Metabolism & Physiological Uses of PUFA's

[Ref: Peter Mayes in "Harper's Biochemistry," 24th ed., (Prentice-Hall: 1996), pp 236-244.]

I. Essential Fatty Acids (EFA's)

- Linoleic Acid (ω-6) 18:2(9,12)

  - This is the precursor to arachidonic acid, 20:4(5,8,11,14)
  - AMDR for ω-6 EFA's is 5% to 10% of Total Calories per day
  - Derived from vegetable sources: corn, peanut, soybean & many plant oils

- α-Linolenic Acid (ω-3) 18:3(9,12,15)

  - This is the precursor to all ω-3 Fatty Acids, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)
  - AMDR for ω-3 EFA's is 0.6% to 1.2% of Total Calories per day
  - Derived from vegetable sources: Frequently found w/ linoleic sources, but particularly, in linseed oil

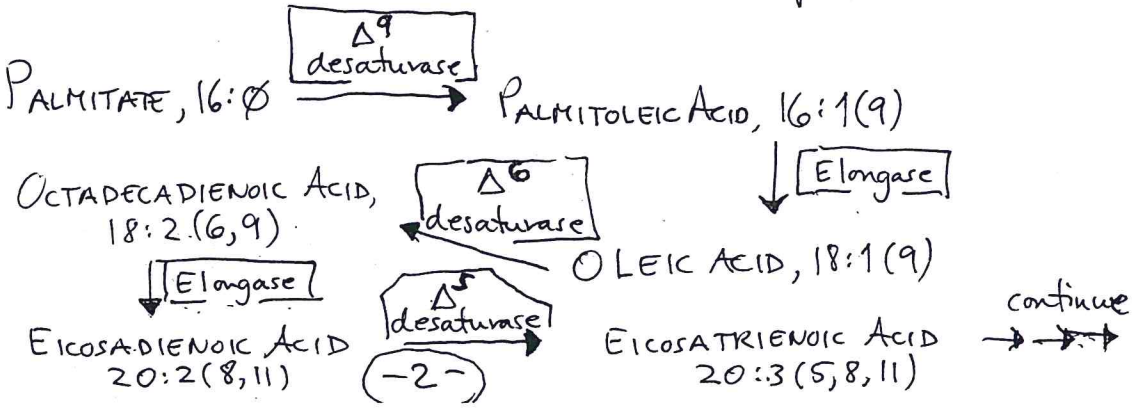
- Note that Arachidonic Acid is nonessential to most mammals b/c it can be formed from linoleic acid. Cats lack the Δ^6-desaturase enzyme required for biosynthesis.

II. Metabolism of PUFA's

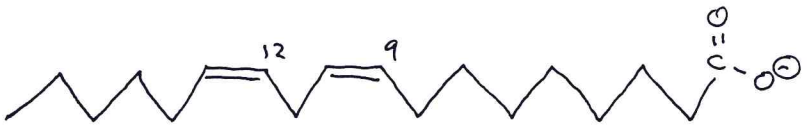
- Elongation & Desaturation

  - Operates in microsomes of differentiated cells capable of derivitizing FA's (hepatocytes, Glial cells, Schwann)
  - Elongation employes malonyl CoA and NADPH in mechanistic rxn like hepatocyte de novo FA synthesis
  - Desaturation (introduction of new double bonds) requires cytochrome activity (holoenzyme with Fe^{2+}/Fe^{3+} heme prosthetic group)
    - Humans possess microsomal Δ^4, Δ^5, Δ^6, and Δ^9 desaturase enzyme activities. In contrast, plants also "possess" (i.e., express genetically) Δ^{12} and Δ^{15} activities. As a consequence of this evolution, humans can not introduce add'l double bonds after the last double bond in the chain, meaning humans cannot synthesize an ω-3 FA from an ω-6 FA, nor an ω-6 from an ω-9 FA.

