Synthesis of fatty acids

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Lippincott’s Biochemistry, Ch. 16

Fatty Acid Synthesis

- Excess carbohydrates and proteins in diet will be used to synthesize fatty acids and stored as TAGs.
- Occurs in liver, lactating mammary glands and adipose tissue
- Requires
  - Carbon Source: Acetyl CoA
  - Reducing Power: NADPH
  - Energy Input: ATP

Why Energy ?

Fatty Acid	Acetyl CoA	Acetyl CoA + n(ATP)
↓	↓	↓
↓	↓	↓
↓	↓	↓
↓	↓	↓
Acetyl CoA	Fatty Acid	Fatty Acid + n(ADP)
ΔG^{o} : -ve	ΔG^{o} : +ve	ΔG^{o} : -ve

Overview of fatty acid synthesis

- 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)

FA Degradation and Synthesis

Acyl CoA $_{(n)}$

↓ Oxidation

↓ Hydration

↓ Oxidation

↓ Thyolysis

Acyl CoA $_{(n-2)}$ + Acetyl CoA

Acyl CoA $_{(n+2)}$

↑ reduction

↑ dehydration

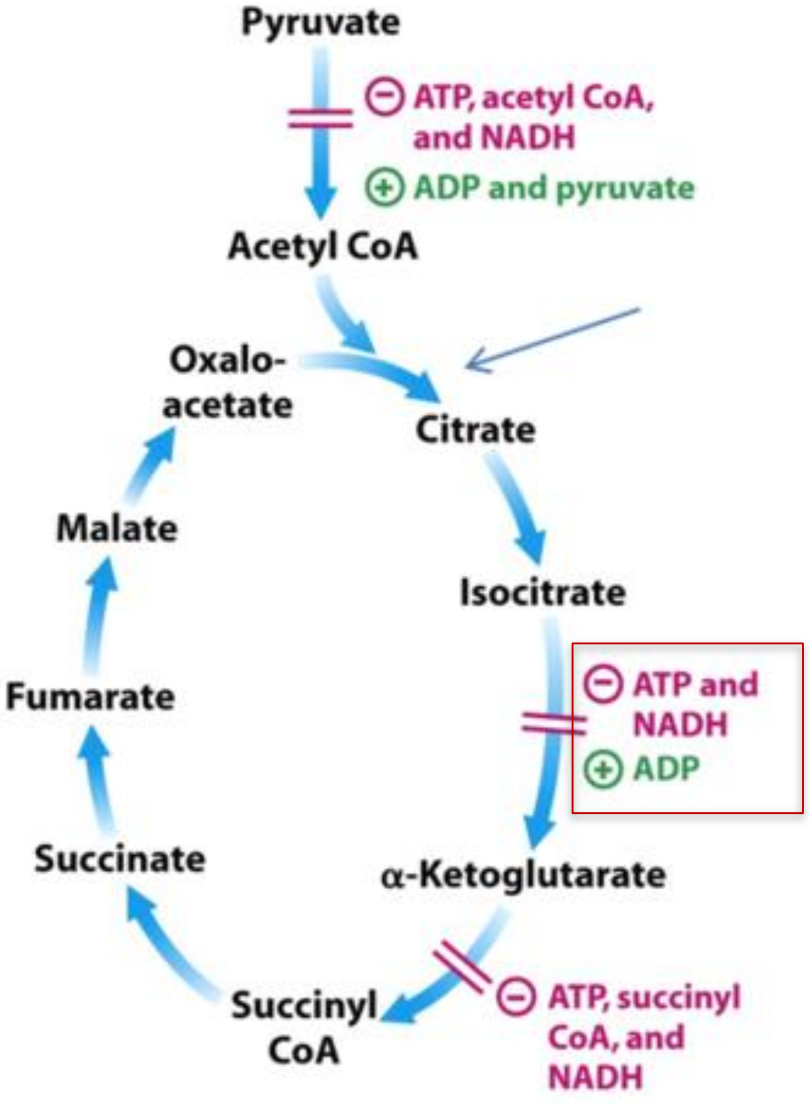
↑ reduction

↑ condensation

Acyl CoA$_{(n)}$ + Malonyl CoA

Acetyl CoA

Transport of acetyl-CoA from mitochondria to cytoplasm



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

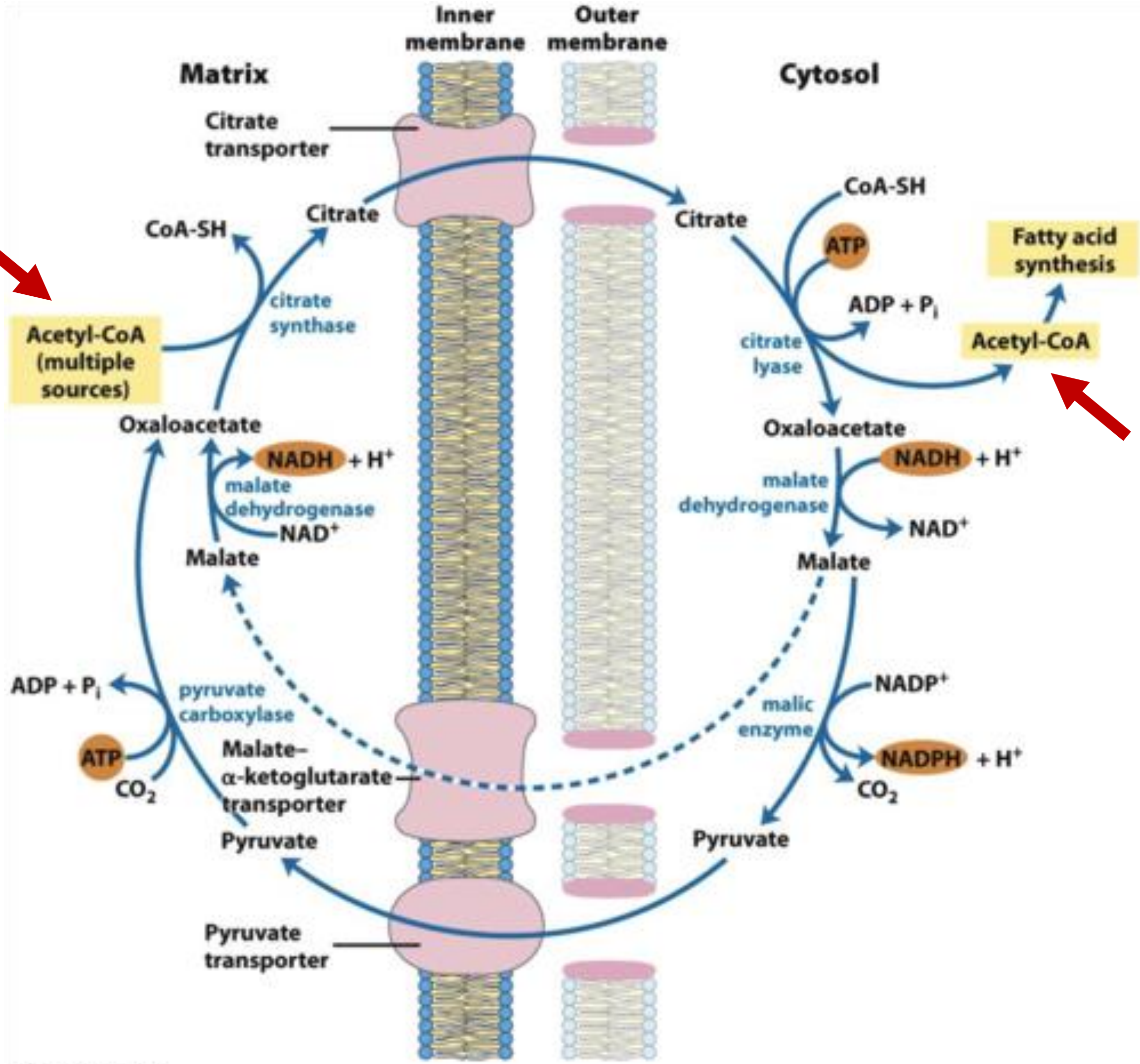
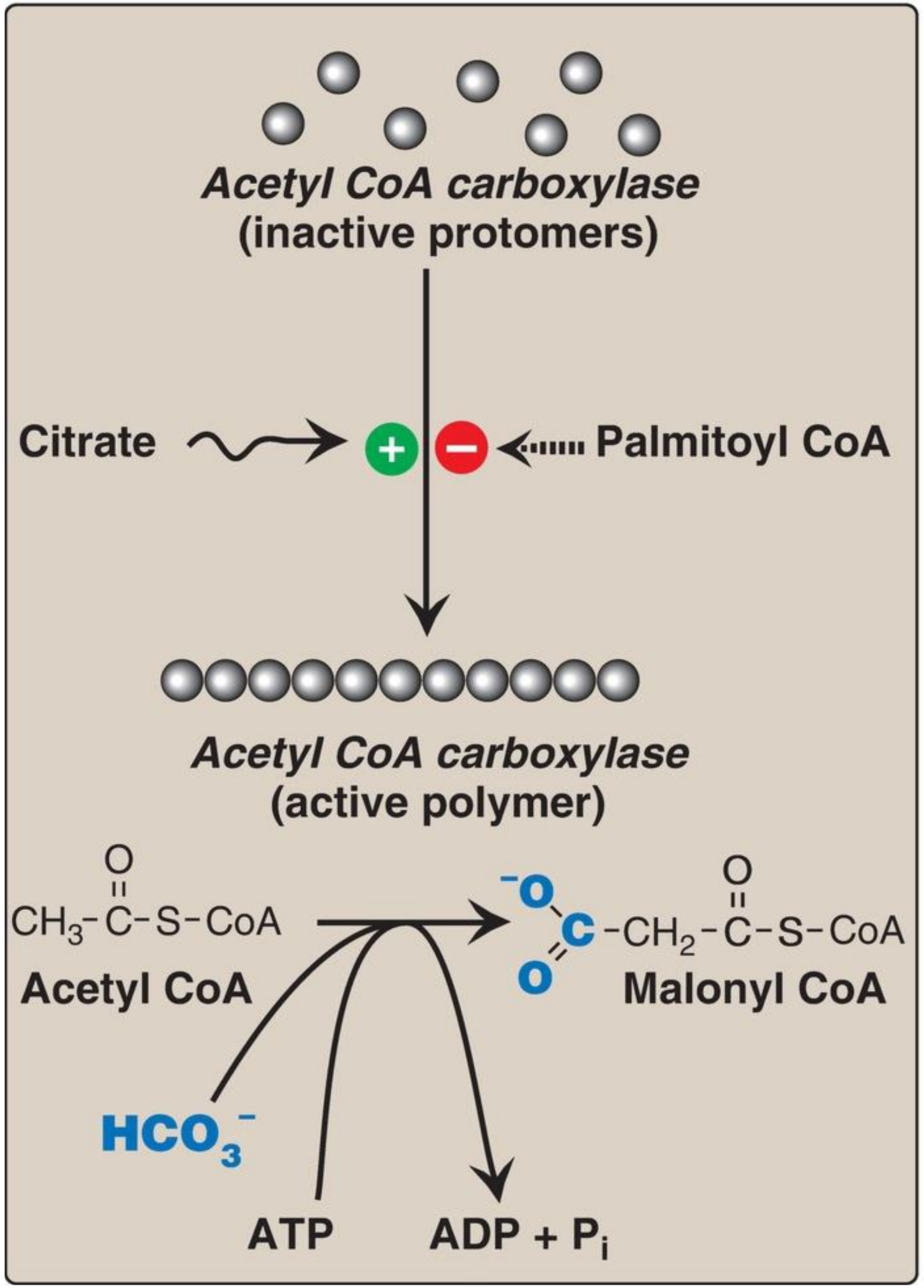


