Metabolism of lipids II:
Synthesis of fatty acids

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Resources

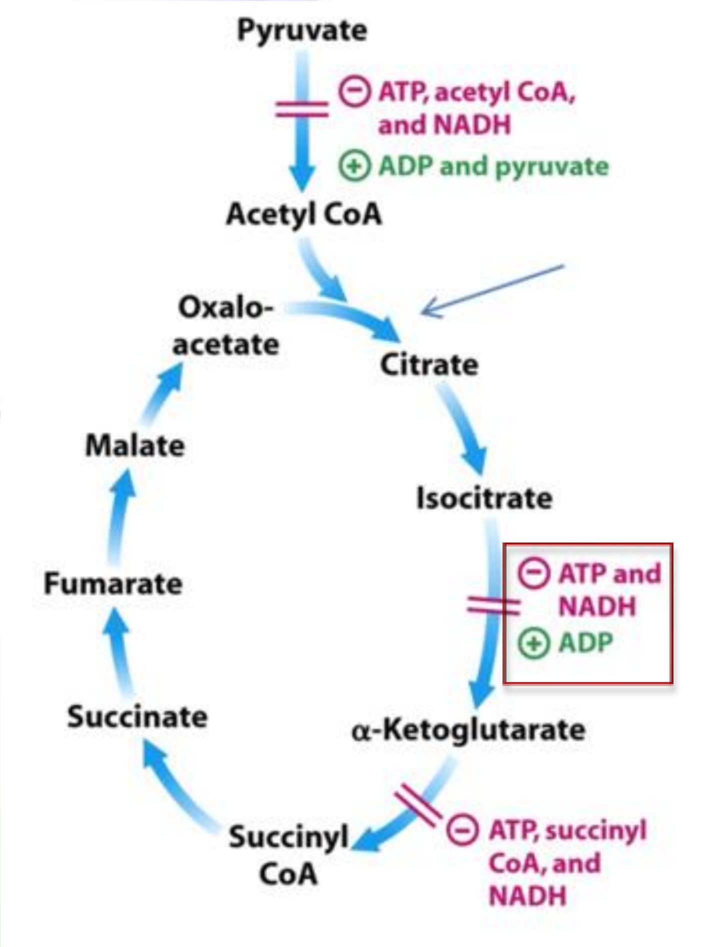
- This lecture
- Lippincott's Biochemistry, Ch. 16

Overview of fatty acid synthesis

Major sites: liver and adipose tissues

- The fatty acids are synthesized by:
  1. Production of malonyl CoA
  2. Binding of acetyl CoA and malonyl CoA to the fatty acid synthase
  3. Condensation of acetyl CoA and malonyl CoA
  4. Elongation of the acyl CoA by 2 carbons per round
     - Reduction, dehydration, reduction
  5. Binding of malonyl CoA
  6. *Repeat steps 3 (acyl CoA), 4, and 5*
  7. Release of the hydrocarbon chain by a thioesterase (TE)

Mitochondria to cytoplasm transport of acetyl-CoA



When ATP increases:

ATP inhibits isocitrate dehydrogenase

Citrate is transported into the cytosol

Citrate is cleaved into oxaloacetate and acetyl CoA by ATP citrate lyase

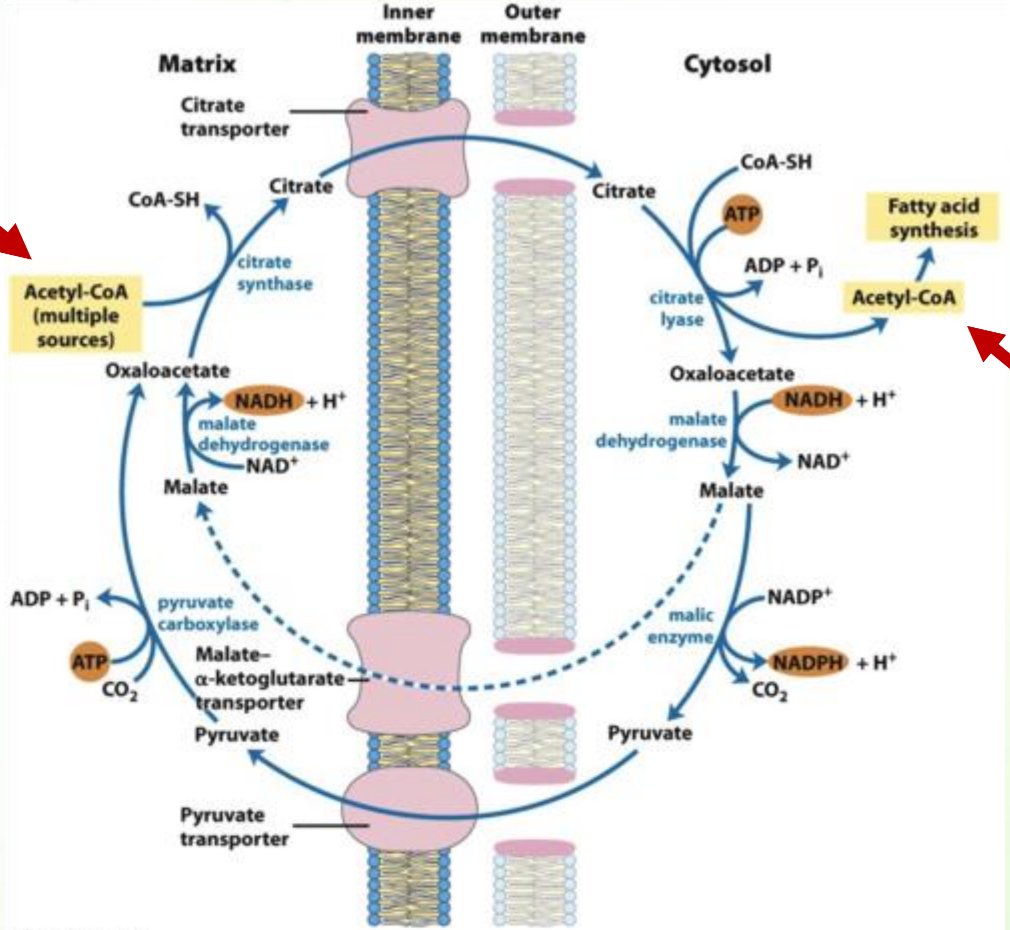


Figure 21-10
Lehninger Principles of Biochemistry, Fifth Edition
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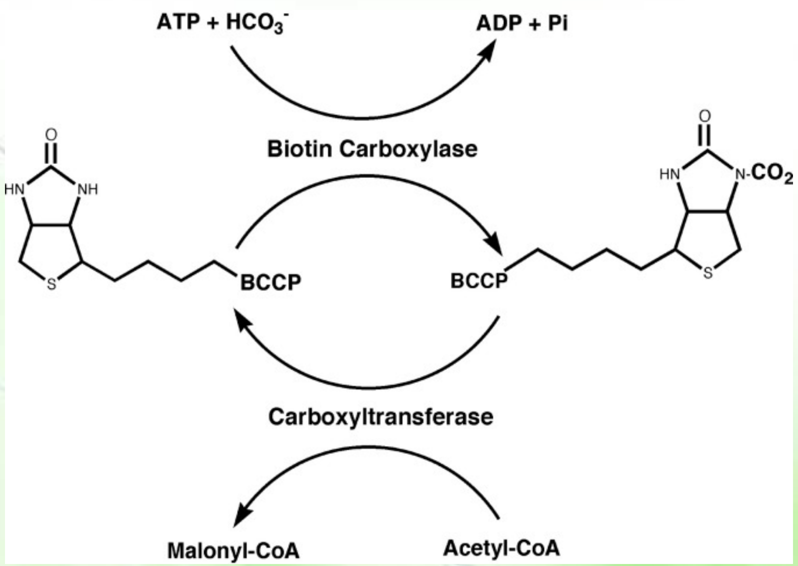
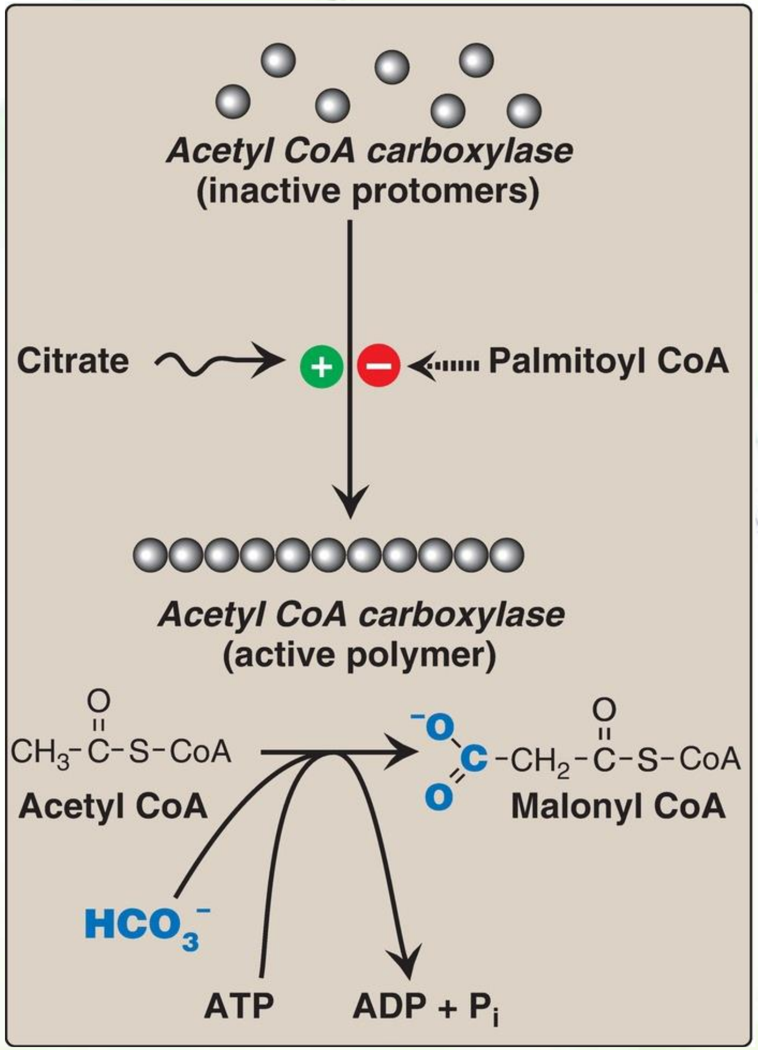
Glucose can be converted to fat, but fat cannot be converted to glucose.

