

Lipid Metabolism: uptake and synthesis

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Edward Wojcik, Ph.D.
Department of Biochemistry and Molecular
Biology
7128 MEB
ewojci@lsuhsc.edu
568-2058

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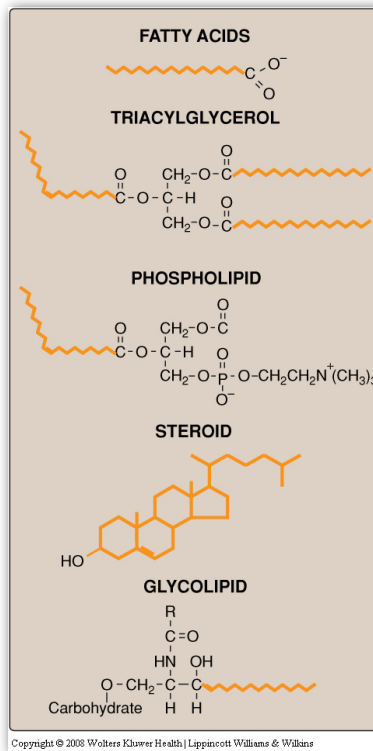
Lipids are water insoluble, heterogeneous molecules

A) Functions

- a) compartmentalize cellular components and biochemical pathways: membranes
- b) storage of metabolic energy
- c) coenzymes
- d) signaling molecules and effectors

B) Hydrophobic, lipophilic

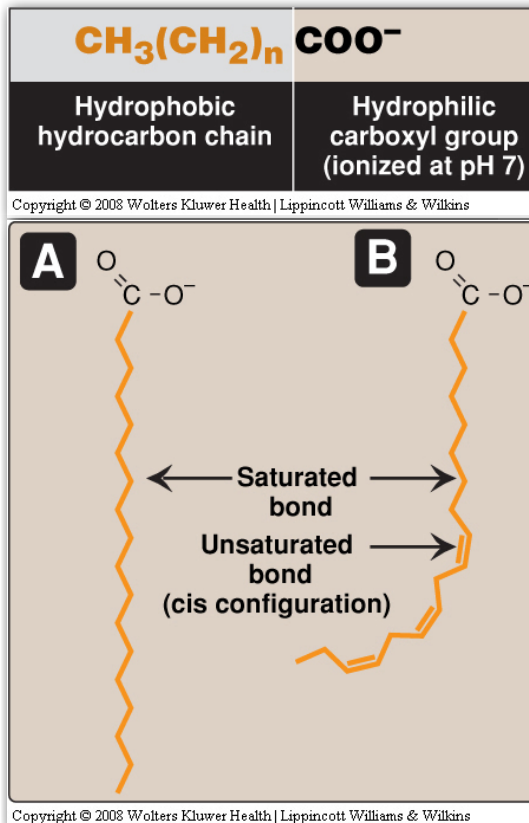
C) Major factor in obesity, diabetes, atherosclerosis



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Fatty Acid Structure

1. Vary in total number of carbons in the acyl chain.
2. Can contain double bonds (normally found in the cis configuration), but are usually unbranched.
3. Always amphipathic due to invariant carbonyl end.

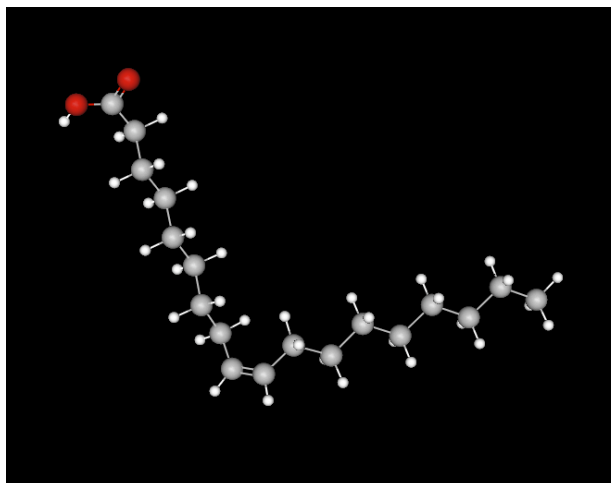


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“ Δ ” nomenclature locates double bonds: counting from the carbonyl end

e.g. cis- Δ (9)-octadecenoic acid

{Oleic Acid}



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Oleic Acid

cis-.delta.9-Octadecenoic acid

cis-Delta(9)-octadecenoic acid

cis-delta(sup 9)-Octadecenoic acid

<i>cis</i>-9-Octadecenoic Acid

Oleic acid (8CI)

(9Z)-Octadecenoic acid

9-Octadecenoic acid, (Z)-

Oleic acid-9,10-t

9-Octadecenoic acid (9Z)-

nchembio.103-comp16

9-cis-Octadecenoic acid

(Z)-Octadec-9-enoic acid

Emersol 220 white oleic acid

9,10-Octadecenoic acid

9-Octadecenoic acid (9Z)- (9CI)

cis-9-Octadecenoic-9,10-3H2 acid

cis-.delta.(sup 9)-Octadecenoic acid

9-Octadecenoic acid (Z)-, sulfurized

9-Octadecenoic acid (9Z)-, sulfurized

9-Octadecenoic-9,10-t2 acid, (Z)-



4-02-00-01641 (Beilstein Handbook Reference)

9-Octadecenoic-9,10-t2 acid, (9Z)- (9CI)

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“Δ” IUPAC nomenclature locates dbl bonds: counting from the carbonyl end

1. cis-Δ(9,12,15)-octadecatrienoic acid
2. n-Hexadecanoic acid
3. cis-Δ(9)-octadecenoic acid
4. cis-Δ(9,12)-octadecadienoic acid

Fatty acids with chain lengths of four to ten carbons are found in significant quantities in milk.

Structural lipids and triacylglycerols contain primarily fatty acids of at least sixteen carbons.

COMMON NAME	STRUCTURE
Formic acid	1
Acetic acid	2:0
Propionic acid	3:0
Butyric acid	4:0
Capric acid	10:0
Palmitic acid	16:0
Palmitoleic acid	16:1(9)
Stearic acid	18:0
Oleic acid	18:1(9)
Linoleic acid	18:2(9,12)
α-Linolenic acid	18:3(9,12,15)
Arachidonic acid	20:4(5, 8,11,14)
Lignoceric acid	24:0
Nervonic acid	24:1(15)

Precursor of prostaglandins

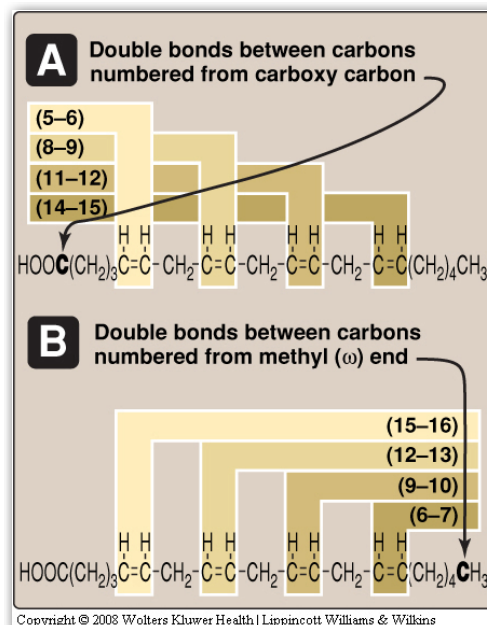
Essential fatty acids

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“ω” [omega] nomenclature marks the first dbl bond from the opposite, or, methyl end

1. ω (omega) carbon numbering – **terminal methyl group is always the omega carbon.** Begin counting at omega carbon (#1); most common are ω-6 or N-6 or n-6 (linoleic) and ω-3 (N-3; n-3) (linolenic) fatty acids. These two are “**essential**” fatty acids.