Figure 21-10
Lehninger Principles of Biochemistry, Fifth Edition

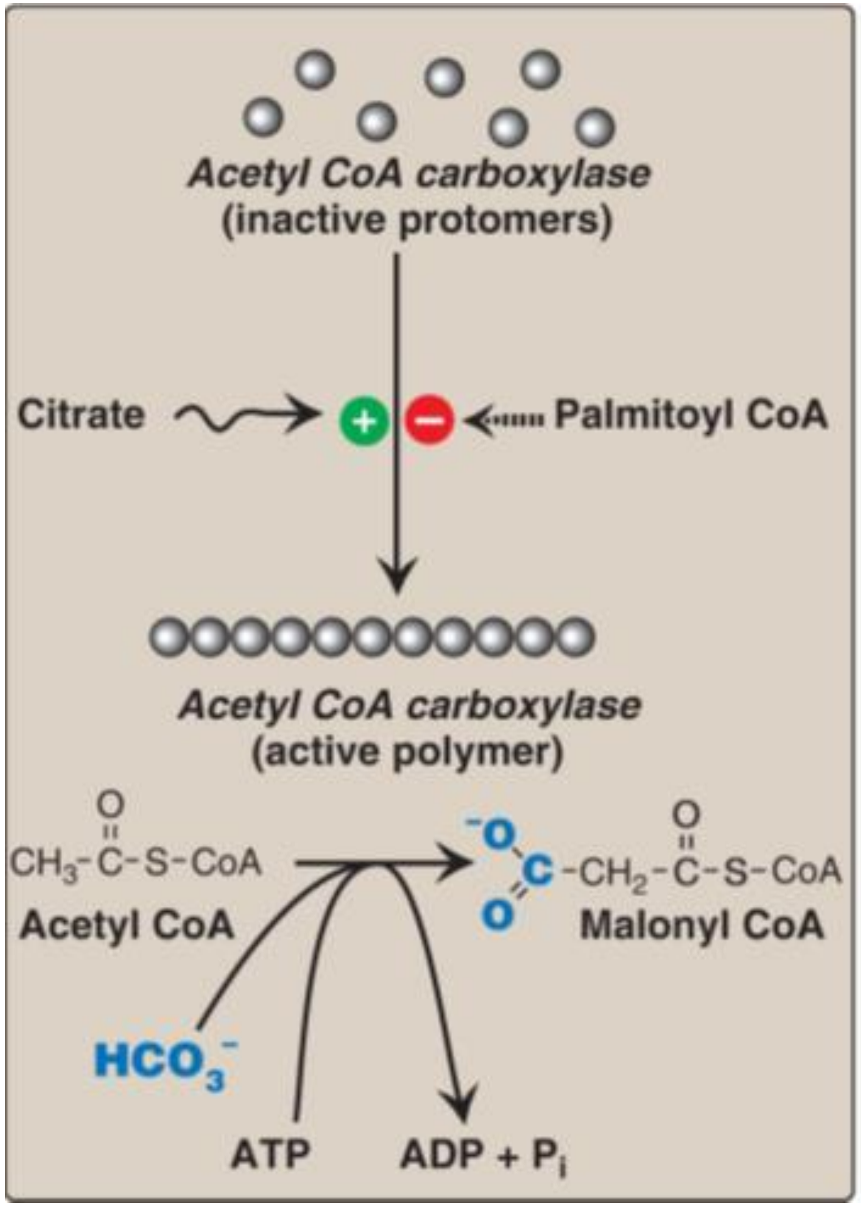
Glucose can be converted to fat, but fat cannot be converted to glucose.