- Example 1: Conversion of palmitic acid to long-chain ω-9 PUFA derivatized products

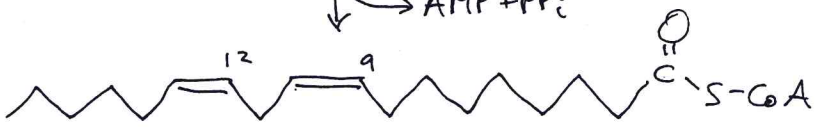


- EXAMPLE 2: Conversion of LINOLEIC ACID TO DIHOMO-γ-LINOLENIC and ARACHIDONIC ACIDS, ω-6 PUFA's



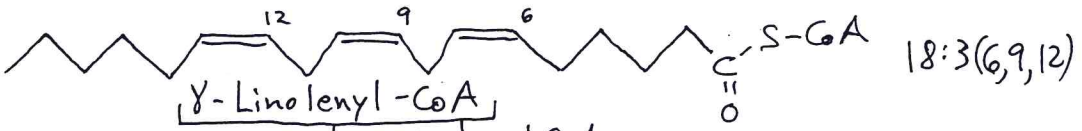
Linoleic Acid

CoASH + ATP → AMP + PP_i — E: fatty acyl CoA synthase



Linoleyl-CoA

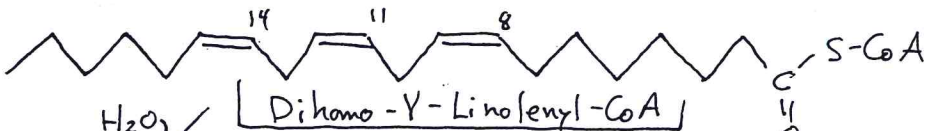
$NADH + H^+$ + O_2 → NAD^+ + $2H_2O$ — E: Δ^6-desaturase



γ-Linolenyl-CoA

malonyl CoA → CoA + CO_2

$2NADPH + 2H^+$ → H_2O + $2NADP^+$ — E: microsomal elongase



Dihomo-γ-Linolenyl-CoA

H_2O → CoASH

Dihomo-γ-linolenic Acid 20:3(8,11,14)

$NADH + H^+$ + O_2 → NAD^+ + $2H_2O$ — E: Δ^5-desaturase

Arachidonyl-CoA

H_2O → CoASH

Arachidonic Acid 20:4(5,8,11,14)

① Eicosanoids of PG_1, TX_1, LT_3 subfamily &
② Signal Transcription of Genetic Traits

① Eicosanoids of PG_2, TX_2, LT_4 & ② Transcription Act

- EXAMPLE 3 : Summary of conversion of α-Linolenic Acid to long-chain ω-3 PUFA's, EPA and DHA

α-linolenyl-CoA 18:3 (9,12,15)

↓ Δ^6-desaturase

octadecatetraenoyl CoA 18:4 (6,9,12,15)

↓ elongase

eicosatetraenoyl CoA 20:4 (8,11,14,17)

↓ Δ^5-desaturase

eicosapentaenoyl CoA 20:5 (5,8,11,14,17)

H_2O → CoASH → EPA

① Eicosanoids of PG_3, TX_3 and LT_5 subfamily

&

② Transcription Activation of Genetic Traits

eicosapentaenoyl CoA → elongase → docosapentaenoyl CoA 22:5 (7,10,13,16,19)

↓ Δ^4-desaturase

docosahexaenoyl CoA 22:6 (4,7,10,13,16,19)

H_2O → CoASH → DHA

① Found in high concentrations in retina, cerebral cortex, testes and sperm

② Retinal rods contain virtually 1 molecule DHA per phospholipid in outer segments. High DHA in retina ⇒ ↑ membrane fluidity ⇒ enhanced action of rhodopsin