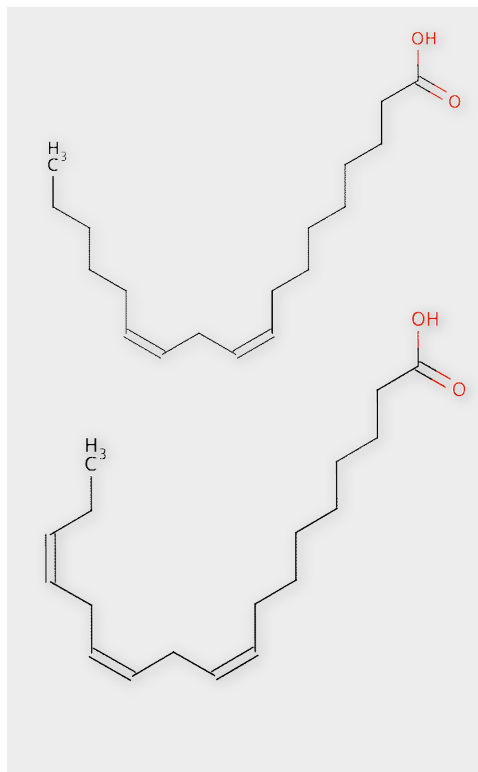


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Examples of essential fatty acids:

(ω -3) **linolenic acid**, *all-cis*-9,12,15-octadecatrienoic acid

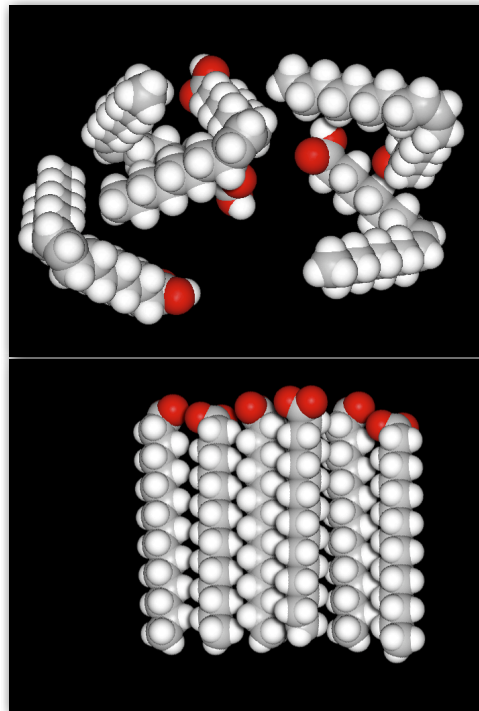
(ω -6) **linoleic acid**, *cis-cis*-9,12-octadecadienoic acid



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Saturated Fatty Acids have higher melting points

1. An example of this includes Olive oil versus candle wax.
2. Degree of saturation of fatty acids greatly affects membrane behavior.

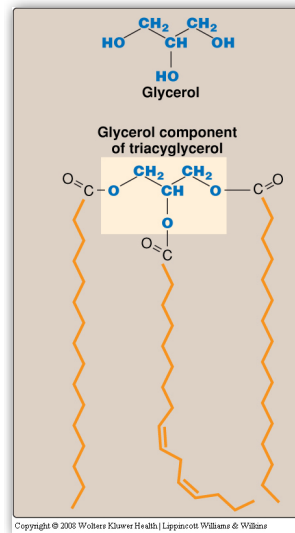


oleic vs stearic acids

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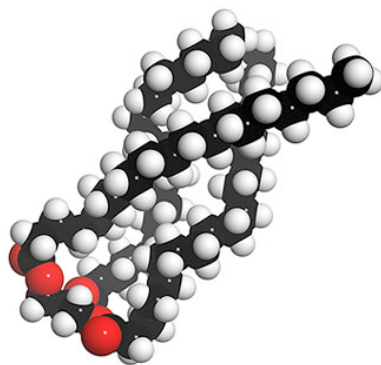
Triacylglycerols (TAG's) are the storage form of fatty acids

1. The majority of our fatty acid intake is from our diet
2. When cellular energy is plentiful, fatty acids can be synthesized de novo
3. The acyl chain on carbon 1 of a TAG is usually saturated, that on carbon 2 is often unsaturated, and that on carbon 3 can be either.



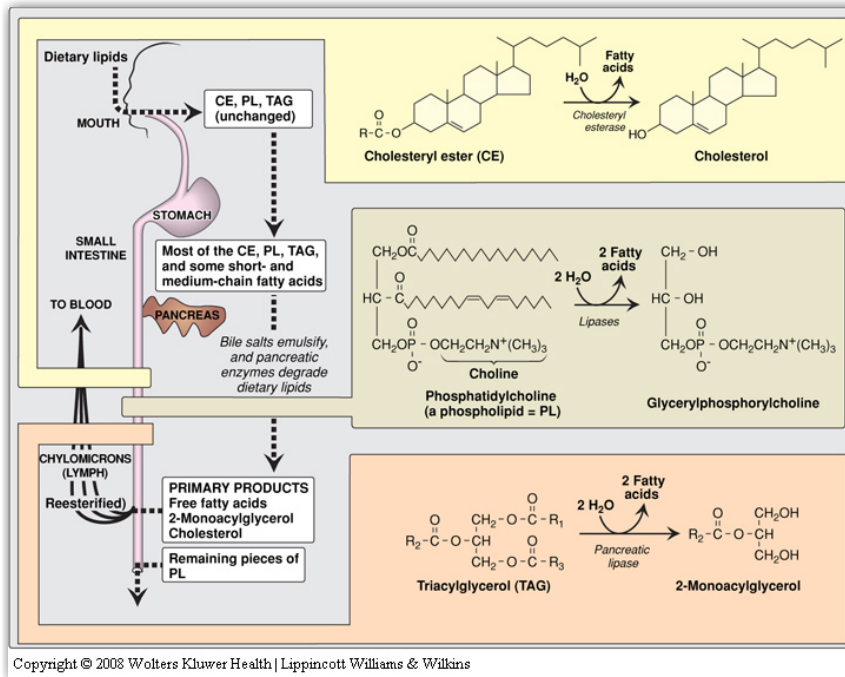
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TAGS don't form membranes, and they cannot be directly absorbed from food (aggregates are too large)



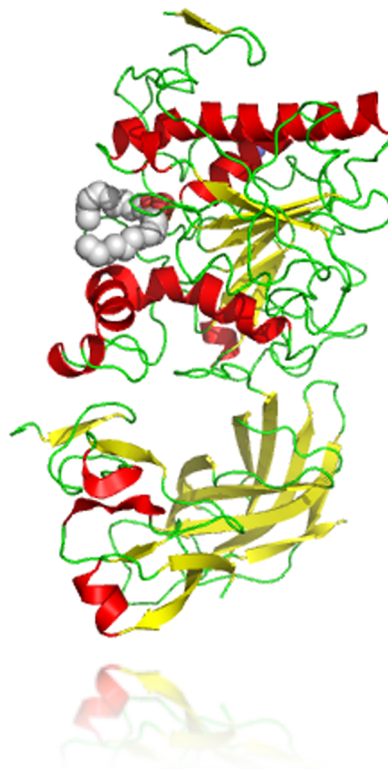
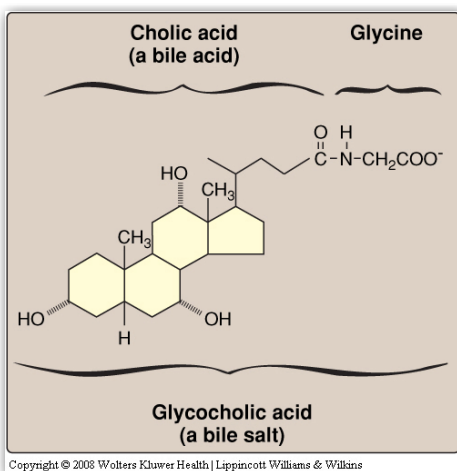
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Fats are broken down to forms that can passage into intestinal mucosal cells



