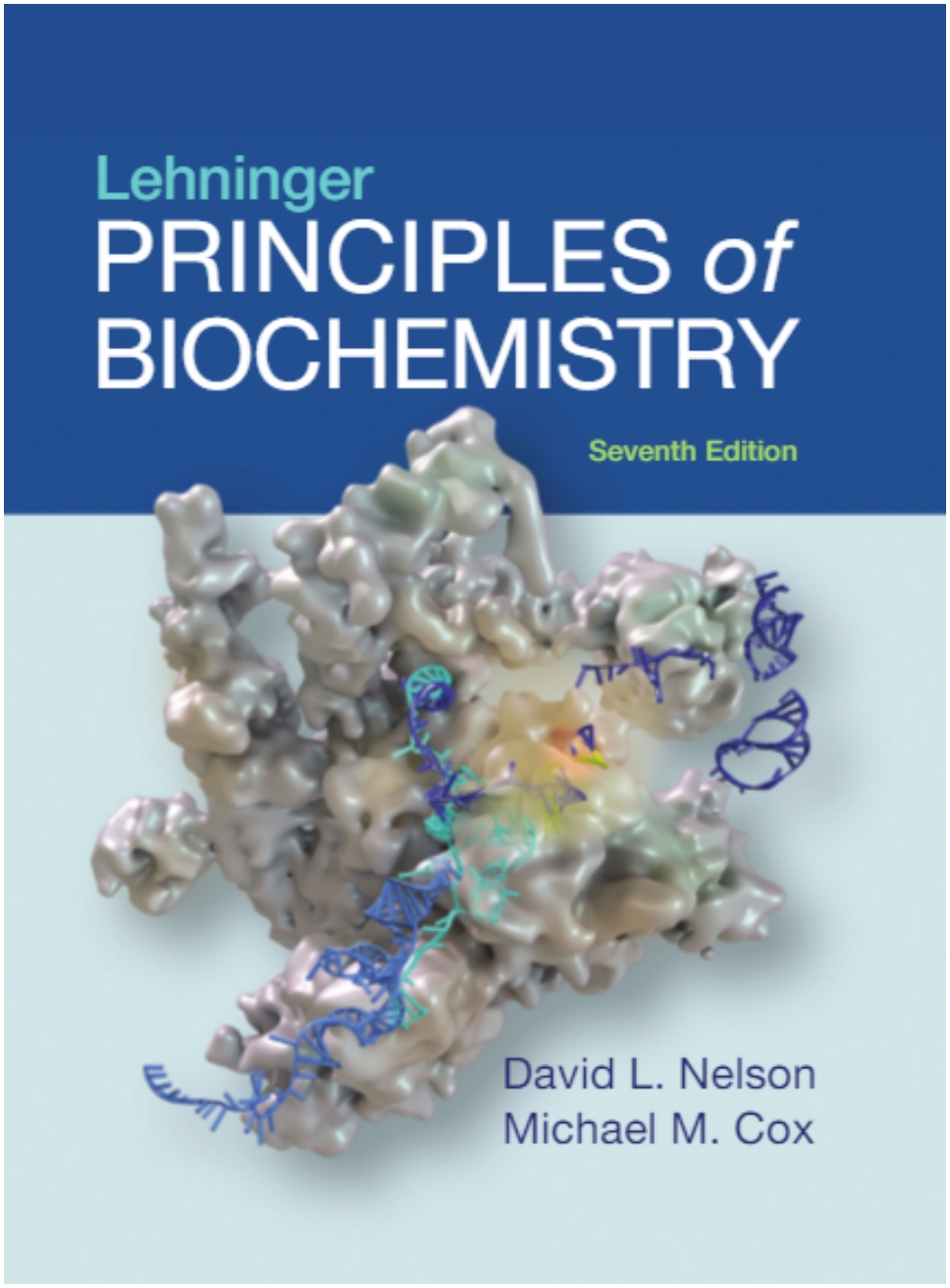
17| Fatty Acid Catabolism



CHAPTER 17:
Fatty Acid Catabolism

Learning goals:

- How fats are digested in animals
- How fats are mobilized and transported in tissues
- How fats are oxidized
- How “ketone bodies” are produced

Oxidation of Fatty Acids Is a Major Energy Source in Many Organisms

- About one-third of our energy needs comes from dietary triacylglycerols.
- About 80% of energy needs of mammalian heart and liver are met by oxidation of fatty acids.
- Many hibernating animals, such as grizzly bears, rely almost exclusively on fats as their source of energy (and water during their long-term sleep)

Hibernating Bears Get the Majority of Their Energy from Stored Fatty Acids

Stouffer Productions/Animals Animals

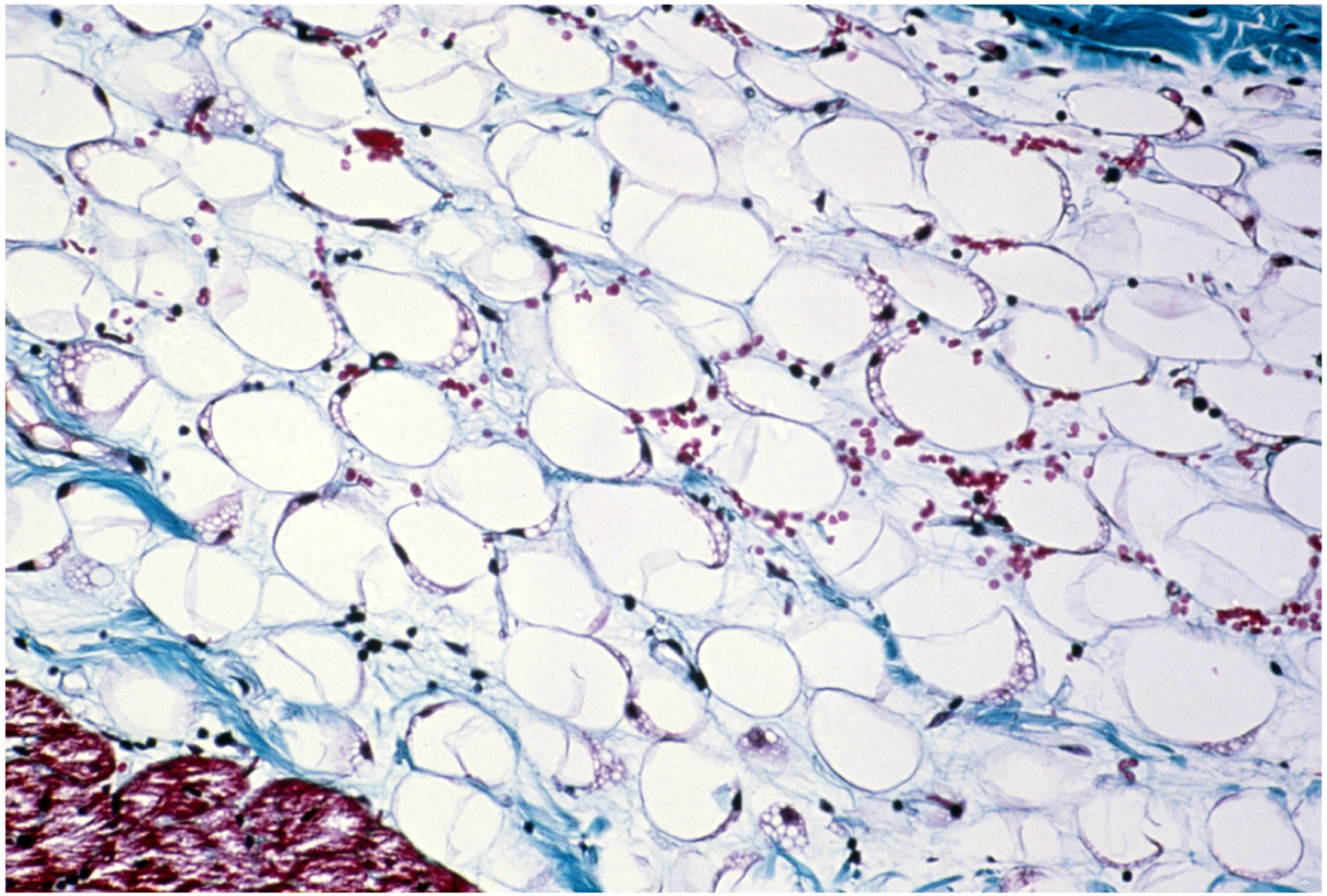
Box 17-1

Lehninger Principles of Biochemistry, Seventh Edition

Fats Provide Efficient Fuel Storage

- The advantage of fats over polysaccharides:
  - Fatty acids carry more energy per carbon because they are more reduced.
  - Fatty acids complex or carry less water because they are nonpolar.
- Glucose and glycogen are for short-term energy needs and quick delivery.
- Fats are for long-term (months) energy needs, good storage, and slow delivery.

