Lecture 9 - Fatty Acid Metabolism

Chem 454: Regulatory Mechanisms in Biochemistry
University of Wisconsin-Eau Claire

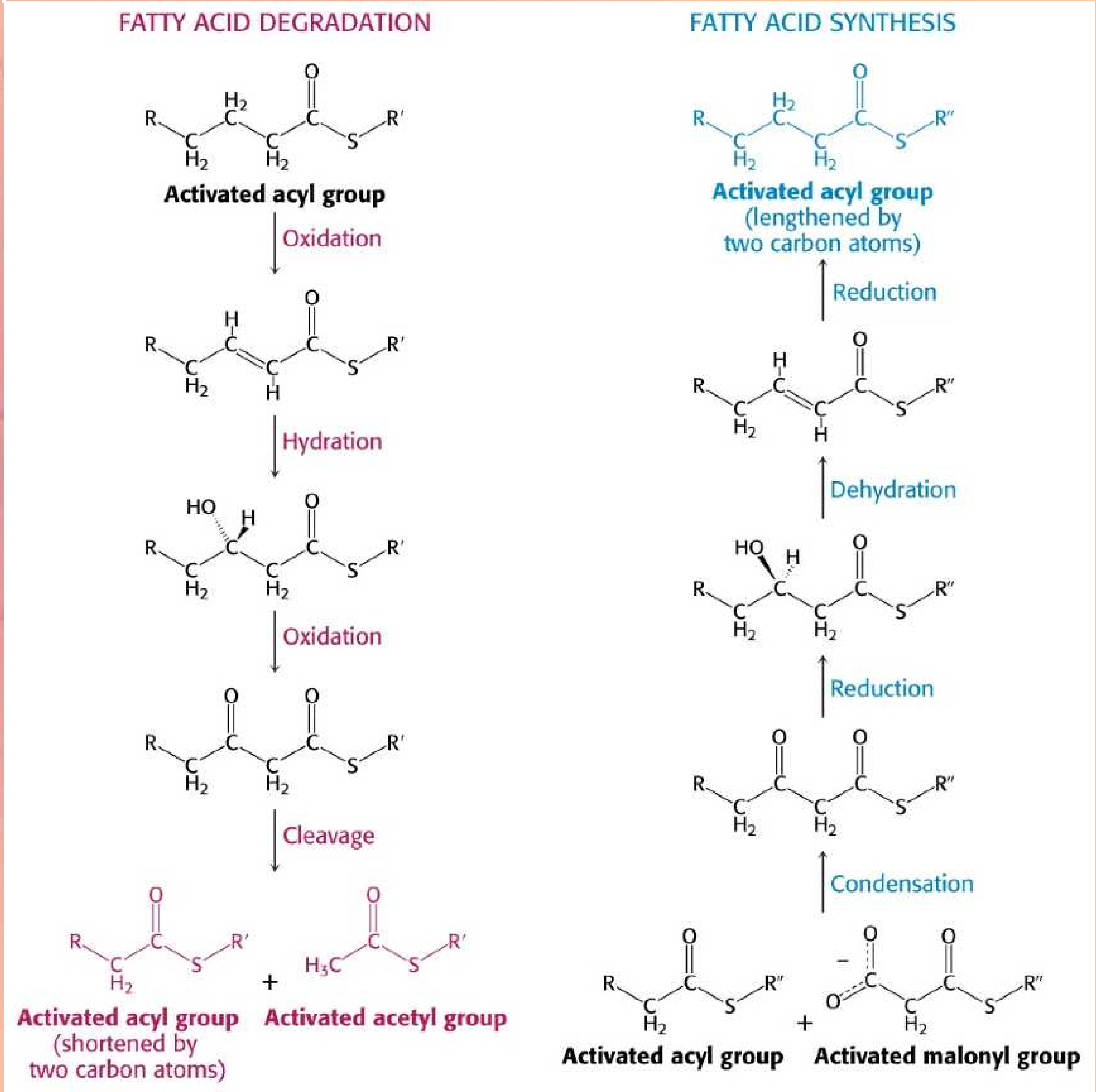
Introduction

Fatty acids play several important roles:

- Building blocks for phopsholipids and glycolipids
- Target proteins to membranes
- High energy source of fuel
- Fatty acid derivatives are used as hormones and intracellular messengers

Introduction

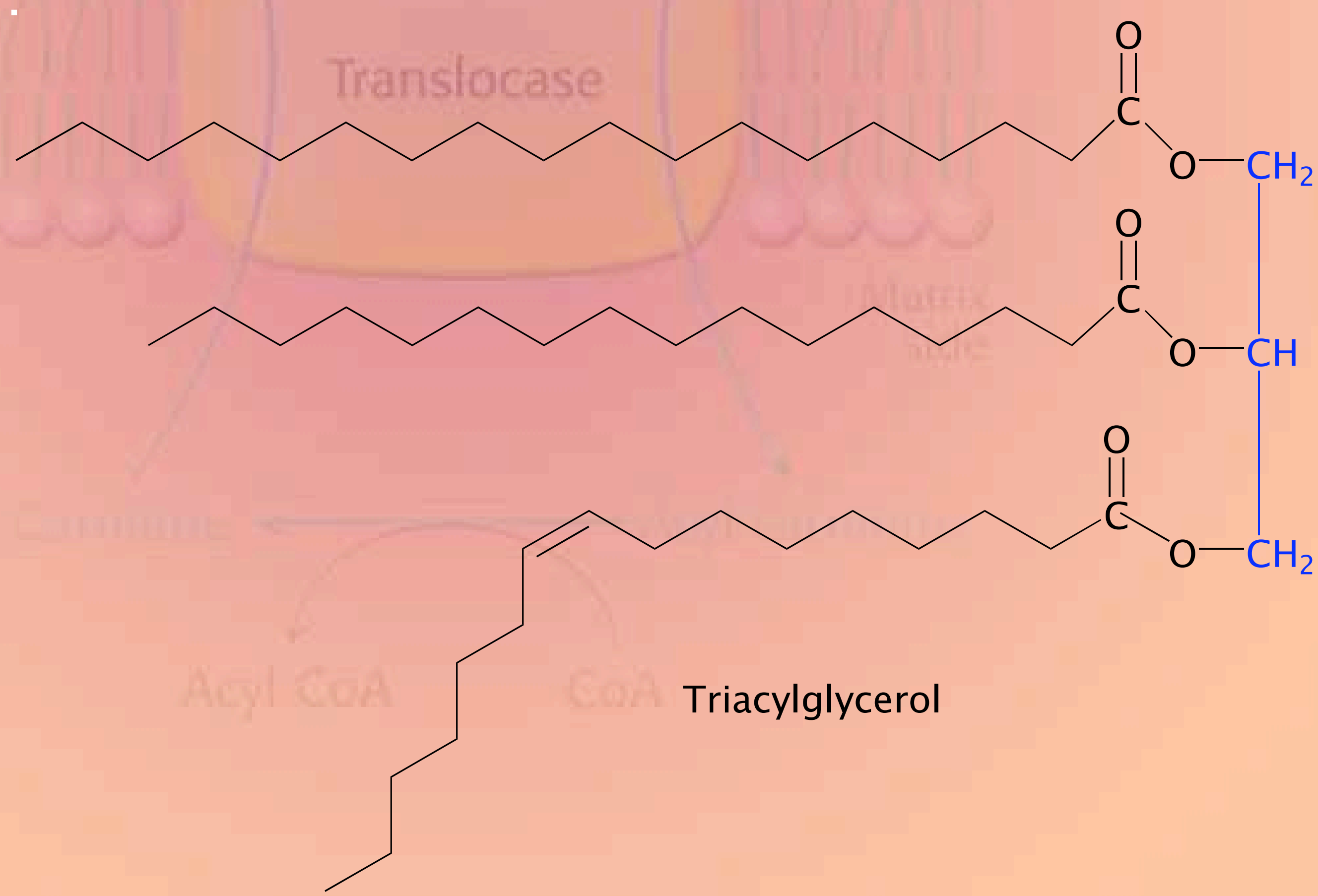
Overview of fatty acid synthesis



1. Triglycerides

Triglycerides are a highly concentrated store of energy

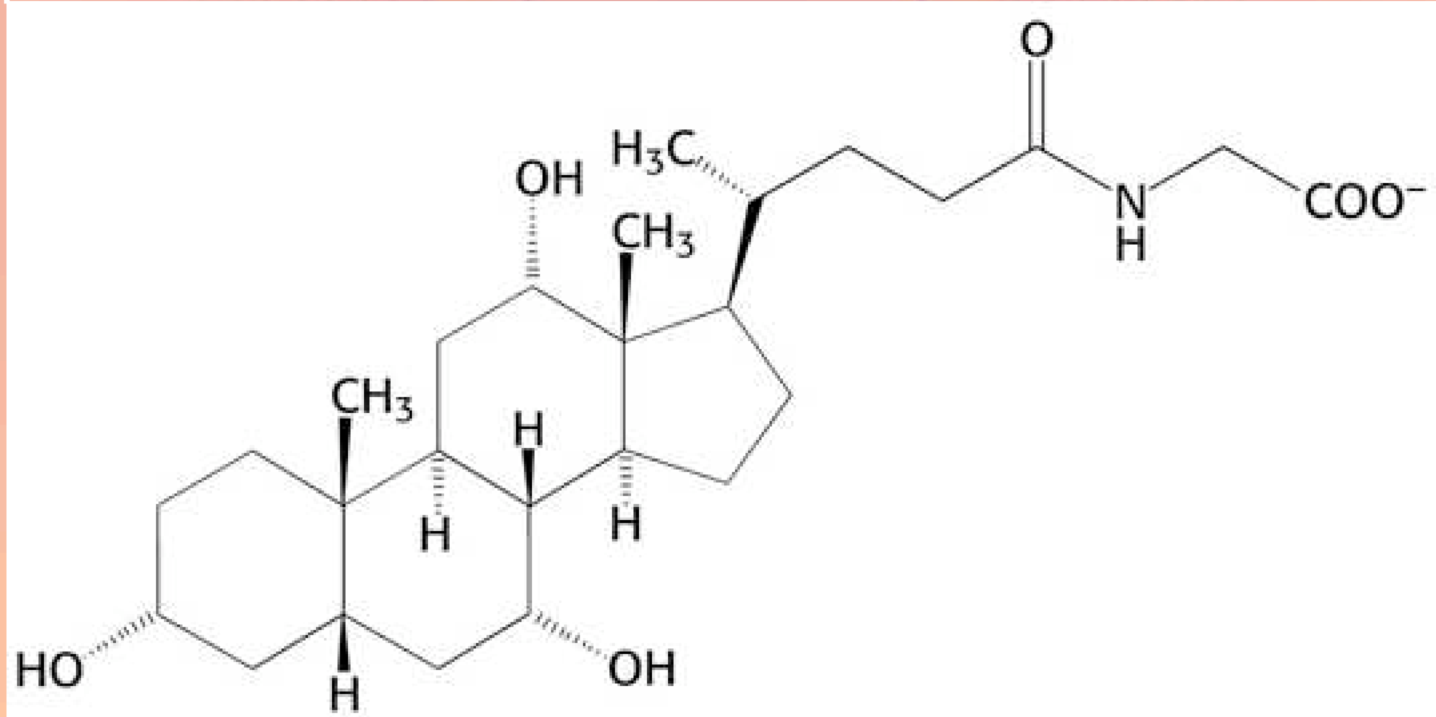
- 9 kcal/g *vs* 4 kcal/g for glycogen
- Glycogen is also highly hydrated, 2 g H_2O/g glycogen



Triacylglycerol

1.1 Pancreatic Lipases

- Dietary triacylglycerols must be broken down before being absorbed by the intestines.
- Bile salts, which act as detergents, are used to solublize the triacylglycerols



Glycocholate

1.1 Pancreatic Lipases

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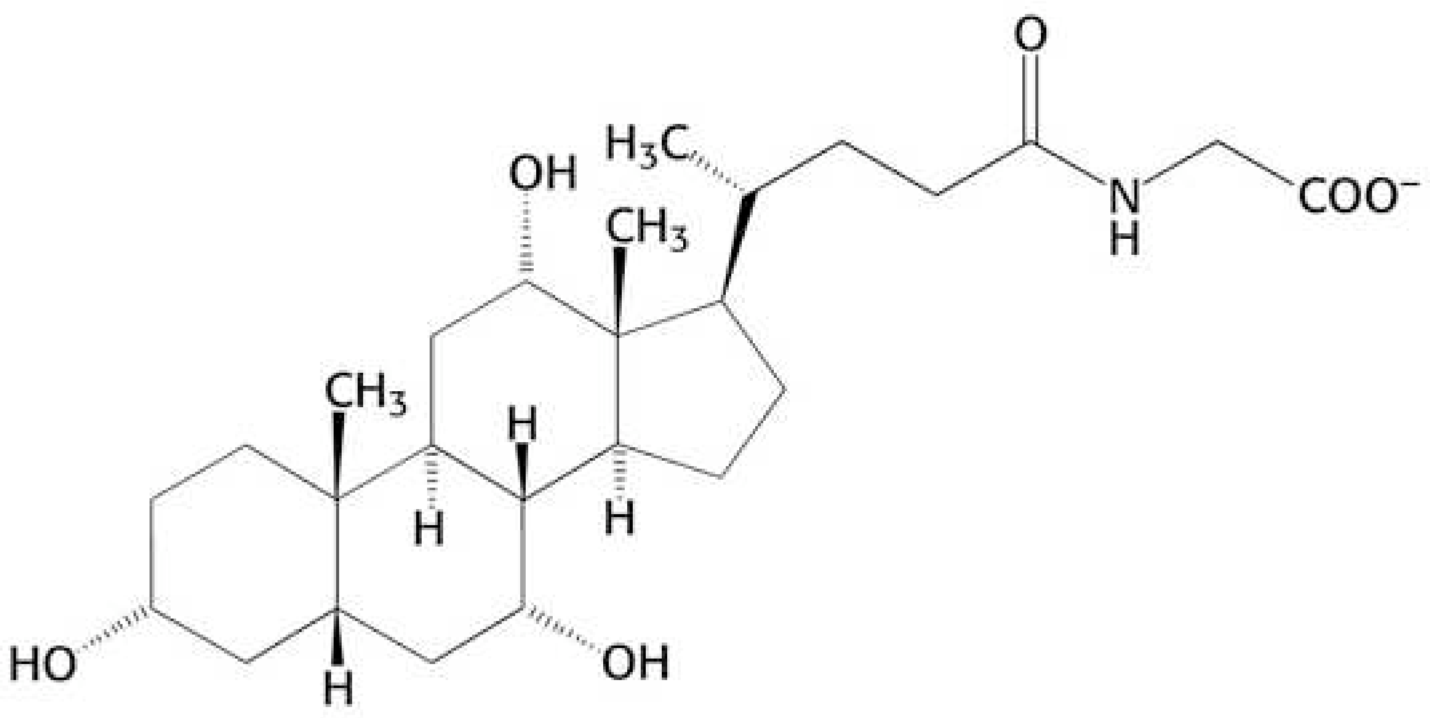
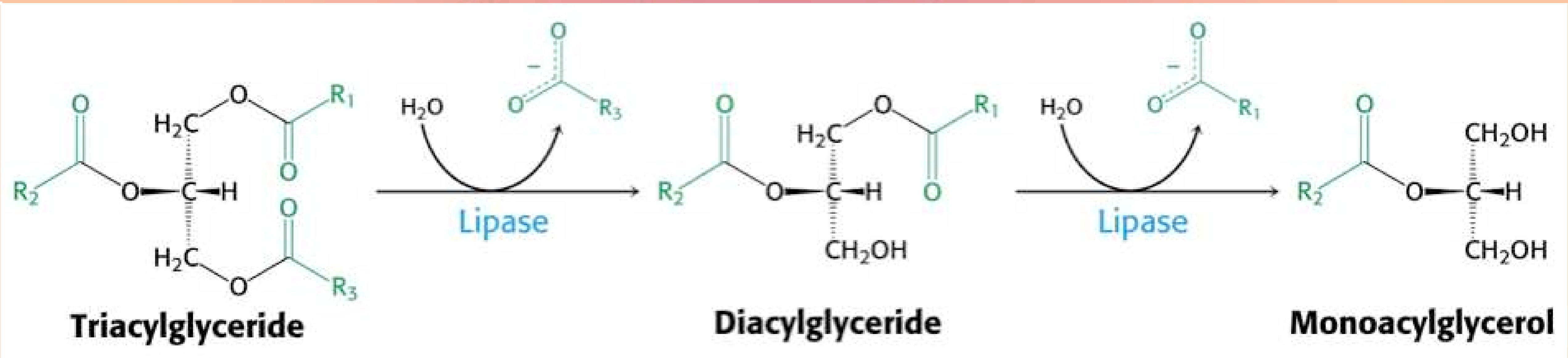


Glycocholate

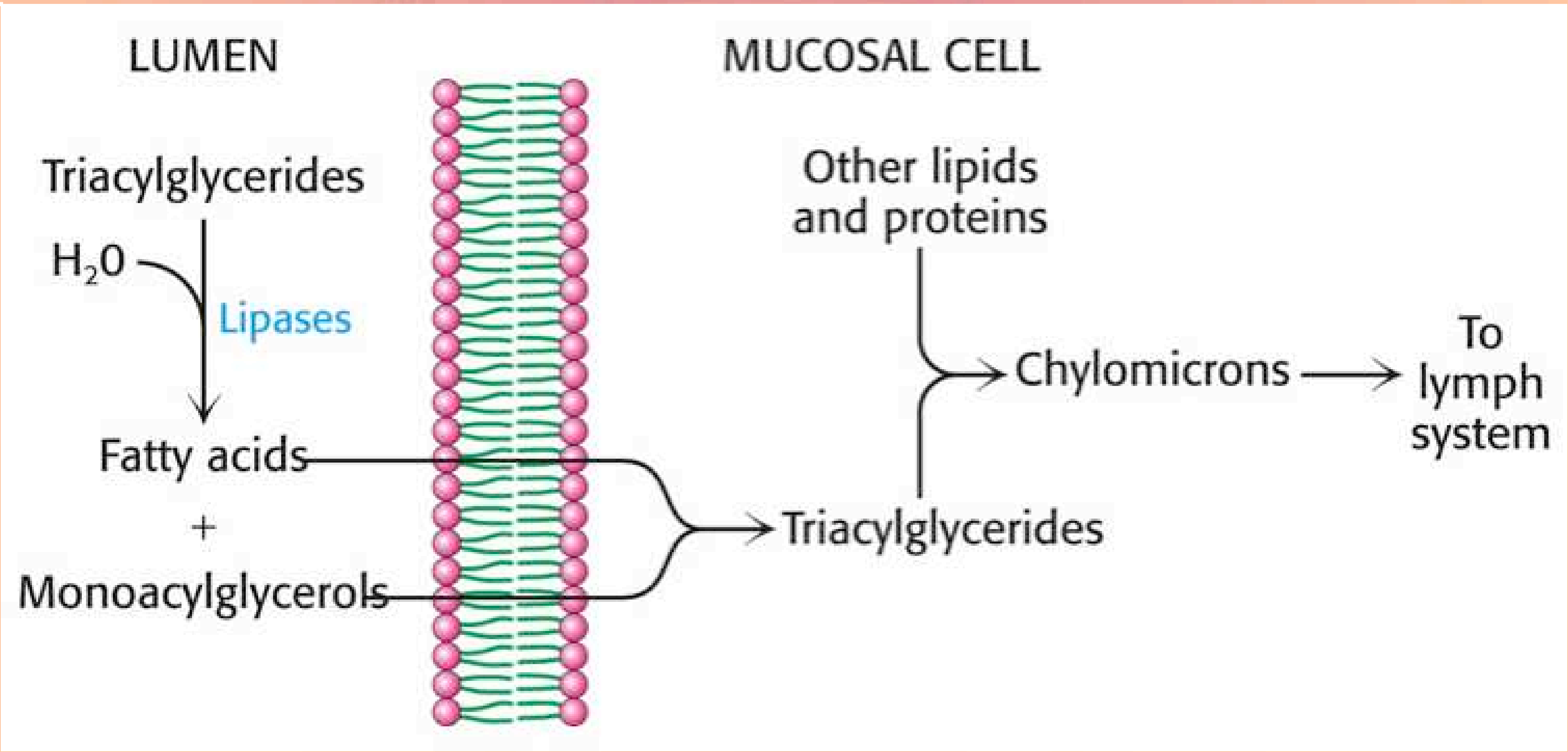
1.1 Pancreatic Lipases

Pancreatic lipases hydrolyze the ester bonds of the triacylglycerols while in the micelles.