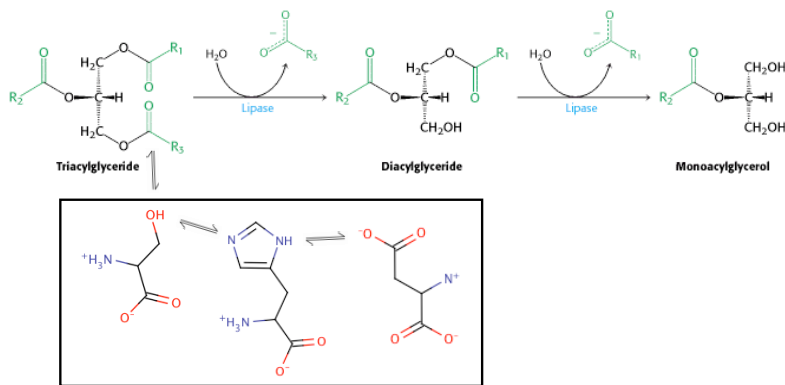
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The critical players for the uptake of fats from the diet are: pancreatic lipase and bile salts



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Mechanism of lipases resembles that of chymotrypsin, with a catalytic triad

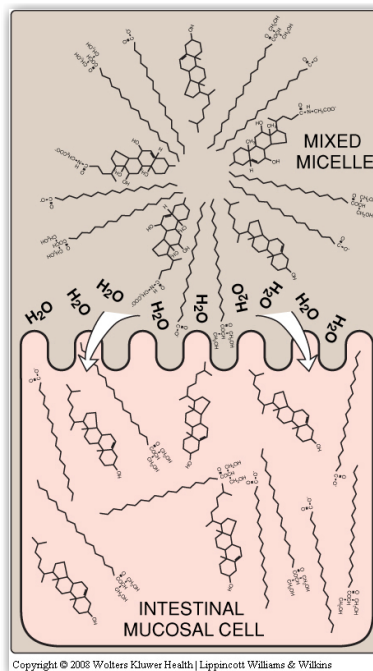


<http://www.angelo.edu/faculty/nflynn/Biochemistry/CT%20Catalytic%20Mechanism.htm>

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Digested fats form mixed micelles in the intestinal lumen

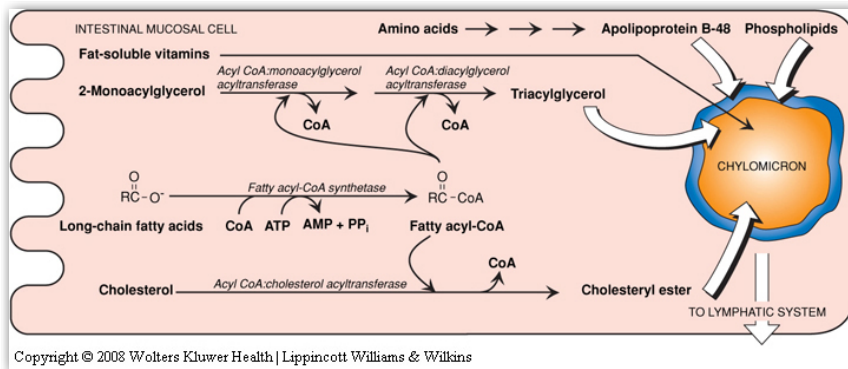
1. Fatty acids, monoacylglycerol and cholesterol can be absorbed by intestinal mucosal cells.
2. After absorption, triacylglycerols are re-formed and cholesterol re-esterified.
3. These [very hydrophobic] compounds are packaged by apolipoproteins into chylomicrons for transport throughout the body via lymphatic and, subsequently, blood stream.
4. Short and medium chain fatty acids can be directly absorbed by intestinal mucosal cells.



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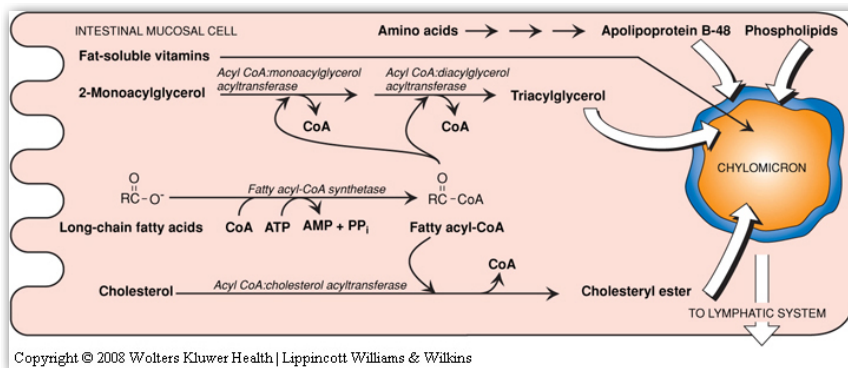
Resynthesis of triacylglycerides and cholesteryl esters at the ER of intestinal mucosal cells



1. Fatty acids are activated by fatty **acyl CoA synthetase** [requires ATP].
2. **Triacylglycerol synthase** re-joins 2-monoacylglycerol with two fatty acyl CoA
3. Cholesterol is re-esterified with fatty acyl CoA by Acyl CoA cholesterol acyltransferase

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Chylomicrons transport TAG's and Cholesterol-esters to peripheral tissues



1. Mature Chylomicrons contain TAG's, cholesterol, cholesterol esters, phospholipids and apolipoprotein B-48.
2. The apolipoprotein stabilizes the particle and increases its solubility. It also prevents multiple particles from coalescing into a large mass.

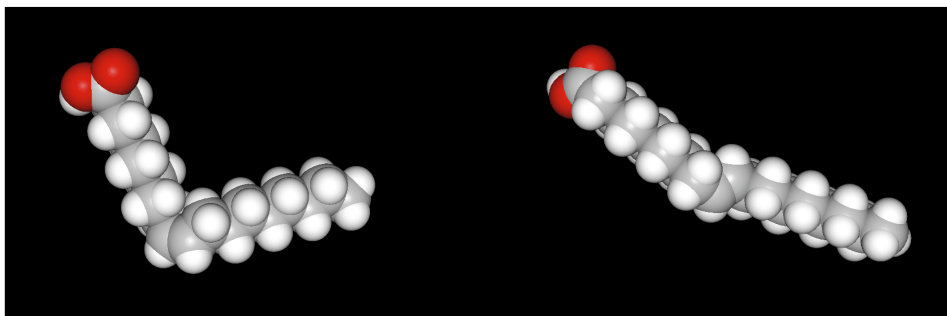
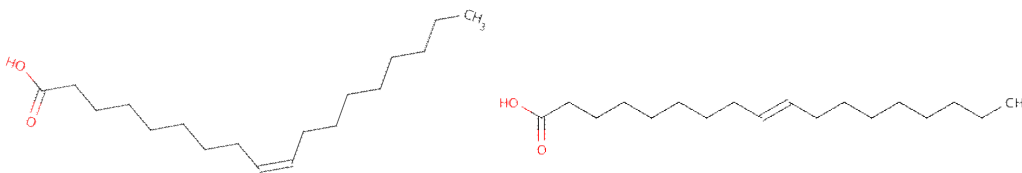
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TAG's in chylomicrons are broken down primarily in the capillaries of skeletal muscle and adipose tissue

1. **Lipoprotein lipase** degrades TAG's into free fatty acids and glycerol
2. Free fatty acids can be absorbed by neighboring cells or transported to other sites by the carrier protein, albumin.
3. Glycerol that is released from triacylglycerol is used **primarily by the liver** to produce **glycerol 3-phosphate** which can be utilized by glycolysis or gluconeogenesis

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Unsaturated bonds are typically in *cis* configuration



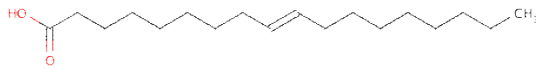
Oleic acid

Elaidic acid

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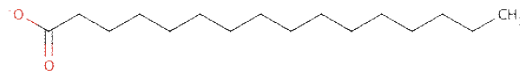
trans fatty acids can also be incorporated into TAG's and phospholipids

