Lipid Metabolism

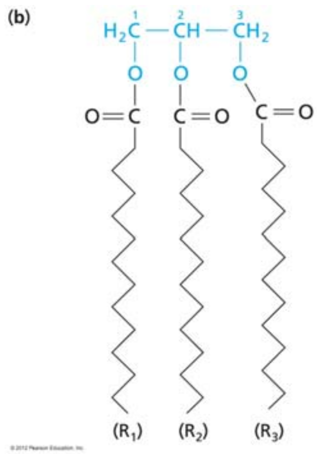
Pratt & Cornely, Chapter 17

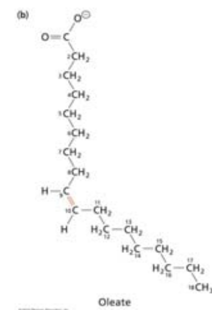
Catabolism Overview

- Lipids as a fuel source from diet
- Beta oxidation
  - Mechanism
  - ATP production
- Ketone bodies as fuel

TAG and FA

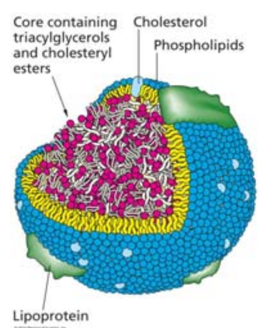
- High energy
  - More reduced
  - Little water content
  - 9 Cal/g vs 4 Cal/g for carbs
- Unsaturated FA
- Glycerol





Digestion

- Cross from intestine into bloodstream



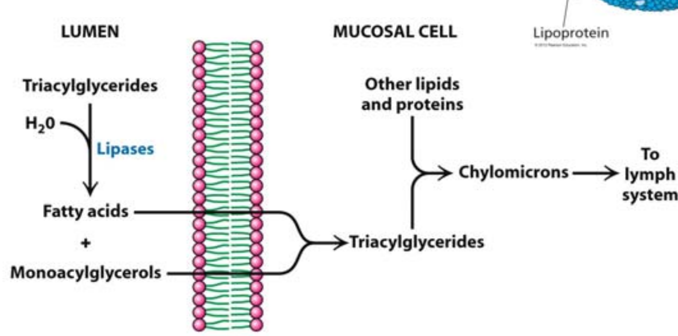


Figure 22.5
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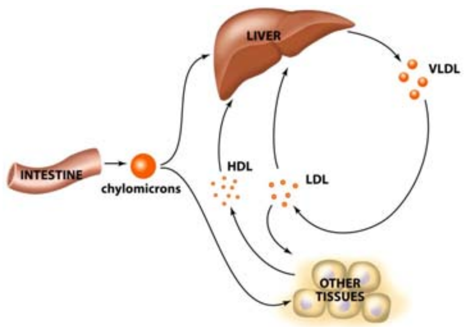
Lipoprotein Metabolism

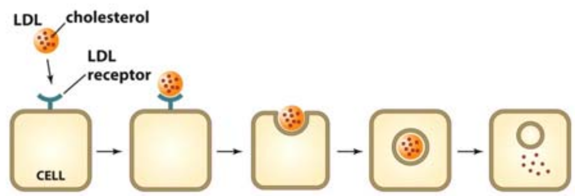


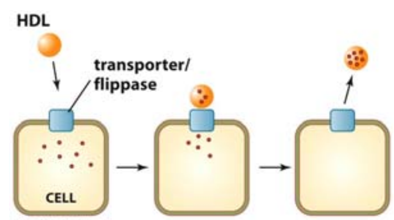
- Liver is the packaging center
- VLDL are sent out of liver
- Constant cycling of LDL in blood
- Genetic cholesterol problem: no LDL receptors in non-liver cells
- HDLs are "good cholesterol"

[TABLE 17-1] Characteristics of Lipoproteins

Lipoprotein	Diameter (Å)	Density ($g \cdot cm^{-3}$)	% Protein	% Triacylglycerol	% Cholesterol and Cholesteryl Ester
Chylomicrons	1000–5000	<0.95	1–2	85–90	4–8
VLDL	300–800	0.95–1.006	5–10	50–65	15–25
IDL	250–350	1.006–1.019	10–20	20–30	40–45
LDL	180–250	1.019–1.063	20–25	7–15	45–50
HDL	50–120	1.063–1.210	40–55	3–10	15–20

