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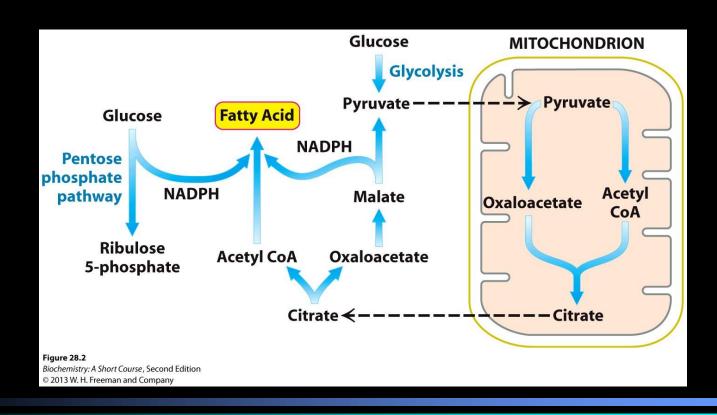
Fatty Acid Synthesis

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

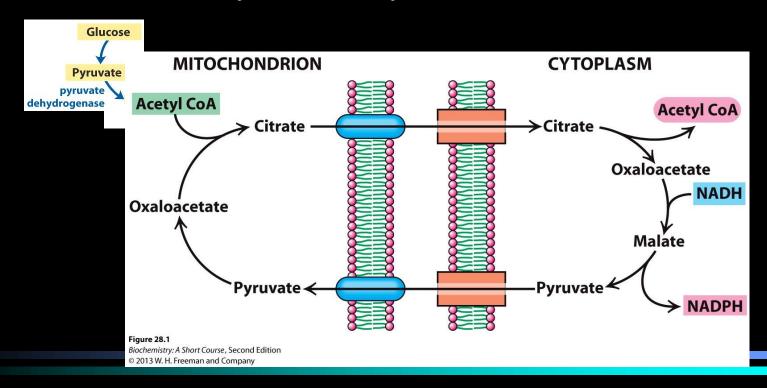
Pathway Integration

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



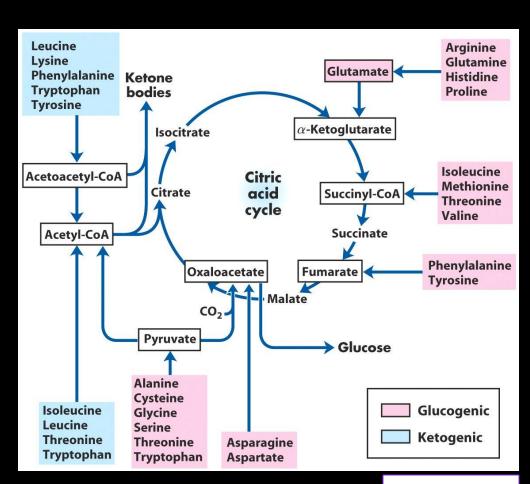
Overlap with carbohydrate metabolism

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

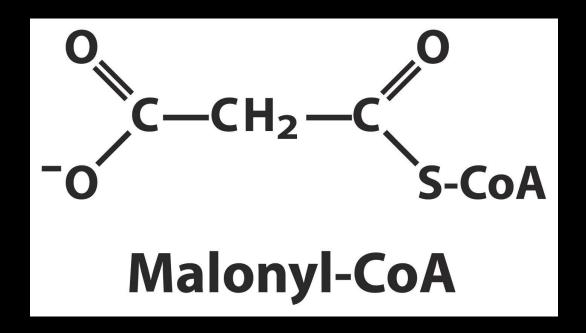


Overlap with protein metabolism

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



The intermediate: malonyl-CoA



→ Malonyl-CoA is an "activated" form of acetyl-CoA used for fatty acid biosynthesis.

carrier → ADP + P Transcarboxylase **Biotin** carrier protein Acetyl-CoA CH 3-Transcarboxylase Biotin carrier **Biotin** protein carboxylase Malonyl-CoA protein Figure 21-1 Lehninger Principles of Biochemistry, Fifth Edition

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Formation of malonyl-CoA

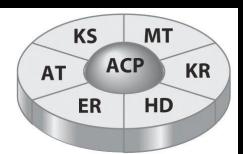
- ★Acetyl-CoA carboxylase has three activities:
- ✓ biotin carrier protein
- √ biotin carboxylase
- √ transcarboxylase
- →Bicarb is phosphorylated, then picked up by biotin
- → Biotin swinging arm transfers CO₂ to acetyl-CoA