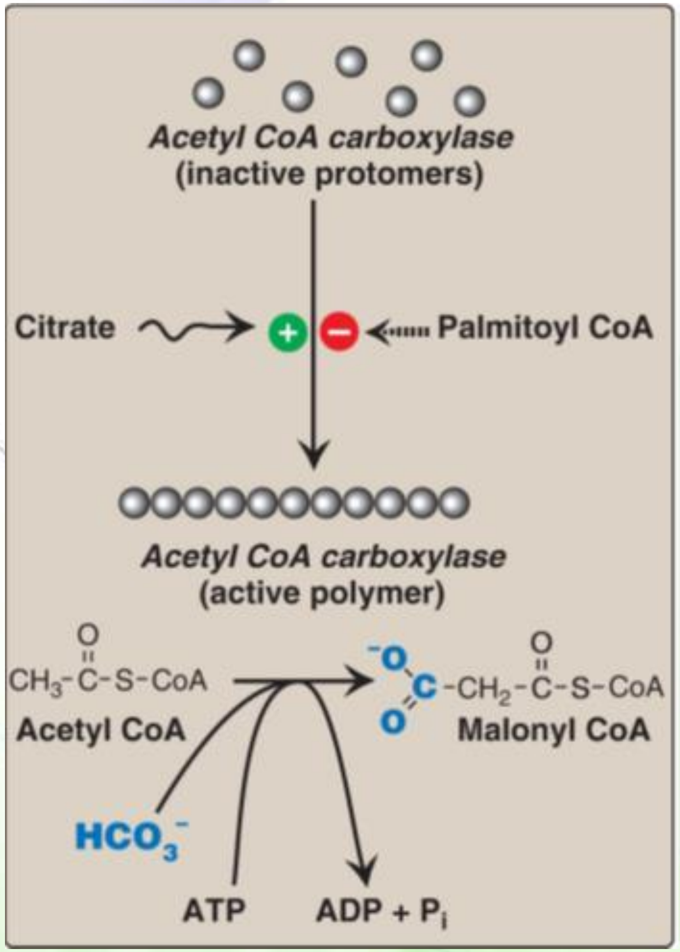
Synthesis of malonyl-CoA

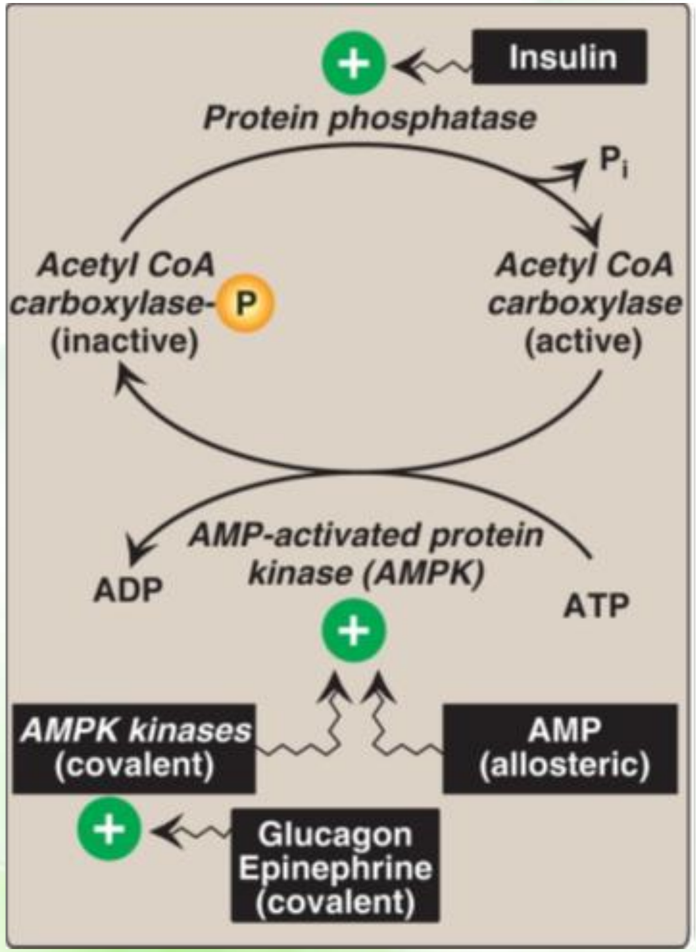
- Acetyl CoA carboxylase (ACC) transfers a carbon from CO_2 (as a bicarbonate) via biotin (vitamin B7), which is covalently bound to a lysyl residue of the ACC.
  - ATP is needed.
  - The reaction is a rate-limiting reaction.
  - ACC is an allosteric enzyme.





Regulation of ACC

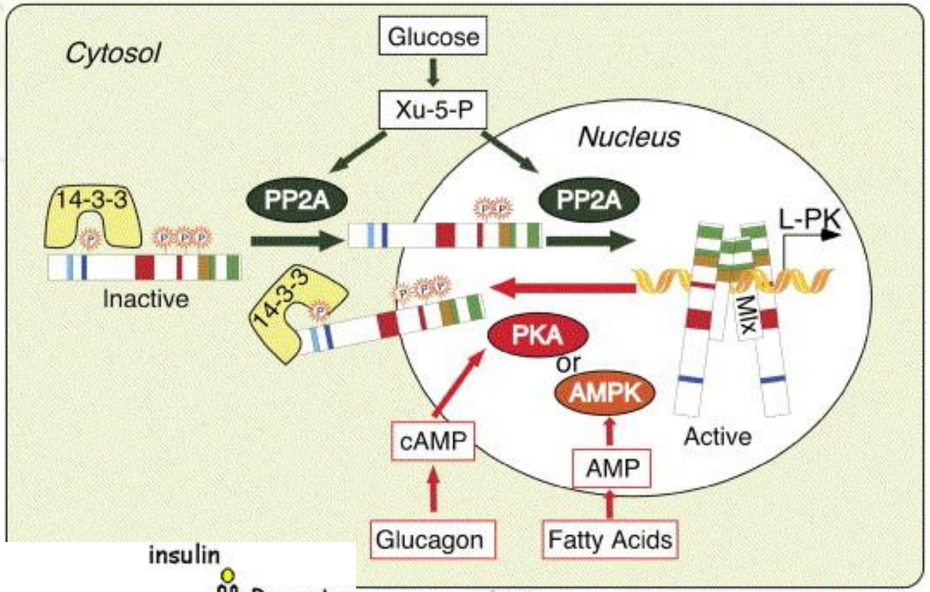


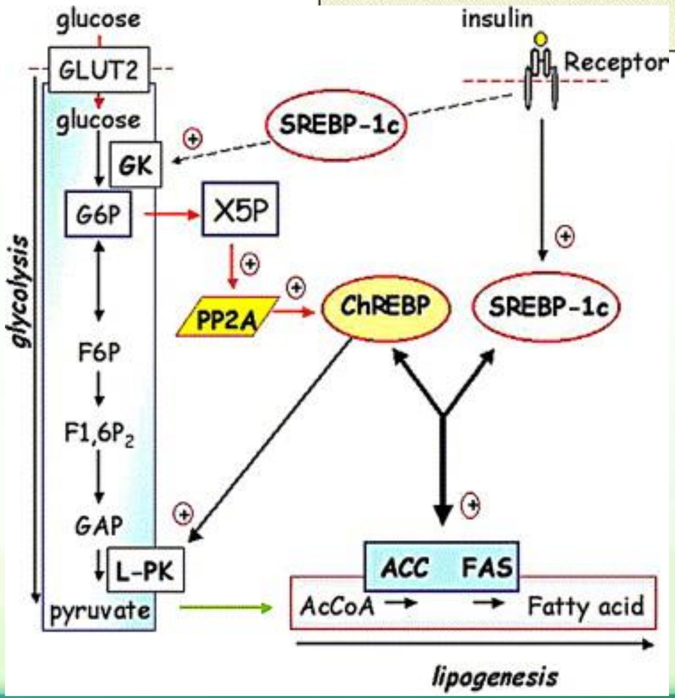


- ACC is inactivated by:
  - Palmitoyl-CoA
  - Phosphorylation by AMPK, which is activated by glucagon and epinephrine.