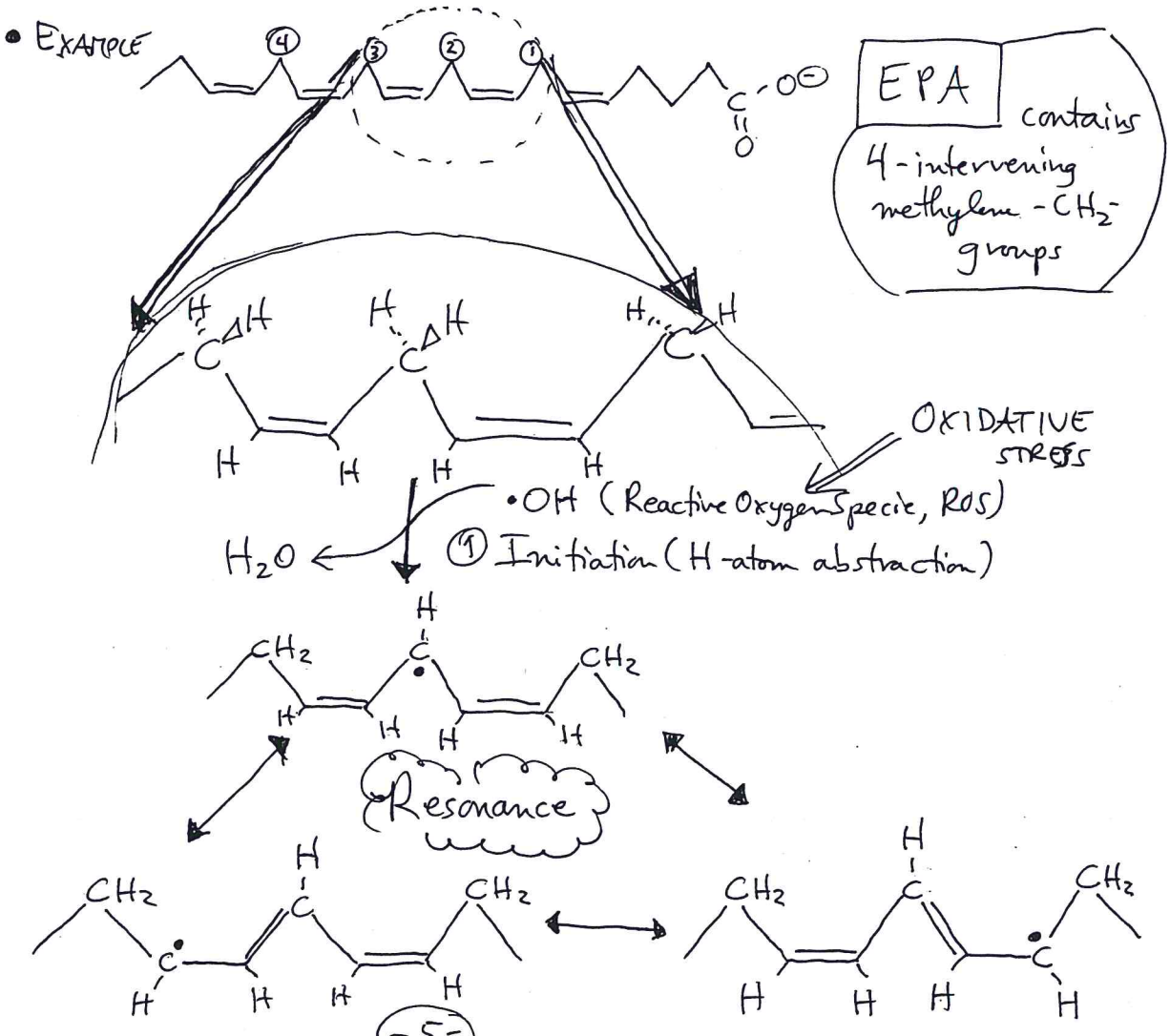
③ Premature infants express low Δ^4-desaturase activity

