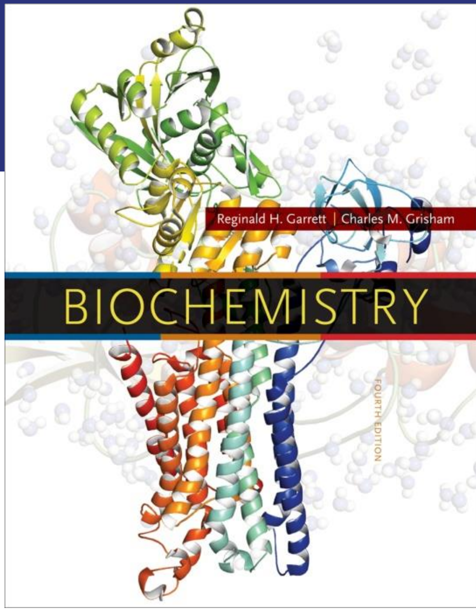


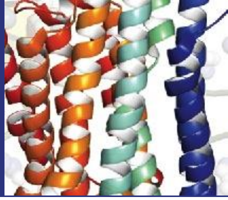
BROOKS/COLE
CENGAGE Learning

Reginald H. Garrett
Charles M. Grisham

Chapter 23
Fatty Acid Catabolism

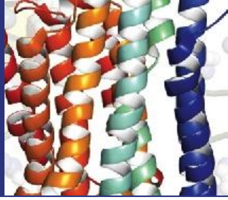
β-oxidation

Essential Questions



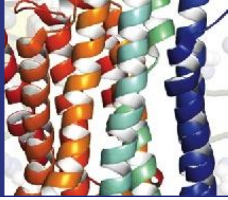
- How are fatty acids catabolized, and how is their inherent energy captured by organisms?

Outline



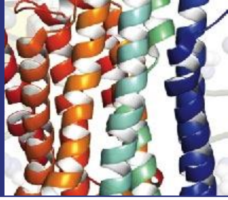
- How are fats mobilized from dietary intake and adipose tissue?
- How are fatty acids broken down?
- How are odd-carbon fatty acids oxidized?
- How are unsaturated fatty acids oxidized?
- Are there other ways to oxidize fatty acids?
- What are ketone bodies, and what role do they play in metabolism?

Why Are Fatty Acids Used by Organisms for Energy Storage?



- Two reasons:
  - The carbon in fatty acids (mostly -CH_2-) is reduced (so its oxidation yields the most energy possible).
  - Fatty acids are not hydrated (as mono- and polysaccharides are), so they can pack more closely in storage tissues

23.1 How Are Fats Mobilized from Dietary Intake and Adipose Tissue?



- Most of the “fats” in diet and in adipose tissue are triglycerides

- Triglycerides represent the major energy input in the modern American diet (but it wasn't always this way)

- Triglycerides are also the major form of stored energy in the body
- See Table 23.1

- Hormones (glucagon, epinephrine, ACTH) trigger the release of fatty acids from adipose tissue

23.1 How Are Fats Mobilized from Dietary Intake and Adipose Tissue?

Figure 23.1 Scanning electron micrograph of an adipose cell (fat cell). Globules of triacylglycerols occupy most of the volume of such cells.

23.1 How Are Fats Mobilized from Dietary Intake and Adipose Tissue?

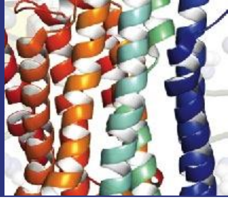


TABLE 23.1 Stored Metabolic Fuel in a 70-kg Person

Constituent	Energy (kJ/g dry weight)	Dry Weight (g)	Available Energy (kJ)
Fat (adipose tissue)	37	15,000	555,000
Protein (muscle)	17	6,000	102,000
Glycogen (muscle)	16	120	1,920
Glycogen (liver)	16	70	1,120
Glucose (extracellular fluid)	16	20	320
Total			660,360

23.1 How Are Fats Mobilized from Dietary Intake and Adipose Tissue?

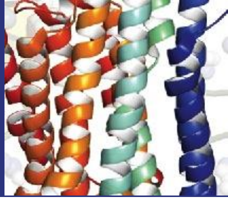
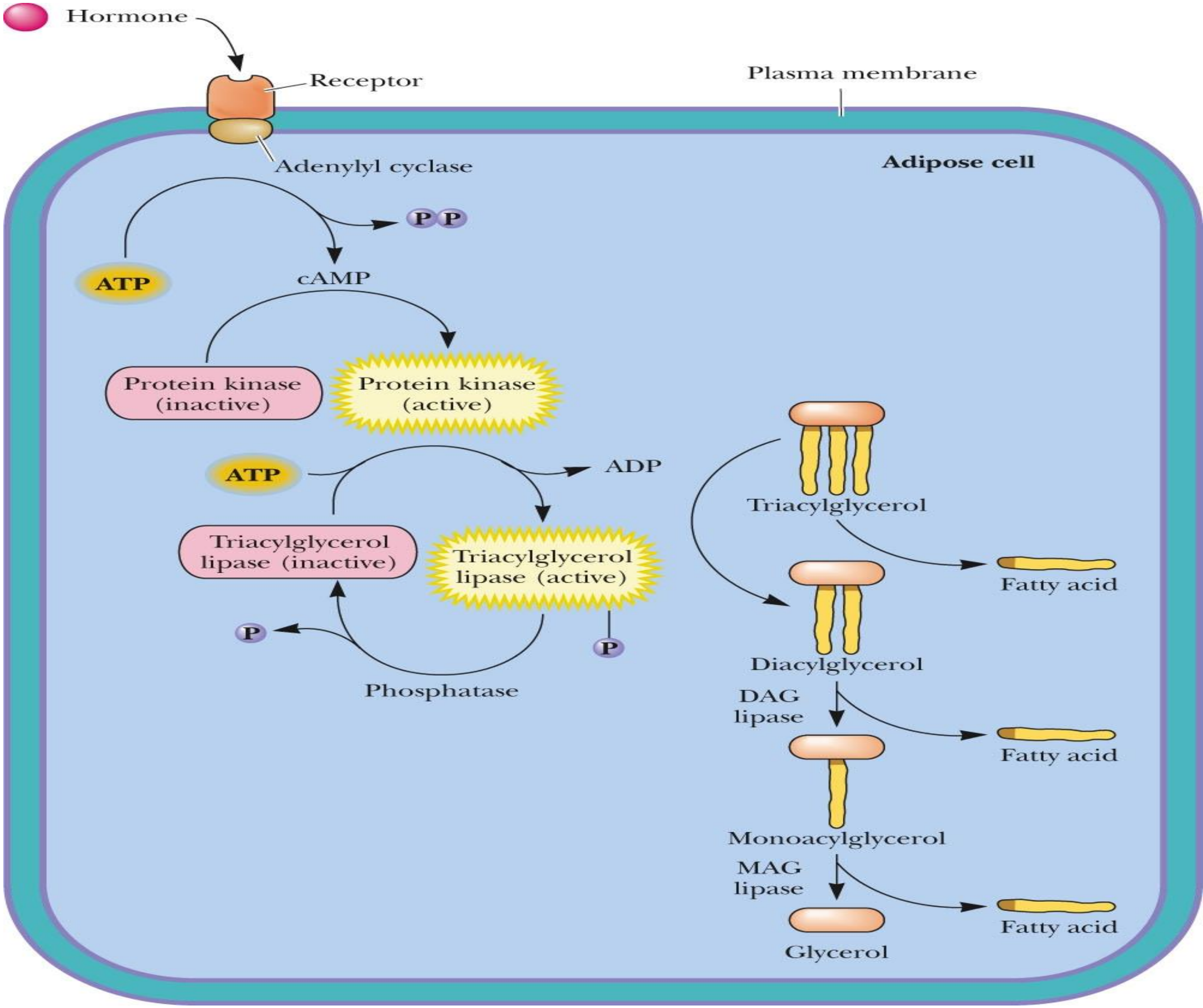


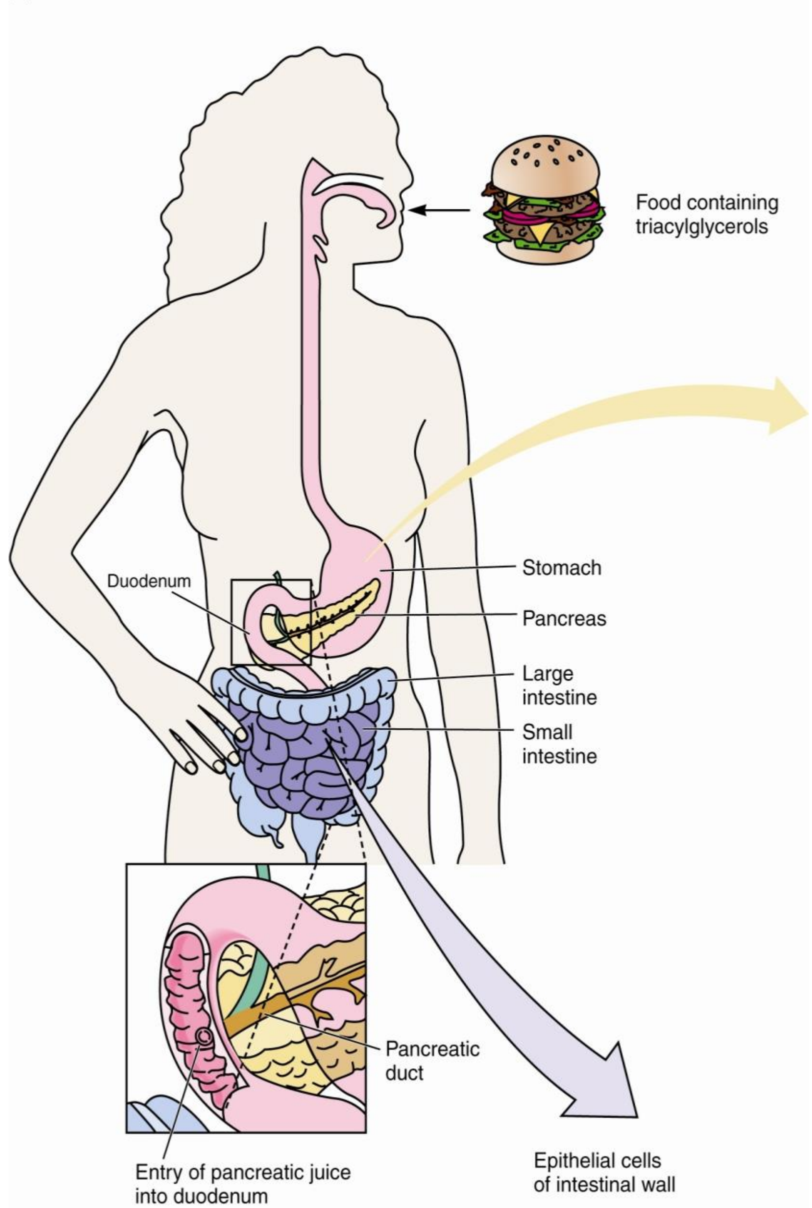
Figure 23.2 Liberation of fatty acids from triacylglycerols in adipose tissue



23.1 How Are Fats Mobilized from Dietary Intake and Adipose Tissue?

Figure 23.3a The pancreatic duct secretes digestive fluids into the duodenum, the first portion of the small intestine.

(a)



23.1 How Are Fats Mobilized from Dietary Intake and Adipose Tissue?

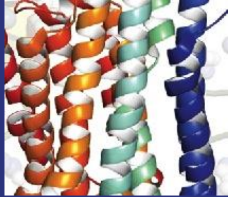
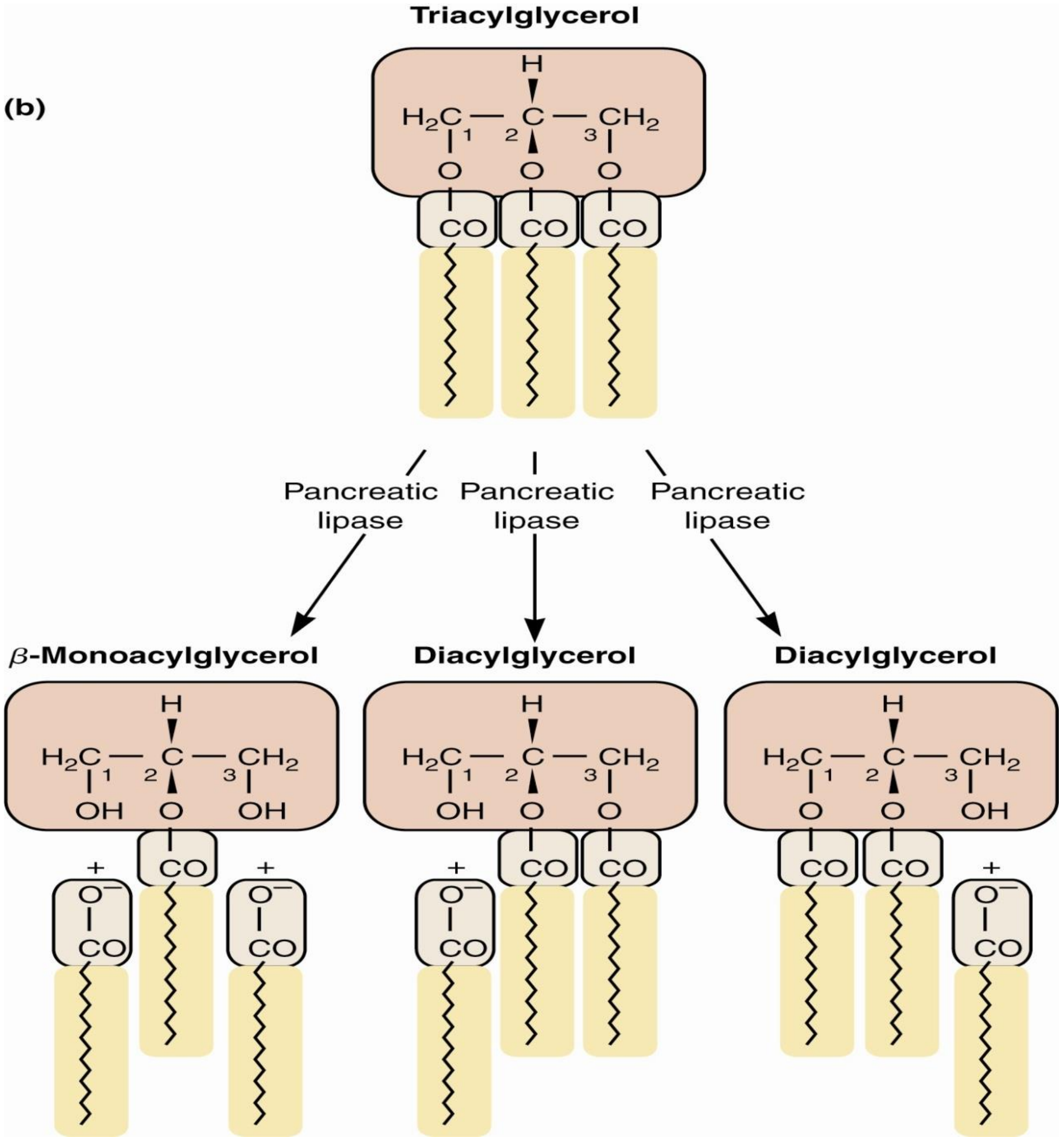
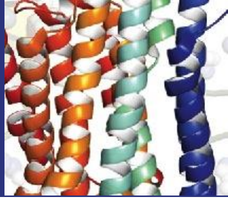


Figure 23.3b Hydrolysis of triacylglycerols by pancreatic and intestinal lipases. Pancreatic lipases cleave fatty acids at the C-1 and C-3 positions. Resulting monoacylglycerols with fatty acids at C-2 are hydrolyzed by intestinal lipases. Fatty acids and monoacylglycerols are absorbed through the intestinal wall and assembled into lipoprotein aggregates termed chylomicrons (discussed in Chapter 24).