1.1 Chylomicrons

In the intestinal mucosal cells, the fatty acids and monoacylglycerides are resynthesized into triacylglycerides and packaged into *chylomicrons*.



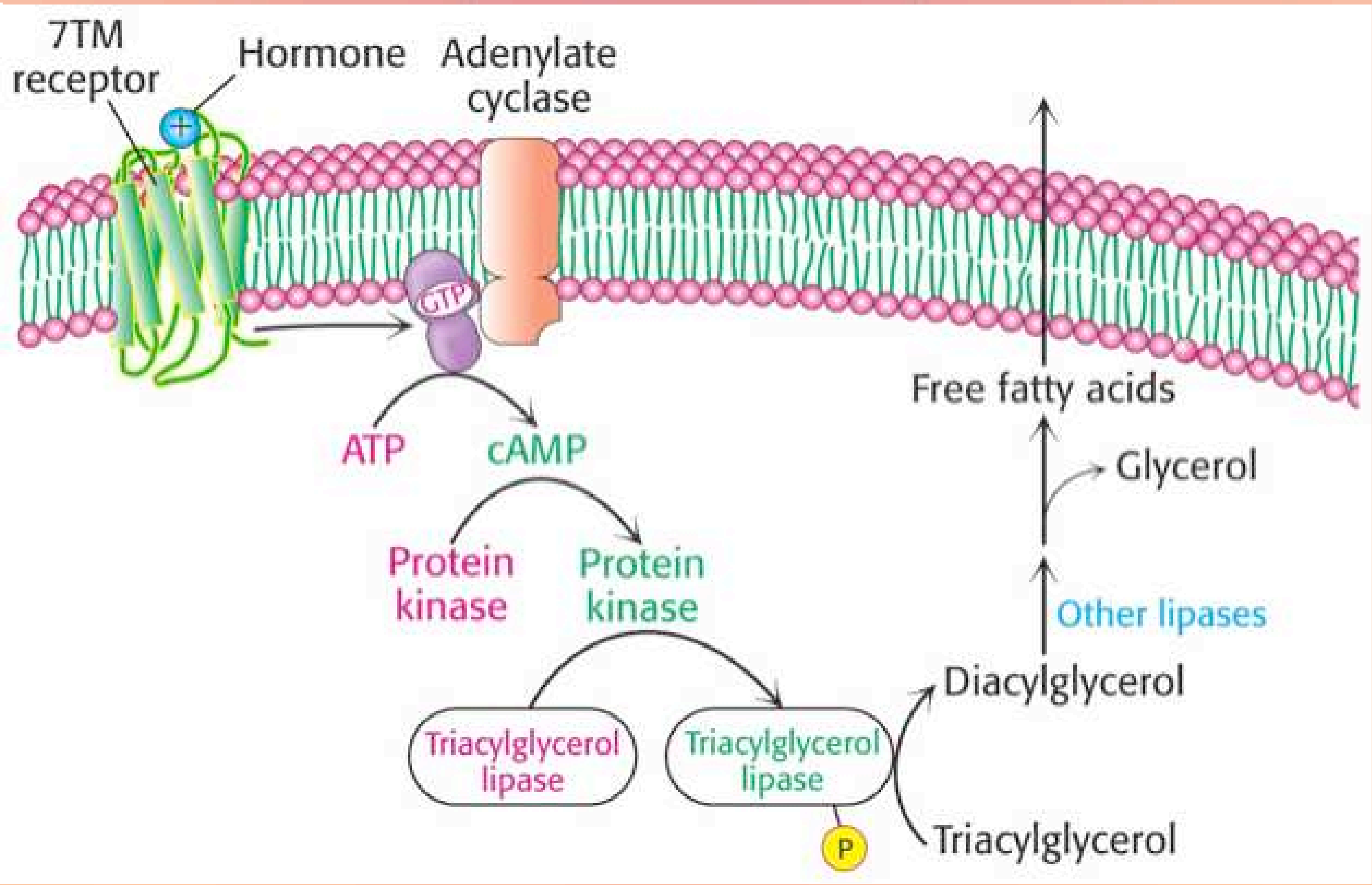
2. Utilization of Fatty Acids as Fuel

Three stages of processing

- Triglycerols are degraded to fatty acids and glycerol in the adipose tissue and transported to other tissues.
- Fatty acids are activated and transported into the mitochondria.
- Fatty acids are broken down into two-carbon acetyl–CoA units and fed into the citric acid cycle.

2.1 Breakdown of Triacylglycerols

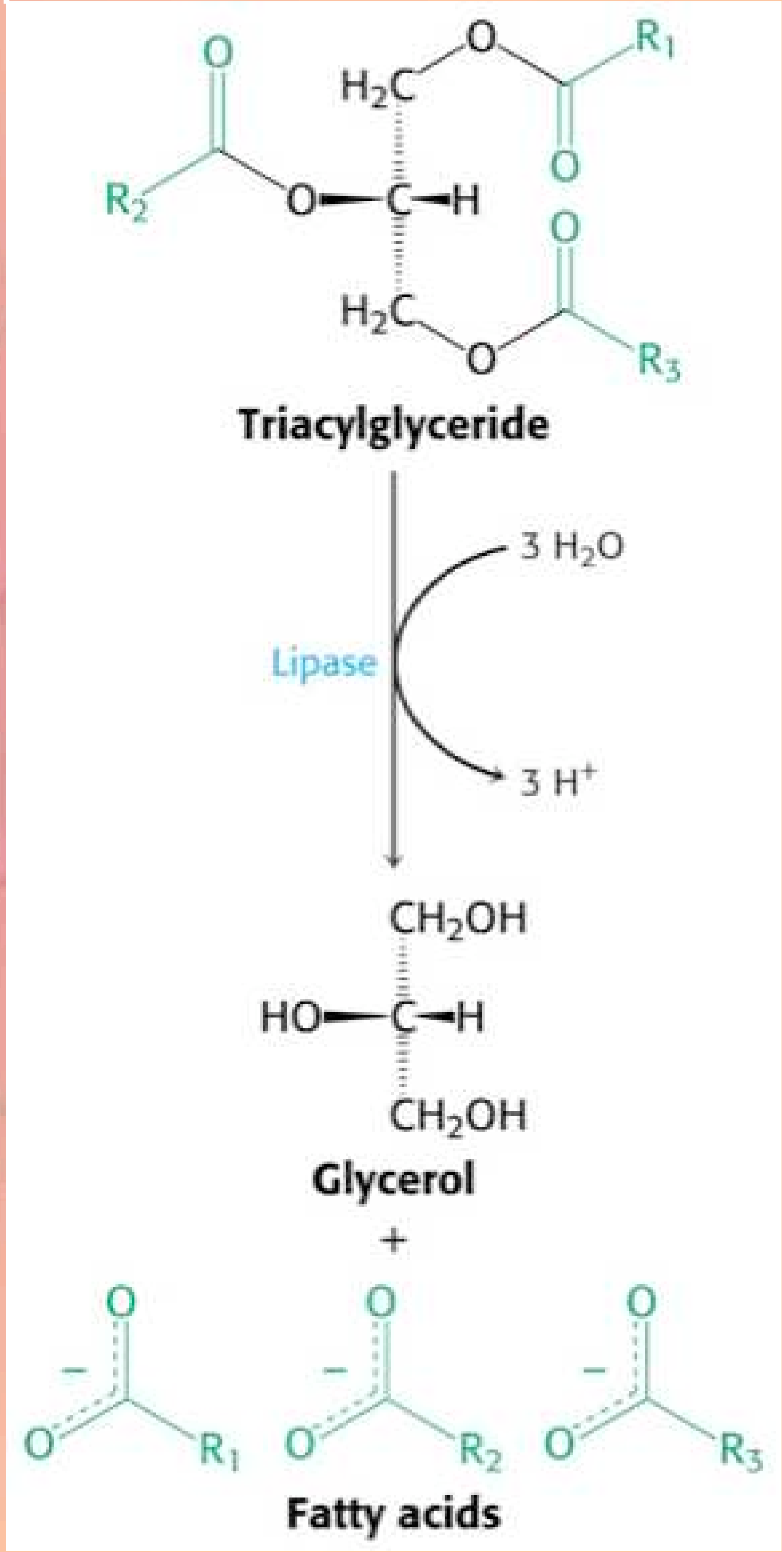
In the adipose tissue, lipases are activated by hormone signaled phosphorylation



2.1 Breakdown of Triacylglycerols

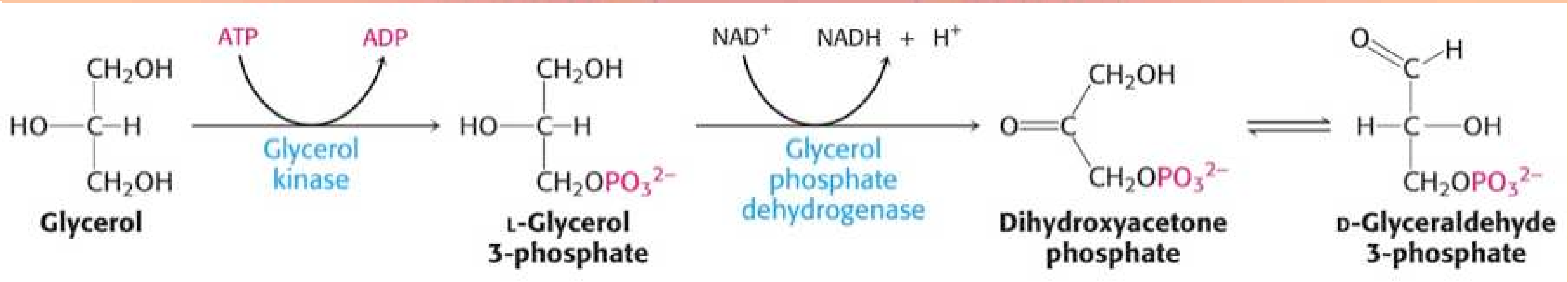
The lipases break the triacylglycerols down to fatty acids and glycerol

- The fatty acids are transportred in the blood by serum albumin



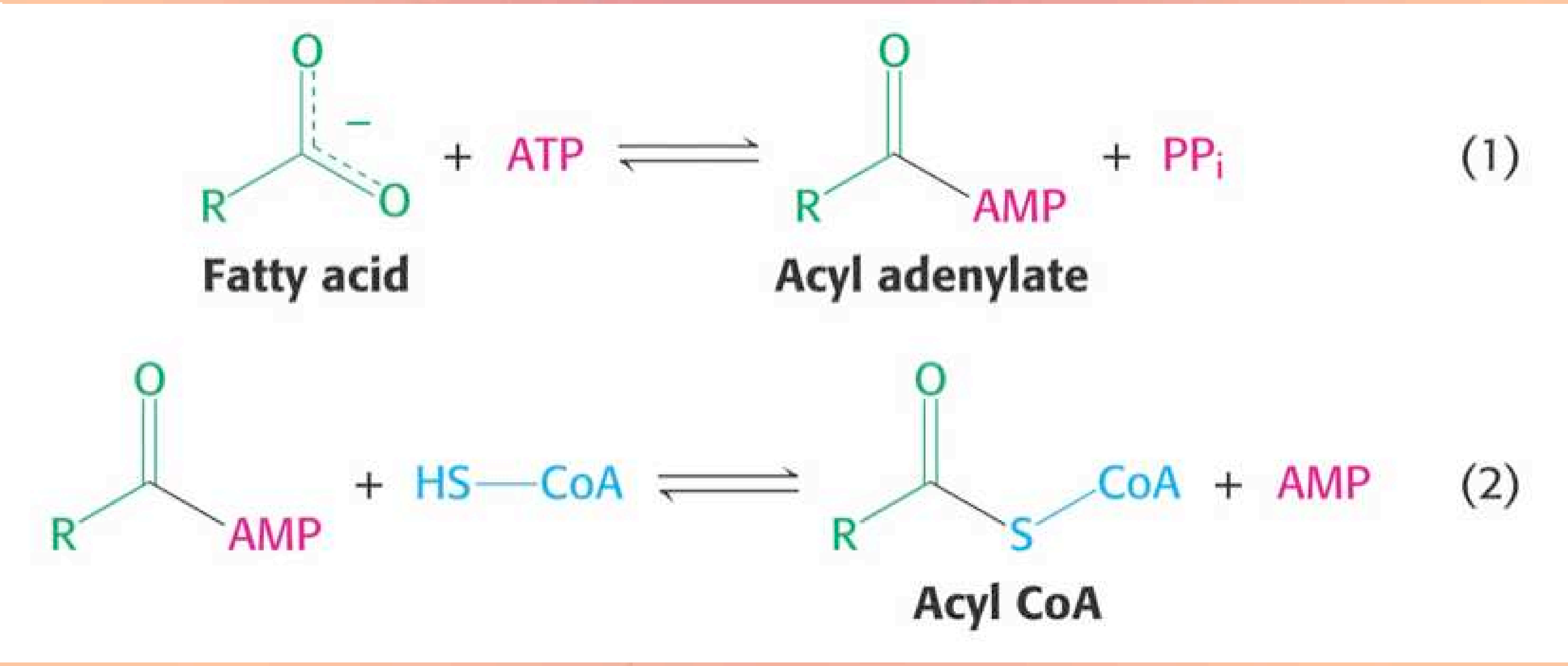
2.1 Breakdown of Triacylglycerols

The glycerol is absorbed by the liver and converted to glycolytic intermediates.



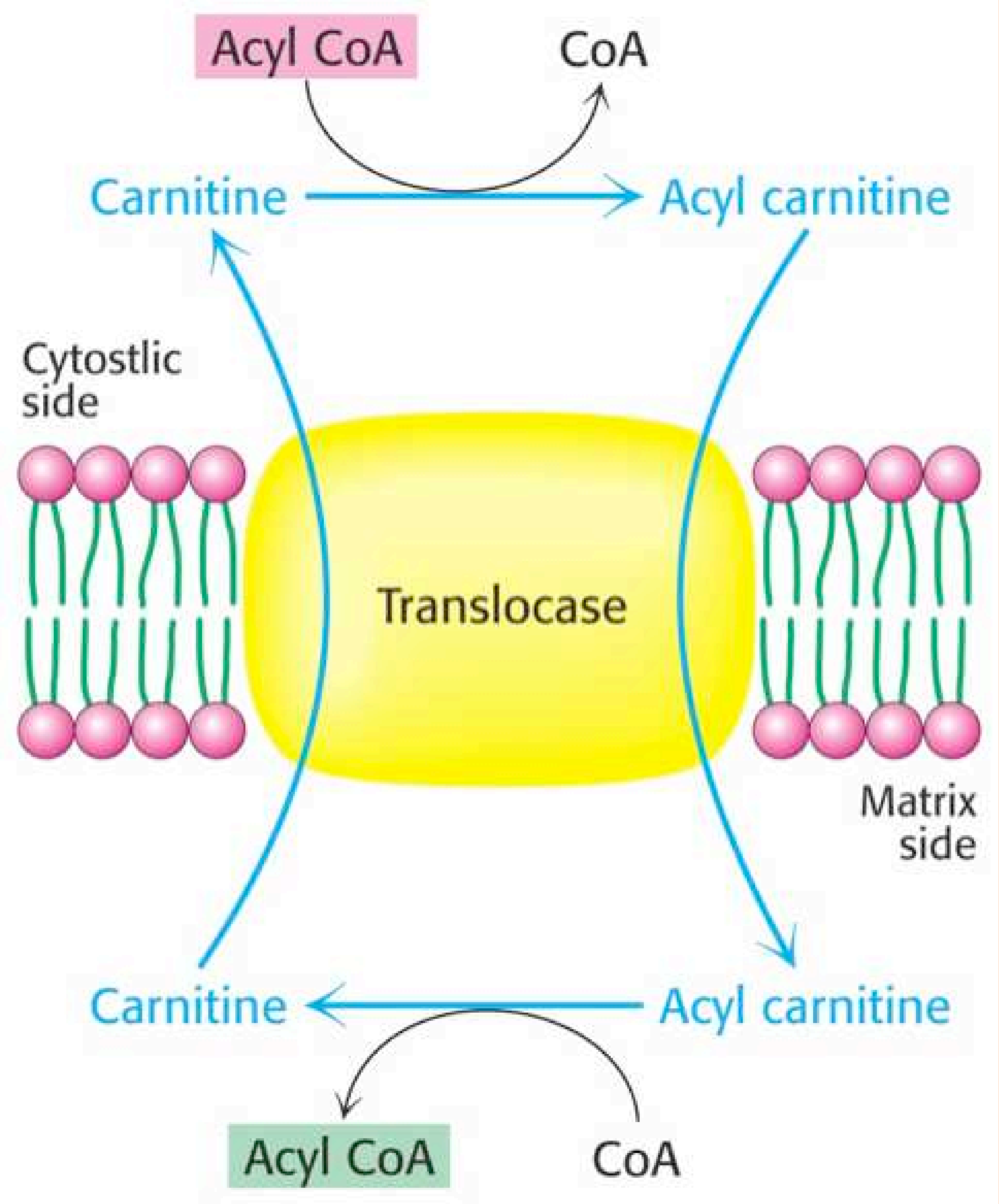
2.2 Activation of Fatty Acids

Acyl CoA synthetase reaction occurs in the on the mitochondrial membrane.