Role of LDL and HDL





Utilization Stage 1: Mobilization

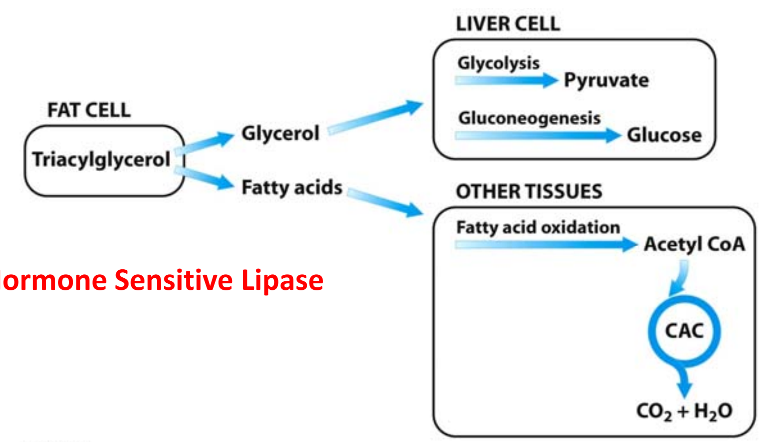


Figure 22.7
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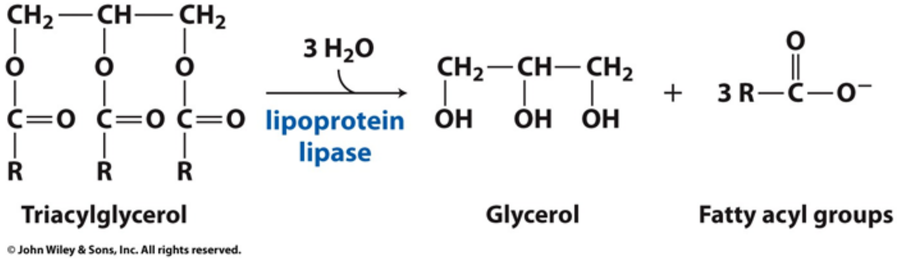
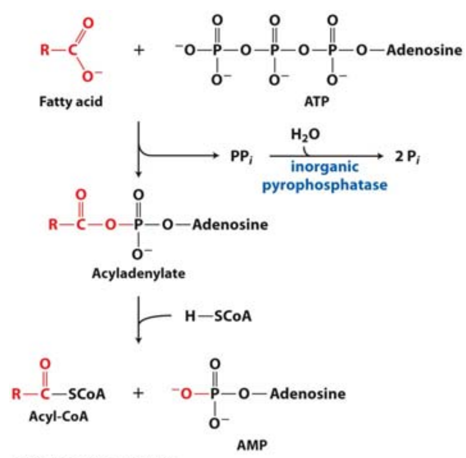
Hormone Sensitive Lipase



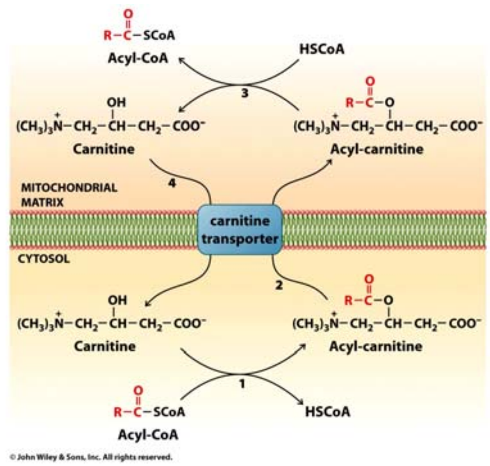
Utilization Stage 2: Activation and Transport into Matrix

- FA must be attached to CoA
- High energy bond
- Costs ATP→ AMP (2 ATP equivalents)



Utilization Stage 2: Transport into Matrix

- Matrix is site of fatty acid breakdown
  - Goes into citric acid cycle
- Carnitine ester: another high energy bond
- Transporter: Major site of regulation of FA degradation

