ANSC/NUTR 618
LIPIDS & LIPID METABOLISM
Fatty Acid Elongation and Desaturation

I. Fatty acid elongation

A. General

1. At least 60% of fatty acids in triacylglycerols are C18.
2. Free palmitic acid (16:0) synthesized in cytoplasm is elongated to stearic acid (18:0) by the addition of a C2 unit at the carboxyl terminal.
3. Virtually all cells contain one or more elongase isoenzymes.

B. Mitochondrial system

1. Palmitic acid is activated to palmitoyl-CoA in the cytoplasm (acyl-CoA synthase).
2. Palmitoyl-CoA is transferred into the mitochondria via the carnitine acyltransferase system.
3. A C2 unit is added by what appears to be a reversal of β-oxidation.
   a. Uses acetyl-CoA as carbon source.
   b. Uses NADH as source of reducing equivalents.
   c. FAD-dehydrogenase in the first step of β-oxidation is replaced by an NAD⁺-reductase.
4. Involved primarily in production of fatty acids for mitochondrial membranes; prefers unsaturated fatty acids as substrates.

C. Microsomal system

1. Palmitate is activated to palmitoyl-CoA in the cytoplasm.
2. Elongase enzymes are located in endoplasmic reticulum (microsomes) (not cytoplasm).
3. A C2 unit is added essentially as in the fatty acid biosynthetic pathway.
   a. Uses acyl-CoA (not acyl-ACP).
   b. Requires MalCoA (not AcCoA) as substrate.
   c. Can use NADH or NADPH as source of reducing equivalents.
   d. Pathway:
      \[
      \text{palmitoyl-CoA} + \text{malonyl-CoA} + 2 \text{NADPH} + \text{H}^+ \rightarrow \text{stearoyl-CoA} + 2 \text{NADP}^+ + \text{CoASH} + \text{CO}_2
      \]
   e. Virtually all fatty acids can be elongated (saturated, monounsaturated, and polyunsaturated).
C. Elongase isozymes

1. Saturated and monounsaturated fatty acids – ELOVL1, 3, and 6  
   (ELOVL = Elongation of Very Long Chain Fatty Acids)

2. Polyunsaturated fatty acids – ELOVL2, 4, and 5

II. Fatty acid desaturation

A. General

1. Usually alternates with fatty acid elongation.

2. Only three desaturases are present (Δ^9-, Δ^6-, and Δ^5-desaturases). There may be two  
   independent Δ^6-desaturases.

3. If substrate fully saturated or is a trans-fatty acid, then first double bond is at C9 (e.g., stearic  
   acid 18:0 to oleic acid 18:1Δ^9)

4. If substrate already unsaturated, then double bonds are inserted between the carboxyl group  
   and the double bond nearest to the carboxyl group. (e.g., linoleic acid 18:2Δ^9,12 to γ-linolenic  
   acid 18: Δ^6,9,12).

5. Desaturation maintains 1,4-diene composition of fatty acid.

6. Desaturation produces cis-double bonds.
B. *Stearoyl-Coenzyme A desaturase (SCD)*

1. SCD is located on the endoplasmic reticulum (microsomes).
   a. SCD1 – liver
   b. SCD2 – adipose tissue
   c. As many as 5 SCD genes in mice and humans
2. SCD contains flavoprotein and cytochrome $b_5$ or cytochrome P-450.
3. Molecular oxygen is partially reduced by the NADH to produce an enzyme-bound superoxide radical, which oxidizes stearoyl-CoA.
4. *SCD can desaturate any saturated fatty acid and many trans-fatty acids.*

![Overall reaction of stearoyl-CoA desaturase](image)

**C. Other desaturases**

1. *Plants*
   a. Starts with the *cis*-9 fatty acid (oleic acid) as substrate.
   b. Oleic acid must be incorporated into phospholipids of plant membranes.
   c. Desaturation is toward the ω-carbon.
   d. There is no Δ$^6$ desaturase activity in most plants.
      1) Arachidonic acid (20:4n-6) does not occur in most plants.
      2) Fatty acid carbon is conserved for the production of α-linolenic acid (18:3n-3).
   e. Most plants cannot elongate α-linolenic acid.
   f. Most plants do not have a Δ$^{15}$ desaturase.
      1) Many terrestrial plants are enriched with α-linolenic acid.
      2) Marine algae are the only organisms that can make large amounts of docosahexanoic acid.
Major pathways for polyunsaturated fatty acid synthesis in plants and algae. *Indicates a pathway found in high levels in marine algae and mosses, but less commonly in other algae or plants. This pathway is now known to be active in some lower fishes.

2. Animals
   
a. Starts with a saturated fatty acid as substrate.
   
b. The fatty acid must be activated to its acyl-CoA thioester.
   
c. The first double bond is always at the Δ⁹ position.
   
c. Desaturation is always toward the carboxyl-carbon.
Important pathways for unsaturated fatty acid formation in mammals. E = elongase; D = desaturase (positional specificity indicated).
3. **Fatty acid biohydrogenation**
   a. The double bond toward the methyl carbon is isomerized to a *trans*-double bond.
   b. The double bond nearest the #1 carbon is reduced (*hydrogenated*).
   c. The *trans*-double bond is reduced, usually producing stearic acid (18:0).
   d. Each reaction is carried out by a different microorganism.

Biohydrogenation.