Fatty acid synthase

→ Fatty acid synthase has seven different enzyme activities

Bacteria, Plants

Seven activities in seven separate polypeptides



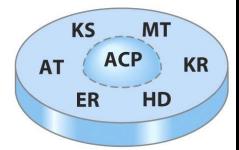
Yeast

Seven activities in two separate polypeptides



Vertebrates

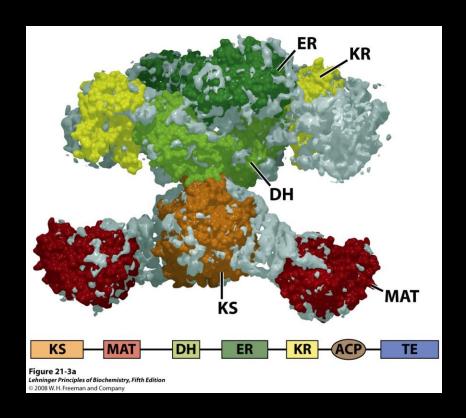
Seven activities in one large polypeptide



Fatty acid synthase

→ Fatty acid synthase has seven different enzyme activities

★Adds two carbons
 every cycle through
 addition of malonyl CoA and loss of CO₂



Fatty acyl synthase

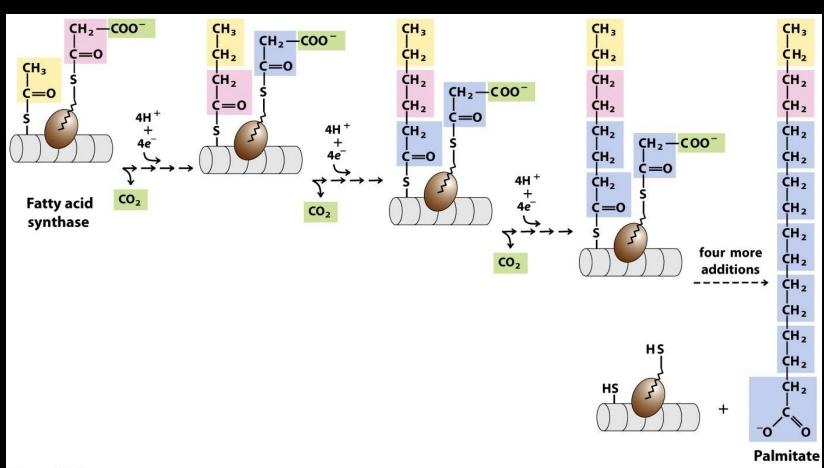
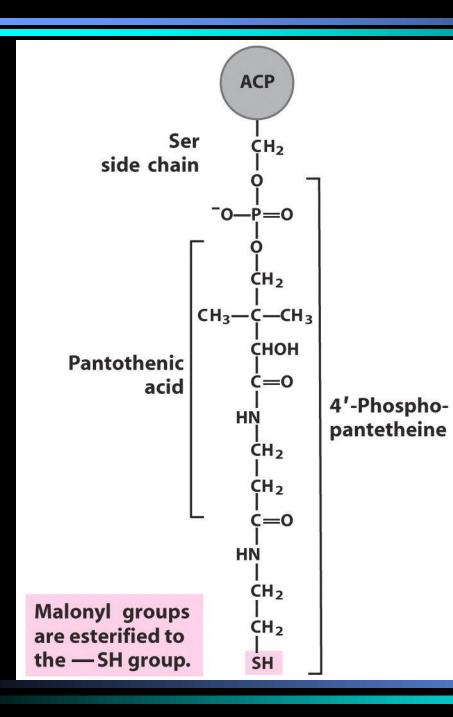


Figure 21-4

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Key Player: acyl carrier protein

