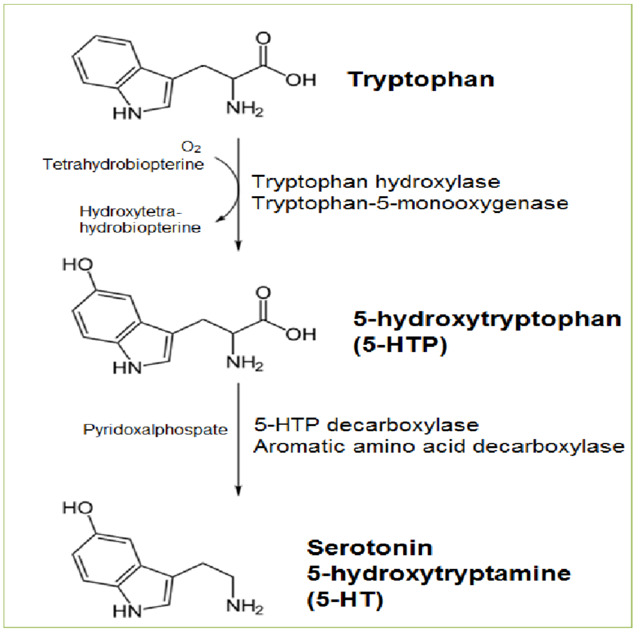
Albinism: 1. Albinism is a congenital disorder characterized in humans by the complete or partial absence of pigment in the skin, hair and eyes. 2. It is a defect in one of several genes that produce or distribute melanine. 3. Due to absence of tyrosinase (Cu containing) enzyme in the melanocyte cells. It is also known as achromia.

Alkeptonuria: Alkaptonuria is a rare inherited disorder. It occurs when your body can't produce enough of an enzyme called homogentisic dioxygenase (HGD). The gene defect makes the body unable to properly break down certain amino acids (tyrosine and phenylalanine). As a result, a substance called homogentisic acid builds up in the skin and other body tissues. Affected individuals may have dark urine or urine that turns black when exposed to air.

Tyrosinemia: Tyrosinemia is a genetic metabolic disorder that causes the body's inability to effectively breakdown the amino acid tyrosine. The inability to breakdown the amino acid is caused by the deficiency of the fumarylacetoacetate hydrolase (FAH) enzyme (Type I), tyrosine aminotransferase enzyme (Type II) and 4-hydroxyphenyl-pyruvate dioxigenase enzyme (Type III) which required for the metabolism of tyrosine. It leads to accumulation of toxic materials in various tissues and finally kidney and liver are destroyed.

Biosynthesis and significance of 5-HT:

1) Serotonin (5-HT) is an important chemical and neurotransmitter in the human body.
2) It is produced in brain.
3) It is believed to help regulate mood and social behavior, appetite and digestion, sleep and memory and function such as vasoconstrictor (smooth construction of muscles).

