A.S.Warsy
Lipids- Structure and Metabolism

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Lipids

Lipids:
- **Heterogenous** group of biomolecules.
- **Water insoluble** (hydrophobic).
- **Soluble** in organic and non-polar solvents acetone, ether, chloroform and benzene.

Functions:
- **Major source of energy** for the body.
- **Storage form of energy**-triglyceride.
- Components of **cell membrane**.
- Some are **hormones** e.g. steroid hormone (cortisol, aldosterone, sex hormones)
- Some **fat-soluble vitamins** have regulatory or coenzyme function.
Classes of lipids

Simple lipids
- e.g.
  - Triglycerides
  - Waxes

Conjugated (complex) lipids
- Phospholipids,
- Glycolipids
- Sphingo- phospholipids
- Lipoproteins.

Derived lipids
- Fatty acids
- Cholesterol
- Ketone bodies

Esters of FA with alcohols

Esters of FA with alcohols and additional group

Obtained on hydrolysis of simplex or complex lipids
Simple Lipids

• These are the esters of fatty acids with various alcohols.

• Further subdivided into neutral fats, and oils and waxes.
  • **Neutral fats** are the esters of long chain fatty acids with glycerol and are called triglycerides or triacylglycerols.
  • **Waxes** are the esters of long chain fatty acids with high molecular weight monohydroxy aliphatic alcohols e.g. Beeswax and carnauba wax.

• Cholesterol esters of palmitic acid (cholesteryl palmitate) is found in blood plasma.

• Esters of hydroxy fatty acids with open chain alcohols are found in skin.
Triglycerides - Neutral fat; the storage form of energy

Fatty acid

Glycerol
Triglycerides

- Triglycerides or triacylglycerols are the esters of fatty acids with trihydric alcohol (glycerol).

- Glycerol with one molecule of fatty acid is called monoglyceride while with three fatty acids is called triglyceride.

- A molecule of triglyceride may contain three similar or dissimilar fatty acids which may be saturated as well as unsaturated.

- Usually the vegetable fats contain greater proportion of unsaturated fatty acids while the animal fats contain large amounts of the long chain saturated fatty acids.

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Compound or conjugated lipids

- Esters of fatty acids with certain other compounds (groups) in addition to glycerol and fatty acids.

- These include phospholipids, glycolipids, proteolipids (lipoproteins) etc.
Conjugated lipids

Phospholipids
Phospholipids: building blocks of membrane, components of signal transduction pathway:

- Phosphatidyl inositol
- Phosphatidyl choline
- Phosphatidyl glycerol
- Phosphatidyl ethanolamine
- Phosphatidyl serine

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Sphingolipids: contain the alcohol sphingosine

Sphingolipids: Structural components of membranes and surface antigens:

**Sphingosine**

\[
\text{CH}_3-(\text{CH}_2)_n-C=C-C-C-\text{CH}_2\text{OH}
\]

**Sphingomyelin**

\[
\begin{align*}
\text{R}_2-\text{C-N-}&\text{CH} \quad \text{H} \\
\text{O} &\text{HC} \quad \text{C}=\text{C} \quad (\text{CH}_2)_m \text{CH}_3 \\
\text{O} &\text{H_2C-O-P-O-CH}_2\text{CH}_2\text{N(CH}_3)_3
\end{align*}
\]
Glycolipid

Glycosphingolipid

Ceramid

Glycosidic bond

Galactose

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Phosphate

Polar lipid molecule
- Polar head
- Nonpolar tails

Glycerol

Phospholipid bilayer
- Water
- Phospholipids
- Water

Phospholipids in single layer
- Water

Fatty acids
Micelle

(a) Palmitic acid

Hydrocarbon end orients away from water

(b) Oil

(c) Water

Ionic end is soluble in water

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Complex lipids

CH₃-(CH₂)₁₂-C=CH-C-C-C=CH₂-OH
   H       H       H

CH₃-(CH₂)ₙ-NH
   (CH₂)ₙ

Ceramide

CH₃-C-O-C-R₁
   H₂-C-O-C-R₂
   H₂-C-O-C-R₃
   O-C-R₄

Cardiolipin

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Cholesterol esters: Structural component of membranes. Precursor of steroid hormones, vitamin D and bile acids.
Derived Lipids

- Substances which are obtained by hydrolysis of the simple and compound lipids.

- These include fatty acids (saturated as well as unsaturated), glycerol, sterols, etc.
Fatty Acids

- Obtained by the hydrolysis of neutral fats (triglycerides).
- Organic monocarboxylic acids with an aliphatic chain containing 4 to 24 carbon atoms.
- The aliphatic chain may be saturated or unsaturated with one or more double bonds.