23.1 How Are Fats Mobilized from Dietary Intake and Adipose Tissue?



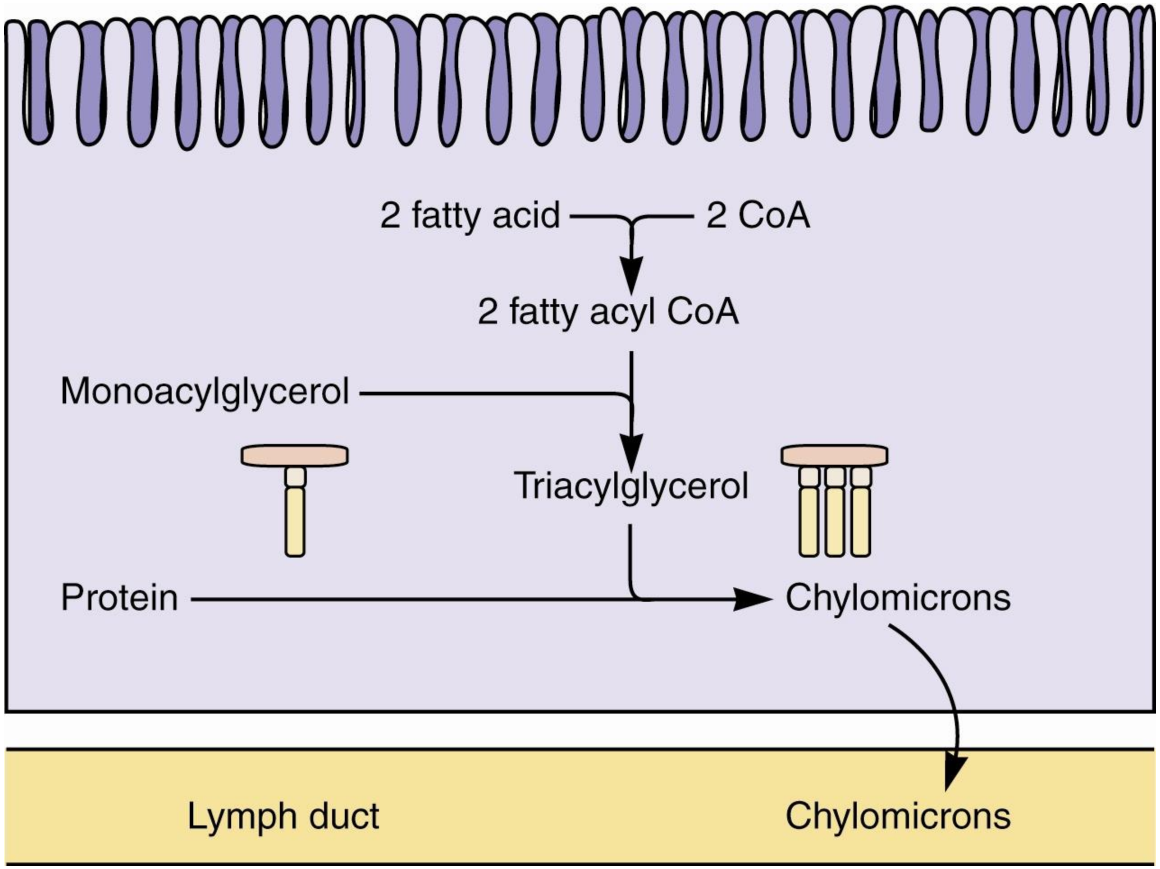


Figure 23.3b Fatty acids and monoacylglycerols are absorbed through the intestinal wall and assembled into lipoprotein aggregates termed chylomicrons (discussed in Chapter 24).

23.1 How Are Fats Mobilized from Dietary Intake and Adipose Tissue?

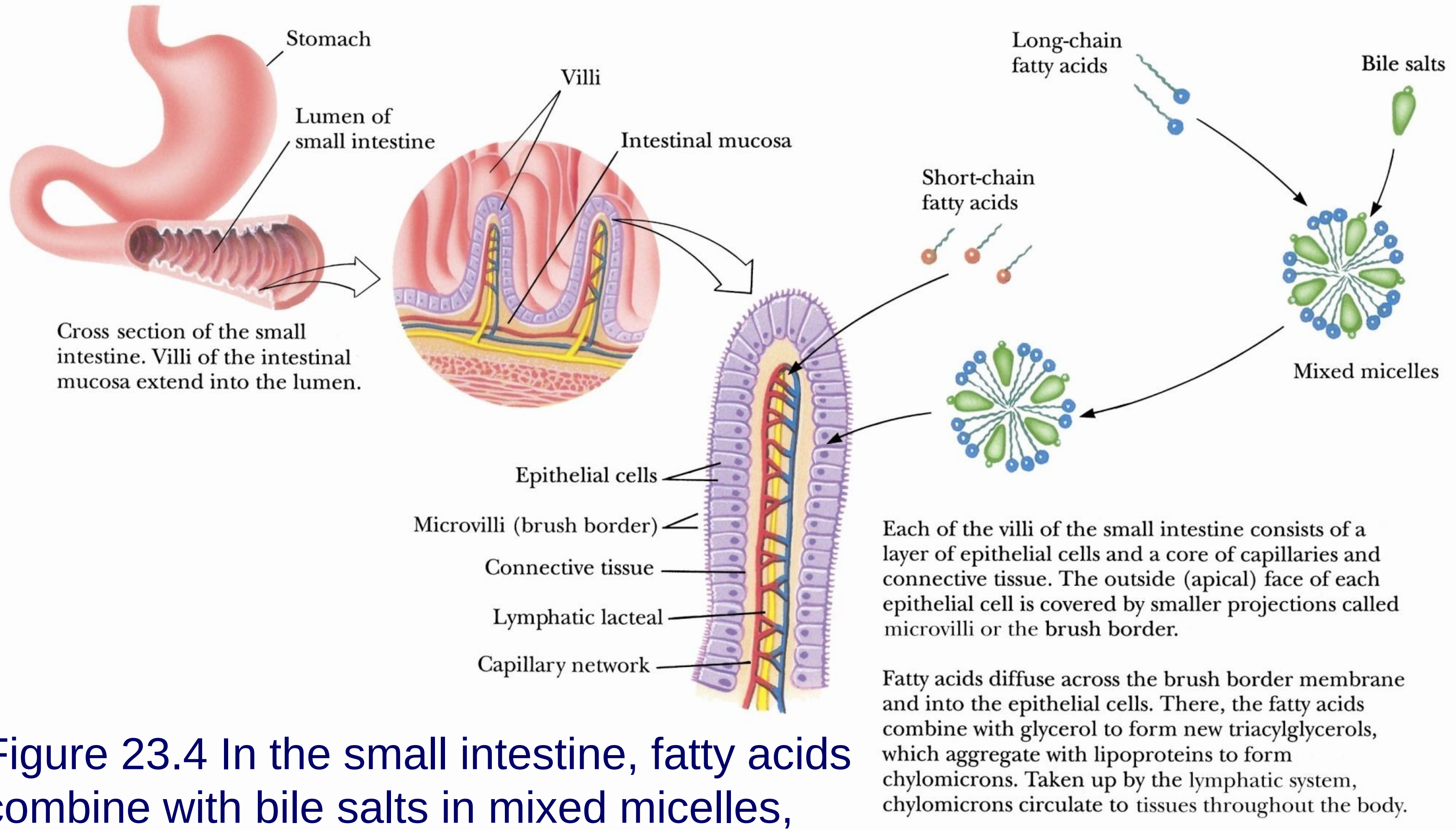
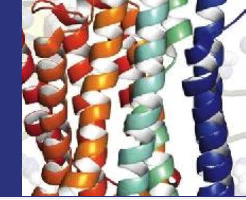


Figure 23.4 In the small intestine, fatty acids combine with bile salts in mixed micelles, which deliver fatty acids to epithelial cells that cover the intestinal villi

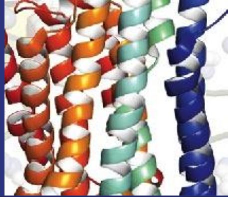
23.2 How Are Fatty Acids Broken Down?



Knoop showed that fatty acids must be degraded by removal of 2-C units

- Albert Lehninger showed that this occurred in the mitochondria
- F. Lynen and E. Reichart showed that the 2-C unit released is acetyl-CoA, not free acetate
- The process begins with oxidation of the carbon that is "β" to the carboxyl carbon, so the process is called "β-oxidation"

23.2 How Are Fatty Acids Broken Down?



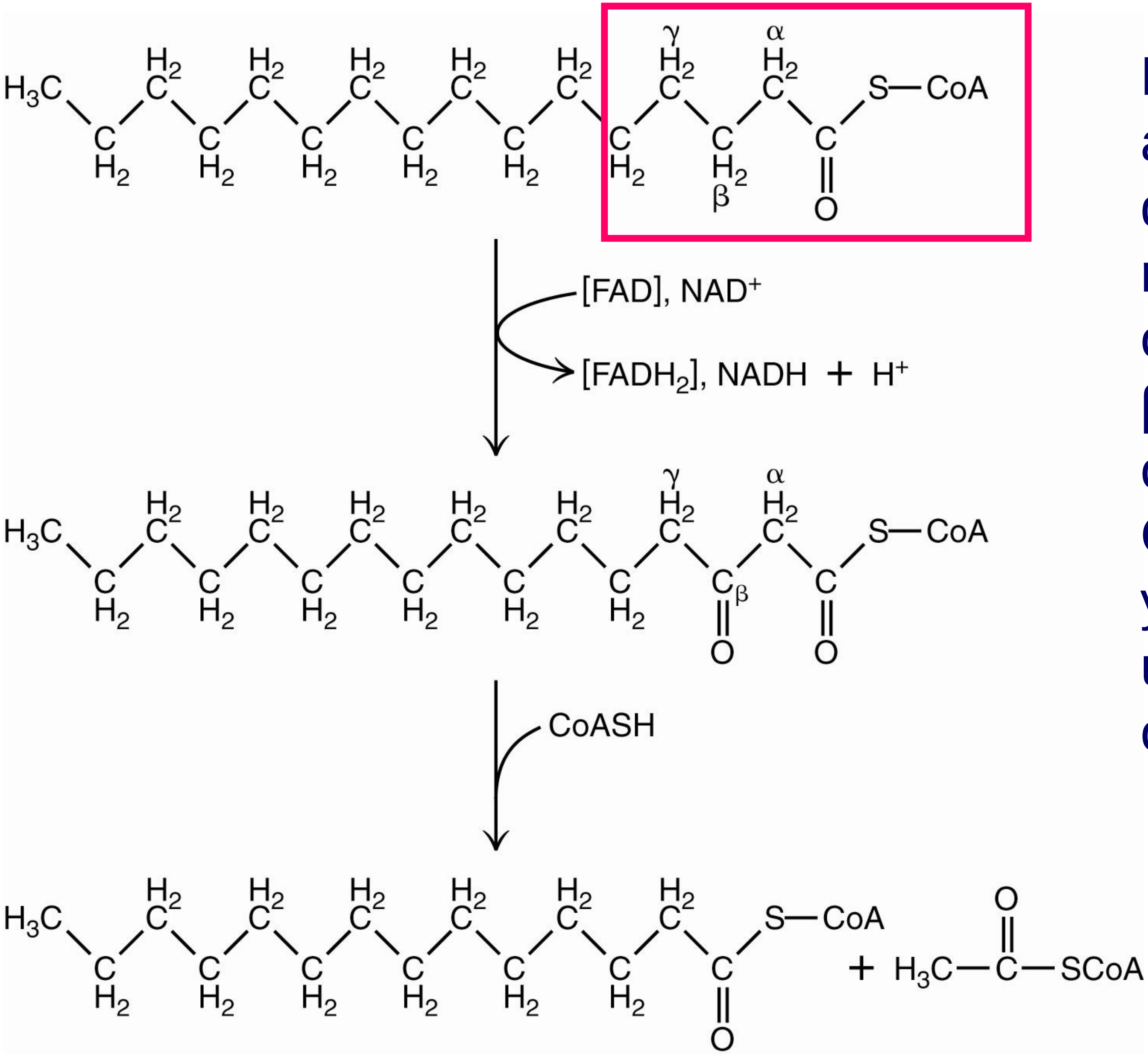
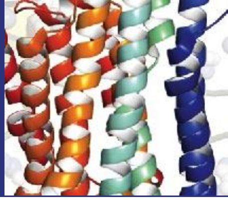


Figure 23.5 Fatty acids are degraded by repeated cycles of oxidation at the β-carbon and cleavage of the C_α-C_β bond to yield acetate units, in the form of acetyl-CoA.

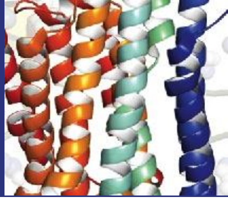
CoA activates FAs for oxidation



Acyl-CoA synthetase condenses fatty acids with CoA, with simultaneous hydrolysis of ATP to AMP and PP_i

- Formation of a CoA ester is expensive energetically
- Reaction just barely breaks even with ATP hydrolysis
- But subsequent hydrolysis of PP_i drives the reaction strongly forward
- Note the acyl-adenylate intermediate in the mechanism

23.2 How Are Fatty Acids Broken Down?



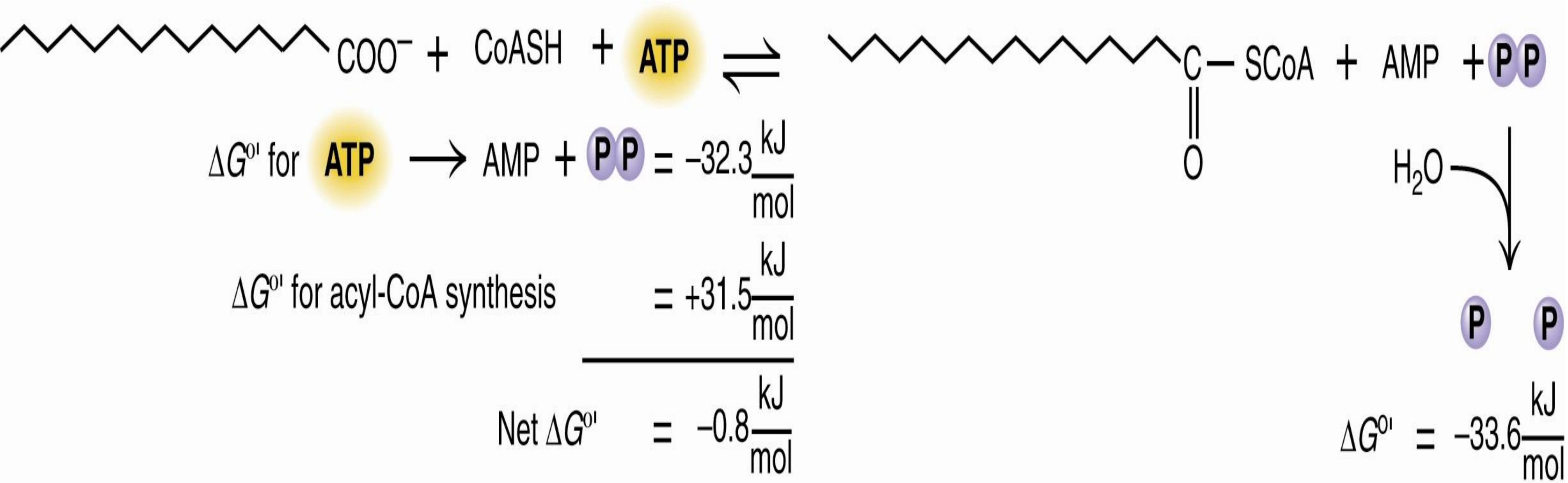


Figure 23.6 The acyl-CoA synthetase activates fatty acids for β-oxidation. The reaction is driven by hydrolysis of ATP to AMP and pyrophosphate and by the subsequent hydrolysis of pyrophosphate.

