

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

I. Fatty acid elongation**A. General**

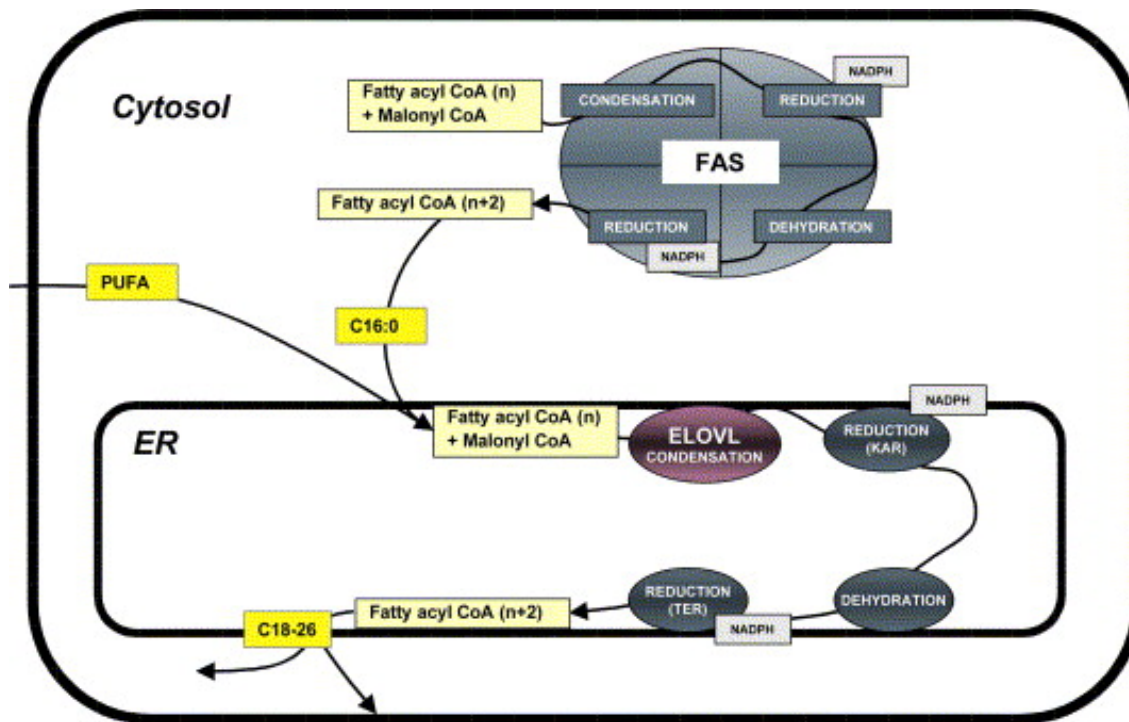
1. At least 60% of fatty acids in triacylglycerols are C18.
2. Free palmitic acid (16:0) synthesized in cytoplasm is elongated to stearic acid (18:0) by the addition of a C2 unit at the *carboxyl* terminal.
3. Virtually all cells contain one or more elongase isoenzymes.