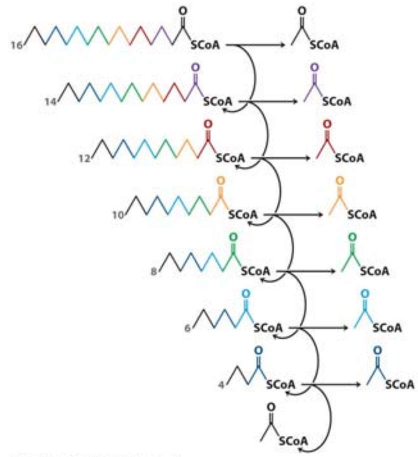


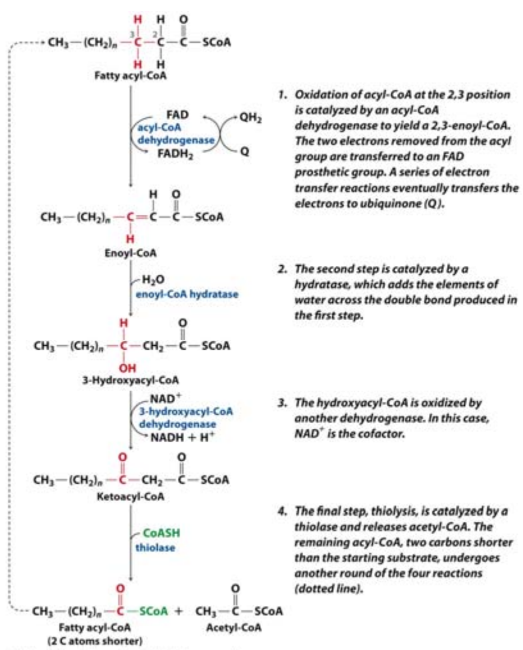
Problem 7

- A deficiency of carnitine results in muscle cramps, which are exacerbated by fasting or exercise. Give a biochemical explanation for the muscle cramping, and explain why cramping increases during fasting and exercise.

Utilization Stage 3: Beta Oxidation

- Four step process
- Production of
  - QH_2
  - NADH
  - Acetyl CoA

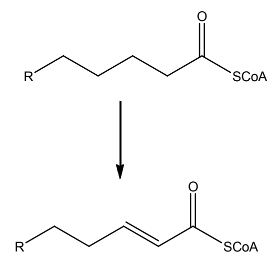




Steps 1-3 are analogous to…

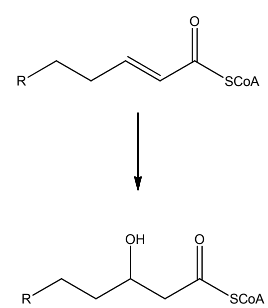
Step 1: Acyl CoA Dehydrogenase

- Similar to succinate DH from citric acid cycle
- Prosthetic $FAD/FADH_2$
- High energy electrons passed on to QH_2
- 1.5 ATP



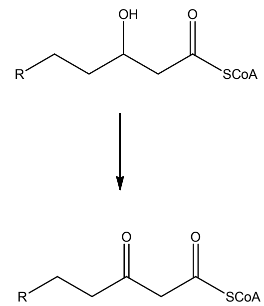
Step 2: Enoyl CoA Hydratase

- Similar to fumarate hydratase from citric acid cycle
- Addition of water
- No energy cost/production



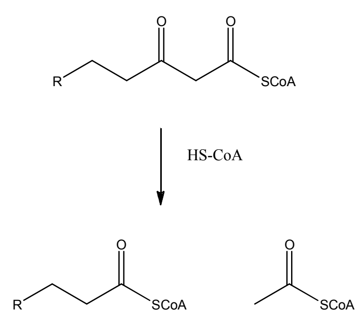
Step 3: 3-hydroxyacyl CoA DH

- Similar to malate DH from citric acid cycle
- Oxidation of secondary alcohol to ketone
- NADH production
- 2.5 ATP



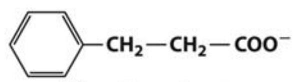
Step 4: Thiolase

- CoA is used as a nucleophile in a “nucleophilic acyl substitution”
- FA shortened by 2 carbons
- Acetyl CoA produced

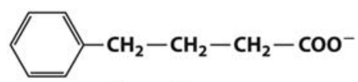


Problem 13

- The β-Oxidation pathway was elucidated in part by Franz Knoop in 1904. He fed dogs fatty acid phenyl derivatives and then analyzed their urine for the resulting metabolites. What metabolite was produced when dogs were fed



Phenylpropionate



Phenylbutyrate

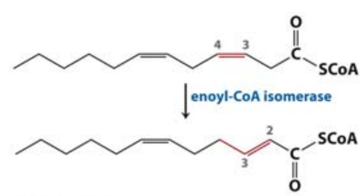
One round of β oxidation	*Citric acid cycle*	*Oxidative phosphorylation*
1 QH_2 →		1.5 ATP
1 NADH →		2.5 ATP
1 Acetyl-CoA →	3 NADH →	7.5 ATP
	1 QH_2 →	1.5 ATP
	1 GTP →	1 ATP
	Total	14 ATP

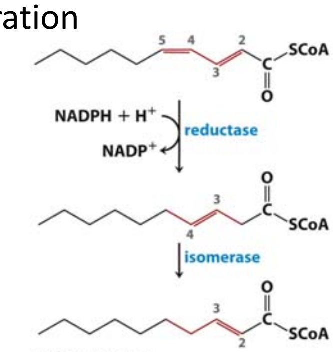
ATP Accounting

- How much ATP is netted from palmitate (16 carbon fatty acid)?
  - Cost 2 ATP to activate to palmitate CoA
  - Run through beta oxidation SEVEN times
    - 7 QH2 = 10.5 ATP
    - 7NADH = 17.5 ATP
  - 8 acetyl CoA produced = 80 ATP
- Total: 106 ATP, or 6.625 ATP per carbon
- Compare to glucose, which is 5.33 ATP per C