Fat Storage in White Adipose Tissue



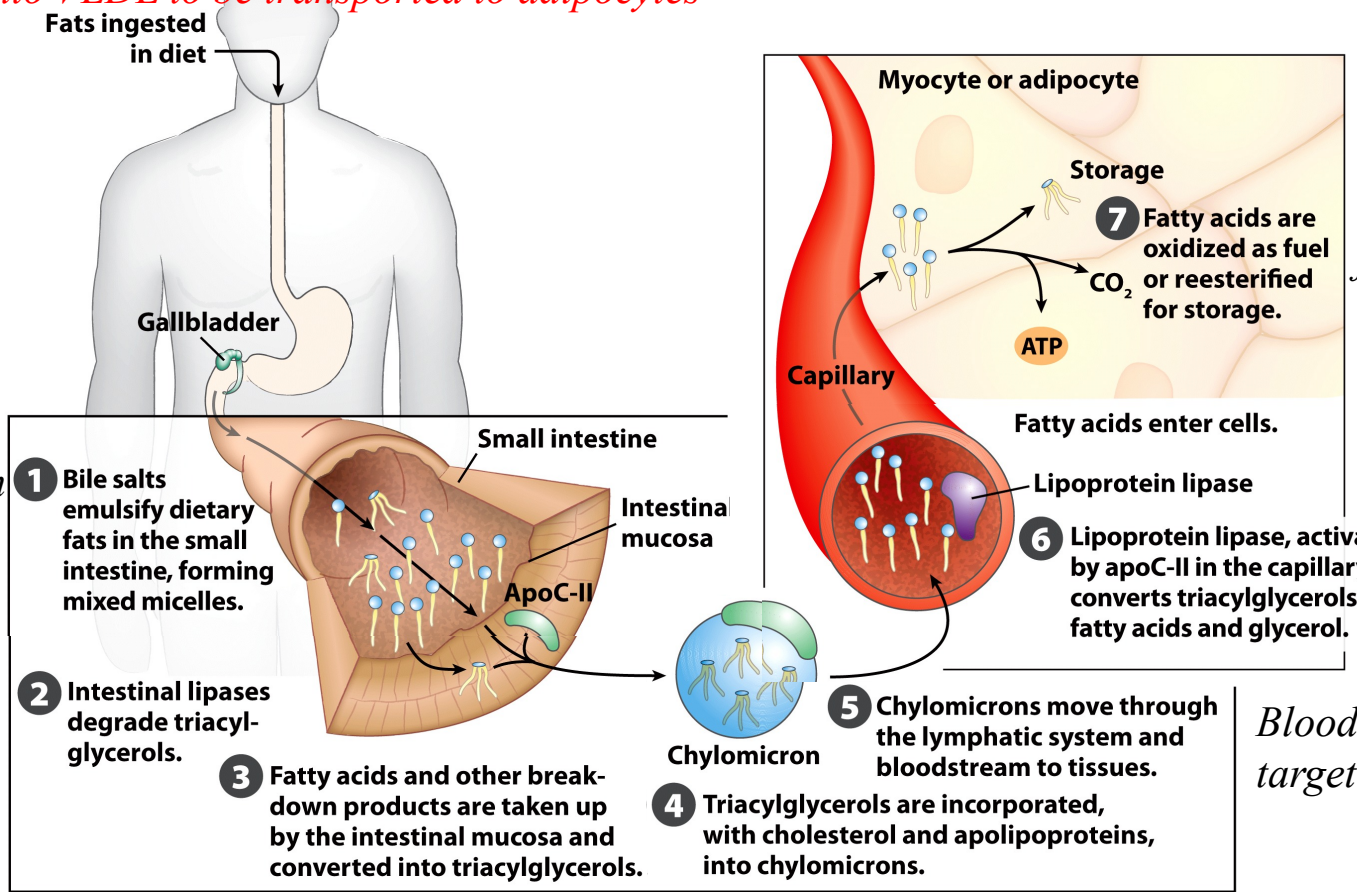
Biophoto Associates/Science Source

Figure 10-3a
Lehninger Principles of Biochemistry, Seventh Edition

Dietary fatty acids are absorbed in the vertebrate small intestine

Remaining chylomicrons go to liver and enter by RME → used for ketone bodies synthesis.

When diet contains more f.a. than needed, liver converts them to TAG and packages them into VLDL to be transported to adipocytes



Emulsification by biological detergents (bile)

Breakdown of TAG to DAG, MAG, FFA and glycerol

Uptake by intestinal cells

Chylomicrons (lipoproteins)

Bloodstream to target tissues

2nd breakdown of TAG

Used for energy (muscles) or reesterified for storage (adipose)

Lipids Are Transported in the Blood as Chylomicrons

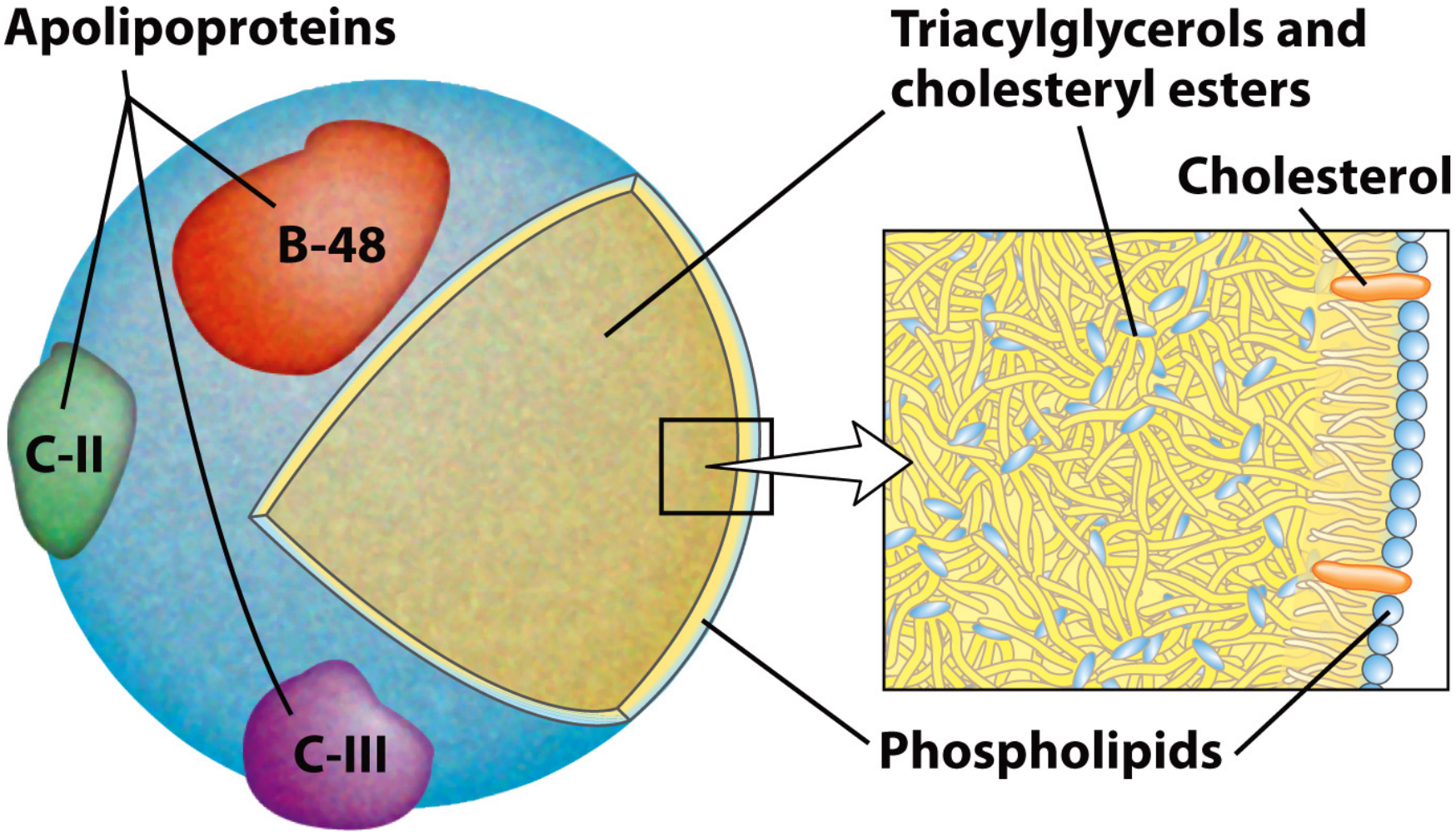


Figure 17-2
Lehninger Principles of Biochemistry, Seventh Edition

Apoliporpotein + lipids particles = **lipoprotein**

Hormones trigger mobilization of stored triacylglycerols

- Hydrolysis of TAGs is catalyzed by lipases
  - can produce MAGs, DAGs, FFA and glycerol
- Some lipases are regulated by hormones glucagon and epinephrine

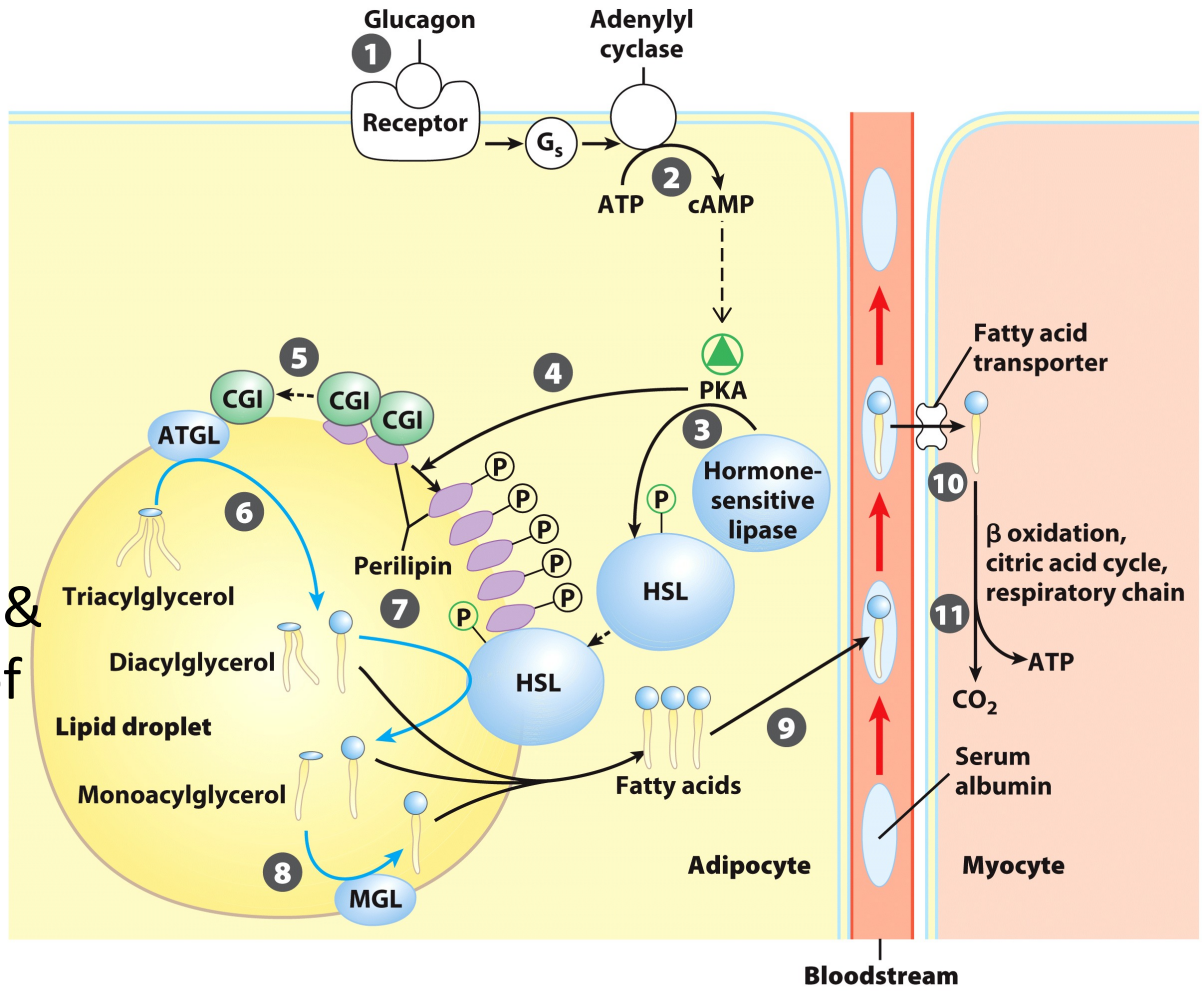
Recall:

- Epinephrine means: "We need energy now"
- Glucagon means: "We are out of glucose"

Hormones trigger mobilization of stored triacylglycerols

- Perilipins – proteins that coat lipid droplets and restrict access to lipids to prevent premature mobilization
- ↓$[glc]_{blood}$ → glucagon →→ PKA → phosphorylation of hormone-sensitive lipase & perilipin → dissociation of CGI and activation of adipose triacylglycerol lipase

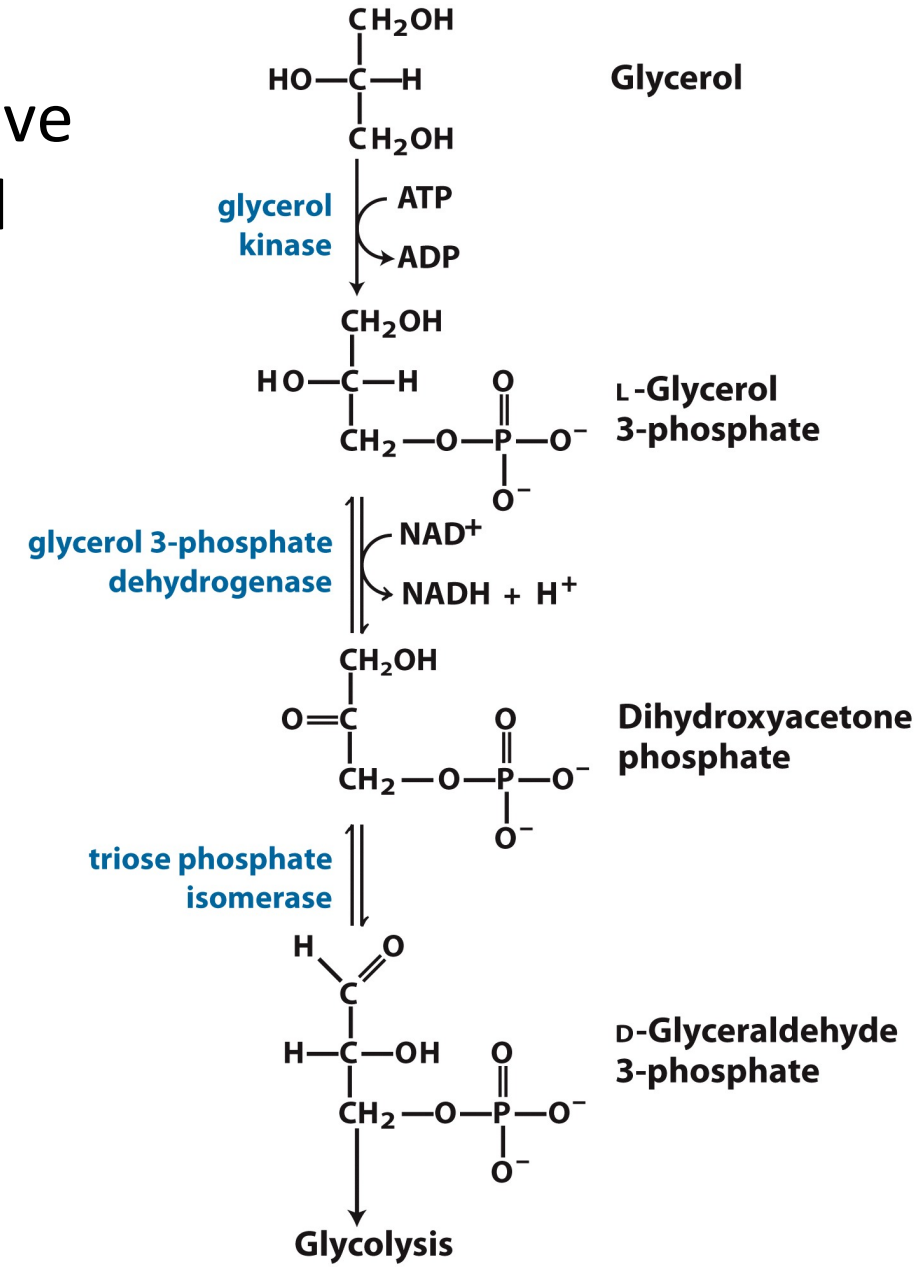
  Monoacylglycerol lipase hydrolyzes MAGs



Serum albumin binds up to 10 f.a. noncovalently

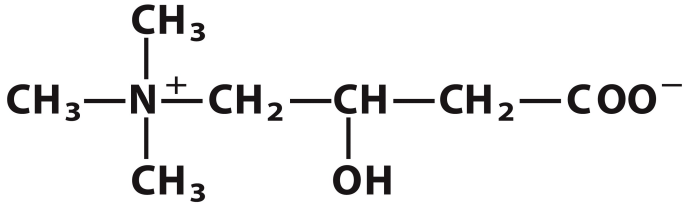
Glycerol from fats enters glycolysis

- Only 5% of biologically-active energy of TAG is in glycerol
- Glycerol kinase activates glycerol at the expense of ATP
- Subsequent reactions recover more than enough ATP to cover this cost
- Allows limited anaerobic catabolism of fats



Fatty Acid Transport into Mitochondria

- Fats are degraded into fatty acids and glycerol in the cytoplasm of adipocytes
- Fatty acids are transported to other tissues for fuel
- β-oxidation of fatty acids occurs in mitochondria
- Small (< 12 carbons) fatty acids diffuse freely across mitochondrial membranes
- Larger fatty acids (most free fatty acids) are transported via acyl-carnitine/carnitine transporter (**carnitine shuttle**)
- Three steps:



Carnitine

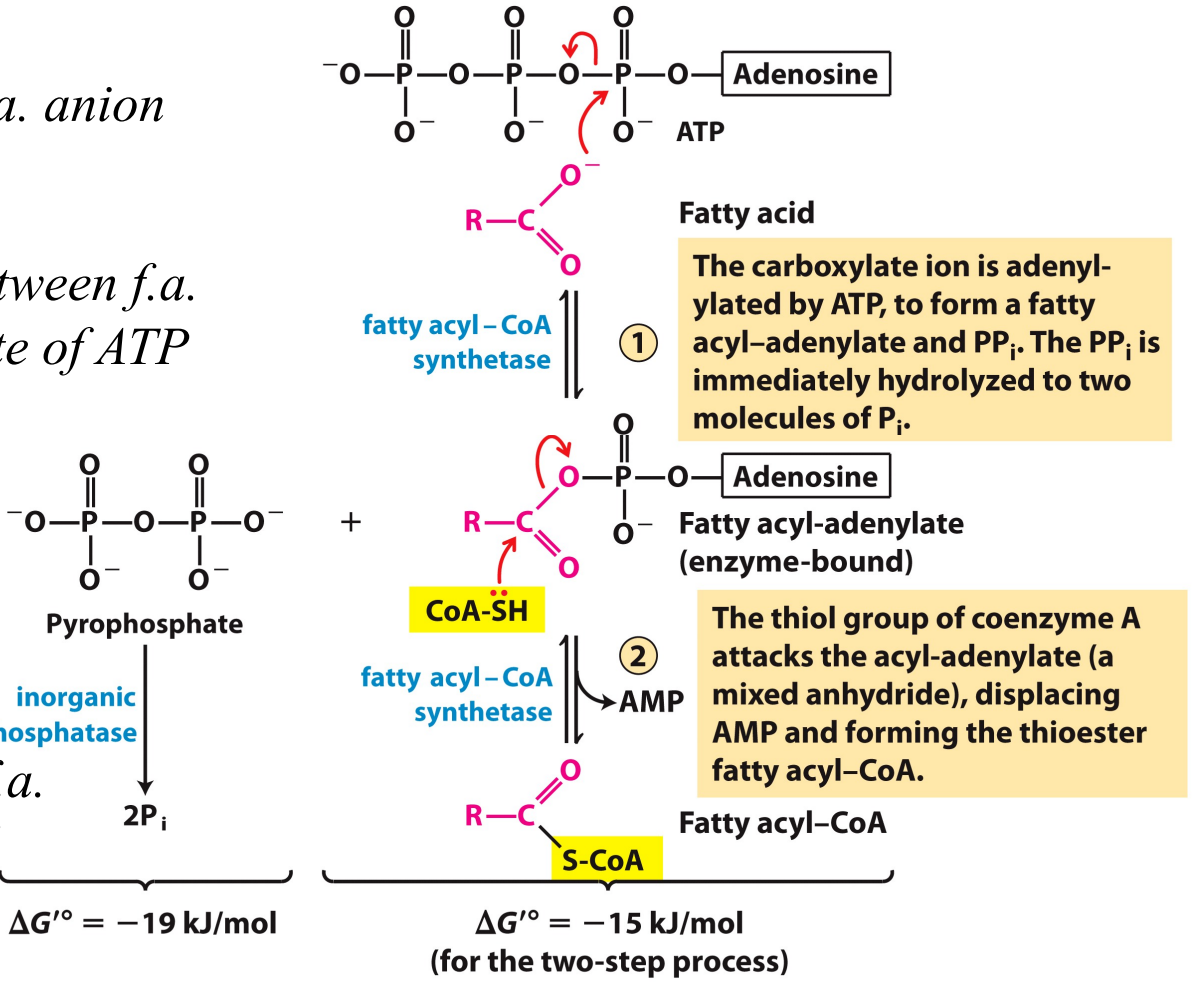
Conversion of a fatty acid to a fatty acyl–CoA (1)