23.2 How Are Fatty Acids Broken Down?

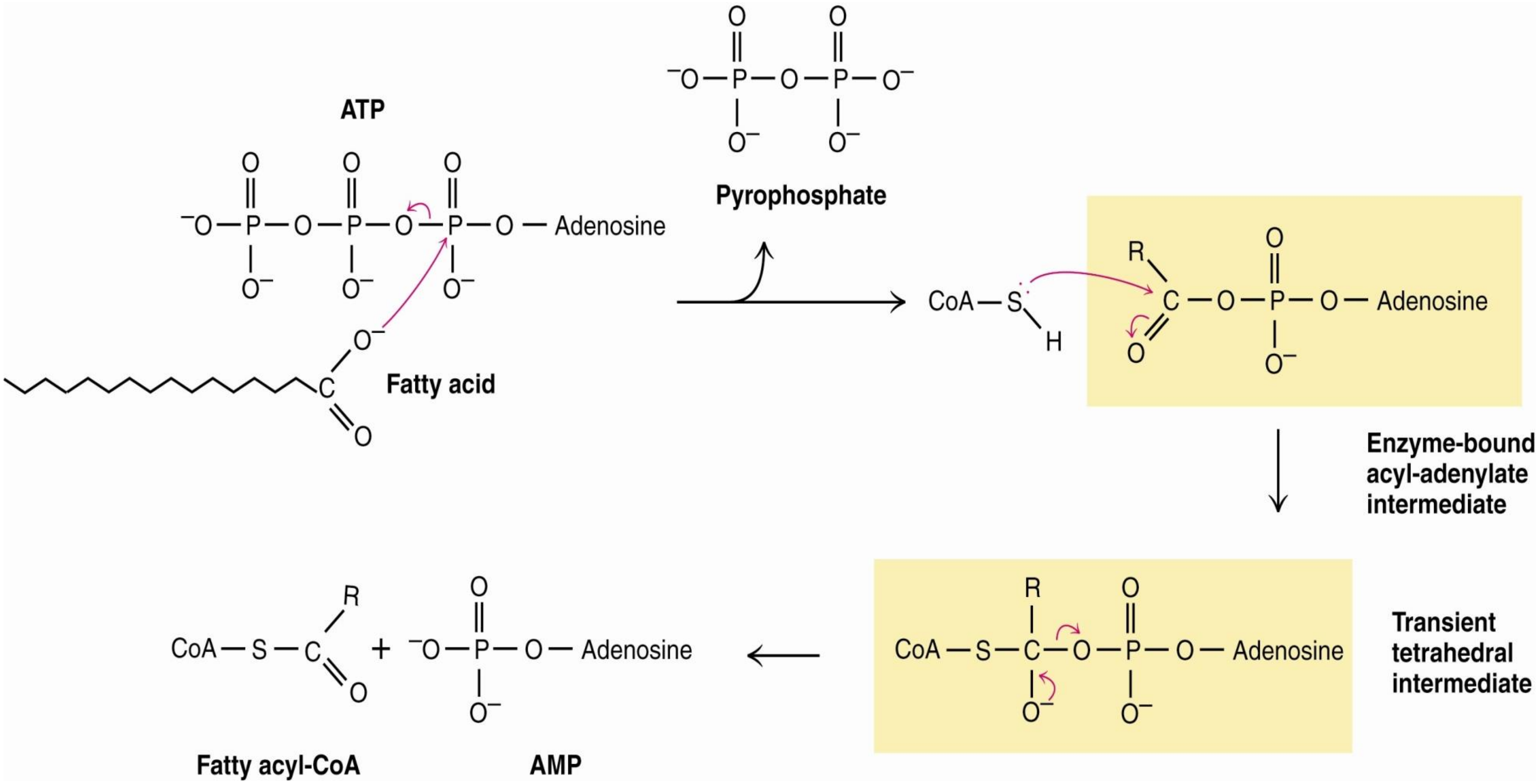
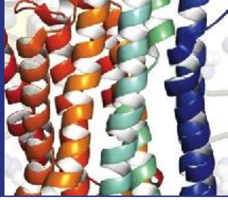


Figure 23.7 The mechanism of the acyl-CoA synthetase reaction involves fatty acid carboxylate attack on ATP to form an acyl-adenylate intermediate. The fatty acyl-CoA thioester product is formed by CoA attack on this intermediate.

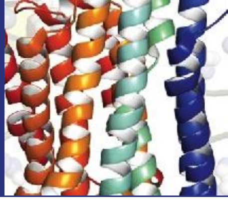
Carnitine as a Carrier



Carnitine carries fatty acyl groups across the inner mitochondrial membrane

- Short chain fatty acids are carried directly into the mitochondrial matrix
- Long-chain fatty acids cannot be directly transported into the matrix
- Long-chain FAs are converted to acyl carnitines and are then transported in the cell
- Acyl-CoA esters are formed inside the inner membrane in this way

Carnitine Carries Acyl Groups Across the Inner Mitochondrial Membrane



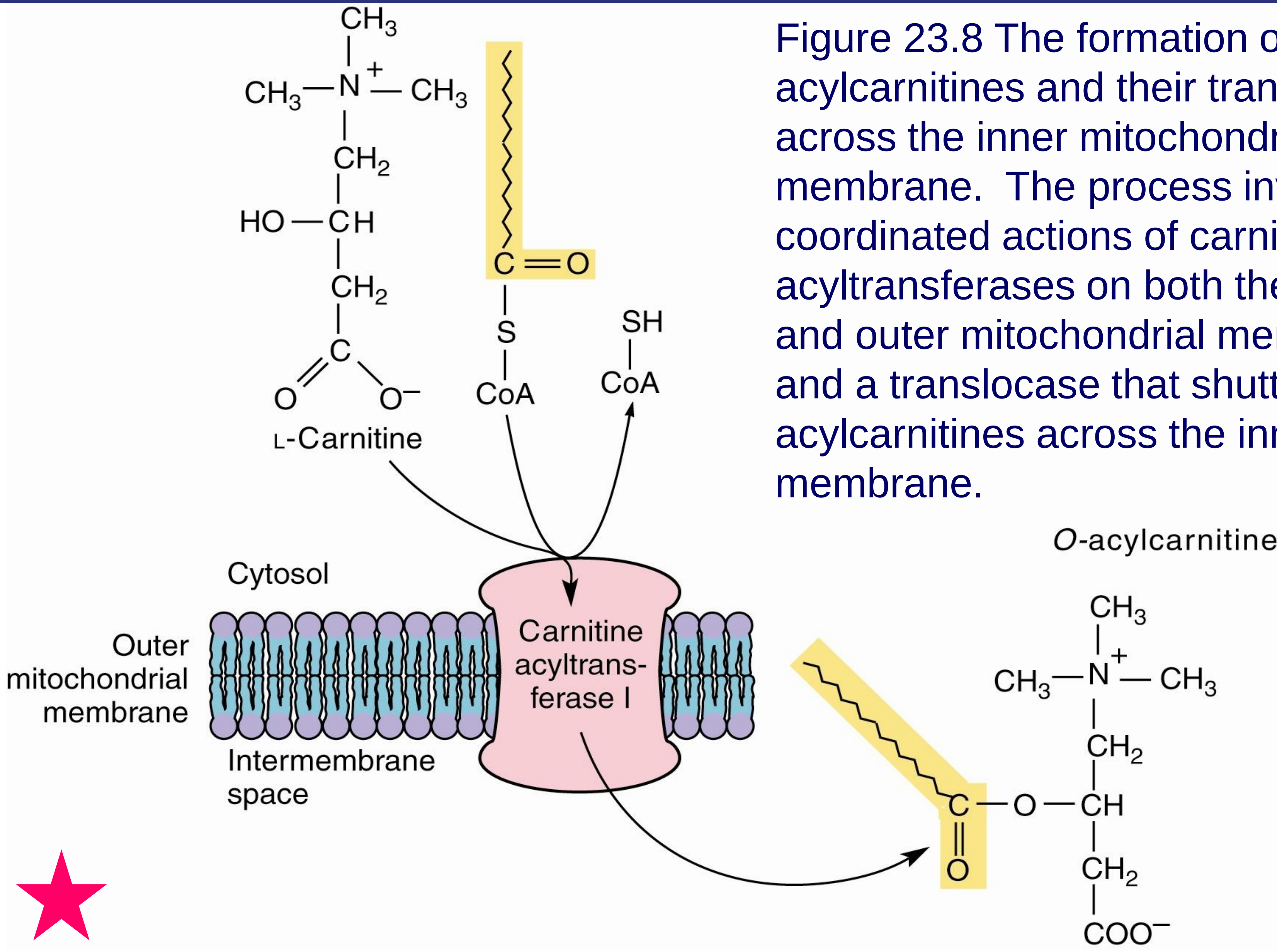
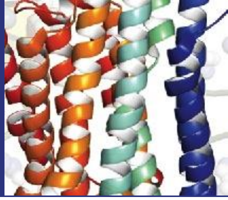
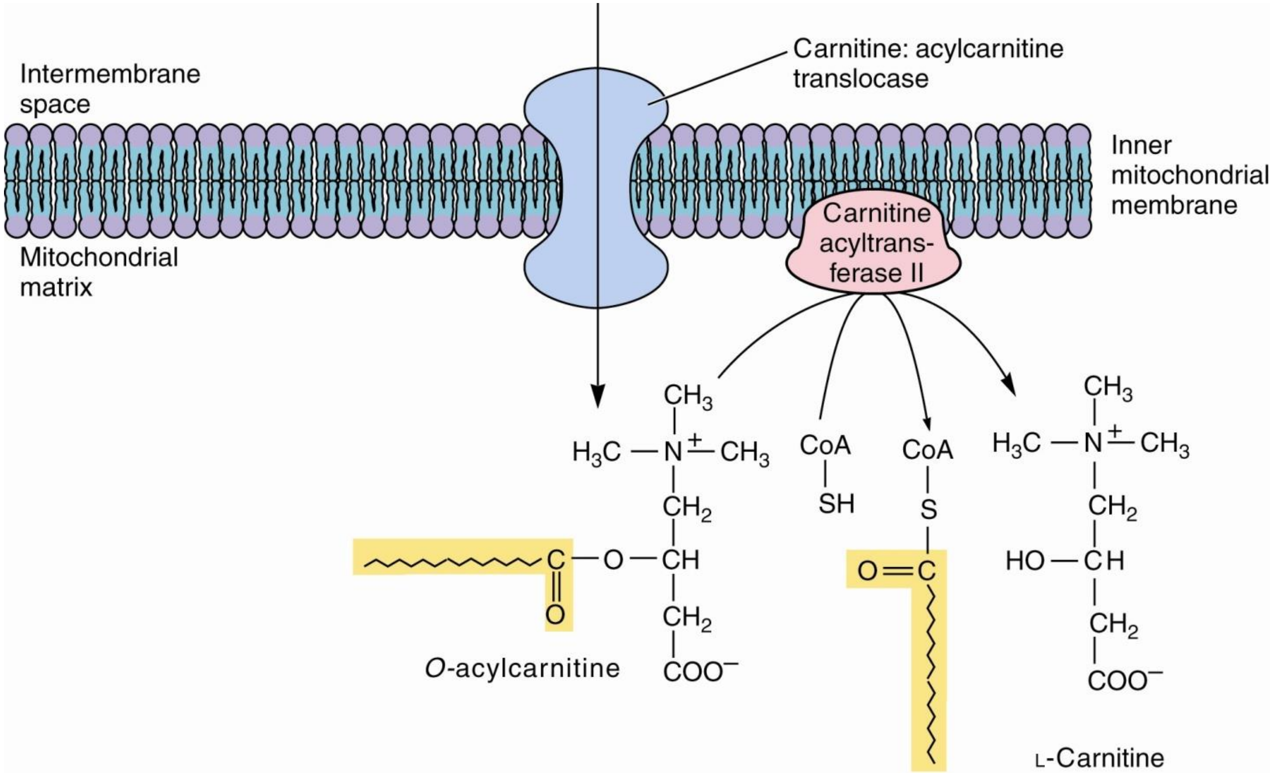


Figure 23.8 The formation of acylcarnitines and their transport across the inner mitochondrial membrane. The process involves the coordinated actions of carnitine acyltransferases on both the inner and outer mitochondrial membranes and a translocase that shuttles O-acylcarnitines across the inner membrane.

Carnitine Carries Acyl Groups Across the Inner Mitochondrial Membrane





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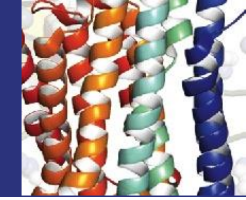
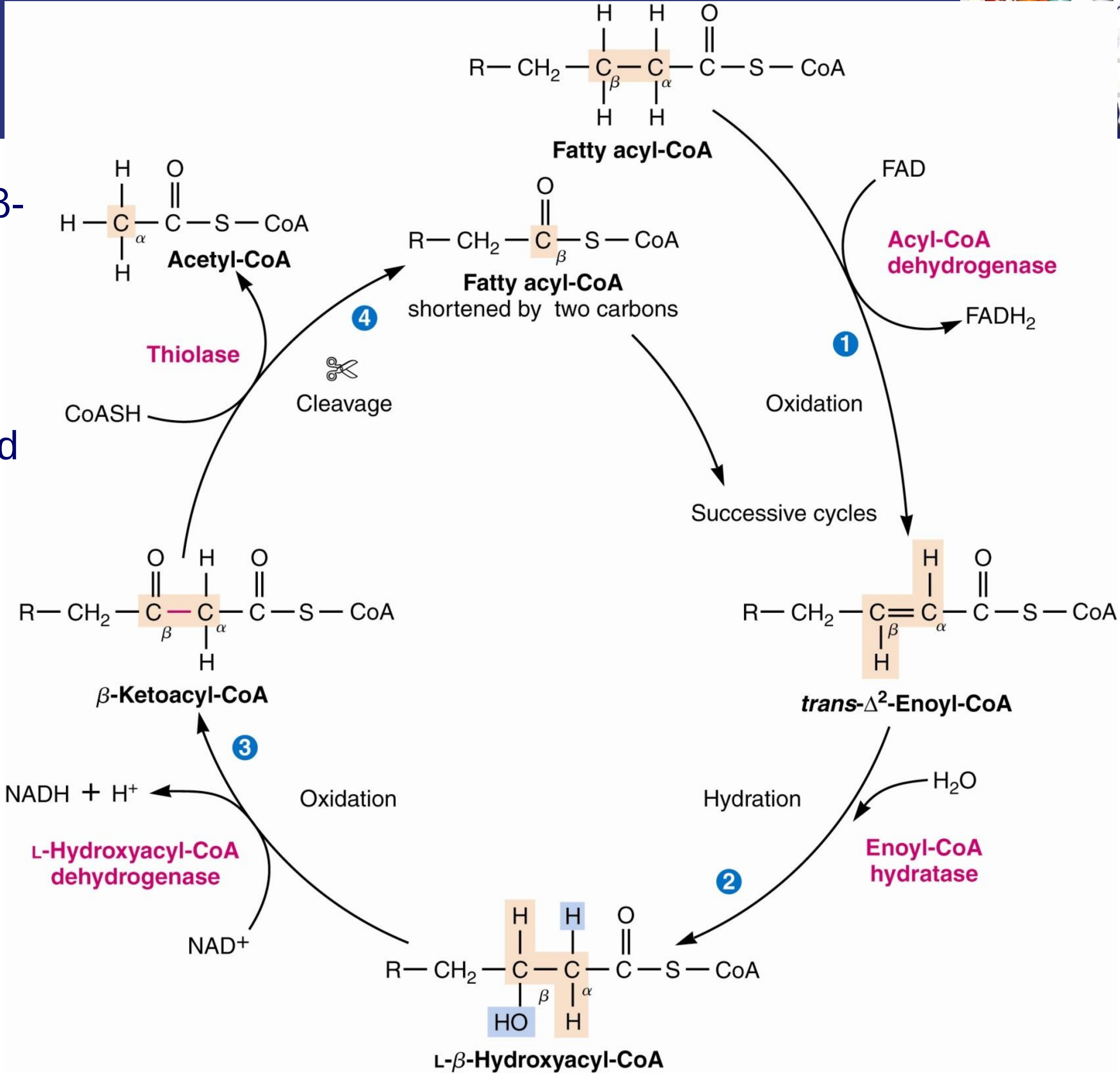
β-Oxidation of Fatty Acids



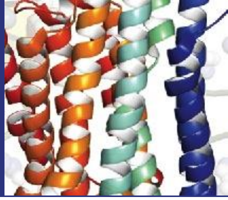
A Repeated Sequence of 4 Reactions

- Strategy: create a carbonyl group on the β-C
- First 3 reactions do that; fourth cleaves the "β-keto ester" in a reverse Claisen condensation
- Products: an acetyl-CoA and a fatty acid two carbons shorter
- The first three reactions are crucial and classic - we will see them again and again in other pathways

Figure 23.9 The β-oxidation of saturate fatty acids involves a cycle of four enzyme-catalyzed reactions.



A Family of Acyl-CoA Dehydrogenases Carry Out the First Reaction of β-Oxidation



- A family of membrane-bound and soluble matrix enzymes
- As a fatty acyl chain is shortened in successive cycles of β-oxidation, it moves from the membrane-bound complex to the family of soluble matrix enzymes (Figure 23.10)
- Mechanism involves proton abstraction, followed by double bond formation and hydride removal by FAD
- Electrons are passed to an electron transfer flavoprotein, and then to the electron transport chain

How Are Fatty Acids Broken Down?