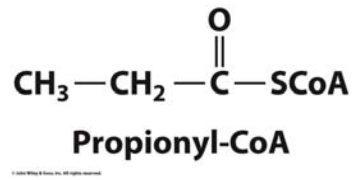
Processing Other FA

- Unsaturated and trans fatty acids
  - Trans is natural intermediate
  - Produce 1.5 ATP less for first unsaturation, 2.5 ATP less for second unsaturation

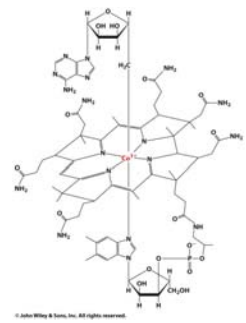




Processing Other FA

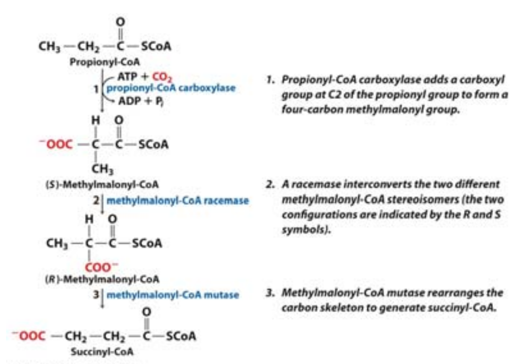


- Odd chain fatty acids
  - Rare, but do occur in diet
  - One of 2 requirements for Vitamin B_{12} (cobalamine) in human diet



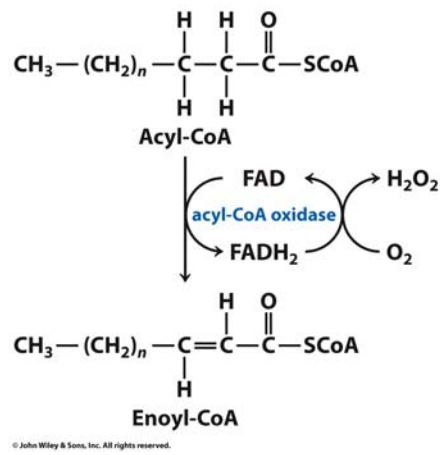
Production of Succinate

- Carboxylase (biotin)
- Rearrangement (vitamin B12-radical)
- Net glucose can be produced



Peroxisome

- Handles long fatty acids
  - Chain shortening
- Branched fatty acids
- Chemistry of first oxidation is different

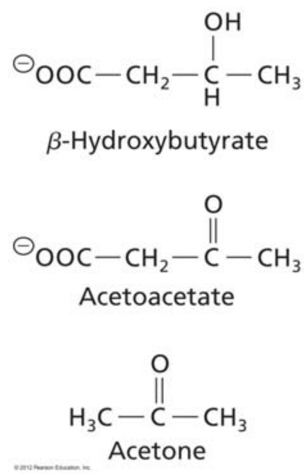


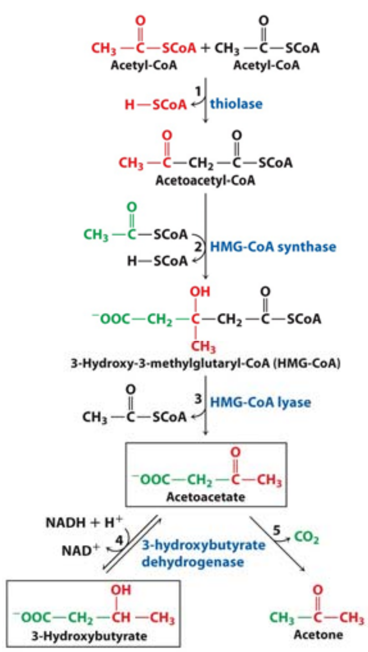
Alternate Fate of Acetyl CoA

- Fasting, Diabetes
  - Glycolysis is down, gluconeogenesis is up
  - Oxaloacetate depleted
  - Citric acid cycle has diminished capacity
  - Acetyl CoA levels build up
- Ketone bodies are formed

Ketone Bodies

- Water soluble form of lipids
- Less potential energy than FA
- Main energy source of brain in starvation
- Also used in muscle and intestine





