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Fatty Acid Synthesis

Overview of fatty acid biosynthesis

- Occurs in the cytosol of certain animal tissues; e.g., liver and mammary gland
- (Also occurs in plants and bacteria)
- Uses acetyl-CoA, NADPH as starting materials
- Produces a pool of palmitic acid (16:0) that can be further modified

Pathway Integration

✦Fatty acid synthesis requires the cooperation of several metabolic pathways.

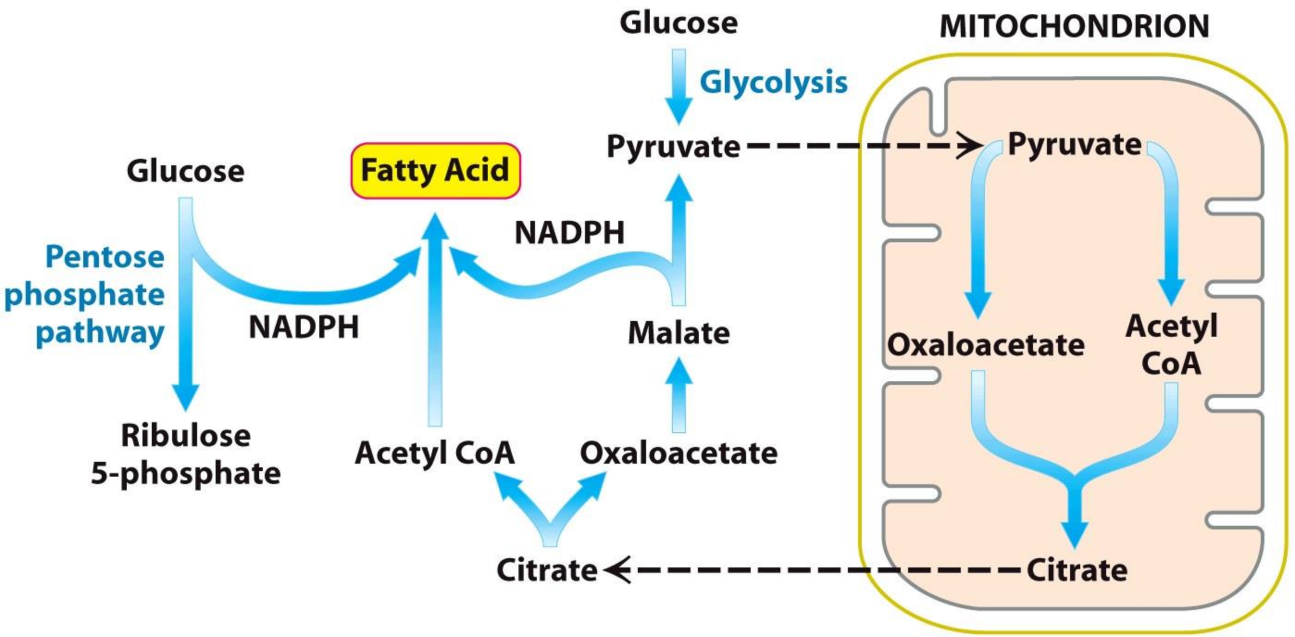


Figure 28.2
Biochemistry: A Short Course, Second Edition

Overlap with carbohydrate metabolism

- Excess carbs are transported to cytosol as citrate
- OA ends up back in the matrix
- Net result is acetyl-CoA in cytosol

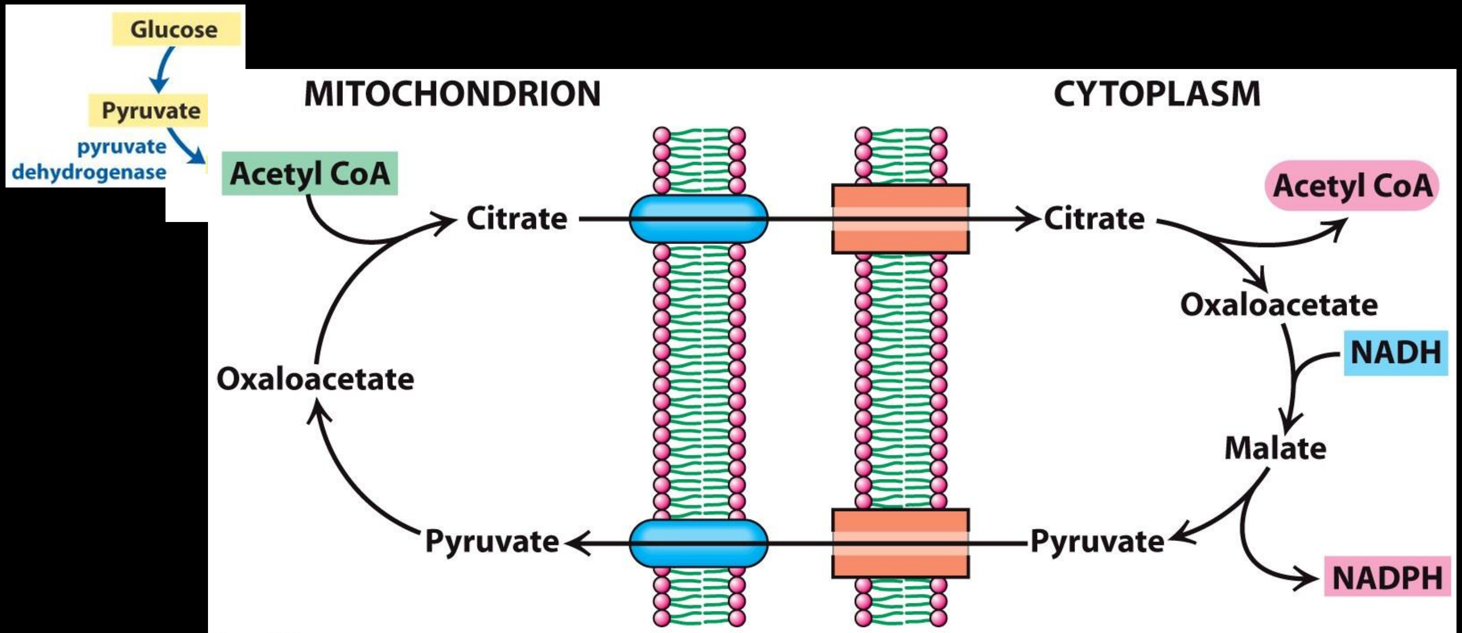


Figure 28.1
Biochemistry: A Short Course, Second Edition

Overlap with protein metabolism

- Amino acid degradation leads to acetyl-CoA or citrate
- Citrate is transported to cytosol
- Net result is acetyl-CoA in cytosol

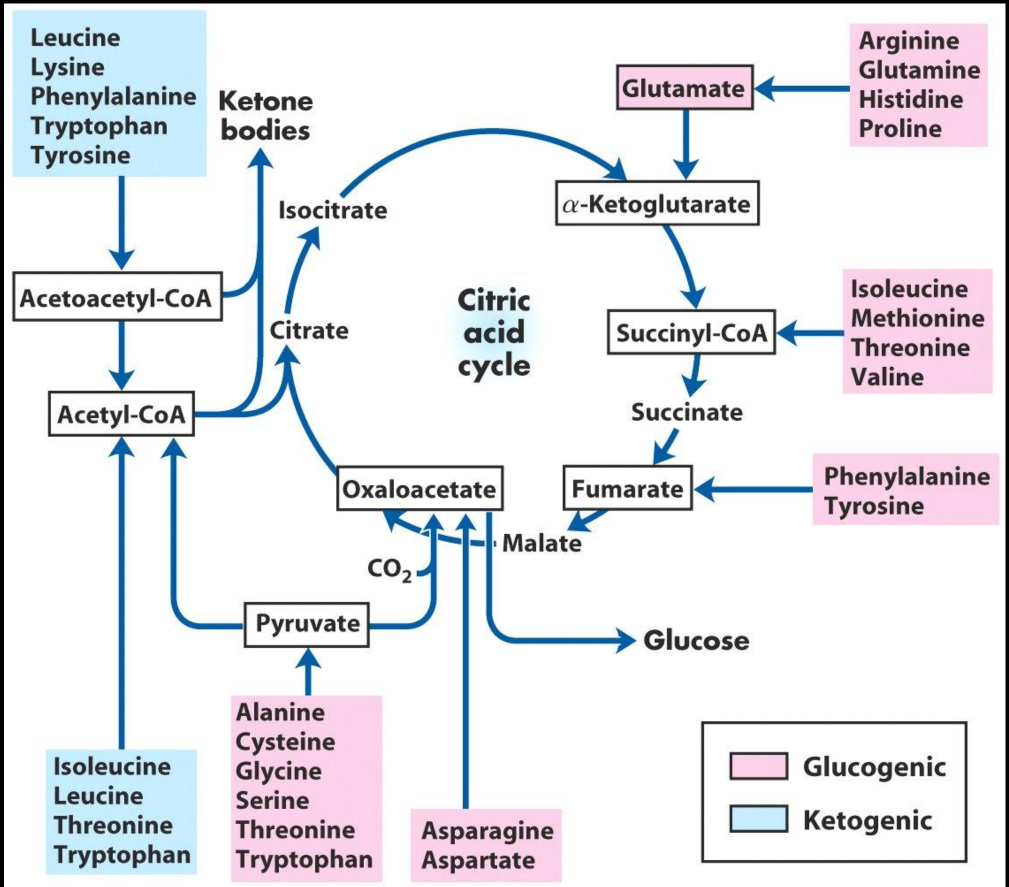
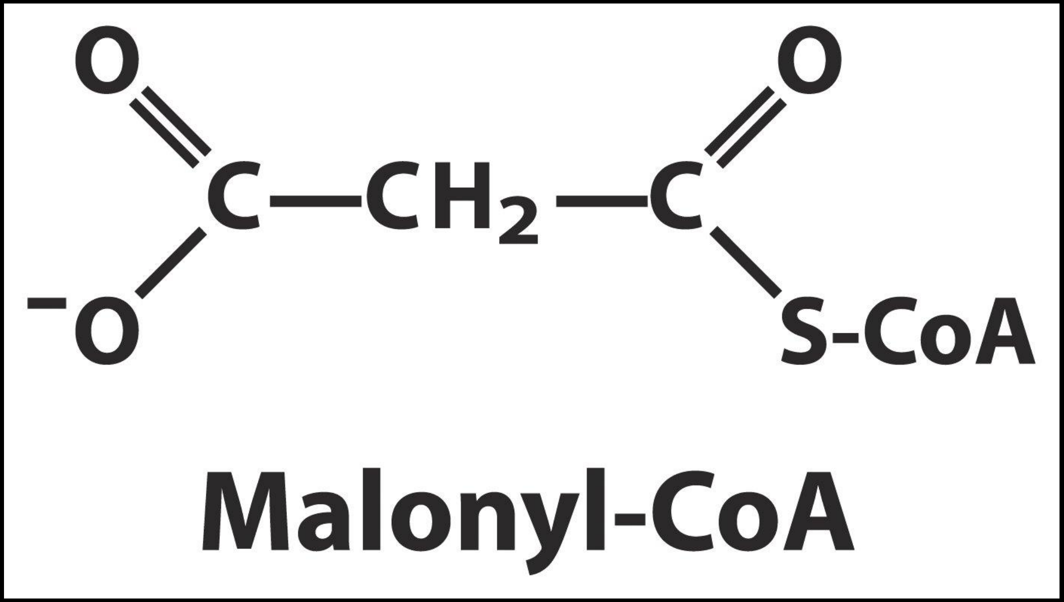


Fig 18-15

The intermediate: malonyl-CoA



- Malonyl-CoA is an “activated” form of acetyl-CoA used for fatty acid biosynthesis.

