Overview of lipid metabolism
# Classification of lipids (examples)

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<th>SIMPLE LIPIDS</th>
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<td><strong>PHOSPHOLIPID</strong></td>
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<td><strong>SPHINGOLIPIDS</strong></td>
<td>STEROID HORMONES</td>
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<td>Phosphosphingolipid</td>
<td>KETONE BODIES</td>
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<td><strong>GLYCOLIPID</strong></td>
<td>FAT SOLUBLE VITAMINS (ADEK)</td>
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<td>Cerebrosides</td>
<td><strong>EICOSANOIDS</strong></td>
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<td>Gangliosides</td>
<td>Prostaglandin</td>
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<td>Sulfatides</td>
<td>Leukotriene</td>
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<td><strong>LIPOPROTEINS</strong></td>
<td><strong>BILE ACIDS/SALTS</strong></td>
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<td>GLYCEROL</td>
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</table>
There is free rotation about C-C bonds in the fatty acid hydrocarbon, except where there is a double bond.

Each cis double bond causes a kink in the chain.

Rotation about other C-C bonds would permit a more linear structure than shown, but there would be a kink.
Simple fat have simple function

- They are neutral lipid
- Storage in adipose tissues
- Insulation
- Store of energy
Triglycerides (triacylglycerols) are synthesized mainly in adipose tissue, liver, and intestines.

Glycerol + 3 FFA $\rightarrow$ TG + H$_2$O
In adipose tissue, breaks down triacylglycerols to free fatty acids and glycerol

**Hormone sensitive lipase**

Cleave a fatty acid from a triglyceride, then other lipase complete the process of lipolysis, and fatty acid are released into the blood by serum albumin

• This enzyme is activated by epinephrine and glucagon and inhibited by insulin
Overview of fatty acid degradation

**FA** = fatty acid

**LPL** = lipoprotein lipase

**HSL** = Hormone sensitive lipase

**FA** from fat cell

**LPL** = Lipoprotein lipase

**Mitochondrion**

**Cell membrane**

**Cytoplasm**

**Capillary**

**Lipoproteins**

**Albumin**

**HSL**

**Overview of fatty acid degradation**
Differences Between Lipogenesis and Lipolysis

1. Intermediates in synthesis are linked to acyl carrier proteins (ACP). In breakdown intermediates linked to coenzyme A (CoA).

2. Synthesis in cytosol; breakdown in mitochondria

3. Enzymes of synthesis are one polypeptide (fatty acid synthase) in animals; For breakdown enzymes are separate

4. Biosynthesis uses NADPH/NADP$^+$; breakdown uses NADH/NAD$^+$ & FAD
Triglycerides TG:

- Triglyceride give energy in case of absence of carbohydrates
- Extra triglycerides are found in the blood after meal TG "gut" >>>>> blood>>>>> adipose
- Elevated in obese or diabetic patients. Level increases from eating simple sugars or drinking alcohol. Associated with heart and blood vessel disease.
Adipose tissue: the link between obesity and cardiovascular disease.

1. Fat or adipose tissue is not a simple storage organ of surplus lipids in form of triglycerides.

2. Chronic overnutrition and lack of physical activity result in excess deposition of adipose tissue which plays a key role in the pathophysiology of cardiovascular disease (CVD).

3. **Leptin** is a **hormone** made by **adipose cells**. When leptin binds to its receptors in our brain, it stimulates the release of appetite-suppressing chemicals.
Complex/Compound Lipids

- Esters of fatty acids with alcohol, containing non-lipid Group (PO₄, Nitrogenous base, or sugar)

- Compound Lipids are Further Classified as:
  1. PHOSPHO-LIPIDS
  2. GLYCO-LIPIDS
  3. PROTEO-LIPIDS (LIPO-PROTEINS)
  4. SULPHO-LIPIDS
PHOSPHOLIPIDS

1. **Glycerophospholipids** (Backbone is Glycerol)

   - Phosphatidic acid is the parent compound for all
   - $\text{PO}_4$ with additional group form Polar head.
   - 2 Fatty acids form non polar tail.
   - Amphipathic molecule
Common Phosphoglycerides:

PA + serine = phosphatidylserine (PS)

PA + ethanolamine = phosphatidylethanolamine (PE, cephalin)