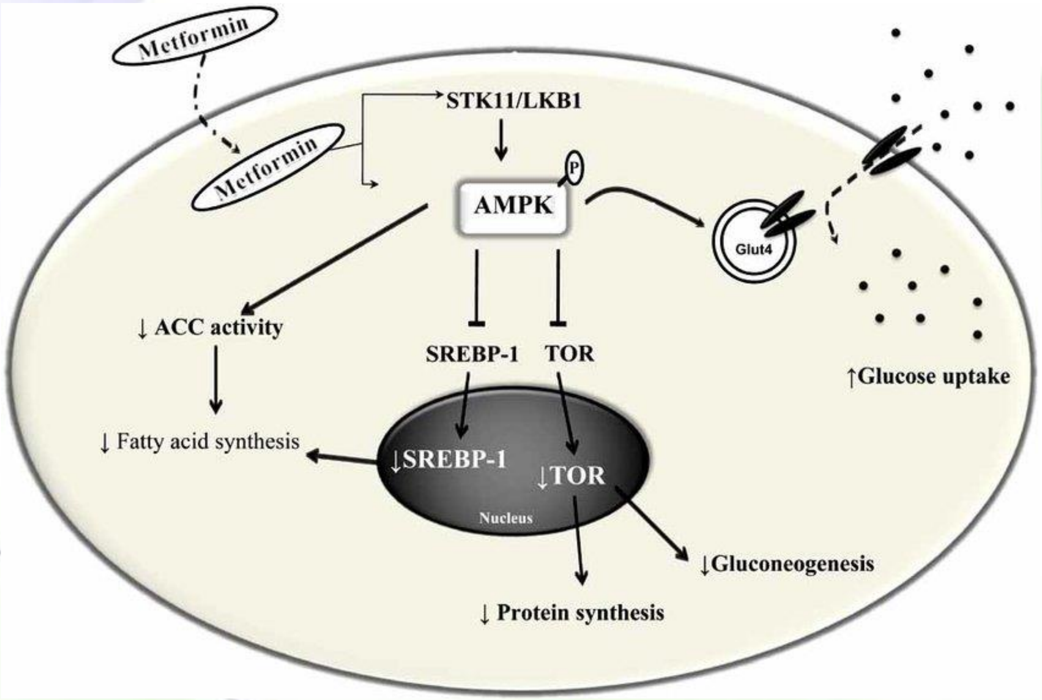
Regulation of ACC synthesis

- ACC synthesis is regulated transcription factors:
  - The carbohydrate response element–binding protein (ChREBP)
    - ChREBP is inactivated by phosphorylation by PKA and AMPK preventing its nuclear localization.
    - It is dephosphorylated by excess glucose.
  - The sterol regulatory element–binding protein-1c (SREBP-1c)
    - SREBP-1 is activated by Insulin.
- Fatty acid synthase, glucokinase, ATP citrate lyase and liver pyruvate kinase are similarly regulated.





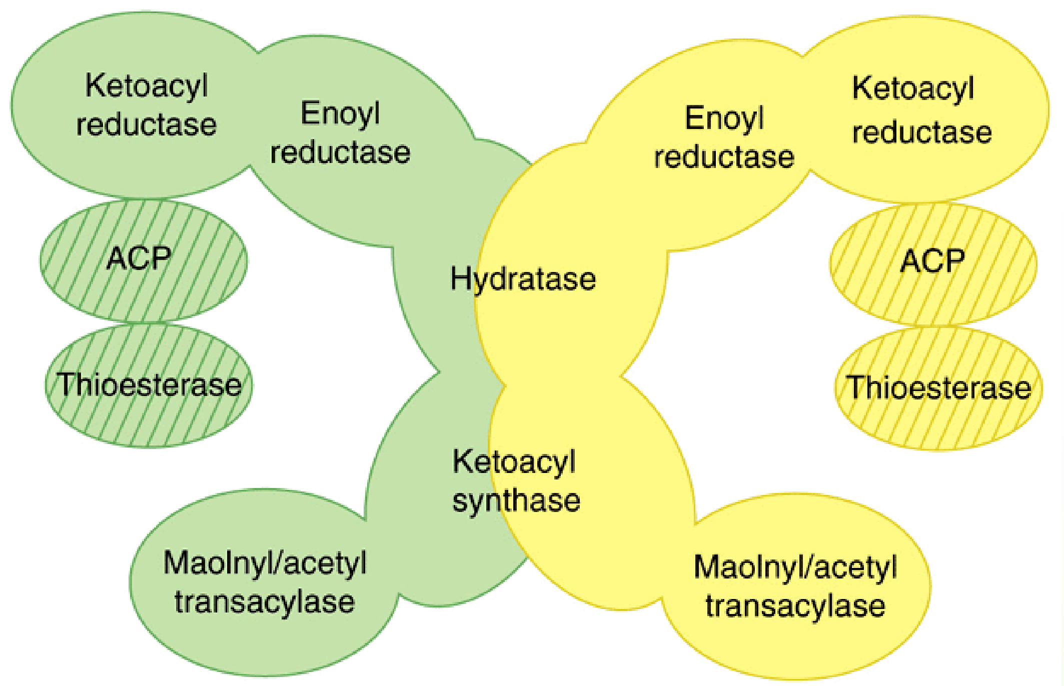
Metformin



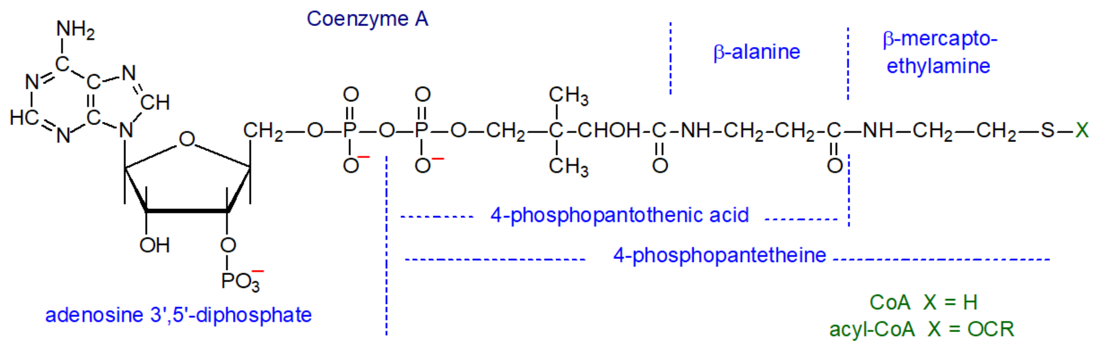
- Metformin lowers plasma TAG through
  - Activation of AMPK, resulting in inhibition of ACC activity (by phosphorylation) and inhibition of ACC and fatty acid synthase expression (by decreasing ChREBP and SREBP-1c).
- It lowers blood glucose by increasing AMPK-mediated glucose uptake by muscle.

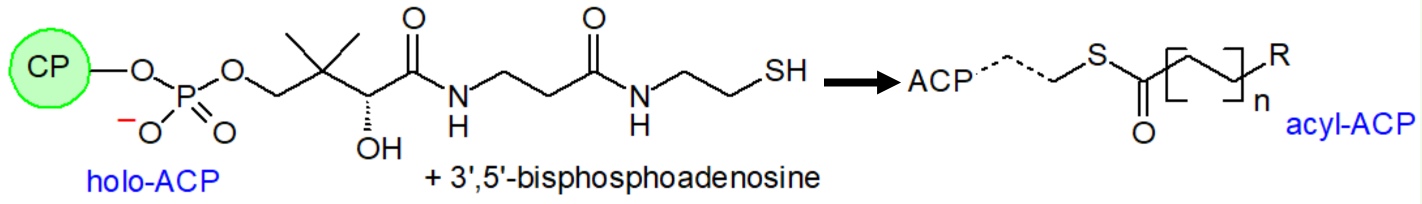
Fatty acid synthase (FAS)