Nucleophilic attack by f.a. anion

Phosphoester linkage between f.a. carboxyl and α phosphate of ATP

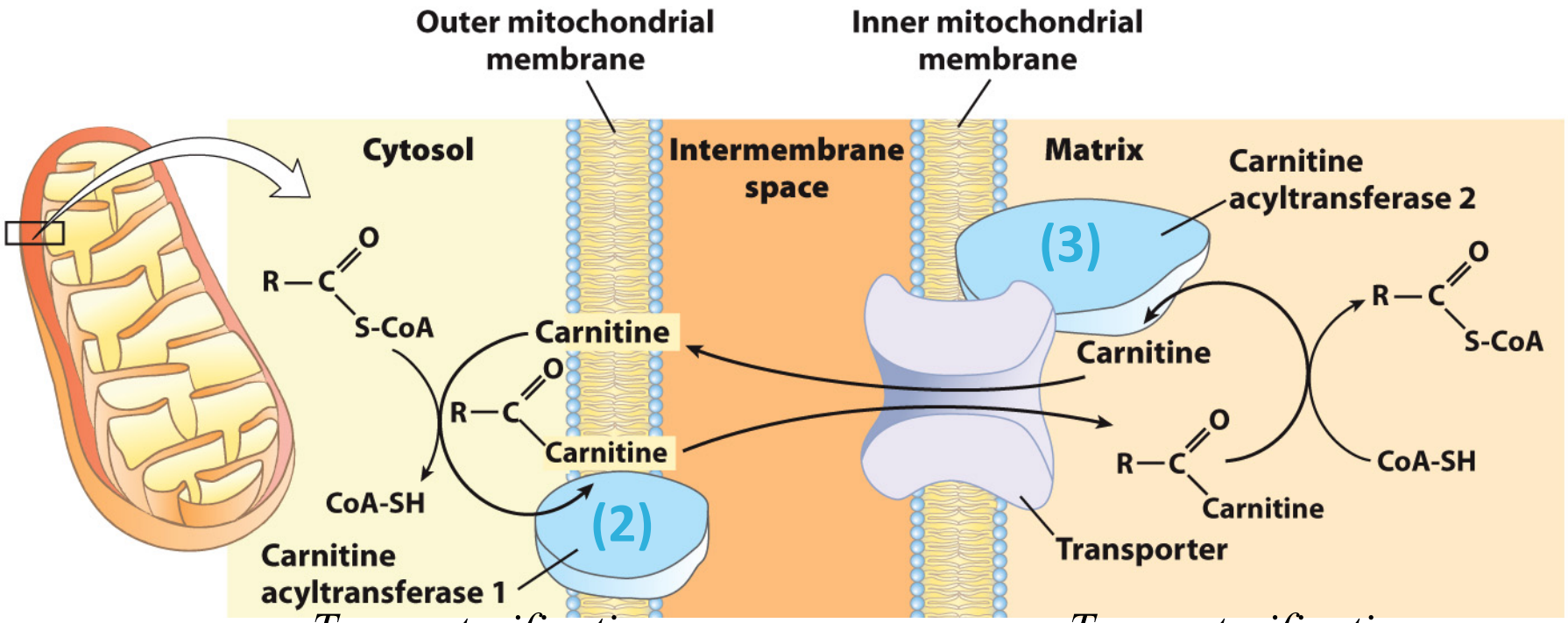
Thioester linkage between f.a. carboxyl and thiol group of CoA-SH

Hydrolysis of PP_i to $2P_i$ is highly exergonic and pulls the first reaction forward



Acyl-Carnitine/Carnitine Transport

Carnitine-mediated entry is the rate limiting step for oxidation of f.a. in mito



2 separate pools of CoA:

Matrix CoA → used mostly in oxidative degradation (pyr, f.a., a.a.)

Cytosolic CoA → used in biosynthesis of f.a.

Stages of Fatty Acid Oxidation

- Stage 1 consists of oxidative conversion of two-carbon units into acetyl-CoA via β-oxidation with concomitant generation of NADH and $FADH_2$
  - involves oxidation of β carbon to thioester of fatty acyl-CoA
- Stage 2 involves oxidation of acetyl-CoA into CO_2 via citric acid cycle with concomitant generation NADH and $FADH_2$
- Stage 3 generates ATP from NADH and $FADH_2$ via the respiratory chain

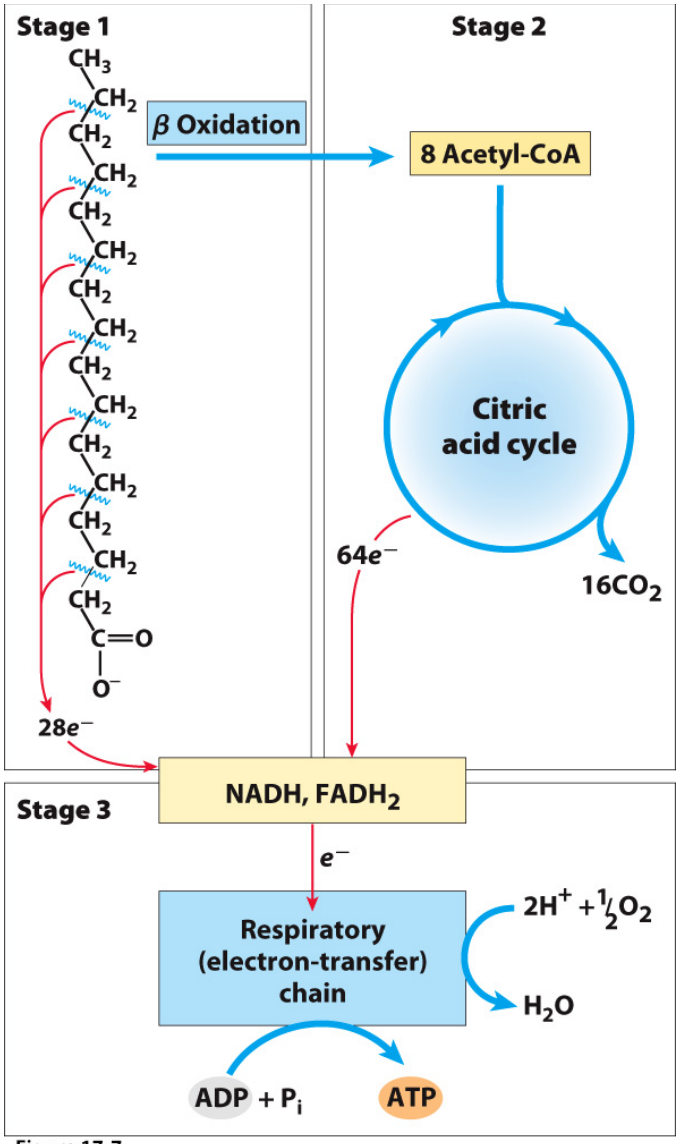


Figure 17-7
Lehninger Principles of Biochemistry, Seventh Edition

The β-Oxidation Pathway

Each pass removes one acetyl moiety in the form of acetyl-CoA.

Formation of each acetyl-CoA requires removal of 4 H atoms {2 e^- pairs and 4 H^+})

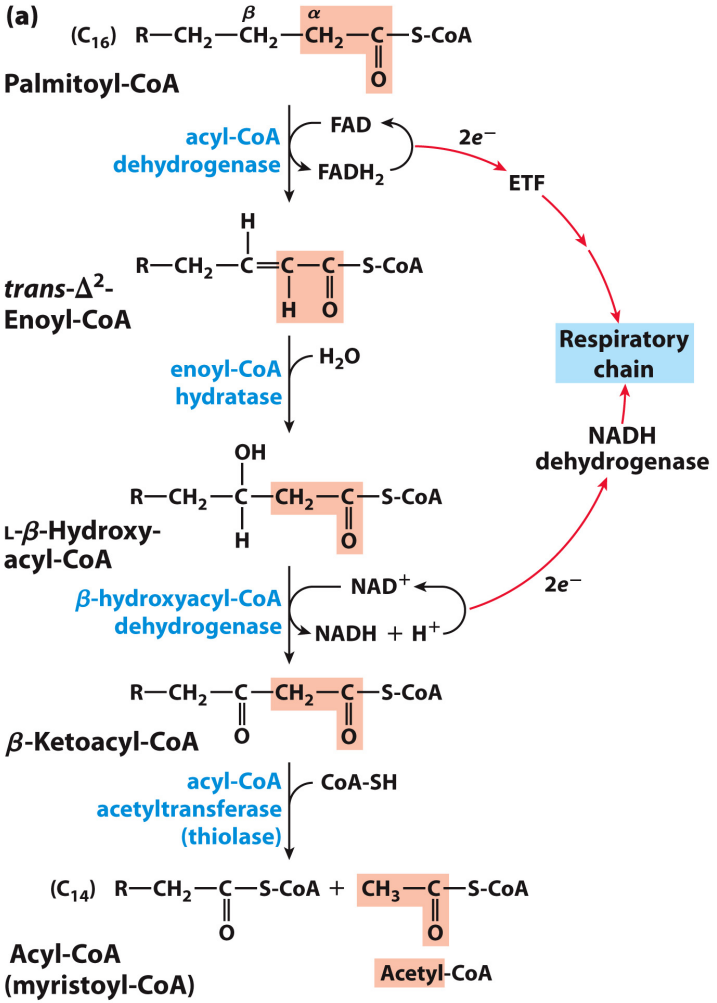
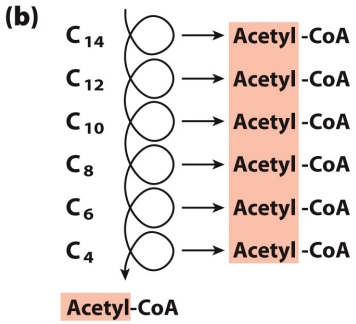


