Chapter 8 Fat
Insoluble in water but relatively soluble in solvents

Classification:
1. Simple lipids: esters of fatty acid with glycerol (fat, oil)
   - esters of fatty acid with alcohol (wax)
2. Compound lipids: esters of fatty acid containing nonlipids such as phosphorus, carbohydrates, and proteins.
   - Include:
     - phospholipids: containing phosphoric acid and N.
     - glycolipids: carbohydrate and other N.
     - lipoprotein.: lipids bound to protein in blood and other tissues.
3. Derived lipids: derived from lipids by hydrolysis. i.e. fatty acid and glycerol.
4. Sterols :lipids with complex phenanthrene-type ring structures.
5. Terpenes
• Structure:
  • Constituent in animal nutrient includes:
    • fatty acid
    • glycerol
  • Mono-glycerides
  • Di-glycerides-
  • Tri-glycerides
  • Phospholipids
  • Animal metabolism : Glycolipids
  .
  • Lipoproteins
  • Sterols
- Fatty acids
  - Consist of carbon from 2 to 24 or more in length.
  - A carboxy group on the end of each chain.
  - General structure: \( RCOOH \), where \( R \) is carbon chain
- Saturated fatty acids
  - Acetic acid (C2)
  - Myristic acid (C14)
- Unsaturated fatty acids: containing double bond
  - Oleic acid (C18:1)
  - Linoleic acid (C18:2)
  - Linolenic acid (C18:3) essential fatty acid
  - Arachidonic acid (C20:4)
  - Eicosapentaenic acid (C20:5)
  - Docosahexaenoic acid (22:6)
- C18:3, C20:5, C22:6, called omega-3 fatty acids
### Table 8.1 Fatty acids most common in plant and animal tissues.

<table>
<thead>
<tr>
<th>ACID</th>
<th>NO. CARBONS</th>
<th>NO. DOUBLE BONDS</th>
<th>ABBREVIATED DESIGNATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Butyric (butanoic)</td>
<td>4</td>
<td>0</td>
<td>C4:0</td>
</tr>
<tr>
<td>Caproic (hexanoic)</td>
<td>6</td>
<td>0</td>
<td>C6:0</td>
</tr>
<tr>
<td>Caprylic (octanoic)</td>
<td>8</td>
<td>0</td>
<td>C8:0</td>
</tr>
<tr>
<td>Capric (decanoic)</td>
<td>10</td>
<td>0</td>
<td>C10:0</td>
</tr>
<tr>
<td>Lauric (dodecanoic)</td>
<td>12</td>
<td>0</td>
<td>C12:0</td>
</tr>
<tr>
<td>Myristic (tetradecanoic)</td>
<td>14</td>
<td>0</td>
<td>C14:0</td>
</tr>
<tr>
<td>Palmitic (hexadecanoic)</td>
<td>16</td>
<td>0</td>
<td>C16:0</td>
</tr>
<tr>
<td>Palmitoleic (octadecenoic)</td>
<td>16</td>
<td>1</td>
<td>C16:1</td>
</tr>
<tr>
<td>Stearic (octadecanoic)</td>
<td>18</td>
<td>0</td>
<td>C18:0</td>
</tr>
<tr>
<td>Oleic (octadeциenoic)</td>
<td>18</td>
<td>1</td>
<td>C18:1</td>
</tr>
<tr>
<td>Linoleic (octadecadenoic)</td>
<td>18</td>
<td>2</td>
<td>C18:2</td>
</tr>
<tr>
<td>Linolenic (eicosanoic)</td>
<td>20</td>
<td>3</td>
<td>C18:3</td>
</tr>
<tr>
<td>Arachidonic (eicosatetraenoic)</td>
<td>20</td>
<td>4</td>
<td>C20:4</td>
</tr>
<tr>
<td>Linoerc (tetracosanoic)</td>
<td>24</td>
<td>0</td>
<td>C24:0</td>
</tr>
</tbody>
</table>
**TABLE 8.2**  Position of double bonds in unsaturated fatty acids.