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

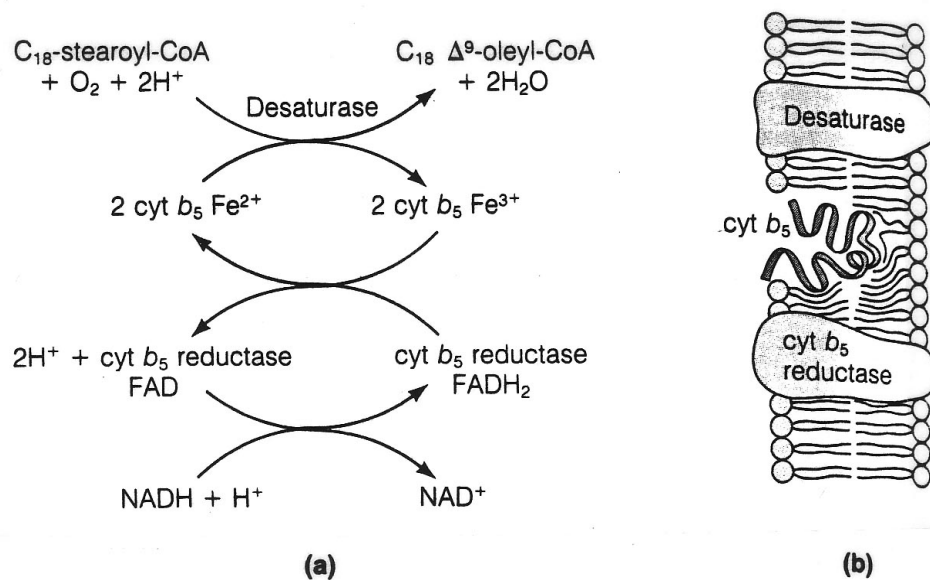
II. Fatty acid desaturation

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 18:1 Δ^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 18:2 $\Delta^{9,12}$ to γ -linolenic acid 18:3 $\Delta^{6,9,12}$).
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.*

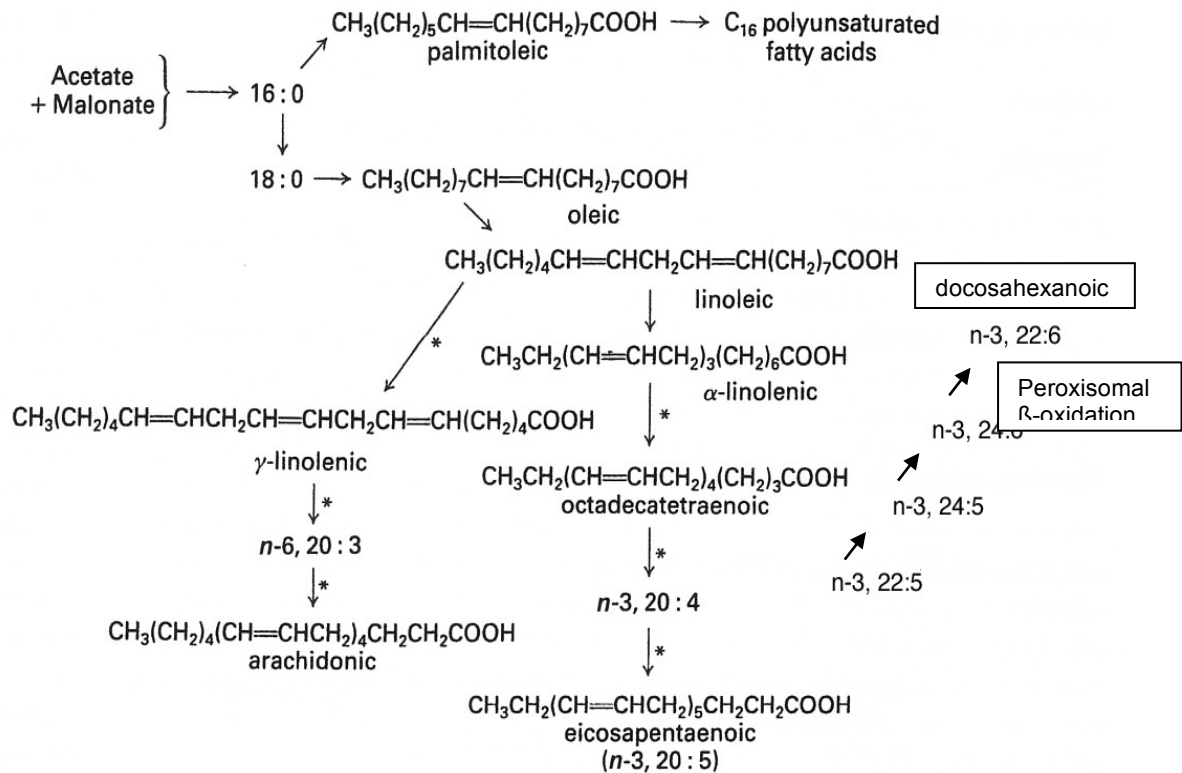


Overall reaction of stearoyl-CoA desaturase

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.