→ "Macro" CoA, carries growing fatty acid chain via thioester

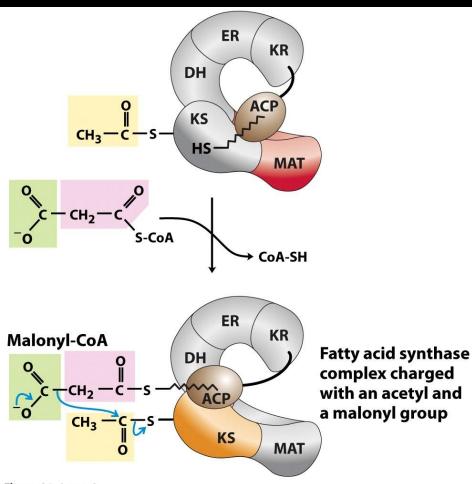
Enoyl-ACP reductase **β-Ketoacyl-ACP** ER reductase **β-Hydroxyacyl-ACP** DH dehydratase **β-Ketoacyl-ACP** HSsynthase MAT Malonyl/acetyl-CoA-**ACP transferase** CoA-SH **Acetyl-CoA** ER KR DH ACP MAT Figure 21-6 part 1

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Initiation Stage

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

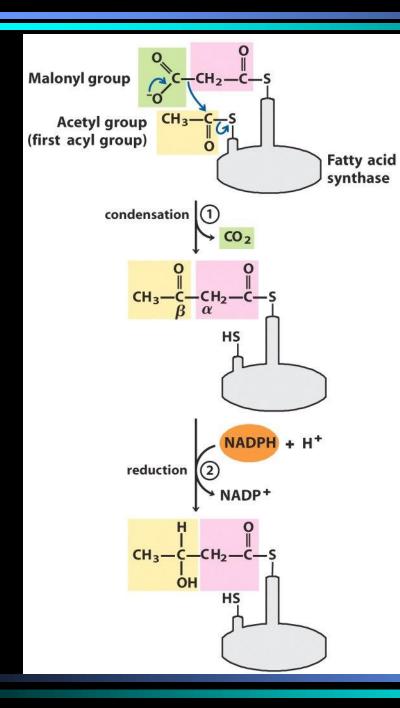
Initiation Stage



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

Figure 21-6 part 2
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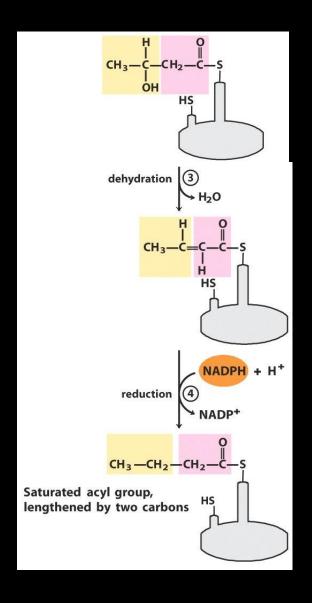


Overview of Assembly Stage

4 steps:

- * Condensation
- *Reduction
- * Dehydration
- *Reduction

Fig 21-2



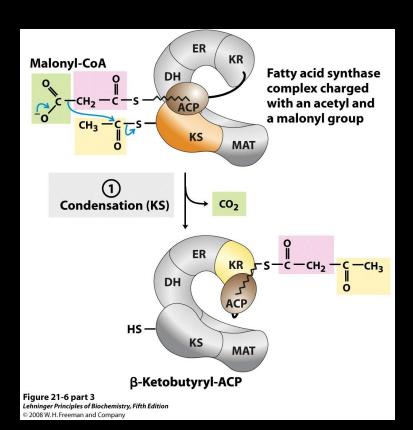
Overview of Assembly Stage

4 steps:

- *Condensation
- *Reduction
- * Dehydration
- *Reduction

Fig 21-2

Step 1: Condensation



✓ Reaction of malonyl group with acetyl group to form acetoacetyl
ACP

✓ Loss of CO₂

Step 2: Reduction to alcohol

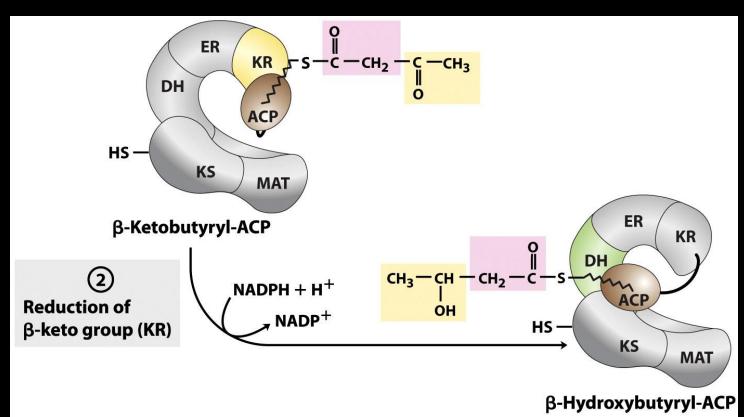
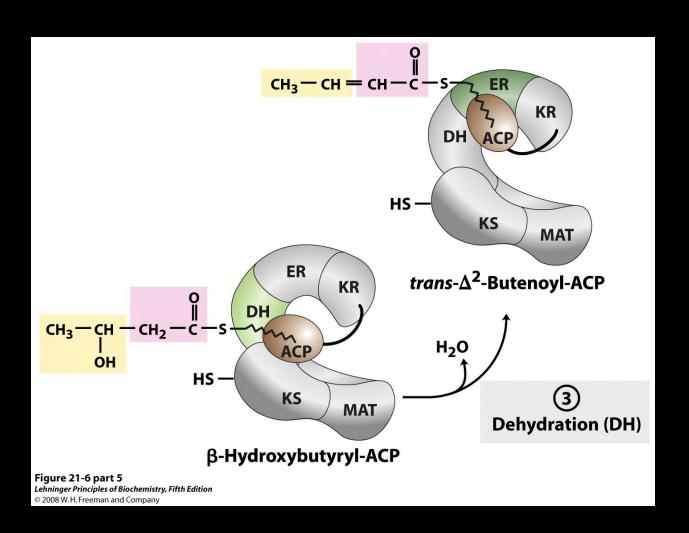


Figure 21-6 part 4
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Step 3: Dehydration



KR DH <mark>СН₃ — СН₂ —</mark> СН₂ — С — S ACP. MAT **Butyryl-ACP** NADP+-Reduction of double NADPH + H⁺ bond (ER) $CH_3 - CH = CH - C - S$ KR DH ACP KS MAT $trans-\Delta^2$ -Butenoyl-ACP Figure 21-6 part 6

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Step 4: Reduction of double bond

Transfer to KS

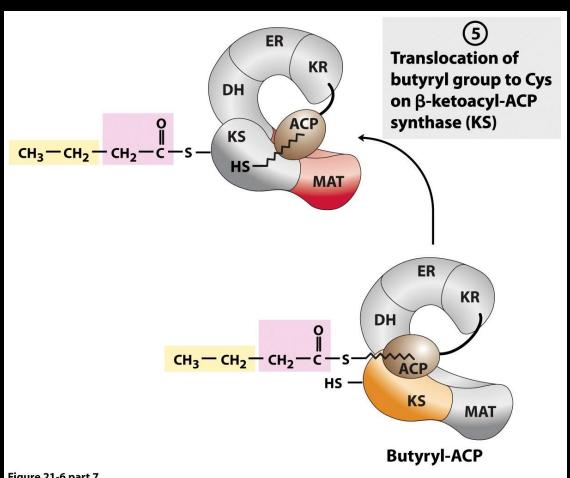


Figure 21-6 part 7
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ER KR DH ACP KS СН₃ — СН₂ — СН₂ — С — **Butyryl group** MAT Malonyl-CoA CoA-SH ER KR KS MAT condensation ER DH HS-KS MAT **β-Ketoacyl-ACP** Figure 21-7

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Next cycle begins

✓ Another malonyl group is linked to ACP

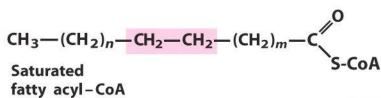
Palmitate 16:0 desaturation elongation **Palmitoleate** 16:1(Δ^9) Stearate 18:0 elongation desaturation Longer saturated fatty acids Oleate 18:1(Δ^9) desaturation \ (in plants only) Linoleate 18:2($\Delta^{9,12}$) desaturation desaturation (in plants only) √-Linolenate 18:3($\Delta^{6,9,12}$) α-Linolenate elongation 18:3($\Delta^{9,12,15}$) **Eicosatrienoate** 20:3($\Delta^{8,11,14}$) desaturation Other polyunsaturated **Arachidonate** 20:4($\Delta^{5,8,11,14}$) fatty acids

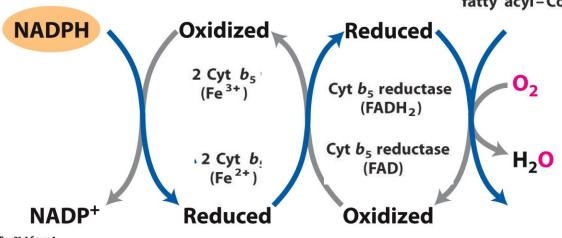
Palmitic acid modifications

- ★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.