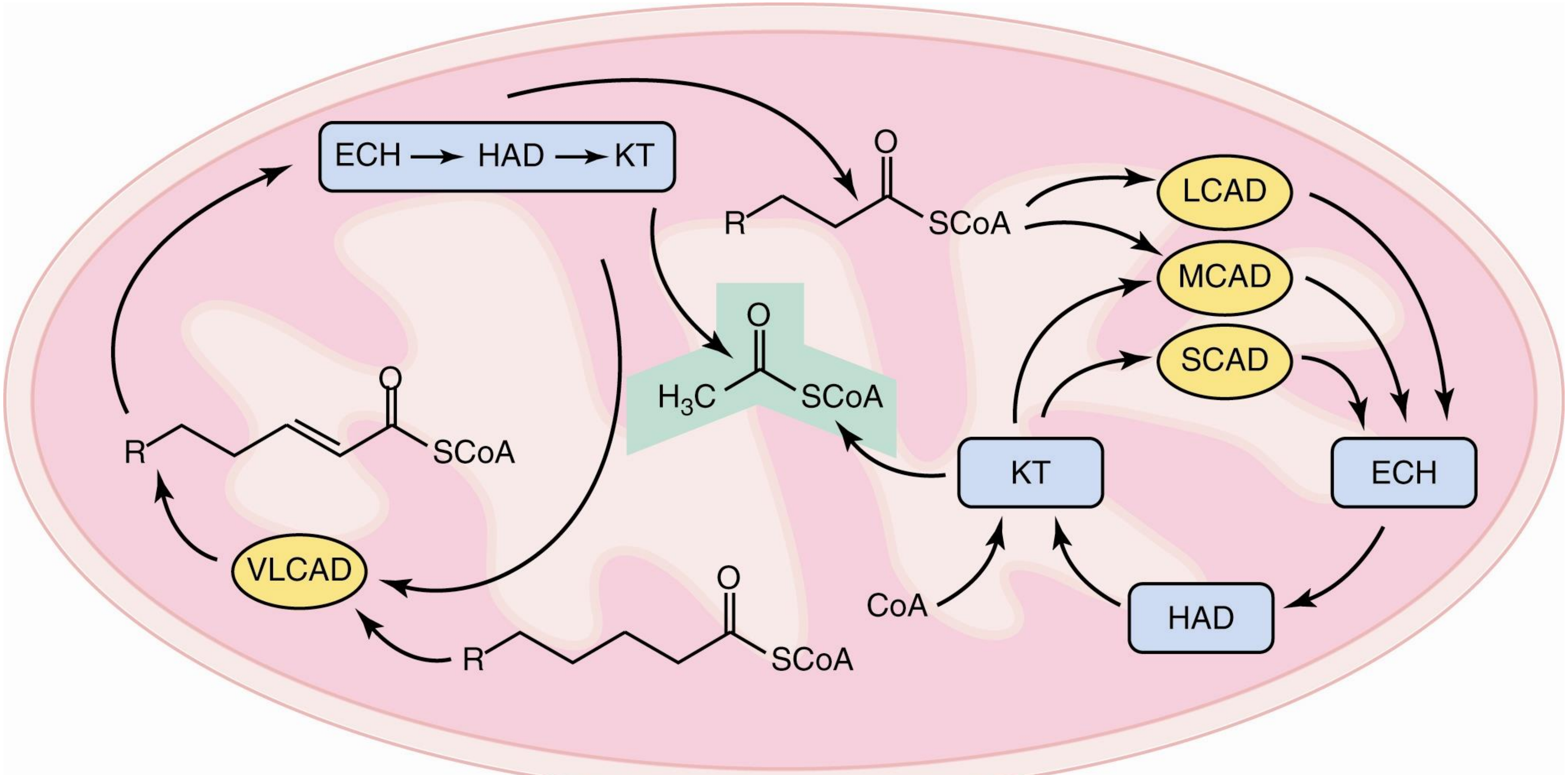
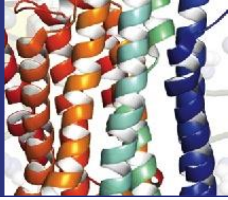


Figure 23.10 Very long-chain fatty acids proceed through several cycles of β-oxidation (left) via membrane-bound enzymes in mitochondria, before becoming substrates for the separate soluble enzymes of β-oxidation (right).

23.2 How Are Fatty Acids Broken Down?



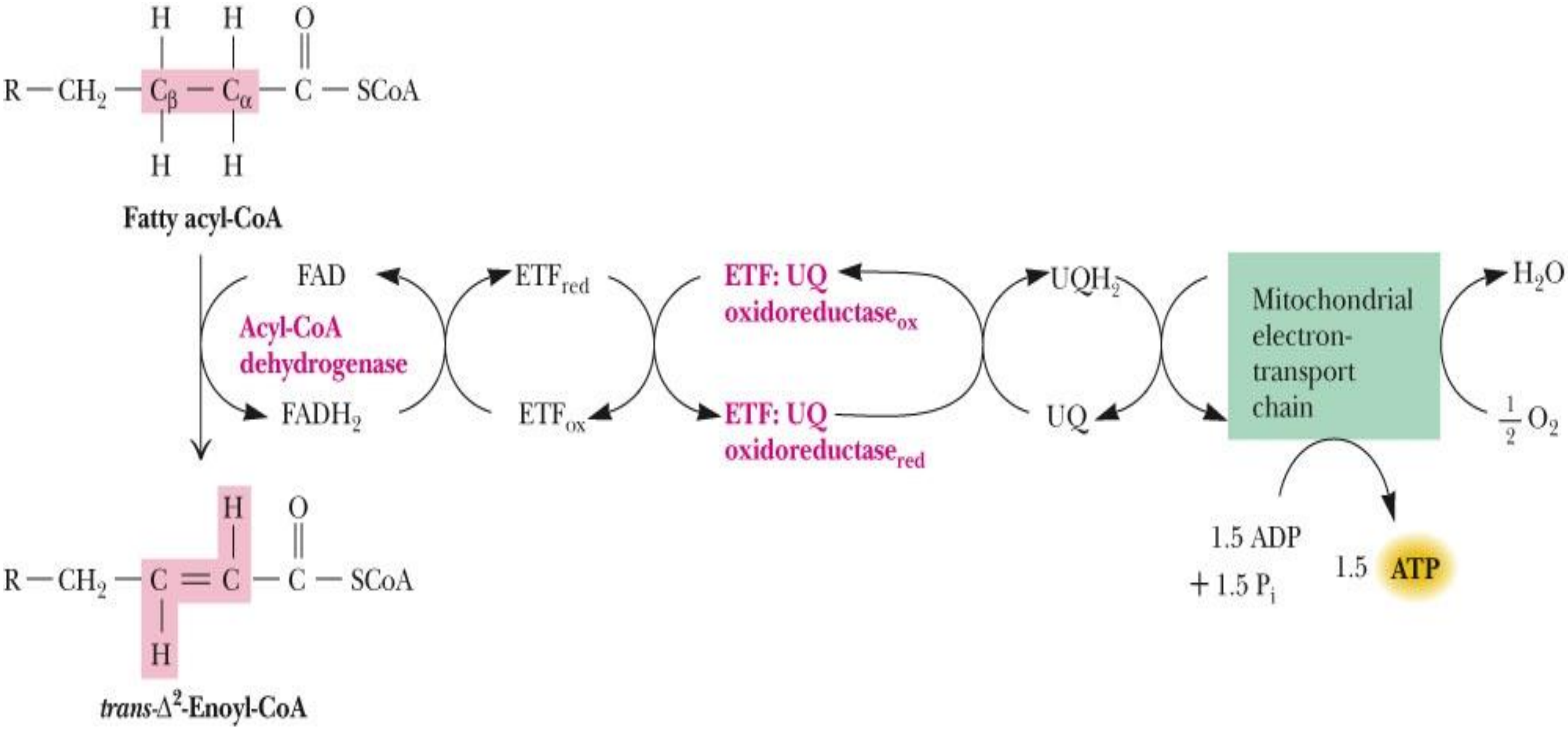
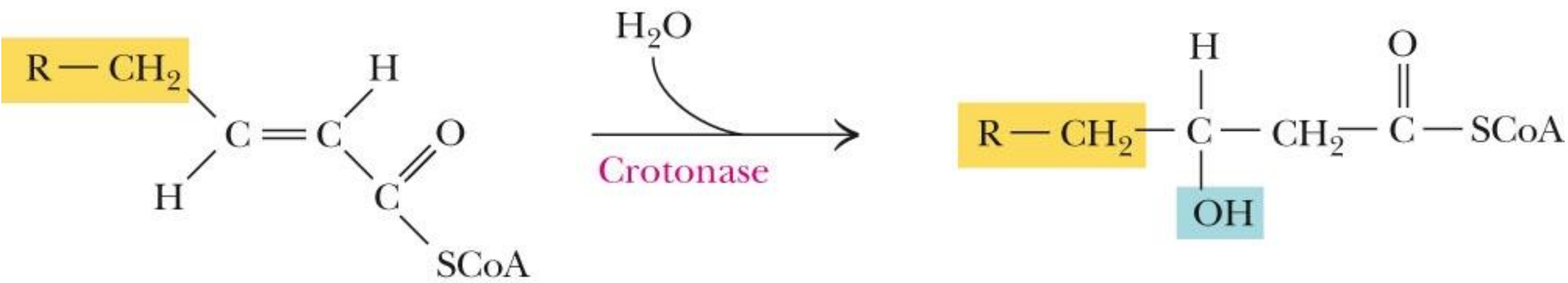


Figure 23.12 The acyl-CoA dehydrogenase reaction. The two electrons removed in this oxidation reaction are delivered to the electron-transport chain in the form of reduced coenzyme Q (UQH_2).

23.2 How Are Fatty Acids Broken Down?

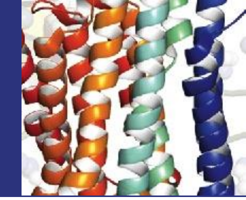
Enoyl-CoA Hydratase Adds Water Across the Double Bond



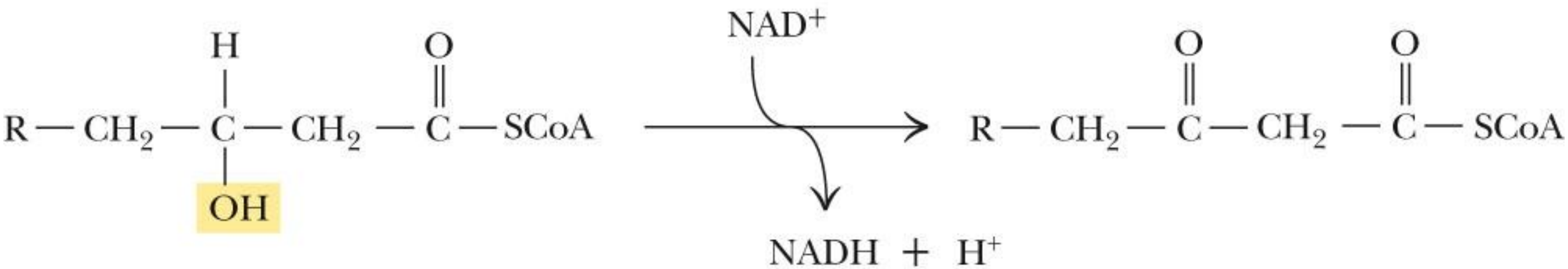
trans-Enoyl-CoA   L-β-Hydroxyacyl-CoA

The next step is the addition of the elements of H_2O across the new double bond in a stereospecific manner, yielding the corresponding hydoxyacyl-CoA. The reaction is catalyzed by **enoyl-CoA hydratase**, also called **crotonase**. These enzymes convert *trans*-enoyl-CoA derivatives to L-β-hydroxyacyl-CoA.

23.2 How Are Fatty Acids Broken Down?



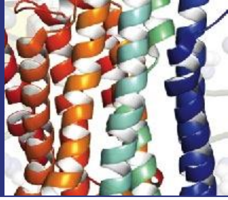
L-Hydroxyacyl-CoA Dehydrogenase Oxidizes the β-Hydroxyl Group



L-β-Hydroxyacyl-CoA β-Ketoacyl-CoA

The third reaction of this cycle is the oxidation of the hydroxyl group at the β-position to produce a β-ketoacyl-CoA derivative. This second oxidation reaction is catalyzed by **L-hydroxyacyl-CoA dehydrogenase**, an enzyme that requires NAD^+ as a coenzyme. NADH produced in this reaction represents metabolic energy. Each NADH produced by this reaction drives the synthesis of 2.5 ATP.

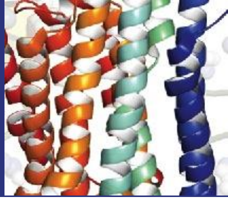
The Fourth Reaction of β-Oxidation: Thiolase



aka β-ketothiolase

- Cysteine thiolate on enzyme attacks the β-carbonyl group
- Thiol group of a new CoA attacks the shortened chain, forming a new, shorter acyl-CoA
- This is the reverse of a Claisen condensation: attack of the enolate of acetyl-CoA on a thioester
- Even though it forms a new thioester, the reaction is favorable and drives other three

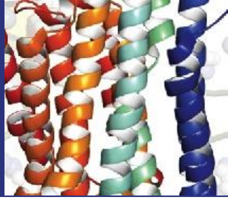
Summary of β-Oxidation



Repetition of the cycle yields a succession of acetate units

- Thus, palmitic acid yields eight acetyl-CoAs
- Complete β-oxidation of one palmitic acid yields 106 molecules of ATP
- Large energy yield is a consequence of the highly reduced state of the carbon in fatty acids
- This makes fatty acids the fuel of choice for migratory birds and many other animals

Complete β-Oxidation of One Palmitic Acid Yields 106 Molecules of ATP



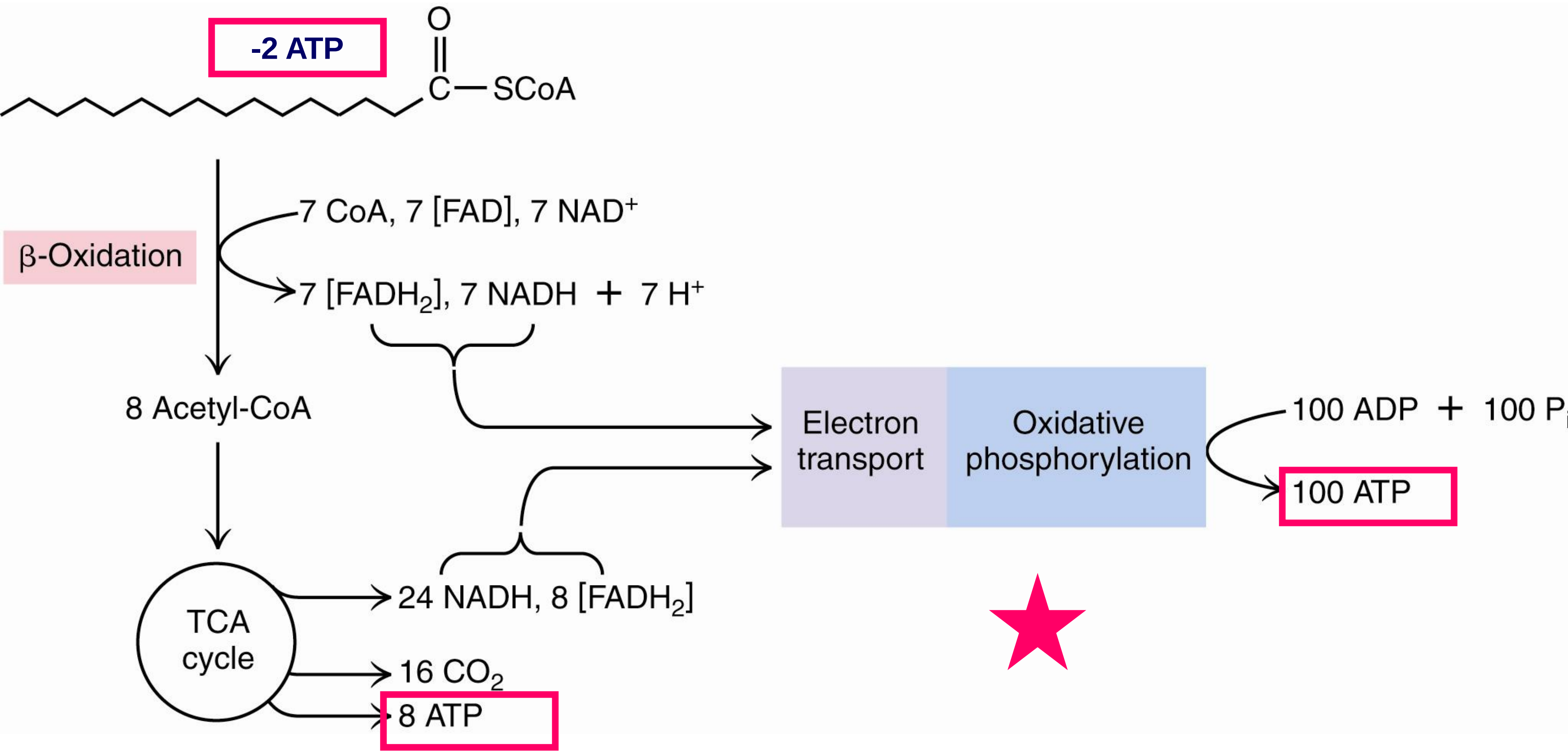
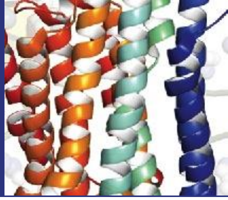


Figure 23.16 Reduced coenzymes produced by β-oxidation and TCA cycle activity provide electrons that drive synthesis of ATP in oxidative phosphorylation. Complete oxidation of palmitoyl-CoA yields a net of 106 ATP.