Elaidic acid



versus

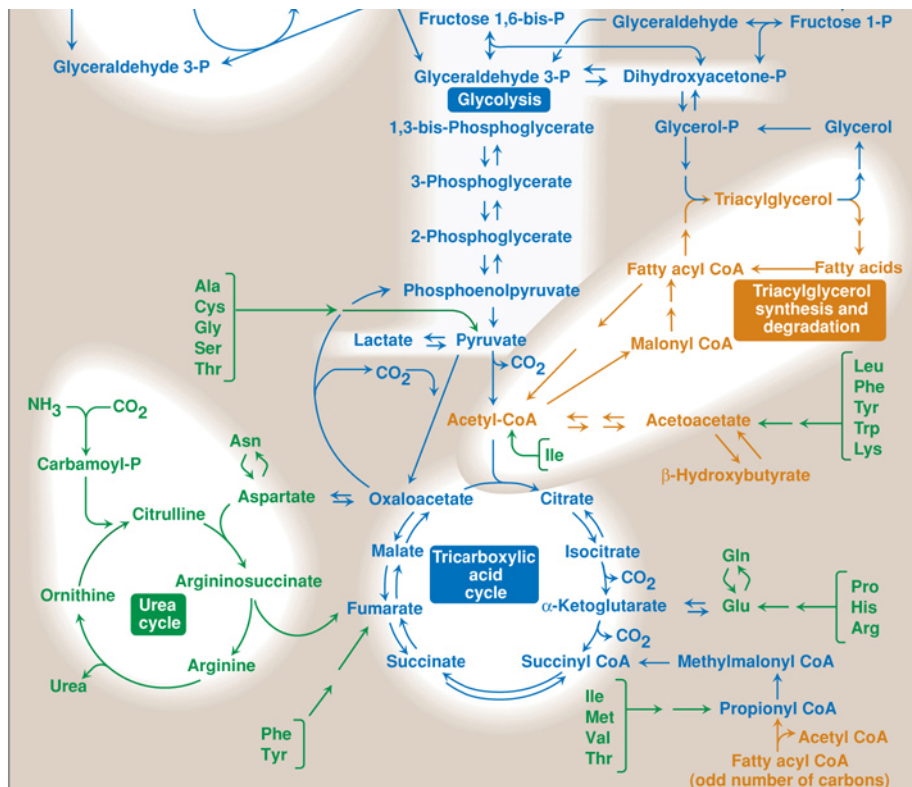
Palmitic acid



Why are *trans* fatty acids unhealthy?

1. epidemiological studies
2. biochemical studies

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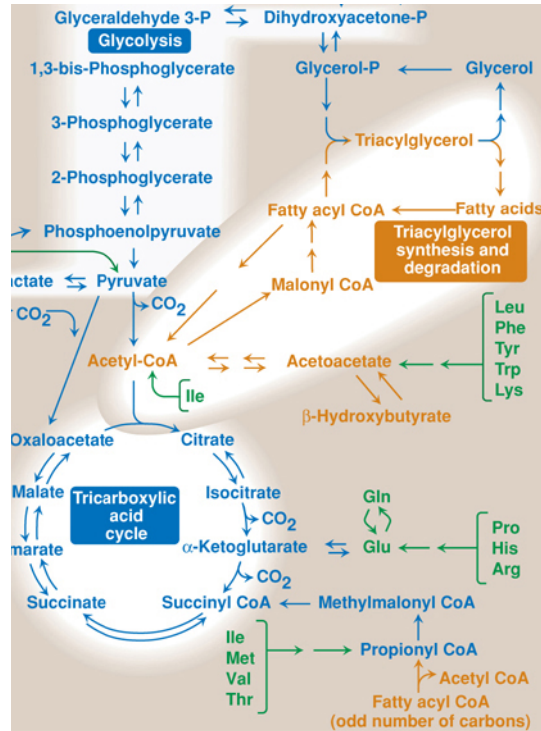


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Fatty acid degradation provides metabolic energy in several ways

1. Via breakdown of acyl chains into a number of Acetyl-CoA molecules.
2. Via recovery of Glycerol-6-phosphate from triacylglycerols.
3. During starvation, hepatocytes divert Acetyl-CoA from the TCA cycle (which is driving gluconeogenesis) towards production of Ketone Bodies (primarily Acetoacetate).



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FATTY ACID BIOSYNTHESIS

1. Sites - major (liver, lactating mammary gland) and minor (adipose tissue, kidney)
2. Precursors and cofactors – acetyl CoA, ATP, NADPH, CO₂
3. Main site of synthesis is in the cytoplasm
4. Cytoplasmic acetyl CoA is from transported mitochondrial acetyl CoA
 1. Citrate shuttle transports acetyl CoA from mitochondria and to cytoplasm (Fig. 16.6) - *mitochondrial citrate synthase* (OAA + Acetyl CoA) → citrate → cytoplasm → cytoplasmic citrate lyase (OAA + Acetyl CoA)
5. acetyl CoA is precursor for fatty acid synthesis; energy charge (ATP levels) must be high in the cell

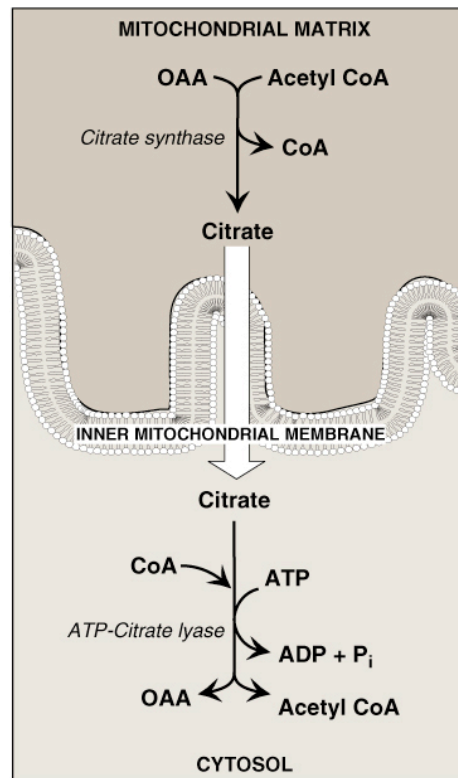


Figure 16.6
Production of cytosolic acetyl CoA.

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6. Carboxylation/decarboxylation – provides energy and mechanism for synthesis (Fig. 16.7) – *acetyl CoA carboxylase* (covalently bound biotin); ATP; CO₂; product is malonyl CoA (3 carbons)

7. Regulation of *acetyl CoA carboxylase* (rate-limiting, committed enzyme)

a) short term - polymerization of dimer (protomer) is stimulated by citrate; inhibited by malonyl CoA and palmitoyl CoA (Fig. 16.7)

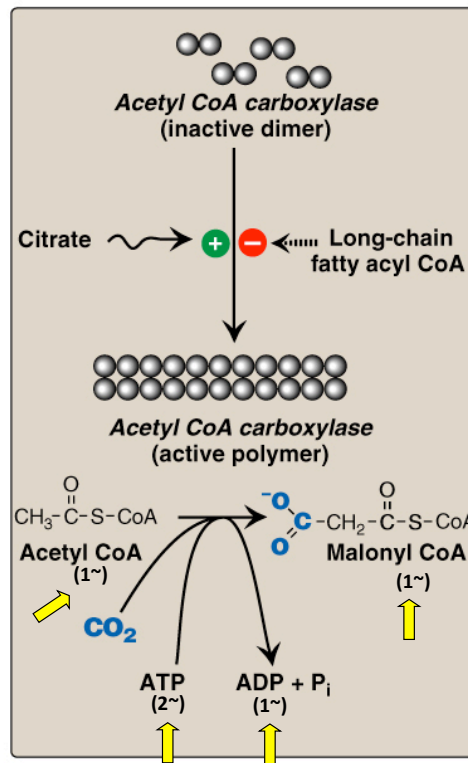


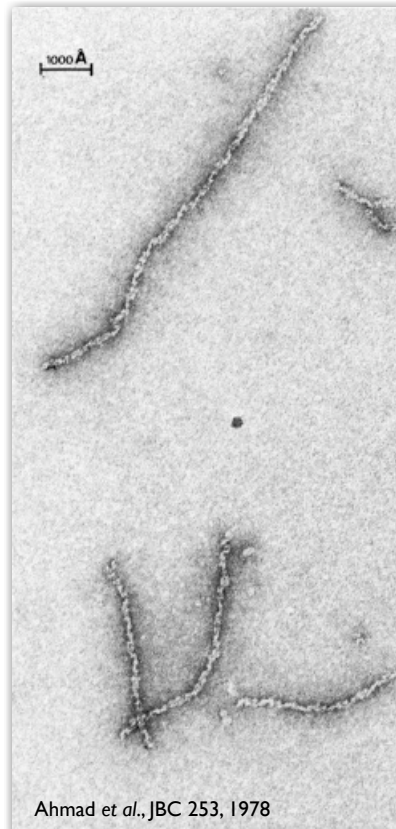
Figure 16.7 Allosteric regulation of malonyl CoA synthesis by *acetyl CoA carboxylase*. The carboxyl group contributed by dissolved CO₂ is shown in blue.