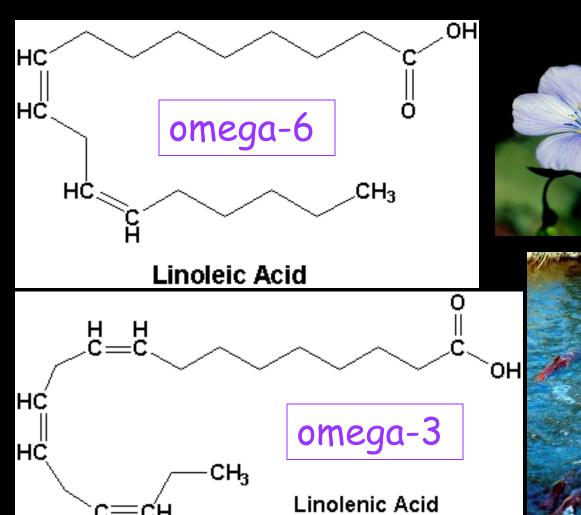


Box 21-1 figure 1

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 $+O_2$ is reduced.

Essential fatty acids







Linoleate 18:2($\Delta^{9,12}$) desaturation desaturation (in plants only) √-Linolenate 18:3($\Delta^{6,9,12}$) α-Linolenate elongation 18:3($\Delta^{9,12,15}$) Eicosatrienoate 20:3($\Delta^{8,11,14}$) desaturation Other polyunsaturated **Arachidonate 20:4**(Δ ^{5,8,11,14}) fatty acids

Linoleic acid modifications

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

Fig 21-12

Phospholipid containing arachidonate phospholipase A₂ Lysophospholipid COO Arachidonate. 20:4(\(\Delta^{5,8,11,14}\) cyclooxgenase activity of COX aspirin, ibuprofen PGG₂ peroxidase activity of COX PGH₂ Other prostaglandins **Thromboxanes** Figure 21-15a Lehninger Principles of Biochemistry, Fifth Edition © 2008 W. H. Freeman and Company

Arachidonic acid as a precursor

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

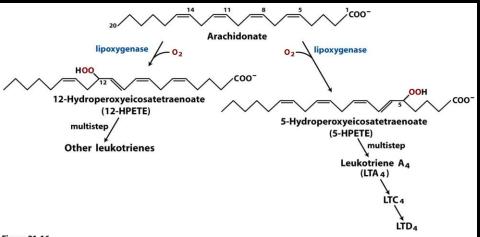


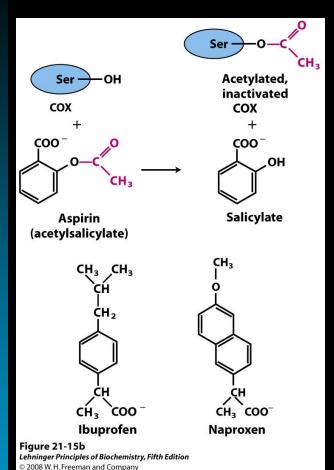
Figure 21-16

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Phospholipid containing arachidonate phospholipase A2 Lysophospholipid COO. Arachidonate. 20:4(\(\Delta^{5,8,11,14} \) cyclooxgenase activity of COX aspirin, ibuprofen PGG₂ peroxidase activity of COX PGH₂ Other prostaglandins **Thromboxanes** Figure 21-15a Lehninger Principles of Biochemistry, Fifth Edition © 2008 W. H. Freeman and Company