Fatty Acid Oxidation is an Important Source of Metabolic Water for Some Animals



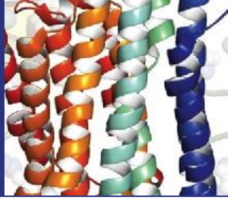
- Large amounts of metabolic water are generated by β-oxidation
- For certain animals – including desert animals (such as gerbils), killer whales (which do not drink seawater), and camels (whose hump is a large fat deposit) – the oxidation of stored fatty acids can be a significant source of dietary water
- Metabolism of fatty acids from such stores provides needed water, as well as metabolic energy, during periods when drinking water is not available

(a) Gerbil

(d) Orca

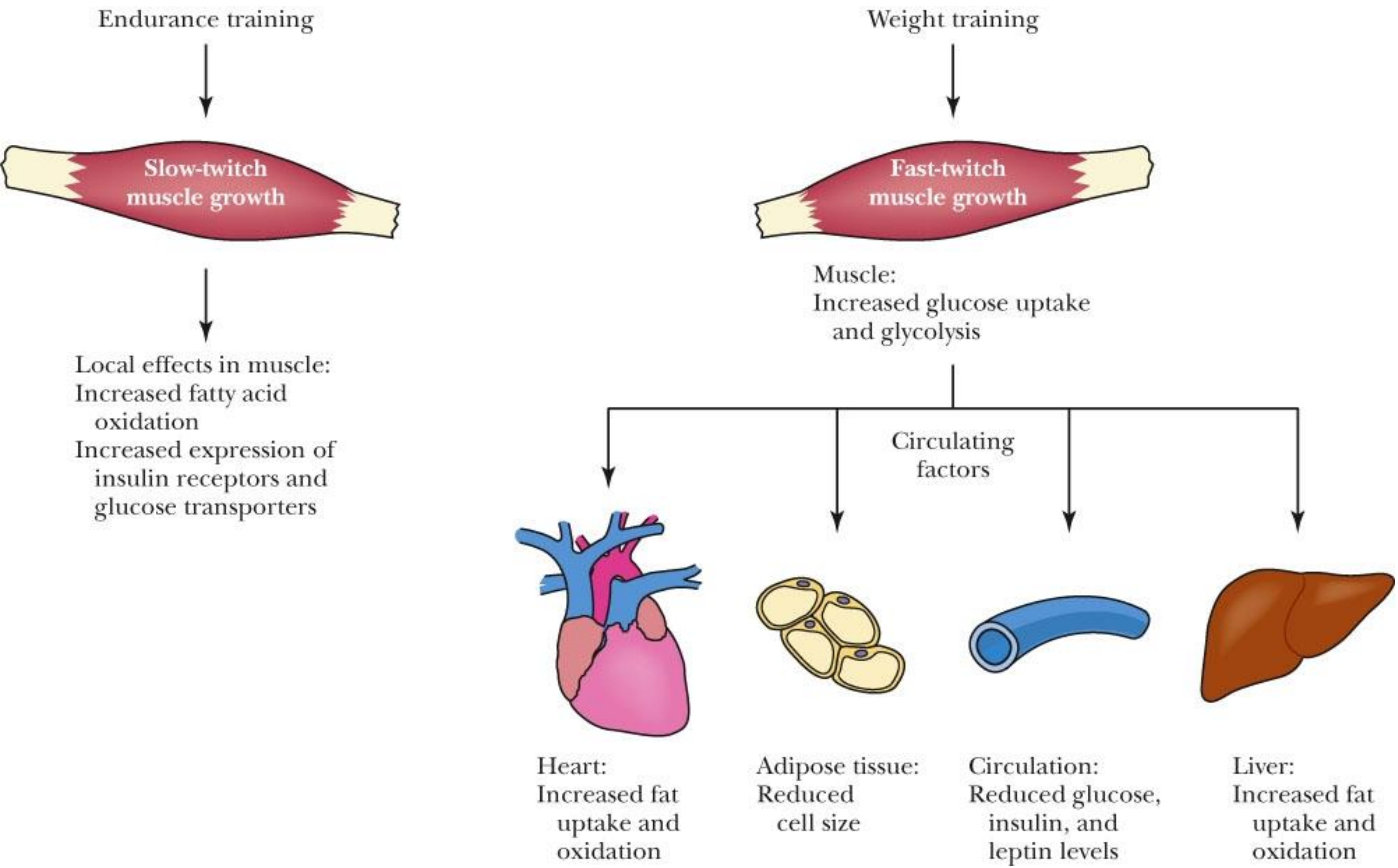
(e) Camels

Exercise Can Reverse the Consequences of Metabolic Syndrome

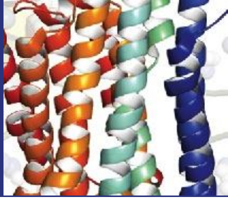


- Metabolic syndrome is a combination of disorders that increase the risk of diabetes and cardiovascular disease
- Insights into how the body deals with high fat and sugar diets are emerging from a variety of studies
- Endurance training increases the mass of slow-twitch muscle, whereas resistance-training builds fast-twitch muscle fibers
- **Slow-twitch muscles** depend on fatty acid oxidation and TCA cycle activity and are **“oxidative”**
- **Fast-twitch muscles** are adapted for short bursts of energy from glycolysis and are **“glycolytic”**

Exercise Can Reverse the Consequences of Metabolic Syndrome



23.3 How Are Odd-Carbon Fatty Acids Oxidized?



β-Oxidation of odd-carbon fatty acids yields ***propionyl-CoA***

- Odd-carbon fatty acids are metabolized normally, until the last three-C fragment - propionyl-CoA - is reached
- Three reactions convert propionyl-CoA to succinyl-CoA
- Note the involvement of biotin and B_{12}
- Note the calculation of catalytic power of the **epimerase reaction**
- **Note pathway** for net oxidation of **succinyl-CoA**

23.3 How Are Odd-Carbon Fatty Acids Oxidized?

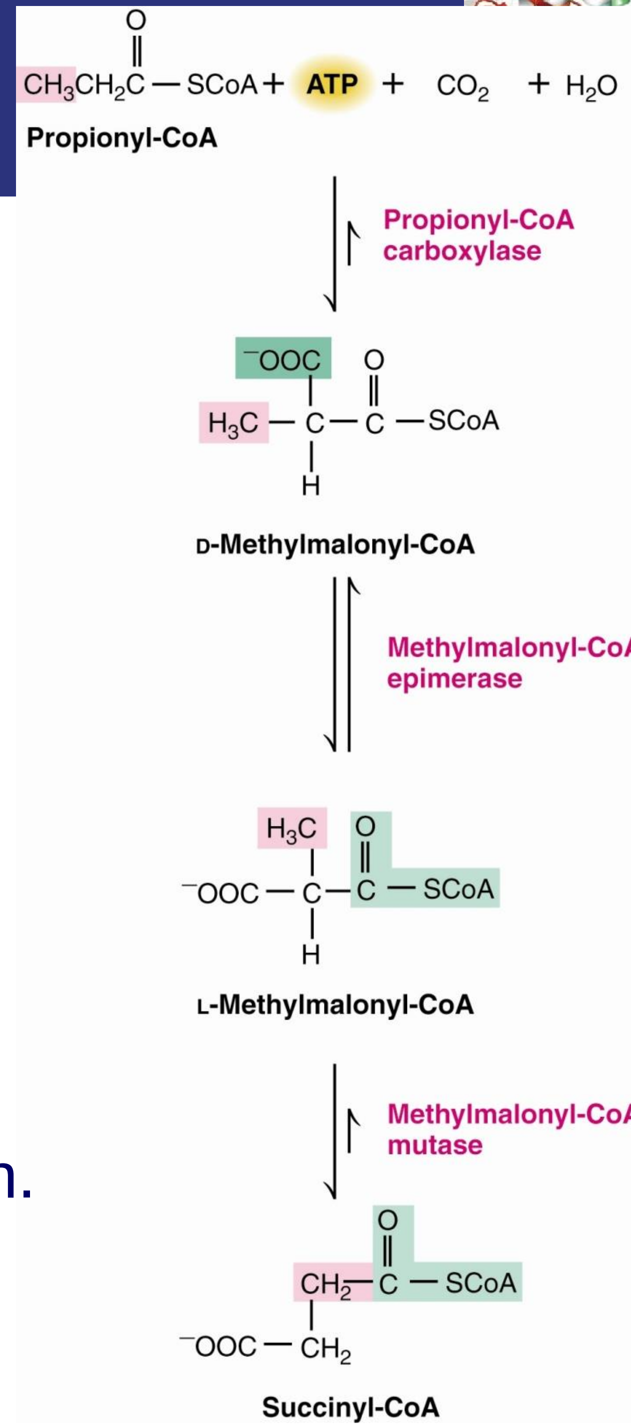
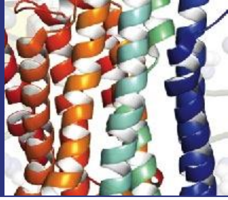


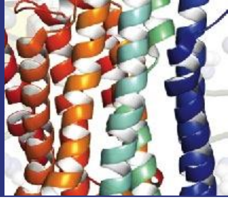
Figure 23.18 The conversion of propionyl-CoA (formed from β-oxidation of odd-carbon fatty acids) to succinyl-CoA is carried out by a trio of enzymes, as shown. Succinyl-CoA can enter the TCA cycle.

Net Oxidation of Succinyl-CoA Requires Conversion to Acetyl-CoA



- Succinyl-CoA derived from propionyl-CoA can enter the TCA cycle
- But TCA cycle intermediates are catalytic and net consumption of succinyl-CoA does not occur directly in TCA
- However, succinyl-CoA from β-oxidation CAN be converted to malate and then transported from the mitochondrial matrix to the cytosol, where it can be oxidatively decarboxylated to pyruvate and CO_2 by malic enzyme
- Pyruvate can then be transported back to the matrix where it can enter the TCA cycle

Net Oxidation of Succinyl-CoA Requires Conversion to Acetyl-CoA



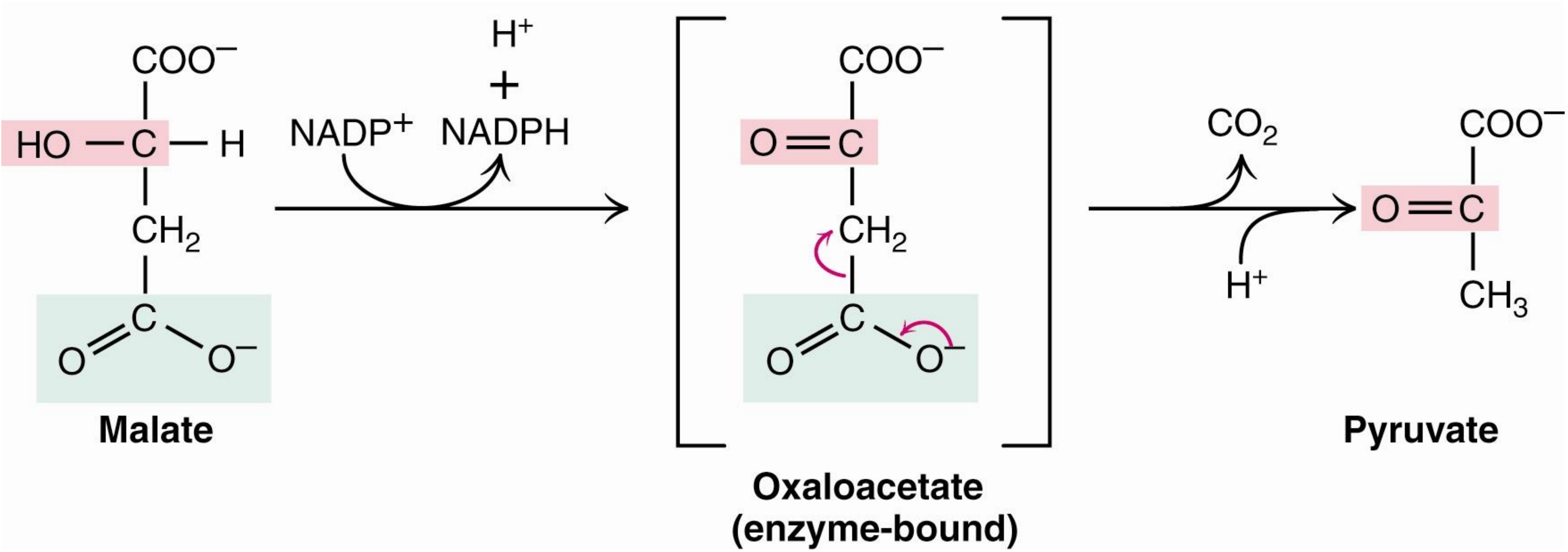
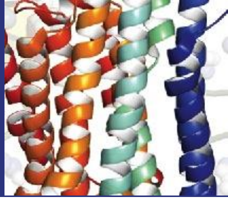


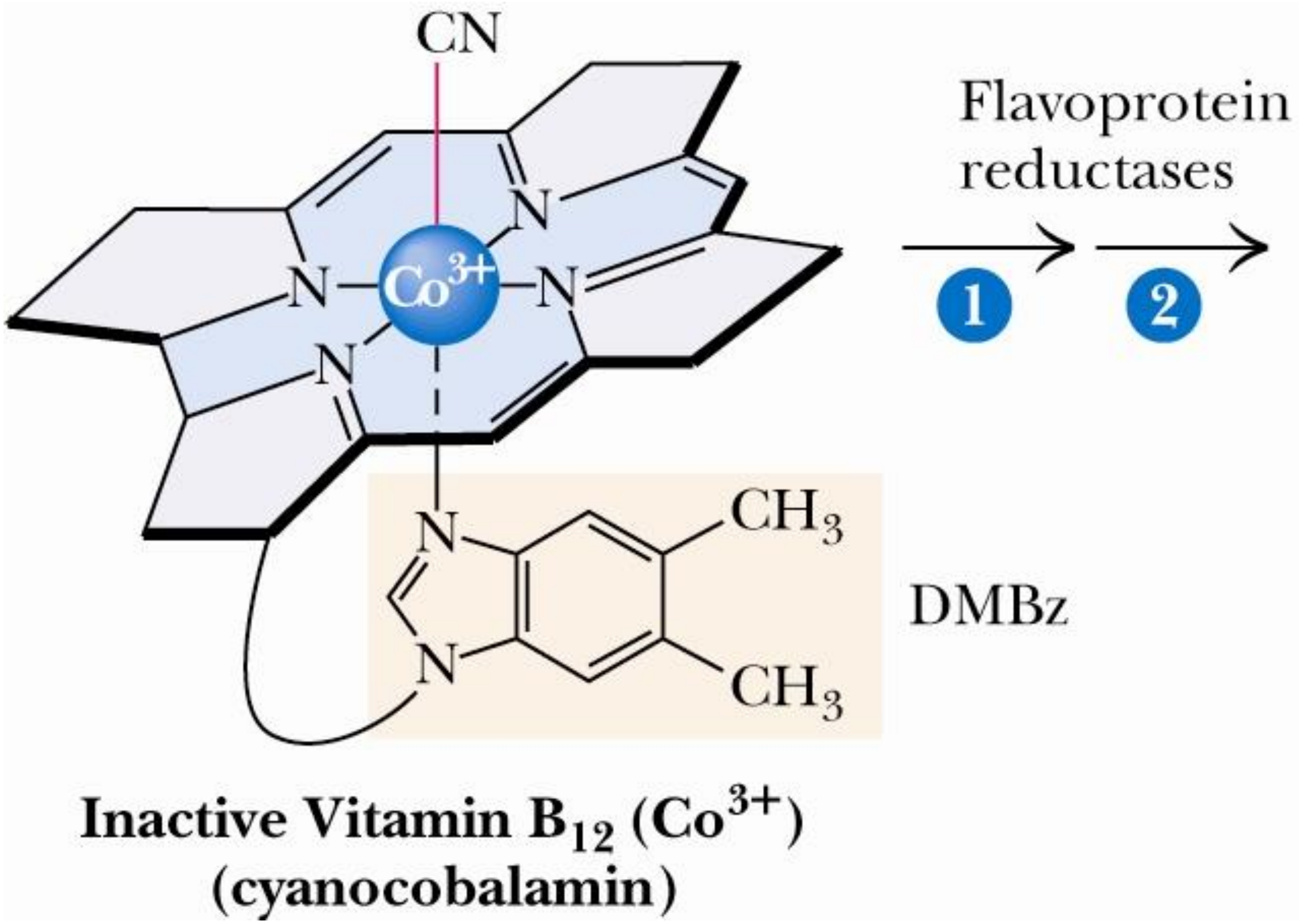
Figure 23.20 The malic enzyme reaction proceeds by oxidation of malate to oxaloacetate, followed by decarboxylation to yield pyruvate.