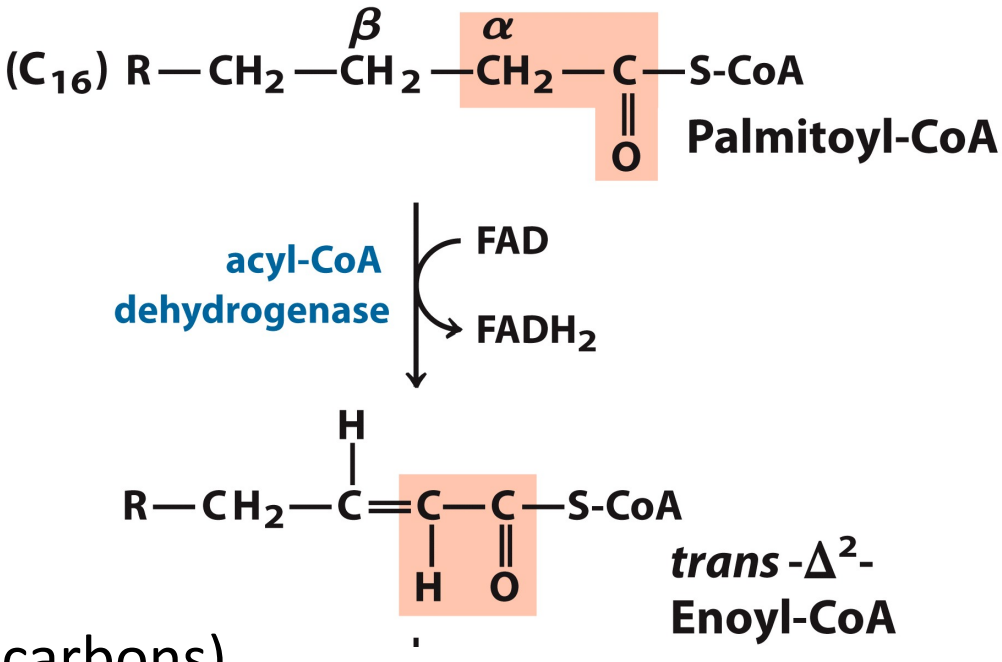
Figure 17-8
Lehninger Principles of Biochemistry, Seventh Edition



Palmitate (C16) undergoes seven passes through the oxidative sequence

Step 1: Dehydrogenation of Alkane to Alkene

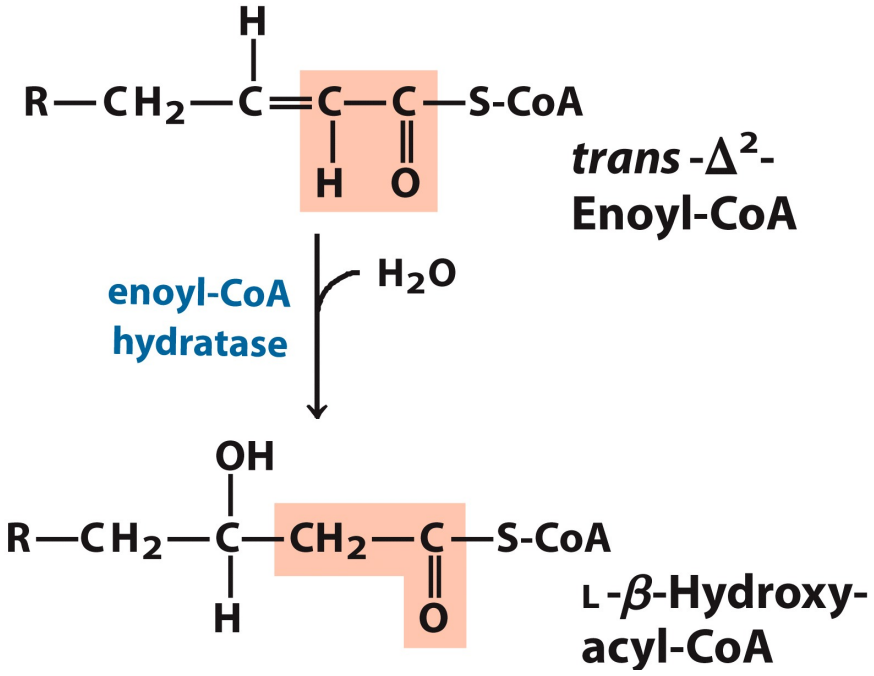
- Catalyzed by isoforms of acyl-CoA dehydrogenase (AD) on the mitochondrial inner membrane
  - Very-long-chain AD (VLCAD, 12–18 carbons)
  - Medium-chain AD (MCAD, 4–14 carbons)
  - Short-chain AD (SCAD, 4–8 carbons)



- Results in *trans double bond*, different from naturally occurring unsaturated fatty acids, between α and β C
- Analogous to succinate dehydrogenase reaction in the CAC
  - Electrons from bound FAD transferred directly to the electron- transport chain via electron-transferring flavoprotein (ETF)

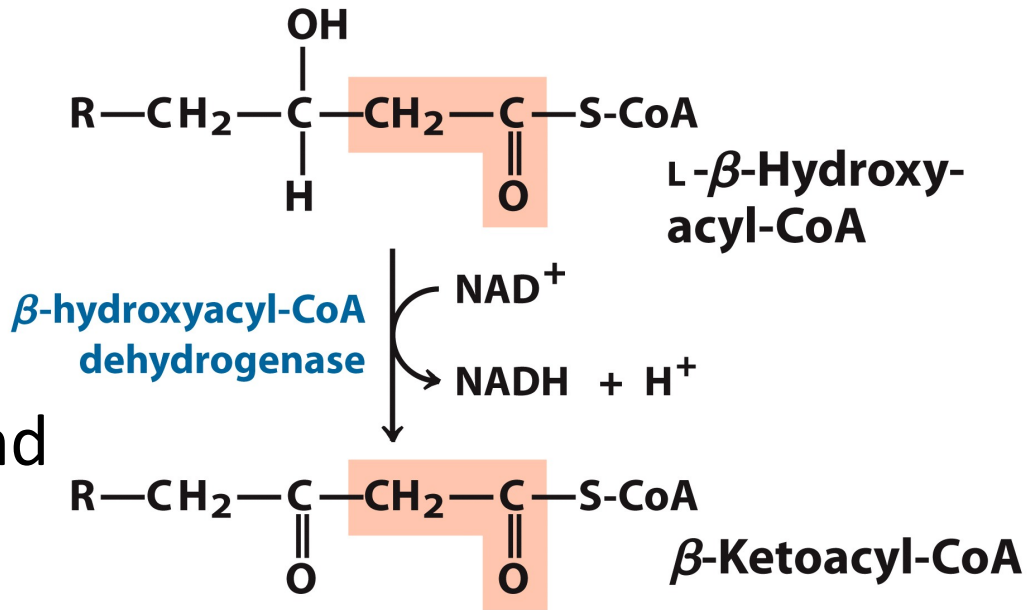
Step 2: Hydration of Alkene

- Catalyzed by two isoforms of enoyl-CoA hydratase:
  - Soluble short-chain hydratase (crotonase)
  - Membrane-bound long-chain hydratase, part of trifunctional complex
- Water adds across the double bond yielding alcohol
- Analogous to fumarase reaction in the CAC
  - Same stereospecificity



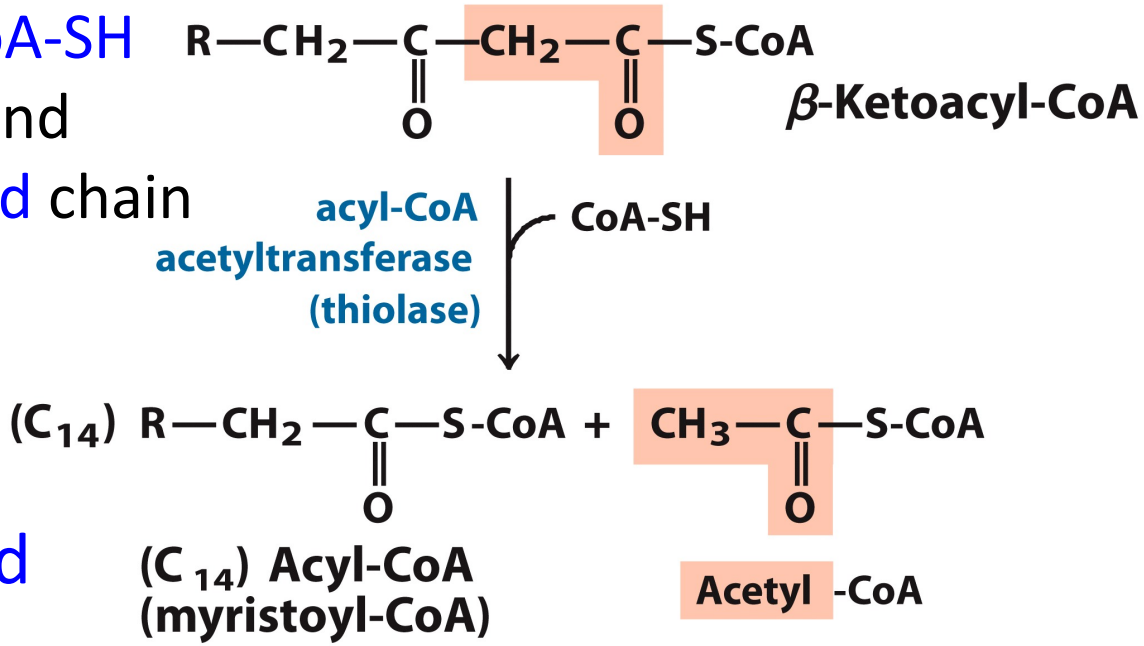
Step 3: Dehydrogenation of Alcohol

- Catalyzed by β-hydroxyacyl-CoA dehydrogenase
- The enzyme uses NAD cofactor as the hydride acceptor
- Only L-isomers of hydroxyacyl CoA act as substrates
- Analogous to malate dehydrogenase reaction in the CAC
- The first three steps create a *much less stable* C-C bond, where the α C is bound to 2 carbonyl groups