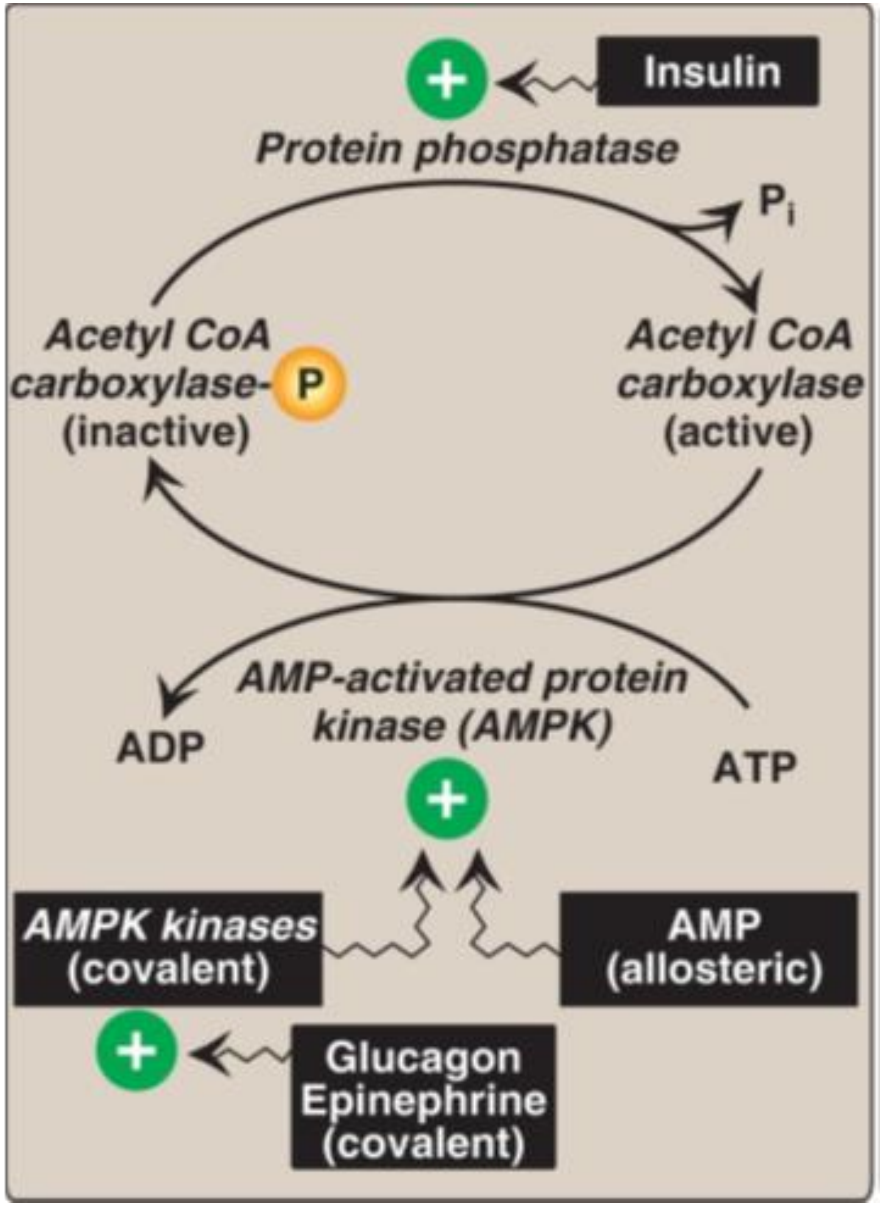
Synthesis of malonyl-CoA

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



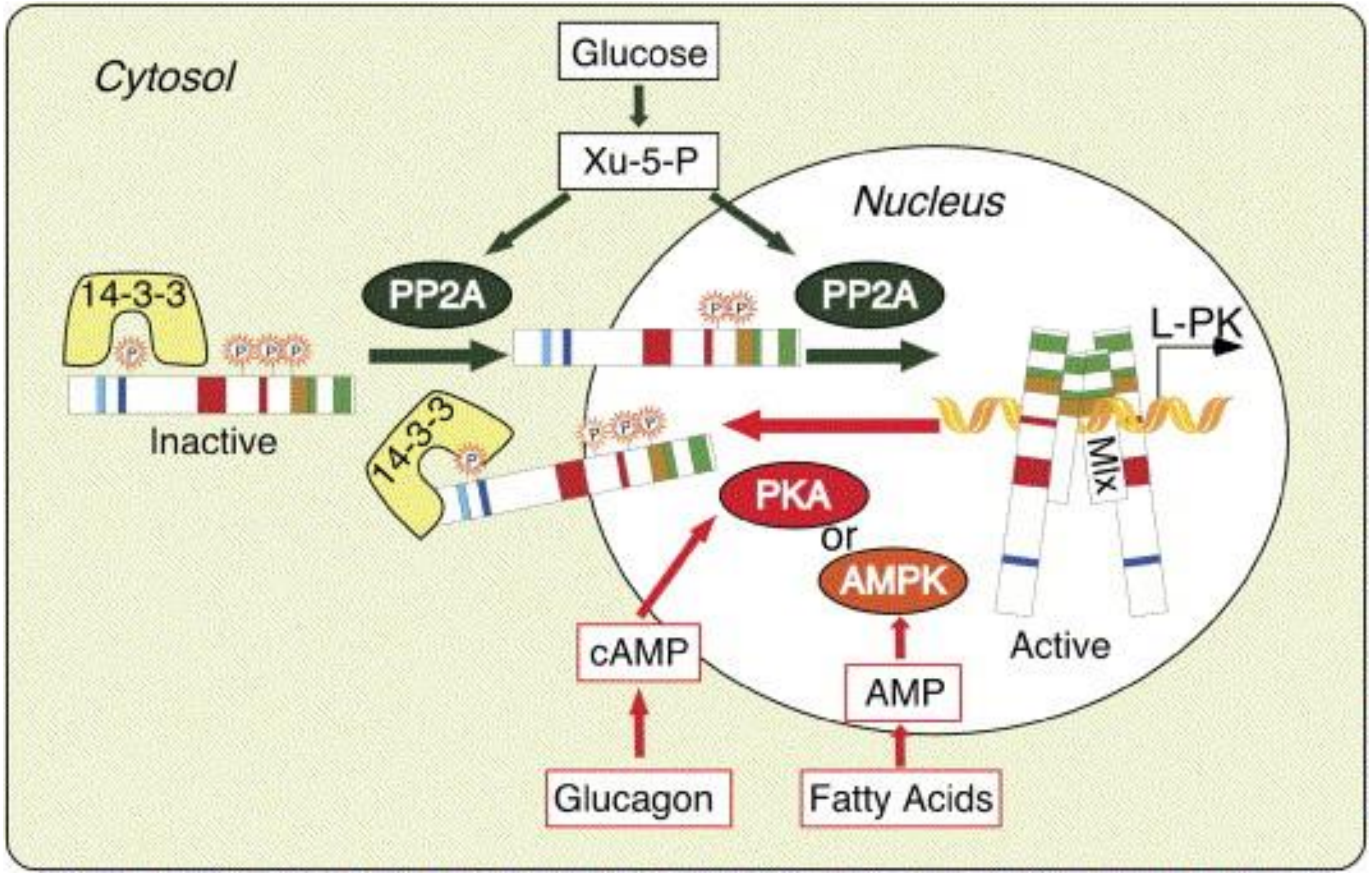
Regulation of ACC

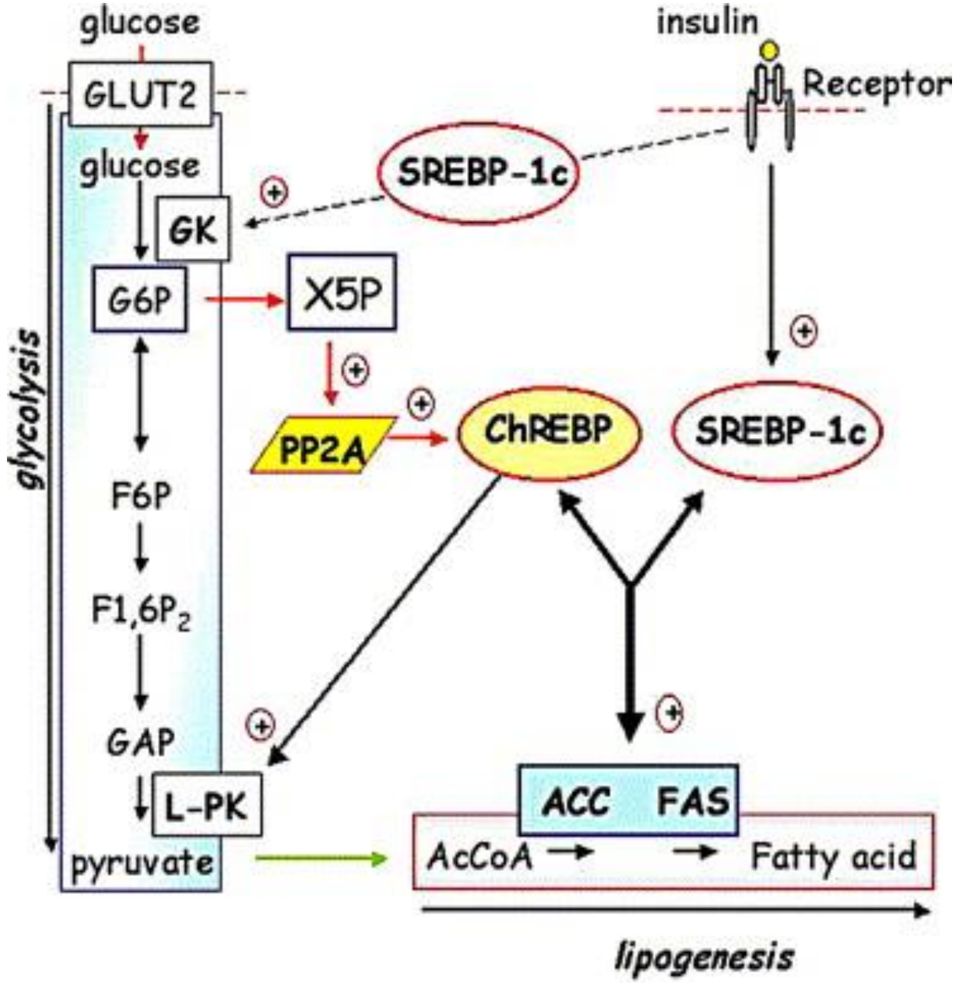




- ACC is **inactivated** by:
  - Palmitoyl-CoA
  - Phosphorylation by AMPK, which is activated by glucagon and epinephrine.

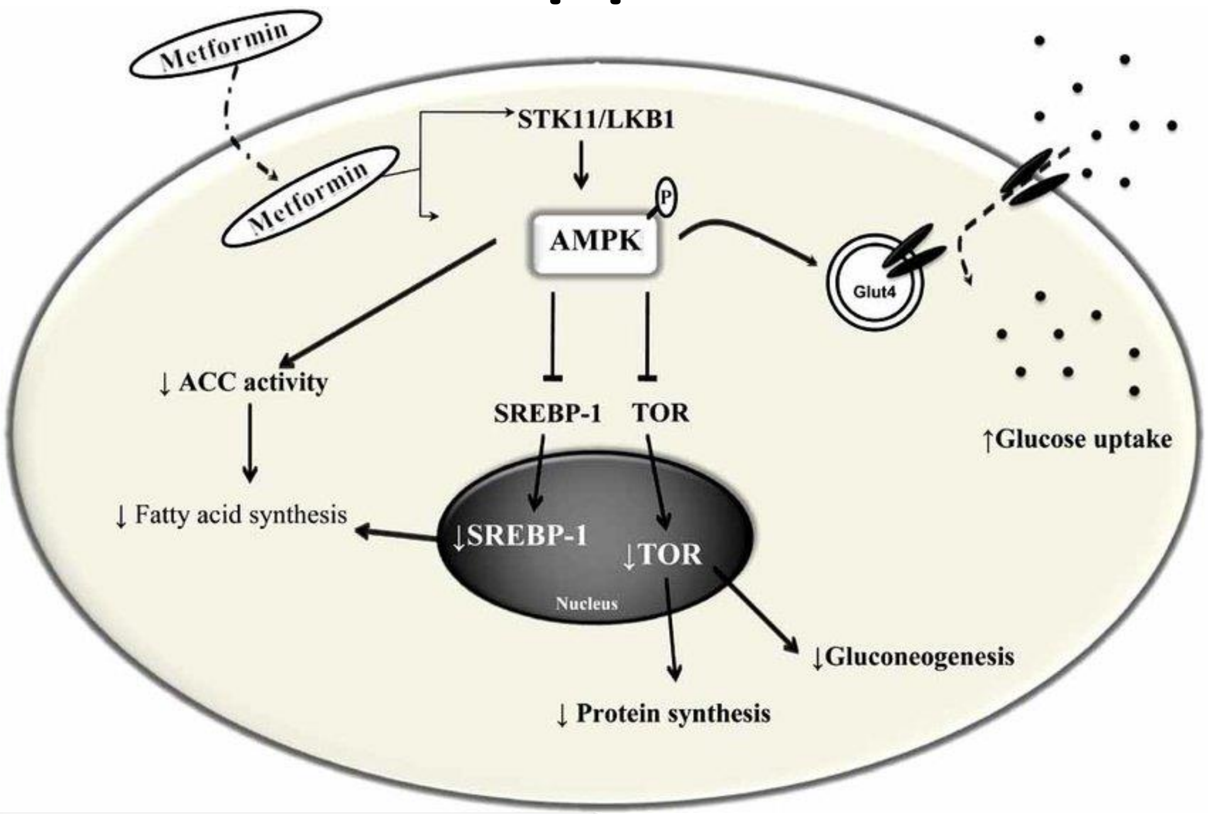
Regulation of ACC synthesis by transcription factors





- 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.

Application: Metformin



- Metformin lowers plasma TAG by:
  - 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.

Application: ACC2 inhibitors

Challenges related to efficacy, selectivity and safety

اكتشاف مثير ضد البدانة

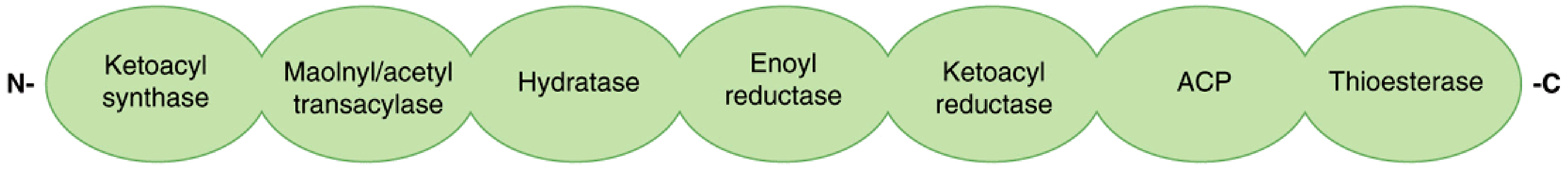
لندن – قدس برس اكتشف الباحثون علاجا مثيرا وقويا ضد البدانة قد يسمح للأشخاص بتناول ما يشاؤون من الطعام دون أن يكتسبوا وزنا إضافيا، بل على العكس يمكنهم تخفيف أوزانهم الزائدة.

وقال الباحثون من كلية بايلور الطبية في تكساس، قالوا إنهم اكتشفوا إنزيما يضعف قدرة الجسم على حرق الدهون، وبالتحكم في هذا الأنزيم، فسيكون بالإمكان السماح للجسم بحرق دهون أكثر.