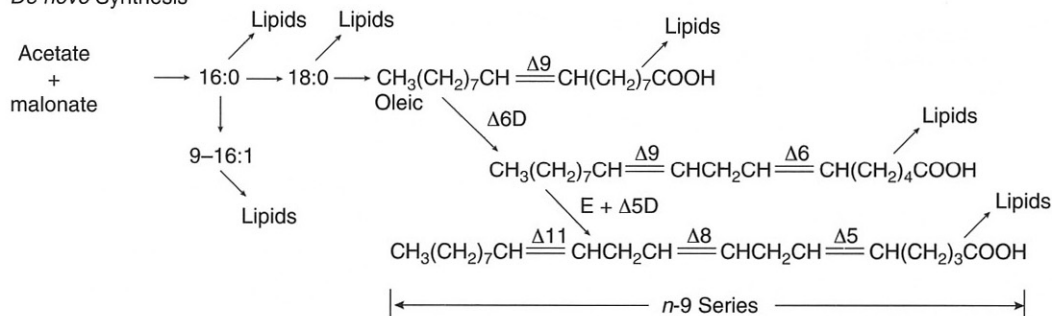


Major pathways for polyunsaturated fatty acid synthesis in plants and algae. *Indicates a pathway found in high levels in marine algae and mosses, but less commonly in other algae or plants.

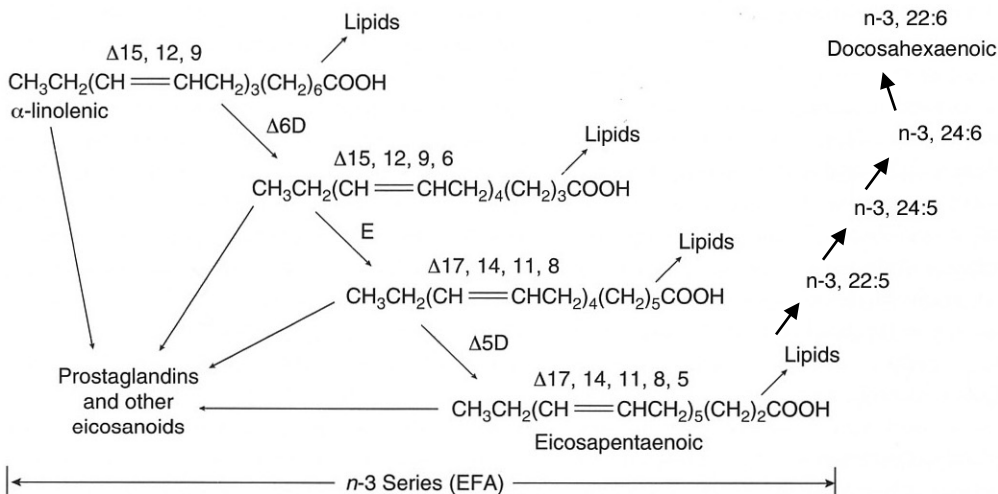
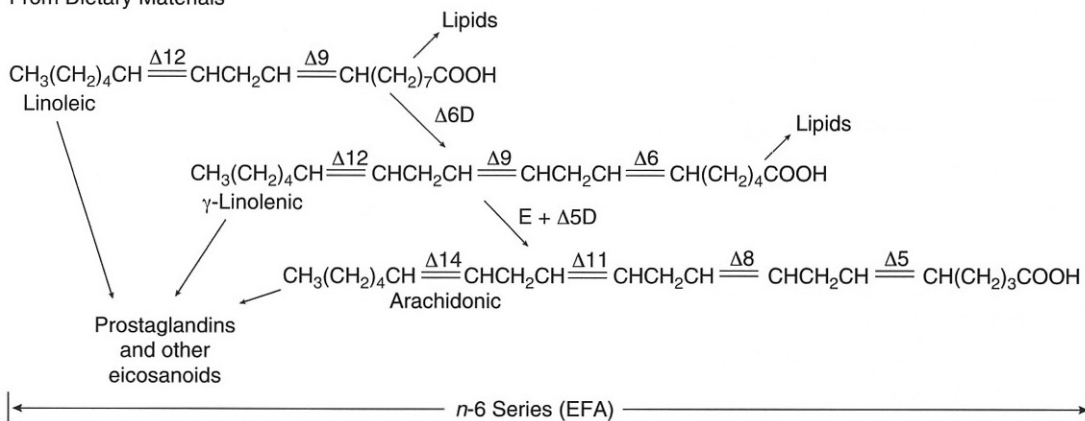
2. Animals

- Starts with a saturated fatty acid as substrate.
- The fatty acid must be activated to its acyl-CoA thioester.
- The first double bond is always at the Δ^9 position.
- Desaturation is always toward the carboxyl-carbon.