Step 4:
Transfer of Fatty Acid Chain

- Catalyzed by acyl-CoA acetyltransferase (thiolase) via covalent mechanism
  - The carbonyl carbon in β-ketoacyl-CoA is electrophilic
  - Active site thiolate acts as nucleophile and releases acetyl-CoA
  - Terminal sulfur in CoA-SH acts as nucleophile and picks up the fatty acid chain from the enzyme
- The net reaction is ***thiolysis*** of a carbon-carbon bond



Fatty Acid Oxidation is Performed by a Single Trifunctional Protein

- Hetero-octamer
  - four α subunits
    - enoyl-CoA hydratase activity
    - β-hydroxyacyl-CoA dehydrogenase activity
    - responsible for binding to membrane
  - four β subunits
    - long-chain thiolase activity
- May allow substrate channeling between enzymes
- Associated with mitochondrial inner membrane
- Processes fatty acid chains with 12 or more carbons
- Shorter chains processed by soluble enzymes in the matrix

Fatty Acid Oxidation Is Performed by a Single Trifunctional Protein

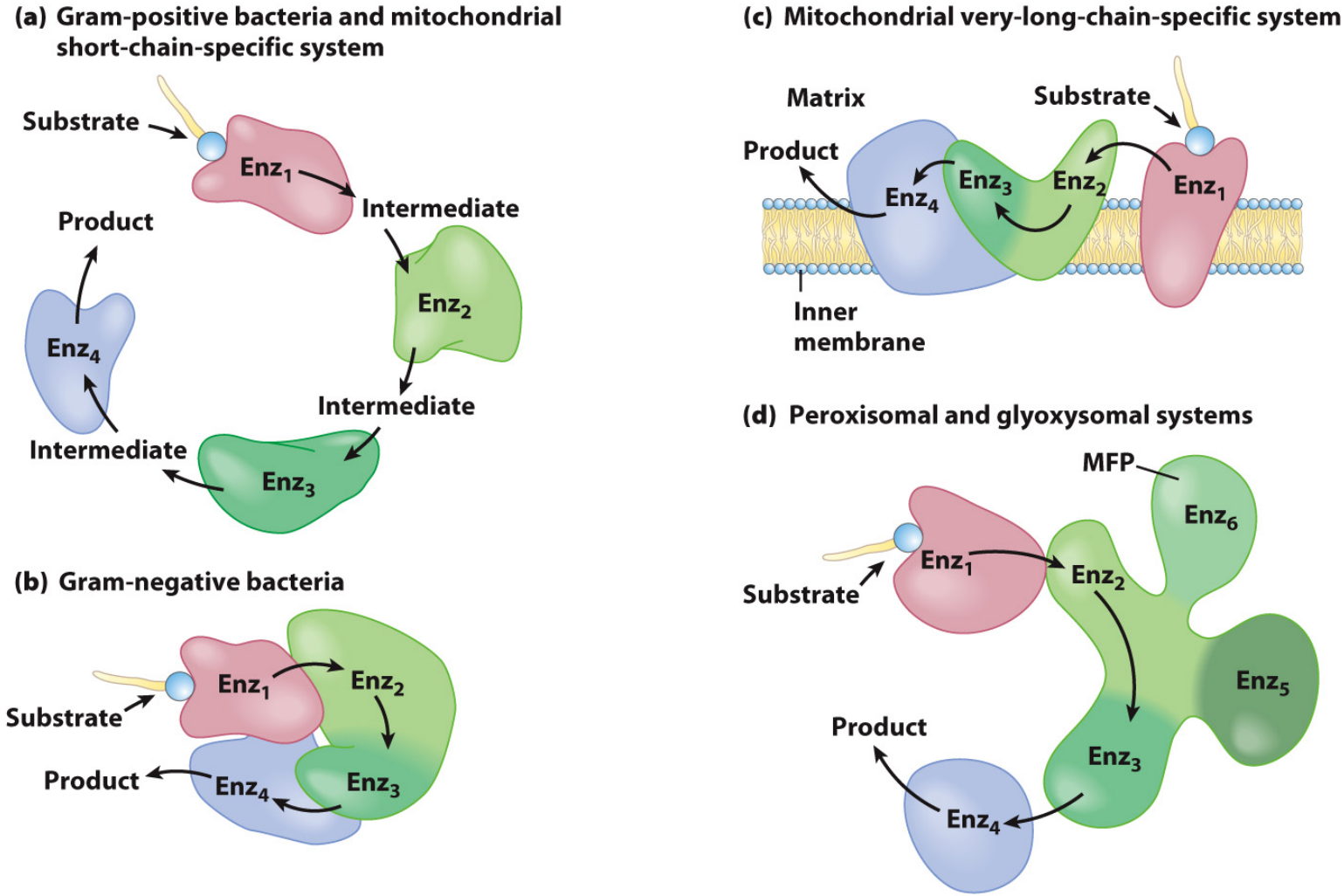


Figure 17-15
Lehninger Principles of Biochemistry, Seventh Edition

Each Round Produces an Acetyl-CoA and Shortens the Chain by Two Carbons

Spiral pathway

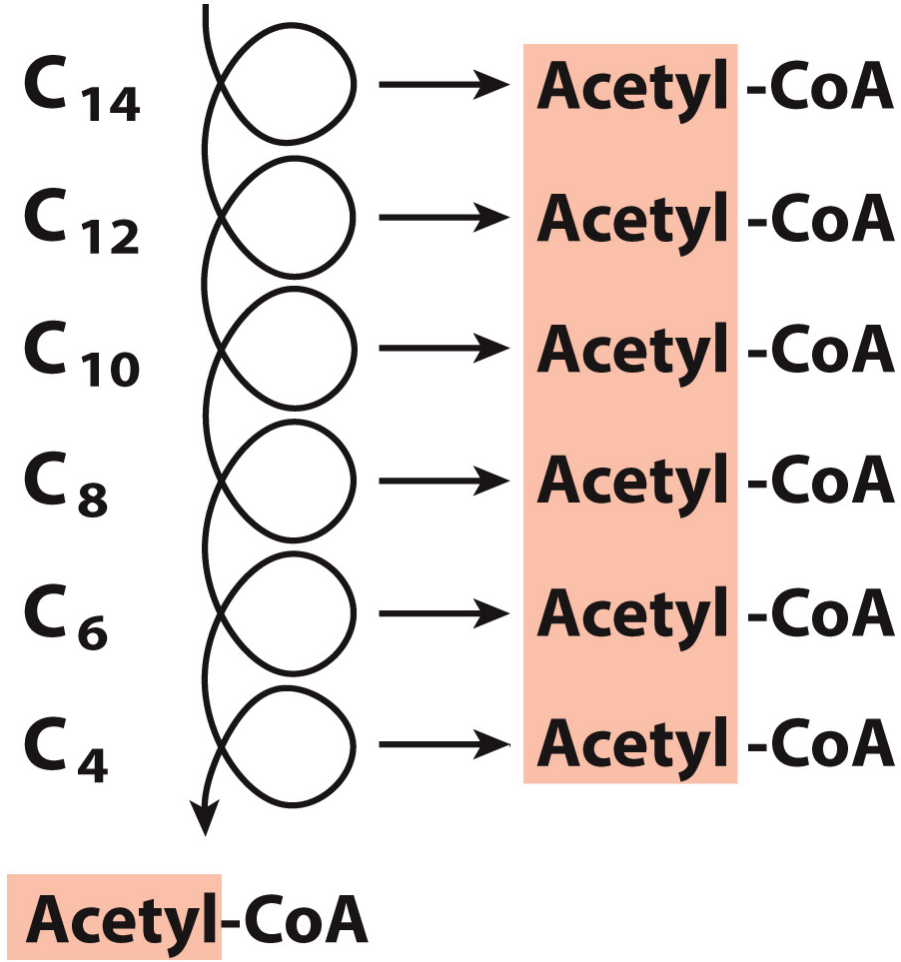


Figure 17-8b
Lehninger Principles of Biochemistry, Seventh Edition

Fatty Acid Catabolism for Energy

- For palmitic acid (C_{16})
  - Repeating the above four-step process six more times (7 total) results in eight molecules of acetyl-CoA
    - $FADH_2$ is formed in each cycle (7 total)
    - NADH is formed in each cycle (7 total)

- Acetyl-CoA enters citric acid cycle and further oxidizes into CO_2
  - This makes more GTP, NADH, and $FADH_2$

- Electrons from all $FADH_2$ and NADH enter ETC

- Transfer of e^-s from $FADH_2$ and NADH to O_2 yields 1 H_2O per pair (camels and hibernating animals!)

Palmitoyl-CoA + 7CoA + $7O_2$ + $28P_i$ + 28ADP → 8 acetyl-CoA + 28ATP + $7H_2O$ (β oxidation)

Palmitoyl-CoA + $23O_2$ + $108P_i$ + 108ADP → CoA + 108ATP + $16CO_2$ + $23H_2O$ (full oxidation)

NADH and $FADH_2$ Serve as Sources of ATP

TABLE 17-1 Yield of ATP during Oxidation of One Molecule of Palmitoyl-CoA to CO_2 and H_2O

Enzyme catalyzing the oxidation step	Number of NADH or $FADH_2$ formed	Number of ATP ultimately formed[a]
β Oxidation		
Acyl-CoA dehydrogenase	7 $FADH_2$	10.5
β-Hydroxyacyl-CoA dehydrogenase	7 NADH	17.5
Citric acid cycle		
Isocitrate dehydrogenase	8 NADH	20
α-Ketoglutarate dehydrogenase	8 NADH	20
Succinyl-CoA synthetase		8[b]
Succinate dehydrogenase	8 $FADH_2$	12
Malate dehydrogenase	8 NADH	20
Total		108

[a]These calculations assume that mitochondrial oxidative phosphorylation produces 1.5 ATP per $FADH_2$ oxidized and 2.5 ATP per NADH oxidized.
[b]GTP produced directly in this step yields ATP in the reaction catalyzed by nucleoside diphosphate kinase (p. 516).