III. Lipid Peroxidation of PUFA's: A Free-Radical Chain Reaction

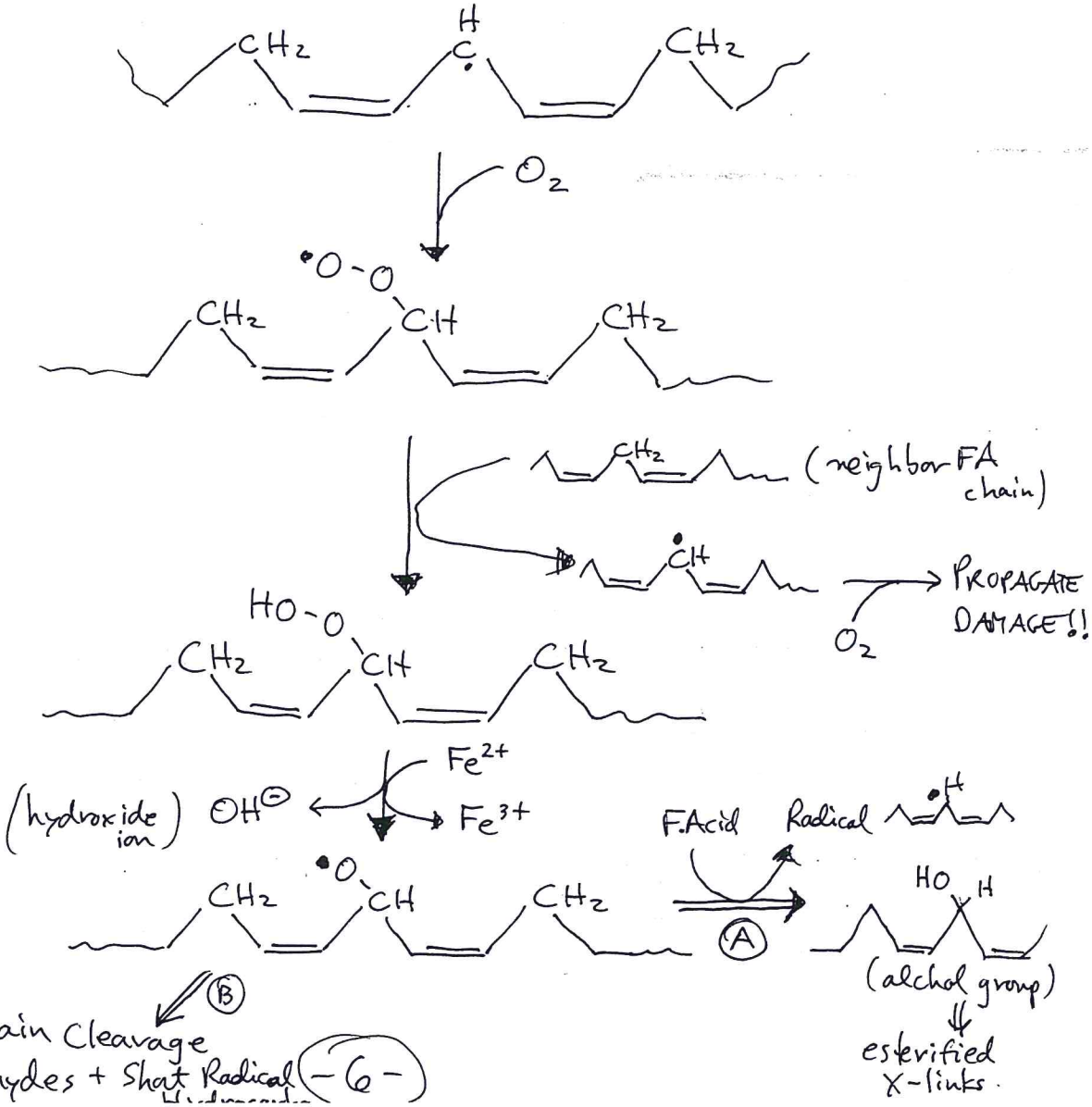
References:
Mayer in "Harper's Biochemistry", pp155-156 (Ch16) and McKee+McKee "Biochemistry: An Intro" 2ded., 1999, pp 316-329.

- The H-atoms of the intervening methylene ($-CH_2$) groups between pairs of double bonds are highly reactive towards free radical oxidation.
- Once H· atom is abstracted from the intervening methylene group, resonance stabilized structures can be formed. The ability to form resonance-stabilized products of H-abstraction fatty acid chain makes oxidation of PUFA's an energetically favorable and kinetically fast reaction