**Fatty acids:** Metabolic fuel, building blocks for triglycerides, phospholipids and sphingolipids. Precursors for prostaglandins.
Derived Lipids

Saturated fatty acids:

\[ \text{CH}_3\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{(CH}_2\text{)}_n\text{-CH}_2\text{-COOH} \]

Unsaturated fat acids:

\[ \text{CH}_3\text{-}(\text{CH}_2\text{)}_n\text{-CH} = \text{CH}\text{-CH}_2\text{-CH} = \text{CH}\text{-}(\text{CH}_2\text{)}_n\text{-COOH} \]
Nomenclature of Fatty Acids

- Named after the name of the hydrocarbon with the same number of carbon atoms, the suffix –oic being substituted for the final –e in the name of the hydrocarbon.

- The saturated fatty acid ends in –anoic, e.g. octanoic acid while the unsaturated fatty acid ends with the suffix –enoic acid, e.g. octadecenoic acid.

- The carbon atoms in the fatty acids are numbered from the –COOH group.

- The carbon atom adjacent to the –COOH is called as α-carbon atom.

- Octadecenoic acid (oleic acid) is written as 18:19, i.e. the fatty acid having 18 carbon atoms with one double bond between carbon atom numbers 9 and 10.

  \[
  \text{CH}_3 - (\text{CH}_2)_7 - \text{CH} = \text{CH} - (\text{CH}_2)_7 - \text{COOH}
  \]

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Saturated Fatty Acids

- Acids containing even number of carbon atoms with the general formula of $C_nH_{2n+1}$.

<table>
<thead>
<tr>
<th>Fatty Acids</th>
<th>Number of C-atoms</th>
<th>Formula</th>
<th>Sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetic acid</td>
<td>2</td>
<td>CH$_3$-COOH</td>
<td>Carbohydrate fermentation</td>
</tr>
<tr>
<td>Butyric acid</td>
<td>4</td>
<td>CH$_3$-(CH$_2$)$_2$-COOH</td>
<td>Butter</td>
</tr>
<tr>
<td>Caproic acid</td>
<td>6</td>
<td>CH$_3$-(CH$_2$)$_4$-COOH</td>
<td>Butter and many fats of plant origin</td>
</tr>
<tr>
<td>Caprylic acid</td>
<td>8</td>
<td>CH$_3$-(CH$_2$)$_6$-COOH</td>
<td>Do</td>
</tr>
<tr>
<td>Capric acid</td>
<td>10</td>
<td>CH$_3$-(CH$_2$)$_8$-COOH</td>
<td>Do</td>
</tr>
<tr>
<td>Lauric acid</td>
<td>12</td>
<td>CH$_3$-(CH$<em>2$)$</em>{10}$-COOH</td>
<td>Coconut oil</td>
</tr>
<tr>
<td>Myristic acid</td>
<td>14</td>
<td>CH$_3$-(CH$<em>2$)$</em>{12}$-COOH</td>
<td>Do</td>
</tr>
<tr>
<td>Palmitic acid</td>
<td>16</td>
<td>CH$_3$-(CH$<em>2$)$</em>{14}$-COOH</td>
<td>Most fats of animal and plant origin</td>
</tr>
<tr>
<td>Stearic acid</td>
<td>18</td>
<td>CH$_3$-(CH$<em>2$)$</em>{16}$-COOH</td>
<td>Do</td>
</tr>
<tr>
<td>Arachidic acid</td>
<td>20</td>
<td>CH$_3$-(CH$<em>2$)$</em>{18}$-COOH</td>
<td>Peanut oil</td>
</tr>
</tbody>
</table>
Unsaturated Fatty Acids

- These have one or more double bonds.
- Those with one double bond are called as monounsaturated fatty acids.
- These are present in nearly all the fats
  e.g. palmitoleic acid and oleic acid.
  \[ \text{CH}_3 - (\text{CH}_2)_5 - \text{CH} = \text{CH} - (\text{CH}_2)_7 - \text{COOH} \]
- Those with more than one double bond are called polyunsaturated fatty acids (PUFA)
  e.g. linoleic acid, linolenic acid and arachidonic.
- Cannot be synthesised in the body therefore are essential in nutrition and
  are also called essential fatty acids.
- These are found in vegetable oils e.g. cotton seed oil, corn oil.
Biological Significance of Essential Fatty Acids

- Essential fatty acids are involved in the esterification of cholesterol and thus help in its transport and metabolism.
- Besides, arachidonic acid is also a precursor of prostaglandins.
- Essential fatty acids are also the constituents of the cell membrane and membrane of the mitochondria.
- These are essential for normal growth and health.
Other Fatty acids

• Some fatty acids either contain hydroxy group or are cyclic in nature and are found in certain biological materials e.g. ricinoleic acid which contain a hydroxy group and is found in castor oil.

• Chaulmoogric acid contains a heterocyclic ring and is found in chaulmoogra oil.

• It is important in the treatment of leprosy.
Physical and Chemical Properties of Fatty Acids

- Short chain fatty acids (from C$_4$ to C$_{10}$) are generally liquid at room temperature while higher fatty acids are solid.