2.3 Transport into Mitochonrial Matrix

Carnitine carries long-chain activated fatty acids into the mitochondrial matrix



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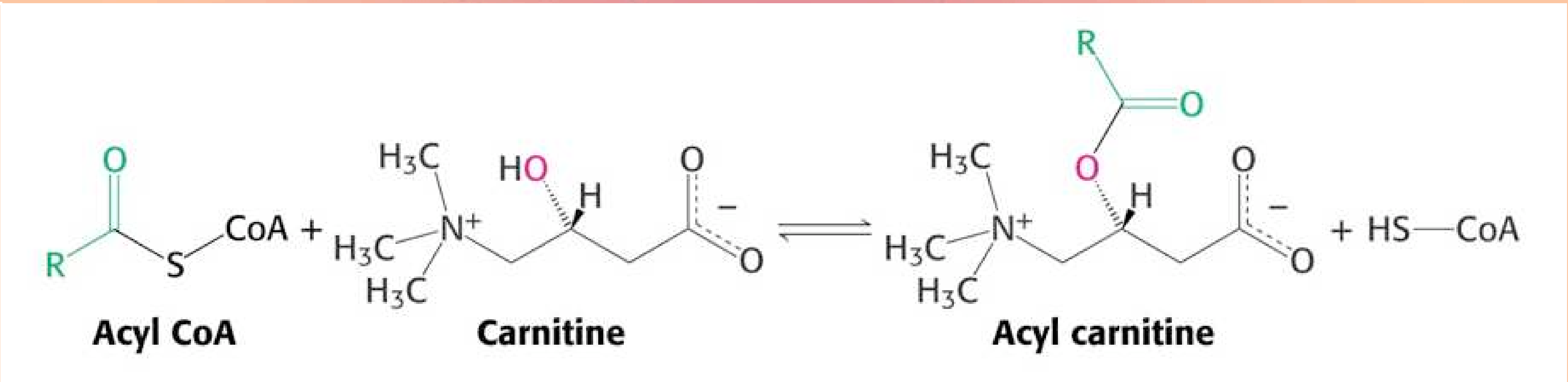
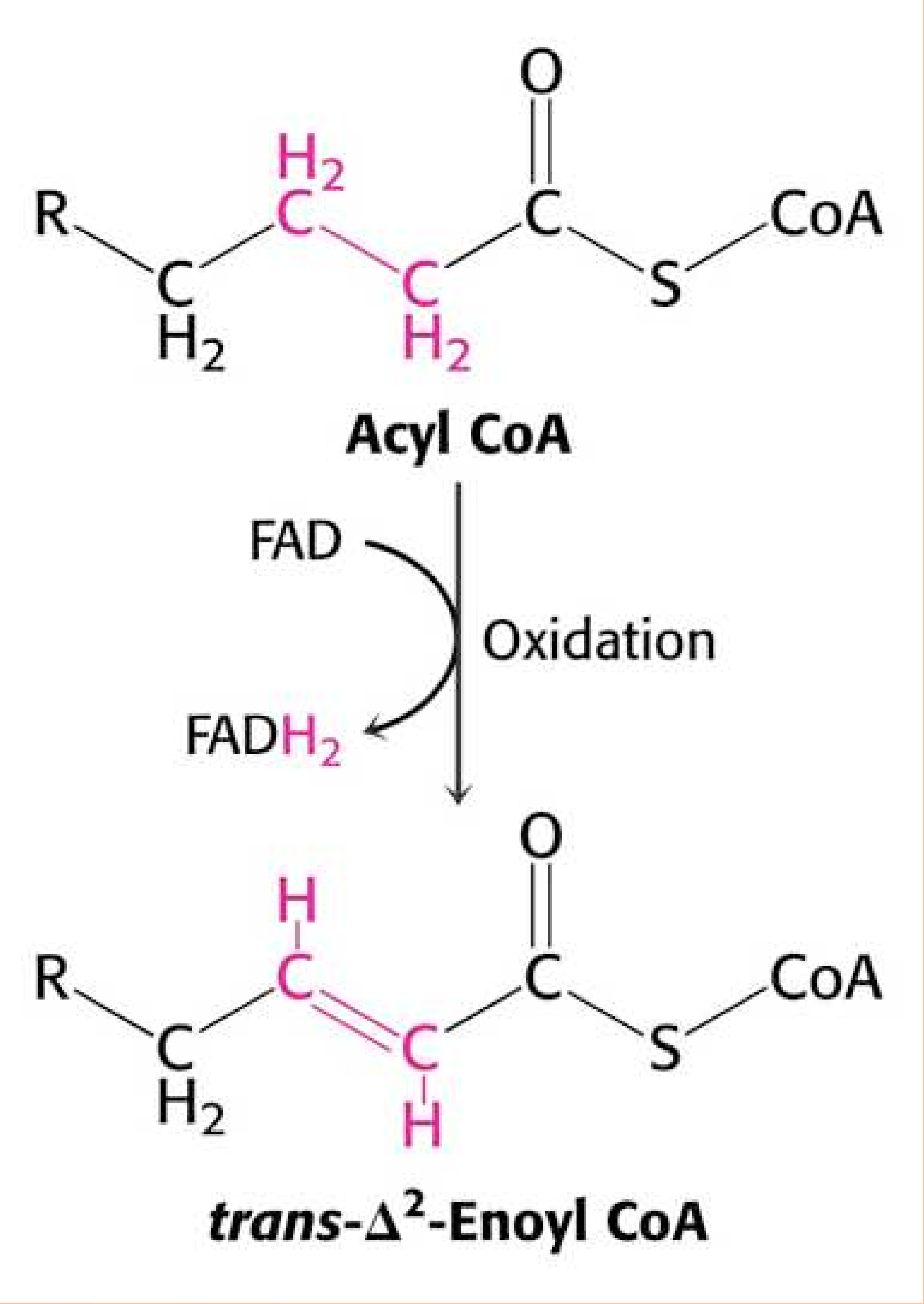


2.4 Fatty acid oxidation

Each round in fatty acid degradation involves four reactions

1. oxidation to *trans*-Δ^2-Enoly-CoA



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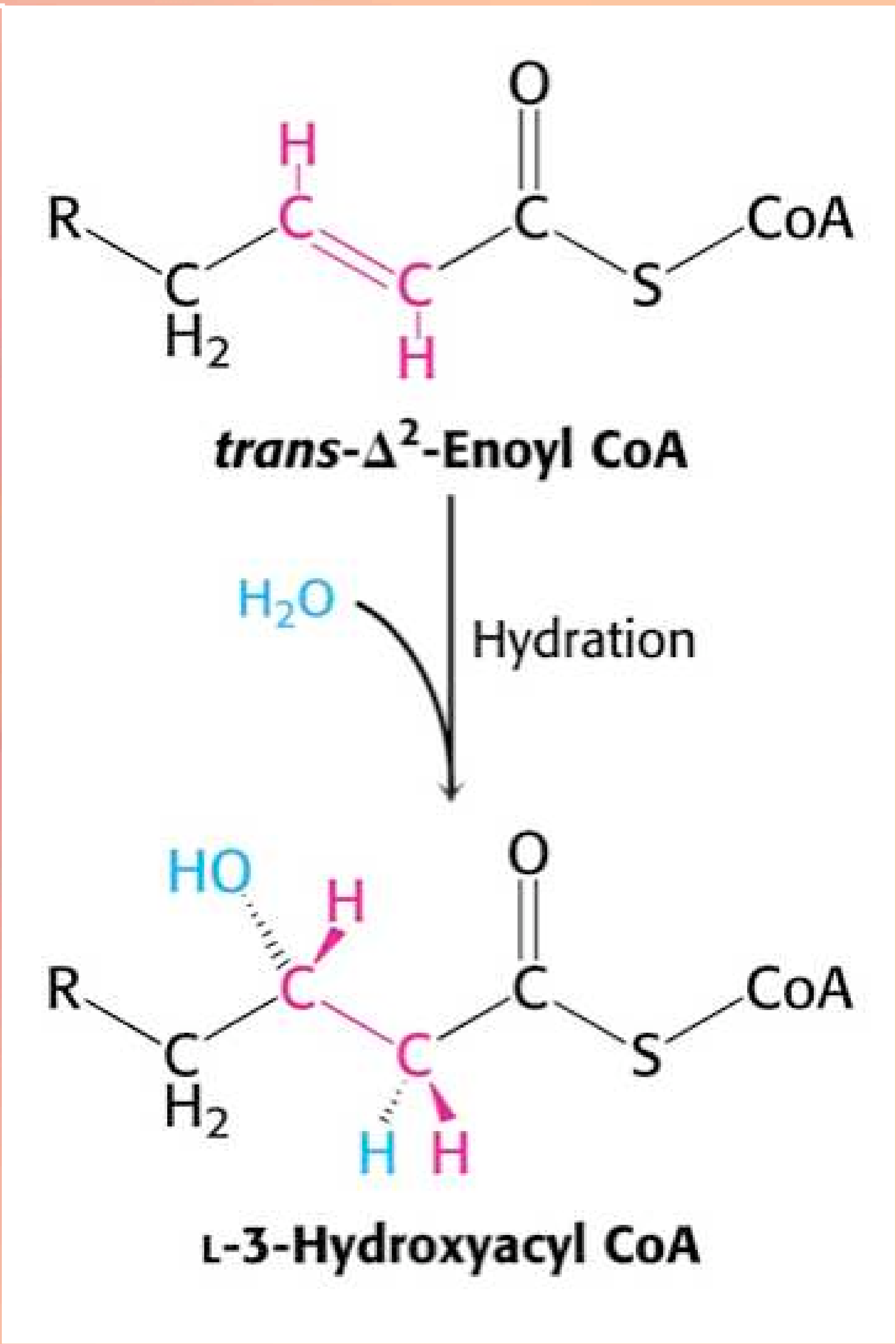
Each round in fatty acid degradation involves four reactions

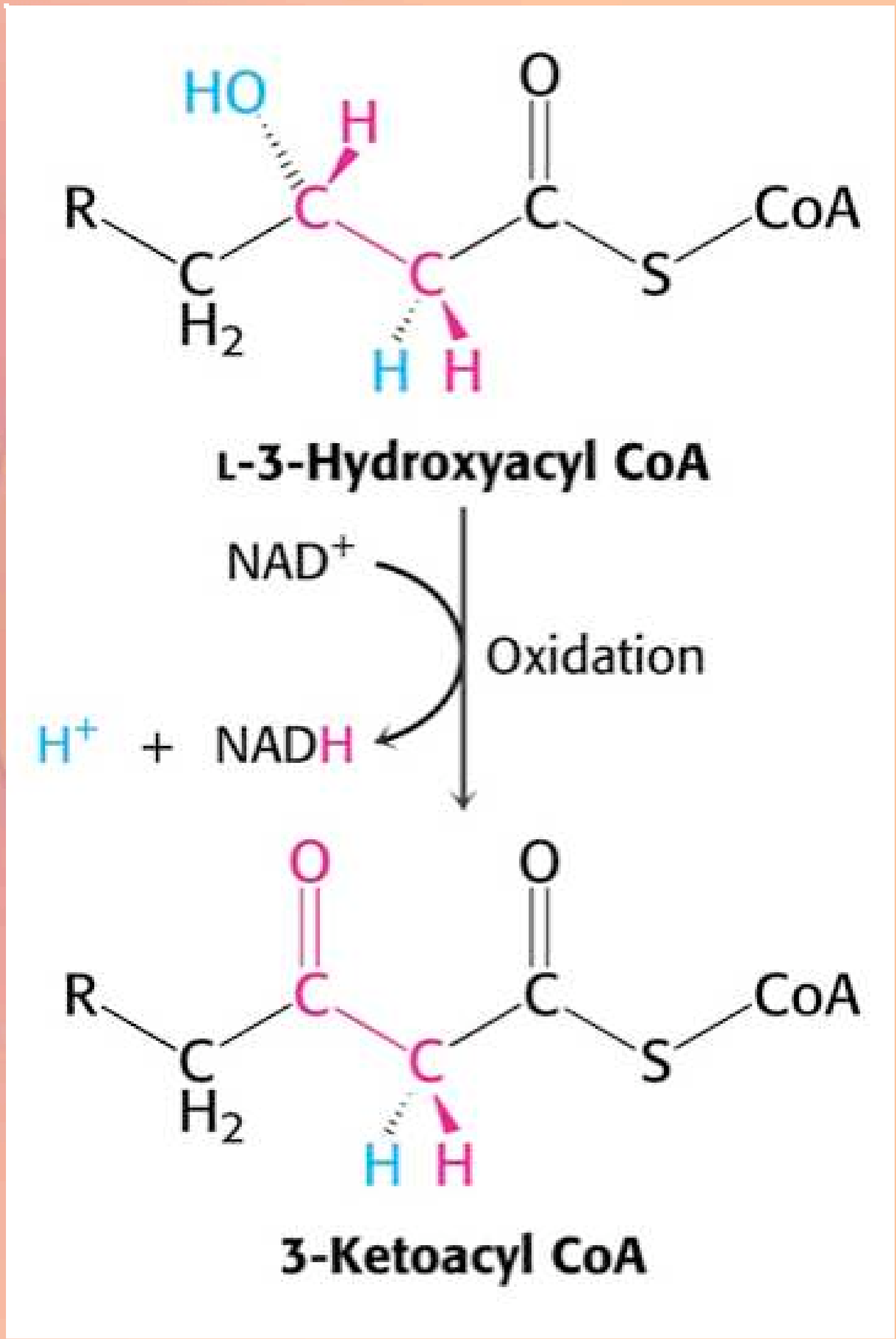
2. Hydration to L-3-Hydroxylacyl CoA



2.4 Fatty acid oxidation

Each round in fatty acid degradation involves four reactions

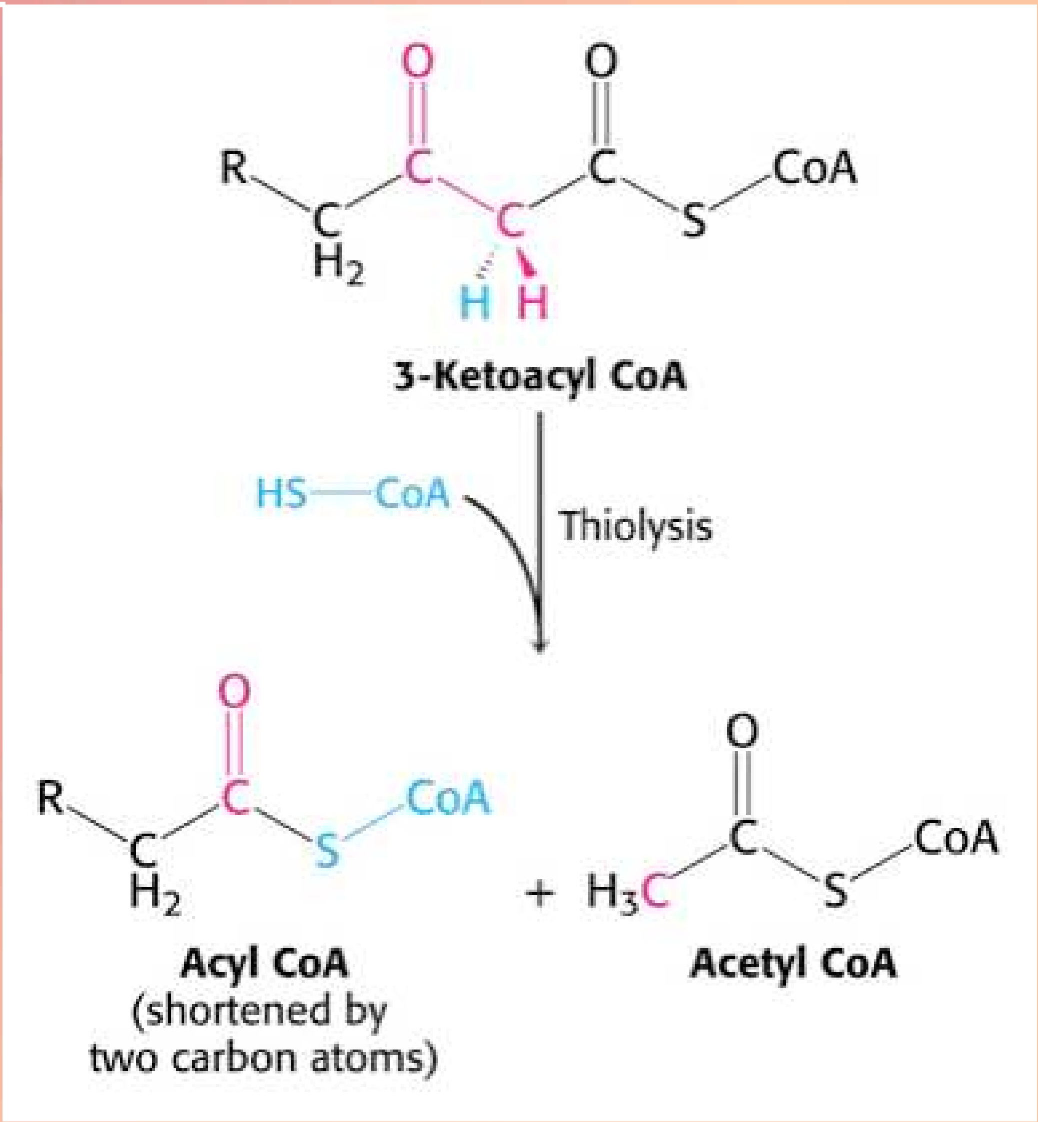
3. Oxidation to 3-Ketoacyl CoA



2.4 Fatty acid oxidation

Each round in fatty acid degradation involves four reactions

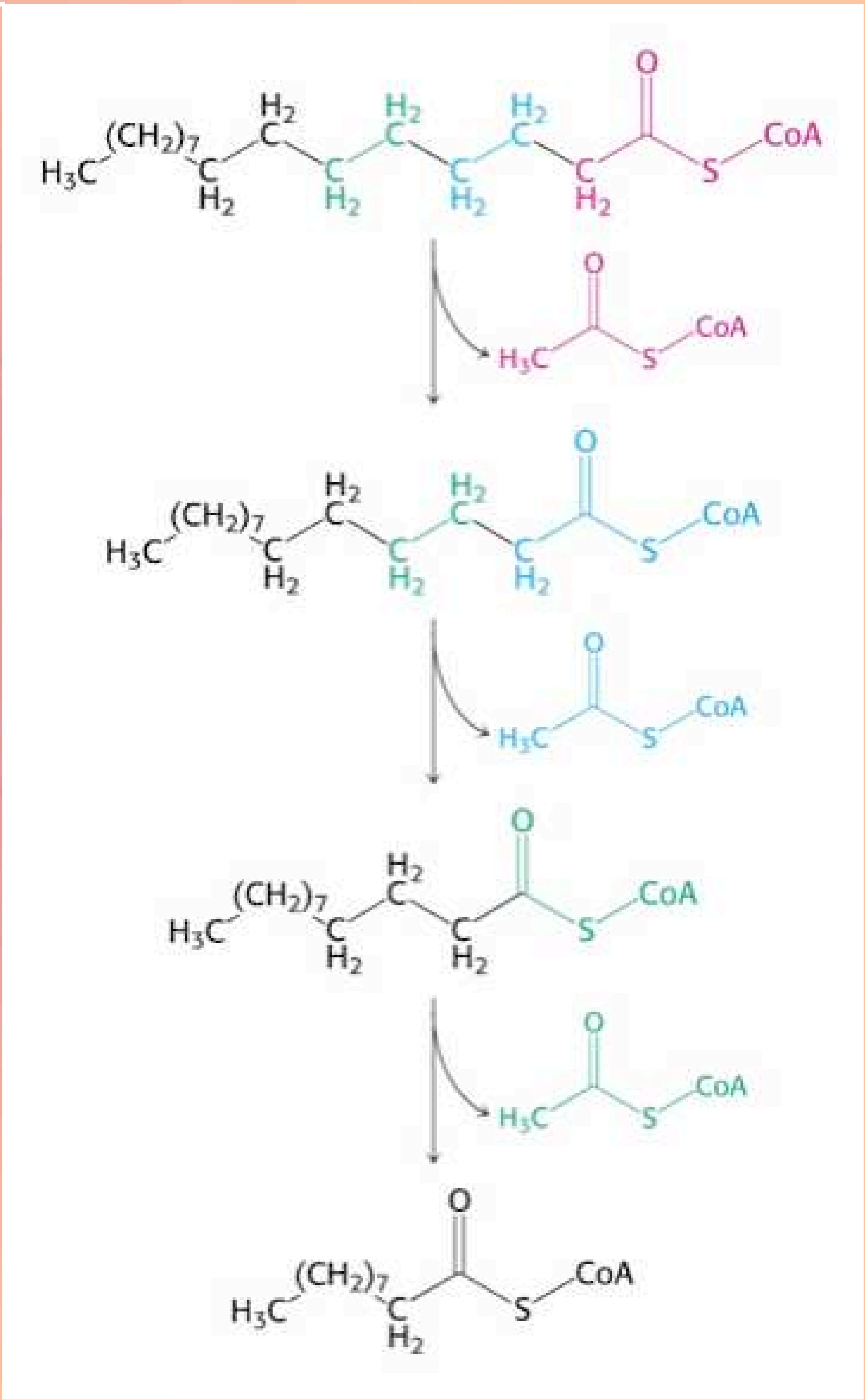
4. Thiolysis to produce Acetyl-CoA



2.4 Fatty acid oxidation

Each round in fatty acid degradation involves four reactions

- The process repeats itself



2.4 Fatty acid oxidation

Each round in fatty acid degradation involves four reactions

TABLE 22.1 Principal reactions in fatty acid oxidation

Step	Reaction	Enzyme
1	Fatty acid + CoA + ATP $\rightleftharpoons$ acyl CoA + AMP + PP_i	Acyl CoA synthetase [also called fatty acid thiokinase and fatty acid:CoA ligase (AMP)]
2	Carnitine + acyl CoA $\rightleftharpoons$ acyl carnitine + CoA	Carnitine acyltransferase (also called carnitine palmitoyl transferase)
3	Acyl CoA + E-FAD $\longrightarrow$ *trans*-Δ^2-enoyl CoA + E-$FADH_2$	Acyl CoA dehydrogenases (several isozymes having different chain-length specificity)
4	*trans*-Δ^2-Enoyl CoA + H_2O $\rightleftharpoons$ L-3-hydroxyacyl CoA	Enoyl CoA hydratase (also called crotonase or 3-hydroxyacyl CoA hydrolyase)
5	L-3-Hydroxyacyl CoA + NAD^+ $\rightleftharpoons$ 3-ketoacyl CoA + NADH + H^+	L-3-Hydroxyacyl CoA dehydrogenase
6	3-Ketoacyl CoA + CoA $\rightleftharpoons$ acetyl CoA + acyl CoA (shortened by C_2)	β-Ketothiolase (also called thiolase)