Similar Mechanisms Introduce Carbonyls in Other Metabolic Pathways

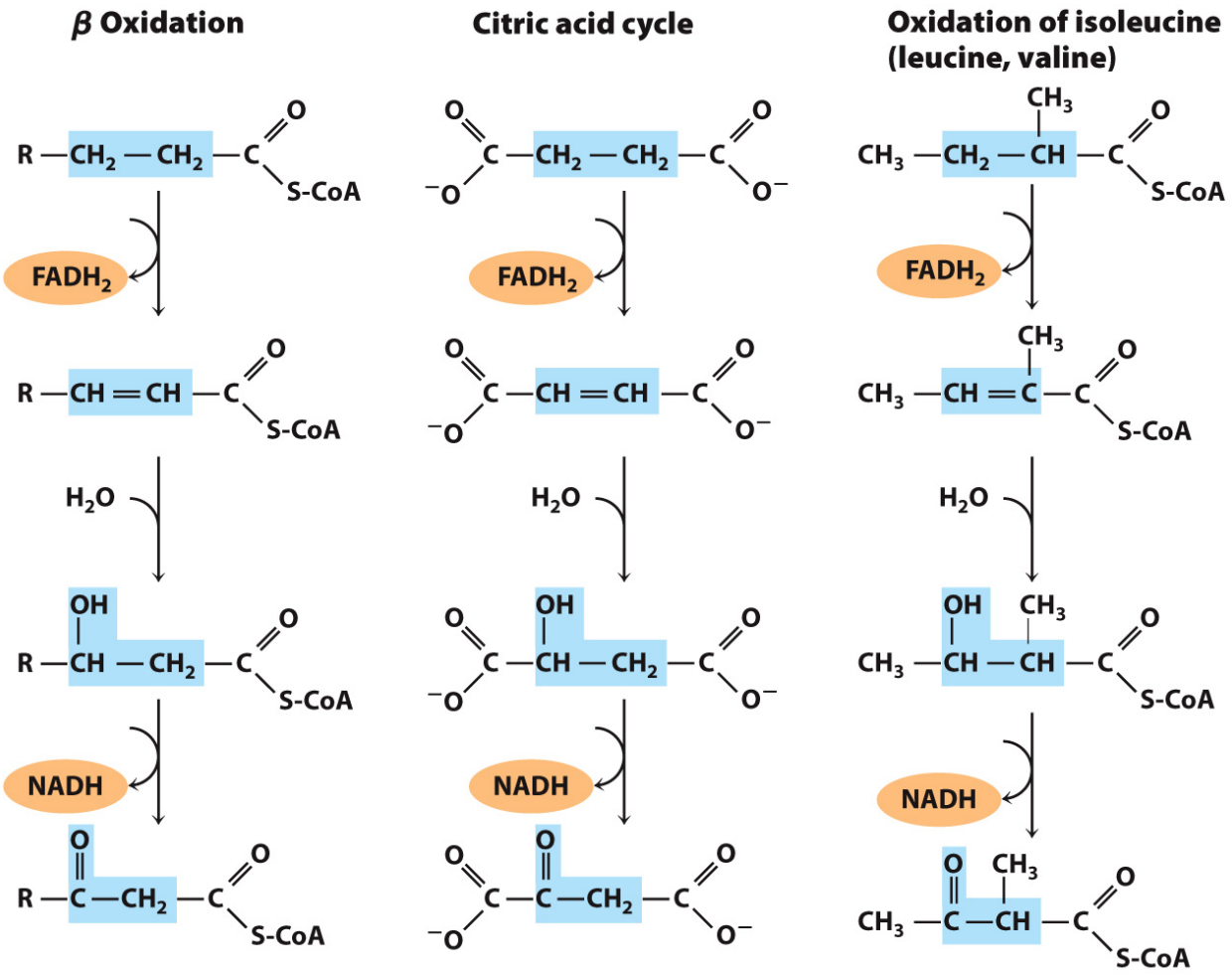


Figure 17-9
Lehninger Principles of Biochemistry, Seventh Edition

Oxidation of Unsaturated Fatty Acids

- Naturally occurring Unsaturated Fatty acids contain **cis** double bonds
  - Are **NOT** a substrate for enoyl-CoA hydratase
- Two additional enzymes are required
  - ***Isomerase:*** converts *cis* double bonds starting at carbon 3 to trans double bonds
  - ***Reductase:*** reduces *cis* double bonds not at carbon 3
- Monounsaturated fatty acids require the isomerase
- Polyunsaturated fatty acids require both enzymes

Oxidation of Monounsaturated Fatty Acids

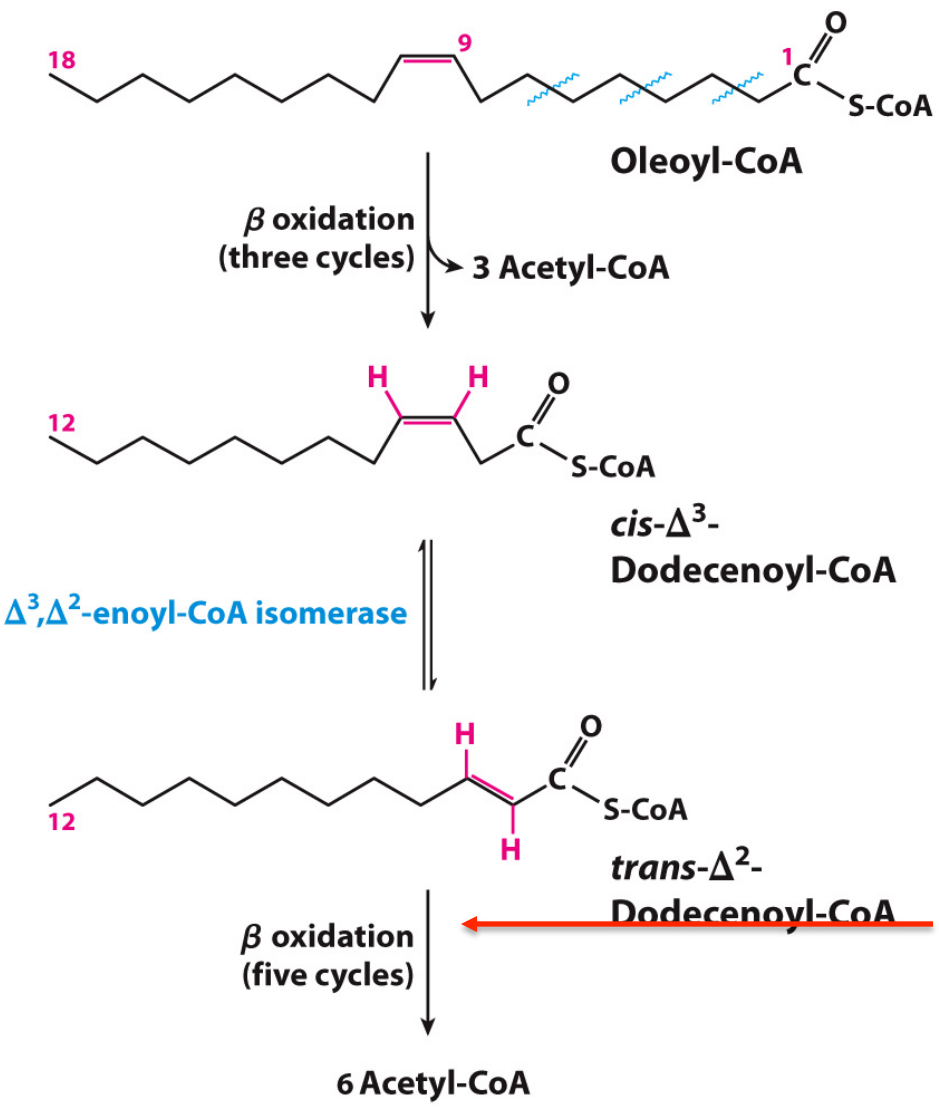


Figure 17-10
Lehninger Principles of Biochemistry, Seventh Edition

Oleate (18:1 Δ^9) converted to oleoyl-CoA and imported into mito via carnitine shuttle

During first of five remaining cycles, acyl-CoA dehydrogenase step is skipped, resulting in 1 fewer $FADH_2$.

Oxidation of Polyunsaturated Fatty Acids

Results in 1 fewer $FADH_2$ after isomerization, but 1 $FADH_2$ is produced during the first step of the next cycle.

NADPH reduces the remaining unsaturated bond, resulting in no further loss of $FADH_2$.