- With alkali, fatty acids form salts which are used as soaps and emulsifying agents.

- Unsaturated fatty acids take up hydrogen and are converted to saturated fatty acids under suitable conditions.

- Due to the different configuration around double bond, unsaturated fatty acids show geometrical (cis-trans) isomerism.
Glycerol

- A trihydric alcohol as it contains three hydroxyl groups.
- Obtained as a bye-product of soap industry.
- Lipolysis of dietary lipids releases glycerol which is converted to glucose in the liver.
Sterols

- Sterols and solid alcohols, i.e. the steroids having an alcoholic group.
- Have cyclopentanoperhydrophenanthrene nucleus also called as steroid nucleus or steroid ring.
- Cholesterol is one of the important steroid present in the body.
- Has 27 carbon atoms, a hydroxyl group (-OH), a double bond, two methyl groups at C10 and C13 and a side chain at C17.
- A precursor of various compounds such as vitamin D₃, bile acids and salts, and adrenocortical and sex hormones.
- Widely distributed in all cells of the body but nervous tissue is rich in cholesterol.
Cholesterol

A steroid structure

Glycocholic acid

Taurocholic acid
Prostaglandins

- Prostaglandins (PGs) are the compounds synthesised from arachidonic acid and other eicosapolyenoic fatty acids having 20 carbon atoms.

- Arachidonic acid undergoes cyclisation at the centre of the carbon chain forming a cyclopentane ring as all the naturally occurring PGs are the derivatives of prostanoic acid.
Prostaglandins

- Six PGs of the E and F series are the primary PGs.
- All the PGs have an –OH group at $C_{12}$ and trans double bond at $C_{13}$.
- Prostaglandins are found in seminal fluid, plasma and other tissues.
- These have pharmacological and biochemical actions and act on smooth muscle, blood vessels and adipose tissues.

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Prostaglandins
Properties of Lipids

Hydrolysis

- Triglycerides can be hydrolysed by acids, alkali or enzymes such as lipases which act on triglycerides and give a mixture of glycerol and free fatty acids.

\[
\text{Lipase} \\
\text{Tripalmitin} \rightarrow \text{Glycerol Palmitic acid}
\]
Properties of Lipids

Saponification

- Hydrolysis of triglycerides by alkali forms soap.
- This is called saponification.
- Sodium and potassium soaps are soluble in water and are used as the emulsifying agents.
- Calcium, magnesium and barium soaps are insoluble.
- The number of mg of KOH required to completely saponify 1g of the oil or fat is called saponification number.

\[
3\text{NaOH} \rightarrow \text{Glycerol Soap}
\]
Halogenation

- Unsaturated fatty acids present in triglycerides accept halogens such as I$_2$ at the double bond.

- This process is known as halogenation.

- Iodine number is a measure of the degree of unsaturation of a fat.

- It is identified as the number of grams of iodine that combines with 100g of a fat.

- High iodine number indicates higher degree of unsaturation of fatty acids present in the fat.

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Rancidity

- Naturally occurring fats particularly from animal sources, on storage in the presence of moist air, give unpleasant smell and develop a characteristic taste and odour.

- It is due to the partial hydrolysis of fats which are further oxidised into aldehydes and ketones.

- This process is called rancidity.

- Certain antioxidants such as vitamin E or vitamin C can prevent oxidation of fats and thus the development of rancidity.
Phospholipids

- Compound lipids containing alcohol, fatty acids, phosphoric acid and a nitrogenous base.
- Derivatives of phosphatidic acid, and include cephalins, lecithins, sphingomyelins, etc.
- Lechinins
- Cephalins
- Phosphatidylinositois
- Plasmalogens
- Sphingomyelins
Lipotropic Factors

Glycolipids

• Cerebrosides
• Gangliosides
• Sulpholipids.
Lipoproteins

- A number of lipids namely glycerides, phospholipids, cholesterol and long chain free fatty acids are present in plasma but being hydrophobic in nature these are insoluble in the aqueous medium.
- These are transported in blood bound to proteins to form hydrophilic complexes known as lipoproteins.
- The protein moiety of lipoproteins is called apolipoprotein or apoprotein.
- There are four major classes of lipoproteins which are important physiologically and are useful in clinical diagnosis. These are:
  - Chylomicrons
    1. Very low density lipoproteins (VLDL)
    2. Low density lipoproteins (LDL), and
    3. High density lipoproteins (HDL)
- Besides, there are free fatty acids bound to albumin.
- Triglycerides are the predominant lipids in chylomicrons and VLDL whereas cholesterol and phospholipids are the predominant lipids in LDL and HDL.
Biological Significance of Lipids

1. Lipids are the important dietary constituents as these have high calorific value.

2. In the body, fats are the efficient source of energy. Fat stored in the adipose tissue is a direct and potential source of energy.