<table>
<thead>
<tr>
<th>ACID</th>
<th>POSITION OF DOUBLE BONDS&lt;sup&gt;a&lt;/sup&gt;</th>
<th>PRECURSOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palmitoleic</td>
<td>9</td>
<td>Palmitic</td>
</tr>
<tr>
<td>Oleic</td>
<td>9, 12</td>
<td>Stearic</td>
</tr>
<tr>
<td>Linoleic</td>
<td>9, 12, 15</td>
<td>None</td>
</tr>
<tr>
<td>Linolenic</td>
<td>5, 8, 11, 14</td>
<td>Linoleic</td>
</tr>
<tr>
<td>Arachidonic</td>
<td>5, 8, 11, 14</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>C atoms are numbered from the carboxyl end.
Conjugated linoleic acid (CLA)
The double bond are conjugated or adjacent to each other and are cis, trans rather than cis, cis as in linoleic acid.

Cis-9,trans-11
It was revealed that cis-9, trans-11 CLA is only a transitory product in biohydrogenation of linoleic acid.
Protective against cancer, diabetes, atherogenesis, obesity.
• Glycerol
• Mono-, Di-, Tri-glycerides (TG)
• (ester of glycerol and fatty acids)
• Properties of TG:
  • saturated fatty acid containing 10 or more carbon are **solid** at room temperature, whereas those with fewer than 10 carbons are **liquid**.
  • TG containing only long chain saturated fatty acid are **solids**, whereas those containing of unsaturated fatty acids are **liquids**.
  • *Saponification number: 皂化一克脂肪所需之KOH之毫克數，
    • 皂化數愈少，表示脂肪酸之鍵數越長。
  •  
  • *Iodine number: 每一百克脂肪之不飽和脂肪酸所能加入之碘的克數。碘價表示脂肪酸不飽和之程度。如Linseed oil之碘價為175至202。
• **Phospholipids**
  Hydrolysis yield fatty acids, phosphoric acid, glycerol and nitrogenous base.
  
  1. L-α-Lecithin
  
  2. Cephalins: similar to lecithin except that choline is replaced by hydroxyethyl amine
  
  3. Sphingomyelins: contain fatty acid, choline, phosphoric acid and nitrogenous base.

• **Sterols**: cholesterol, ergosterol (yield D2 when irradiated), 7—dehydrocholesterol (yield D3 when irradiated), bile acid, androgens, estrogen, progesterones.
L-α-lecithin

\[
\begin{align*}
\text{H}_2\text{C}&\text{-O}\text{-P}\text{-OCH}_2\text{CH}_2\text{N}^+\text{(NH}_3)_3 \\
\text{O} & \\
\text{H}_2\text{C}&\text{-O}\text{-P}\text{-OCH}_2\text{CH}_2\text{N}^+\text{(NH}_3)_3 \\
\end{align*}
\]
Functions of lipids:

1. Serve as a source of essential fatty acid.
2. Serve as carrier of the fat-soluble Vitamins.
4. Energy supply

- The amount of utilizable energy is related to their digestibility, true digestibility of fat exceeds 80%.
- Total dietary lipid content < 10%, because higher proportion of metabolic fecal lipids on a low-fat diet. ∴ apparent dig. of fat < 80%.
Essential fatty acids (EFA)

- Linoleic acid and linolenic acid cannot be synthesized by animal tissues or not in sufficient amounts to prevent pathological changes, so must be supplied in the diet.

- Arachidonic acid (C 20:4) be synthesized from linoleic acid (C 18:2).