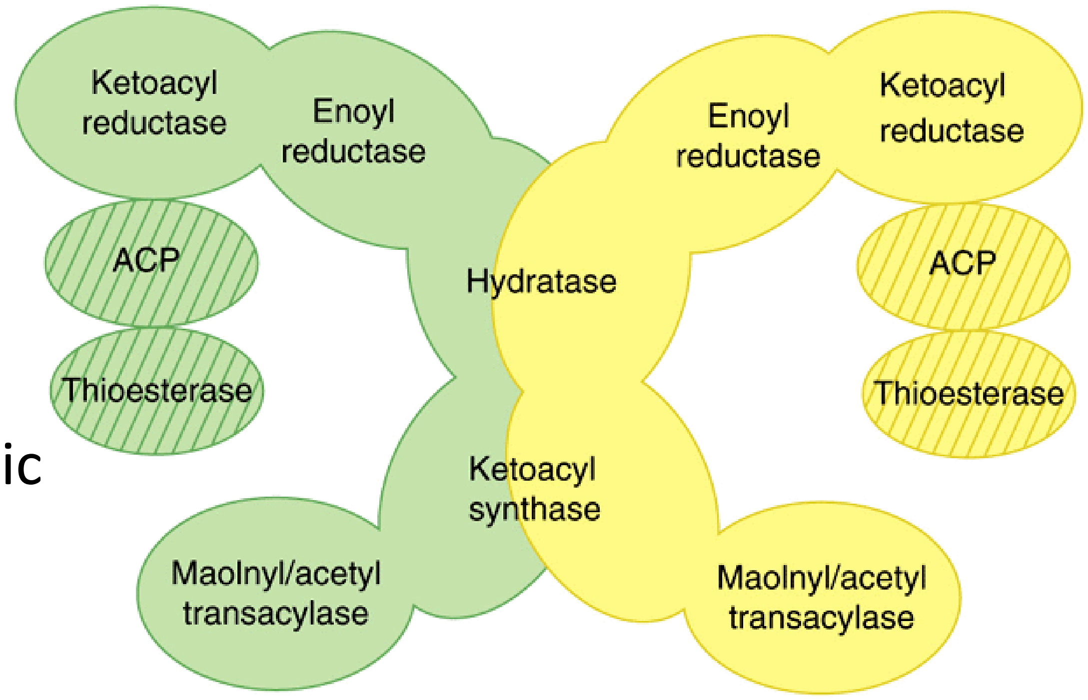
وقال الباحثون إن الفئران المهندسة وراثيا، التي ينقصها إنزيم «أسيتل – كو ايه كاربوكسيليز ٢» أو ما يعرف اختصارا بـ ,ACC2 تستطيع تناول كميات أكثر من الطعام بحوالي ٤٠ في المائة، وتزن أقل بنحو ١٥ في المائة، مقارنة مع غيرها من الحيوانات.

وسجل الدكتور صالح وكيل، كبير الباحثين، في مجلة «العلوم» الأمريكية، أن هذا الأنزيم ACC2 قد يكون هدفا لإنتاج أدوية تنظم حرق الدهون في الجسم، لذلك فقد يلعب دورا مهما في عمليات تنظيم البدانة، وعلاج السكري، وحتى في حالات استخدام وتراكم الدهون التي تزيد خطر الإصابة بتصلب الشرايين، مشيرا الى أن الفئران التي ينقصها ذلك الجين تبدو سعيدة وحيوية وتتناسل بشكل جيد.

Fatty acid synthase (FAS)



Sequence of enzyme domains in primary structure of fatty acid synthase monomer

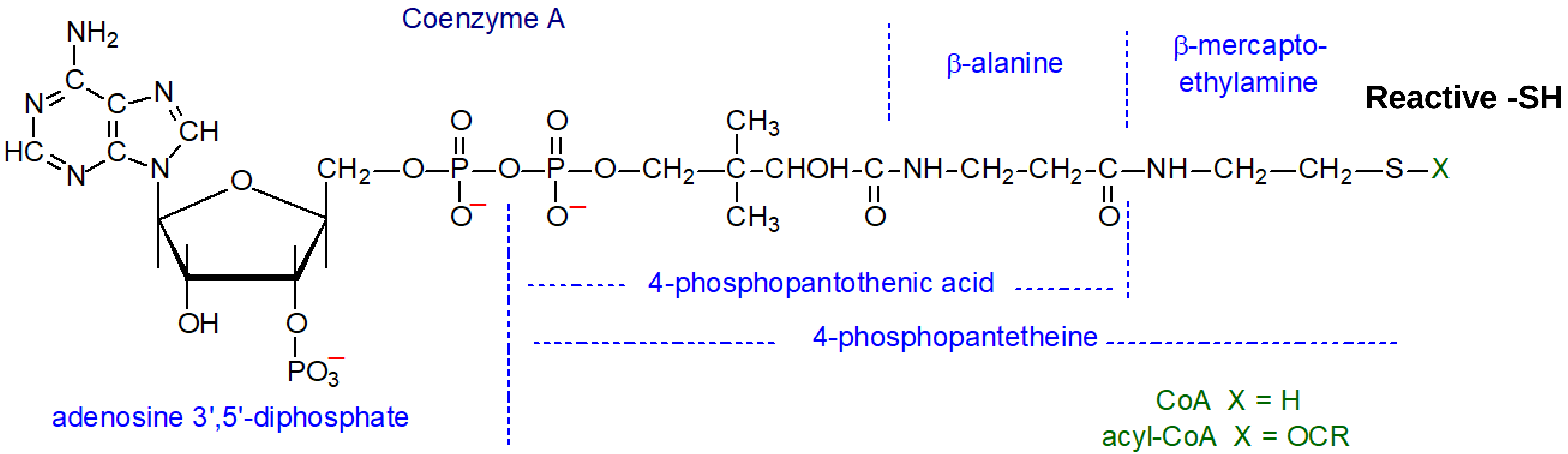


Fatty acid synthase homodimer

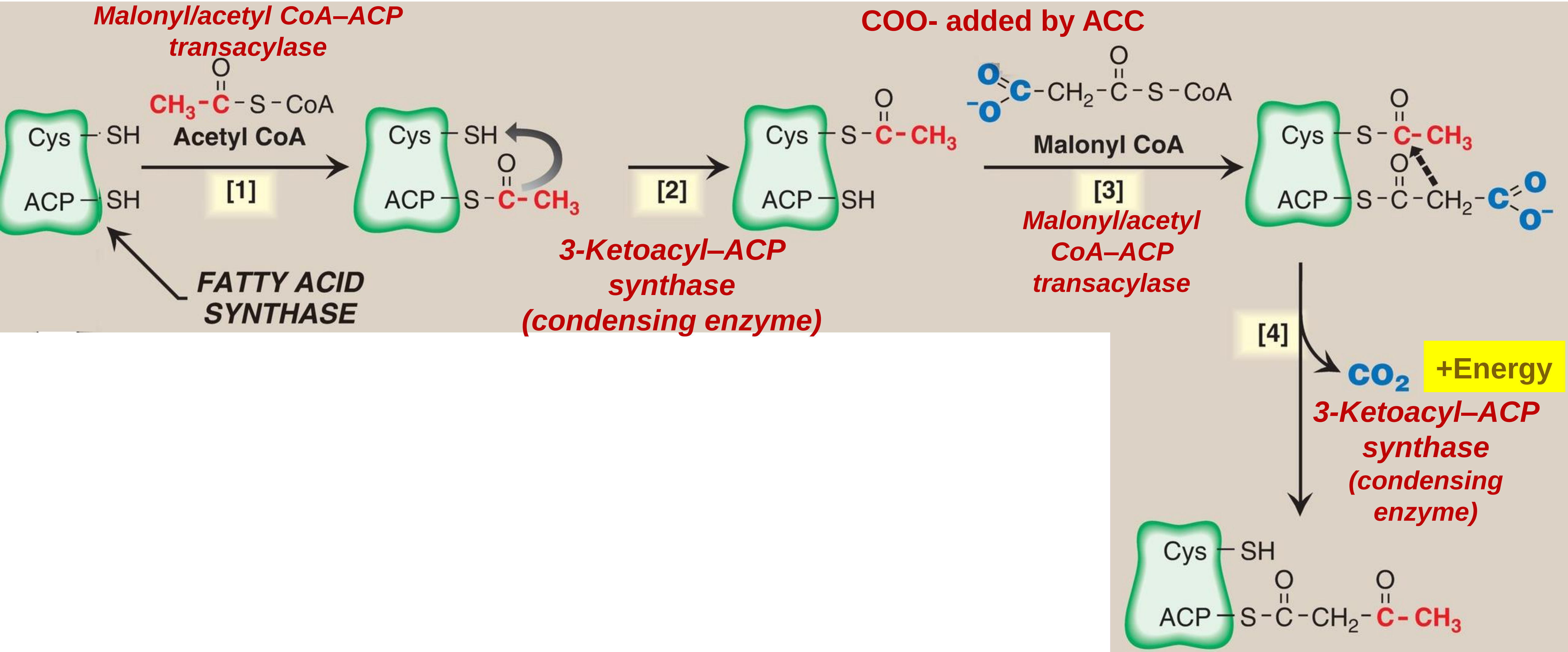
- A multifunctional, homodimeric enzyme complex
- Each FAS monomer is multicatalytic with six enzymic domains and a domain for binding a phosphopantetheine-containing acyl carrier protein (ACP) domain.

Fatty acid synthase (FAS)

- 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.