2.5 ATP Yield

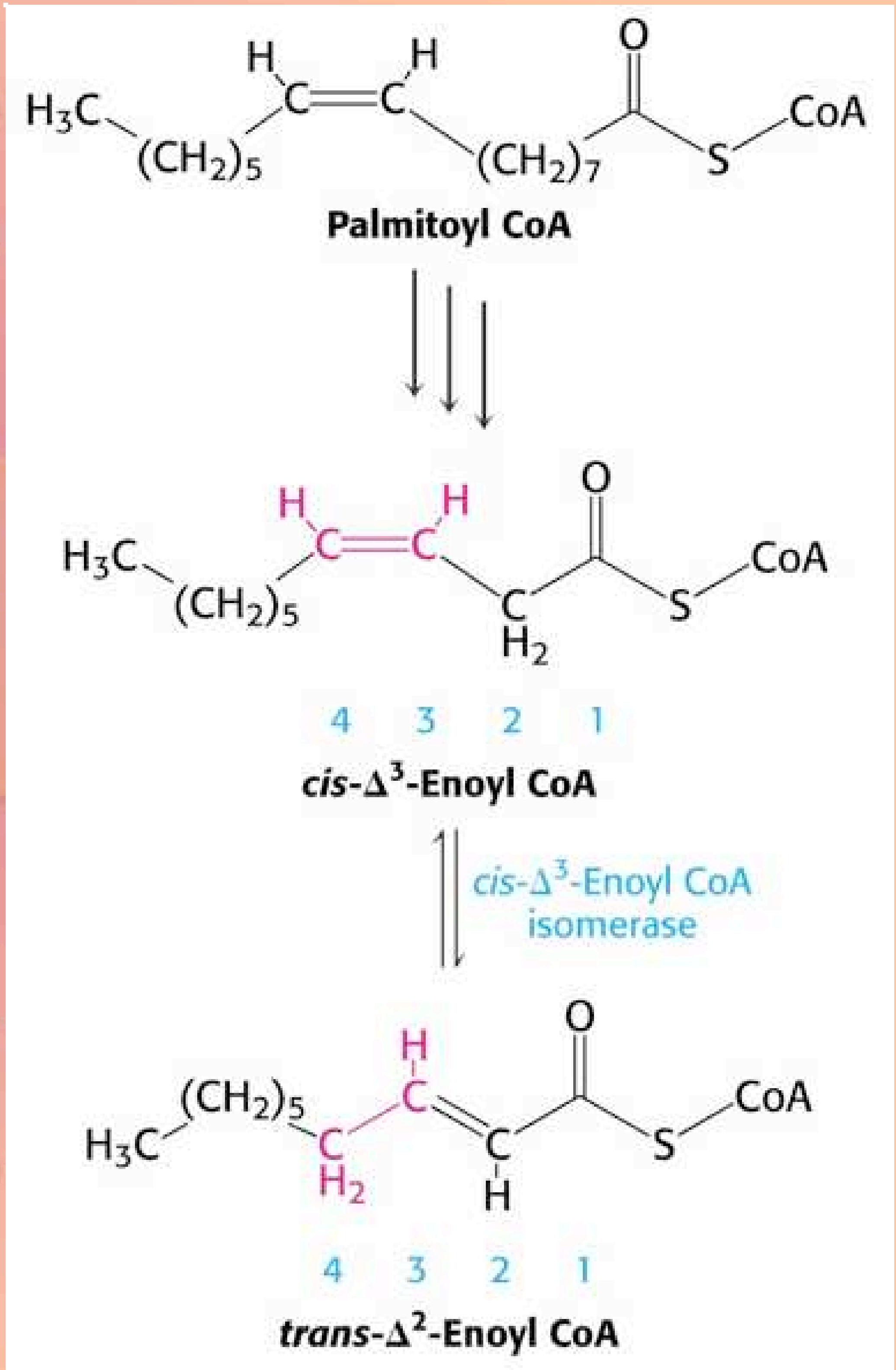
The complete oxidation of the sixteen carbon palmitoyl–CoA produces 106 ATP's

$$\text{Palmitoyl–CoA} + 7\ \text{FAD} + 7\ \text{NAD}^{+}\ \ 7\ \text{CoASH} + H_2O \longrightarrow$$

$$8\ \text{Acetyl–CoA} + 7\ \text{FADH}_2 + 7\ \text{NADH} + 7\ H^{+}$$

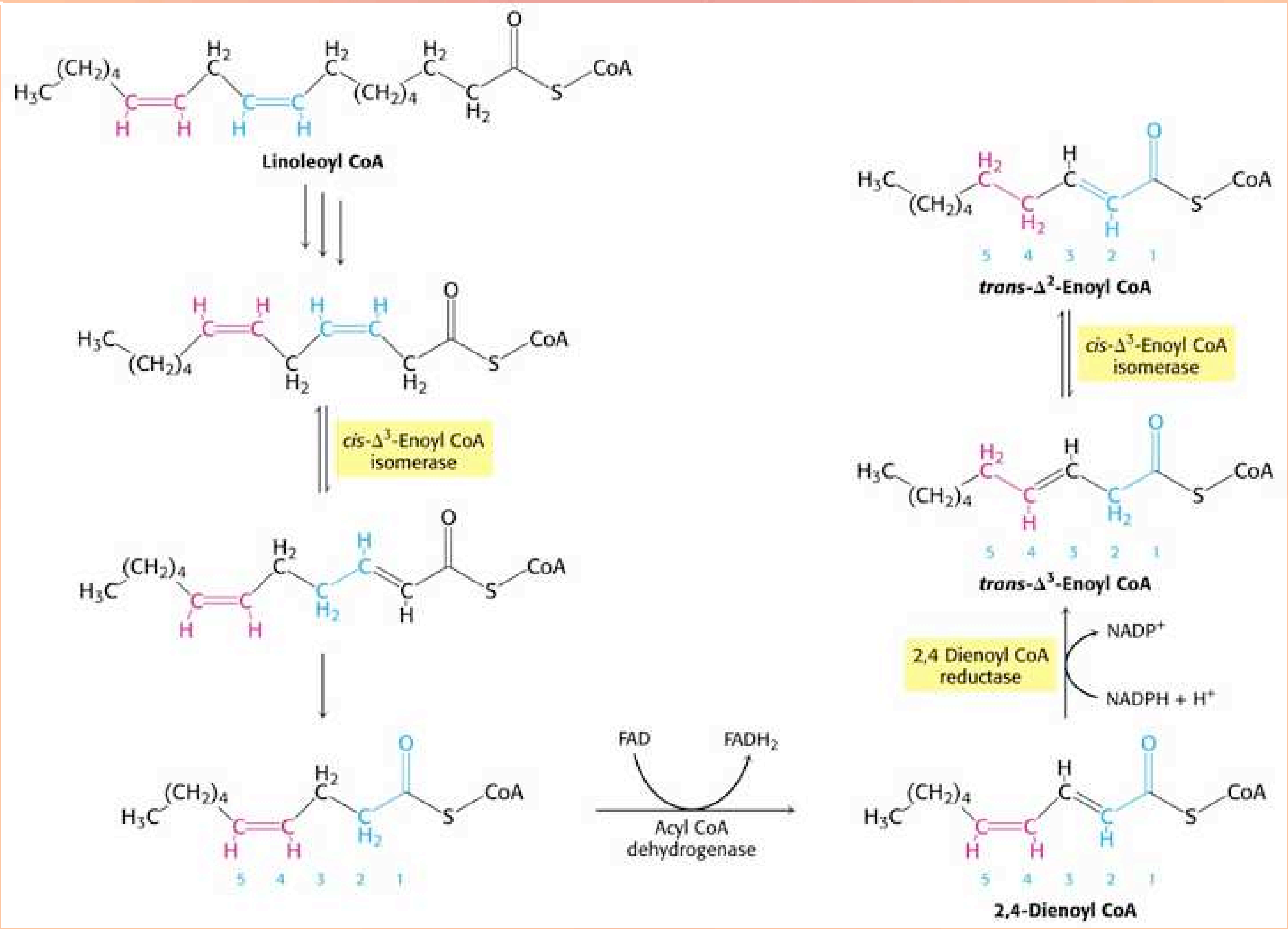
3.1 Special Cases

Unsaturated fatty acids (monounsaturated)

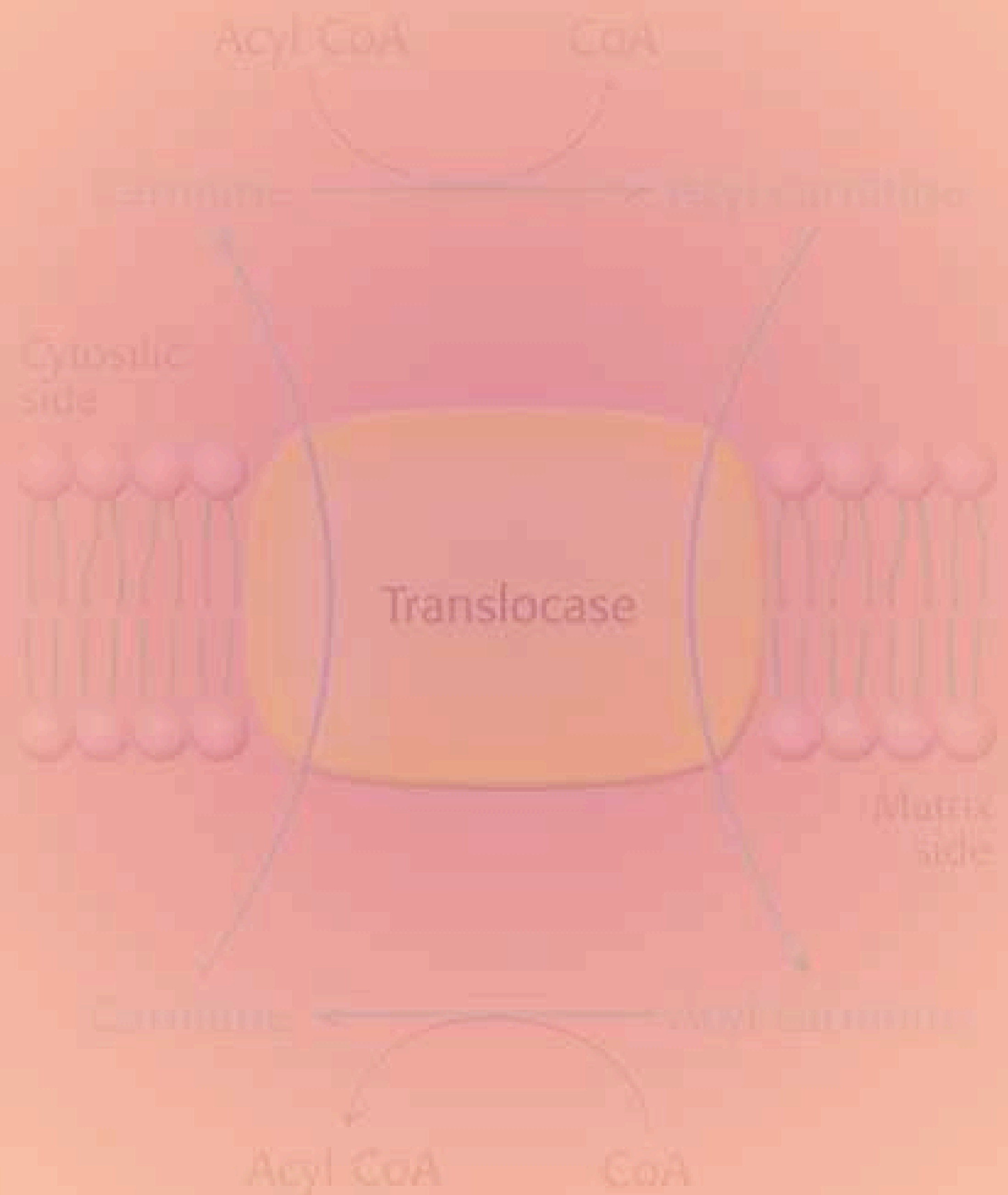


3.1 Special Cases

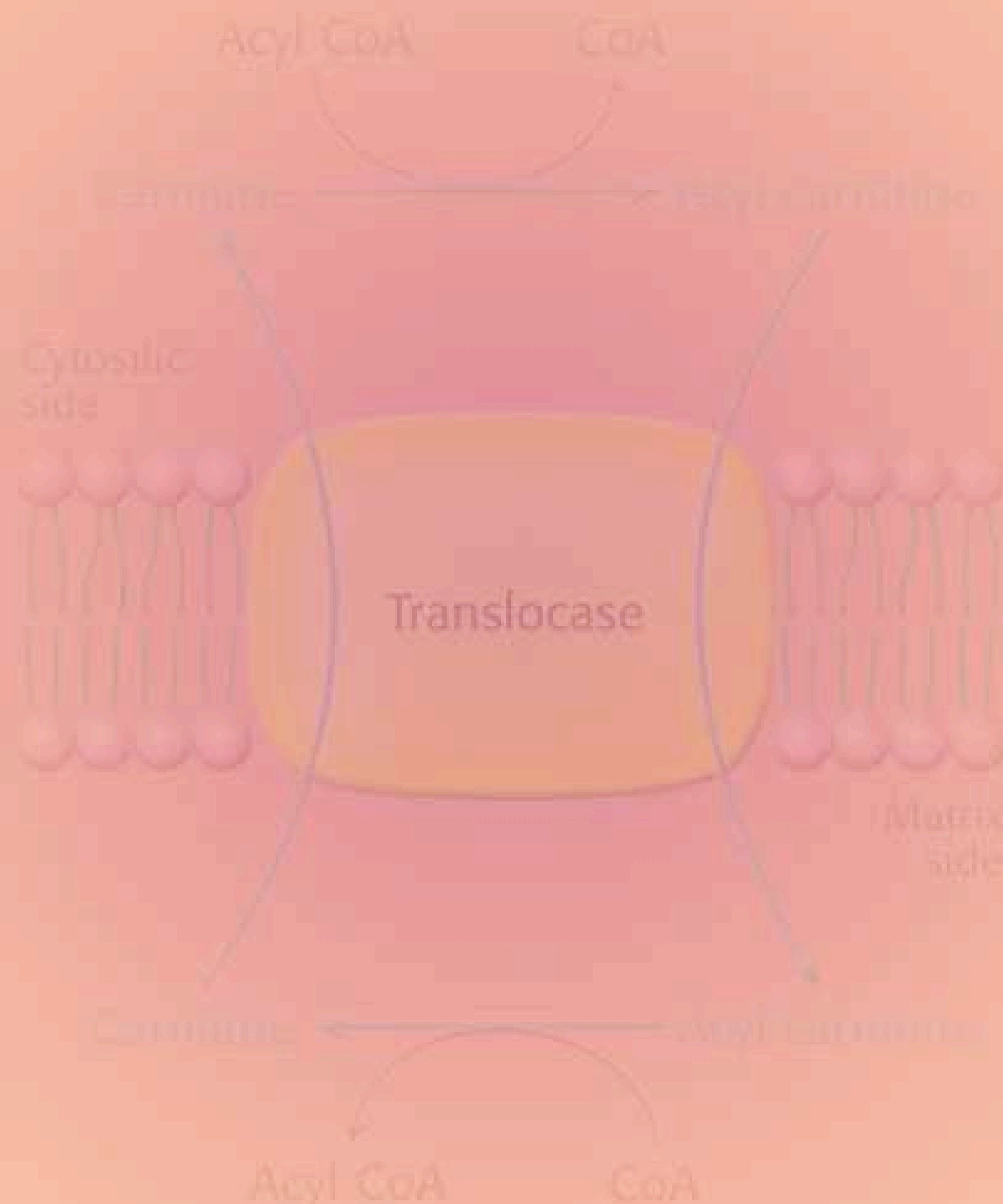
Unsaturated fatty acids (polyunsaturated)



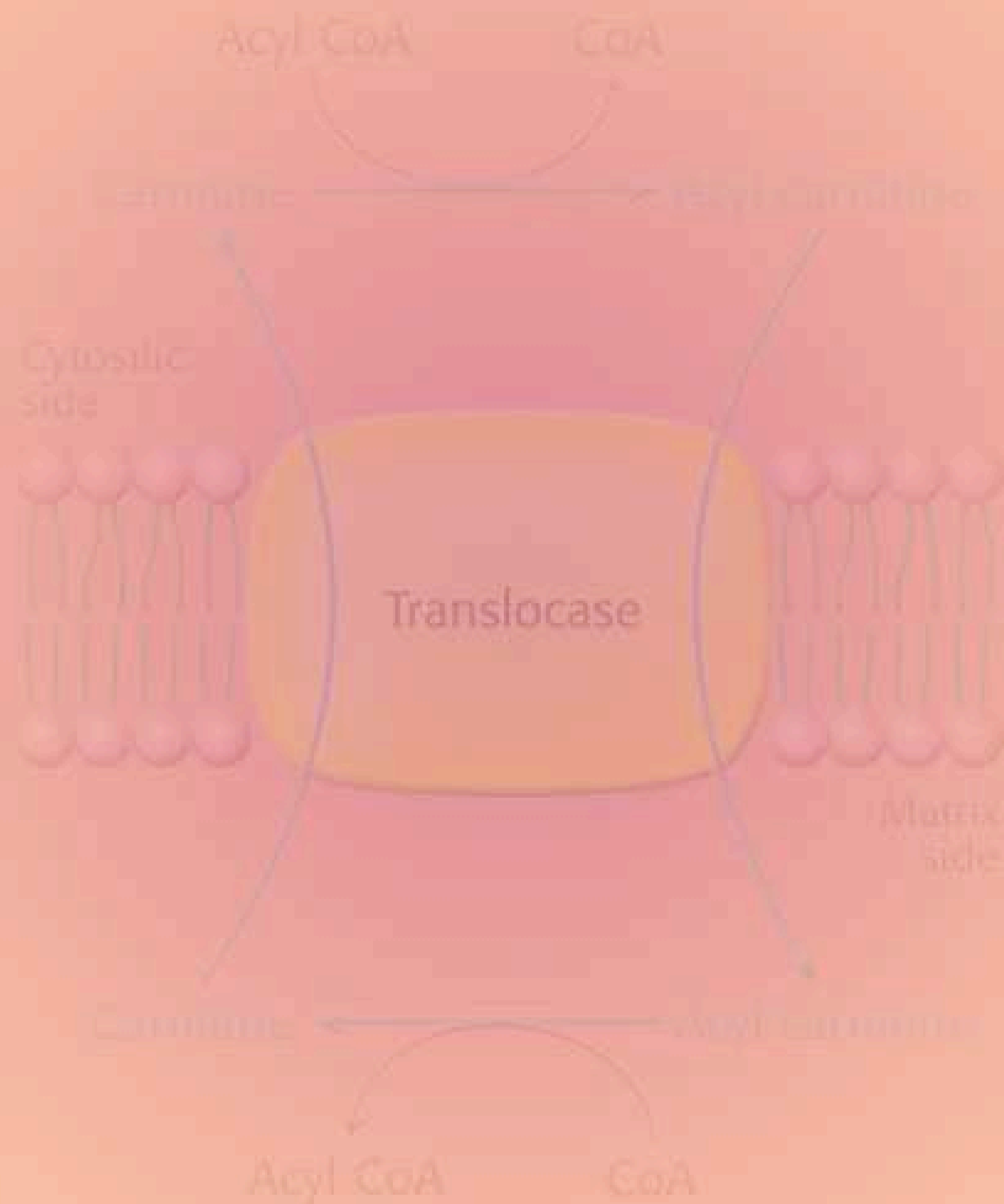
3.2 Odd-Chain (skip)



3.3 Propionyl-CoA (skip)



3.4 Peroxisomes (skip)



3.5 Ketone Bodies

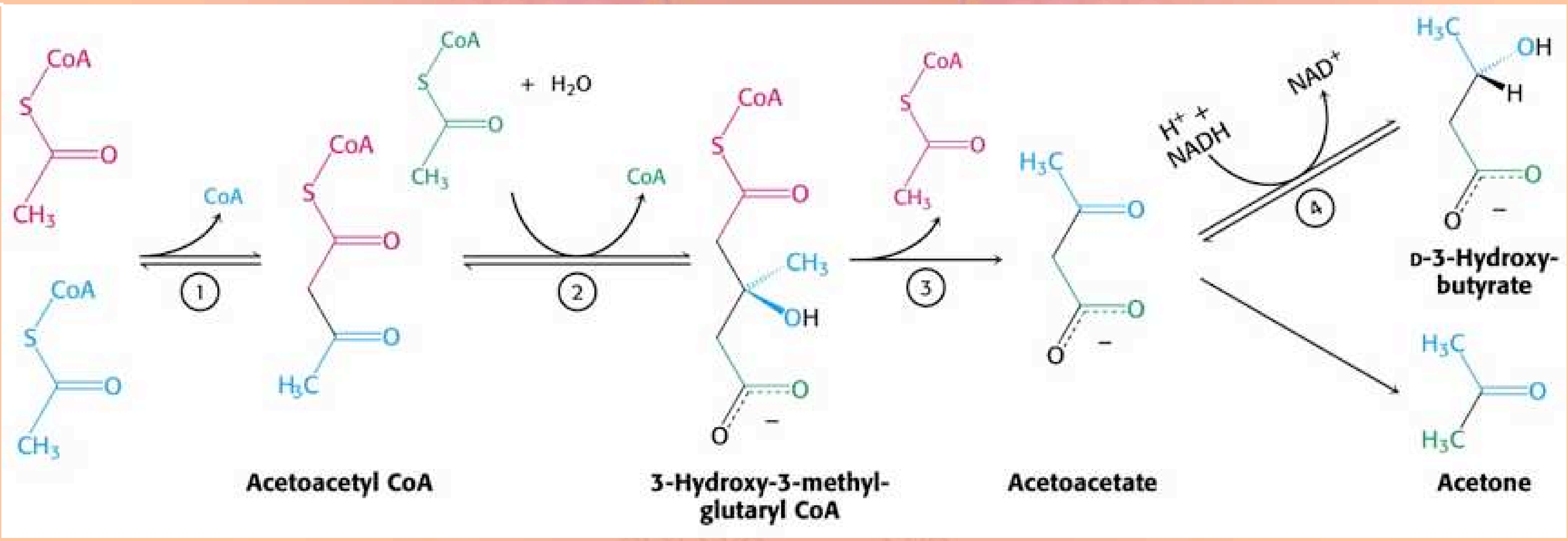
Use of fatty acids in the citric acid cycle requires carbohydrates for the the production of oxaloacetate.