- EFA function in body:
  - *An integral part of the lipid-protein structure of cell membrane.
  - *Play an important part in the structure of several compounds called eicosanoids (including prostaglandins and eicosanoids).
  - Eicosanoids include prostaglandins, lower blood pressure, stimulate smooth muscle contraction, inhibit norepinephrine, induced release of fatty acid from adipose.
EFA缺乏之臨床症狀

- Dermatitis.
- Skin lesions.
- Growth failure.
- Reproduction failure
- Elevation of triene: tetraene ratio of tissue fatty acid (比例 >0.4, 顯示EFA缺乏 (rat), 豬餵與無脂飼糧, 在心, 肝, 脂肪組織中triene: tetraene比例增加。.
- Edema.
- Subcutaneous hemorrhage.
- Poor feathering.
- EFA缺乏較易出現於非反芻動物及幼小反芻動物。
5. Carrier of the fat-soluble Vitamins

• Fat soluble Vitamins are dispersed in micelles similar to those formed in the absorption of fatty acids
Absorption

- Fig 8.2 showed digestion and absorption of lipids.

* Bile acid is secreted from liver, it facilitate digestion and absorption, are reabsorbed readily from lower jejunum and ileum and recycled to the liver.

* Common bile acid: cholic acid
  - deoxycholic
  - taurocholic
  - glycocholic
Figure 8.2 Schematic diagram of the major conversions that occur in transport of lipids across the intestinal mucosal cell during absorption.
2. Main site of absorption of lipid:
   • proximal jejunum, some absorption occur alone the GI tract.
(1). Short fatty acid (C2 to C10), glycerol are absorbed by passive transport into the mesenteric blood and pass to the portal blood system.

(2). Monoglycerides and long-chain fatty acid enter to brush border and the core of intestinal mucosal cell by diffusion.
(3). Some TG may be absorbed intact as a fine emulsion of particles.

(4). Phospholipid are hydrolyzed to FFA, the remainder of the lysophospholipid is absorbed intact.

(5). Free cholesterol is absorbed readily.
3. After entering the epithelial cell

(1) long-chain FA + COA + ATP $\rightarrow$ fatty acyl-COA.

(2) fatty acyl COA + Monoglyceride $\rightarrow$ Diglyceride.

(3) Diglyceride + fatty acyl – COA $\rightarrow$ Triglyceride (only fatty acid of C12 or grater chain)
(4) Triglyceride + phospholipide + free cholesterol + protein $\rightarrow$ chylomicron.

(5) chylomicron leave the mucosal cell by pinocytosis and enter the lacteals via intercellular space and then to the lymphatic system
4. Transport and deposition

- Blood lipid consist of
  - (1). chylomicron.
  - (2). lipid from mobilized depot stores.
  - (3). from body tissues, especially liver and adipose tissues.

- Blood lipid are transported as lipoprotein
- Lipoprotein

- (1) High-density lipoprotein (HDL): 高蛋白質，低脂質。
- (2) Low-density lipoprotein (LDL)
- (3) Very low-density lipoprotein (VLDL).
- (4) Chylomicron (lowest density).

除 chylomicron 由 dietary fat 而來，LDL, HDL 均由肝、小腸合成
<table>
<thead>
<tr>
<th>LIPOPROTEIN CLASS&lt;sup&gt;a&lt;/sup&gt;</th>
<th>DENSITY RANGE (g/ml)</th>
<th>ELECTROPHORETIC MOBILITY</th>
<th>PROTEIN</th>
<th>TRIGLYCERIDE</th>
<th>CHOLESTEROL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chylomicrons</td>
<td>&lt;0.94</td>
<td>Origin</td>
<td>1-2</td>
<td>85-95</td>
<td>1-3</td>
</tr>
<tr>
<td>VLDL (beta lipoprotein)</td>
<td>0.94-1.006</td>
<td>Prebeta</td>
<td>6-10</td>
<td>50-65</td>
<td>4-8</td>
</tr>
<tr>
<td>LDL (beta lipoprotein)</td>
<td>1.006-1.063</td>
<td>Beta</td>
<td>18-22</td>
<td>4-8</td>
<td>6-8</td>
</tr>
<tr>
<td>HDL (alpha lipoprotein)</td>
<td>1.063-1.21</td>
<td>Alpha</td>
<td>45-55</td>
<td>2-7</td>
<td>3-5</td>
</tr>
</tbody>
</table>