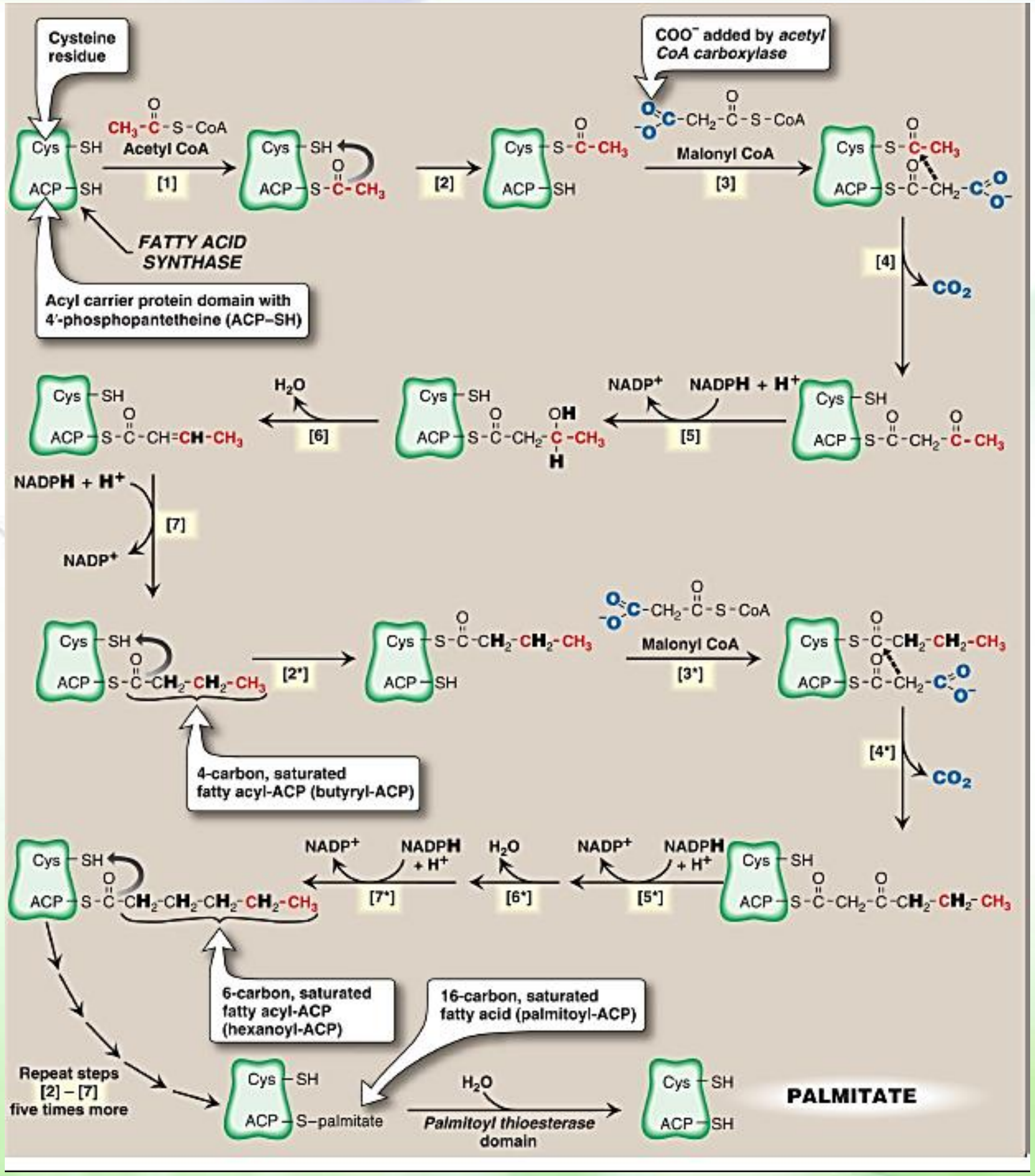
- A multifunctional, homodimeric enzyme
- Each FAS monomer is multicatalytic with six enzymic domains and a domain for binding a phosphopantetheine-containing acyl carrier protein (ACP) domain.
- Phosphopantetheine, a derivative of pantothenic acid (vitamin B5), carries acyl units on its terminal thiol (–SH) group and presents them to the catalytic domains of FAS.
- It also is a component of CoA.

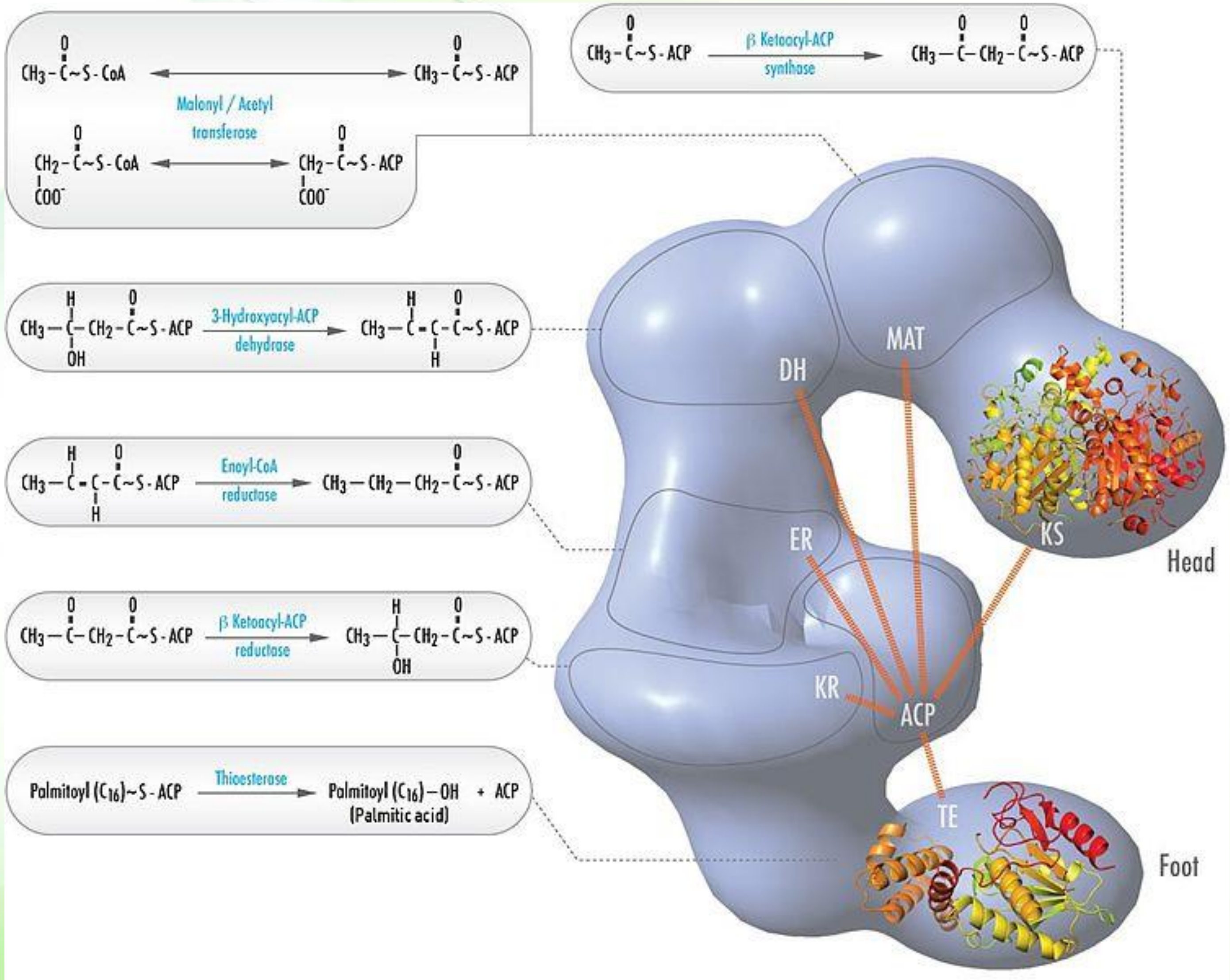


Fatty acid synthase homodimer

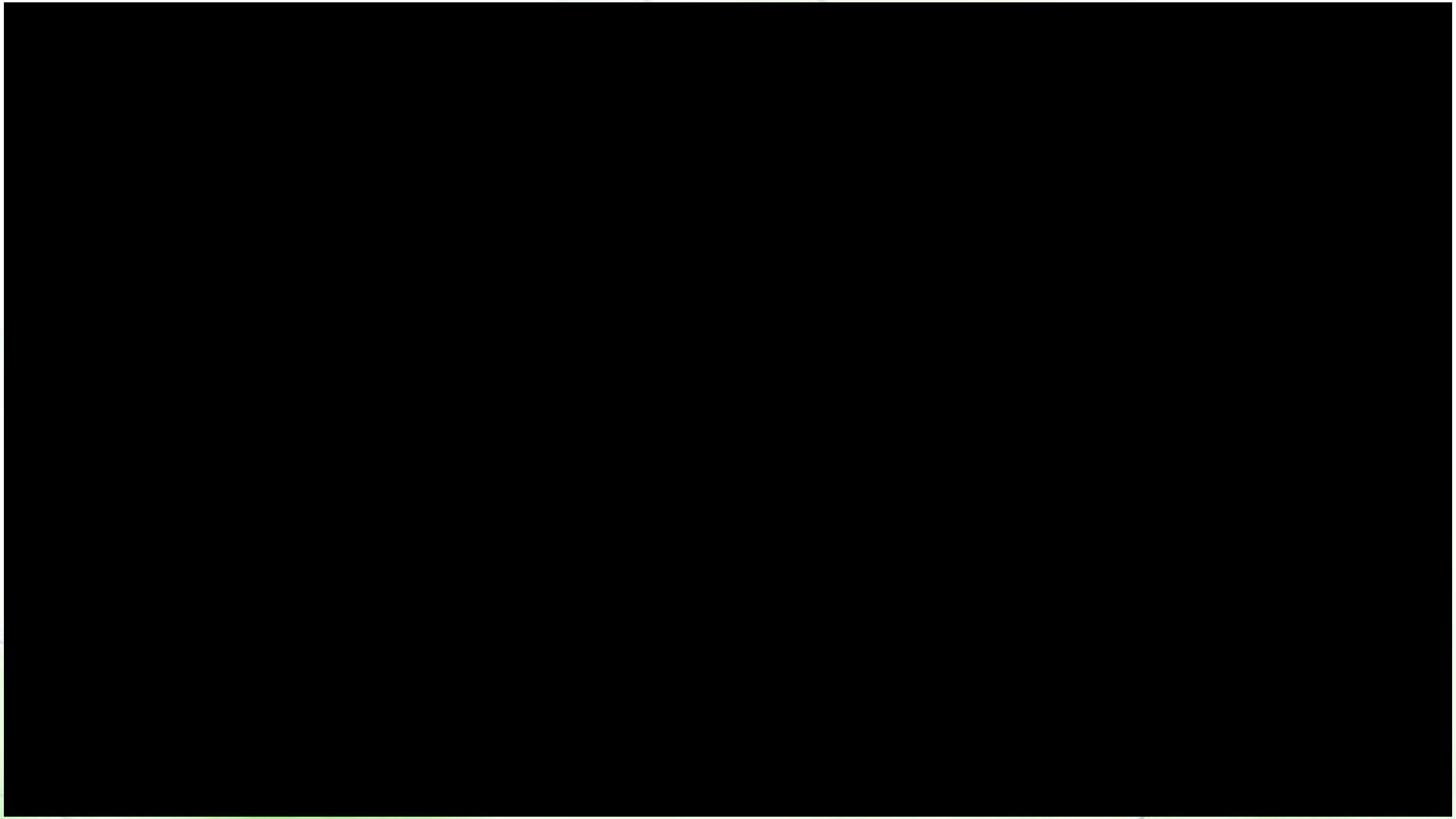





Cysteine residue
COO⁻ added by acetyl CoA carboxylase
Acetyl CoA
Malonyl CoA
[1]
[2]
[3]
[4]
CO2
FATTY ACID SYNTHASE
Acyl carrier protein domain with 4'-phosphopantetheine (ACP–SH)
Cys
ACP
H2O
[6]
NADP+
NADPH + H+
[5]
[7]
[2*]
[3*]
[4*]
[5*]
[6*]
[7*]
4-carbon, saturated fatty acyl-ACP (butyryl-ACP)
6-carbon, saturated fatty acyl-ACP (hexanoyl-ACP)
16-carbon, saturated fatty acid (palmitoyl-ACP)
Repeat steps [2] – [7] five times more
S–palmitate
Palmitoyl thioesterase domain
PALMITATE