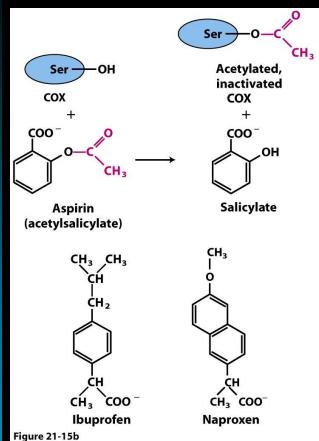
Arachidonic acid as a precursor

- **→**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

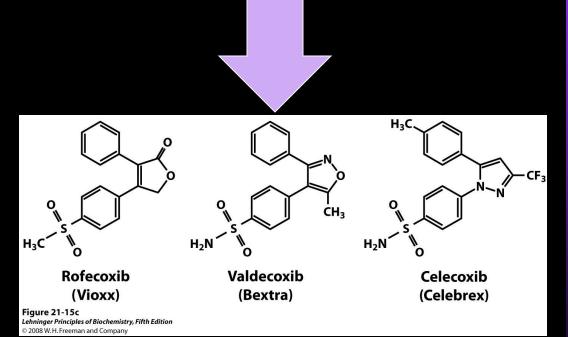
→ Many analgesics are inhibitors of prostaglandin synthesis (via COX).



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Arachidonic acid as a precursor

Increased specificity for COX-2



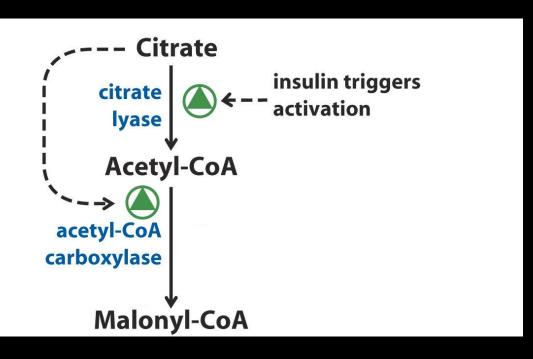
Control of fatty acid synthesis

★ 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.

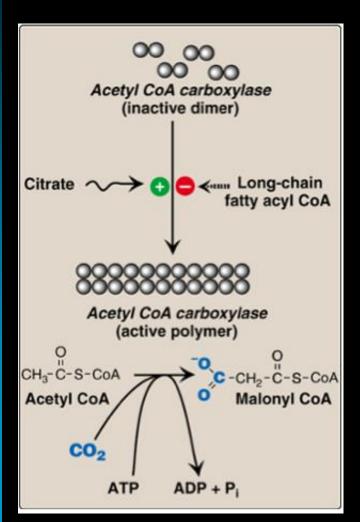


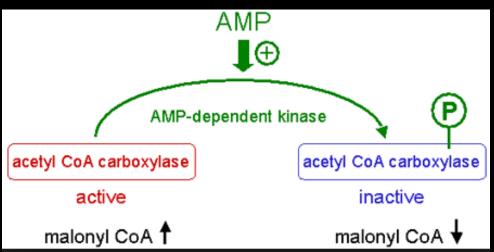
Insulin and citrate stimulate FA synthesis

Control of fatty acid synthesis



Acetyl-CoA Carboxylase





glucagon, epinephrine trigger phosphorylation/ inactivation

Reciprocal control

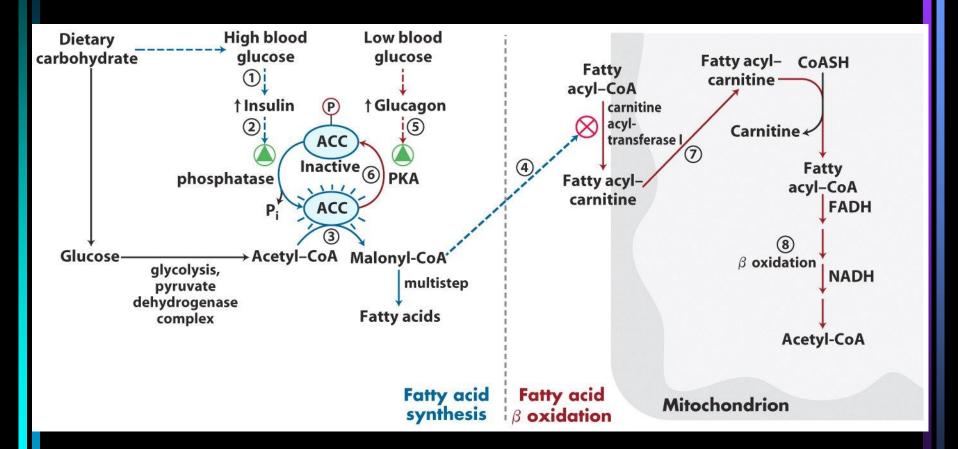


Fig 17-13