<sup>a</sup>VLDL denotes very low-density lipoprotein, LDL low-density lipoprotein, and HDL high-density lipoprotein. From Schaefer and Levy (1985).
• *Blood lipid 之組成及濃度受下列因子影響
• dietary lipid type and quantity.
• endogenous synthesis in liver.
• species age and endocrine status of the individual.
• *Fat deposition mainly in adipose tissue
• 脂肪組織由碳水化合物及脂質合成脂肪, 亦能氧化脂肪酸, 因此
• adipose tissue 之脂肪屬於動態。
• Depot fat (adipose tissue) accumulated from late prenatal life to maturity.
• Early TG accretion in lean tissue and bone:
  • Hyperplasia (increase in cell number)
  • Hypertrophy (increase in cell size)
Fatty acid and Triglyceride Metabolism.

- Biosynthesis site: liver, mammary gland, adipose tissue. Liver is the central organ for lipid interconversion and metabolism.
- mouse, rat: 一半之脂肪合成在肝
- chicken: 全部之脂肪合成在肝
- pig: 全部之脂肪合成在脂肪組織
- cow, sheep: 肝及脂肪組織各一半( 以醋酸
為主要之合成基質，其次為乳酸 )
- Synthesis of fatty acids by liver and adipose tissue follows similar pathways.
The metabolism of lipid in the liver

- *synthesis of fatty acid from carbohydrate.
- *synthesis of fatty acid from lipogenic amino acids.
- *synthesis of cholesterol from acetyl-COA.
- *synthesis of phospholipids.
- *synthesis of lipoprotein.
- *synthesis of ketone body.
- *degradation of fatty acid.
- *degradation of phospholipids.
- *removal of phospholipids and cholesterol from blood.
- *lengthening and shortening of fatty acids.
- *saturating and desaturating of fatty acids.
- *control of depot lipid and liver lipid storage.
Fatty acid biosynthesis

- Primary substrate: glucose → glycolytic cycle → pyruvate.
- Oxaloacetate isomers: pyruvate → acetyl COA (derived from carbohydrate, protein, and degraded fat).

1. Acetyl COA + oxaloacetate → citrate → pass through the mitochondrial matrix → cytosol.
2. Acetyl COA + ACP (acyl carrier protein) → acetyl-ACP + COA.
3. Malonyl COA + ACP → malonyl-ACP(3) + COA
4. Acetyl-ACP + Malonyl-ACP → Acetoacetyl-ACP(4) + CO₂
5. Acetoacetyl ACP + 2NADPH₂ → Butyl-ACP(4) + NADP⁺ + H₂O
6. From Malonyl COA to Butyl ACP(4) repeated seven times to form C₁₆ palmitate, and further elongation can form C₁₈, C₂₀, C₂₂.
Figure 8.3  Fatty acid biosynthesis. Note the enzymes involved at various stages. The interrelationships between glucose and lipid metabolism are also shown. From Zeisel (1993; J. Nutritional Biochemistry 4: 550 (1993)).
Desaturation of FA

• C18:0 to C18:1, C16:0 to C16:1
  (Desaturation at 9,10-position)
• Inability to synthesize C18:2, C18:3 and C20:4
• C18:2 provide C20:3, C20:4 and C22:5
• C18:3 provide C20:5, C22:5 and C22:6
TG Biosynthesis
Figure 8.4 Triglyceride biosynthesis. Note the enzymes involved at various stages. From Mersmann (1986).
Triglyceride catabolism

- TG in adipose tissue is a dynamic state with continuous synthesis and degradation (lipolysis).
- Lipoprotein lipase (LPL) is a major enzyme responsible for hydrolysis of circulating TG in chylomicron and VLDL.
- Lipoprotein lipase activity is high \(\rightarrow\) animal in the fed state.
- Lipoprotein lipase activity is low \(\rightarrow\) animal in the fast state.
- Lipolysis is stimulated by epinephrine, synthetic \(\beta\)-agonist, somatotropin (growth hormone).
- Lipolysis is inhibited \(\alpha\)-adrenergic receptor on adipose cell.
- TG \(\rightarrow\) glycerol + fatty acid.
Fatty acid catabolism.