Formation of malonyl-CoA

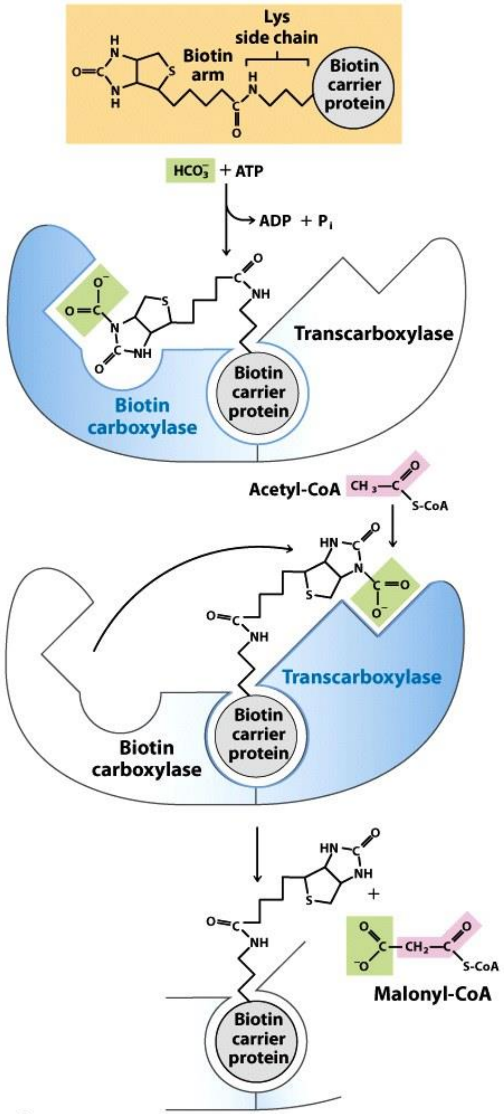


Figure 21-1
Lehninger Principles of Biochemistry, Fifth Edition

✦Acetyl-CoA carboxylase has three activities:

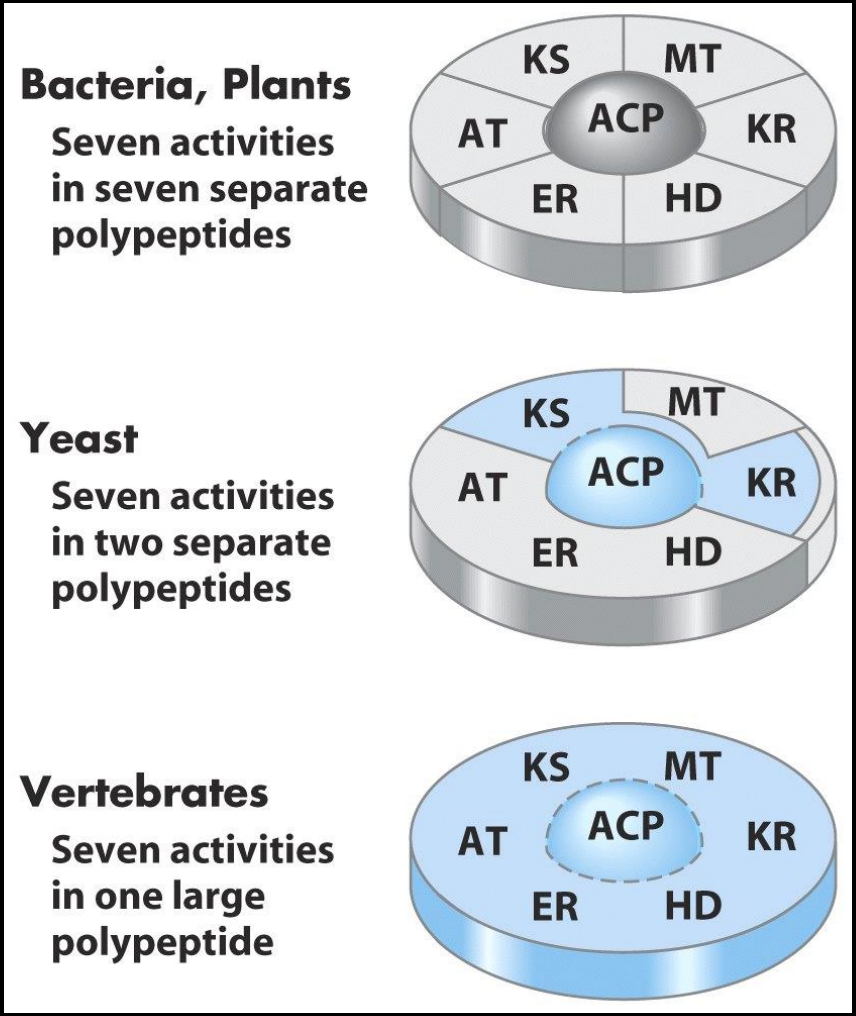
✓biotin carrier protein
✓biotin carboxylase
✓transcarboxylase