During starvation or diabetes, OAA is used to make glucose

- Fatty acids are then used to make ketone bodies (acetoacetate and D–3–hydroxybutarate)

3.5 Ketone Bodies

Ketone bodies, acetoacetate and 3–hydroxybutarate are formed from Acetyl–CoA



3.6 Ketone Bodies as a Fuel Source

The liver is the major source of ketone bodies.

- It is transported in the blood to other tissues

Acetoacetate in the tissues

- Acetoacetate is first activated to acetoacetate by transferring the CoASH from succinyl-CoA.
- It is then split into two Acetyl-CoA by a thiolase reaction

3.7 Fatty Acids Cannot be Used to Synthesize Glucose

Even though the citric acid cycle intermediate oxaloacetate can be used to synthesize glucose, Acetyl–CoA cannot be used to synthesize oxaloacetate.

- The two carbons that enter the citric acid cycle as Acetyl–CoA leave as CO_2.

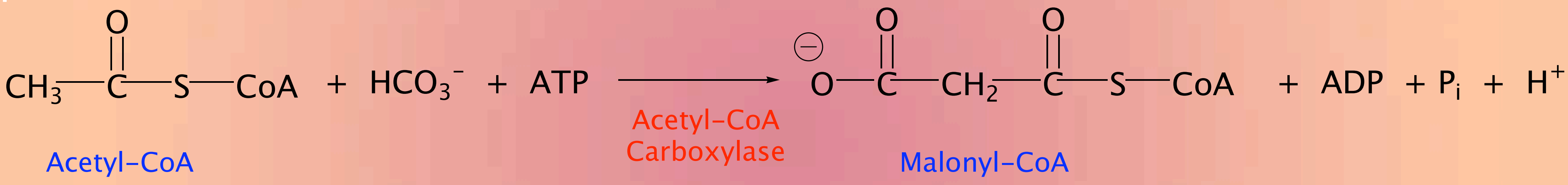
4. Fatty Acid Synthesis.

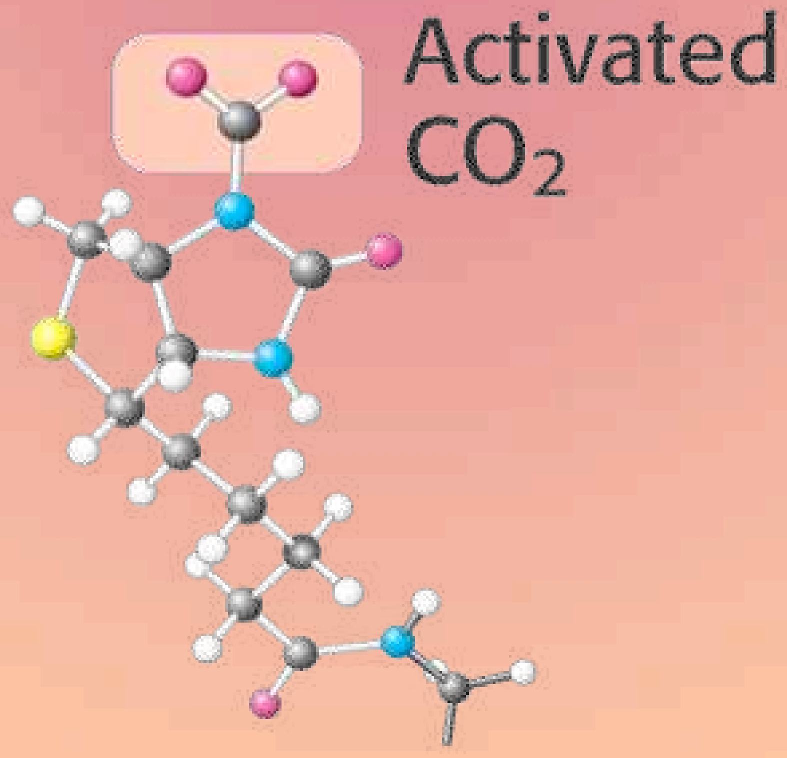
Fatty acid are synthesized and degraded by different pathways.

- Synthesis takes place in the cytosol.
- Intermediates are attached to the acyl carrier protein (ACP).
- In higher organisms, the active sites for the synthesis reactions are all on the same polypeptide.
- The activated donor in the synthesis is malonyl-ACP.
- Fatty acid reduction uses NADPH + H^+.
- Elongation stops at C_{16} (palmitic acid)

4.1 Formation of Malonyl Coenzyme A

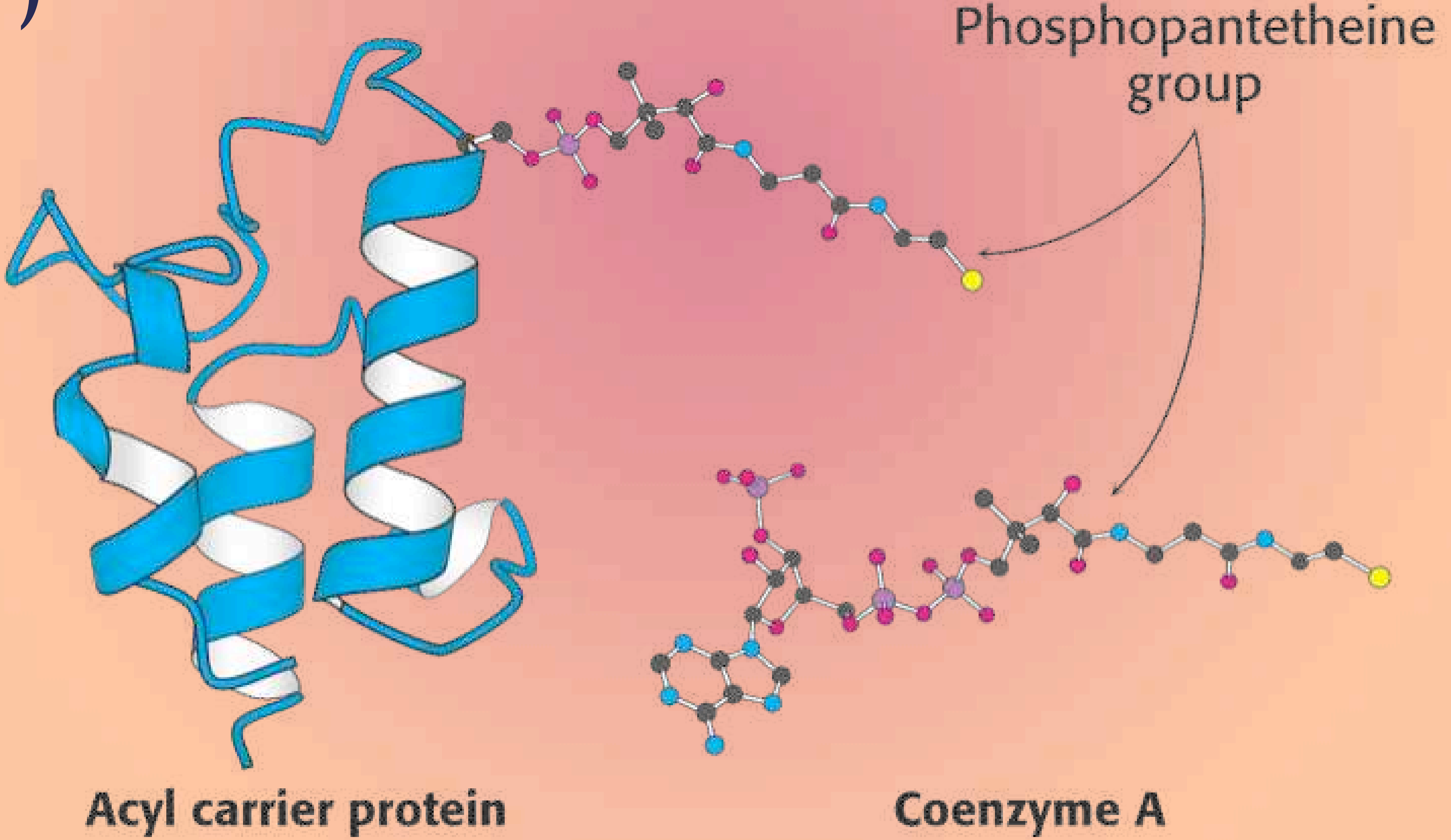
Formation of malonyl-CoA is the committed step in fatty acid synthesis.





4.2 Acyl Carrier Protein

The intermediates in fatty acid synthesis are covalently linked to the acyl carrier protein (ACP)



4.3 Elongation

In bacteria the enzymes that are involved in elongation are separate proteins; in higher organisms the activities all reside on the same polypeptide.

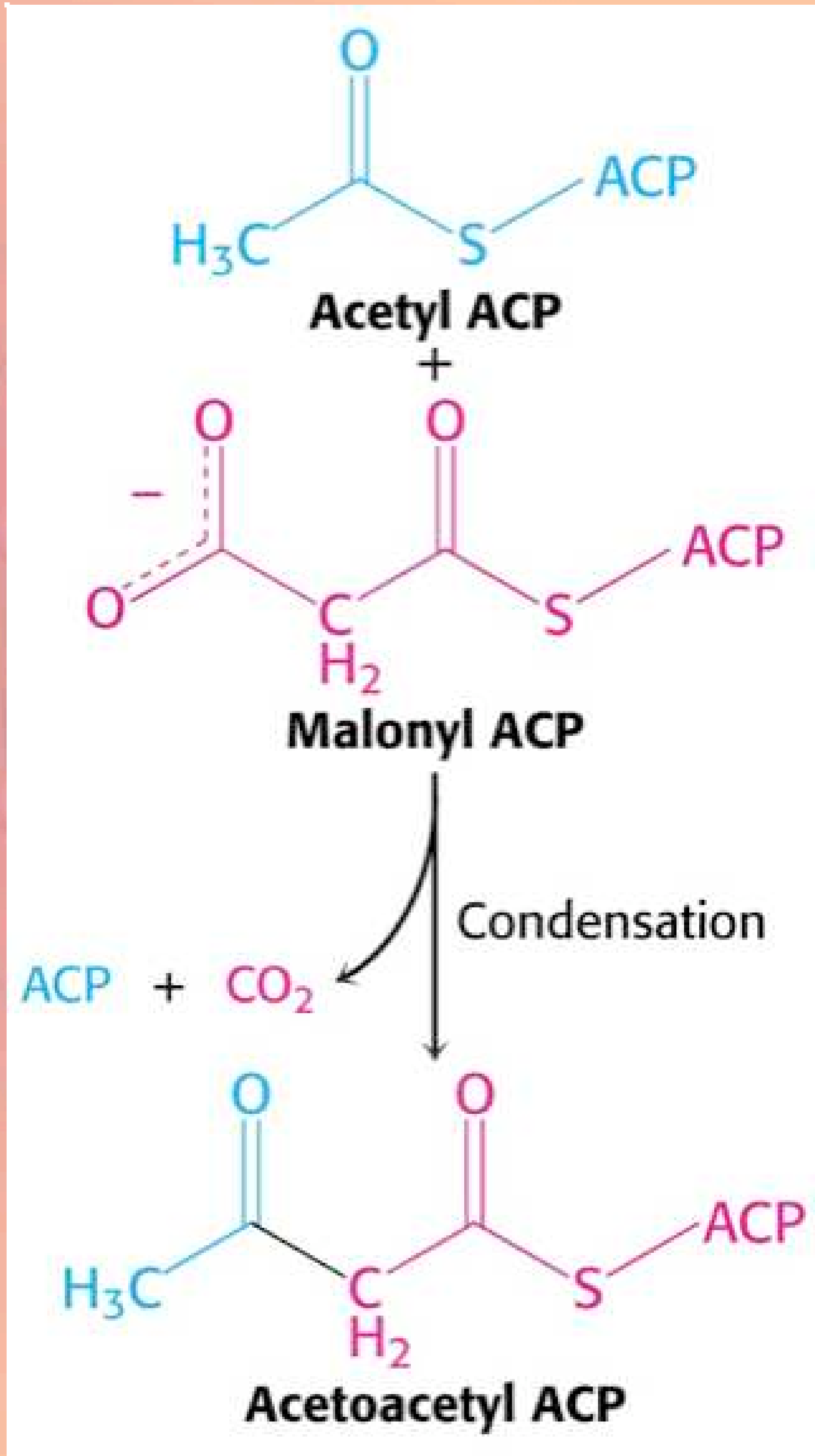
- To start an elongation cycle, Acetyl–CoA and Malonyl–CoA are each transferred to an acyl carrier protein

$$\text{Acetyl–CoA} + \text{ACP} \underset{\text{Acetyl transacylase}}{\rightleftharpoons} \text{Acetyl–ACP} + \text{CoA}$$

$$\text{Malonyl–CoA} + \text{ACP} \underset{\text{Malonyl transacylase}}{\rightleftharpoons} \text{Malonyl–ACP} + \text{CoA}$$

4.3 Elongation

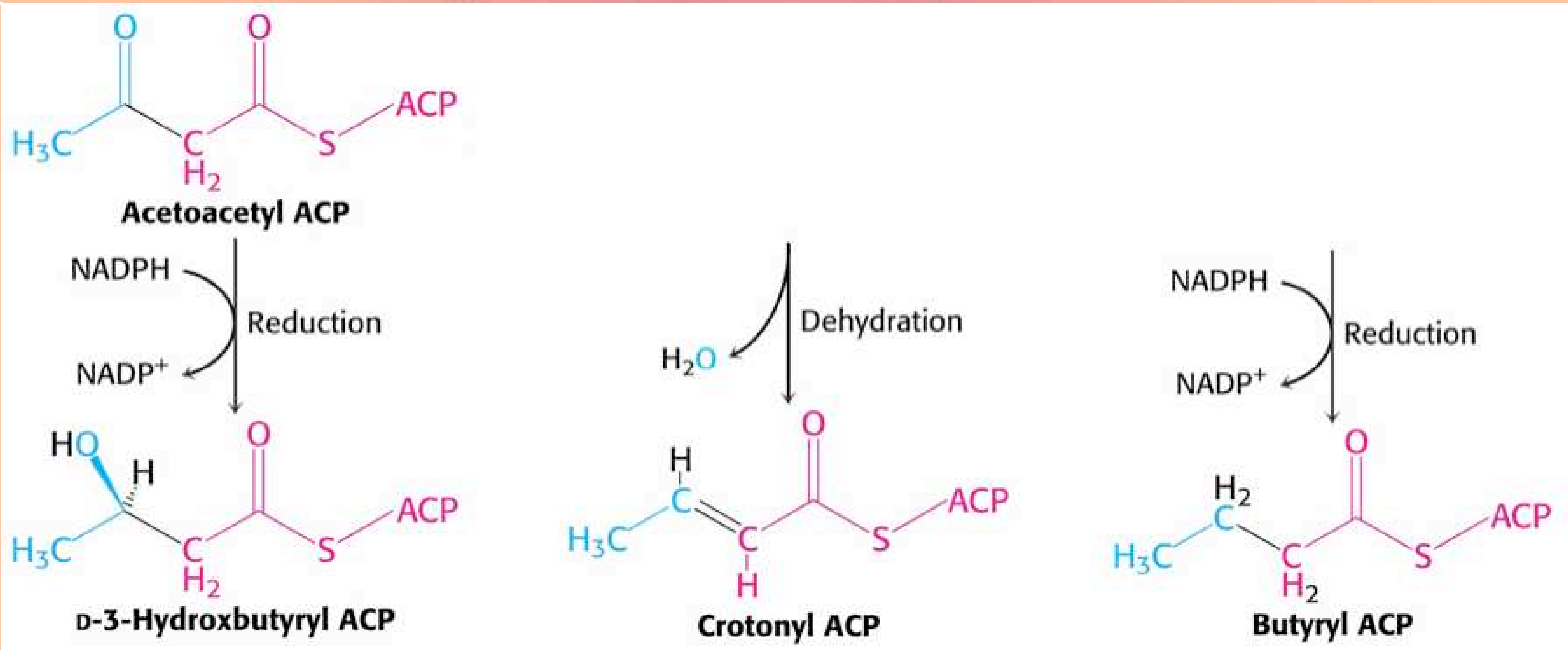
Acyl-malonyl ACP condensing enzyme forms Acetoacetyl-ACP.



4.3 Elongation

The next three reactions are similar to the reverse of fatty acid degradation, except

- The NADPH is used instead of NADH and $FADH_2$
- The D-enantiomer of Hydroxybutarate is formed instead of the L-enantiomer



4.3 Elongation

The elongation cycle is repeated six more times, using malonyl-CoA each time, to produce palmityl-ACP.

A thioesterase then cleaves the palmityl-CoA from the ACP.