1. Fatty acid are transported via the blood to body tissues to be used as an oxidative energy source.
2. Occurred in the mitochondria of skeletal muscle, liver, cardiac muscle, adipose tissue.
3. CO₂ and Ketones as product.
4. Carboxyl 端開始, 每次移去2個碳, 產生acetyl COA.
   - Acetyl COA released → 1. 再合成脂肪酸.
   - 2. 合成steroids, ketones.
   - 3. 進入TCA.
5. 氧化過程包括COA esterification形成acyl-COA, 再進行dehydrogenase移去氫, 產生acetyl COA。
6. Oxidation pathway as shown Fig.8.5
Figure 8.5 Breakdown of a fatty acid is an oxidative process; that is, hydrogens are removed by the actions of enzymes (dehydrogenases). The fatty acid here (caproic acid, which has a six-carbon chain) is not broken down in its free form but is in the form of an ester of CoA (top). After oxidation and hydration (first three steps), two carbon units split off from the chain in the form of acetyl-CoA (last step). The remaining chain, still in the form of a CoA fatty acid ester can go through the whole process again. Thus, a fatty acid of any length can be disassembled two units at a time until it is all reduced to acetyl-CoA or, if an odd-length acid, to propionyl-CoA. Adapted from Green (1960).
Steroid metabolism

*Steroid basic ring structure, they include sterol, cholesterol and ergosterol, bile acids.

*飼糧中含量最多之steroid是cholesterol,

*cholesterol之合成原料為acetyl CoA, biosynthesis in liver. Regulation of biosynthesis is by dietary intake,

higher intake → depress the activity of HMG COA reductase (the rate-limiting enzyme in synthesis) in liver and ileum.

cholesterol 經由fecal bile acid, fecal steroid, bile salt之方式排出. Excretion of cholesterol in the bile and its conversion to bile acids. cholesterol can be used for steroid hormone (progesterone, adrenal cortical hormone, testosterone, estrogen) synthesis.

bile salt即bile acid與taurine, glycine結合(conjugation)形成,包括taurocholic及glycocholic acid。
phospholipid metabolism

- 動物體內含量最多之 phospholipid 為 lecithin (phosphotidyl choline)
- phospholipid 經 carboxyl ester 及 phosphate ester 之水解, fatty acid 氧化成 acetyl COA 進入 TCA cycle, glycerol 進入 glycolysis pathway 或再作爲 TG, 或 phospholipid 合成用.
Ketones

- Acetyl CoA → Acetoacetyl CoA

- Acetoacetic acid → Acetone

- β -Hydroxybutyric acid

- Formation of ketones is a continuous process. Provide a supply of energy for use by tissue.
Lipid deposition.

- is related to number of adipose cell and to their individual size.
- preadipocytes can proliferate postnatally, even adulthood.
- postnatal increase in adipocyte number varies among species,
- Obese swine have more small adipocytes than lean swine.
- body fat deposition is a dynamic phenomenon.
  - 1.anatomical ( adipocyte size and number )
  - 2.biochemical ( lipogenesis and lipolysis)
Abnormal in metabolism of lipids.

- *遺傳引起之血液中* lipoprotein *含量過高, 稱 familial hyperlipoproteinemia,
- 包括血液中* lipoprotein, cholesterol, TG之含量.
- *因肝中缺乏* LDL 之* cell surface receptor,因此不能從血液中排除 LDL, 因此血中 LDL 濃度較正常者為高。同時在肝中產生更多之 LDL並以 VLDL型態釋放至血液中
- In the normal liver, LDL receptor bind the VLDL and degrade them.
Fatty livers

- 因肝功能異常，使lipid蓄積於肝中而形成。
- 由正常5%提高至30%以上。
- 餵飼high-fat or high-cholesterol diet.