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6. Carboxylation/decarboxylation – provides energy and mechanism for synthesis (Fig. 16.7) – *acetyl CoA carboxylase* (covalently bound biotin); ATP; CO₂; product is malonyl CoA (3 carbons)

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Ahmad et al., JBC 253, 1978

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- b) phosphorylation – glucagon and epinephrine stimulate phosphorylation = inactive; high insulin and carbohydrates promote dephosphorylation = active (Fig. 16.8)
- c) long term - enzyme levels; increased by high carbohydrate, low fat diet (high citrate activates); inhibited by low carbohydrate, high fat diet. Same is true for fatty acid synthase

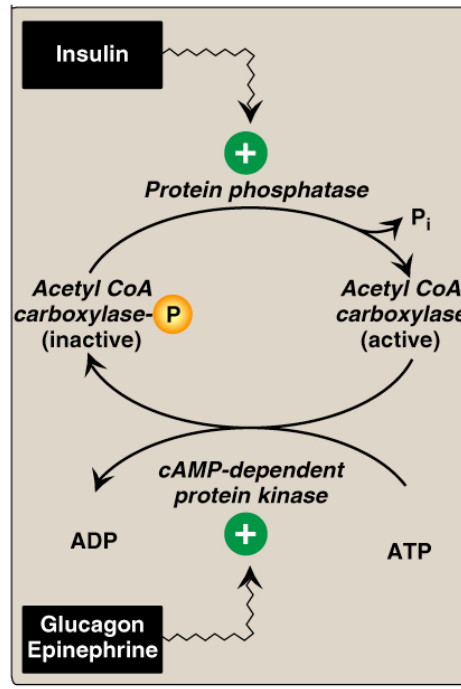
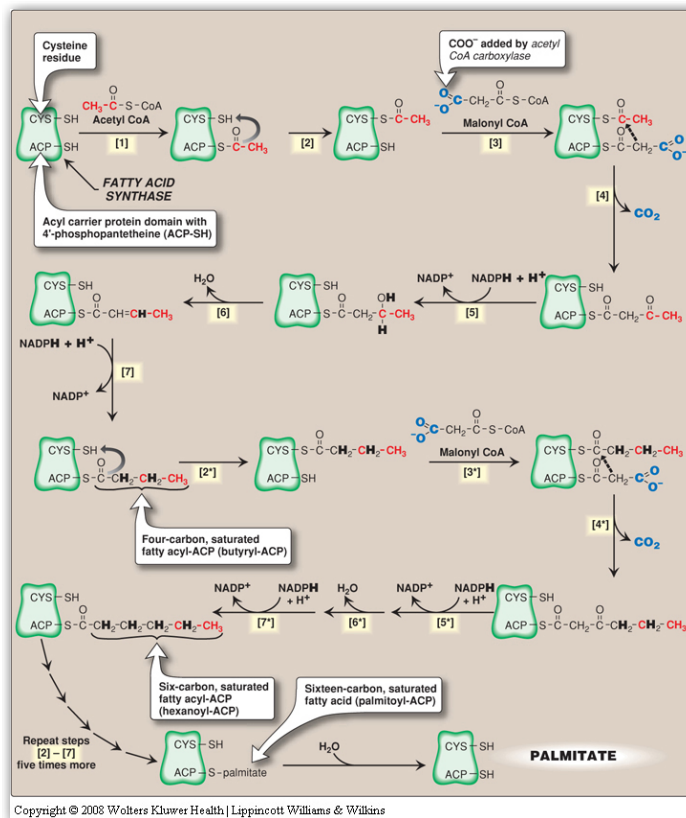


Figure 16.8 Hormone-mediated, covalent regulation of acetyl CoA carboxylase.

Fatty acid synthase

1. multifunctional enzyme with seven (6) different catalytic activities.
2. It is composed of a single polypeptide chain!
3. It has a special domain, the ACP, (acyl carrier protein) which covalently binds a 4'-phosphopantetheine molecule.



Domain 1 [substrate entry]

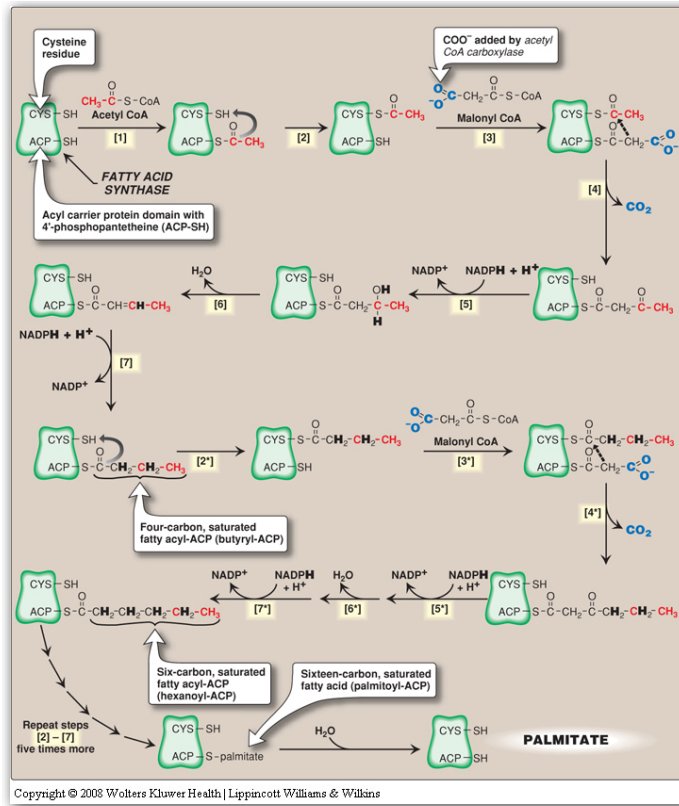
- (1) malonyl/acetyl transferase
- (2) 3-Ketoacyl-ACP synthase

Domain 2 [the reduction unit]

- (3) 3-Ketoacyl-ACP reductase
- (4) 3-Hydroxyacyl-ACP dehydratase
- (5) Enoyl-ACP reductase

Domain 3 [the palmitate release unit]

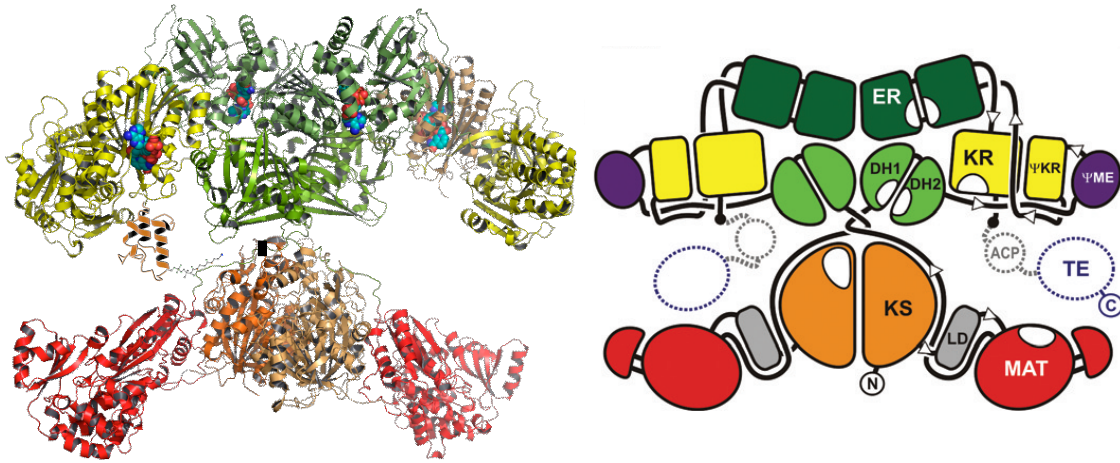
- (6) ACP (acyl carrier protein domain)
Palmitoyl thioesterase