The Activation of Vitamin B_{12}



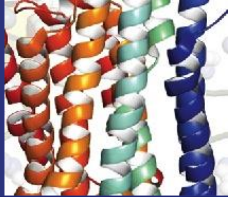
- Conversion of inactive vitamin B_{12} to active 5'-deoxyadenosylcobalamin involves three steps
- Two flavoprotein reductases convert Co^{3+} to Co^{2+} and then to Co^{+}
- Co^{+} is a powerful nucleophile, which can attack the C-5’ of ATP to form 5-deoxyadenosylcobalamin
- This is one of only two known adenosyl transfers in biological systems (the other is the formation of S-adenosylmethionine – see Chapter 25)

The Activation of Vitamin B_{12}

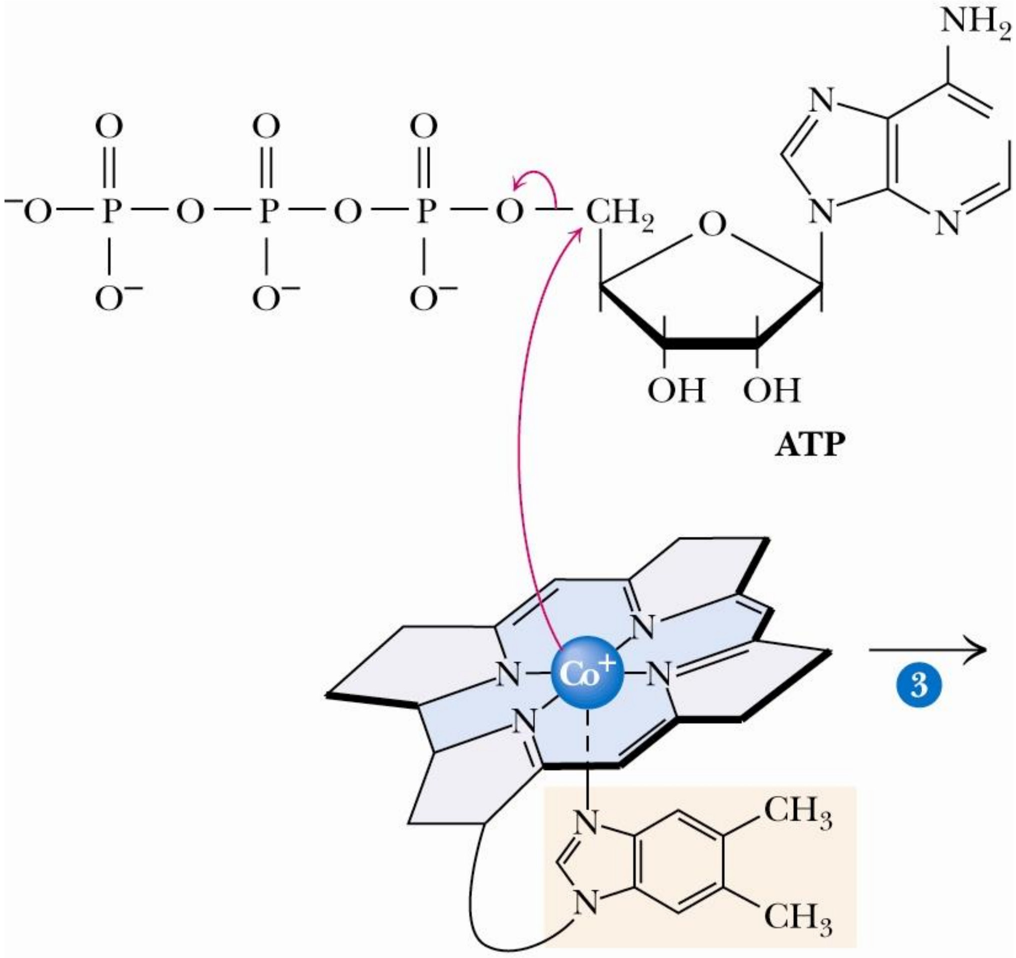


Formation of the active coenzyme form of B_{12} is initiated by the actionof flavoprotein reductases.

The Activation of Vitamin B_{12}

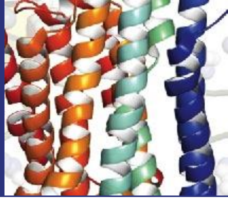


Formation of the active coenzyme form of B_{12} is initiated by the actionof flavoprotein reductases. The resulting Co^{+} species, dubbed a supernucleophile, attacks the 5'-carbon of ATP in an unusual adenosyl transfer.



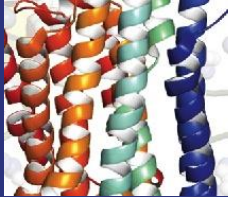
Supernucleophile (Co^{+})

Can Natural Antioxidants in Certain Foods Improve Fat Metabolism?

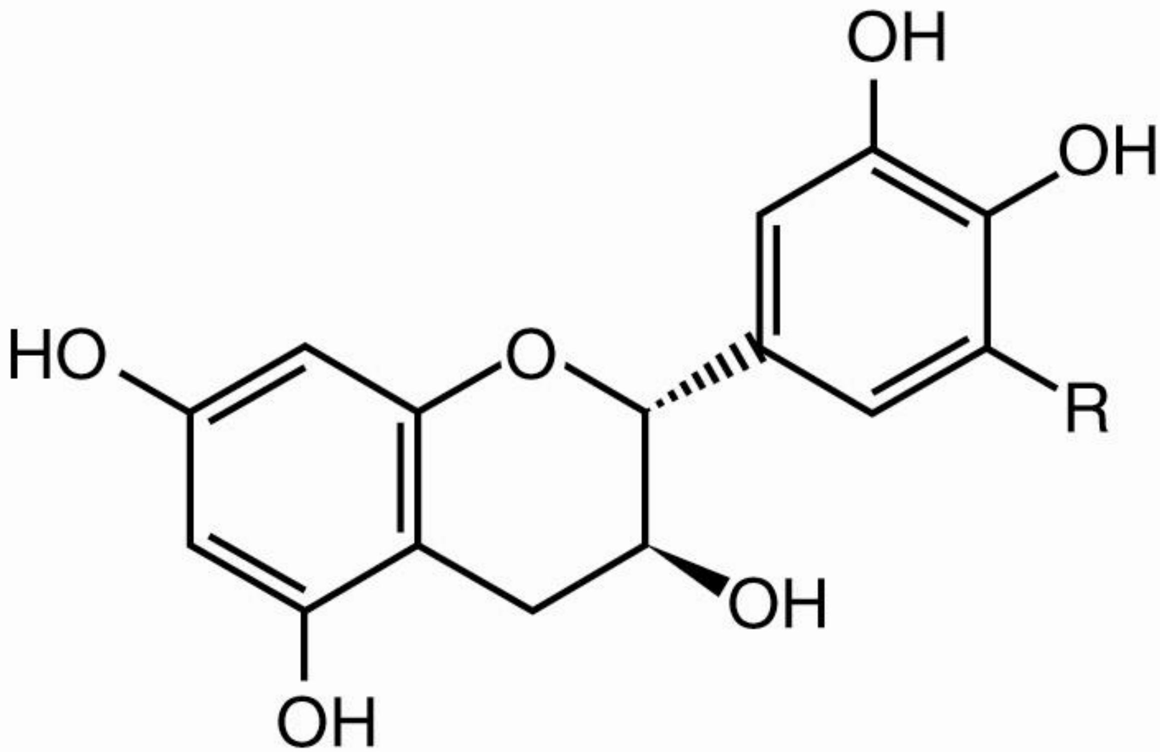


- Beneficial effects have been attributed in recent years to polyphenolic compounds in foods such as chocolate, red wine, and tea
- Principal among these are the **catechins**
- Takatoshi Murase has shown that green tea extract added to diets of rats increased muscle glycogen, decreased muscle fatty acid synthesis, and increased muscle fatty acid oxidation
- Exercise endurance was also increased, suggesting that fatty acids can be an energy source in muscle

Can Natural Antioxidants in Certain Foods Improve Fat Metabolism?



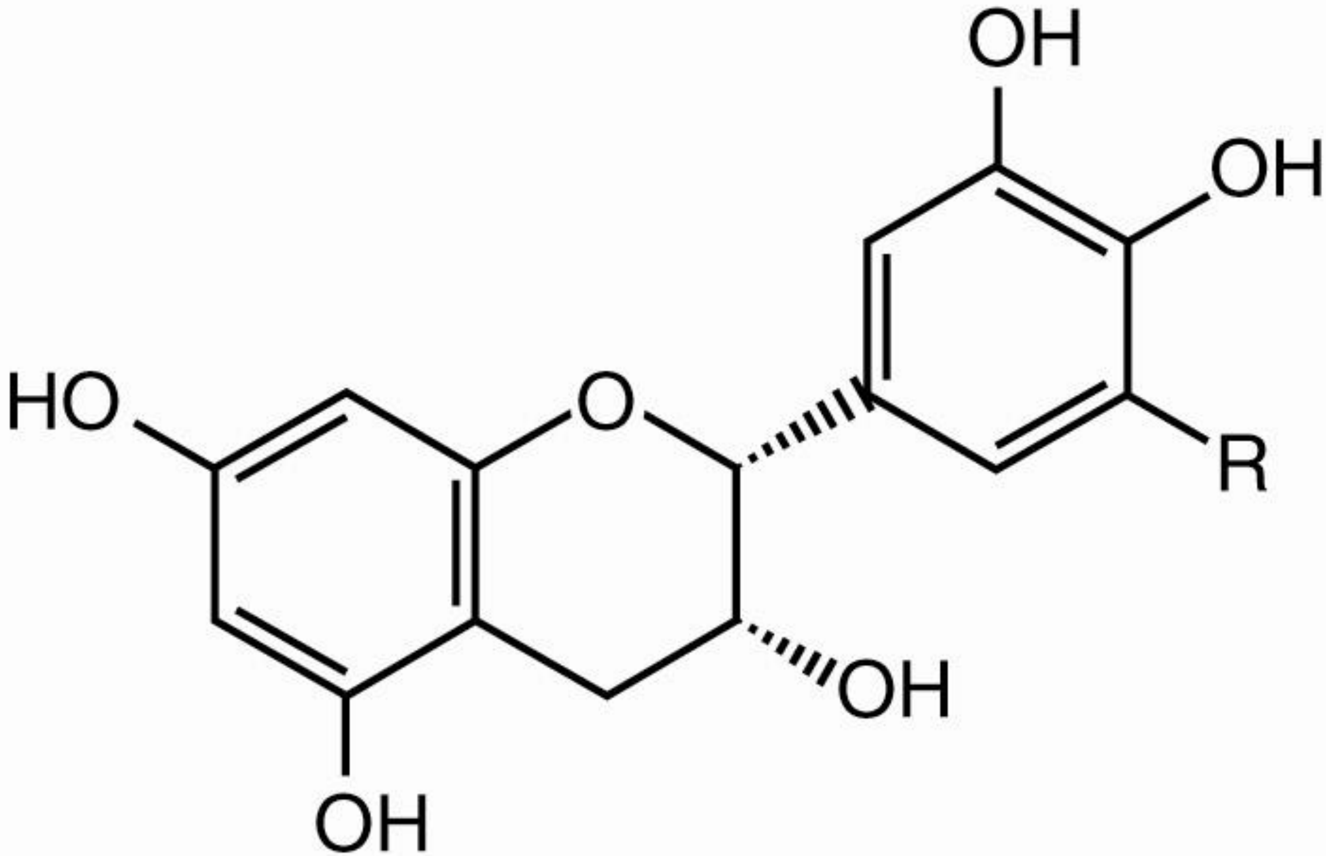
(a) R = H (+)-catechin,
R = OH (+)-gallocatechin (GC)



Catechins found in black and green tea.

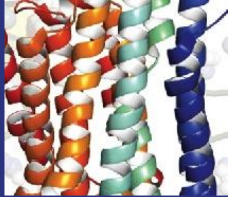
Can Natural Antioxidants in Certain Foods Improve Fat Metabolism?

(b) R = H (–)-epicatechin,
R = OH (–)-epigallocatechin (EGC)



Catechins found in black and green tea.

23.4 How Are Unsaturated Fatty Acids Oxidized?



Consider monounsaturated fatty acids:

- Oleic acid, palmitoleic acid
- Normal β-oxidation for three cycles
- cis-Δ^3 acyl-CoA cannot be utilized by acyl-CoA dehydrogenase
- **Enoyl-CoA isomerase** converts this to trans- Δ^2 acyl CoA
- β-oxidation continues from this point

23.4 How Are Unsaturated Fatty Acids Oxidized?

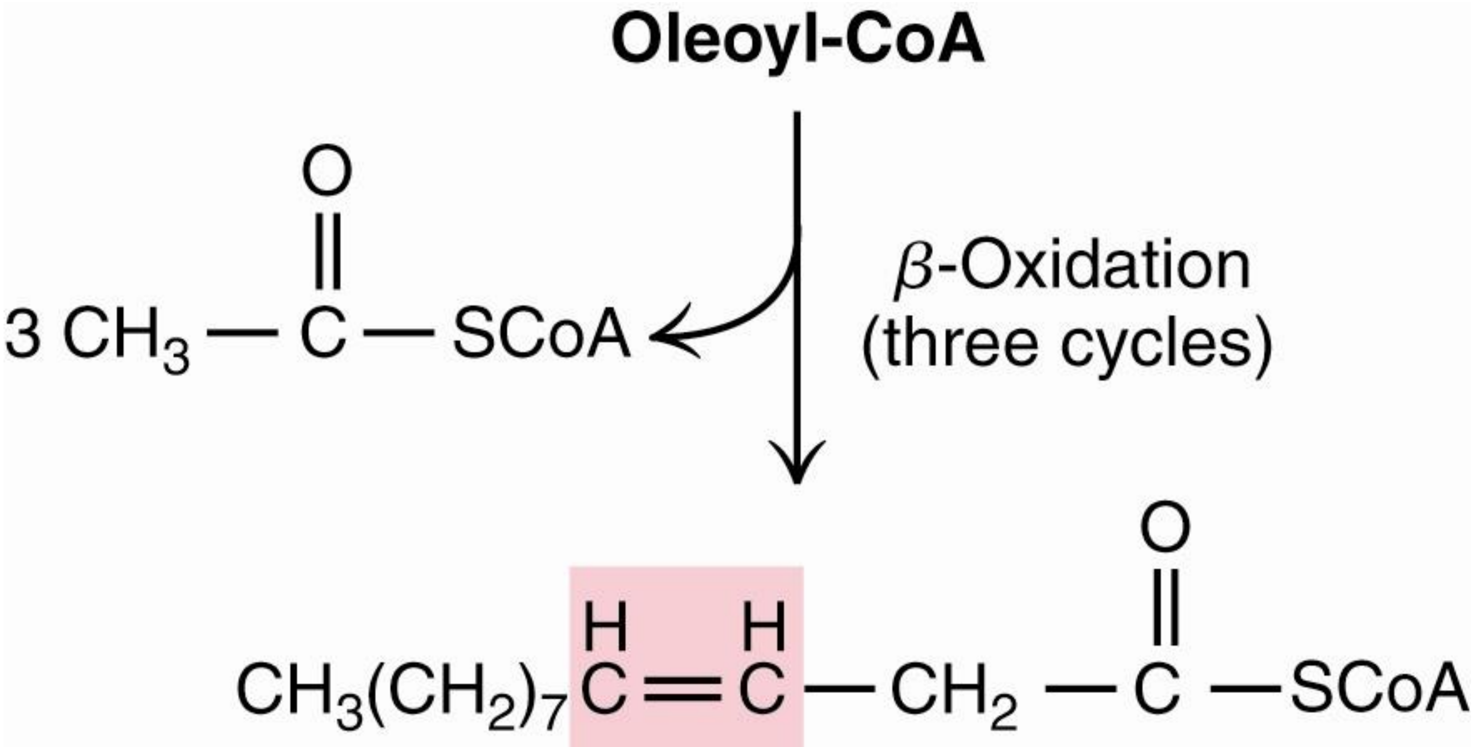


Figure 23.21 β-Oxidation of unsaturated fatty acids. In the case of oleoyl-CoA, three β-oxidation cycles produce three molecules of acetyl-CoA and leave cis-Δ^3-dodecenoyl-CoA. Rearrangement of enoyl-CoA isomerase gives the trans-Δ^2 species, which then proceeds normally through the β-oxidation pathway.