4.4 Multifunctional Fatty Acid Synthase

Domain 1

- Substrate entry (AT & MT) and condensation unit (CE)

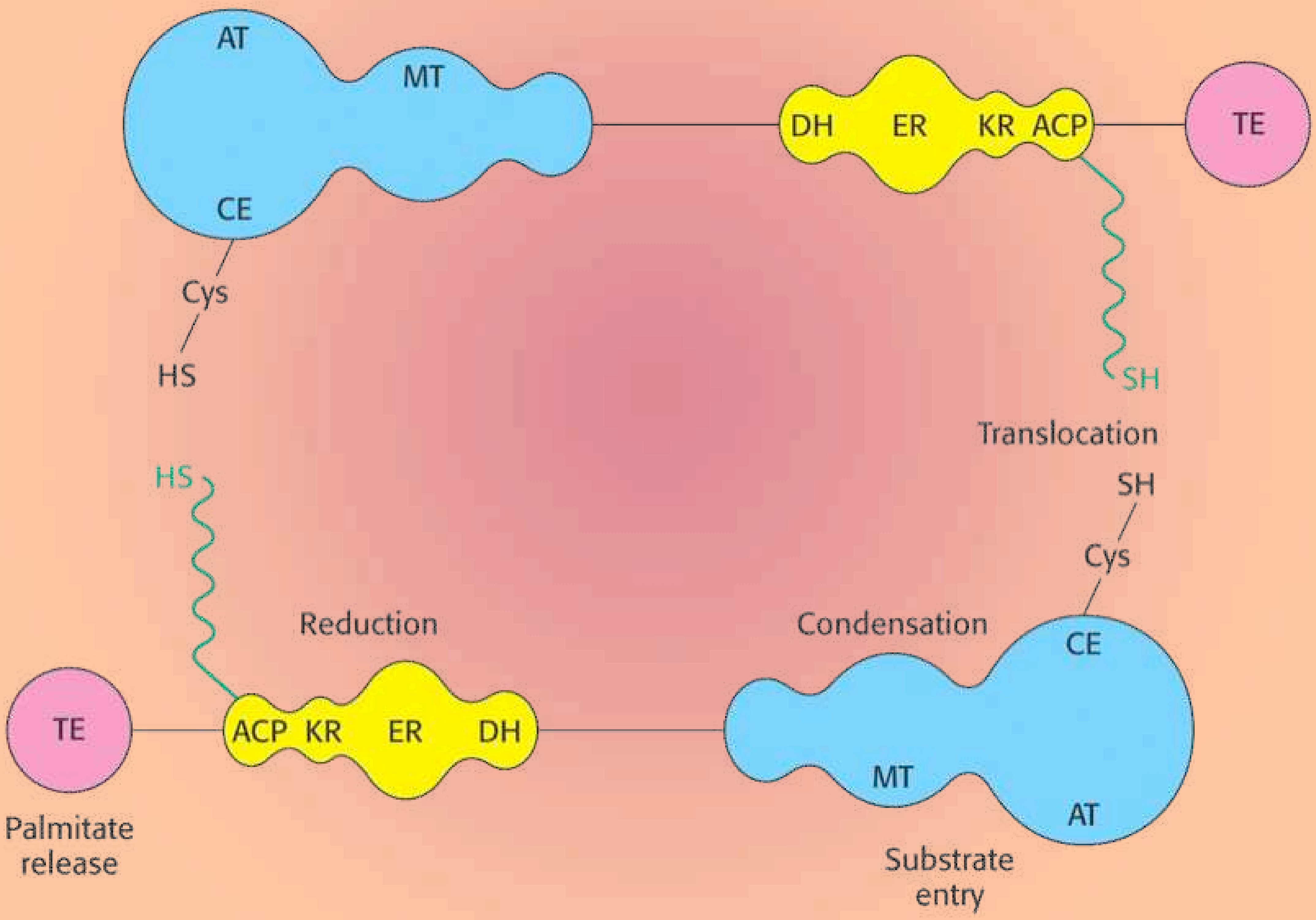
Domain 2

- Reduction unit (DH, ER & KR)

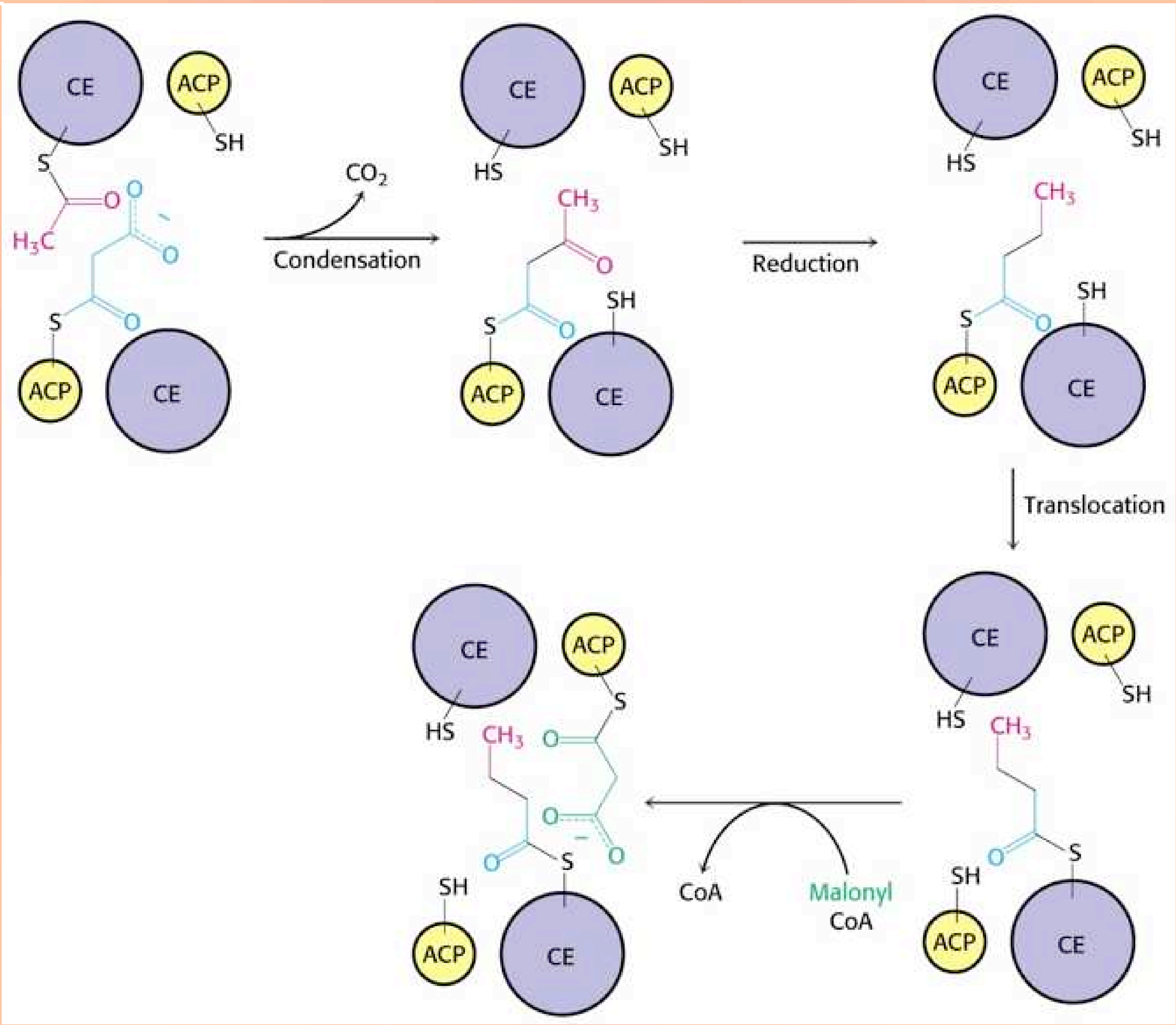
Domain 3

- Palmitate release unit (TE)

4.4 Multifunctional Fatty Acid Synthase

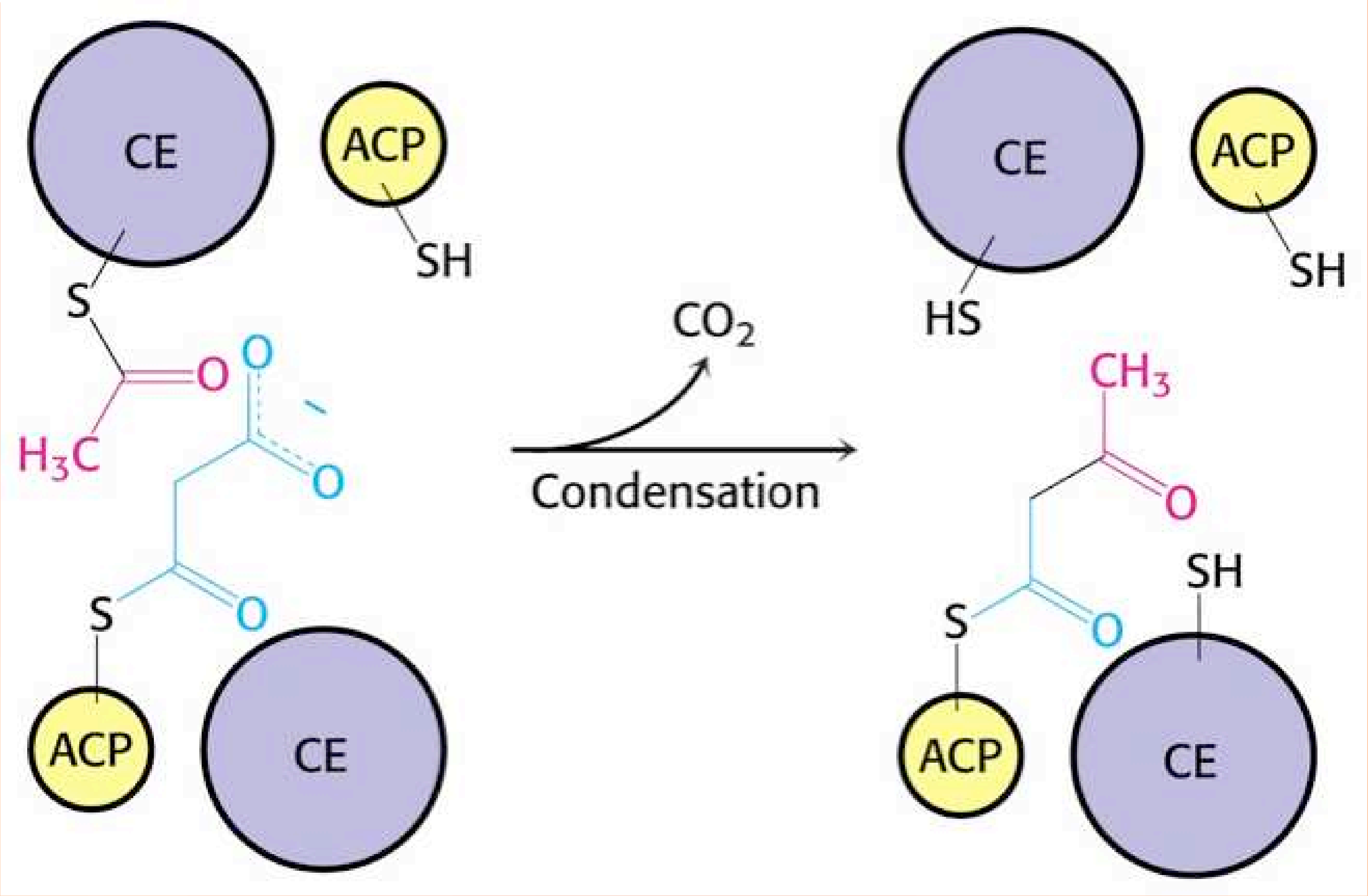


4.5 Fatty Acid Synthase Mechanism



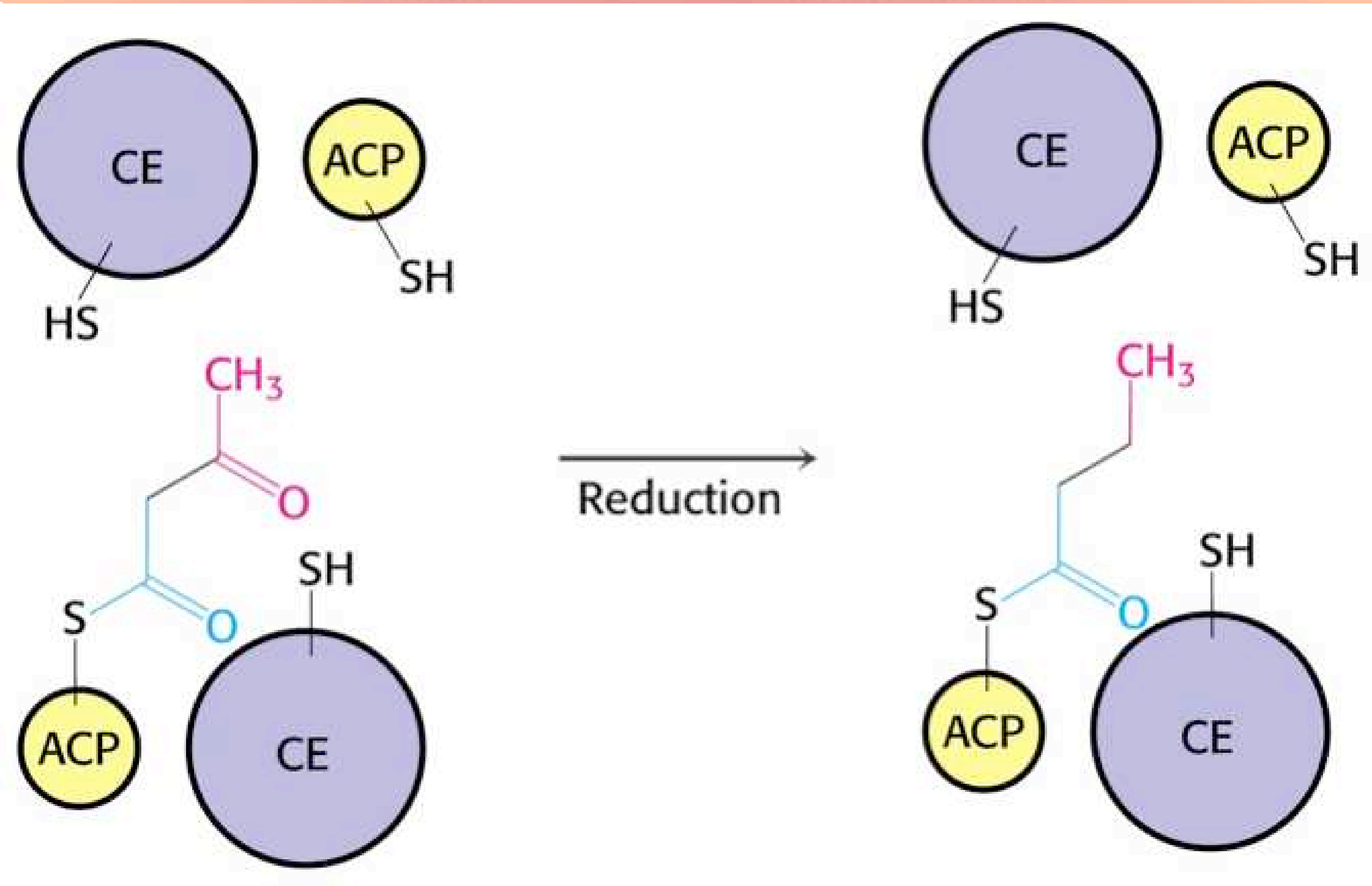
4.5 Fatty Acid Synthase Mechanism

Condensation of Acyl–CoA with Malonyl–CoA:



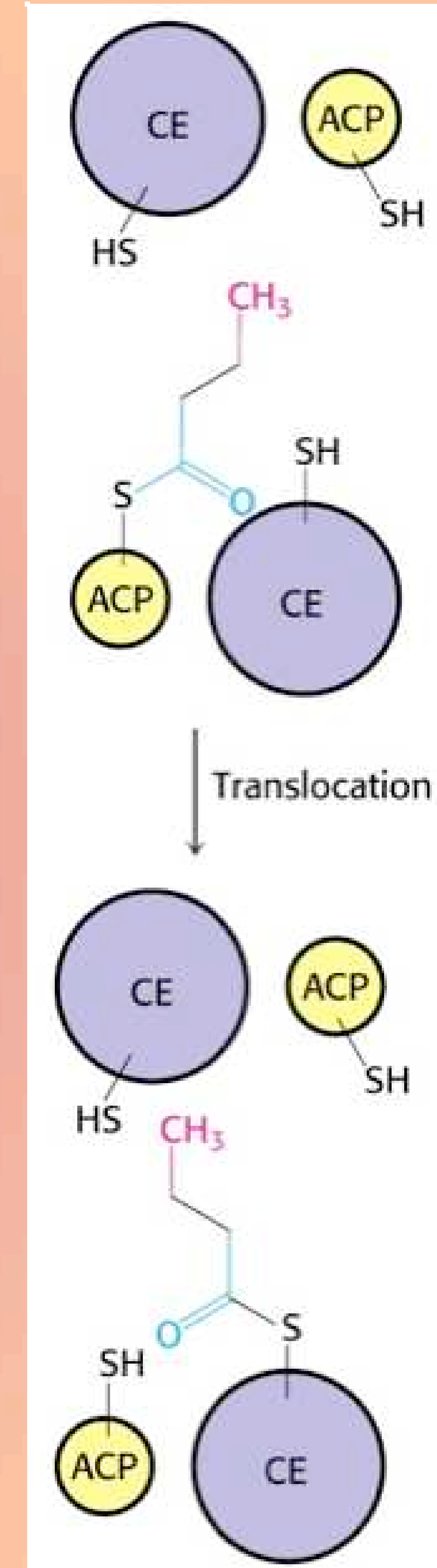
4.5 Fatty Acid Synthase Mechanism

Reduction of the acetoacetate unit:



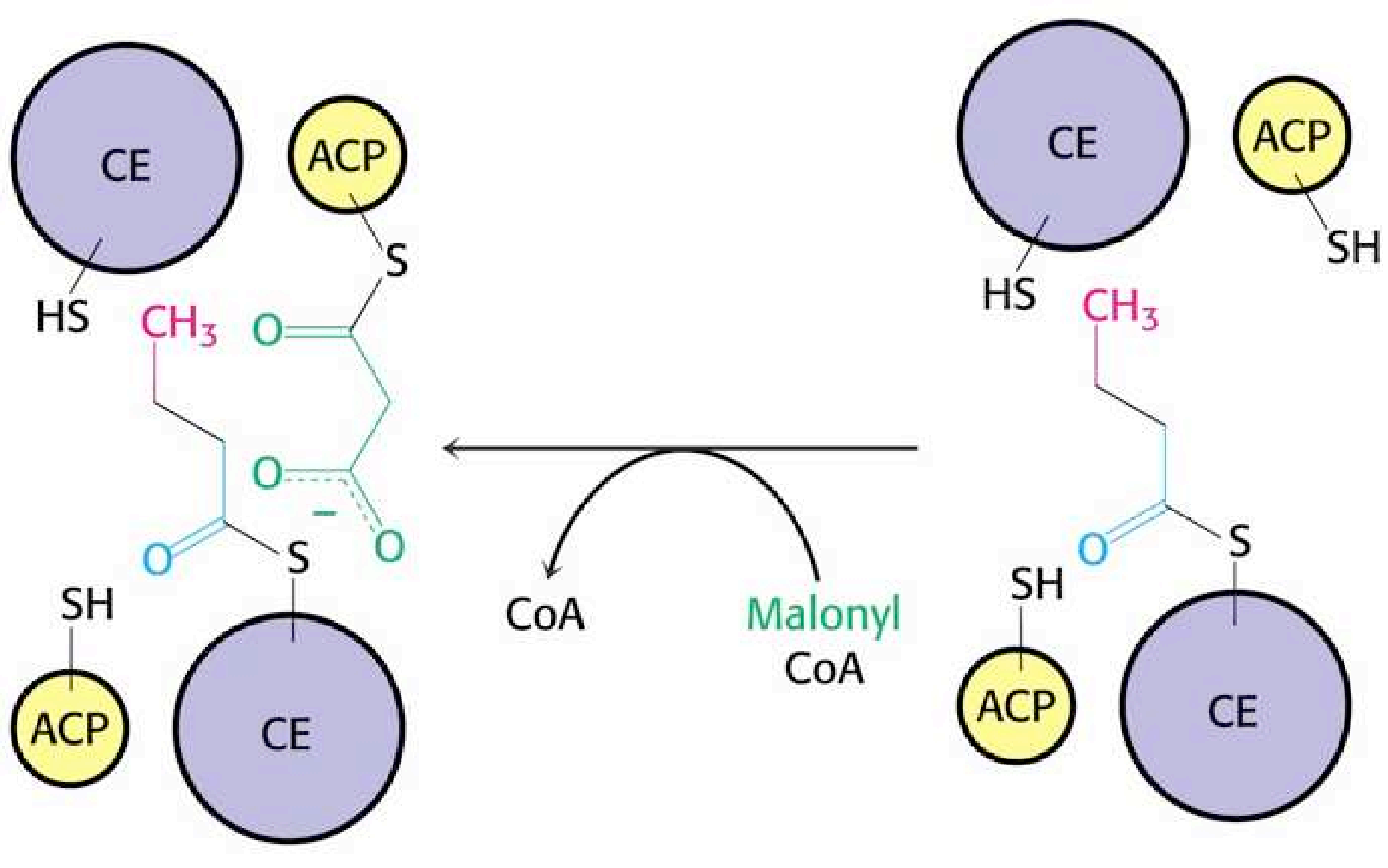
4.5 Fatty Acid Synthase Mechanism

Translocation to the condensing enzyme



4.5 Fatty Acid Synthase Mechanism

Transfer of Malonyl group to the other ACP:



4.6 Stoichiometry of FA synthesis

The stoichiometry of palmitate synthesis:

- Synythesis of palmitate from Malonyl-CoA

$$\text{Acetyl-CoA} + 7\ \text{malonyl-CoA} + 14\ \text{NADPH} + 20\ H^+ \longrightarrow \text{palmitate} + 7\ CO_2 + 14\ NADP^+ + 8\ \text{CoA} + 6\ H_2O$$

- Synthesis of Malonyl-CoA from Acetyl-CoA

$$7\ \text{Acetyl-CoA} + 7\ CO_2 + 7\ \text{ATP} \longrightarrow 7\ \text{Malonyl-CoA} + 7\ \text{ADP} + 7\ P_i + 14\ H^+$$

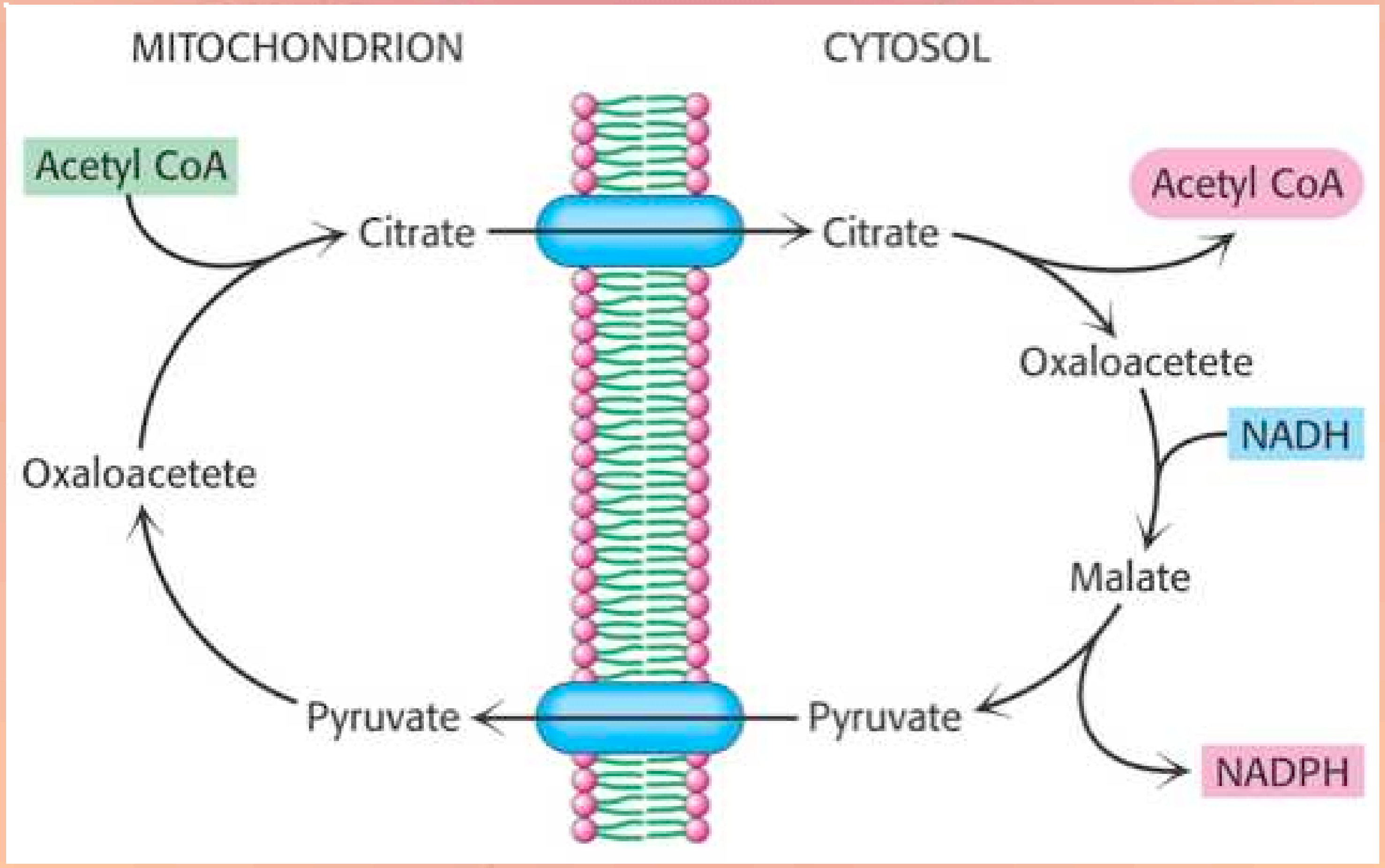
- Overall synthesis

$$\text{Acetyl-CoA} + 7\ \text{ATP} + 14\ \text{NADPH} + 6\ H^+ \longrightarrow \text{palmitate} + 14\ NADP^+ + 8\ \text{CoA} + 6\ H_2O + 7\ \text{ADP} + 7\ P_i$$

4.7 Citrate Shuttle

Acetyl–CoA is synthesized in the mitochondrial matrix, whereas fatty acids are synthesized in the cytosol

- Acetyl–CoA units are shuttled out of the mitochondrial matrix as citrate:



$$\text{Citrate} + \text{ATP} + \text{CoA} + H_2O \xrightarrow[\text{Citrate Lyase}]{} \text{Acetyl–CoA} + \text{ADP} + P_i + \text{Oxaloacetate}$$

4.8 Sources of NADPH

The malate dehydrogenase and NADP$^+$–linked malate enzyme reactions of the citrate shuttle exchange NADH for NADPH

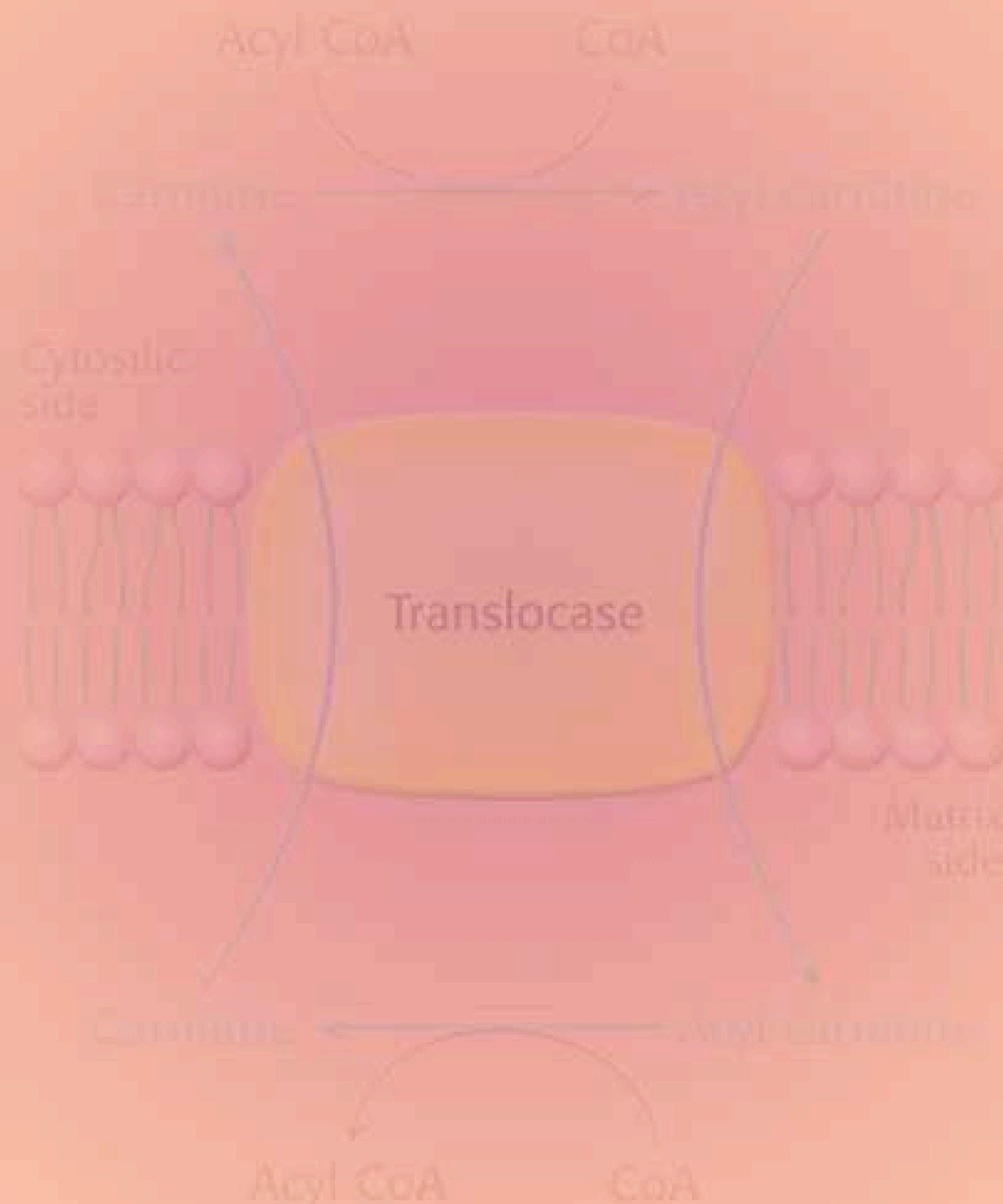
$$\text{Oxaloacetate} + \text{NADH} + H^+ \xrightarrow[\text{Malate Dehydrogenase}]{} \text{Malate} + \text{NAD}^+$$

$$\text{Malate} + \text{NADP}^+ \xrightarrow[\text{NADP}^+\text{–linked Malate Enzyme}]{} \text{Pyruvate} + CO_2 \;\; \text{NADPH}$$

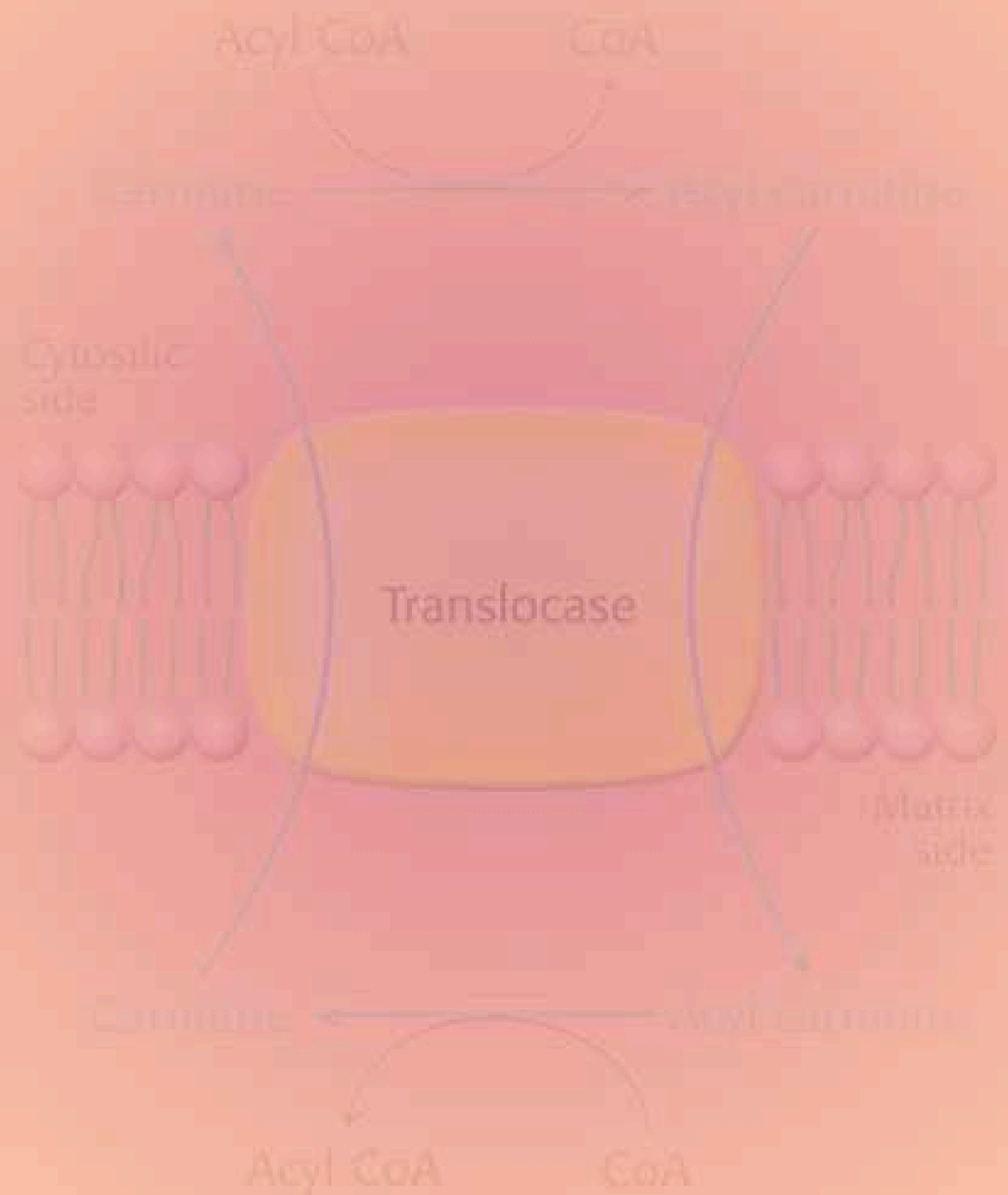
$$\text{Pyruvate} + CO_2 + \text{ATP} + H_2O \underset{\text{Pyruvate Carboxylase}}{\rightleftharpoons} \text{Oxaloacetate} + \text{ADP} + P_i + 2\,H^+$$

$$\text{NADP}^+ + \text{NADH} + \text{ATP} + H_2O \rightleftharpoons \text{NADPH} + \text{NAD}^+ + \text{ADP} + P_i + H^+$$

4.9 Fatty Acid Synthase Inhibitors (skip)



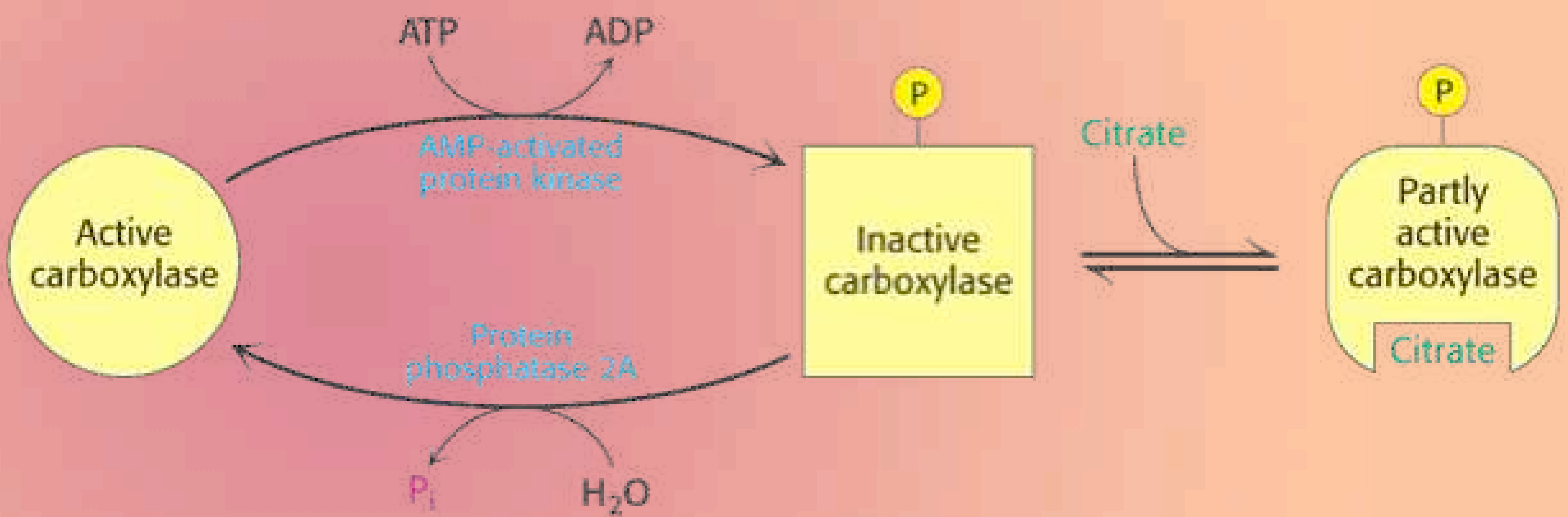
4.10 Variations on a Theme (skip)