Malonyl / Acetyl transferase
β Ketoacyl-ACP synthase
3-Hydroxyacyl-ACP dehydrase
Enoyl-CoA reductase
β Ketoacyl-ACP reductase
Thioesterase
Palmitoyl (C16)~S-ACP
Palmitoyl (C16)–OH + ACP
(Palmitic acid)
DH
MAT
KS
ER
KR
ACP
TE
Head
Foot

Ketoacyl synthase (KS)
Malonyl/acetyltransferase (AT)
Dehydrase (DH)
Enoyl reductase (ER)
Ketoacyl reductase (KR)
Thioesterase (TE)
Acyl carrier protein (ACP)



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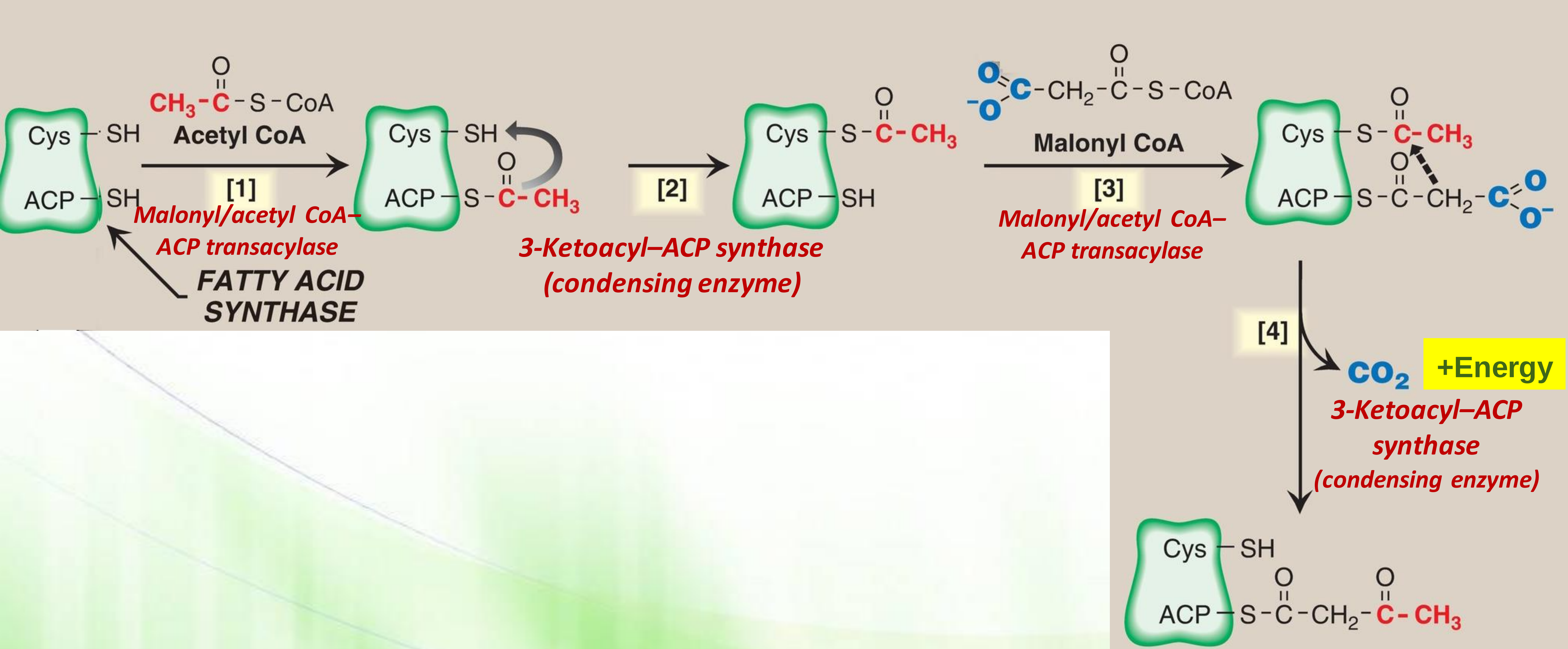
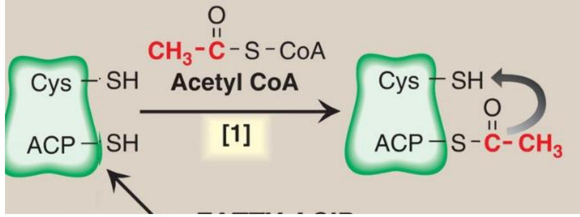
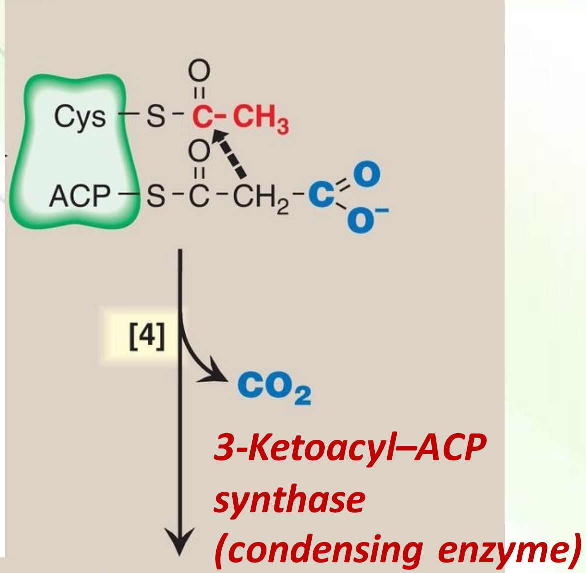
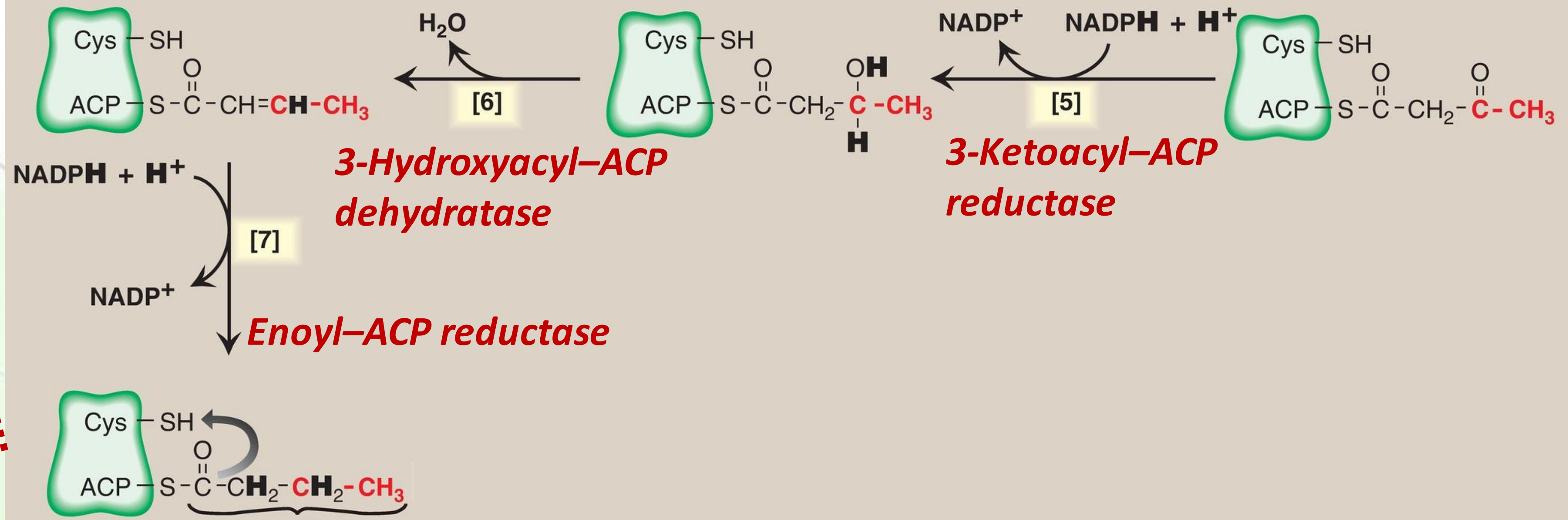