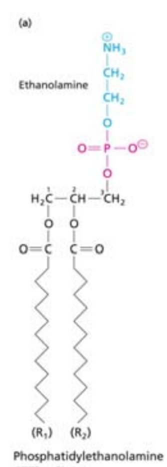
1. *Two molecules of acetyl-CoA condense to form acetoacetyl-CoA. The reaction is catalyzed by a thiolase, which breaks a thioester bond.*
2. *The four-carbon acetoacetyl group condenses with a third molecule of acetyl-CoA to form the six-carbon 3-hydroxymethylglutaryl-CoA (HMG-CoA).*
3. *HMG-CoA is then degraded to the ketone body acetoacetate and acetyl-CoA.*
4. *Acetoacetate undergoes reduction to produce another ketone body, 3-hydroxybutyrate.*
5. *Some acetoacetate may also undergo nonenzymatic decarboxylation to acetone and CO_2.*

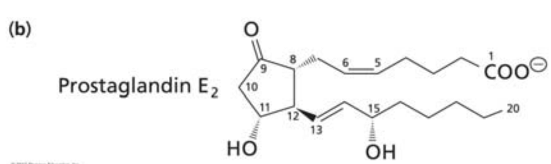
Anabolism Overview

- Fatty acid synthesis
- Fatty acid synthesis regulation
- Cholesterol

Biosynthesis of Lipids

- Triacylglyerides as fuels
- Glycerophospholipids in membrane
- Prostaglandins as signal molecules
- Cholesterol and derivatives

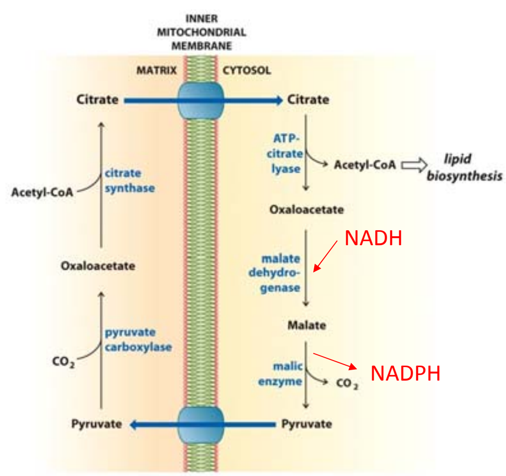




Fatty Acid Synthesis

- Opposite of beta oxidation in the sense that 2-carbon acetate units are linked to form even-chain, saturated fatty acids
- Differs from Fatty acid degradation
  - In cytoplasm, not matrix
  - Acyl carrier protein rather than CoA
  - Enzymes linked in a complex
  - Utilizes NADPH
  - Energetically linked to ATP hydrolysis

Transport to Cytoplasm



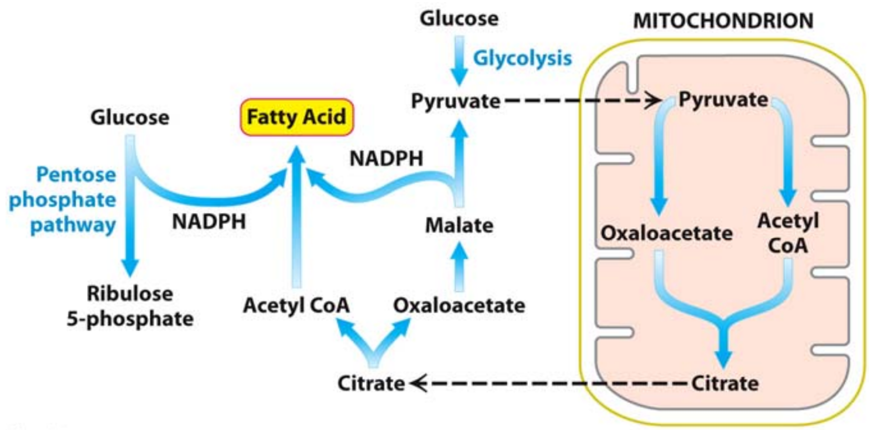


Figure 28.2
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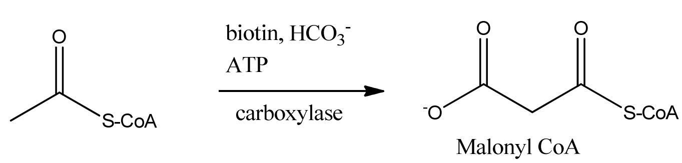
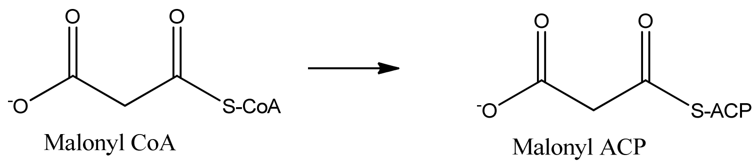
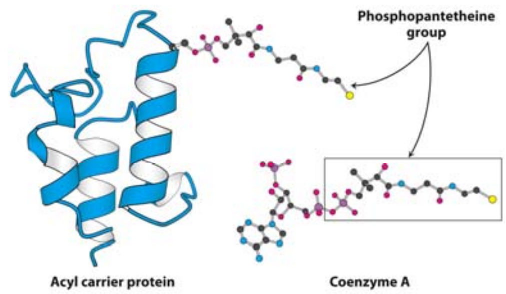
Activation of Acetyl Group