23.4 How Are Unsaturated Fatty Acids Oxidized?

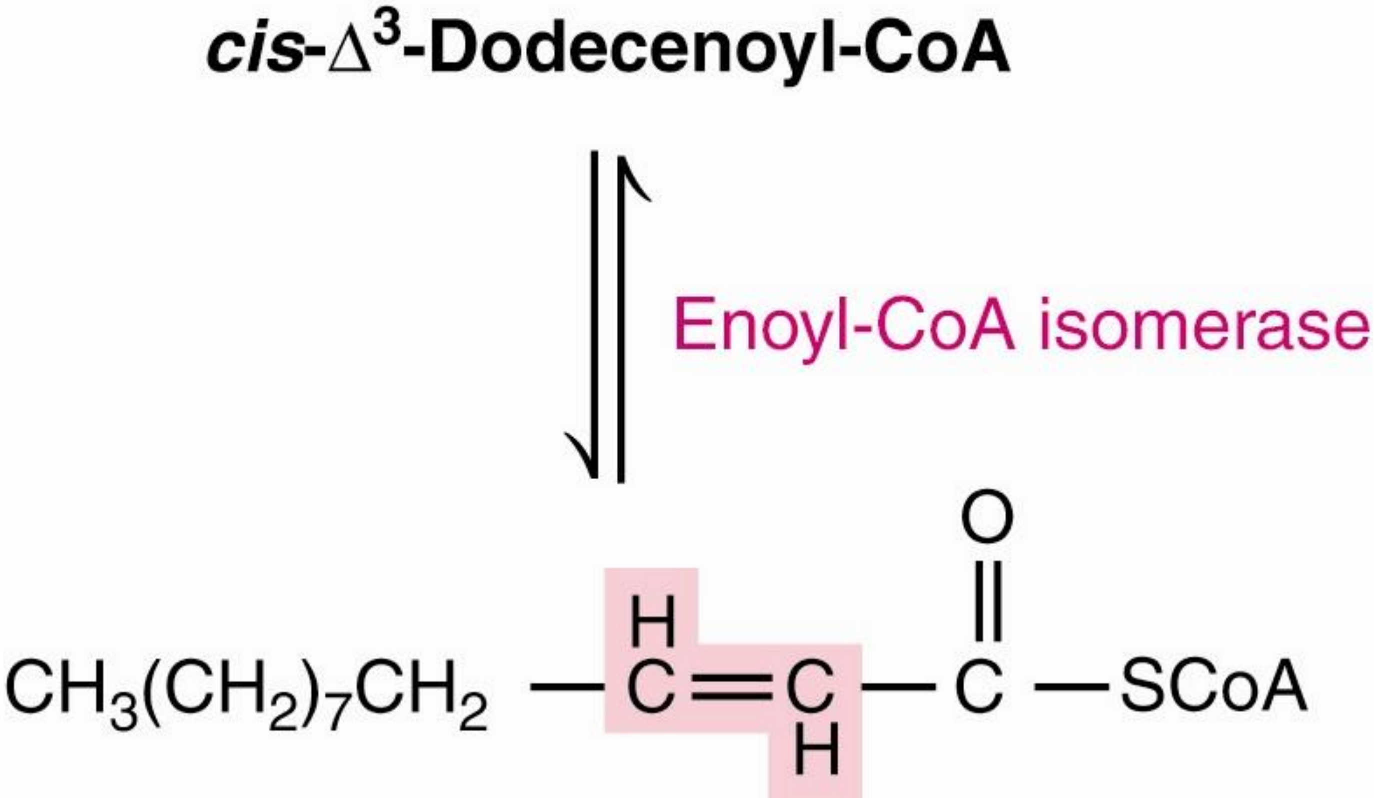
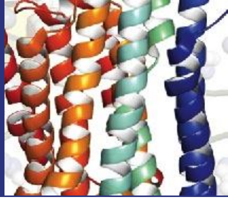


Figure 23.21 β-Oxidation of unsaturated fatty acids. In the case of oleoyl-CoA, three β-oxidation cycles produce three molecules of acetyl-CoA and leave cis-Δ^3-dodecenoyl-CoA. Rearrangement of enoyl-CoA isomerase gives the trans-Δ^2 species, which then proceeds normally through the β-oxidation pathway.

Degradation of Polyunsaturated Fatty Acids Requires 2,4-Dienoyl-CoA Reductase



- Degradation of polyunsaturated fatty acids is slightly more complicated
- The process is the same as for oleic acid, through 3 cycles of β-oxidation
- Enoyl-CoA isomerase then converts the cis-Δ^3 double bond to a trans-Δ^2 double bond
- Which permits 1 more round of β-oxidation
- But the resulting trans-Δ^2, cis-Δ^4 structure is a problem
- **2,4-Dienoyl-CoA reductase** solves this problem

Degradation of Polyunsaturated Fatty Acids

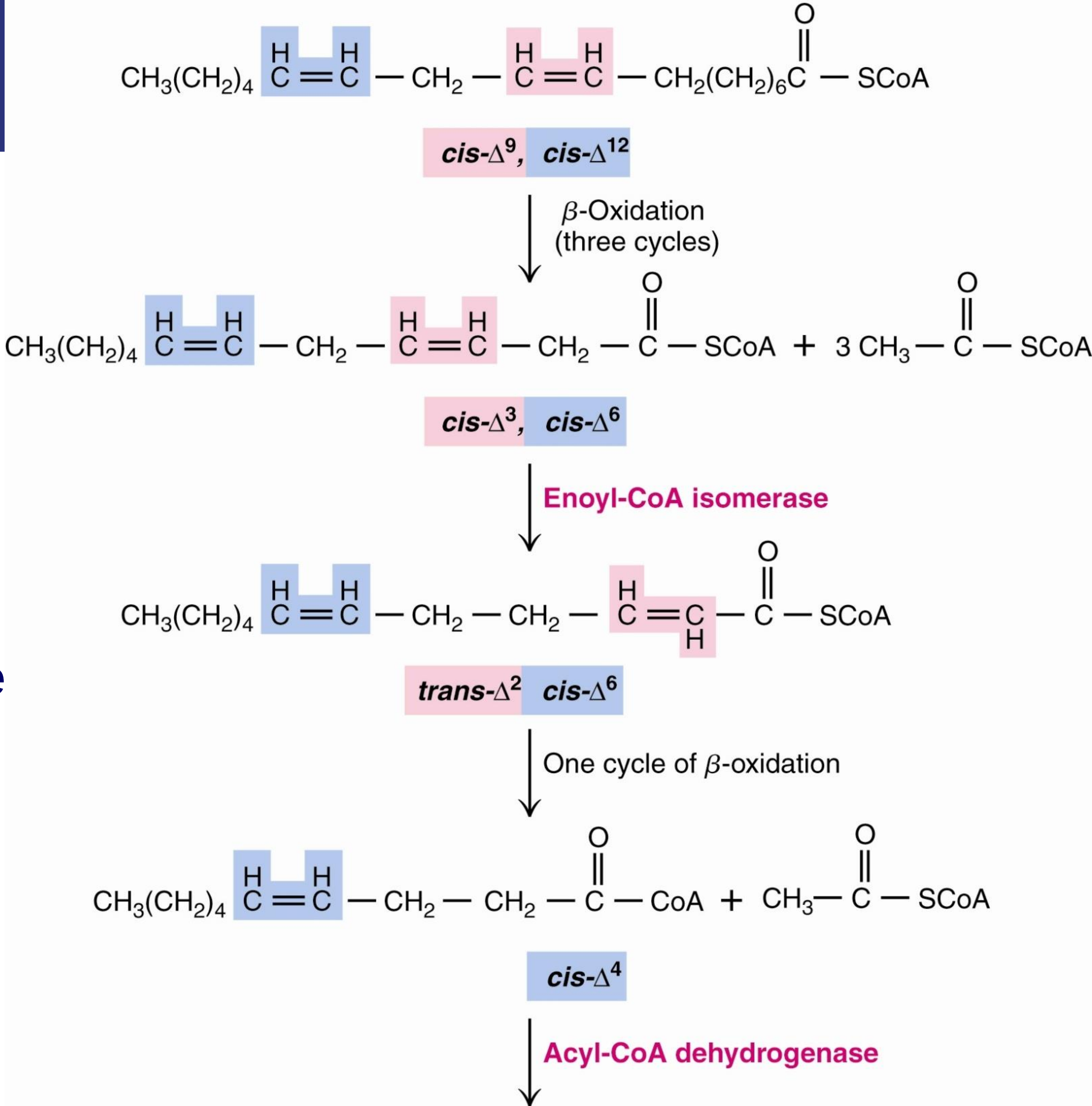


Figure 23.22 The oxidation pathway for polyunsaturated fatty acids in mammals.

Degradation of Polyunsaturated Fatty Acids Requires 2,4-Dienoyl-CoA Reductase

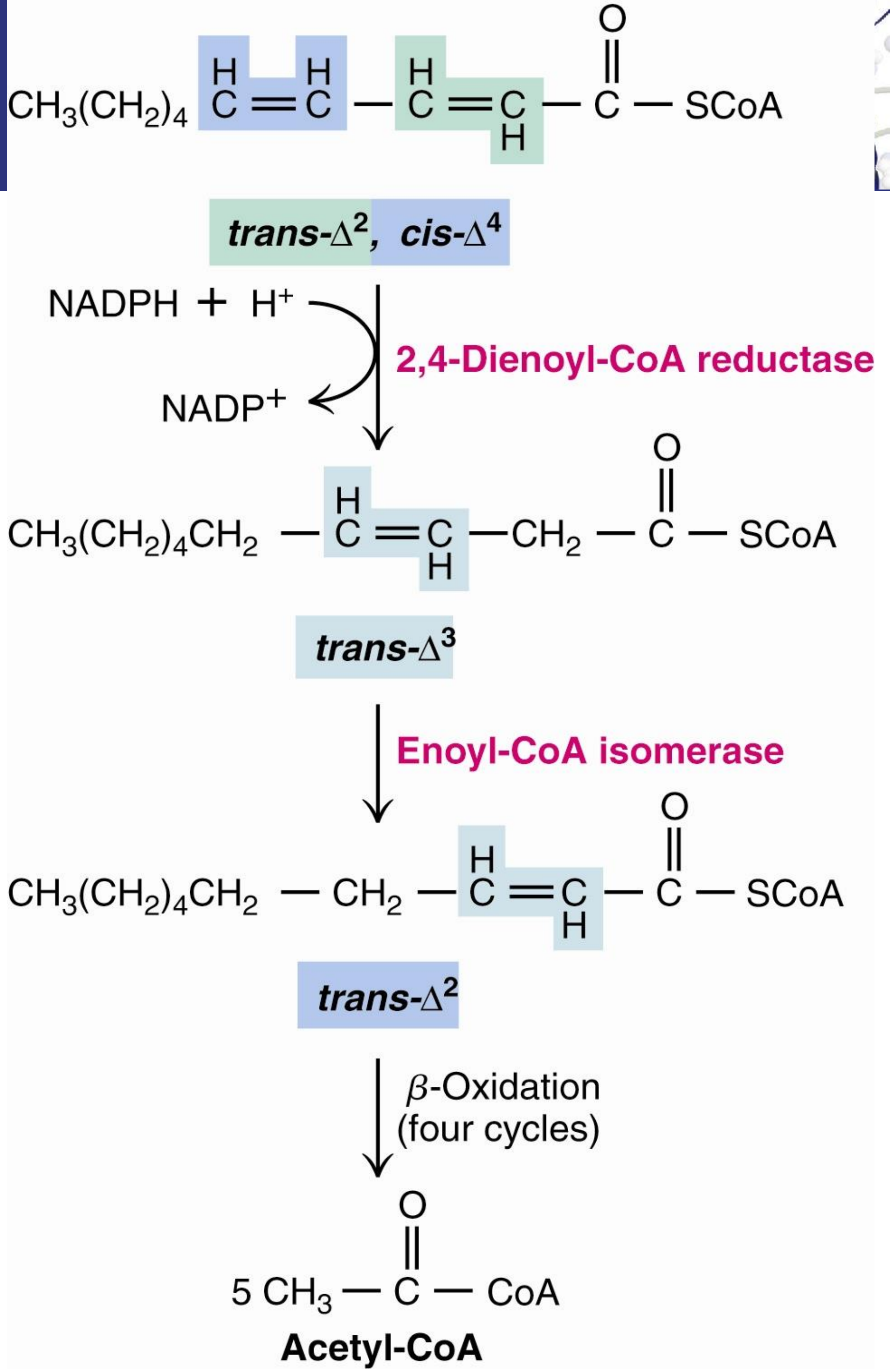
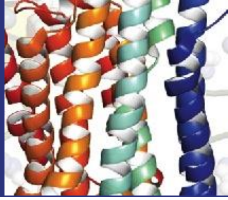


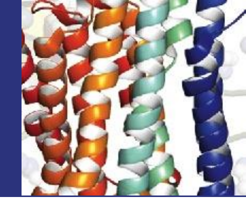
Figure 23.22 The oxidation pathway for polyunsaturated fatty acids in mammals.

23.5 Are There Other Ways to Oxidize Fatty Acids?



- **Peroxisomal β-oxidation** requires FAD-dependent **acyl-CoA oxidase**
- Branched-chain fatty acids are degraded via **α-oxidation**
- **ω-Oxidation** of fatty acids yields small amounts of dicarboxylic acids

Peroxisomal β-oxidation requires FAD-dependent acyl-CoA oxidase



- Peroxisomes are organelles that carry out flavin-dependent oxidations, regenerating oxidized flavins by reaction with O_2 to produce H_2O_2
- Similar to mitochondrial β-oxidation, but initial double bond formation is by acyl-CoA oxidase

  NOT acyl-CoA dehydrogenase
- Electrons go to O_2 rather than e^- transport
- Fewer ATPs result

Peroxisomal β-oxidation requires FAD-dependent acyl-CoA oxidase

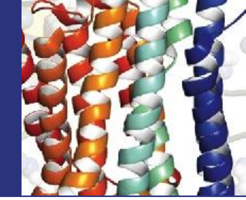
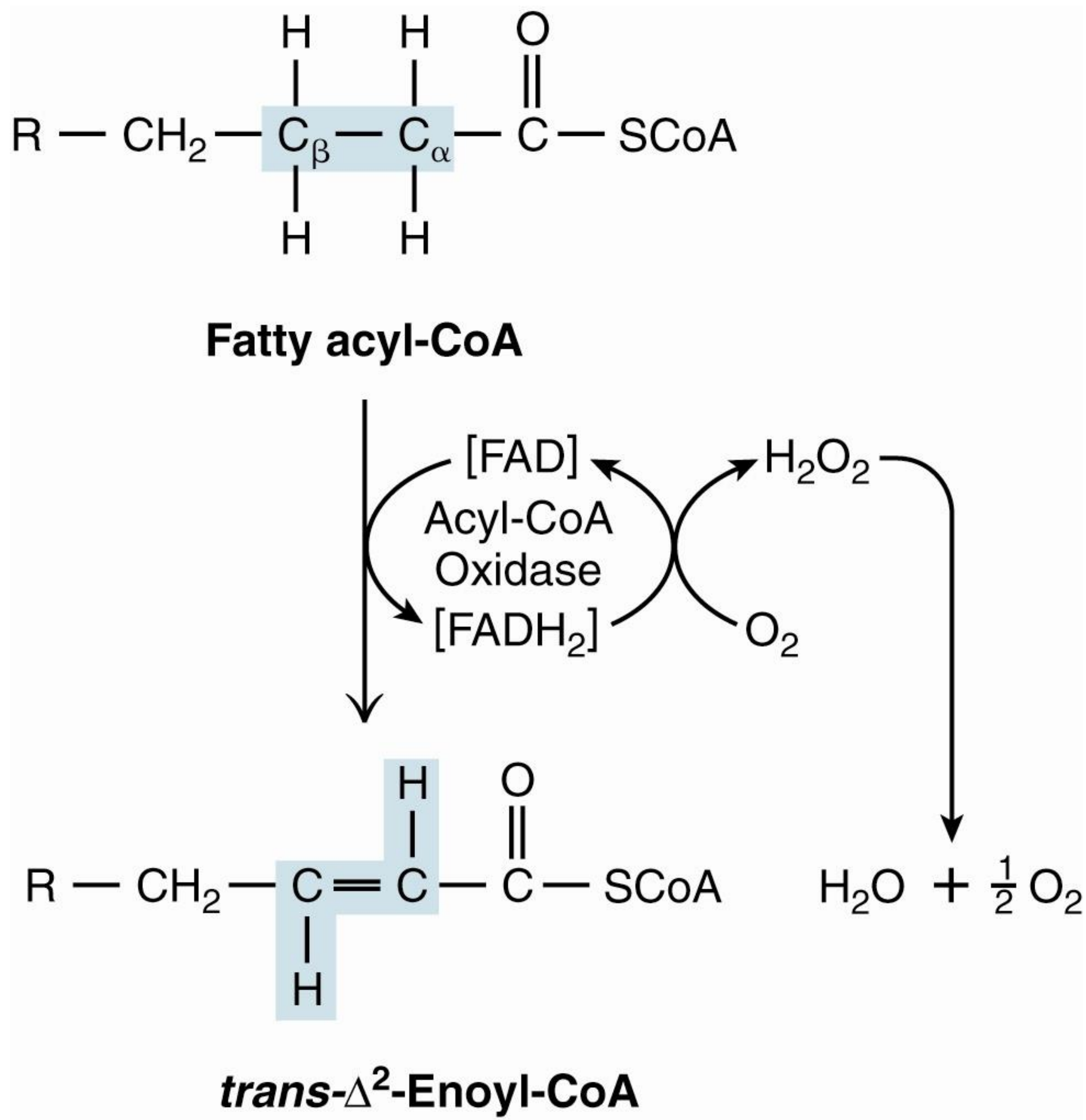
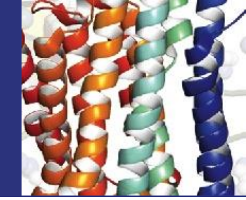


Figure 23.23 The acyl-CoA oxidase reaction in peroxisomes. Electrons captured as FADH2 are used to produce the hydrogen peroxide required for degradative processes in peroxisomes and thus are not available for eventual generation of ATP.