✦Bicarb is phosphorylated, then picked up by biotin

✦Biotin swinging arm transfers CO_2 to acetyl-CoA

Fatty acid synthase

- Fatty acid synthase has seven different enzyme activities



Fatty acid synthase

- Fatty acid synthase has seven different enzyme activities

- Adds two carbons every cycle through addition of malonyl-CoA and loss of CO_2

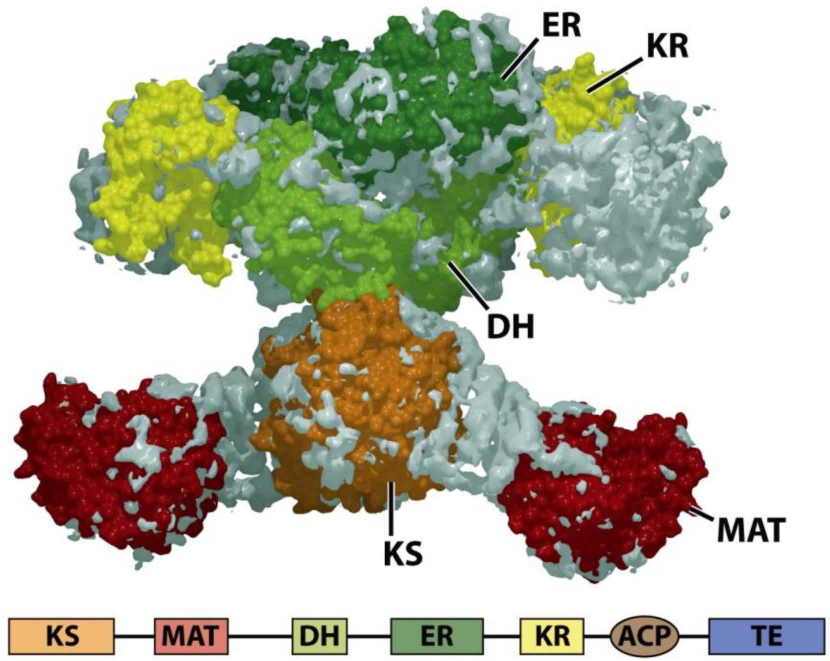


Figure 21-3a
Lehninger Principles of Biochemistry, Fifth Edition

Fatty acyl synthase

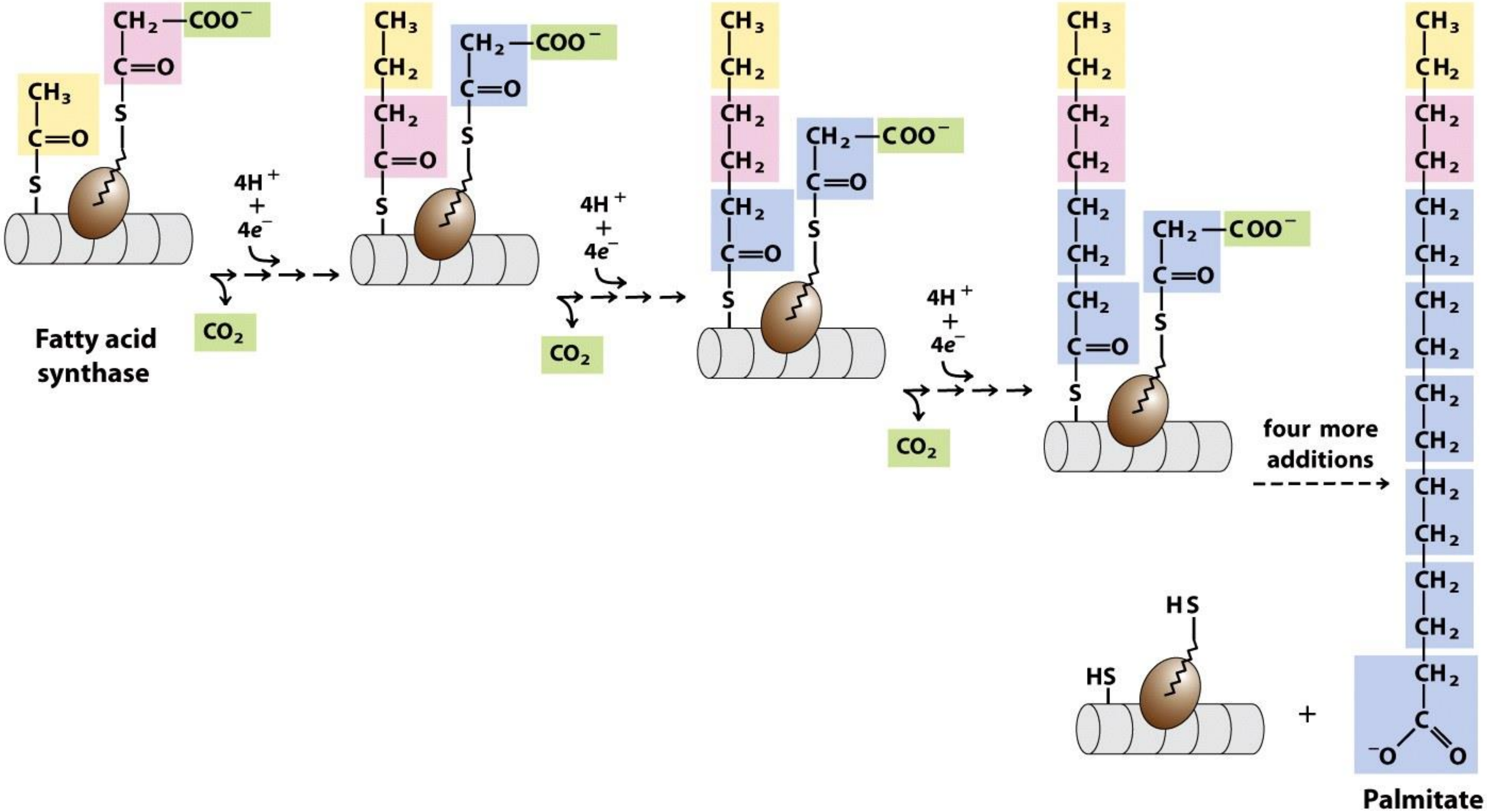
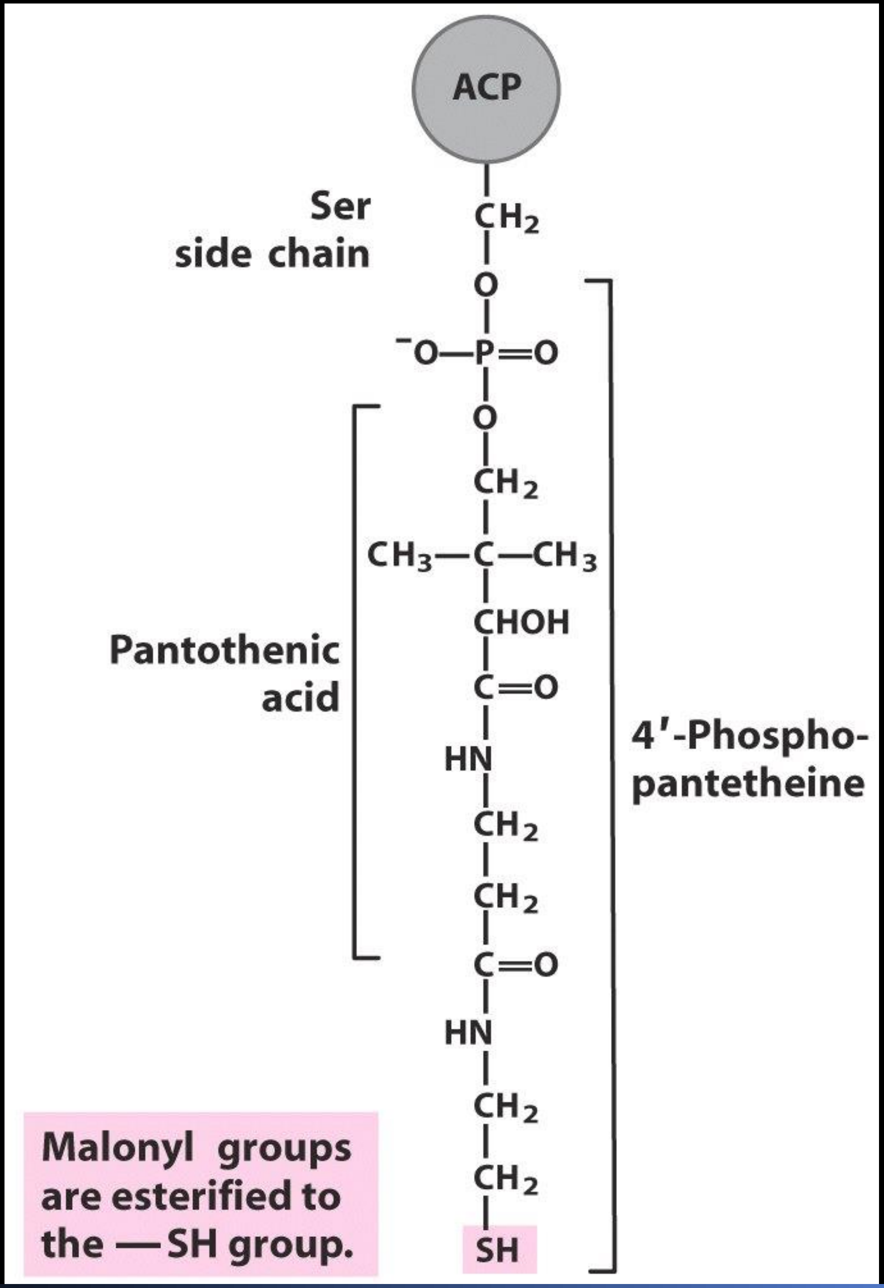


Figure 21-4
Lehninger Principles of Biochemistry, Fifth Edition

Key Player: acyl carrier protein



- “Macro” CoA, carries growing fatty acid chain via thioester

Initiation Stage

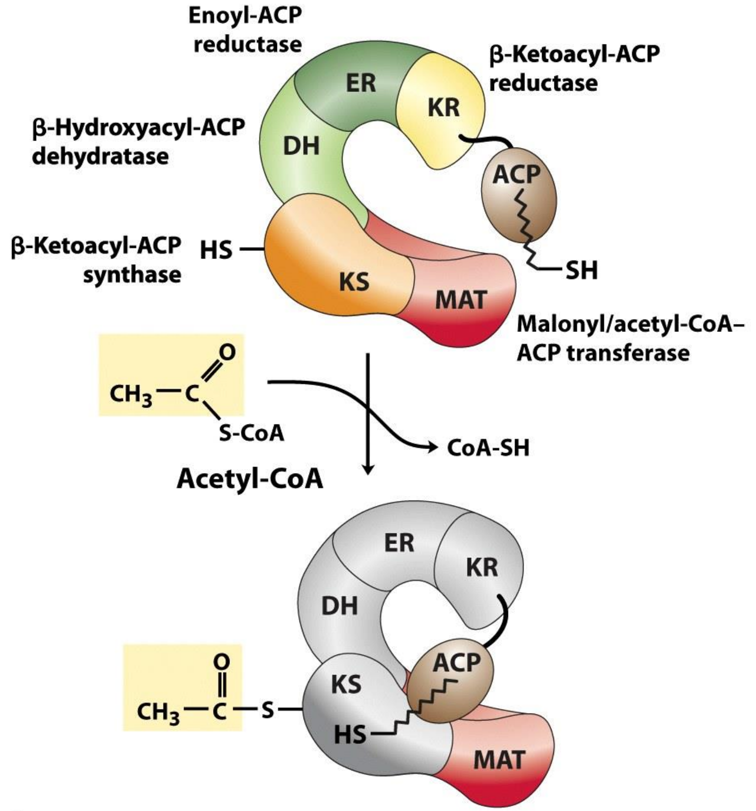


Figure 21-6 part 1
Lehninger Principles of Biochemistry, Fifth Edition

Step 1: loading of acetyl-CoA onto fatty acid synthase

Initiation Stage

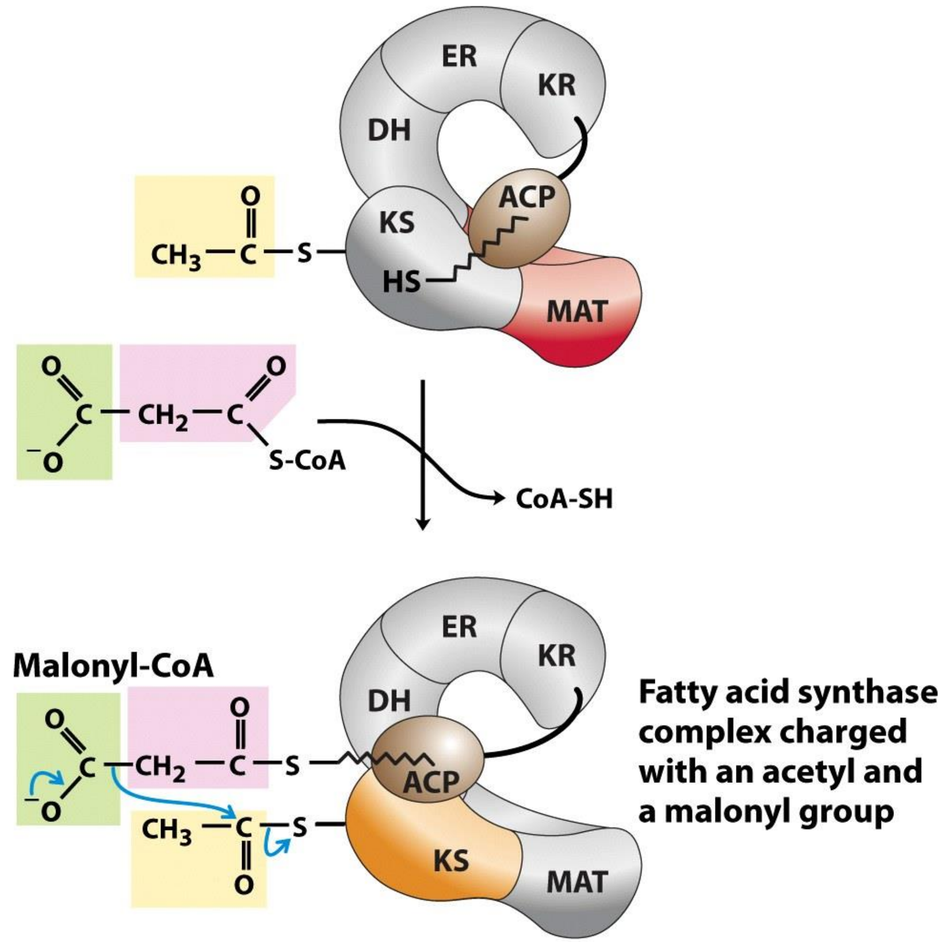
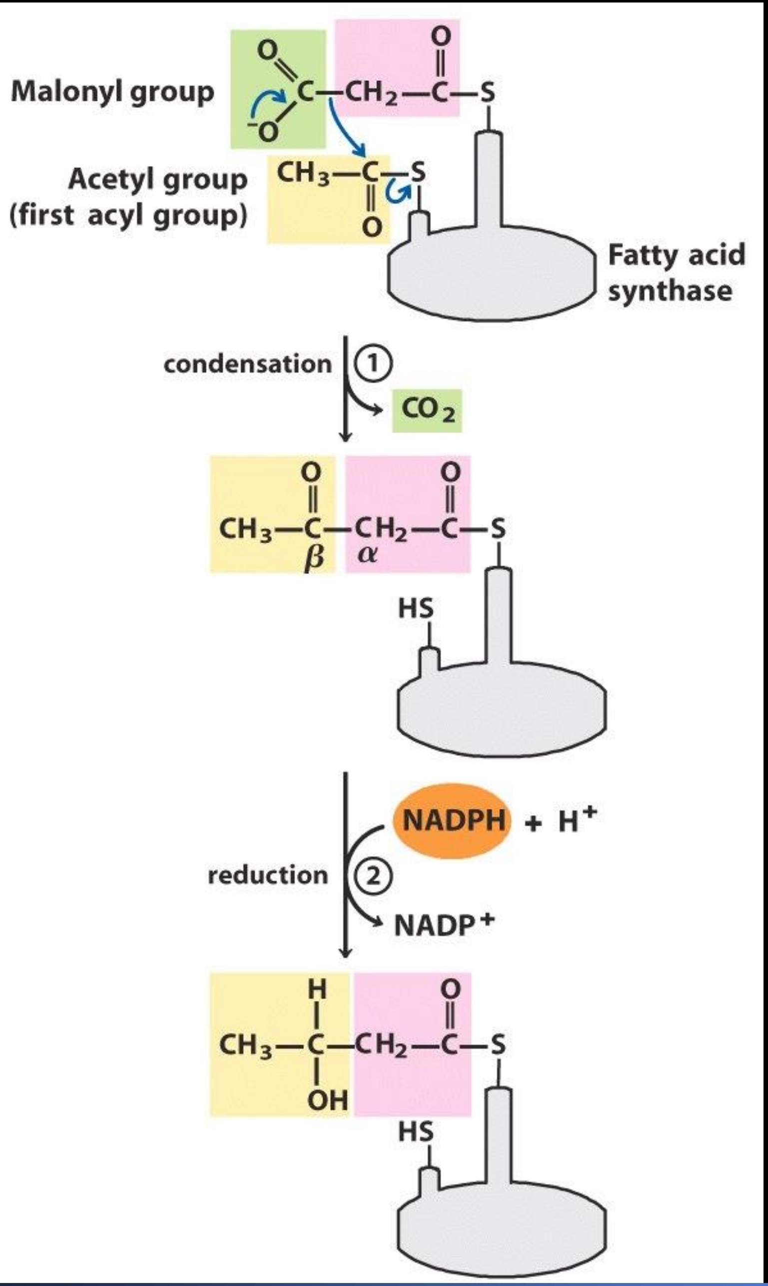