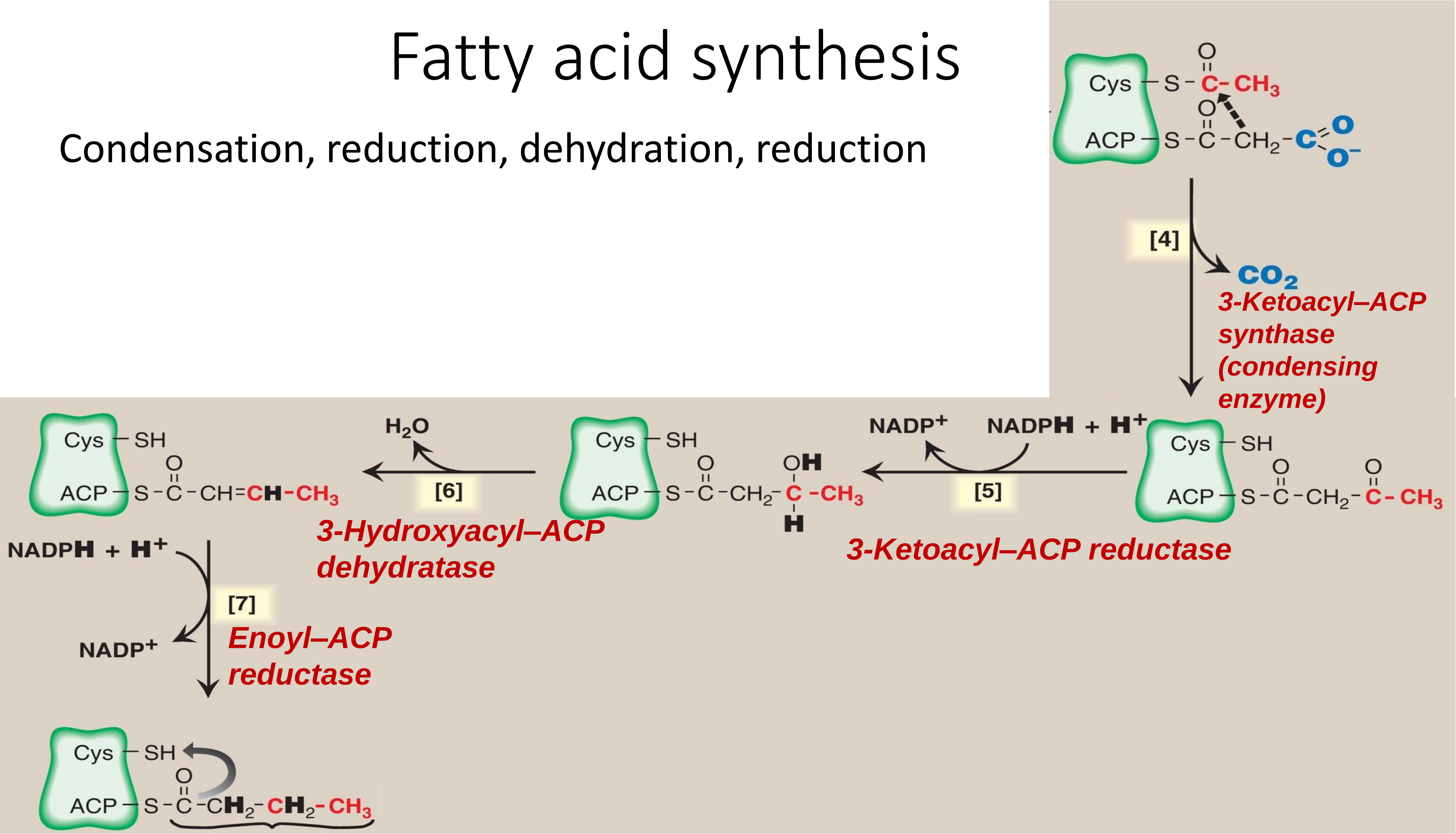


Fatty acid synthesis

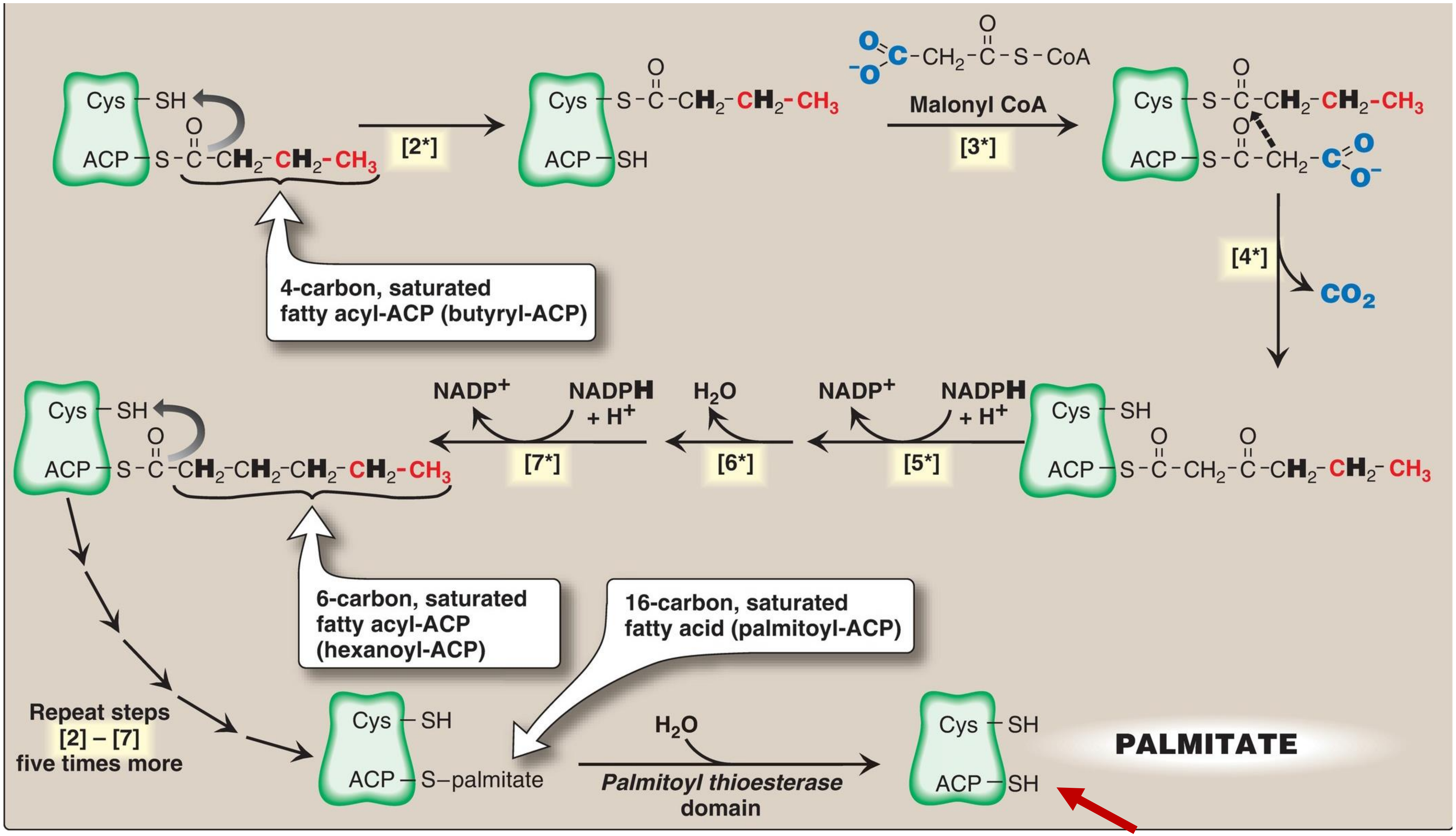


Fatty acid synthesis

Condensation, reduction, dehydration, reduction

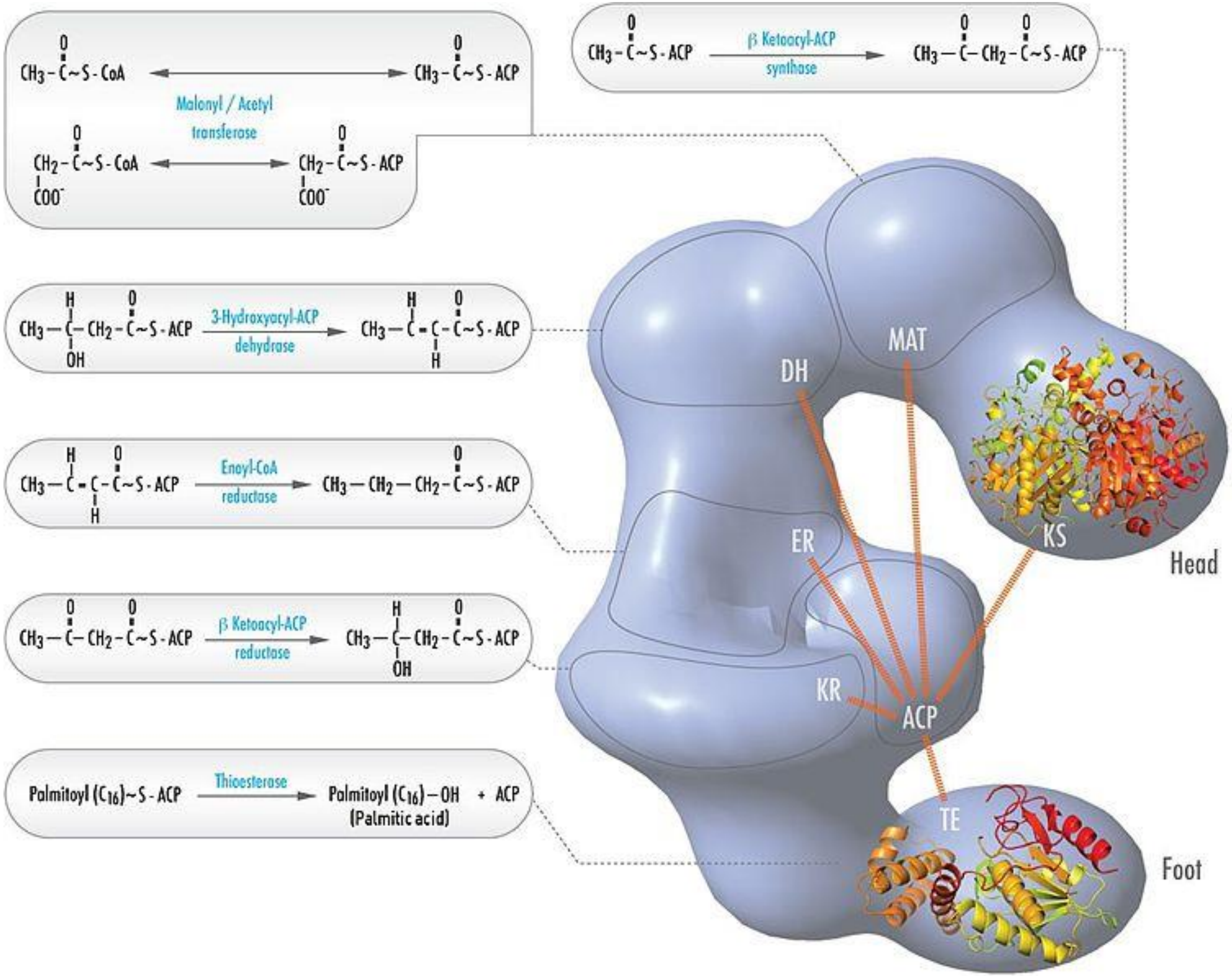


Fatty acid synthesis



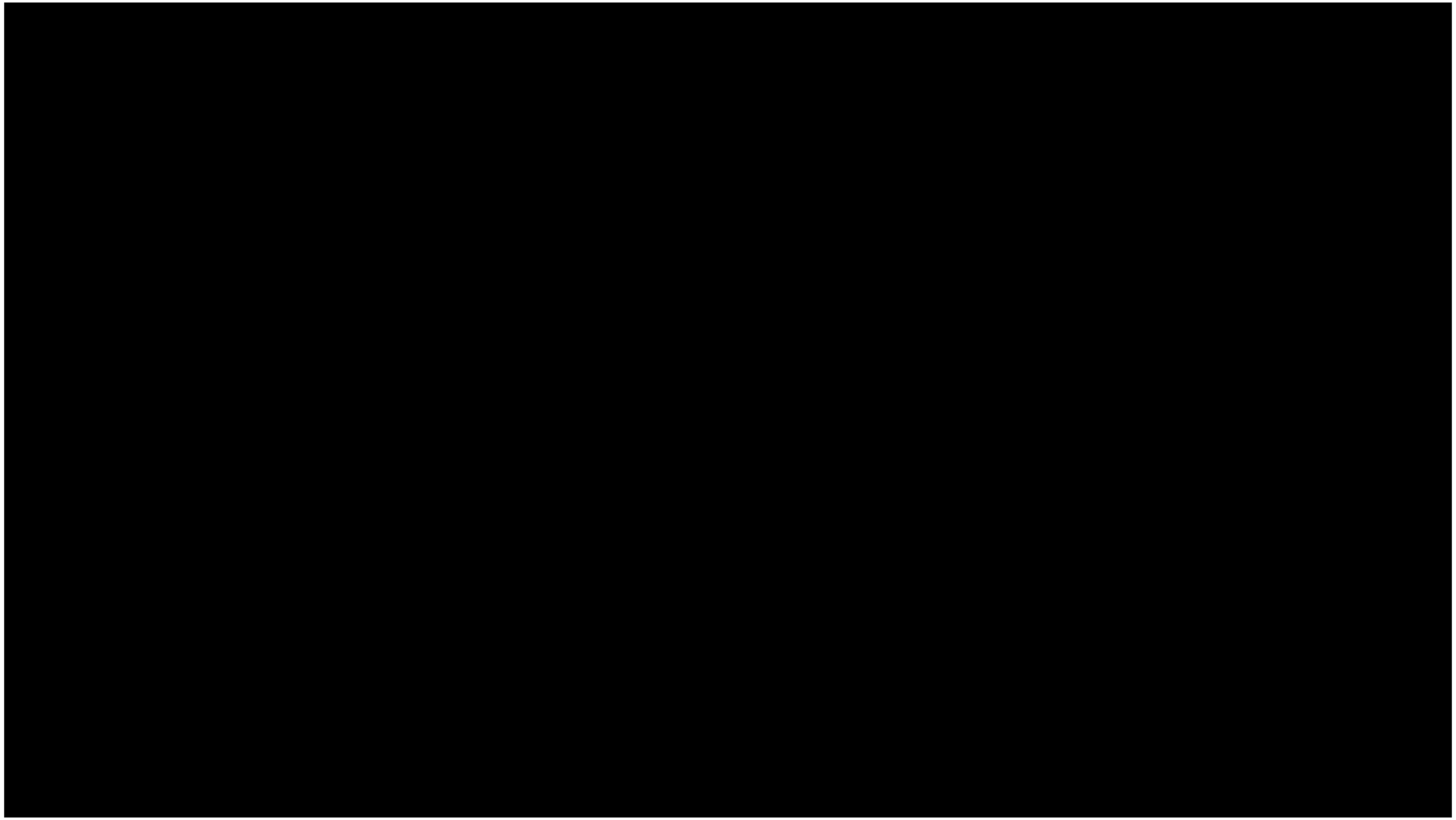
The lactating mammary gland terminates lengthening the chain EARLY.

Fatty acid synthesis



Fatty acid synthesis

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



The stoichiometry of palmitate synthesis

- **Stoichiometry of palmitate synthesis:**

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

- **Malonyl-CoA synthesis:**