PA + choline = phosphatidylcholine (PC, lecithin)

PA + glycerol = phosphatidylglycerol (PG)

PA + inositol = phosphatidylinositol (PI)
Types of Glycero-phospholipids

• depending upon the type of head alcohol Common Glycerophospholipids are

1. Phosphotidyl Choline. (Lecithin)
   1. Forms component of cell membrane
   2. Decrease surface tension of aqueous later of lung
   3. Detergent property solubilize cholesterol in bile

2. Phosphotidyl Ethanol amine. (Cephalin)
   1. Brain lipid
Types of Glycero-phospholipids

3. Phosphotidyl Serine.
   Apoptosis (Programmed cell death)

4. Phosphotidyl Inositol
   1. Precursor of Second Messengers

5. Phosphatidyl Glycerol.

6. Cardiolipin.
   3. Mitochondrial Membranes
Plasmalogens

- **Plasmalogens** are a type of *ether phospholipid* characterized by the presence of fatty alcohol with an ether linkage at the C-1 position of glycerol, instead of ester-linked fatty acid.

- Enriched in polyunsaturated fatty acids at the C-2 position of the glycerol backbone.
Plasmalogens

In human heart tissue, nearly 30–40% glycerophospholipids are plasmalogens.

They can protect mammalian cells against the damaging effects of reactive oxygen specie

Plasmalogens are effective as endogenous antioxidants.

It has potent physiologic actions (platelet activation; inflammatory responses; bronchoconstriction)
2. **Sphingolipids** (backbone is Sphingosine)

Fatty acid forms amide linkage with amino group of sphingosine = Ceramide (this is also a precursor for glycolipids)

- Esterification of carbon 1 of ceramide by phosphorylcholine = sphingomyelin
  - (important component of myelin in nerves)
### GLYCOLIPIDS

**Sphingolipid (general structure)**

- **Sphingosine**
  - \[ HO-^{3}CH-CH=CH-(CH_{2})_{12}-CH_{3} \]
  - \[ O \]
  - \[ ^{2}CH-\text{N} \]
  - \[ ^{1}CH_{2}-O-X \]

- **Fatty acid**

**Table: Name of Sphingolipid, Name of X, Formula of X**

<table>
<thead>
<tr>
<th>Name of Sphingolipid</th>
<th>Name of X</th>
<th>Formula of X</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceramide</td>
<td>—</td>
<td>—H</td>
</tr>
<tr>
<td>Sphingomyelin</td>
<td>Phosphocholine</td>
<td>[ -\text{P}-\text{O}-\text{CH}<em>{2}-\text{CH}</em>{2}-\text{N}(\text{CH}<em>{3})</em>{3} ]</td>
</tr>
<tr>
<td>Neutral glycolipids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucosylcerebroside</td>
<td>Glucose</td>
<td></td>
</tr>
<tr>
<td>Lactosylceramide (a globoside)</td>
<td>Di-, tri-, or tetrasaccharide</td>
<td></td>
</tr>
<tr>
<td>Ganglioside GM2</td>
<td>Complex oligosaccharide</td>
<td></td>
</tr>
</tbody>
</table>
Ceramides + Sugar residue (β-glycosidic bond)

1. **Cerebrosides**

**Glucosylcerebrosides**
Ceramides + Glucose
Non neuronal accumilate in Liver (GAUCHER’S Disease)

**Galactosylcerebrosides**
Ceramides + Galactose
Neuronal tissues- White matter

**Sulfatides**
Ceramides + Galactose + Sulfate
Ceramides + Sugar residue (β-glycosidic bond)

2. **Gangliosides**
   - Ceramides + branched oligosaccharides
   - Have acidic sugar (Sialic Acid/NANA)
   - Glc-Gal-GalNA-Gal .......................GM1
     NANA
   - Glc-Gal-GalNA-Gal .......................GM2
     NANA
   - Glc-Gal-  .........................GM3
     NANA
Derived lipid
What is Cholesterol?