Branched-Chain Fatty Acids Are Degraded Via α-Oxidation

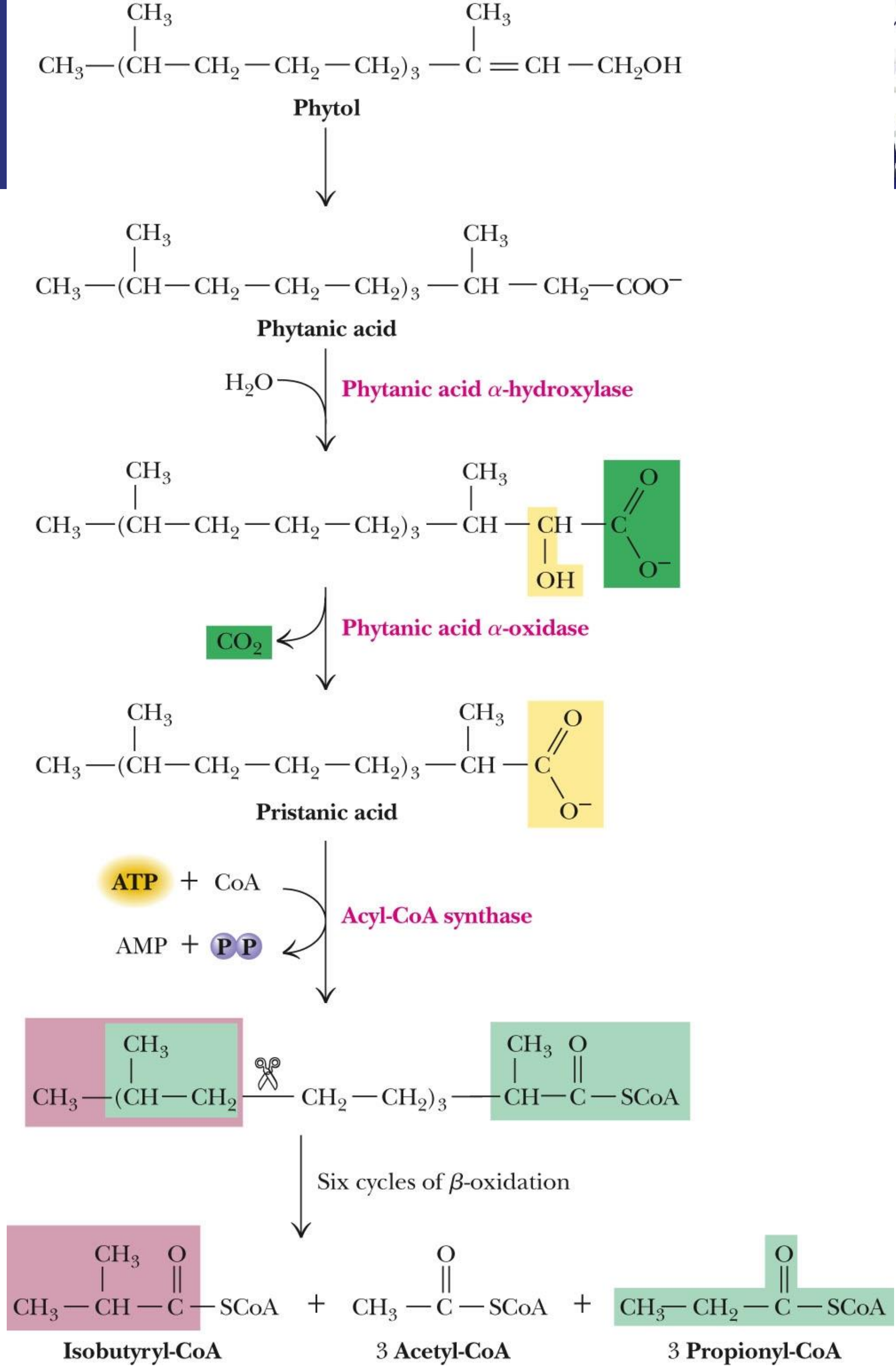


An alternative to β-oxidation is required

- Branched chain FAs with branches at odd-number carbons are not good substrates for β-oxidation
- **α-oxidation** is an alternative
- **Phytanic acid α-oxidase** decarboxylates with oxidation at the alpha position
- β-oxidation occurs past the branch

Branched-chain fatty acids are degraded via α-oxidation

Figure 23.24 Branched-chain fatty acids are oxidized by α-oxidation, as shown for phytanic acid. The product of the phytanic acid oxidase, pristanic acid, is a suitable substrate for normal β-oxidation. Isobutyryl-CoA and propionyl-CoA can both be converted to succinyl-CoA, which can enter the TCA cycle.



ω-Oxidation of fatty acids yields small amounts of dicarboxylic acids

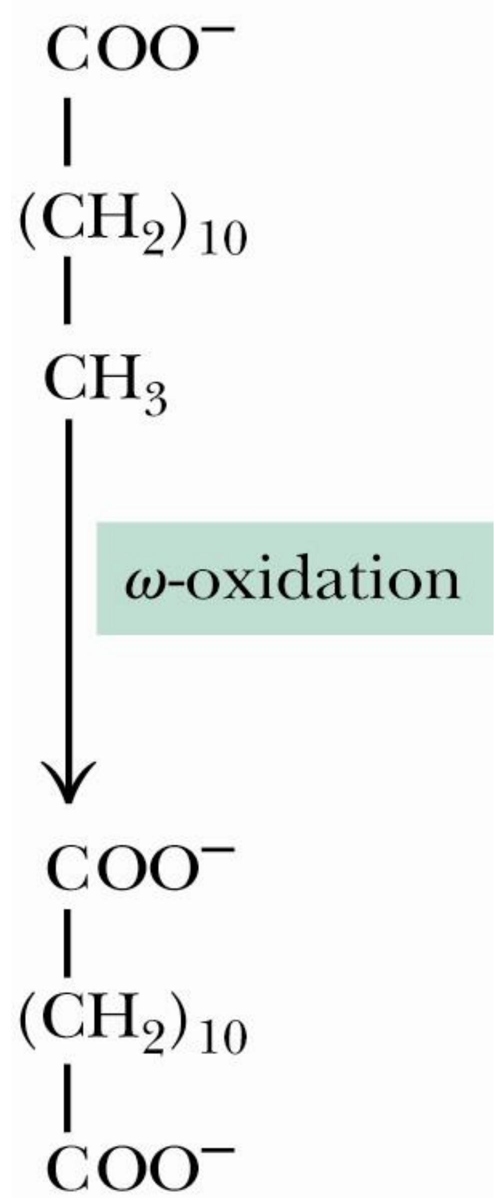
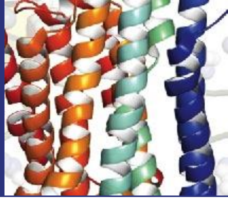


Figure 23.25 Dicarboxylic acids can be formed by oxidation of the omega carbon of fatty acids in a cytochrome P-450-dependent reaction.

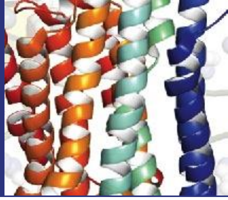
23.6 What Are Ketone Bodies, and What Role Do They Play in Metabolism?



A special source of fuel and energy for certain tissues

- Some of the acetyl-CoA produced by fatty acid oxidation in liver mitochondria is converted to **acetone**, **acetoacetate** and **β-hydroxybutyrate**
- These are called **ketone bodies**
- Source of fuel for brain, heart and muscle
- Major energy source for brain during starvation
- Synthesis in Figure 23.26
- They are transportable forms of fatty acids

23.6 What Are Ketone Bodies, and What Role Do They Play in Metabolism?



- Synthesis of ketone bodies occurs only in the mitochondrial matrix
- First step - Figure 23.26 - is reverse thiolase
- Second reaction makes HMG-CoA
- These reactions are mitochondrial analogues of the (cytosolic) first two steps of cholesterol synthesis
- Third step - **HMG-CoA lyase** - is similar to the reverse of citrate synthase

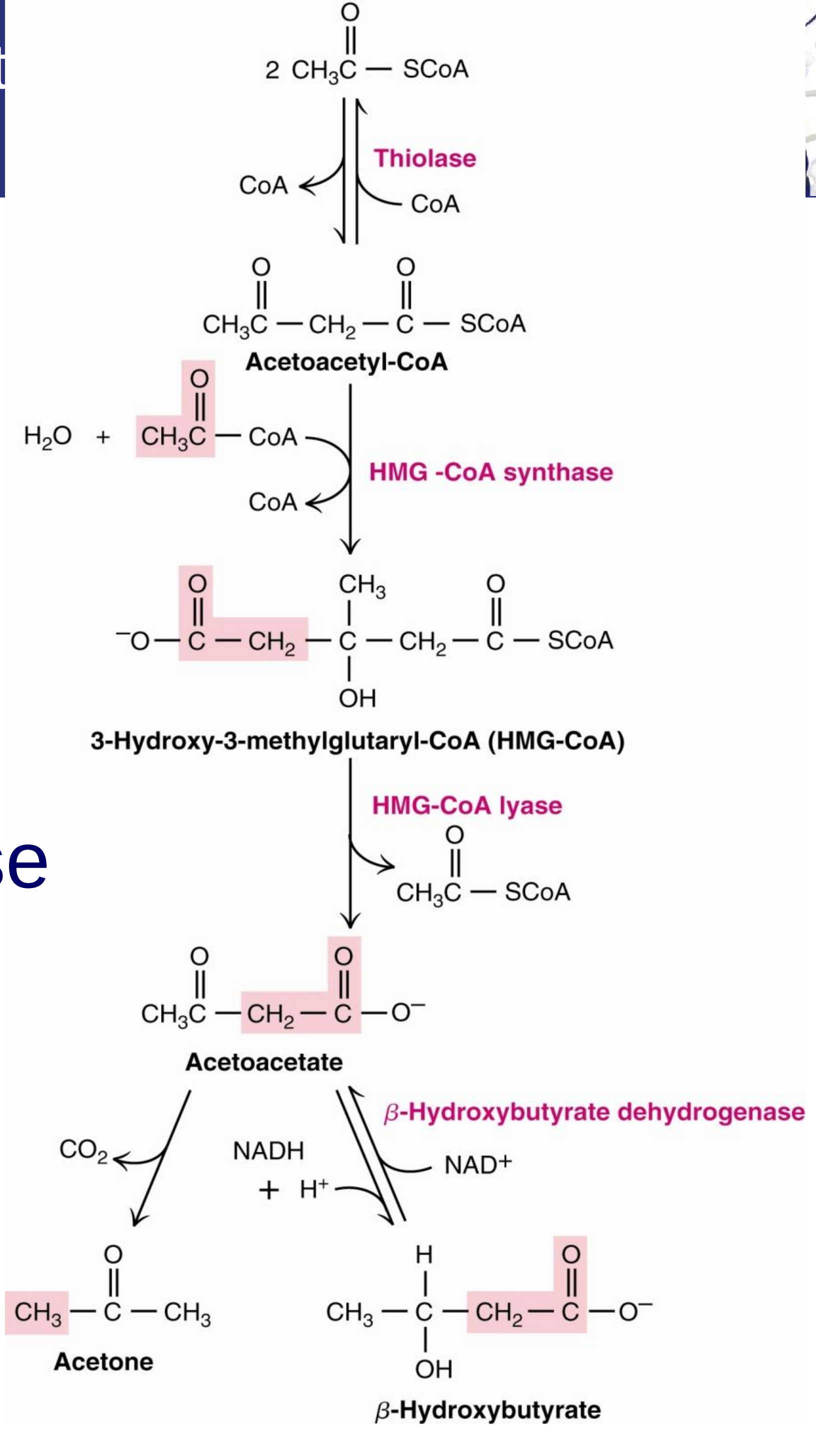
23.6 What Are Ketone Bodies, & What Role Do They Play in Metabolism?

reverse thiolase

HMG-CoA

reverse of citrate synthase

Figure 23.26 The formation of ketone bodies, synthesized primarily in liver mitochondria.



23.6 What Are Ketone Bodies, & What Role Do They Play in Metabolism?

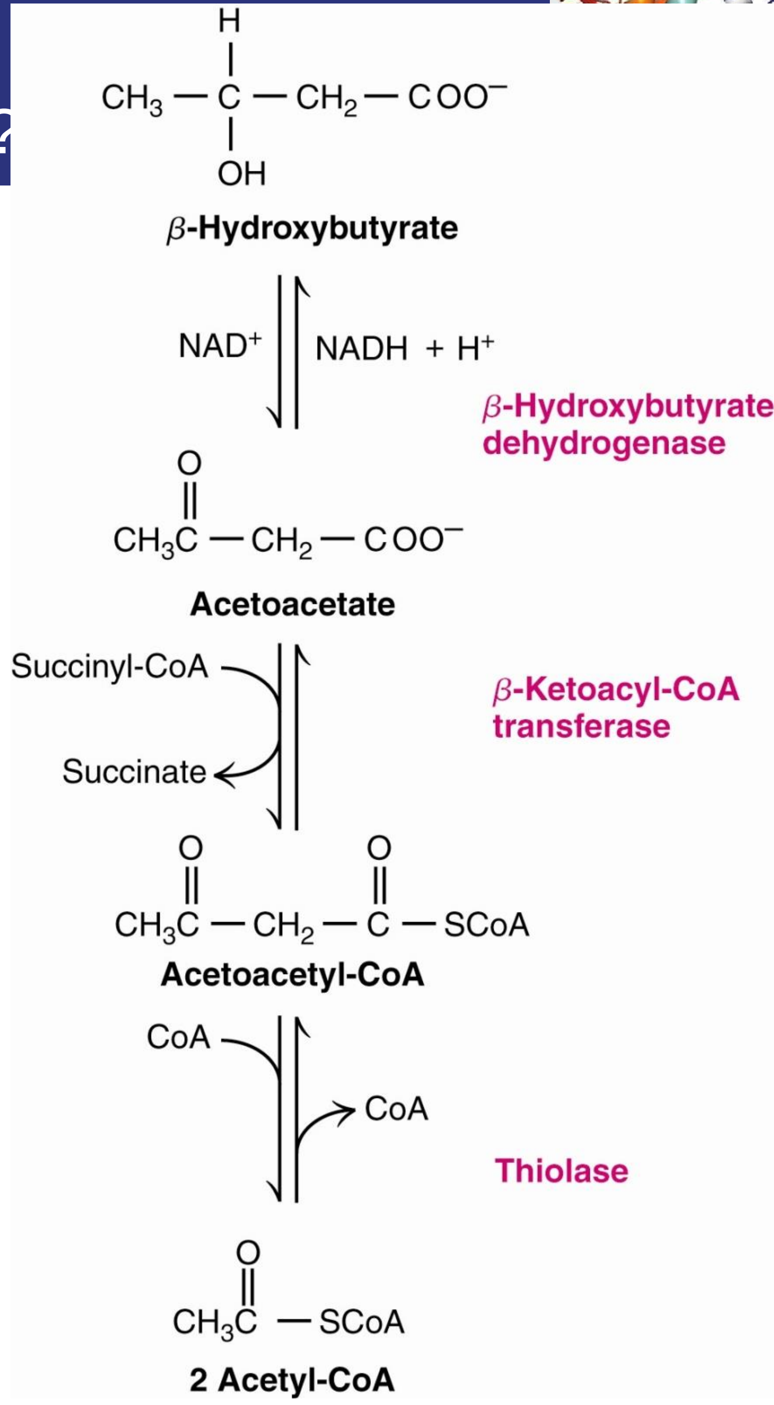
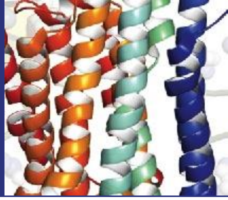


Figure 23.27 Reconversion of ketone bodies to acetyl-CoA in the mitochondria of many tissues (other than liver) provides significant metabolic energy.

Ketone Bodies and Diabetes



"Starvation of cells in the midst of plenty"

- Glucose is abundant in blood, but uptake by cells in muscle, liver, and adipose cells is low
- Cells, metabolically starved, turn to gluconeogenesis and fat/protein catabolism
- In type I diabetics, OAA is low, due to excess gluconeogenesis, so Acetyl-CoA from fat/protein catabolism does not go to TCA, but rather to ketone body production
- Acetone can be detected on breath of type I diabetics

富人低消費