Cys
ACP
SH
SH
CH3-C-S-CoA
Acetyl CoA
[1]
Malonyl/acetyl CoA–
ACP transacylase
FATTY ACID
SYNTHASE
[2]
3-Ketoacyl–ACP synthase
(condensing enzyme)
Malonyl CoA
[3]
Malonyl/acetyl CoA–
ACP transacylase
[4]
CO2
+Energy
3-Ketoacyl–ACP
synthase
(condensing enzyme)

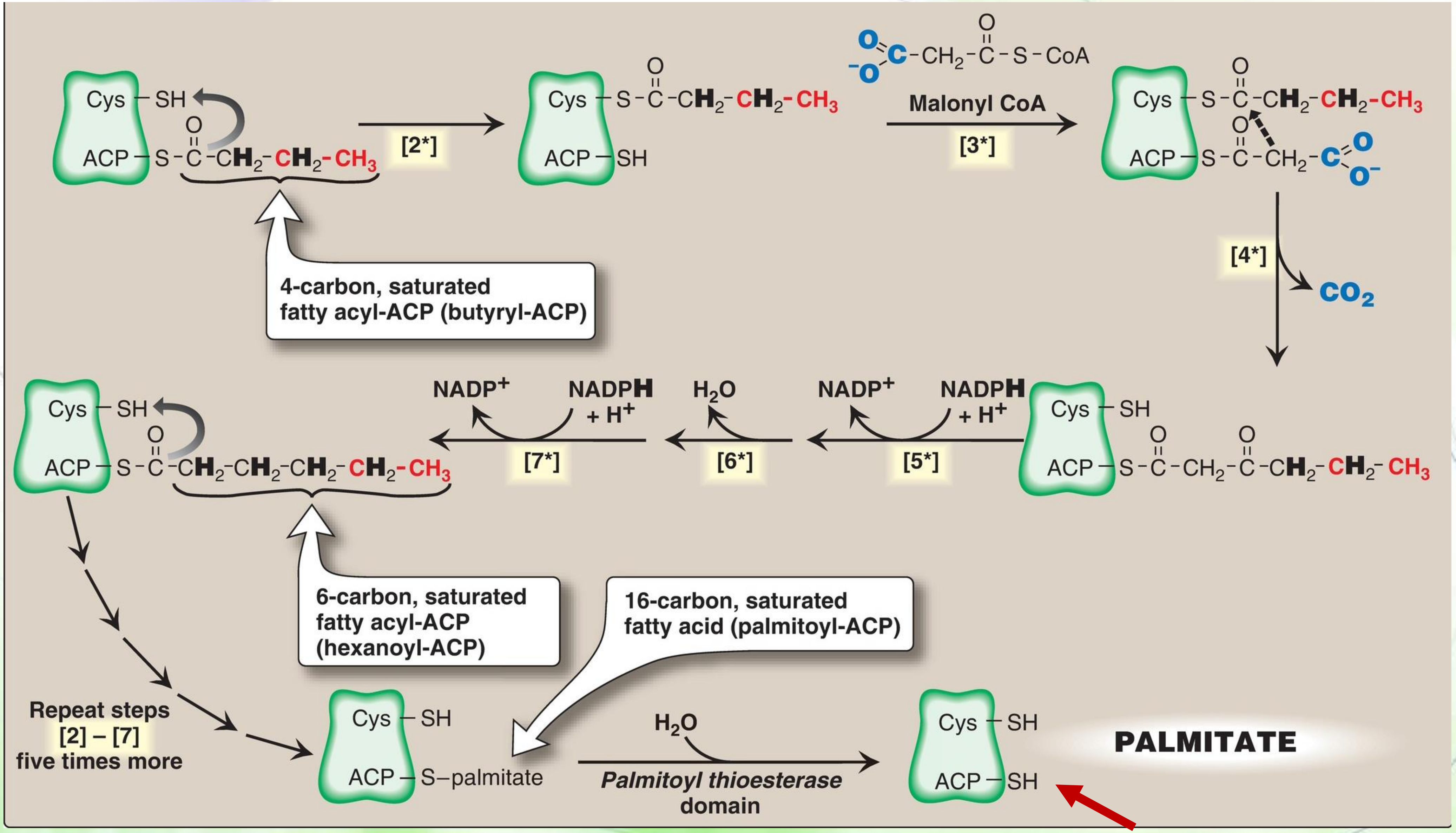
Condensation, reduction, dehydration, reduction







Compare to the first reaction in the previous slide



The lactating mammary gland terminates lengthening the chain EARLY.

The stoichiometry of palmitate synthesis

- **Stoichiometry of palmitate synthesis:**

  Acetyl-CoA + 7 malonyl-CoA + 14 NADPH + 14H^+ ⟶ palmitate + 7CO_2 + 14$NADP^+$ + 8CoA + 6H_2O

- **Malonyl-CoA synthesis:**

  7 Acetyl-CoA + 7CO_2 + 7ATP ⟶

  7 malonyl-CoA + 7ADP + 7P_i + 7H^+

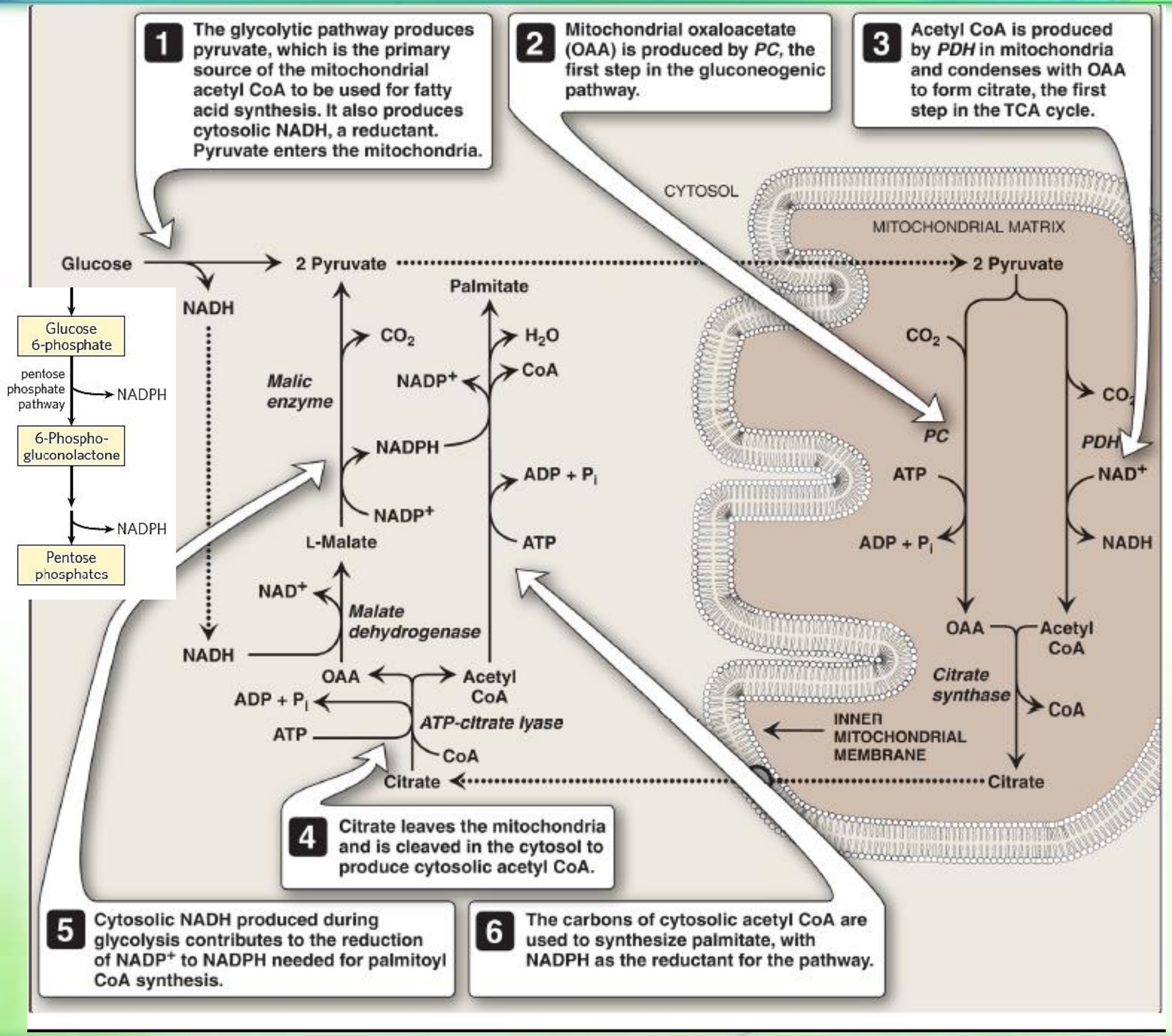
- **Overall stoichiometry of palmitate synthesis:**