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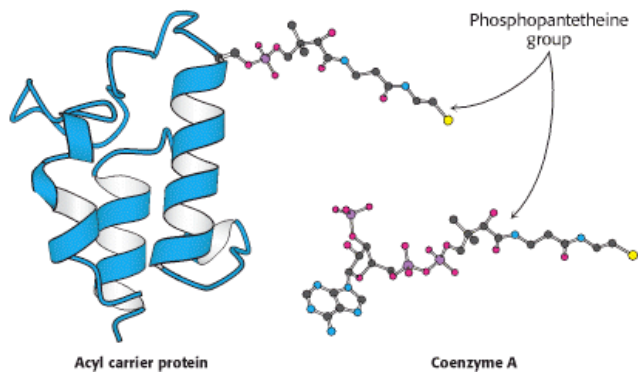


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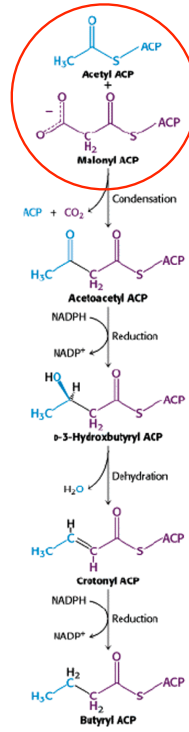
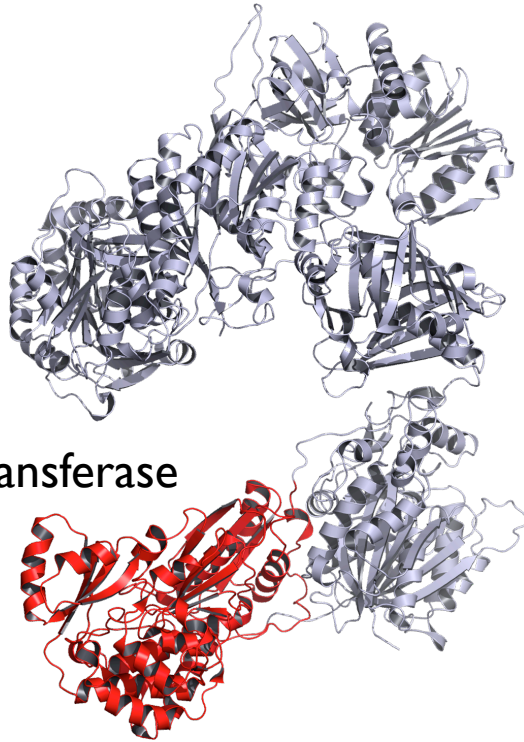
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Fatty acid synthase ACP domain with phosphopantetheine prosthetic group



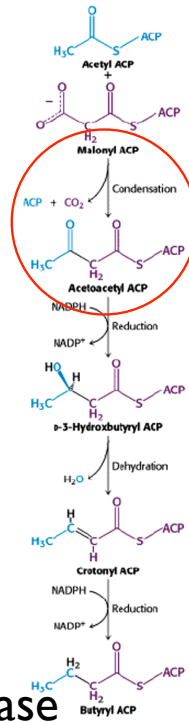
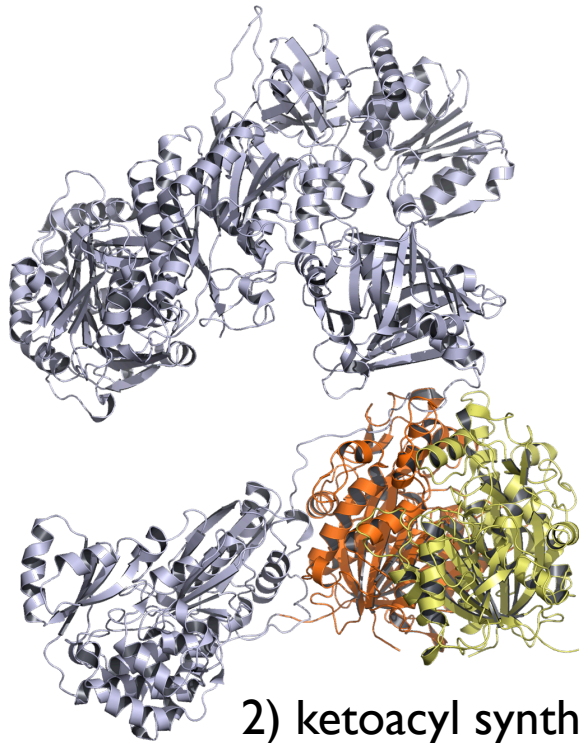
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1) malonyl transferase



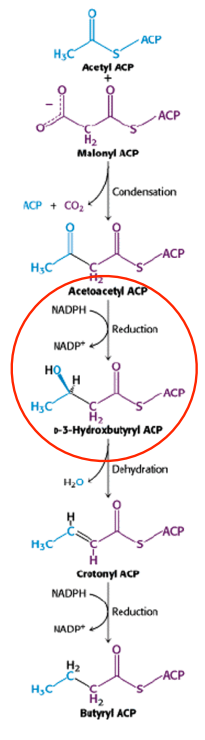
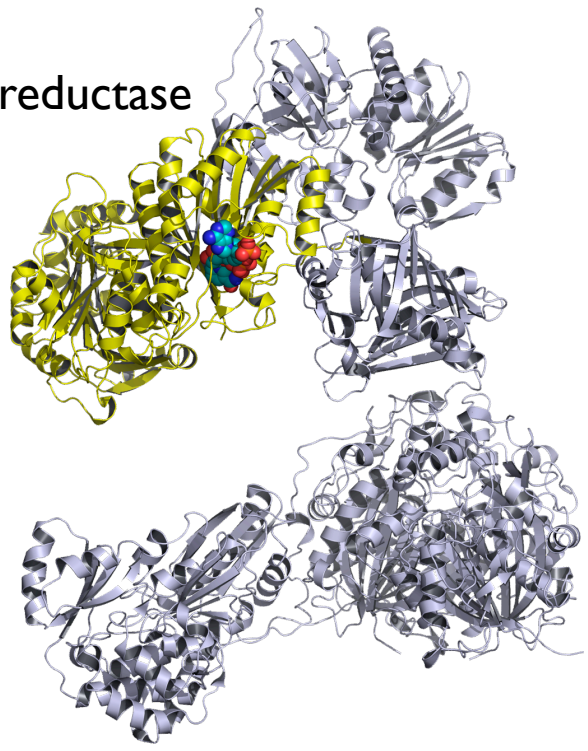
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2) ketoacyl synthase

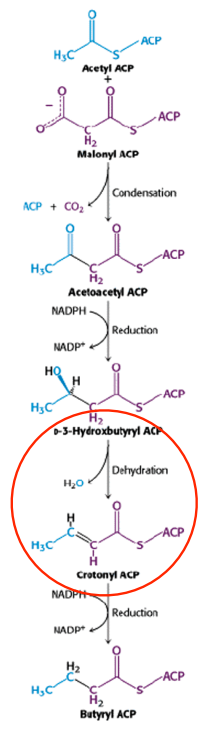
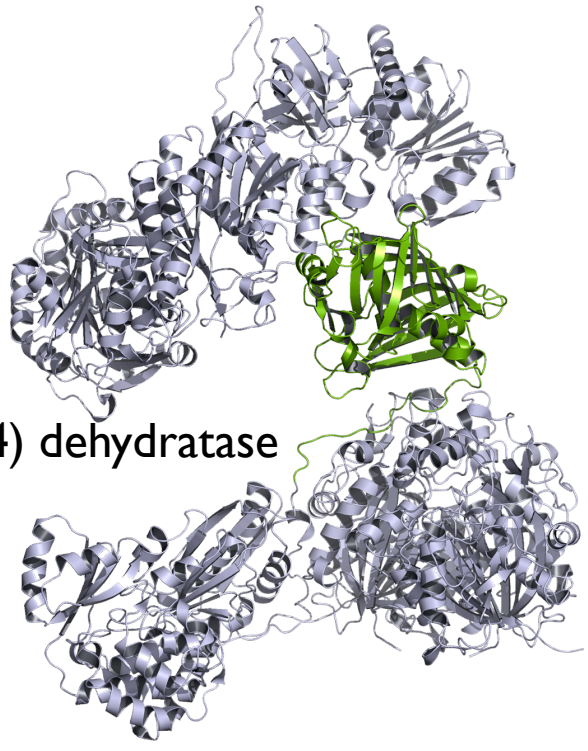