- Example

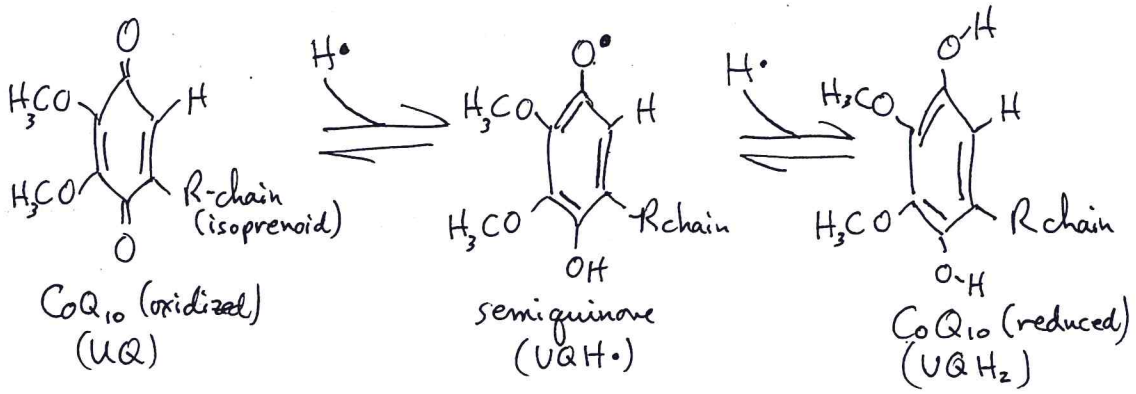


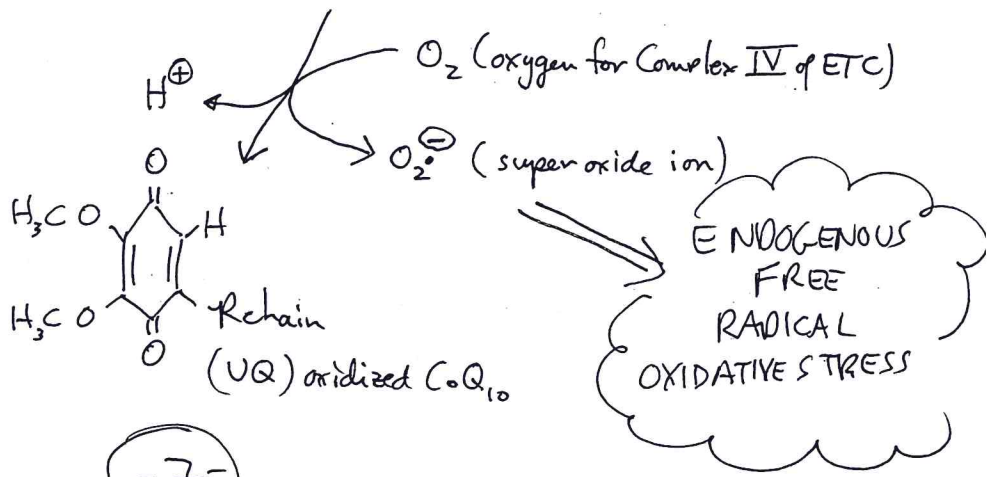
- The free radical hydrocarbon chain becomes more easily formed for those PUFA molecules containing more intervening methylene $-CH_2-$ groups (i.e., PUFA's with more total double bonds).
- After formation of the free radical hydrocarbon chain reacts with available O_2, forming a peroxy radical ($-C-OO^{\bullet}$). This organic peroxy abstracts neighboring H-atom from a nearby fatty acid chain, thus propagating the chain reaction.