  8 Acetyl-CoA + 14 NADPH + 7ATP + 7H^+ ⟶

  palmitate + 14$NADP^+$ + 8CoA + 6H_2O + 7ADP + 7P_i

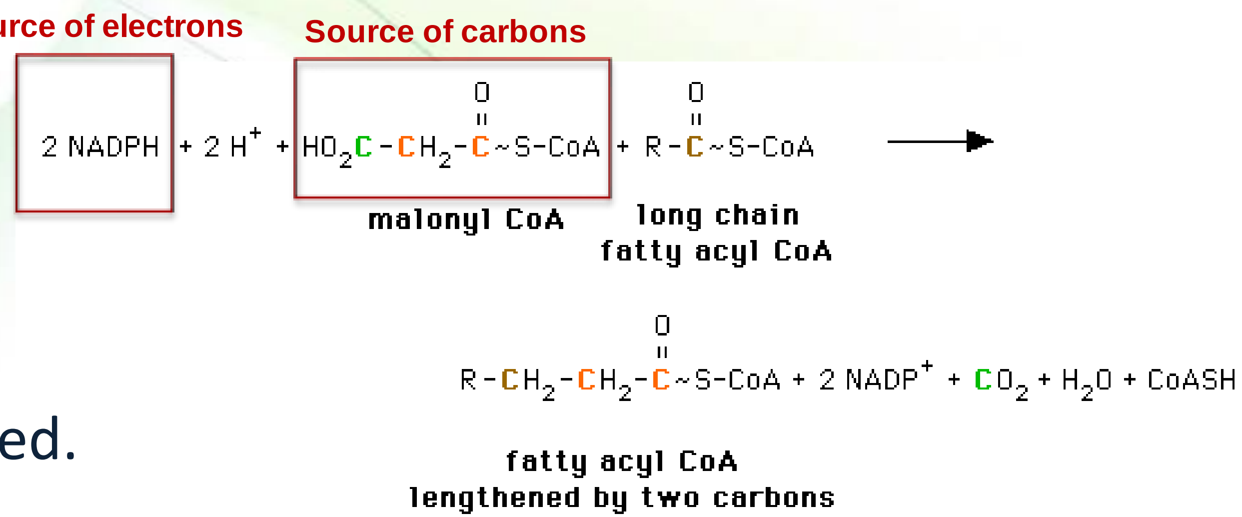
Sources of molecules

- Acetyl CoA
  - Pyruvate
- NADH *(for oxaloacetate to malate)*
  - Glycolysis
- NADPH:
  - Pentose phosphate pathway
  - Malate to pyruvate

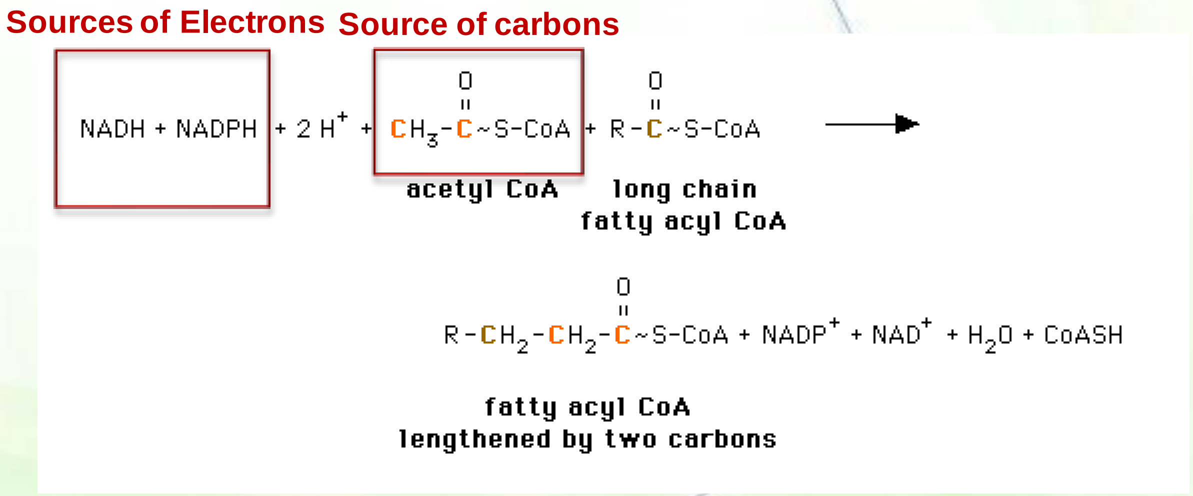


Further elongation

- Location: smooth endoplasmic reticulum
- Different enzymes are needed.
- Two-carbon donor: Malonyl CoA
- Source of electrons: NADPH
- No ACP or multifunctional enzyme is needed.



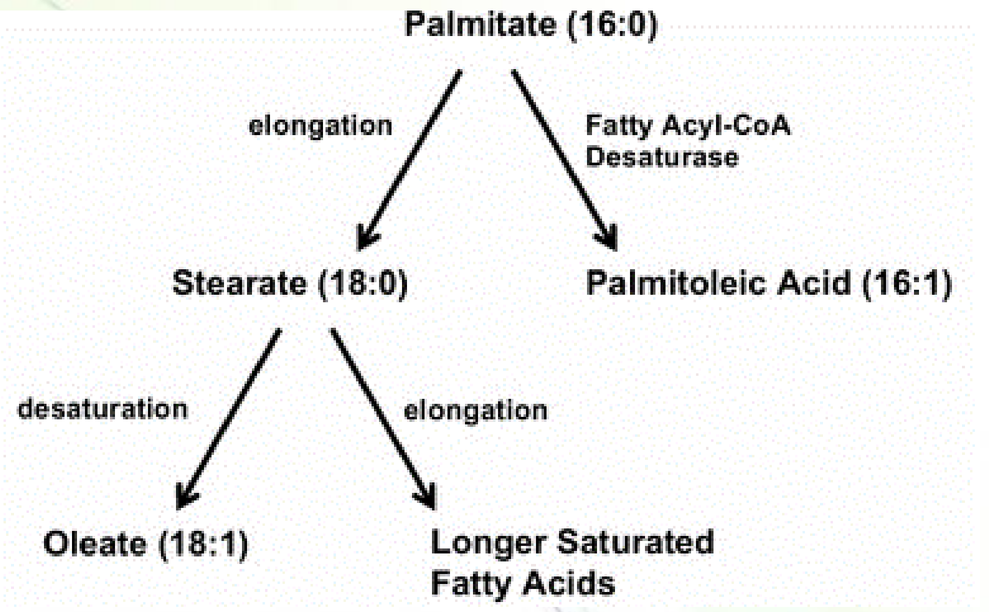
- Note: the brain has additional enzymes allowing it to produce the very-long-chain fatty acids ([VLCFA] over 22 carbons)

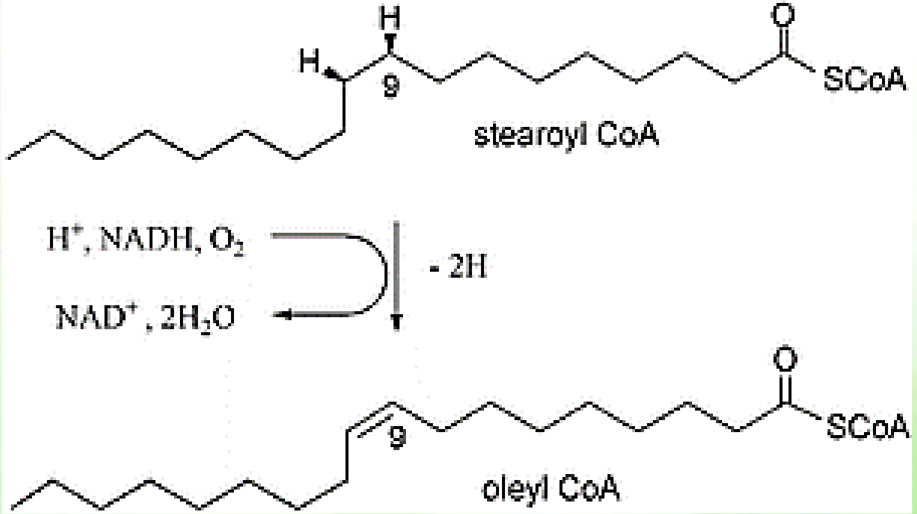


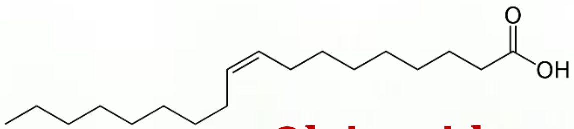
- Location: mitochondria
- Two-carbon donor: Acetyl CoA
- Source of electrons: NADPH and NADH
- Substrates: fatty acids shorter than 16

Chain desaturation

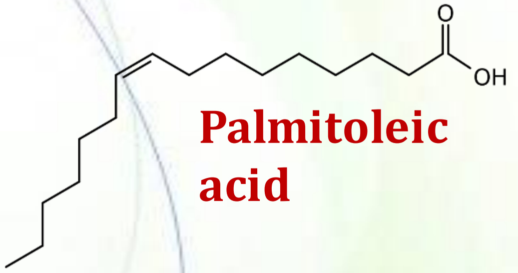
- Enzymes: fatty acyl CoA desaturases
- Substrates: long-chain fatty acids
- Location: smooth endoplasmic reticulum
- Acceptor of electrons: oxygen (O_2), cytochrome b5, and its flavin adenine dinucleotide (FAD)-linked reductase
- Donor of electrons: NADH
- The first double bond is inserted between carbons 9 and 10, producing oleic acid, 18:1(9), and small amounts of palmitoleic acid, 16:1(9).