3. Fats present in subcutaneous tissues and around certain organs act as the insulating material.

4. Nervous tissue is rich in fats.

5. Lipids, in the form of lipoproteins, are the important cellular constituents and occur in cell membrane, mitochondria and cytoplasm. Lipoproteins are also essential for the transport of lipids in blood.

6. Lipids are the source of fat soluble vitamins (vitamins A, D, E and K) and of essential fatty acids.

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Composition of chylomicron:
- TG = 88% = Total lipids 98-99%
- PL = 8%
- CE = 3%
- C = 1%
- Protein = 1-2%

Chylomicron Synthesis and Secretion:
From intestinal mucosal cells.
Chylomicrons are released by exocytosis into lymphatic capillaries and then enter general circulation.

**Time Course of TG Absorption**
- Dietary intake of lipids
- Time (hours): 3, 6, 9
- Serum TG (mg/L): 1000, 200, 100
- May be as high as 1000 mg/dl depending on amount of lipid in diet

Therapeutic uses of medium chain TG
TG with medium chain FA are used for patients with malabsorption syndrome, as they can be absorbed intact and hydrolysed in intestinal mucosa and absorbed directly into portal blood.
Abnormalities in Lipid Digestion and Absorption

- **Bile salt deficiency:** Due to liver diseases, obstruction in bile duct, overgrowth of intestinal bacteria (cause ↓ emulsification). Leads to lipid malabsorption (stools with chalky, clay colour).

- **Pancreatic enzyme deficiency:** Secondary to pancreatitis or CF. Weight loss and steatorrhea.

- **Defective chylomicron synthesis:** Due to decrease synthesis of Apoprotein B-48 (protein in chylomicron). Leads to accumulation of TG in intestine and decrease chylomicron in blood (abetalipoproteinemia).
TG in chylomicron are degraded to glycerol + FFA by Lipoprotein lipase in the luminal surface of capillary bed.

**Diagram:**
- **Chylomicron** → **Lipase** → **FFA + Glycerol**
  - **FFA + Glycerol** → **Taken up by liver**
  - **Chylomicron remnants** → **Taken up by liver**
    - • Taken up by peripheral tissues (muscles, adipocytes).
    - • May bind to albumin and transported to other cells.

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Lipid Metabolism

**Digestion and Absorption of Lipids**

- Digestion of dietary lipids start in the small intestine where these are first emulsified by the bile salts.
- After emulsification, lipids are hydrolysed by the lipolytic enzymes such as pancreatic lipase, phospholipase and cholesterol esterase, present in the pancreatic juice.
- Pancreatic lipase removes fatty acids from dietary triglycerides.
- The end products of hydrolysis consists of a mixture of free fatty acids, glycerol and mono- and diglycerides in addition to some undigested fats.
- These are absorbed into the intestine and reform triglycerides which are passed on to lymphatic system and reach systemic circulation through the thoracic duct.
- Short chain fatty acids are absorbed as such into the portal vein.
- Dietary phospholipids are completely hydrolysed by phospholipases in the intestinal lumen to free fatty acids, glycerol, phosphoric acid and the nitrogenous bases.

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Lipid Metabolism

Digestion and Absorption of Lipids

• These are absorbed along with the digestive products of the triglycerides.
• Phospholipids are resynthesised in the intestinal mucosa and form part of the chylomicrons.
• Cholesterol is absorbed in the free form.
• The cholesterol esters are hydrolysed by cholesterol esterase secreted in the pancreatic juice.
• Cholesterol and free fatty acids are then absorbed from the intestine.
• Cholesterol is re-esterified in the intestinal mucosa and passes along with triglycerides in the form of chylomicrons to the lymph vessel.
• After absorption, lipids are either oxidised mainly in the liver or are stored in the depot (adipose tissue).
Major pathways of lipid metabolism

1. **β-oxidation.** For breakdown of fatty acid to acetyl CoA in mitochondria. Produces ATP.
2. **De novo synthesis of fatty acids:** From acetyl CoA by fatty acid synthetase complex. Occurs in cytoplasm.
3. **Triglyceride synthesis:** From glycerol-3-phosphate + fatty acyl CoA. In liver and adipose tissue synthesis used ATP and NADPH.
4. **Ketone body formation:** ↑ During starvation and diabetes mellitus (Due to ↑ Acetyl CoA, but ↓ carbohydrate derived oxaloacetate, so acetyl CoA cannot give energy via TCA cycle).
   - Synthesised by liver and used by brain, heart, etc.
5. **Cholesterol synthesis:** From acetyl CoA.
6. **6Phospholipid synthesis.**
7. **Synthesis of prostaglandins and thromboxanes.** In all tissues.
   - Local hormones
   - Variety of functions
   - Synthesised from C20 (Arachidonic acid).