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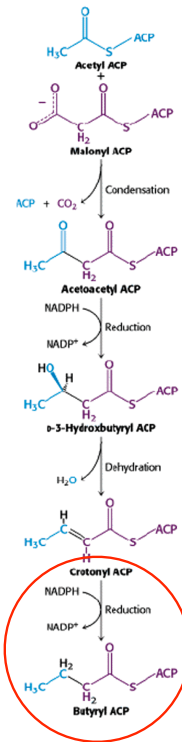
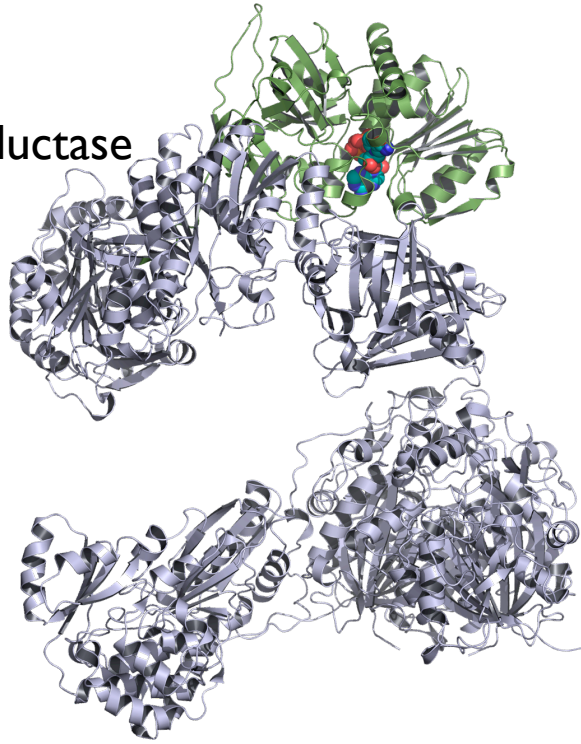
3) ketoacyl reductase



4) dehydratase

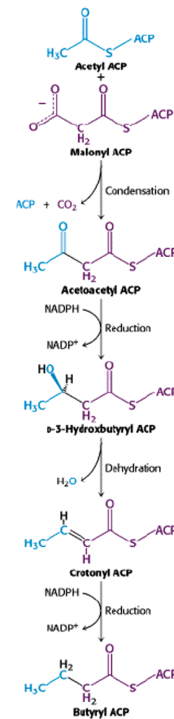
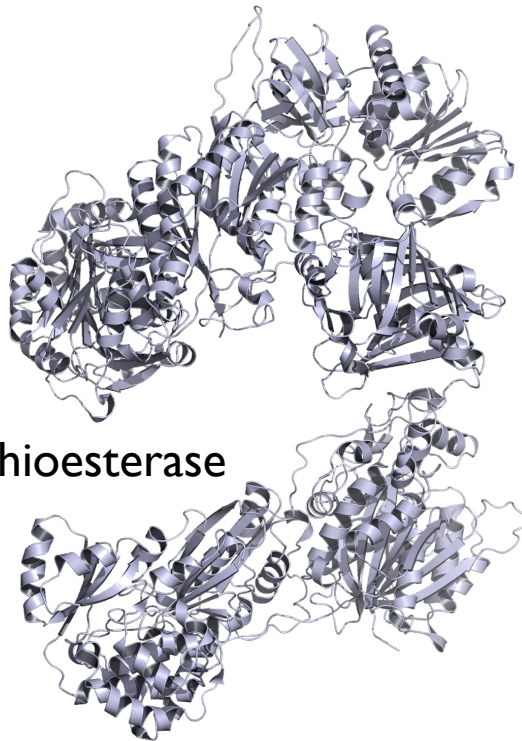


5) enoyl reductase



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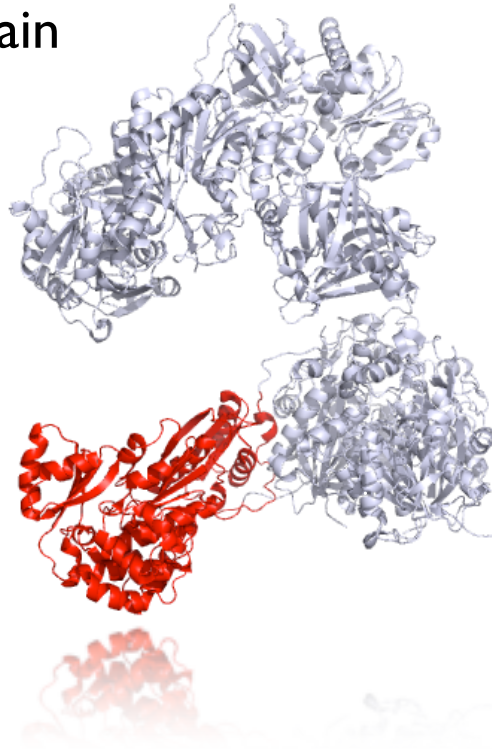
6) thioesterase



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malonyl transferase domain

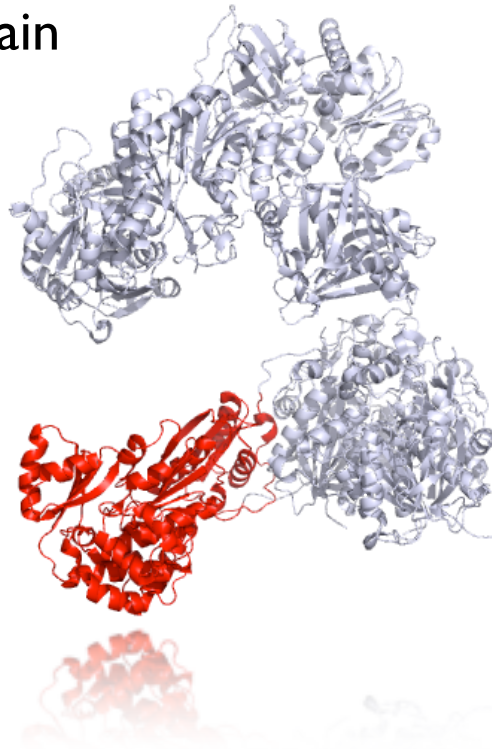
1. transfers short chain acyl-CoA to ACP domain
2. uses both acetyl-CoA and malonyl-CoA with equal efficiency
3. can also utilize propionyl-CoA to form odd-length fatty acids



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malonyl transferase domain

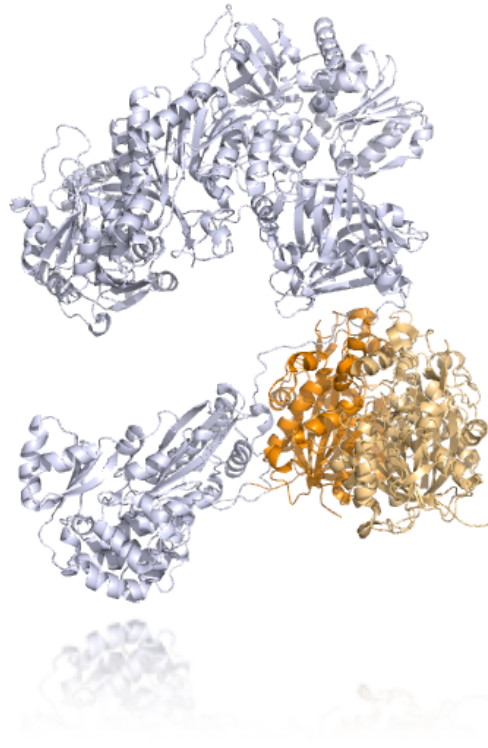
If malonyl transferase really can't distinguish between acetyl-CoA and malonyl-CoA, what happens if it binds and transfers several acetyl-CoA's in succession to ACP, instead of malonyl-CoA?