Oleic acid

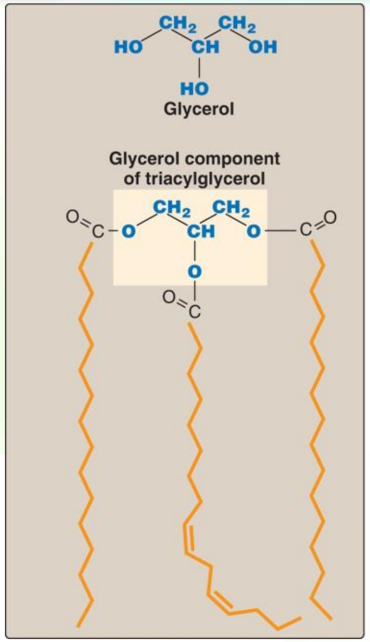


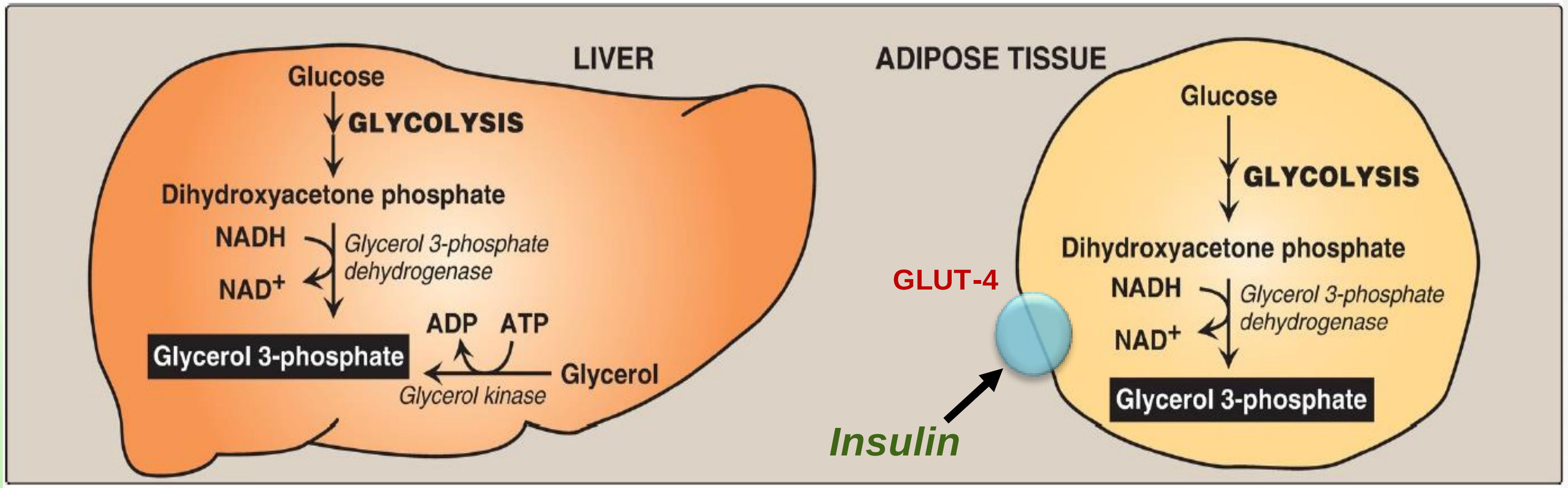
Palmitoleic acid

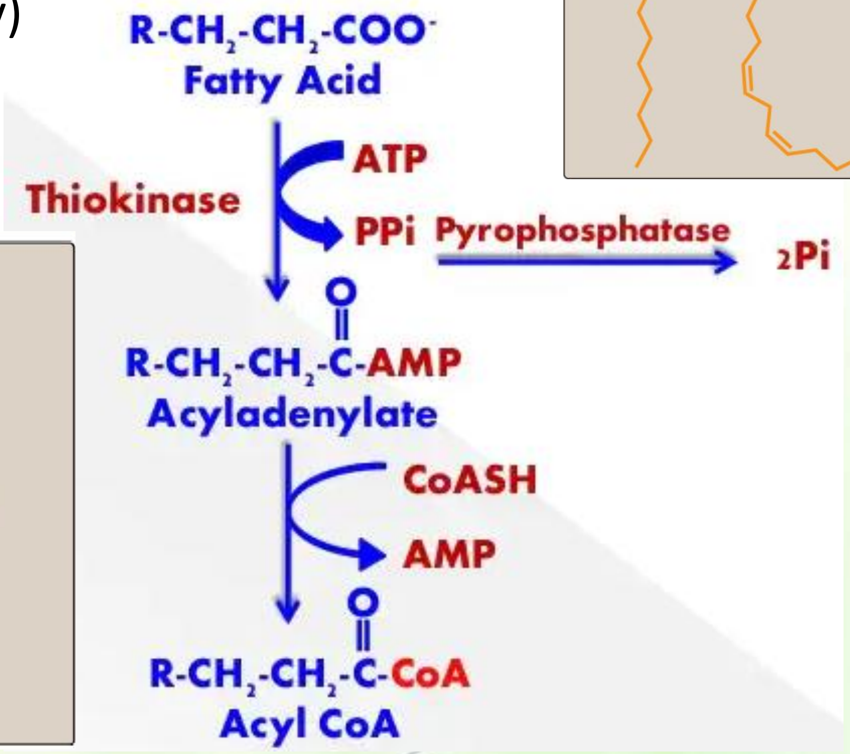
Humans have carbon 9, 6, 5, and 4 desaturases but cannot introduce double bonds from carbon 10 to the ω end of the chain. Therefore, the polyunsaturated ω-6 linoleic acid and ω-3 linolenic acid are essential.

Triacylglycerol structure and synthesis

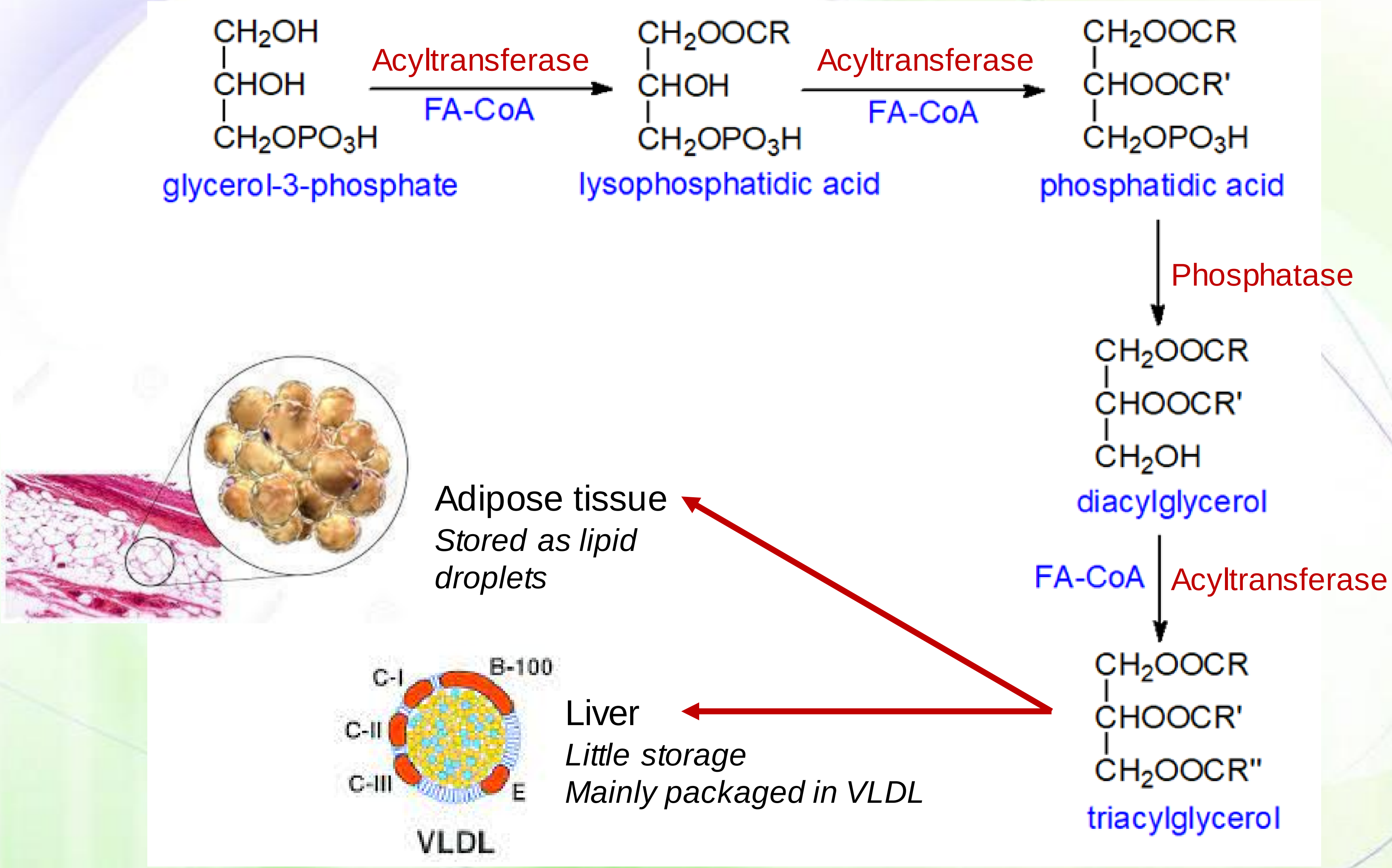
- The fatty acid on carbon 1 is typically saturated, that on carbon 2 is typically unsaturated, and that on carbon 3 can be either.
- Synthesis involves three steps:
  - Glycerol 3-phosphate synthesis
    - Liver (2 mechanisms) vs. adipose tissue (one mechanism only)
  - Activation of fatty acids
  - Synthesis of triacylglycerol







Synthesis of triacylglycerol



Intestinal mucosal cells

- In addition to these two pathways (as in the liver), TAG is synthesized via the MAG pathway in the intestinal mucosal cells.