- Acetyl CoA carboxylase (analogous to pyruvate carboxylase of gluconeogenesis)
- Requires biotin, ATP
- A regulation step—shifts fuel away from CAC



Transfer to Acyl Carrier Protein





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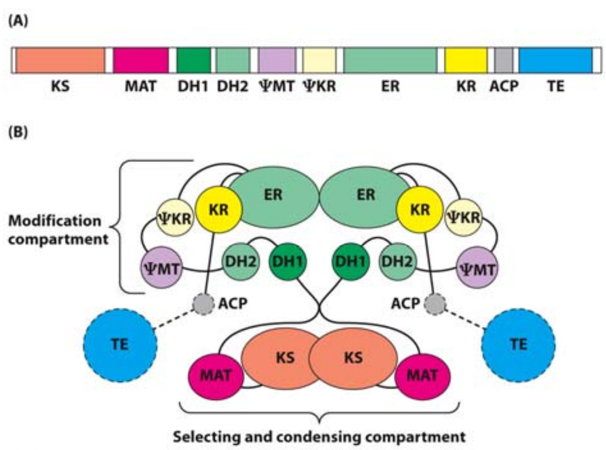
Multifunctional Enzyme: Fatty Acid Synthase



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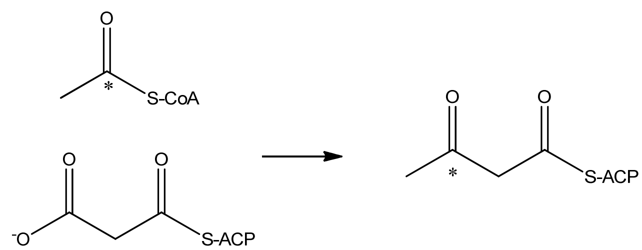
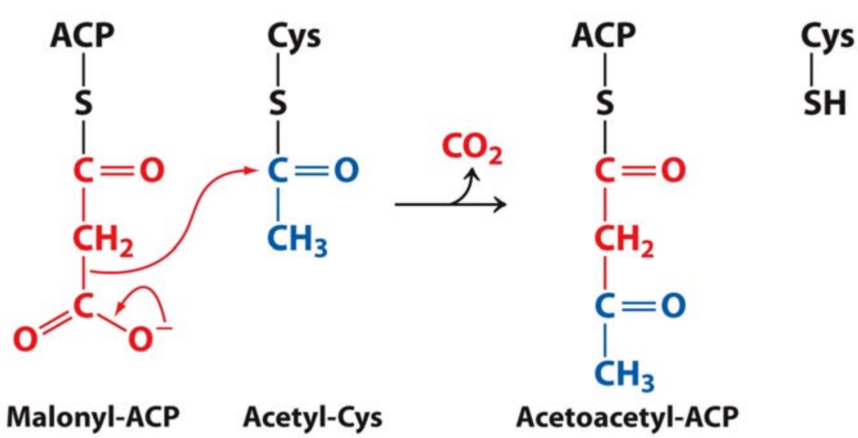
Four Step Elongation

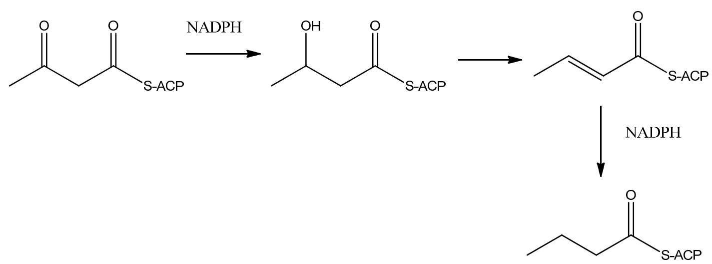
- Step 1: Condensation
  - Loss of CO_2 drives reaction to completion
  - All happens on enzyme complex
  - Mechanism:





Steps 2-4: Opposite of beta Oxidation

- Input of 2 NADPH
- Major use of PPP



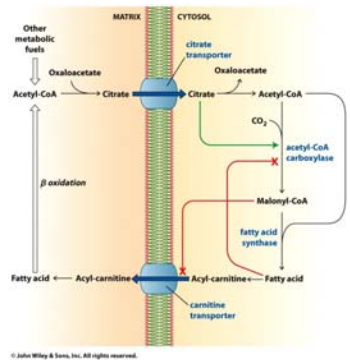
Synthesis of Palmitate

$$\text{Acetyl CoA} + 7\ \text{Malonyl CoA} + 14\ \text{NADPH} + 20\,\text{H}^{\oplus} \longrightarrow$$
$$\text{Palmitate} + 7\ CO_2 + 14\ \text{NADP}^{\oplus} + 8\ \text{HS–CoA} + 6\ H_2O$$

- 16-carbon fatty acid produced in major synthesis complex
- **Problem 31:** What is the ATP cost of synthesizing palmitate from acetyl-CoA?