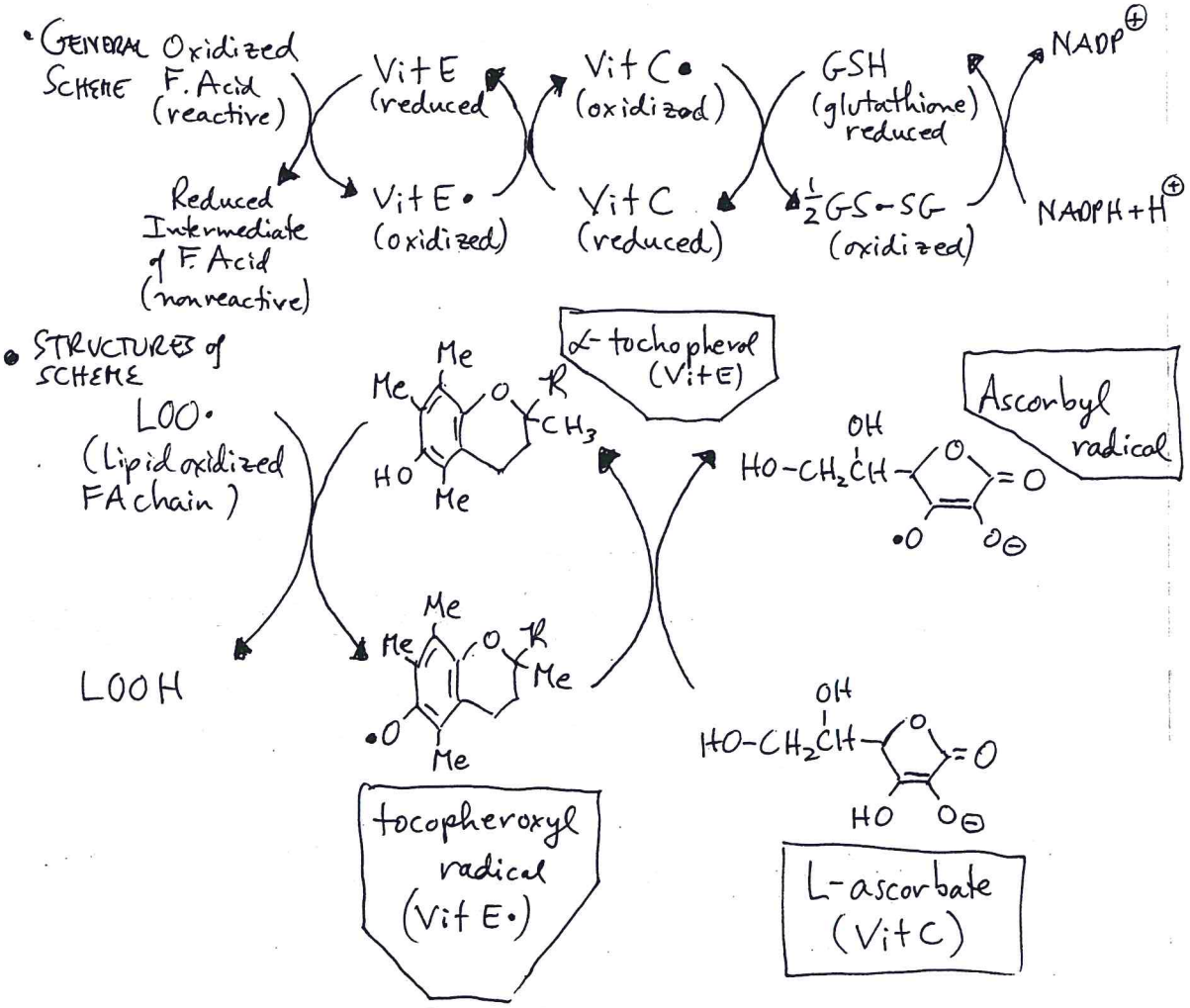
IV Antioxidants & Oxidative Stress

- Enzymes of catalase and superoxide dismutase (SOD) are capable of reducing the activities of the reactive oxygen species (ROS's) by eliminating them via redox reactions.
- Note that endogenous production of ROS's occurs in association with the respiratory burst of phagocytosis during the inflammatory response to injury and infection. [Ref: Champe et al, Lippincott Biochem, Ch 13, p 148]
- Superoxide ion ($O_2^{\bullet -}$) is a free radical also produced during the ETC in the mitochondrial inner membrane upon reaction with the semiquinone intermediate of CoQ_{10}.





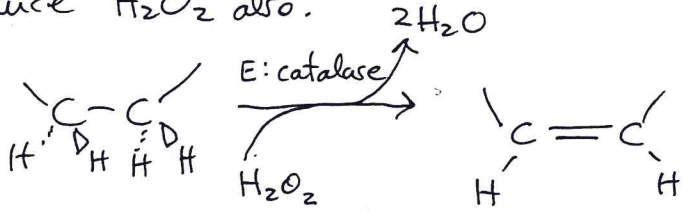
- Tocopherols (Vit E), β-carotene, CoQ10 and polyphenol phytochemicals are lipid ~~soluble~~ soluble. These can halt the propagation steps of the free radical chain reaction, thus minimizing the extent of damage.
- Vit C, urate and glutathione (GSH) are important water soluble antioxidants to help maintain the reduction activities of the lipid soluble vitamins and cofactors. [Reference: Seaman, "Clinical Nutrition for Pain, Inflammation and Tissue Healing," 1988.]



- The antioxidant enzymes prevent the initiation step of the free radical chain reactions by reducing the aggressive, strong oxidizing ROS's before they are able to initiate the 1ST H-atom abstraction rxn.
- Catalase is an Fe-supported enzyme found in most cells, especially erythrocytes. It catalyzes the disproportionation of hydrogen peroxide

$$2\,H_2O_2 \xrightarrow[(Fe\text{-}heme)]{E:\ catalase} 2\,H_2O + O_2$$

whenever H_2O_2 levels are concentrated and elevated. Catalase is abundant within peroxisomes, and it can use available hydrocarbons as H-atom sources to reduce H_2O_2 also.



- Superoxide dismutase (SOD) is found as two isoenzymes within cells. The mitochondrial form employs the Mn-containing isozyme, whereas the cytosol utilizes the Cu-Zn containing isozyme. (Lou Gehrig's disease, ALS, is known to result from a genetic deficiency coding for this Cu-Zn cytosolic form of SOD, McKee+McKee "Biochemistry" p. 324)

$$2O_2^{\ominus\bullet} + 2H^{\oplus} \xrightarrow{\text{E: SOD}} H_2O_2 + O_2$$

Cofactors:
① Mn (mitosol)
② Cu-Zn (cytosol)

Note the H_2O_2 produced may be disproportionated by catalase, or by the next enzyme, GSH peroxidase.

- Glutathione peroxidase is an antioxidant Se-containing enzyme present in numerous aqueous phase fluid compartments of a cell, especially in the cytosols and mitosols of most cells. Note that this enzyme activity is also expressed in support of the conversion of the endoperoxide, PGG_i, to the hydroxylated intermediate, .. PGH_i, in the synthesis of eicosanoids.