  7 Acetyl-CoA + $7CO_2$ + 7ATP ⟶

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

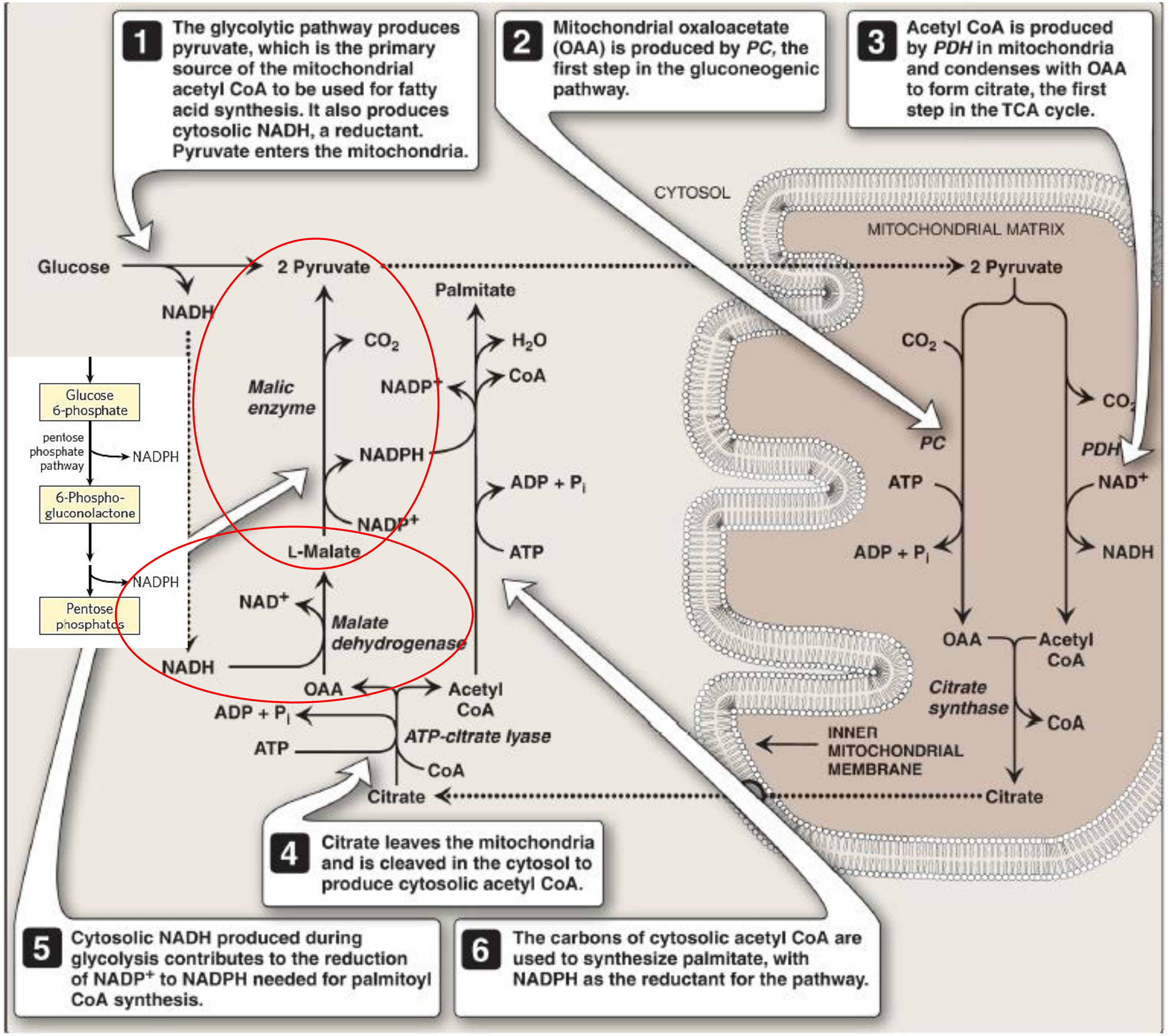
- **Overall stoichiometry of palmitate synthesis:**

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

  palmitate + $14NADP^+$ + 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



Regulation of FA Oxidation & Synthesis

OXIDATION

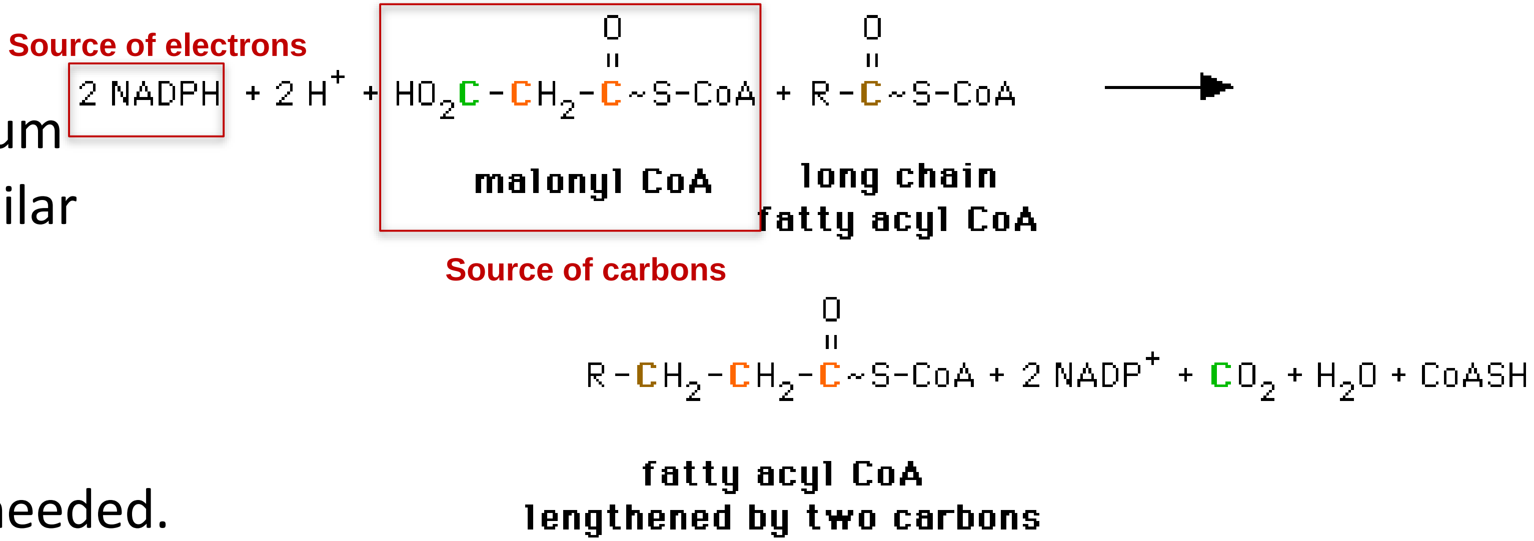
- **Supply of Fatty Acids**
  -Hormonal Control
- **Entry into Mitochondria**
- **Availability of NAD^+**

SYNTHESIS

- **Regulation of ACC**
  -Allosteric Mechanism
  - Phosphorylation
- **Amounts of Enzymes**