Figure 21-6 part 2
Lehninger Principles of Biochemistry, Fifth Edition

Step 2: loading of malonyl-CoA onto fatty acid synthase



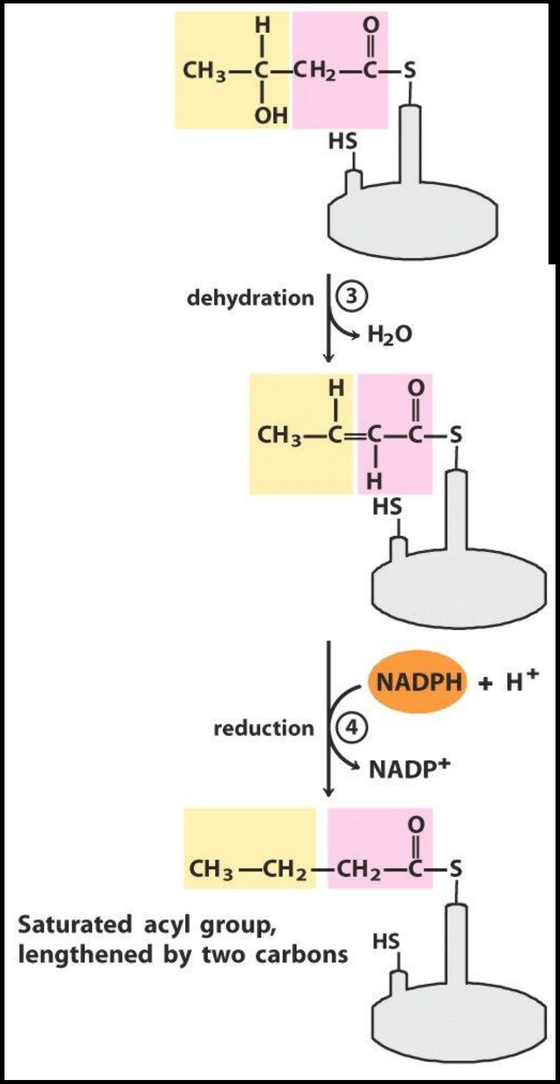
Overview of *Assembly Stage*

4 steps:

- ★Condensation
- ★Reduction
- ★Dehydration
- ★Reduction

Fig 21-2

Overview of Assembly Stage



4 steps:

★Condensation
★Reduction
★Dehydration
★Reduction

Fig 21-2

Step 1: Condensation

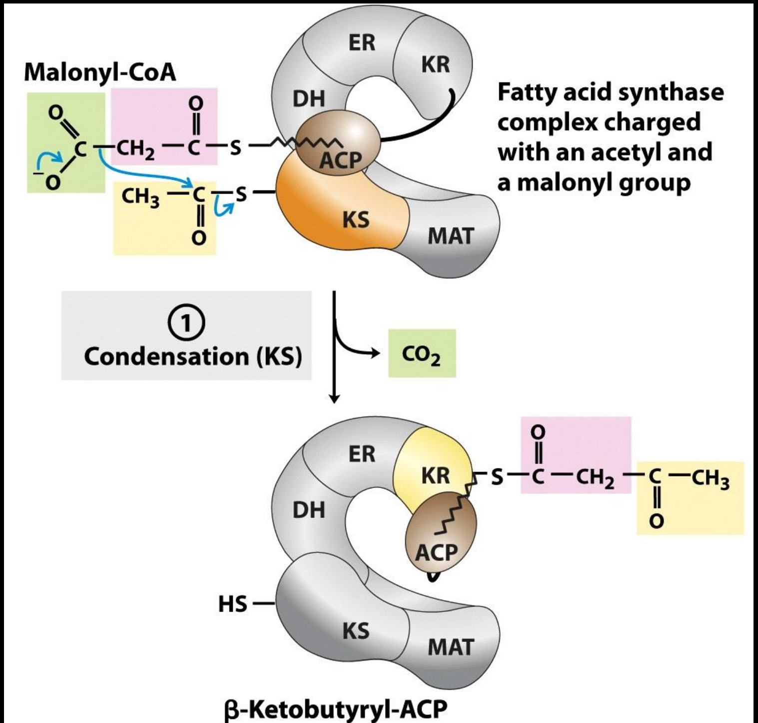


Figure 21-6 part 3
Lehninger Principles of Biochemistry, Fifth Edition

- ✓Reaction of malonyl group with acetyl group to form acetoacetyl-ACP
- ✓Loss of CO_2