- Steroids are derived lipids in which the basic or principle structure is **Cyclopentano Perhydro Phenanthrne Nucleus**
- **(CPPP Nucleus)**
  (Steroid Nucleus)
- **Examples:**
  - Steroid hormones, Vitamin D etc.
Cholesterol is white waxy compound

Widely distributed in almost all the tissues of the body especially in brain, other nervous tissues, adrenals and liver.
Important biological functions Of Cholesterol

• One of the important members of membrane lipids.
• Precursor of Steroids & Vitamin D.
• Forms Adrenal hormones
• Forms Bile acids and salts
• **Relation with various diseases like:**
  – Hypertension
  – Diabetes Mellitus
  – Thyroid Diseases.
Cholesterol

- 27-C cyclic isoprene unit, derived from acetyl CoA
- Phenanthrene nucleus
- Cyclopentane ring
- OH gp at 3\textsuperscript{rd} C
- Double bond at 5\textsuperscript{th} position
- Aliphatic chain at C-17
- Methyl gp at C18,19.
Within intestinal cells (and other body cells) some of the absorbed cholesterol is esterified to fatty acids, forming **cholesteryl esters**.

(R = fatty acid hydrocarbon in diagram above)

The enzyme that catalyzes cholesterol esterification is **ACAT** (Acyl CoA: Cholesterol Acyl Transferase).
Derived lipid

Synthesis of ketone bodies (ketogenesis)

- **substrate**: acetyl-CoA
- **product**: acetoacetate, 3-hydroxybutyrate, acetone
- **function**: energy substrate for extrahepatal tissues
- **subcelullar location**: matrix of mitochondria
- **organ location**: liver

Excessive production of ketone bodies is typical during starvation or diabetes mellitus:

↑ lipolysis → ↑ FA → β-oxidation of FA → excess of acetyl-CoA → ↑ ketogenesis
Use of ketone bodies by the extrahepatal tissues

- acetoacetate and 3-hydroxybutyrate are reconverted to acetyl-CoA (→ citric acid cycle)
- is located in matrix of mitochondria of the peripheral tissues
- is significant in skeletal muscles, heart and also in the brain if lack of Glc occurs
Blood Lipid Levels are Related to Risk of CVD
Triglycerides

- The most diet-responsive blood lipid
- Should be $\leq 150$ mg/dL in fasting state
Blood Lipids (Lipoproteins)

- Lipids (fat) cannot mix with water
- Blood is high in water
- Lipids cannot travel in blood without help
- Lipoproteins are formed to carry lipids
Lipoproteins combine

- Lipids (triglycerides, cholesterol)
- Protein
- Phospholipids
Lipoproteins

- Distinguished by size and density
- Each contains different kinds and amounts of lipids and proteins
  - The more lipid, the lower the density
  - The more protein, the higher the density
Lipoprotein Summary

Classification of Lipoproteins

Chylomicron and Chylomicron remnant
1000 nm

VLDL Very Low Density Lipoprotein
70 nm

IDL Intermediate Density Lipoprotein
40 nm

LDL Low Density Lipoprotein
20 nm

HDL High Density Lipoprotein
10 nm

"Bad" (Non-HDL)

"Good"
Pathophysiology of Atherosclerosis

- Vessel lining is injured (often at branch points) →
- Plaque is deposited to repair injured area →
- Plaque thickens, incorporating cholesterol, protein, muscle cells, and calcium (rate depends partly on level of LDL-C in the blood) →
Atherosclerosis

- Arteries harden and narrow as plaque builds, making them less elastic.
- Increasing pressure causes further damage.
- A clot or spasm closes the opening, causing a heart attack.
Pathophysiology of Atherosclerosis
Heart Attack (Myocardial Infarction)
Heart Attack (Myocardial Infarction)

• When blood supply to the heart is disrupted, the heart is damaged
• May cause the heart to beat irregularly or stop altogether
• 25% of people do not survive their first heart attack
Recommended blood lipids

- Total cholesterol: <200 mg/dL (WHO-<150)
- LDL cholesterol: <130 mg/dL
- HDL cholesterol: >35 mg/dL
- Triglycerides: <200 mg/dL
Effect of lipids on lipoproteins and CVD risk

• **Dietary cholesterol**
  – No effect on blood cholesterol

• **Saturated fats**
  – Raise LDL

• **Trans fats**
  – Raise LDL and lower HDL

• **Monounsaturated fats**
  – Lowers LDL

• **Omega-3 (n-3) polyunsaturated fats**
  – Lowers blood cholesterol