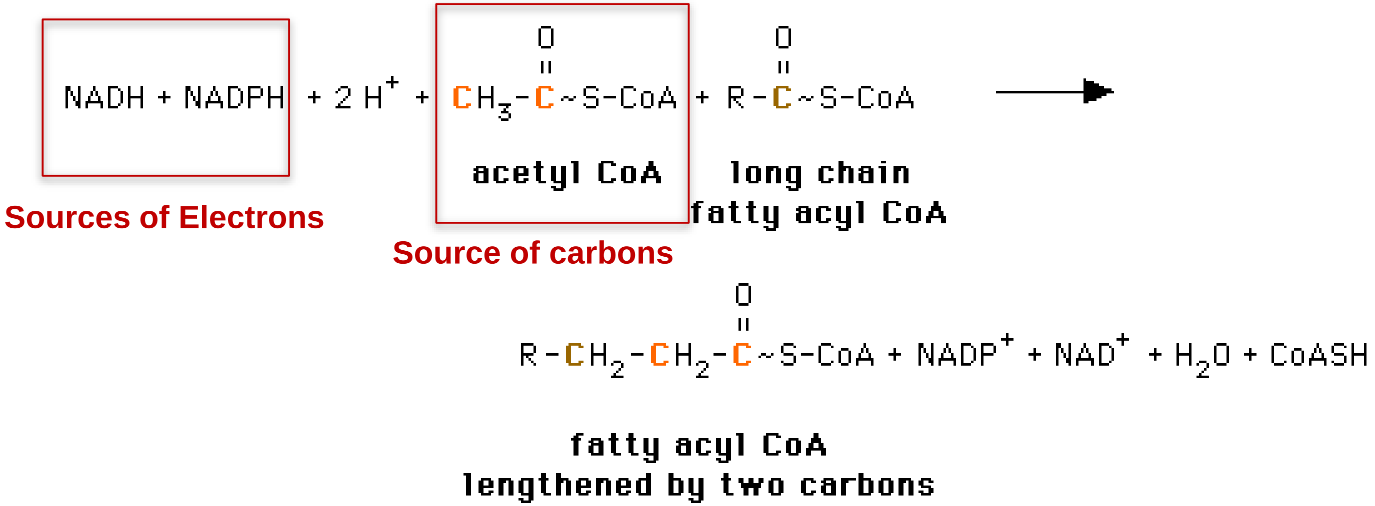
Further elongation of fatty acids

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



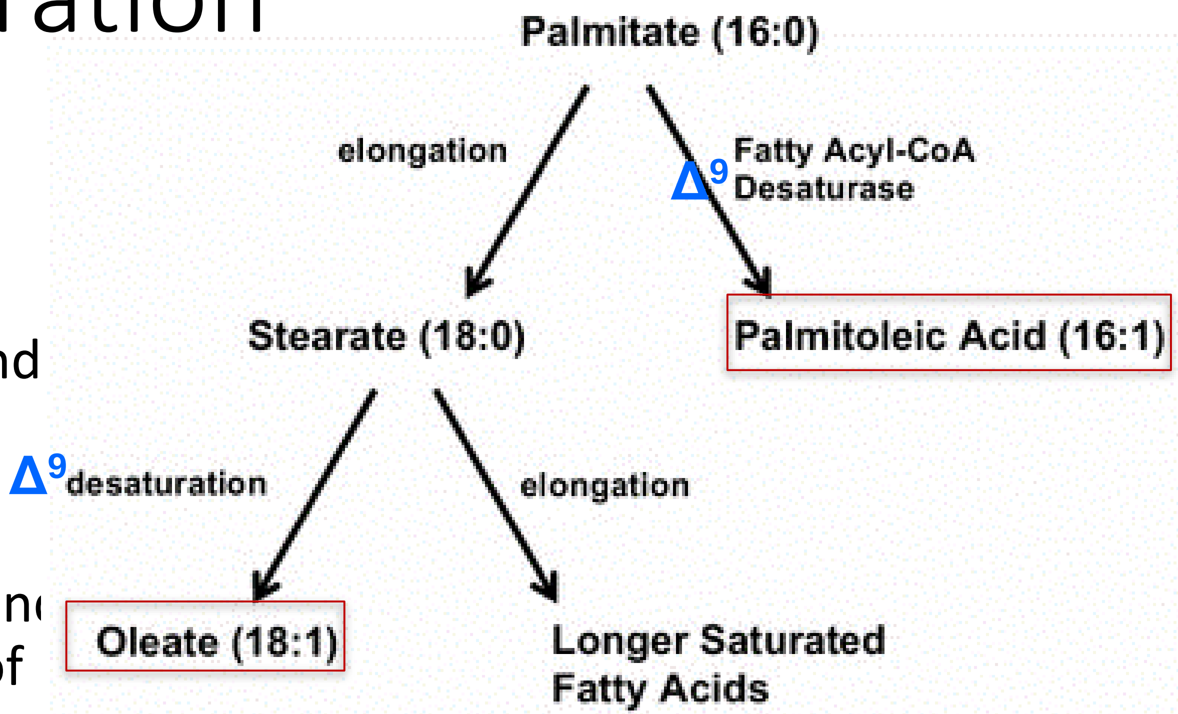
- Note: the brain has additional enzymes allowing it to produce the very-long-chain fatty acids ([VLCFA] over 22 carbons)

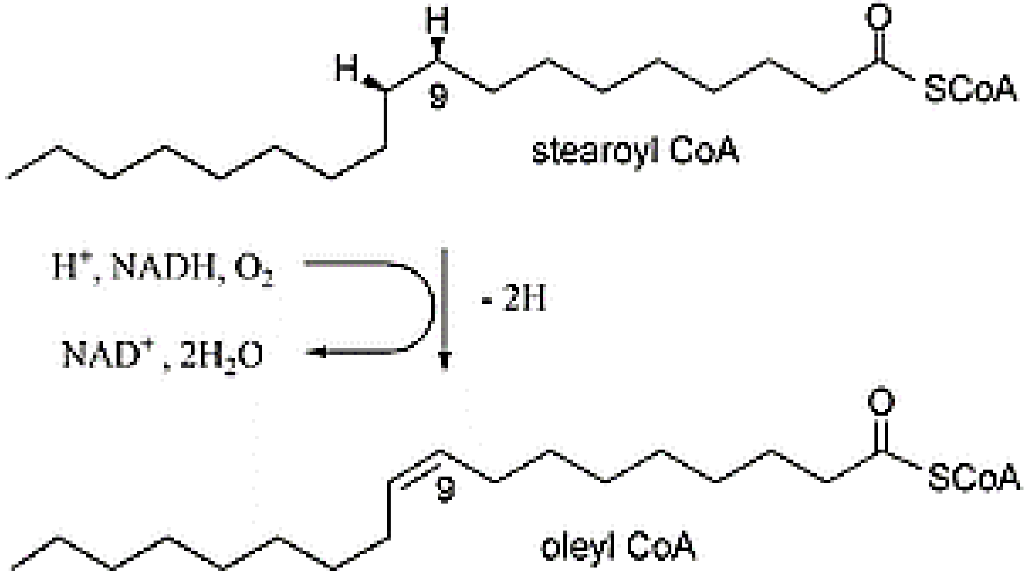
- Location: mitochondria
- Two-carbon donor: Acetyl CoA
- Source of electrons: NADPH and NADH
- Substrates: fatty acids shorter than 16



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 FAD-linked reductase
- Donor of electrons: NADH
- The first double bond is inserted between carbons 9 an 10, producing oleic acid, 18:1(9), and small amounts of palmitoleic acid, 16:1(9).



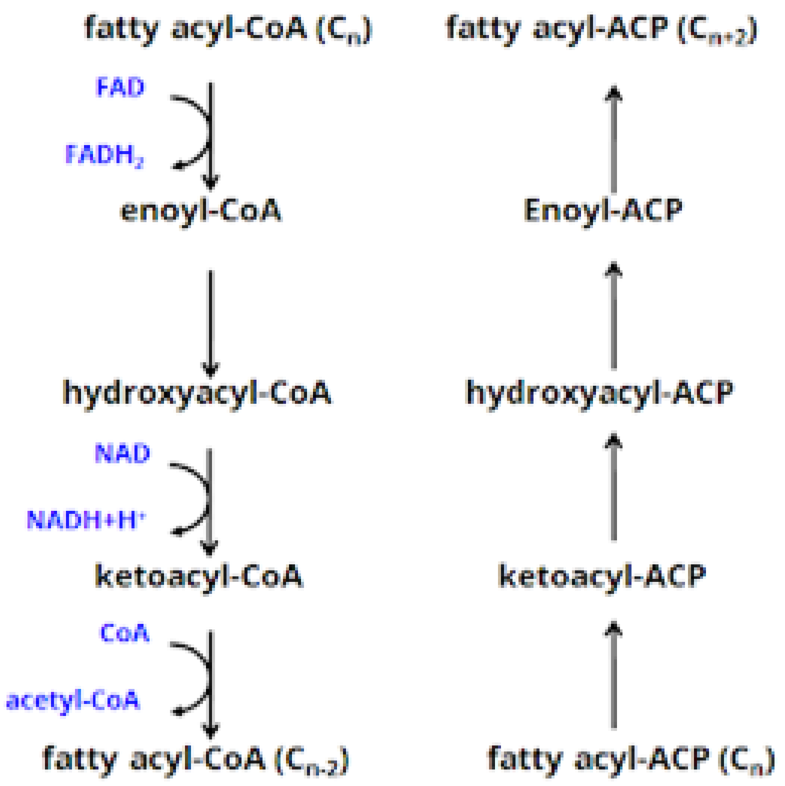


Humans have carbon 9, 6, 5, and 4 desaturases but cannot introduce double bonds from carbon 10 to the ω end of the chain. Therefore, the polyunsaturated ω-6 linoleic acid and ω-3 linolenic acid are essential.