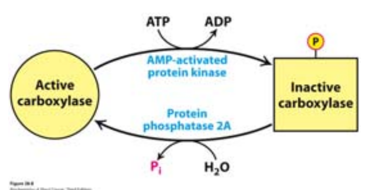
Regulation

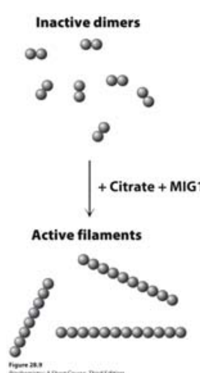
- Logic of Regulation
  - **Acetyl CoA carboxylase**
    - Citrate is acetyl CoA equivalent
    - Fatty Acid is feedback inhibition
  - **Carnitine Transporter**
    - Malonyl CoA

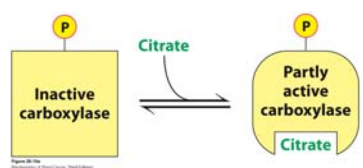


Regulation of AcetylCoA Carboxylase

- AMPK
- Citrate
- Hormone level







Explain this graph…

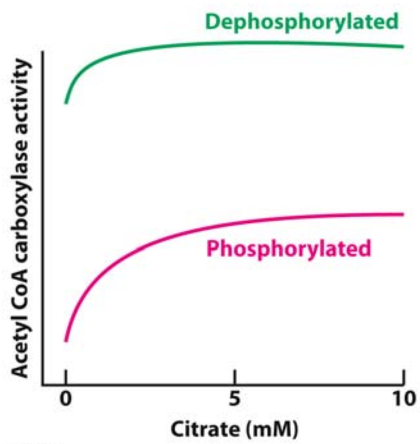


Figure 28.10b
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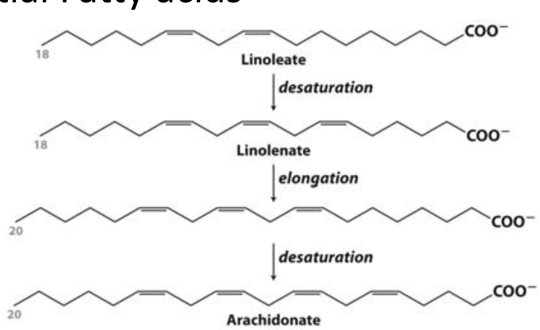
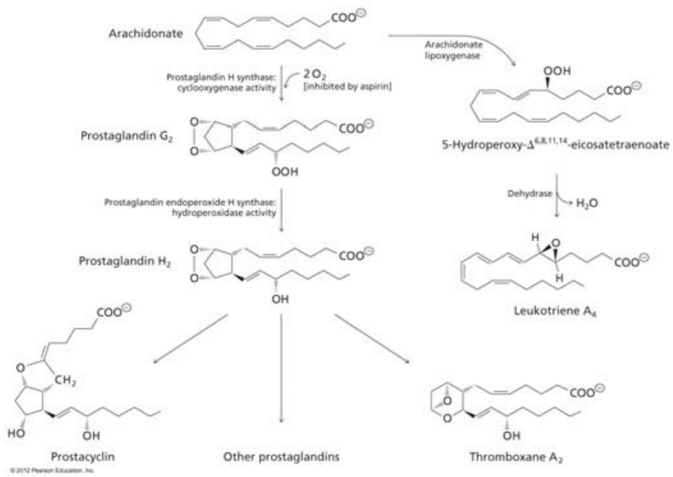
Post-synthesis Modification

- Elongations possible with other enzymes
- Many organisms can make odd-chain fatty acids
- Essential Fatty acids