De novo Synthesis



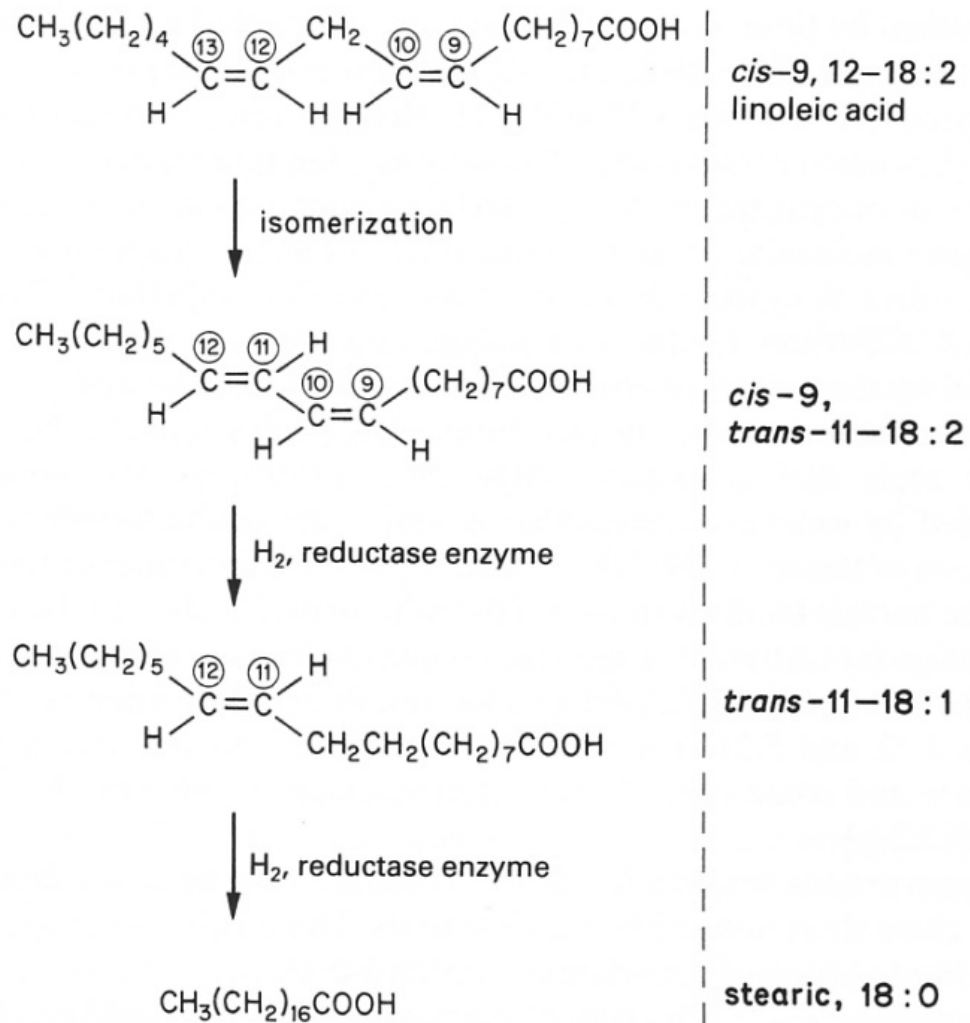
From Dietary Materials



Important pathways for unsaturated fatty acid formation in mammals. E=elongase; D=desaturase (positional specificity indicated).

3. *Fatty acid biohydrogenation*

- The double bond toward the methyl carbon is isomerized to a *trans*-double bond.
- The double bond nearest the #1 carbon is reduced (*hydrogenated*).
- The *trans*-double bond is reduced, usually producing stearic acid (18:0).
- Each reaction is carried out by a different microorganism.



Biohydrogenation.