Step 2: Reduction to alcohol

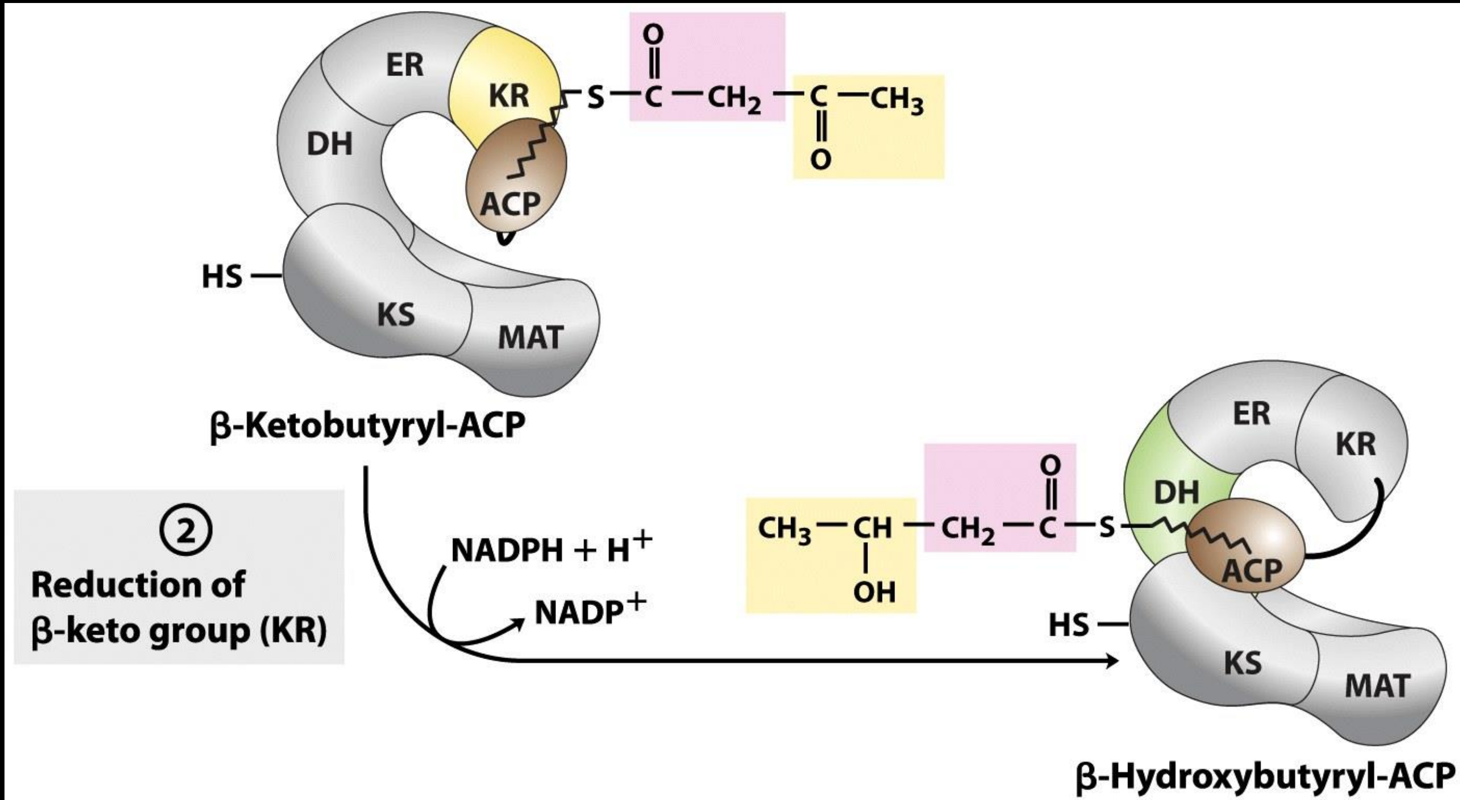


Figure 21-6 part 4
Lehninger Principles of Biochemistry, Fifth Edition

Step 3: Dehydration

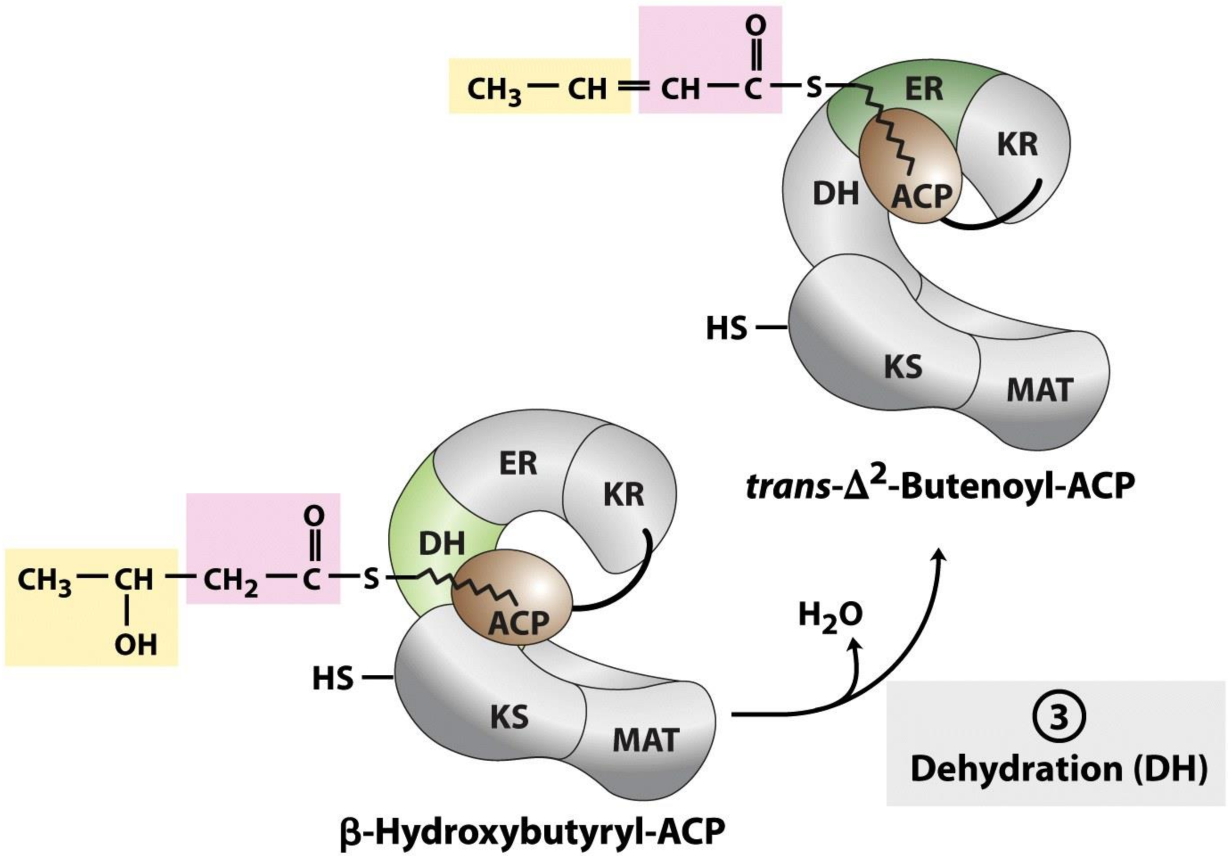


Figure 21-6 part 5
Lehninger Principles of Biochemistry, Fifth Edition

Step 4: Reduction of double bond

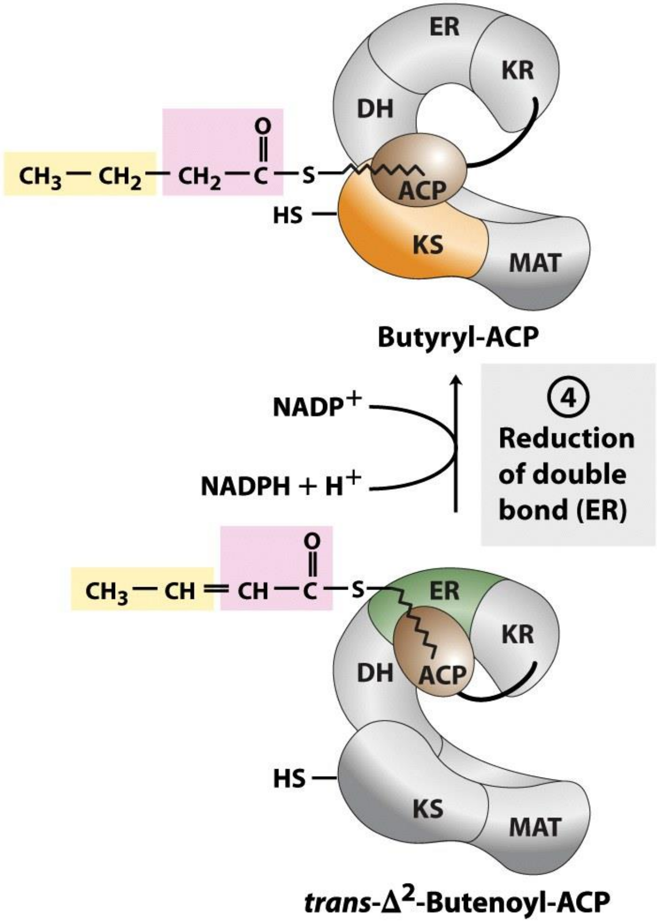


Figure 21-6 part 6
Lehninger Principles of Biochemistry, Fifth Edition

Transfer to KS

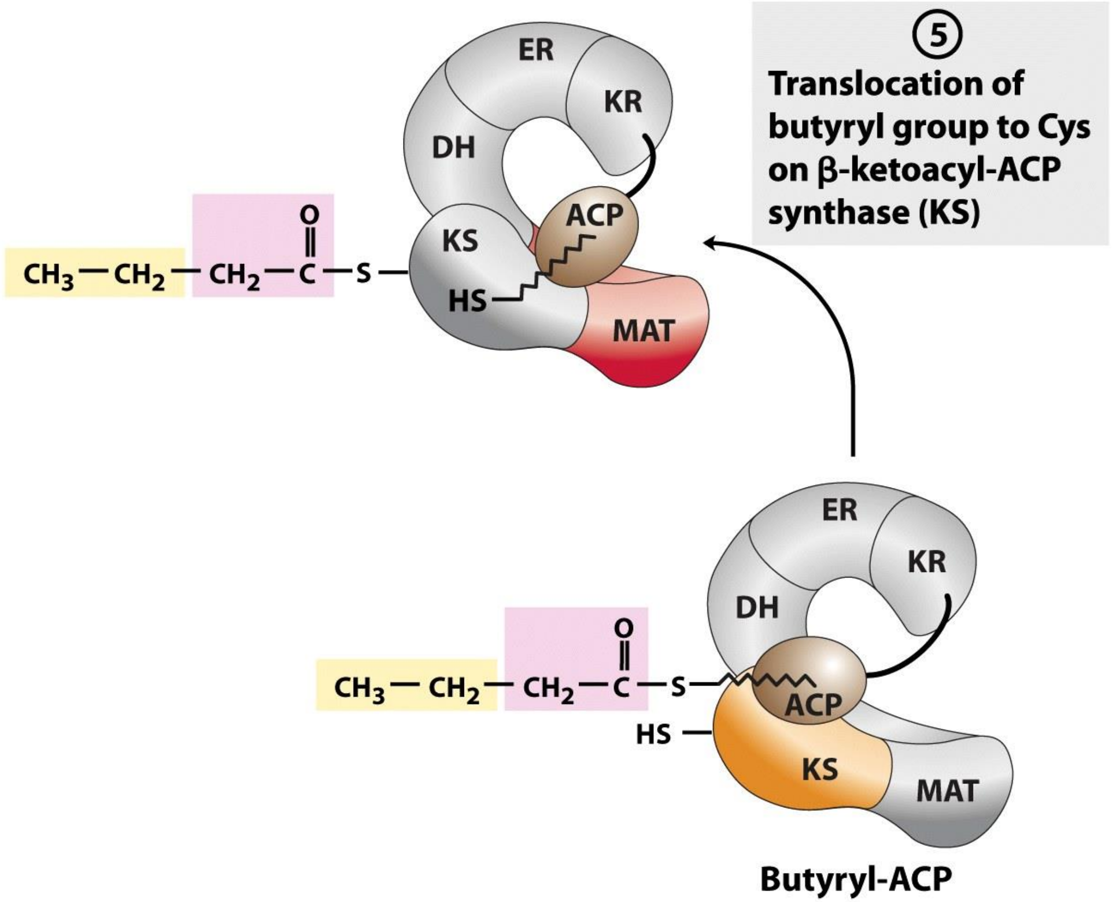


Figure 21-6 part 7
Lehninger Principles of Biochemistry, Fifth Edition

Next cycle begins

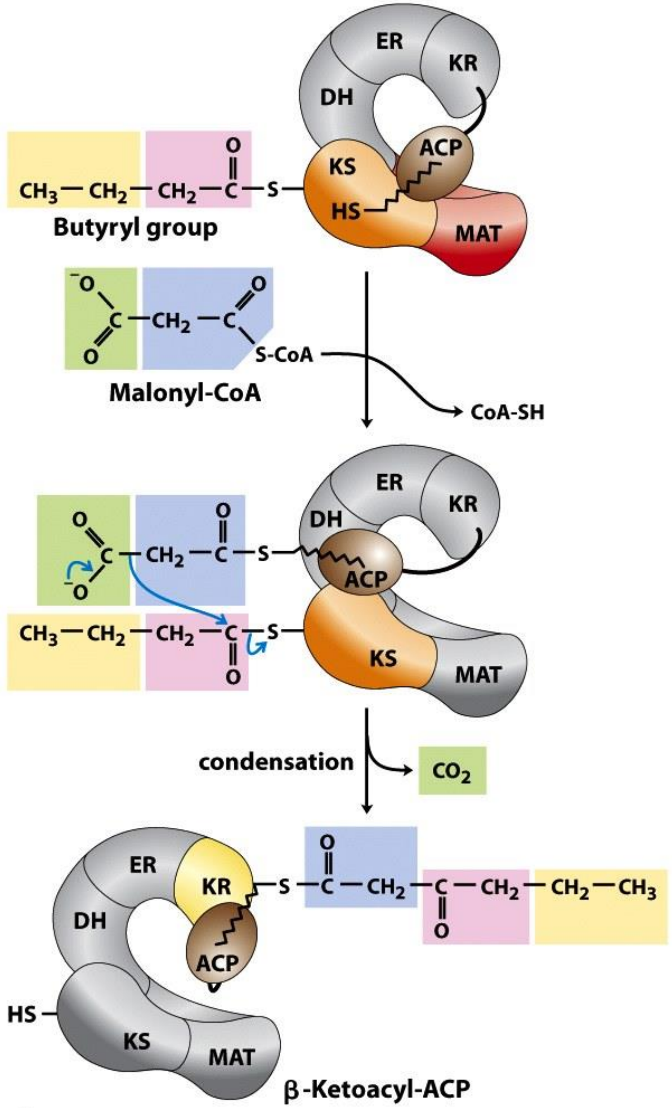
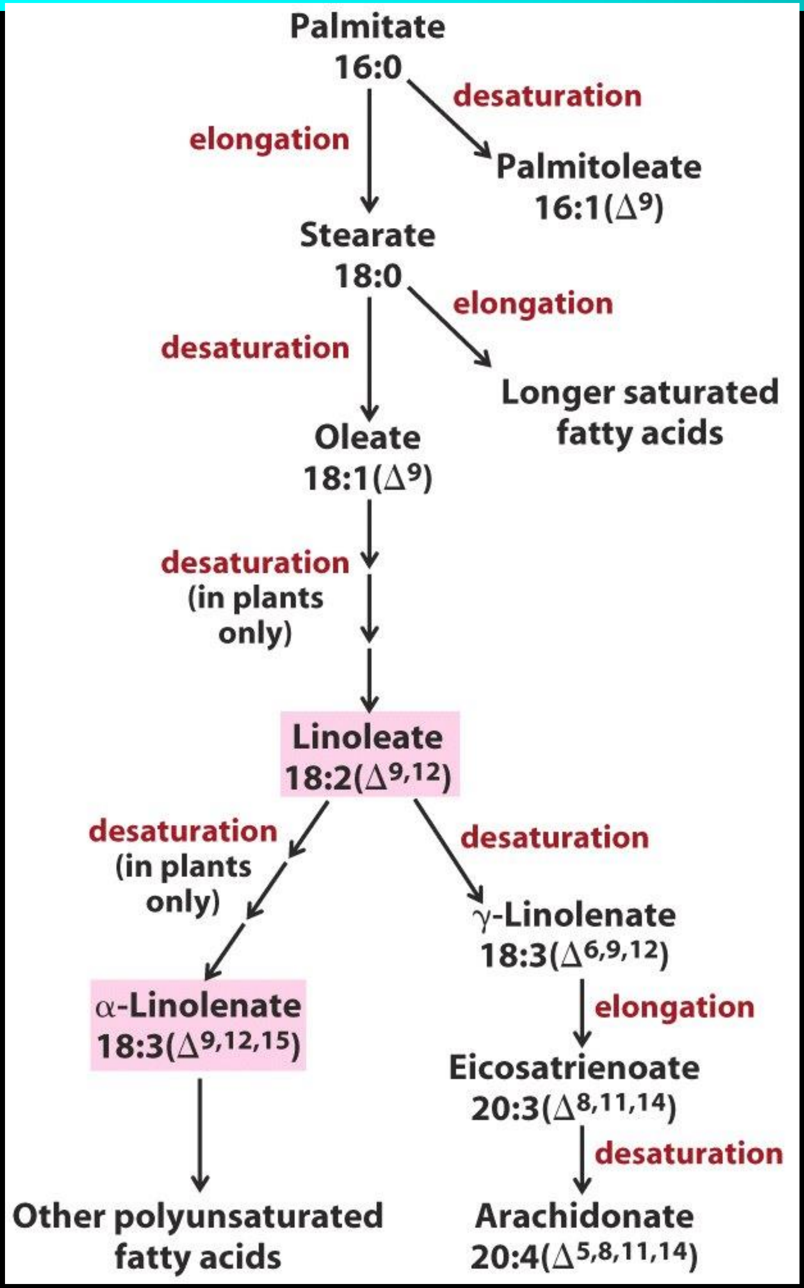