- Increase liver lipogenesis caused by excessive carbohydrate or Vit B complex ( biotin, B2, B1 )

- Increase mobilization of lipid from adipose tissue caused by diabete starvation, hypoglycemia, homone output.

  Decrease transport of lipid from liver to other tissue caused by deficiency of choline, pantothenic acid, inositol, protein, methionine, threonine.

- cellular damage to the liver.
- Vit E, Se deficiency.
- liver poisons.
Atherosclerosis

degenerative change in the blood vessels and heart

• 與serum cholesterol concentration有關.
• 餵食animal fat ( saturated fat ), egg (cholesterol )有關.
• Reduce fat and cholesterol intake, high ratio (2:1) of polyunsaturated to saturated fatty acid in the diet能有效避免.

• 飼料中M+P／S之比例為1.0／1.0或以上, 表示植物性油脂攝取較動物性油脂為高 (mono(M), polysaturated (P) fatty acid).

• Fish oils含高量之ω-3 fatty acids (polyunsaturated fatty acid)含linolenic acid (C 18:3), eicosapentalnoic acid (EPA) (C 20:5) and docosahexaenoic acid (DHA) (C 22:6),此些ω-3脂肪酸能增加血液凝固的時間, ω-3 fatty acid 之含量於海水魚含量多。

• 血液中LDL濃度高能增加人類atherosclerosis, 而HDL(與運動有關)則有降低之效果。
Oxidation of fatty acid to acetyl Co A

• The major part of the energy derived from fat is provided by the fatty acids. Their degradation is that of $\beta$-oxidation.

• $\beta$-oxidation is a progressive shortening of the carbon chain by removal of two carbon atoms at a time.

• Fatty acyl-CoA in the cytosol and then transferred into mitochondria as a complex with carnitine and then release acetyl-CoA.
Fatty acid
\[ R.(CH_2)_n.CH_2.CH_2.CH_2.CO_2^- \]
\[ \text{ATP} \]
\[ \text{HS-CoA} \]
\[ 2PP_i + AMP \]
\[ \Rightarrow \]
\[ H_2O \]
\[ \text{Fatty acyl-CoA ligase} \]

Acyl-CoA
\[ R.(CH_2)_n.CH_2.CH_2.CH_2.CO_2^- \]
\[ \text{FAD} \]
\[ \text{FADH}_2 \]
\[ \text{Acyl-CoA dehydrogenase} \]

Enoyl-CoA
\[ R.(CH_2)_n.CH:CH.CH_2.CO_2^- \]
\[ \text{H}_2O \]
\[ \text{Enoyl-CoA hydratase} \]

\[ \beta \]-Hydroxyacyl-CoA
\[ R.(CH_2)_n.CHOH.CH_2.CH_2.CO_2^- \]
\[ \text{NAD}^+ \]
\[ \text{NADH} \]
\[ (+H^+) \]
\[ \beta \]-Hydroxyacyl-CoA dehydrogenase

\[ \beta \]-ketoacyl-CoA
\[ R.(CH_2)_n.COH.CH_2.CH_2.CO_2^- \]
\[ \text{H}_2\text{O} \]
\[ \text{HS-CoA} \]
\[ \text{Acetyl-CoA acyl transferase} \]

\[ \text{R.(CH_2)_n.CH:CH.CH_2.CO_2^- + CH_3COS.CoA} \]

Acyl-coenzyme A Acetyl-coenzyme A
Fig. 9.11 β-oxidation of palmitate.
其 pass way and energy

<table>
<thead>
<tr>
<th></th>
<th>Moles ATP</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mole palmitate to palmitoyl-CoA</td>
<td>2</td>
</tr>
<tr>
<td>1 mole palmitoyl-CoA to 8 moles acetyl-CoA</td>
<td>35</td>
</tr>
<tr>
<td>8 moles acetyl-CoA to carbon dioxide and water</td>
<td>96</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>131 2</strong></td>
</tr>
<tr>
<td><strong>Net gain of ATP per mole of palmitate</strong></td>
<td><strong>129</strong></td>
</tr>
</tbody>
</table>