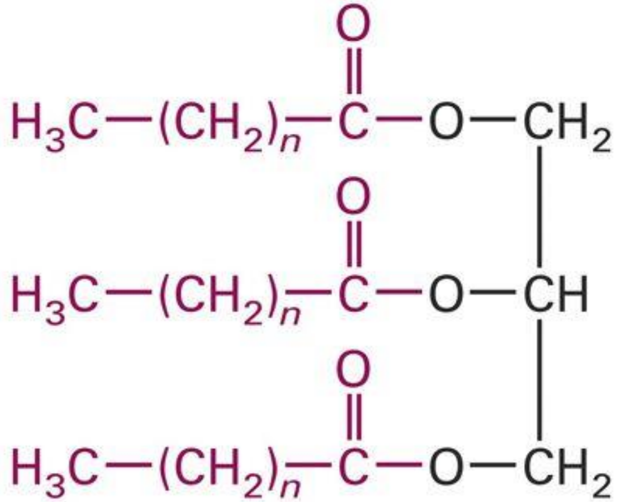
- ✓ Formation of polyunsaturated FA by elongation and desaturation
- ✓ Additional double bonds can be introduced by Δ^4 desaturase, Δ^5 desaturase and Δ^6 desaturase

FA Synthesis vs. degradation

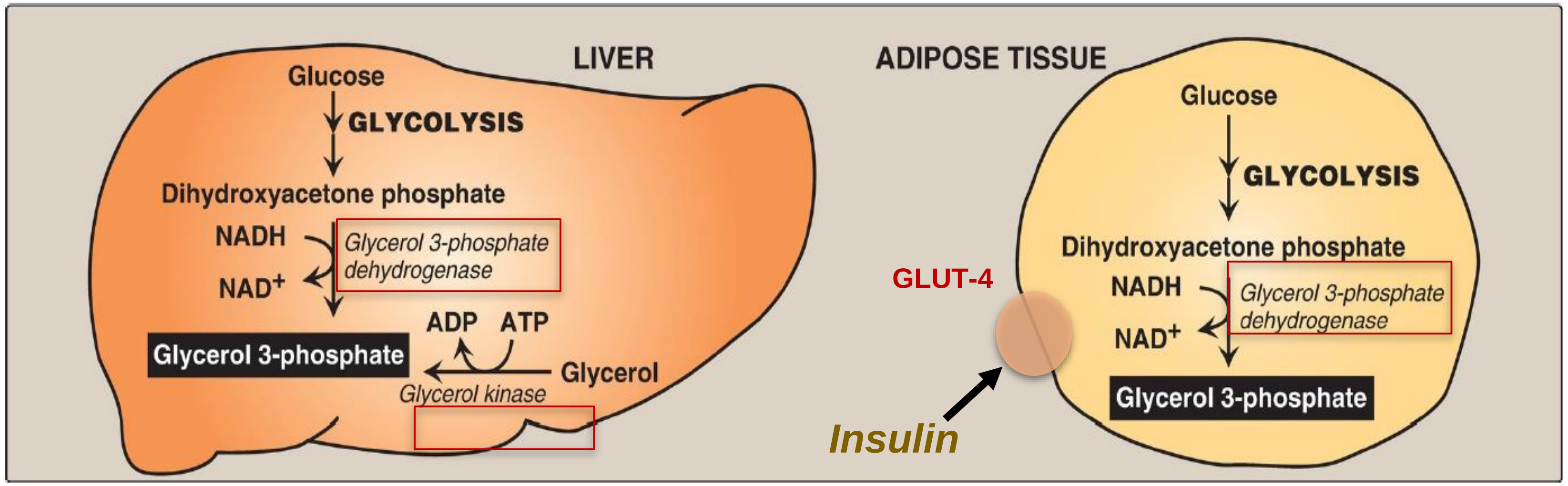
VARIABLE	SYNTHESIS	DEGRADATION
Greatest flux through pathway	After carbohydrate-rich meal	In starvation
Hormonal state favoring pathway	High insulin/glucagon ratio	Low insulin/glucagon ratio
Major tissue site	Primarily liver	Muscle, liver
Subcellular location	Cytosol	Primarily mitochondria
Carriers of acyl/acetyl groups between mitochondria and cytosol	Citrate (mitochondria to cytosol)	Carnitine (cytosol to mitochondria)
Phosphopantetheine-containing active carriers	Acyl carrier protein domain, coenzyme A	Coenzyme A
Oxidation/reduction coenzymes	NADPH (reduction)	NAD^+, FAD (oxidation)
Two-carbon donor/product	Malonyl CoA: donor of one acetyl group	Acetyl CoA: product of β-oxidation
Activator	Citrate	—
Inhibitor	Palmitoyl CoA (inhibits *acetyl CoA carboxylase*)	Malonyl CoA (inhibits *carnitine palmitoyltransferase-I*)
Product of pathway	Palmitate	Acetyl CoA
Repetitive four-step process	Condensation, reduction dehydration, reduction	Dehydrogenation, hydration dehydrogenation, thiolysis

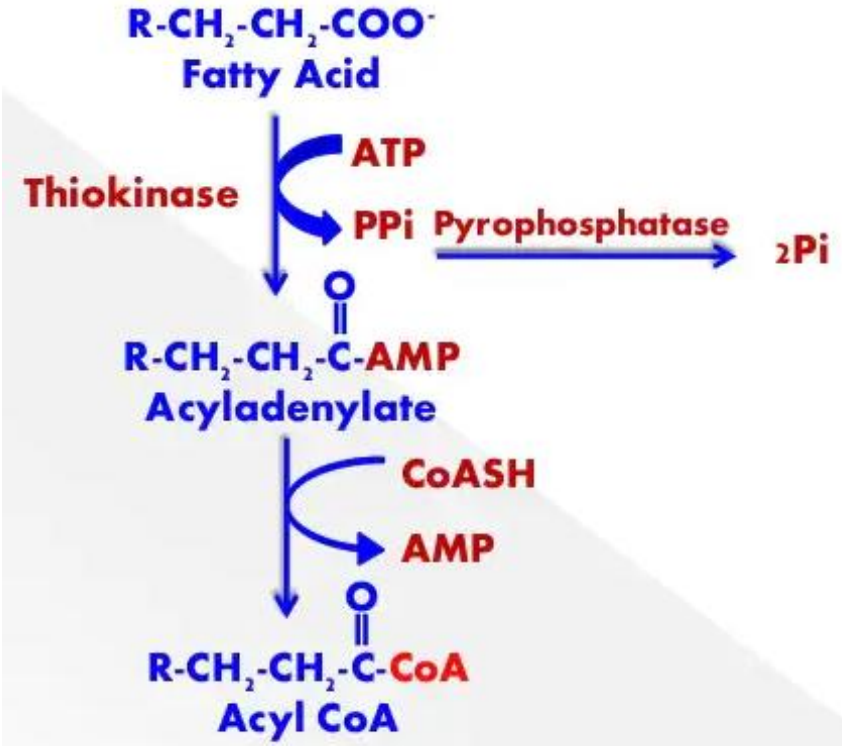


Triacylglycerol structure and synthesis

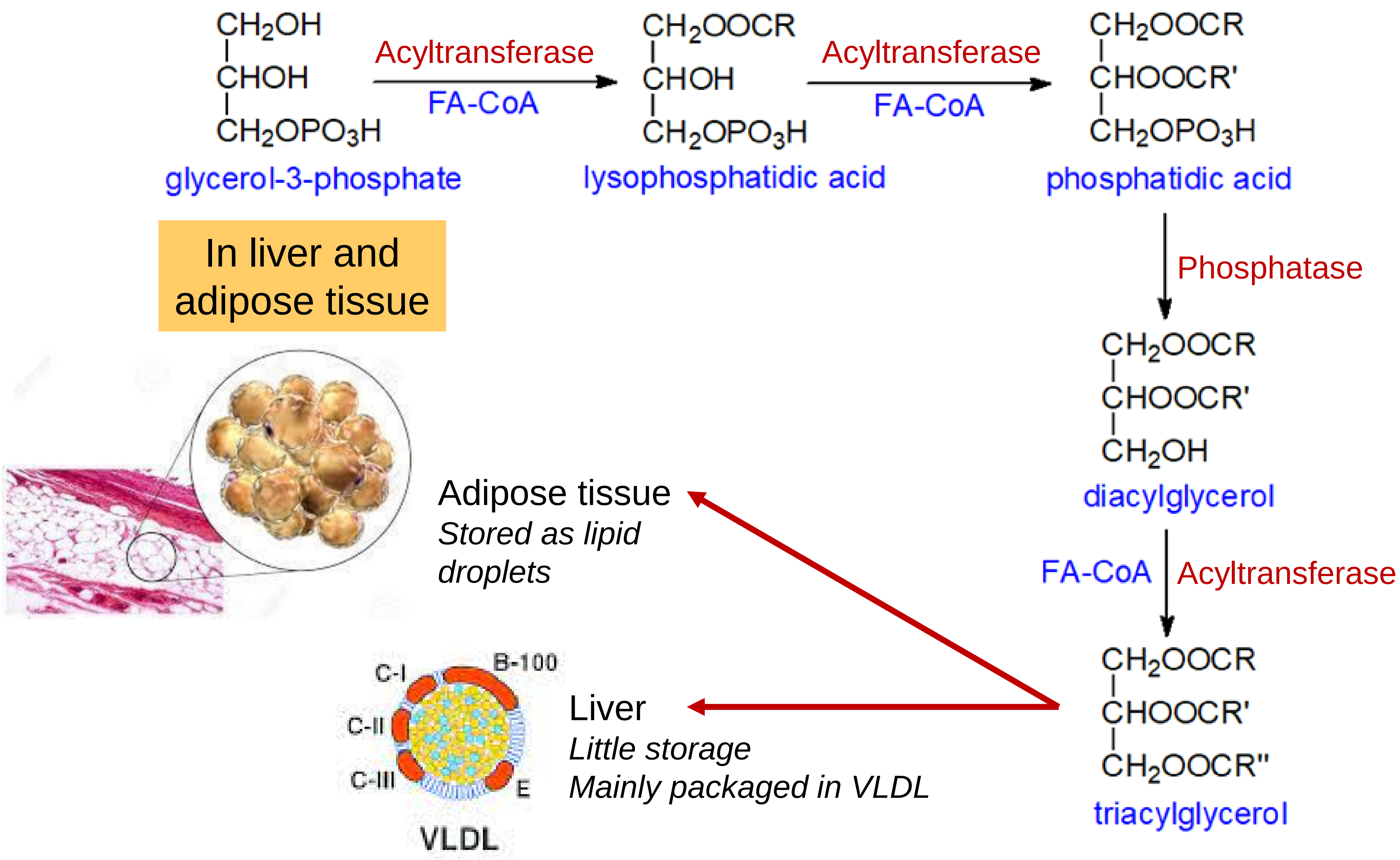


- The fatty acid on carbon 1 is typically saturated, that on carbon 2 is typically unsaturated, and that on carbon 3 can be either.
- Synthesis involves three steps:
  - Glycerol 3-phosphate synthesis
    - Liver (2 mechanisms) vs. adipose tissue (one mechanism only)
  - Activation of fatty acids
  -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





Synthesis of triacylglycerols



TAG resynthesis in intestinal mucosal cells

- In addition to these two pathways, TAG is synthesized via the MAG pathway in the intestinal mucosal cells during absorption.