Figure 21-7
Lehninger Principles of Biochemistry, Fifth Edition

- ✓Another malonyl group is linked to ACP



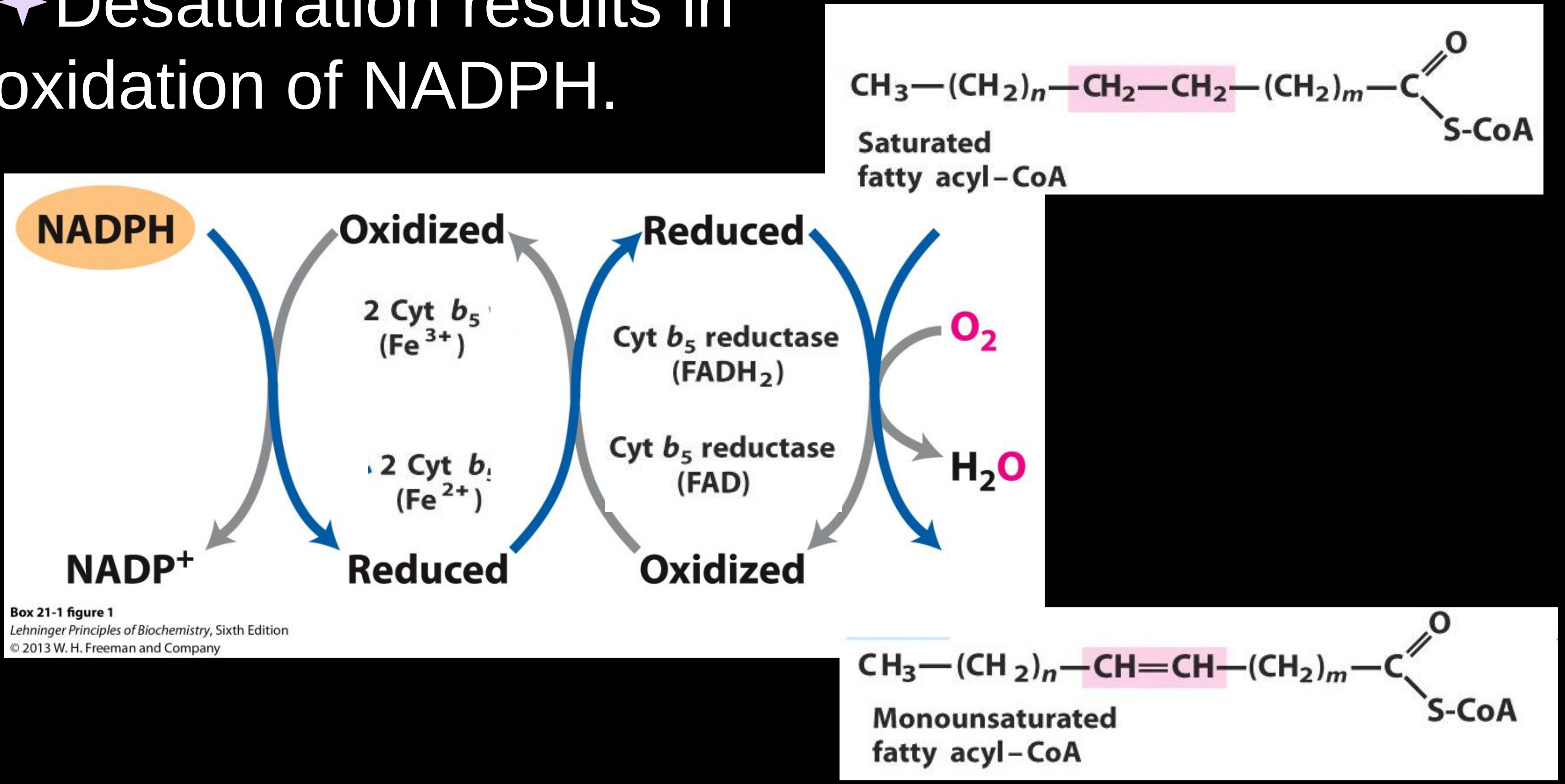
Palmitic acid modifications

- Cell makes a pool of palmitic acid that it can elongate and/or desaturate in the ER.

- Elongation system is very similar to synthesis: 2C units added from malonyl-CoA.

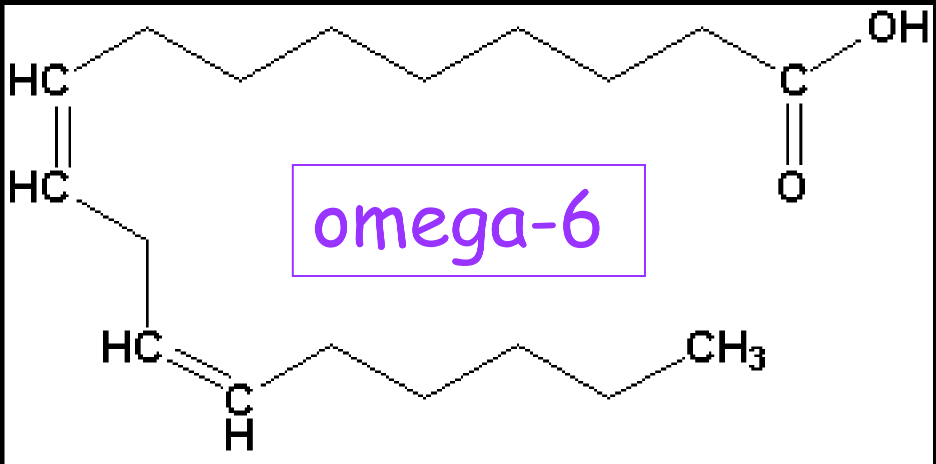
Desaturase reaction

- Desaturation results in oxidation of NADPH.

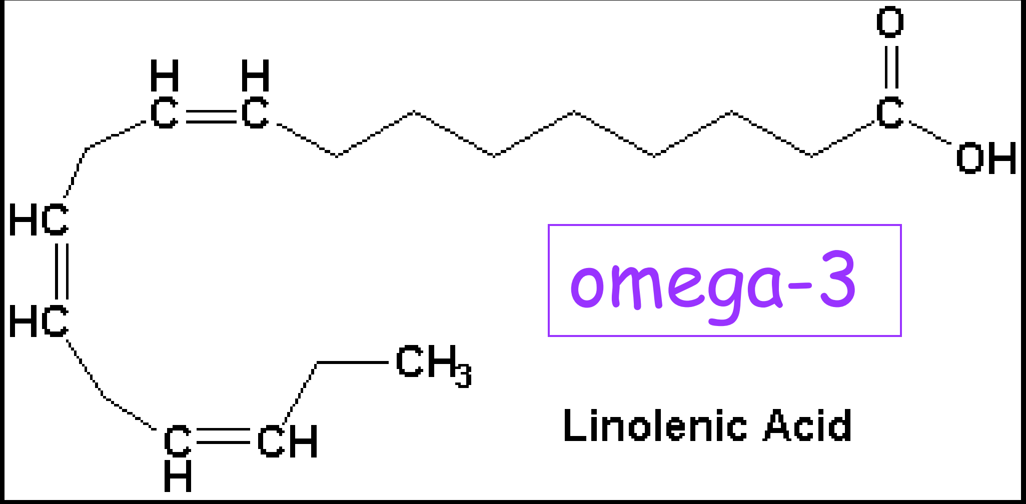


- O_2 is reduced.

Essential fatty acids



Linoleic Acid



Linolenic Acid

Linoleic acid modifications

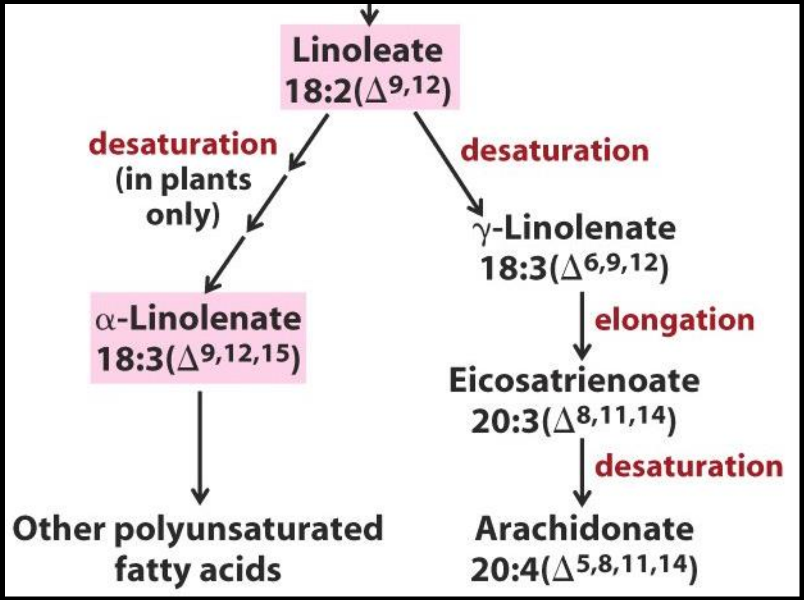


Fig 21-12

✦Linoleic acid can be modified to form essential precursors such as arachidonic acid.