**Coordinate regulation of fatty acid oxidation and fatty acid synthesis:**

- Glycerol
- Acetyl CoA → FA → TG
- Insulin + Glucagon – Citrate + Palmitoye CoA +
Fatty Acid - Metabolism

Fatty acid synthesis (primarily in liver)

Fatty acid storage and mobilization (An adipose tissue)

Fatty acid oxidation (Most tissues)

FA synthesis $\uparrow$ by insulin $\downarrow$ by glucagon

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Lipid Metabolism

Oxidation of Fatty Acids

- Oxidation of fatty acids takes place in mitochondria where the various enzymes for fatty acid oxidation are present close to the enzymes of the electron transport chain.

- Oxidation of fatty acid is known as β-oxidation.

- Oxidation of fatty acids occur at the β-carbon atom resulting in the elimination of the two terminal carbon atoms as acetyl CoA leaving fatty acyl CoA which has two carbon atoms less than the original fatty acid.
Lipid Metabolism

β-Oxidation of Fatty Acids

• First step in the oxidation of fatty acid is the activation of fatty acid, in cytoplasm.
• Fatty acid activation occurs in the presence of ATP and is catalysed by a thiokinase (acyl CoA synthetase).
• Thiokinases are found both inside as well as outside of the mitochondria.
• Several thiokinases are known, each of which is specific for a group of fatty acids.
• These are:
  • Acetyl CoA thiokinase for activating acetic, propionic and acrylic acids.
  • Short chain fatty acid activating enzymes for fatty acids with 4-12 carbon atoms, and
  • Long chain fatty acid activating enzymes for unsaturated as well as long chain saturated fatty acids.

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Lipid Metabolism

B-Oxidation of Fatty Acids

Acyl CoA Synthetase (Thiokinase)

Fatty Acid ⇒ Fatty acyl CoA

CoA  ATP  Mg^{2+}  AMP + PP
Lipid Metabolism

Role of Carnitine

• Fatty acyl CoA is impermeable to inner mitochondrial membrane while enzymes for β-oxidation are present in the mitochondria.
• Therefore after activation, the fatty acid (fatty acyl CoA) interacts with carnitine which helps in its translocation across the inner mitochondrial membrane.
• In the presence of carnitine palmityl acyl transferase I, present on the outer surface of the inner mitochondrial membrane, fatty acyl CoA interacts with carnitine and forms acylcarnitine.
• It passes through the inner membrane and is transferred to intramitochondrial CoA to reform fatty acyl CoA.
• This reaction is catalysed by carnitine palmityl transferase II present on the inner surface of the inner mitochondrial membrane.

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Lipid Metabolism

Role of Carnitine in β-oxidation

Fatty acid

Acyl CoA

Outer side

CoA

Carnitine

Carnitine Palmityl Transferase I

Acylcarnitine

Mitochondrial membrane

CoA

Carnitine Palmityl Transferase II

Acyl CoA

Inner side

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Fatty Acid Oxidation ($\beta$-oxidation)

- Occurs in mitochondrial matrix.
- FA from cytoplasm is transferred to mitochondrial matrix by carnitine in mitochondrial membrane.
- $\beta$-oxidation has 4 steps:
  - Dehydrogenation (FAD-dependent)
  - Hydration
  - Dehydrogenation (NAD-dependent)
  - Cleavage
    (Remove 2C as acetyl CoA)
- Acetyl CoA produced:
  $\beta$-oxidation
   \[
   \text{Palmatyl CoA} \rightarrow 8 \text{ Acetyl CoA}
   \]
   (C16) 7 times
- Enters TCA cycle
- Produces CO$_2$, ATP, H$_2$O

\[
\text{Palmityl CoA} + 7 \text{ NAD}^+ + 7 \text{ FAD} + 7 \text{ CoASH} \rightarrow \\
8 \text{ Acetyl CoA} + 7 \text{ NADH} + 7 \text{ FADH}_2
\]

Palmityl CoA on complete oxidation gives 129 moles of ATP

**Regulation**
- ↑ by insulin, ↓ by glucagon, ↓ by malonyl CoA
Fat stores in neonates:

Human beings are born with fat stores, which begin to accumulate during thirtieth week of gestation.

Expansion of Adipose Tissue and Obesity:

- Rate of fat-cell formation rapid in early life.
- ↑ fat storage → ↑ fat cells.
- Obese children have 2-3 times more fat cells than normal weight children.
- Obesity results from increase in fat in fat cells during middle age.
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Phospholipase A₁

H₂C – O – C – R₁

Phospholipase A₂

H – O – C – R₂

Phospholipase C

H₂C – O – P – O – X

Phospholipase D

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ATP Production During β-Oxidation of Palmitic Acid

- If palmitic acid \((C_{15}H_{31}COOH)\) undergoes β-oxidation it releases 8 molecules of acetyl CoA in seven rounds of the oxidative process.
- In each round of β-oxidation one molecule of FADH\(_2\) and one molecule of NADH+H\(^+\) are produced which generates 2 and 3 ATP molecules, respectively.
- Thus a total of 35 ATP are obtained in 7 rounds of the oxidative process.
- In addition, each acetyl CoA molecule, when oxidised in citric acid cycle, gives 12 molecules of ATP.
- Therefore, additional 96 molecules of ATP are produced from 8 molecules of acetyl CoA.
- Thus a total of 131 molecules of ATP are formed from palmitic acid.
- As two high energy phosphate bonds are hydrolysed (from one molecule of ATP which is changed to AMP), 2 molecules of ATP are used in the activation of a molecule of fatty acid.
- Therefore there is a net yield of 129 molecules of ATP when a molecule of palmitic acid (fatty acid with 16 carbons) is completely oxidised.