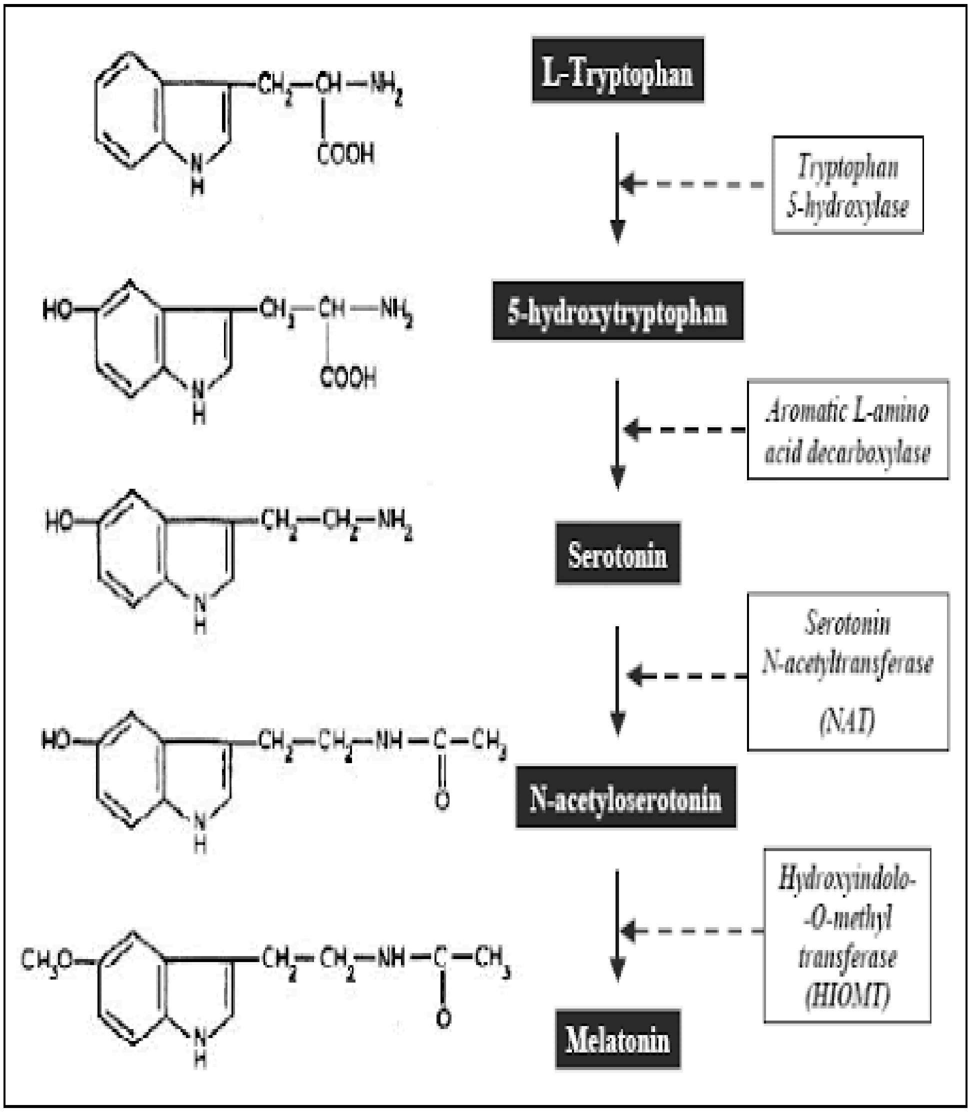


Biosynthesis and significance of melatonin:

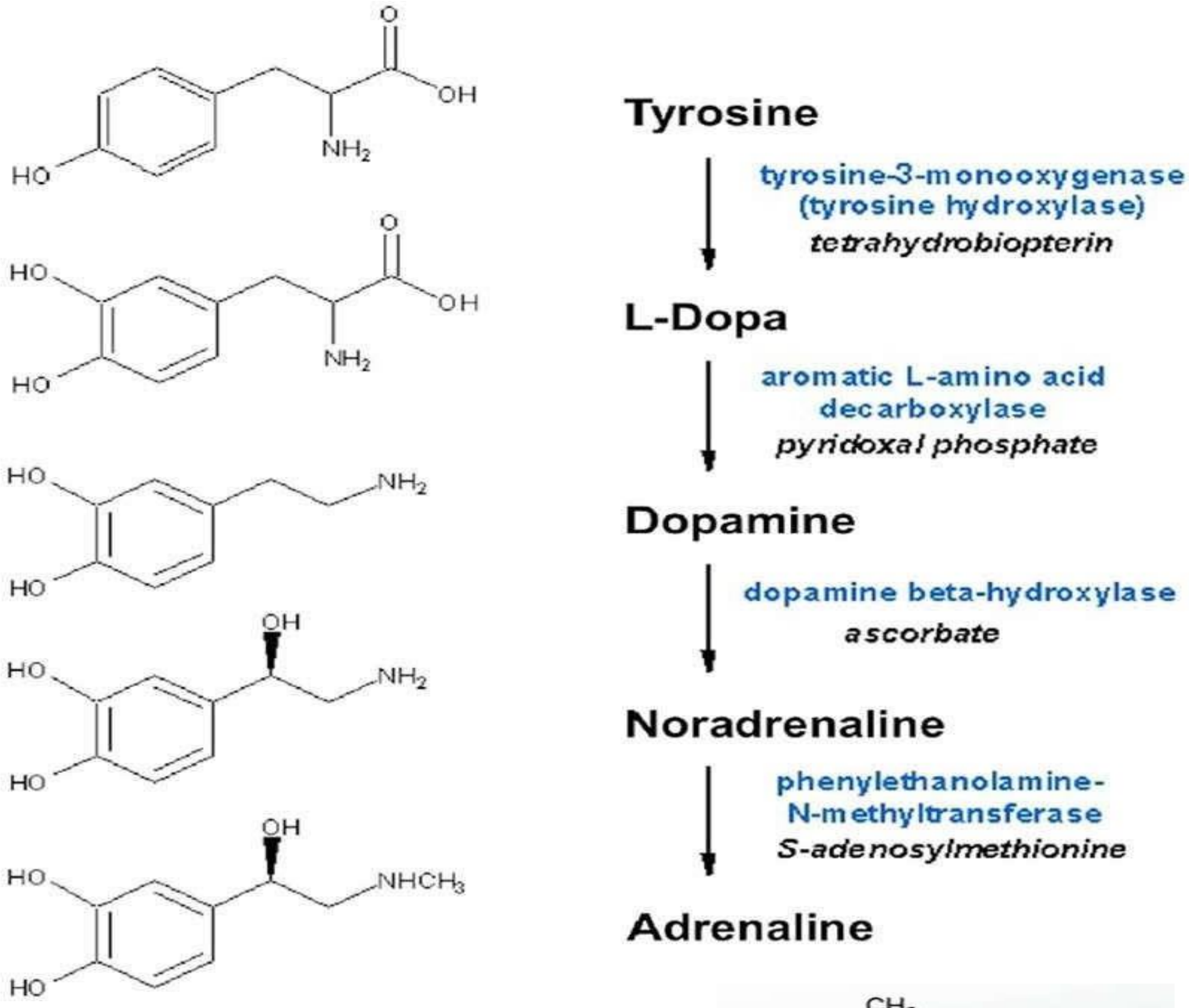
1. In humans, melatonin plays an important role in the regulation of sleep cycles (i.e., circadian rhythm).