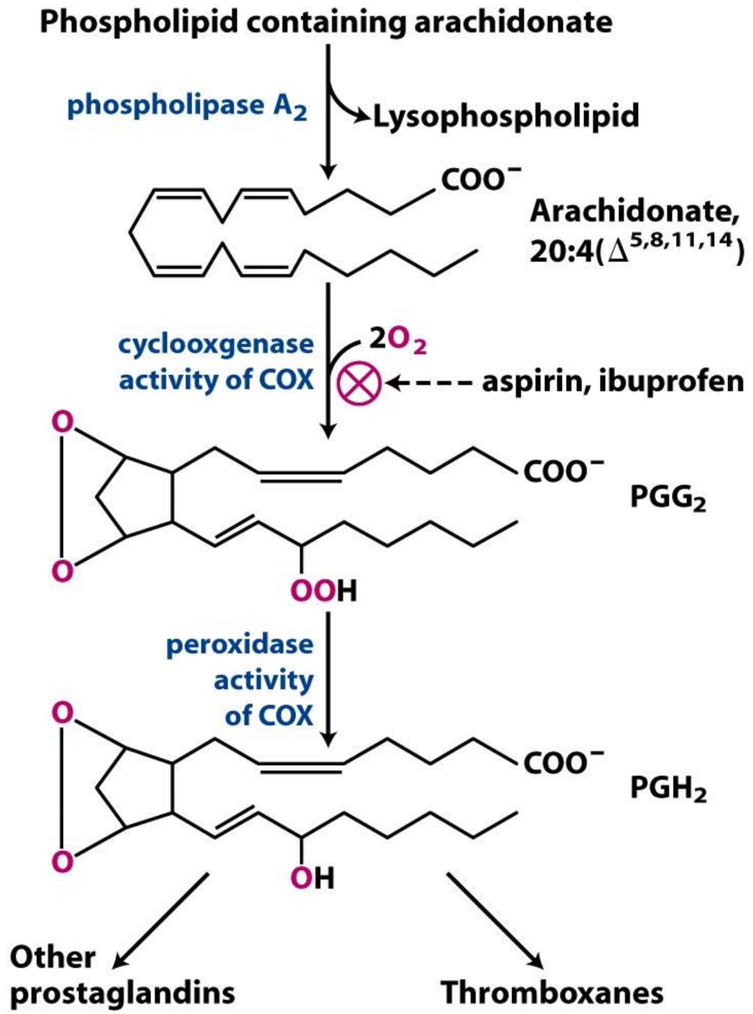


Figure 21-15a
Lehninger Principles of Biochemistry, Fifth Edition

Arachidonic acid as a precursor

- Arachidonic acid is used to make prostaglandins, thromboxanes, and leukotrienes.

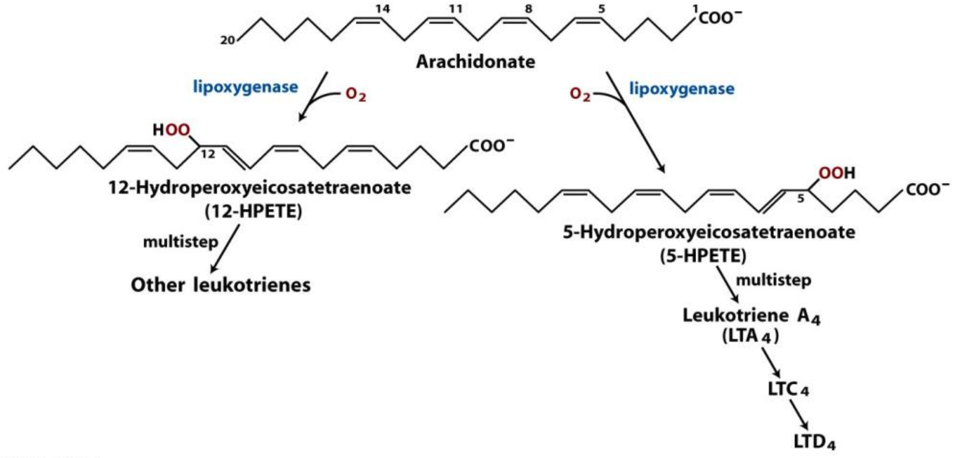


Figure 21-16
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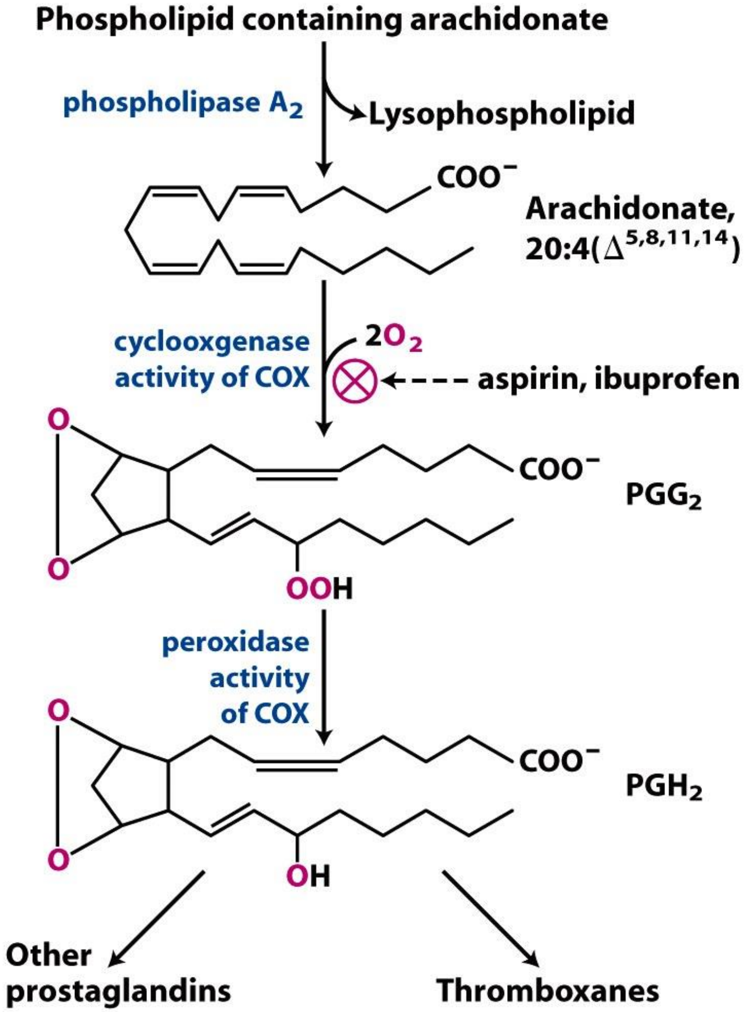

Figure 21-15a
Lehninger Principles of Biochemistry, Fifth Edition

Arachidonic acid as a precursor

✦Two isozymes of COX:

☑COX-1 makes "good" prostaglandins that maintain the GI tract.
☑COX-2 makes "bad" prostaglandins that cause pain and inflammation.

Arachidonic acid as a precursor

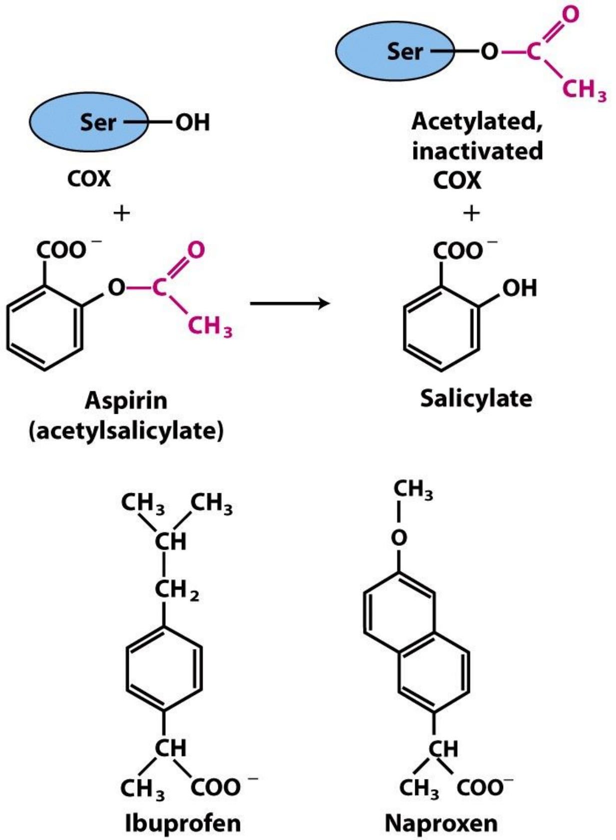

Figure 21-15b
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- Many analgesics are inhibitors of prostaglandin synthesis (via COX).

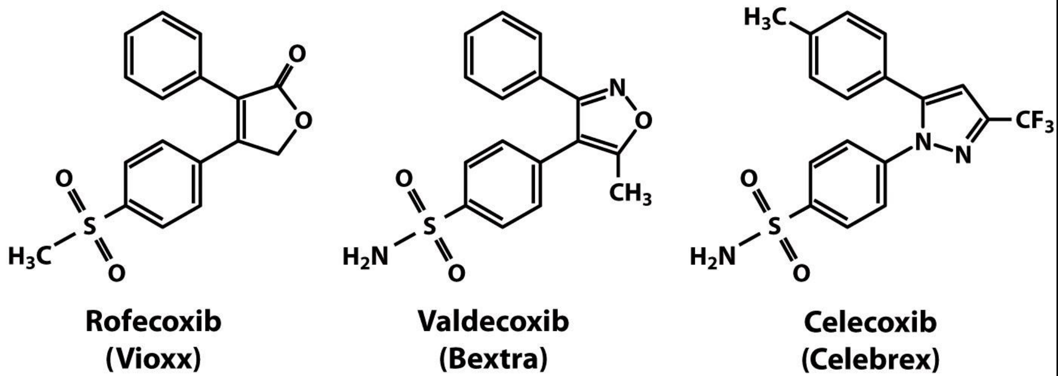

Figure 21-15c
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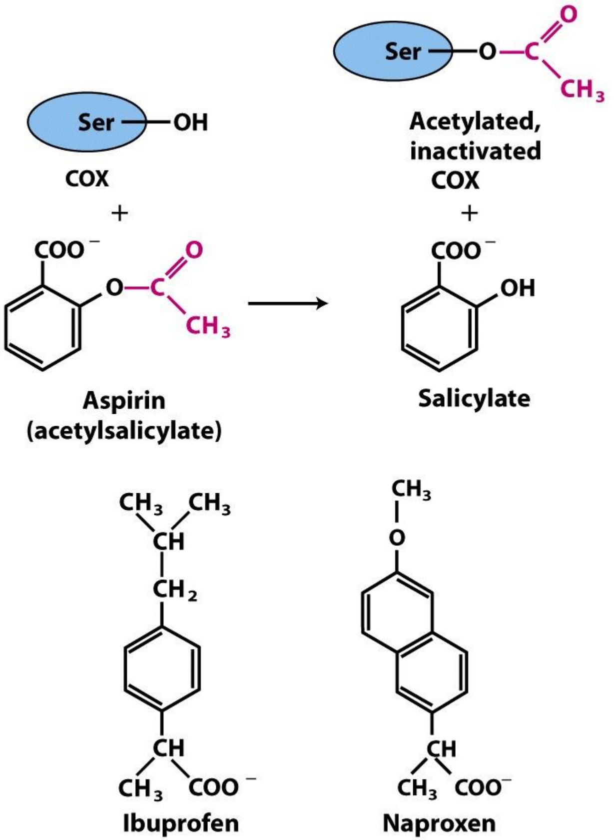

Figure 21-15b
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Arachidonic acid as a precursor

Increased specificity for COX-2

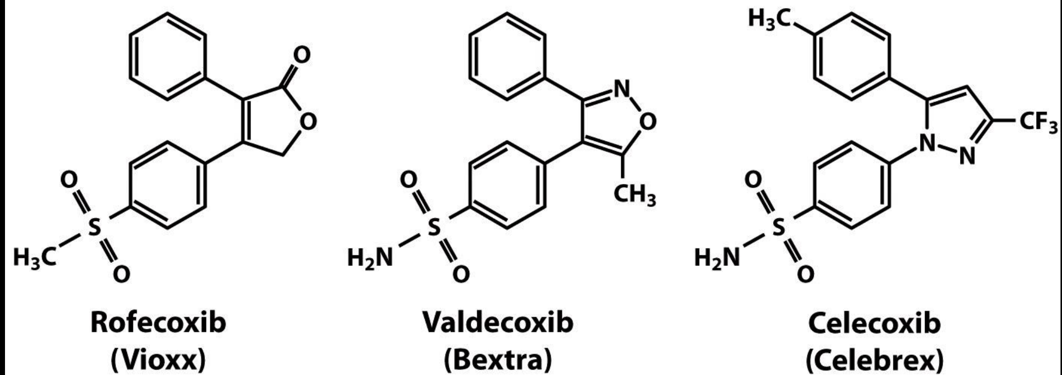

Figure 21-15c
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Control of fatty acid synthesis

- When an organism has more than enough metabolic fuel to meet its energy needs, the excess is converted to fatty acids and stored as triglycerides.