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Oxidation of Fatty Acids with Odd Number of Carbon atoms

- Fatty acids with odd number of carbon atoms are also oxidised by the process $\beta$-oxidation removing 2 carbons as acetyl CoA in each round of the oxidative process.
- In addition a molecule of propionyl CoA containing 3 carbon atoms is also formed.

\[
\text{Fatty acid} \quad \xrightarrow{\beta\text{-oxidation}} \quad \text{Acetyl CoA + Propionyl CoA}
\]

\[
\text{Acetyl CoA + Propionyl CoA} \quad \xrightarrow{} \quad \text{Methylmalonyl CoA}
\]

\[
\text{Methylmalonyl CoA} \quad \xrightarrow{} \quad \text{Succinyl CoA}
\]

- Propionyl CoA is converted to succinyl CoA and enters citric acid cycle.
Oxidation of Unsaturated Fatty Acids

- **Enoyl CoA Isomerase** – It catalyses a reversible shift of the double bond from cis to trans configuration.

- **β-Hydroxyacyl CoA epimerase** - Oxidation of polyunsaturated fatty acids yields D-stereoisomer of β-hydroxyacyl CoA to L-β-hydroxyacyl CoA for its further oxidation to produce acetyl CoA.
Metabolic Fates of Acetyl CoA

- In the normal metabolic process, Acetyl CoA is mainly used in the Kreb cycle.
- The other fates of acetyl CoA include the synthesis of fatty acids and cholesterol.
- Besides, a small quantity of acetyl CoA is also converted to ketone bodies in the liver.

Glucose $\rightarrow$ Pyruvate

Acetyl CoA

- Kreb cycle
- Fatty acids
- Cholesterol
- Ketone bodies

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Biosynthesis of Fatty Acids

• Mammals can synthesize major portion of the saturated as well as the monounsaturated fatty acids.

• There are three systems for the synthesis of fatty acids –
  i) De novo synthesis of fatty acids in cytoplasm.
  ii) Chain elongation in mitochondria, and
  iii) Chain elongation in microsomes.
De novo Synthesis of Fatty Acids

- This is the actual process for the biosynthesis of fatty acids in liver, mammary gland and adipose tissue.
- The enzyme system uses acetyl CoA as the starting material for the synthesis of medium chain fatty acids (such as palmitic acid).
- Synthesis occurs in cytoplasm mostly by the reversal of the β-oxidation process.

![Acetyl CoA → Fatty Acids](image)
Chain Elongation in Mitochondria

- De novo Synthesis forms palmitic acid which is used as a starting material for the synthesis of higher fatty acids in mitochondria.
- Chain elongation of palmitic acid in mitochondria takes place by the successive additions of acetyl CoA.
- Condensation of palmityl CoA with acetyl CoA forms $\beta$-ketostearyl CoA which utilises NADPH+H$^+$ and is reduced to $\beta$-hydroxystearyl CoA.
- Removal of a molecule of water converts $\beta$-hydroxystearyl CoA to $\alpha$-$\beta$-unsaturated stearyl CoA which is reduced to stearyl CoA by using NADPH+H$^+$. 

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Chain Elongation in Microsomes

• The process of chain elongation in microsomes is similar to fatty acid biosynthesis (De novo synthesis) in the cytoplasm. Although it also utilises malony CoA but uses CoA instead of ACP as the acyl carrier.

• Medium chain saturated fatty acids and monounsaturated fatty acids with C\textsubscript{18} (oleic acid) are used for chain elongation.
Fatty Acid Synthesis

- From Acetyl CoA
  
  8 Acetyl CoA + 7ATP + 14NADPH + 14H⁺ + H₂O
  
  Palmitic Acid + 8 CoA + 7ADP + 7 Pi + 14 NADP⁺
  
  (C16)

- Occurs in cytosol.
- Requires Fatty acid synthetase complex:
- 4 Reactions: Condenstation
  Reduction
  Dehydration
  Reduction

Steps repeated several times. Each time increase 2C in FA chain.

Control of F.A. synthesis

Acetyl CoA carboxylase ← Inhibited by palmityl CoA

Activated by citrate.