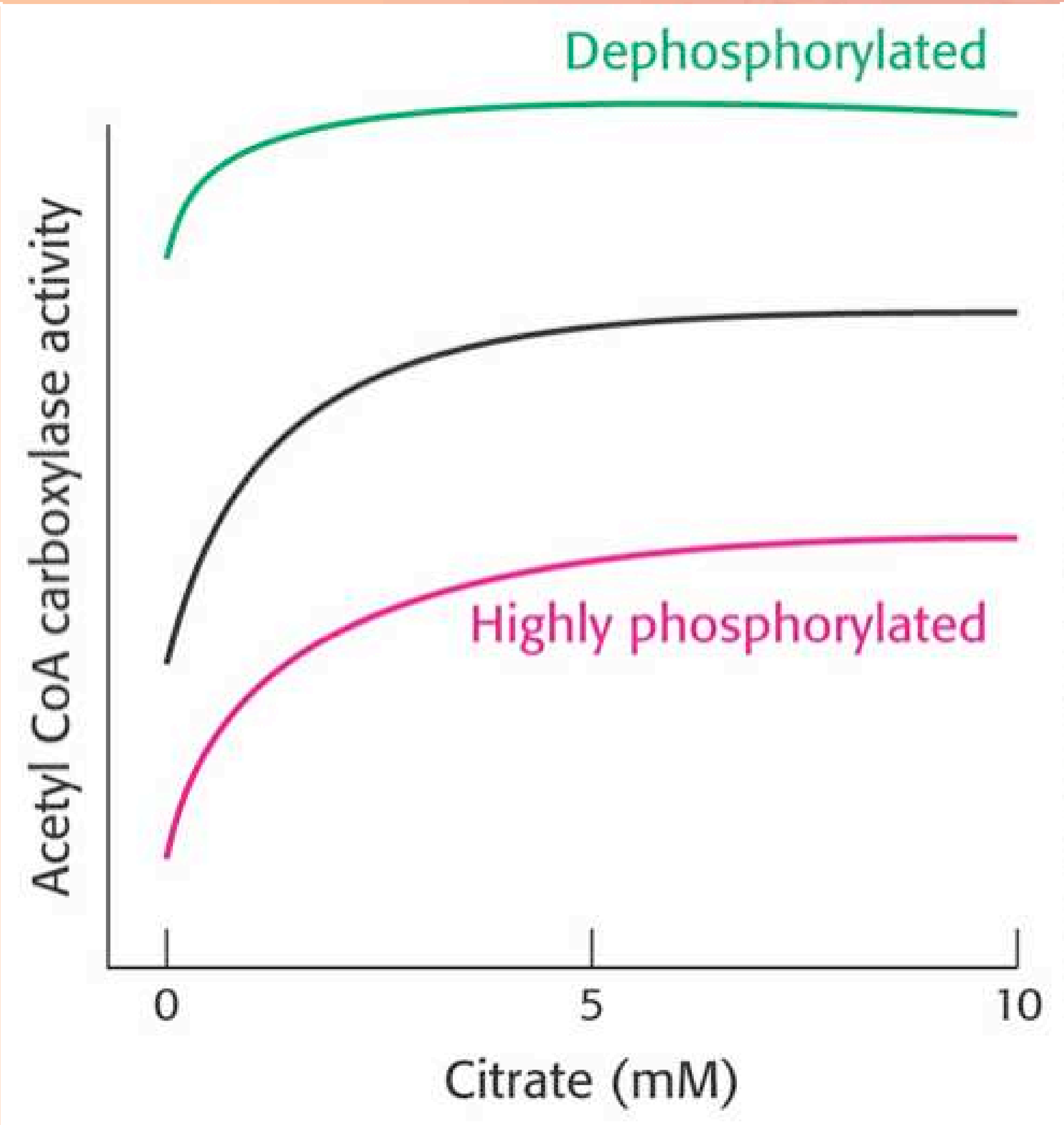
5. Regulation of Fatty Acid Synthesis

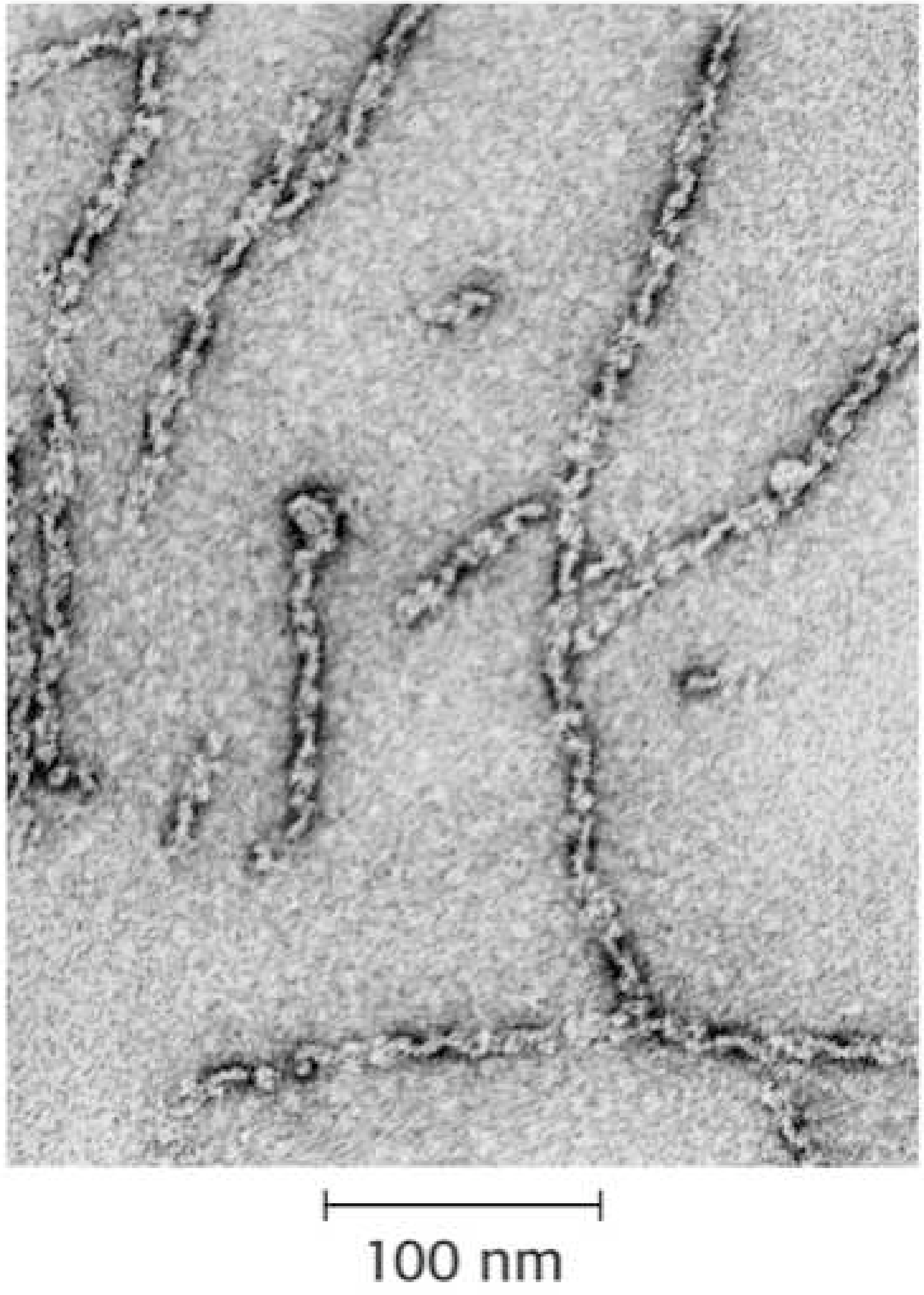
Regulation of Acetyl carboxylase

- Global
  - + insulin
  - - glucagon
  - - epinephrine
- Local
  - + Citrate
  - - Palmitoyl-CoA
  - - AMP



5.1 Regulation of Fatty Acid Synthesis





6. Elongation and Unsaturation

Endoplasmic reticulum systmes introduce double bonds into long chain acyl–CoA's

- Reaction combines both NADH and the acyl–CoA's to reduce O_2 to H_2O.

6.1 Elongation and Unsaturation

Elongation and unsaturation convert palmitoyl–CoA to other fatty acids.

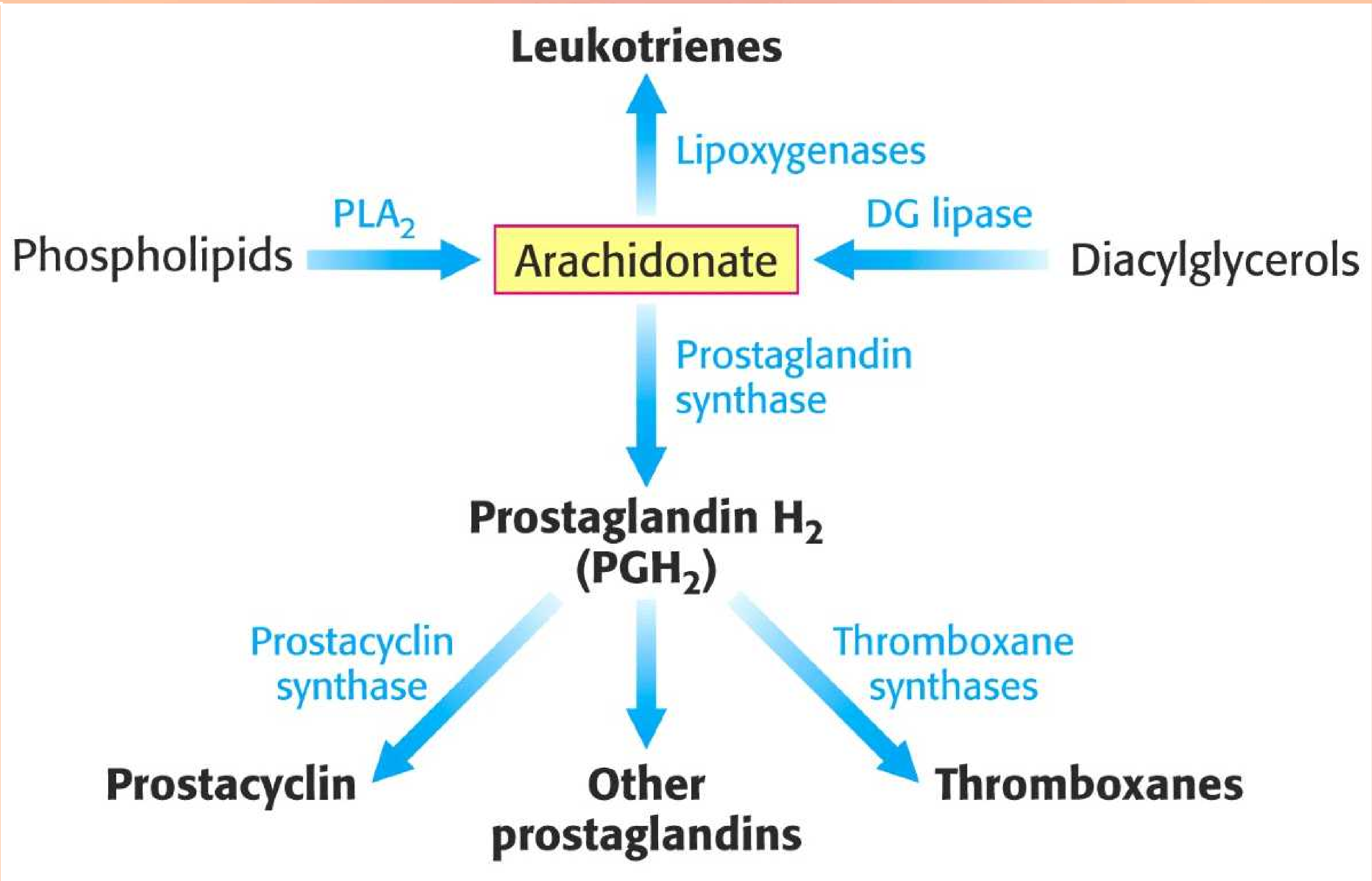
- Reactions occur on the cytosolic face of the endoplasmic reticulum.
- Malonyl–CoA is the donor in elongation reactions

6.2 Eicosanoid Hormones

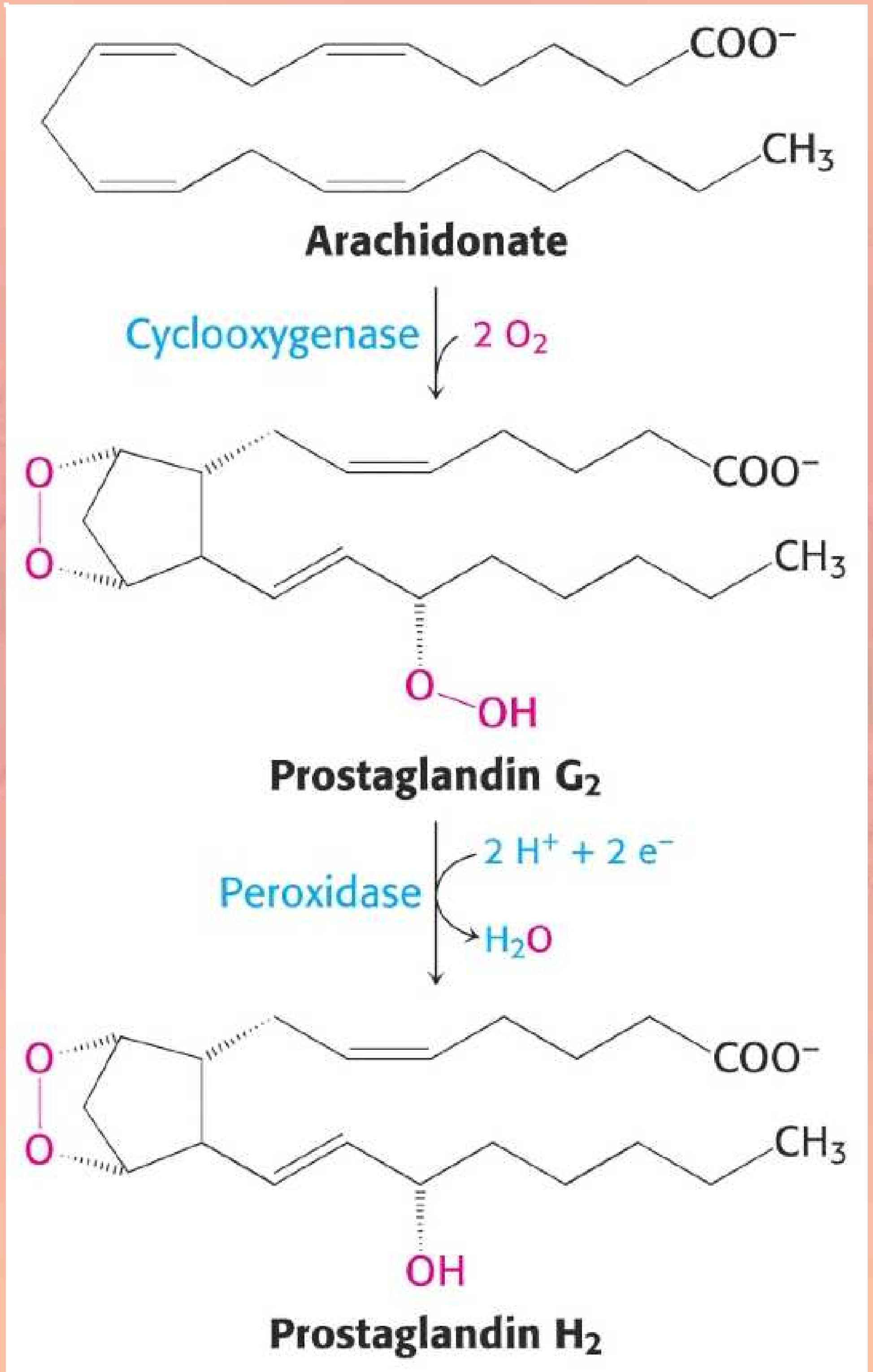
Eicosanoid horomones are synthesized from arachadonic acid (20:4).

- Prostaglandins
  - 20-carbon fatty acid containing 5-carbon ring
  - Prostacyclins
  - Thromboxanes
- Leukotrienes
  - contain three conjugated double bonds

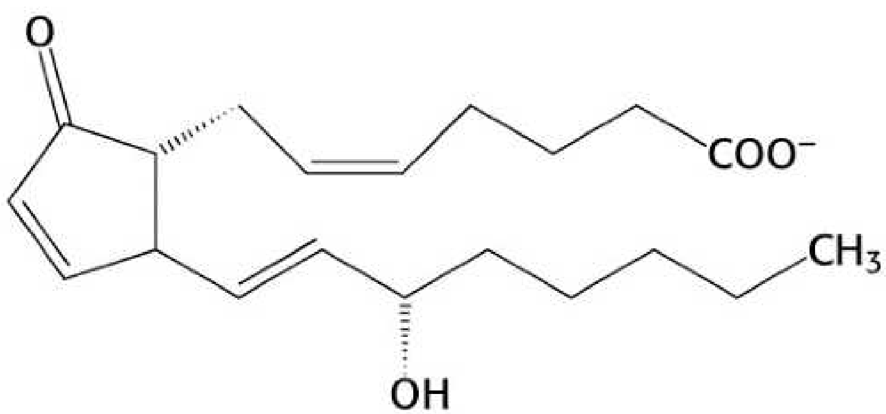
6.2 Eicosanoid Hormones



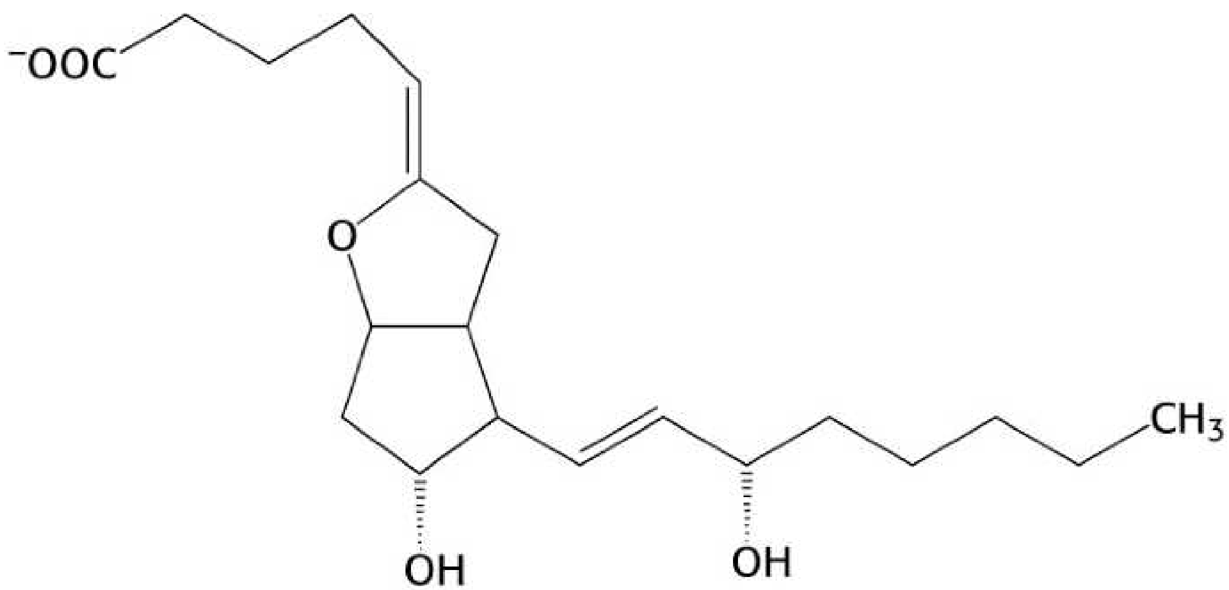
6.2 Eicosanoid Hormones



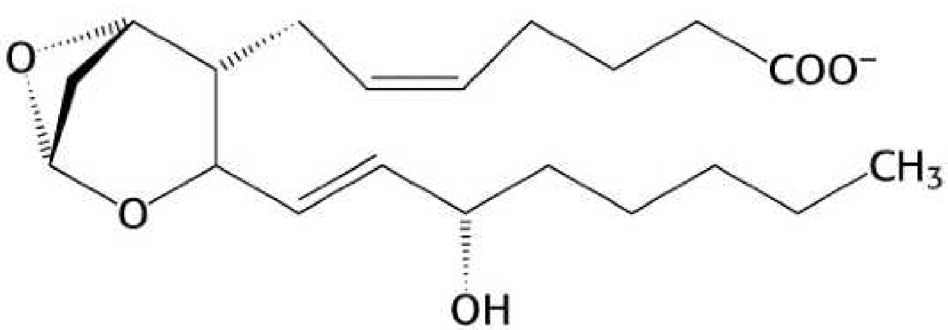
6.2 Eicosanoid Hormones



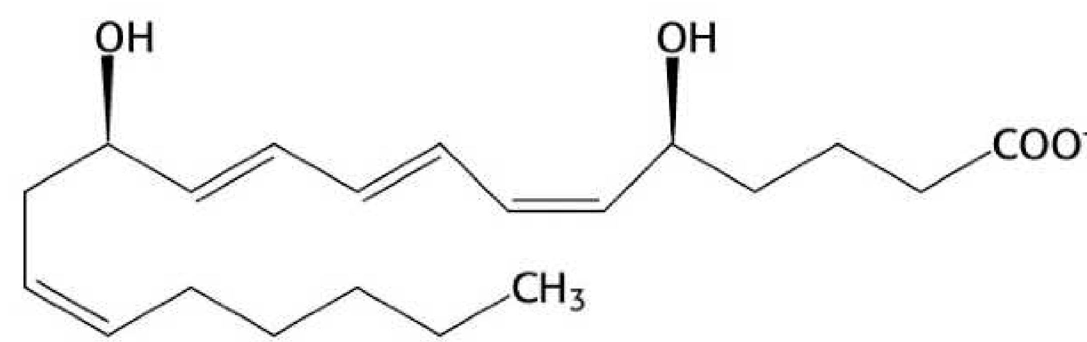
Prostaglandin A_2



Prostacylin (PGI_2)



Thromboxane A_2 (TXA_2)



Leukotriene B_4