Insulin and citrate stimulate FA synthesis

Control of fatty acid synthesis

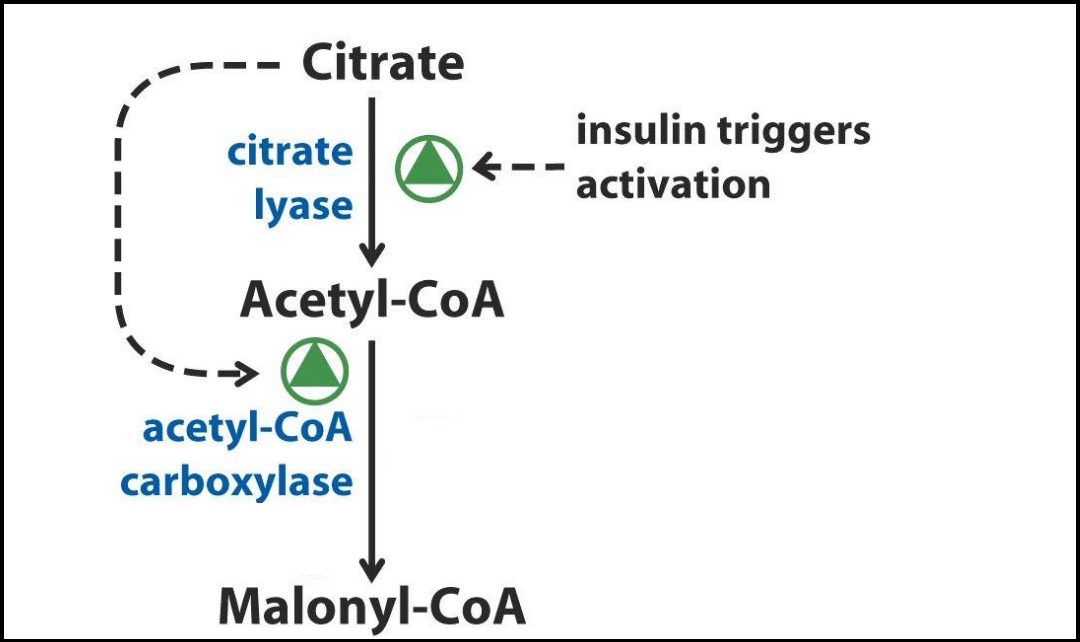
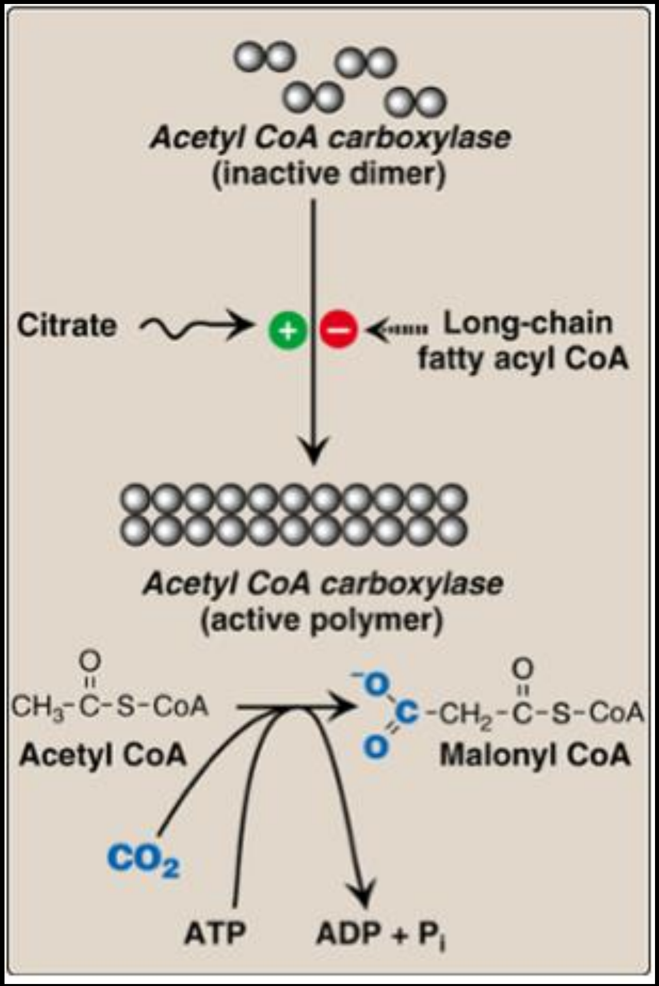
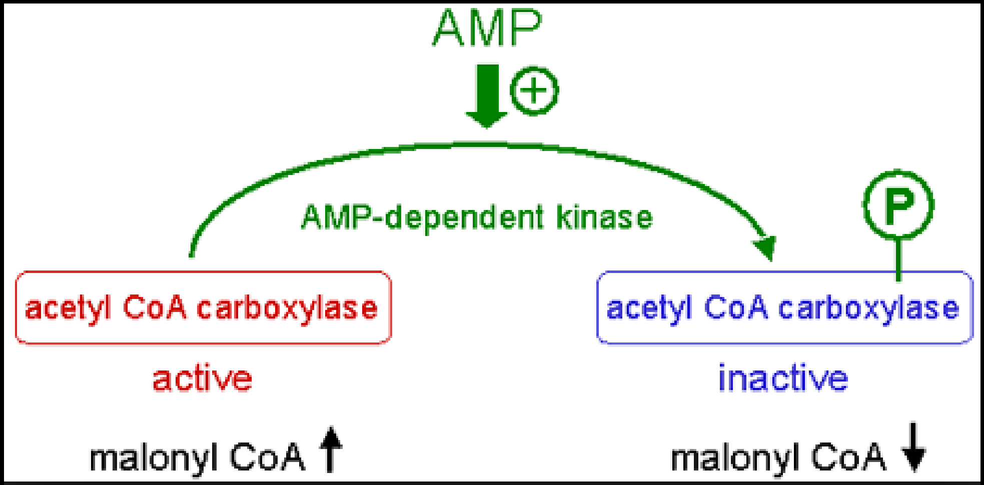


Fig 21-11

Acetyl-CoA Carboxylase





**glucagon,
epinephrine
trigger phosphorylation/
inactivation**

Reciprocal control

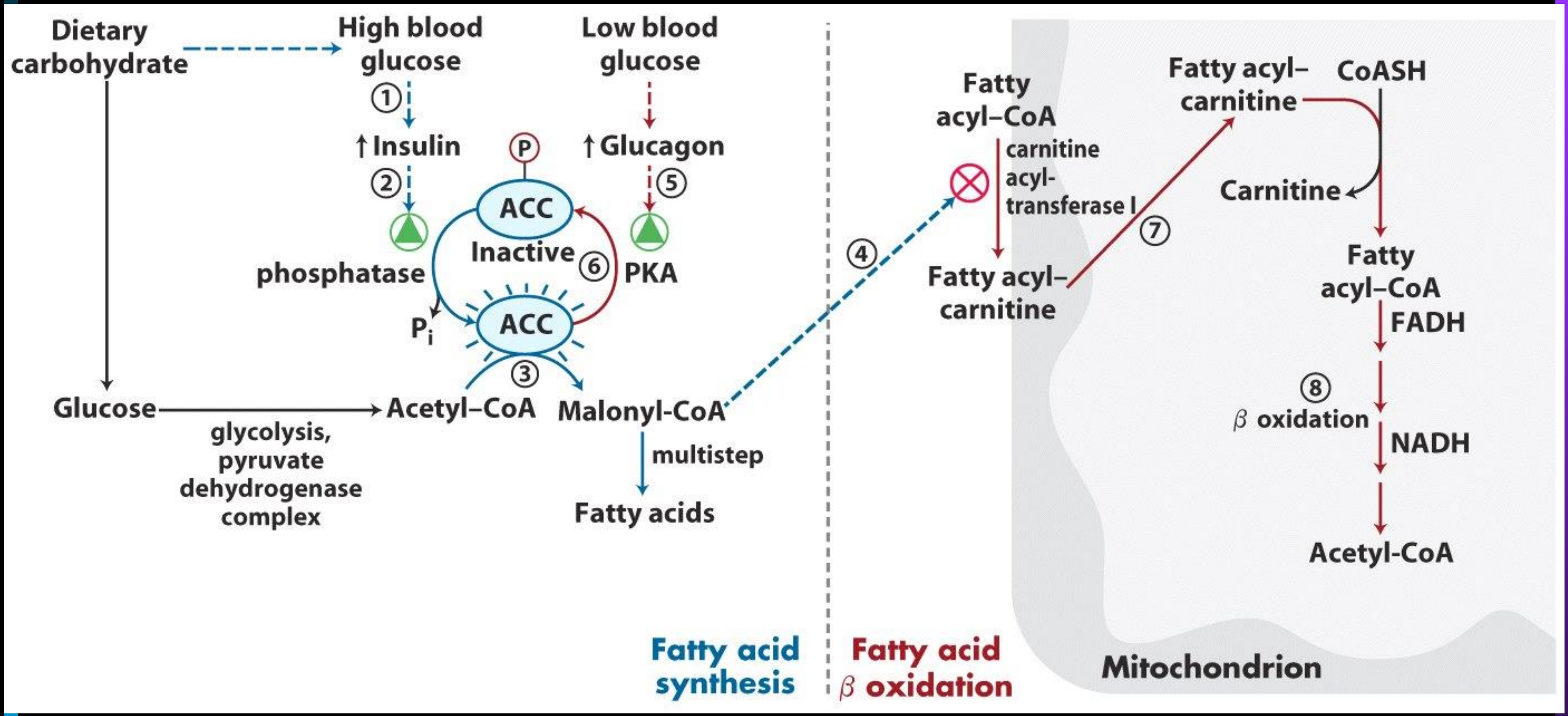


Fig 17-13