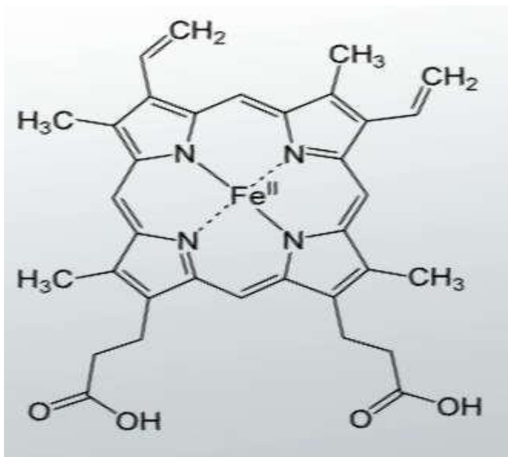
2. Melatonin is released by the pineal gland in the brain during the nighttime hours,

3. It induces physiological changes that promote sleep, such as decreased body temperature and respiration rate.



Biosynthesis of Dopamine adrenaline and noradrenaline





Biological significance of Dopamine

A. Dopamine belongs to catecholamines

B. Epinephrine and norepinephrine are synthesized from dopamine.

C. It plays significance role in learning, behavior changes, regulation of hormones, motor control etc.

D. It controls flow of information from other areas of brain.

E. It plays role in movement.

Biological significance of adrenaline and noradrenaline

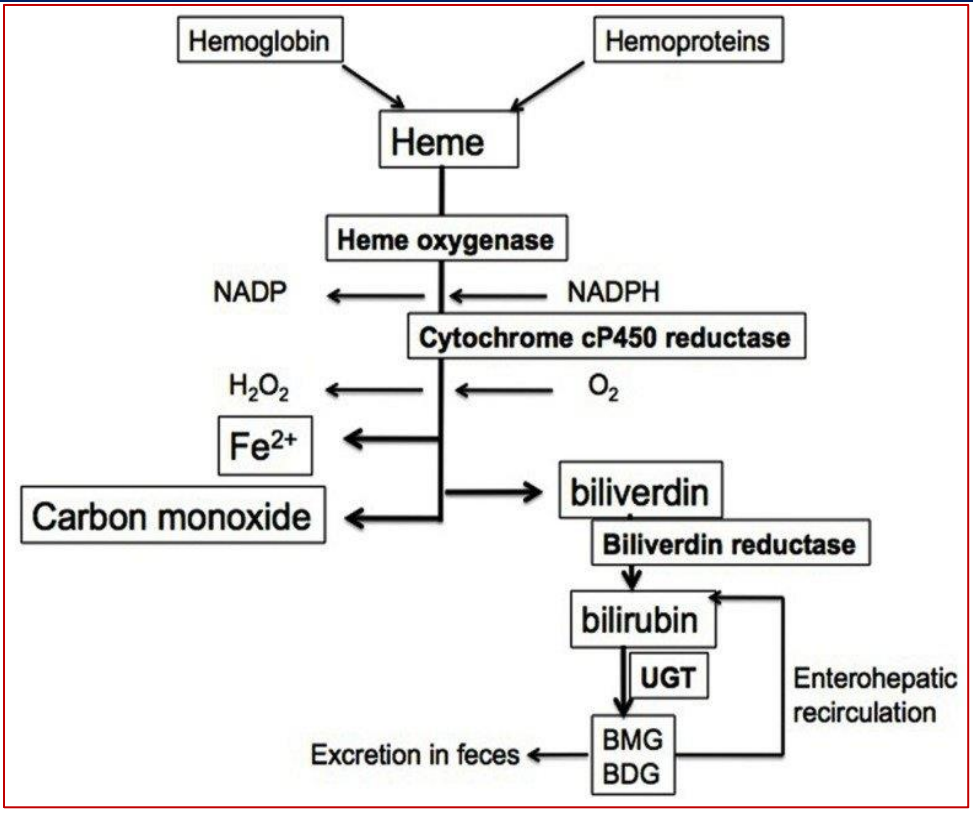
1. Adrenaline (Epinephrine) produced in adrenal gland whereas Noradrenaline (norepinephrine) is secreted from certain neurons of brain as well as adrenal gland.
2. Both are example of catecholamines.
3. Noradrenaline is the main neurotransmitter of the sympathetic nerves in the cardiovascular system.
4. Both are the example of catecholamines.
5. Noradrenaline is the main neurotransmitter of the sympathetic nerves in the cardiovascular system.
6. Adrenaline is the main hormones secreted by the adrenal medulla.
7. Noradrenaline is used to increase and maintain blood pressure in acute situations like cardic arrest etc.
8. Adrenaline is used to treat low blood pressure associated with septic shock, allergic reaction etc.

Catabolism of heme (or Haem):

1. It consist of an iron ion co-ordinated to a porphyrin of hemoglobin and acting as a ligand.

2. Heme break down takes place in macrophages of reticuloendothelial system of spleen and liver.

3. The catabolism of heme is shown in below flow charts.



Hyperbilirubinemia and jaundice:

Hyperbilirubinemia is a condition in which there is too much bilirubin (a yellow coloured pigment) in the blood. When red blood cells break down, a substance called bilirubin is formed. Babies are not easily able to get rid of the bilirubin and it can build up in the blood and other tissues and fluids of the baby's body.

It causes yellowing of the skin, eyes and other tissues. This condition is known as **jaundice** (bilirubin > 2 mg/100ml).

Types of jaundice:

- **Hemolytic jaundice**: a condition due to excessive hemolysis of blood.
- **Parenchymatous jaundice**: a condition due to liver cell damage.
- **Obstructive jaundice**: a condition due to presence of tumors in biliary tract.

Very Short Answer Questions (2 marks)

1. Define Atherosclerosis.
2. What is Transamination?
3. What are lipotropic factors?
4. Define Ketosis.
5. What is Deamination?

Short Answer Questions (5 marks)

1. What is biological significance of Cholesterol?
2. Write short note on formation and utilization of Ketone bodies.
3. Define the terms ketonemia, ketouria, ketosis and ketocidosis.
4. Write the disorders of Lipid metabolism.
5. What is the difference between Transamination and Deamination?
6. Write the disorders of phenylalanine and tyrosine.-

Long Answer Questions (10marks)

1. Describe the digestion and absorption of dietary lipids.
2. Give an account of β – oxidation of saturated even carbon fatty acid (Palmitic acid) along with its energetic and regulation.
3. Describe denovo synthesis of saturated long chain fatty acid and its regulation.
4. Enumerate the ketone bodies. Describe the formation and fate of ketone bodies. Add a note on ketosis.
5. Give an account of synthesis and significance of biological substances of Amino acid metabolism.
6. Explain denovo synthesis of cholesterol and its regulation. Add a note on cholesterol lowering drugs.