↑ by insulin
↓ by glucaon
Triacylglycerol Synthesis

Phosphatidic acid

H₂O

phosphatidic acid phosphatase

Pi

1,2-Diacylglycerol

CoA-S-fatty acid

acyltransferase

CoA-SH

Triacylglycerol

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Extra Hepatic Tissue

KB’s are:
- Acetoacetate
- β-hydroxybutyrate
- Acetone
- Normal level in blood = 0.2 mM
- When conc. exceeds 1-3 mM → being to be taken by extra hepatic tissue.
- After fasting 3 days conc. = 3 mM
  3 weeks conc. = 7 mM
- Brain can use KB instead of glucose.
- ↑ Synthesis in starvation and DM.
- ↑ KB (10-20 mM) → Ketoacidosis
- Ketonemia → Ketonuria.
Cholesterol Metabolism

- Nearly 0.3 g of cholesterol is daily absorbed from diet.
- Ingested cholesterol is absorbed with other lipids and incorporated into chylomicrons and VLDL.
- More than 80% of it is esterified in the intestinal mucosa and is transported with lipoproteins.
- Cholesterol content in normal human blood varies from 150 to 250 mg/100 ml, being equally distributed between plasma and erythroytes.
- A large quantity of cholesterol is also synthesised (about 1g/day) in the extramitochondrial compartment of the cell by using Coa.
- The important sites for cholesterol biosynthesis include liver, skin, intestine, adrenal cortex and testis.

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Metabolic Fates of Cholesterol

Acetyl CoA → Acetyl CoA → Steroid Hormone

Vitamin D

Bile acids and Bile salts
Cholesterol Metabolism

- **Source:**
  - Diet
  - Endogenous synthesis

- **Diet:**
  - Foods rich in cholesterol
  - Eggs:
    - Whole = 550 mg/200 gm
    - Egg yolk = 1500 mg/100 gm
    - Liver = 300 mg/100 gm
    - Lobster and oysters = 200 mg/10 gm
    - Butter = 280 mg/100 gm
    - Cheese = 100 mg/100 gm

- Cholesterol intake should be limited to no more than 100 mg/1000 Kcal, with a total cholesterol of no more than 300 mg/day.
De novo synthesis of cholesterol

- Normal adults synthesise ~ 1g chol./day
- Site of synthesis: Primary site – Liver.
  - other tissues: Adrenal cortex, ovaries and testes.
- Synthesised from Acetyl CoA.

18 Acetyl CoA + 18 ATP + 16 NADPH + 4O₂ + 16H⁺ →
→ cholesterol + 9CO₂ + 16 NADP⁺ + 18 ADP + 18 Pi
4 major steps in synthesis of cholesterol:

1. **Formation of Hydroxymethyl glutaryl CoA** (HMG CoA)
   
   Thiolase
   
   2 Acetyl CoA (2c) → Acetoacetyl CoA (4c) HMG CoA synthesise HMG CoA (C₆)

2. **Conversion of HMG CoA to isoprenoids**
   
   HMG CoA reductase
   
   HMG CoA → Mevalonic Acid
   
   Control of Chol. synthesis (Rate limiting step) → inhibited by ↑ cholesterol.
   
   Mevalonic Acid → CO₂
   
   ATP ATP ATP → Isopentenyl-P-P (CS)

   Inhibitors of HMG CoA reductase are used to treat hypercholesterolaemia. Lovastatin and mevinolin are analogues of HMG CoA and competitive inhibitors of HMG CoA reductase.
3. **Condensation of Isoprenoid to form Squalene**

- Isopentenyl Pyrophosphate (C5) and Dimethylallyl pyrophosphate (C5)
- Geranyl-P-P
- Isopentenyl PP (CS)
- Farensyl-P-P
- NADPH
- Squalene (C30)

4. **Conversion of Squalene to Cholesterol**

- Squalene
- HO C2
- HO C27
- C30 Lanosterol
- 3CD2

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Regulation of cholesterol synthesis

Rate of cholesterol synthesis depends on:
- Overall calorie intake
- Uptake of cholesterol from chylomicron and LDL
- Hormones (insulin, glucagon, cortisol, T3)

\[
\text{LDL} \rightarrow \downarrow \text{HMG CoA reductase}
\]

\[
\text{1LD} \rightarrow \downarrow \text{chol. synthesis} \uparrow \text{ACAT} \uparrow \text{Storage of C}
\]

Chylomicron remnants
\[
\downarrow \text{LDL receptor synthesis} \downarrow \text{uptake of C}
\]

Effect of Chylomicron & LDL uptake on cellular cholesterol level

Formation of cholesterol esters

\[
\text{ACAT}
\]

\[
\text{Cholesterol + Fatty acyl CoA} \quad \text{Cholesterol}
\]

\[
\text{ACAT}
\]

\[
\text{OR Cholesterol + Lecithin} \quad \text{esters and CoASH}
\]

LCAT: Lecithin cholesterol Acyl transferase
ACAT: Acyl CoA: Cholesterol Acyl transferase
Central Role of Liver in Cholesterol Balance

Sources of hepatic cholesterol
- Diet
- Extrahepatic tissue
- Denovo synthesis

Cholesterol in Liver
- Chylomicron Remnants
- HDL and Remnants of VLDL
- From Acetyl CoA

Fate of cholesterol
- Esterification and packing into VLDL → blood
- Bile acid (major)
- Free cholesterol in bile

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Cholesterol

Cholesterol is a waxy fat carried through the bloodstream by lipoproteins.