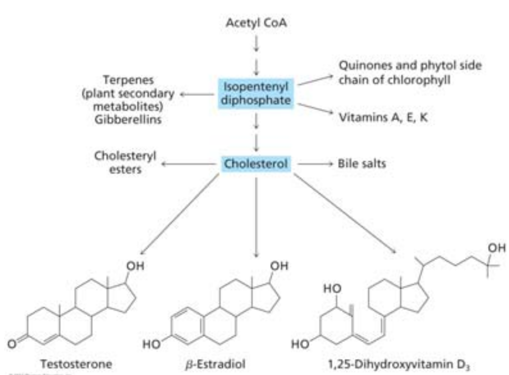


Prostaglandins and COX Inhibitors



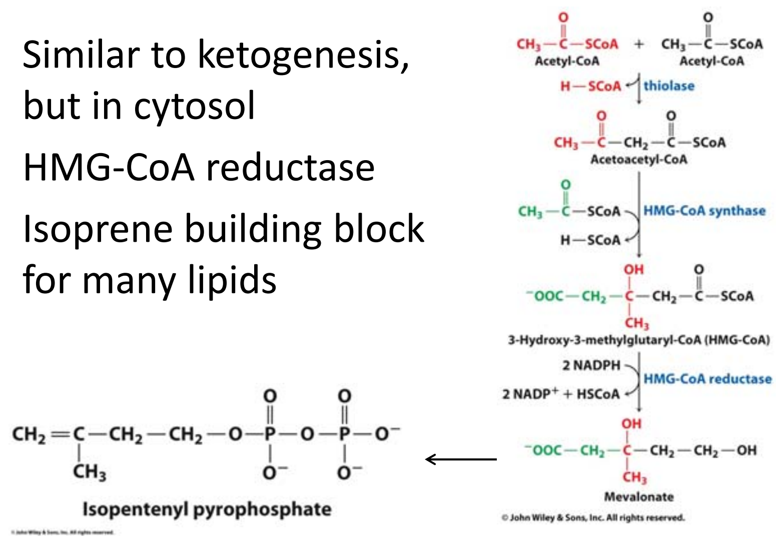
Cholesterol Biosynthesis

- Three Stages: Acetyl CoA→Isopentyl diphosphate→Squalene→Cholesterol

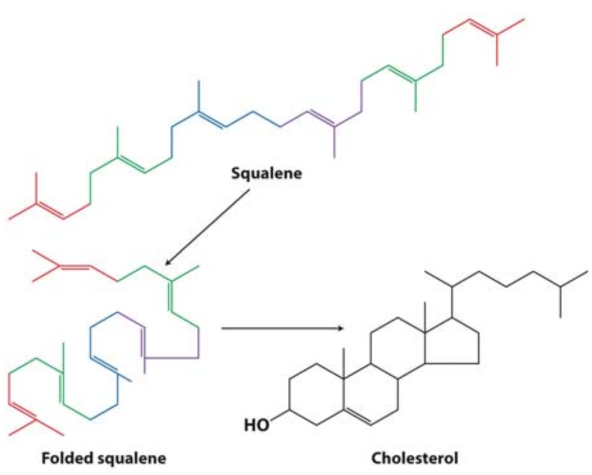


Stage 1

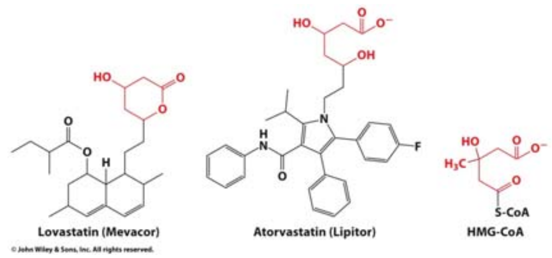
- Similar to ketogenesis, but in cytosol
- HMG-CoA reductase
- Isoprene building block for many lipids



Stages 2 and 3



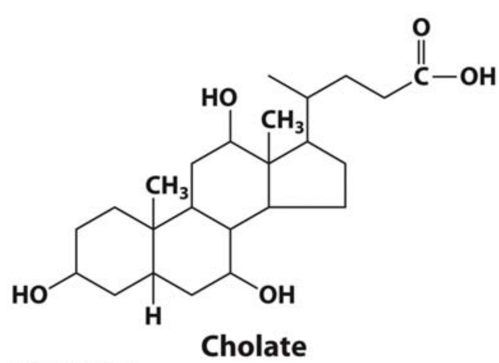
Medical Applications



- Statins inhibit HMG-CoA Reductase
- Problem: inhibits all steroid biosynthesis

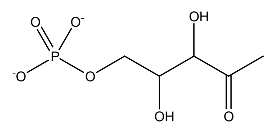
Medical Applications

- Another strategy for lowering cholesterol is to trap bile salts in intestine so that cholesterol is diverted

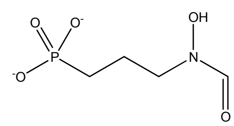


Medical Applications

- Parasites like malaria make isopentenyl diphosphate through a different mechanism
- A competitive inhibitor can selectively kill malaria



intermediate in cholesterol biosynthesis



competitive inhibitor