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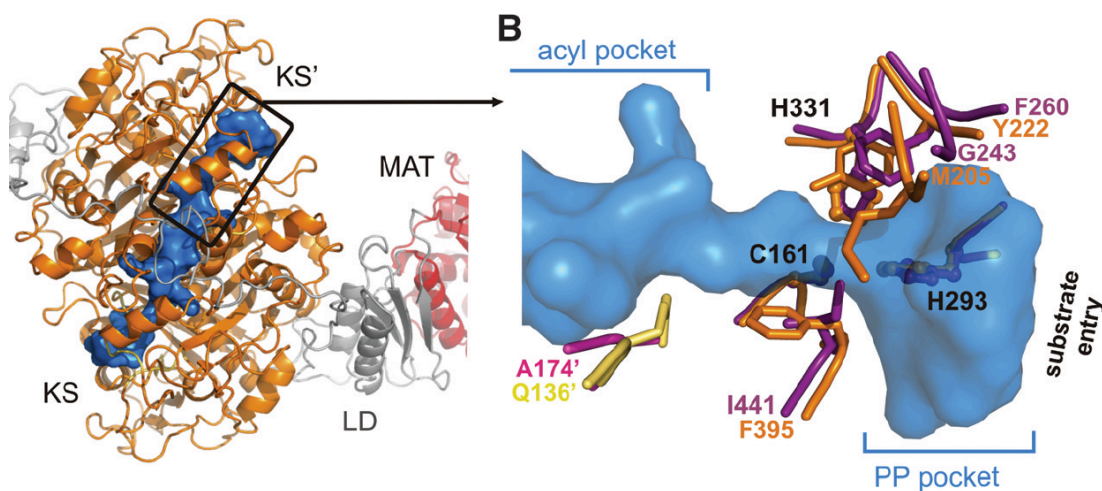
3-Ketoacyl-ACP-synthase

1. catalyzes the committed step in **acyl chain elongation**, but is not rate-limiting for **fatty acid synthesis** (acetyl CoA carboxylase)
2. somehow measures the growing chain and terminates elongation at 16 carbons.

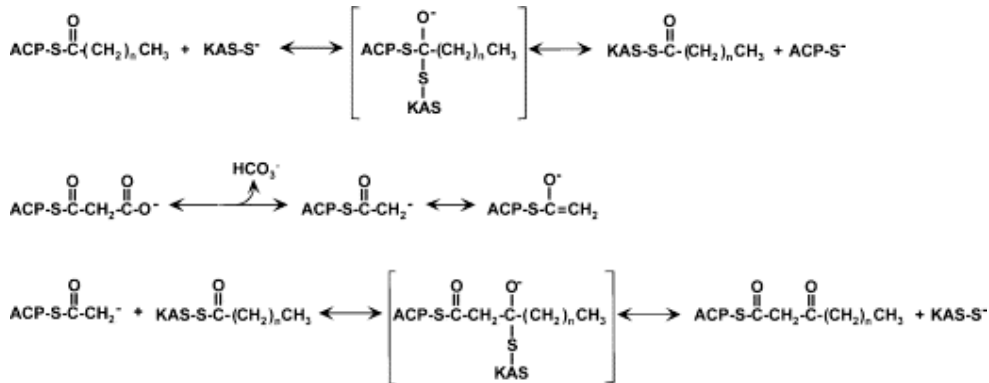


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The deep pocket within ketoacyl synthase, in combination with thioesterase, are postulated to limit acyl chain length synthesis to 16 carbons



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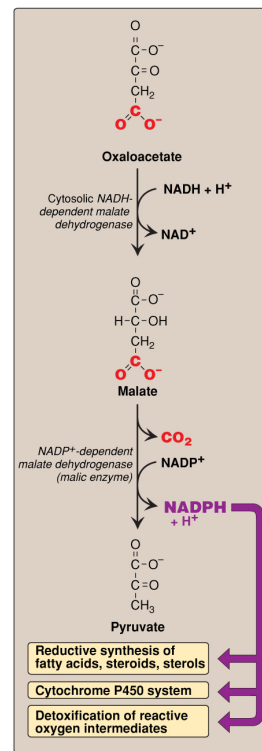
Summary of fatty acid synthesis

8 acetyl CoA + 14 NADPH + 14 H⁺ + 7 ATP



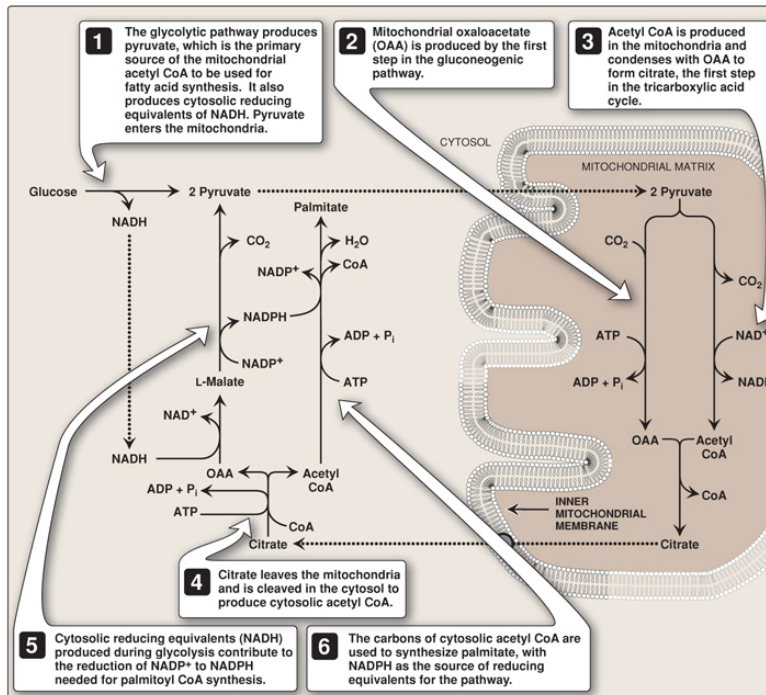
palmitic acid (16:0) + 8 CoA + 14 NADP⁺ + 7 ADP + 7 Pi + 7 H₂O

- I. The major suppliers of NADPH for fatty acid synthesis are:
 - a) the hexose monophosphate shunt
 - b) cytoplasmic malate dehydrogenase



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Summary of fatty acid synthesis



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1. Additional two-carbon units can be added to palmitate by separate enzyme systems contained in the ER and mitochondria.
2. Certain cell types in the brain can add up to a total of 24 carbon units to an acyl chain
3. Enzymes present in the ER (mixed-function oxidases) are responsible for desaturating fatty acids using NADPH as a cofactor

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1: [Subcell Biochem.](#) 2008;49:169-194.

Fatty Acid Synthase Activity in Tumor Cells.

[Little JL](#), [Kridel SJ](#).

While normal tissues are tightly regulated by nutrition and a carefully balanced system of glycolysis and fatty acid synthesis, tumor cells are under significant evolutionary pressure to bypass many of the checks and balances afforded normally. Cancer cells have high energy expenditure from heightened proliferation and metabolism and often show increased lipogenesis. Fatty acid synthase (FASN), the enzyme responsible for catalyzing the ultimate steps of fatty acid synthesis in cells, is expressed at high levels in tumor cells and is mostly absent in corresponding normal cells. Because of the unique expression profile of FASN, there is considerable interest not only in understanding its contribution to tumor cell growth and proliferation, but also in developing inhibitors that target FASN specifically as an anti-tumor modality. Pharmacological blockade of FASN activity has identified a pleiotropic role for FASN in mediating aspects of proliferation, growth and survival. As a result, a clearer understanding of the role of FASN in tumor cells has been developed.

PMID: 18751912 [PubMed - as supplied by publisher]