HDL
High-density lipoproteins
"Good cholesterol"

LDL
Low-density lipoproteins
"Bad cholesterol"

"Good cholesterol (HDL) is stable and carries "bad" cholesterol (LDL) away from the arteries. "Bad" cholesterol (LDL) sticks to artery walls and contributes to plaque build-up."
Fate of Cholesterol in Human Body

- Cholesterol has no use in providing energy. Cannot be degraded completely.
- Major path of excretion of cholesterol is formation of bile acids and salts in liver and excretion.

*Gallstones* → When components of bile precipitate. Most common gallstone have ~ 80% cholesterol. (When bile is supersaturated with cholesterol).

*Treatment of hypercholesterolaemia with cholestyramine (resin)*

Oral intake of cholestyramine: binds bile acids in intestine and prevents the reabsorption by enterohepatic circulation.

∴ ↑ synthesis of bile acids from cholesterol in liver → ↓ cholesterol.

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**Ketone Bodies**

• Acetoacetate, β-hydroxybutyrate and acetone.
• The process of the formation of ketone bodies is called **ketogenesis**.
• In a normal man, concentration of ketone bodies in blood is usually less than 3 mg/100 ml.
• In certain conditions such as during prolonged starvation or in impaired glucose oxidation (such as in diabetes mellitus), fat becomes the source of energy and its degradation is greatly accelerated.
• It results in the excessive production of acetyl CoA which cannot be fully utilised by the liver through Kreb cycle due to lack of oxaloacetate and is converted to ketonebodies.
• The clinical condition resulting from the increased biosynthesis of ketone bodies is called **ketosis**.
• These abnormal metabolites are diffused into the blood in greater concentration (**ketonemia**) and appear in urine (**ketonuria**).
Formation of Ketone Bodies

2 Acetyl CoA → Acetoacetyl CoA

Thiolase

Acetoacetate → Acetyl CoA

HMG CoA Lyase

Acetyl CoA → HMG CoA

H₂O HMG CoA Synthetase

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Formation of Ketone Bodies

Acetoacetate

NadH + H^+ Dehydrogenase NAD^+

B-Hydroxybutyrate

CO₂

Acetone
Utilisation of Ketone Bodies

- Acetoacetate and β-hydroxybutyrate can be used as a source of energy in kidney and muscle.

- Although glucose is a major fuel for brain in the well nourished state but during starvation even brain utilises ketone bodies.

- These are transported from liver to the extrahepatic tissues and are oxidised by Kreb cycle.

- The oxidation of ketone bodies to CO$_2$ and H$_2$O is called ketolysis.
Role of Liver in Lipid Metabolism

• Lipids are though mainly stored in the adipose tissue, liver has a central role in lipid metabolism.
  1. Liver is the important site for the synthesis of fatty acids from acetyl CoA, obtained from the oxidation of glucose.
  2. It is also the important site for the biosynthesis of cholesterol from acetyl CoA, obtained from the oxidation of carbohydrates, fatty acids and certain amino acids.
  3. Liver is also the site for the synthesis of the various plasma lipoproteins and phospholipids as well as for their removal.
  4. Formation of ketone bodies occurs in liver.
  5. It is also the site for fatty acid chain elongation, shortening of fatty acid chain, and for the removal as well as introduction of the double bond in a fatty acid.
  6. Liver is the sole site for the synthesis of bile acids from cholesterol.
  7. Liver is also important for the oxidation of fatty acids (β-oxidation).
Hormonal Control of Lipid Metabolism

**Insulin:**
- Insulin stimulates HMP shunt reactions and increases the supply of NADPH which is essential for the synthesis of long chain fatty acids and cholesterol.
- Insulin also increases the synthesis of triglycerides in liver as well as adipose tissue.
- Since insulin is the main hormone which stimulates glucose utilisation, it also depresses ketogenesis and increases the supply of oxaloacetate for utilization of acetyl CoA via Kreb cycle.

**Glucocorticoids:**
- These hormones increase the rate of release of fatty acids from adipose tissue which in turn leads to ketogenesis and increases cholesterol synthesis.

**Thyroid Hormones:**
- Administration of thyroid hormones reduces plasma lipoproteins, cholesterol and phospholipids but in insulin deficiency thyroid hormones increase the release of fatty acids from the adipose tissue and cause ketogenesis.