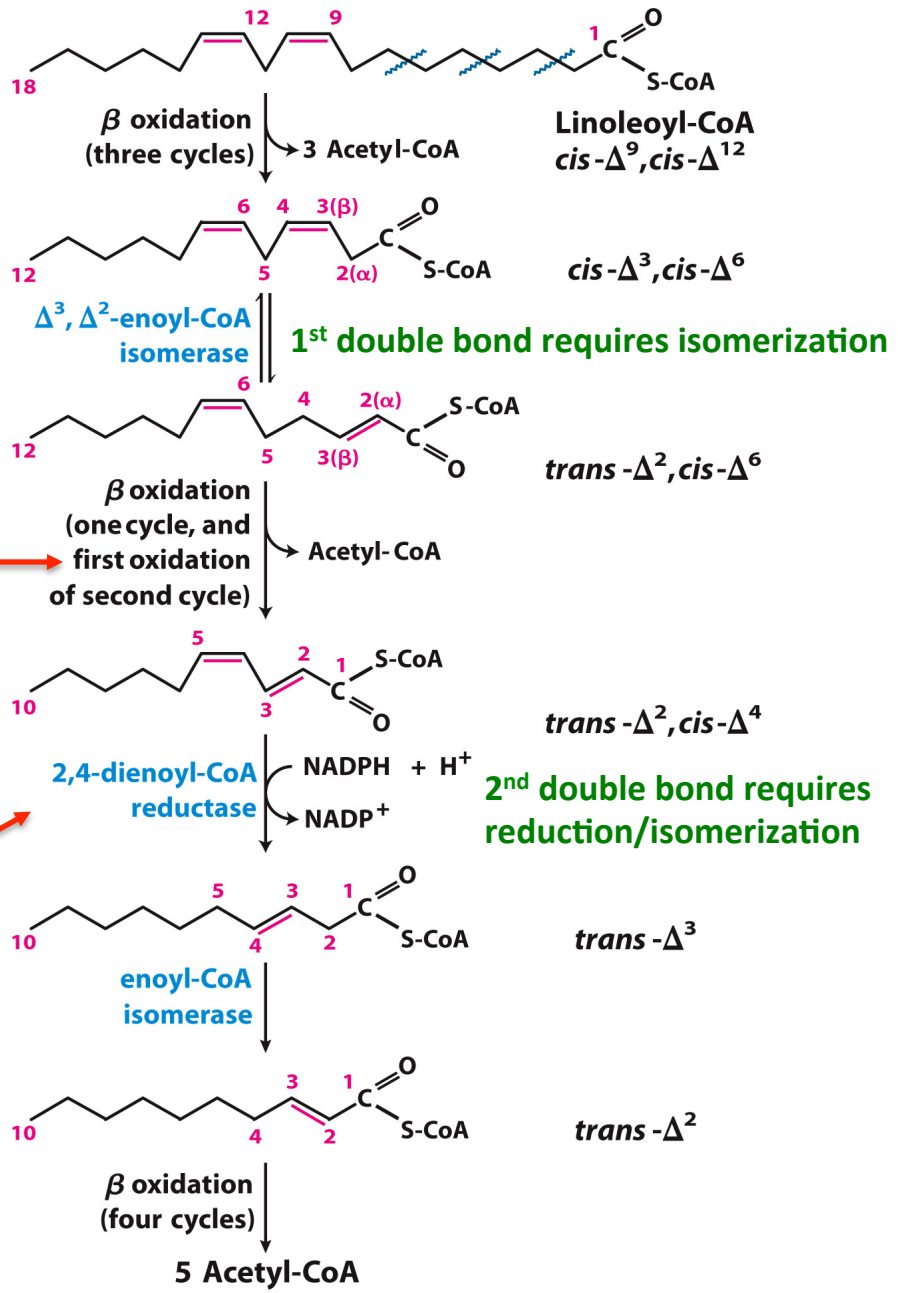


Figure 17-11
Lehninger Principles of Biochemistry, Seventh Edition

Oxidation of Odd-Numbered Fatty Acids

- Most dietary fatty acids are even-numbered.
- Many plants and some marine organisms also synthesize odd-numbered fatty acids.
- Propionyl-CoA (3-carbon compound) forms during final cycle of β oxidation of odd-numbered fatty acids.
- Bacterial metabolism in the rumen of ruminants also produces propionyl-CoA.
- Oxidation is identical to even-numbered long-chain fatty acids, but the last pass through β-oxidation is a fatty acyl-CoA with a 5-C fatty acid that is cleaved to give acetyl-CoA and propionyl-CoA

Oxidation of Propionyl-CoA

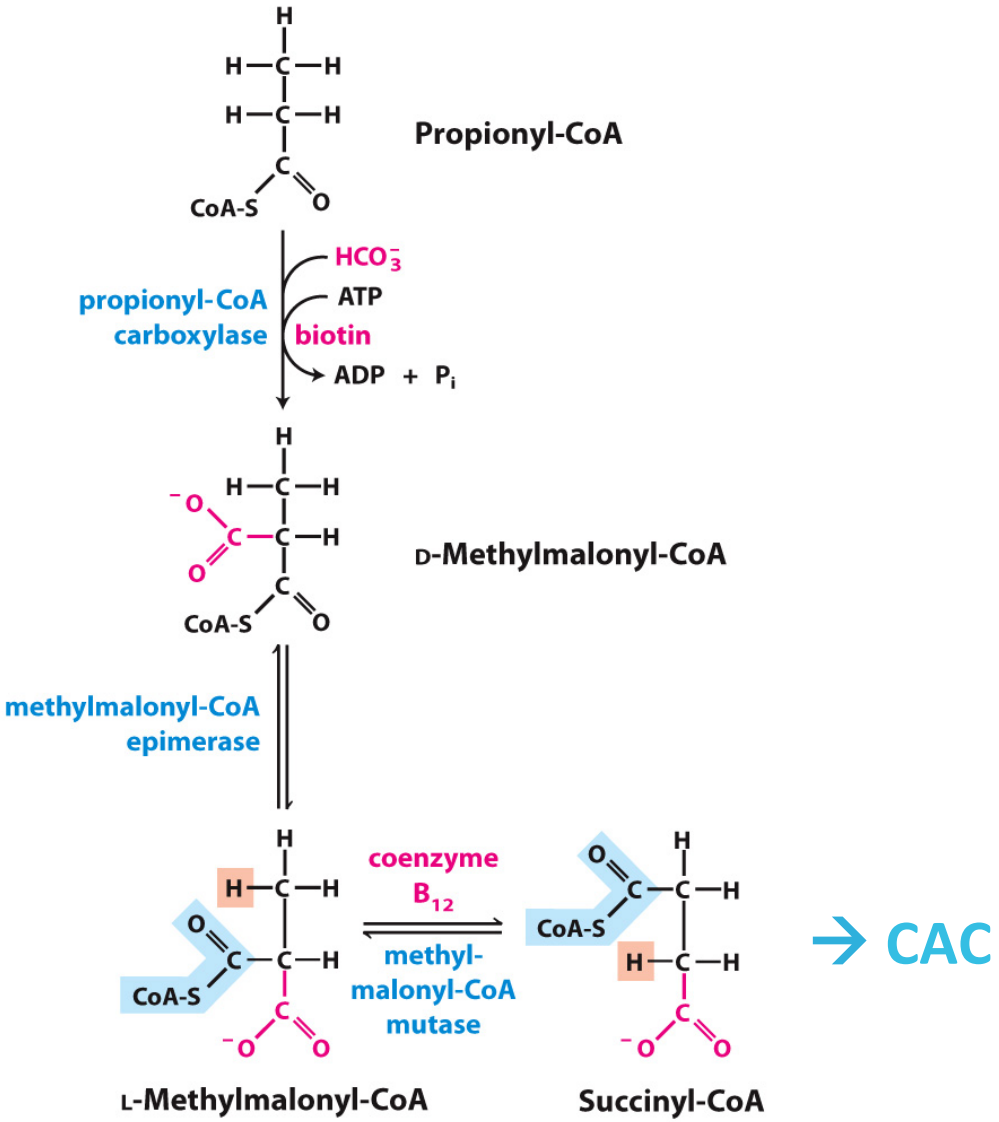


Figure 17-12
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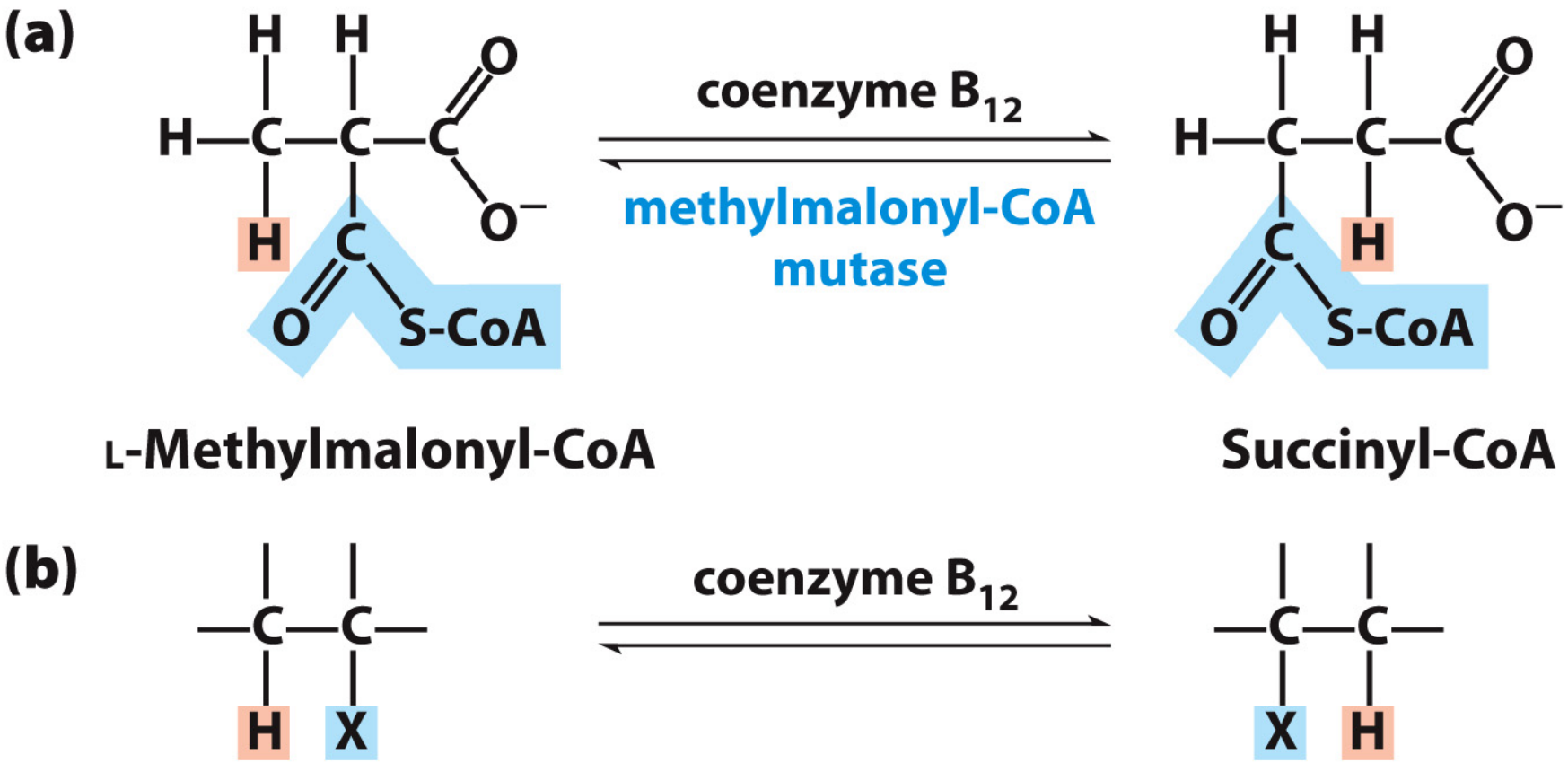
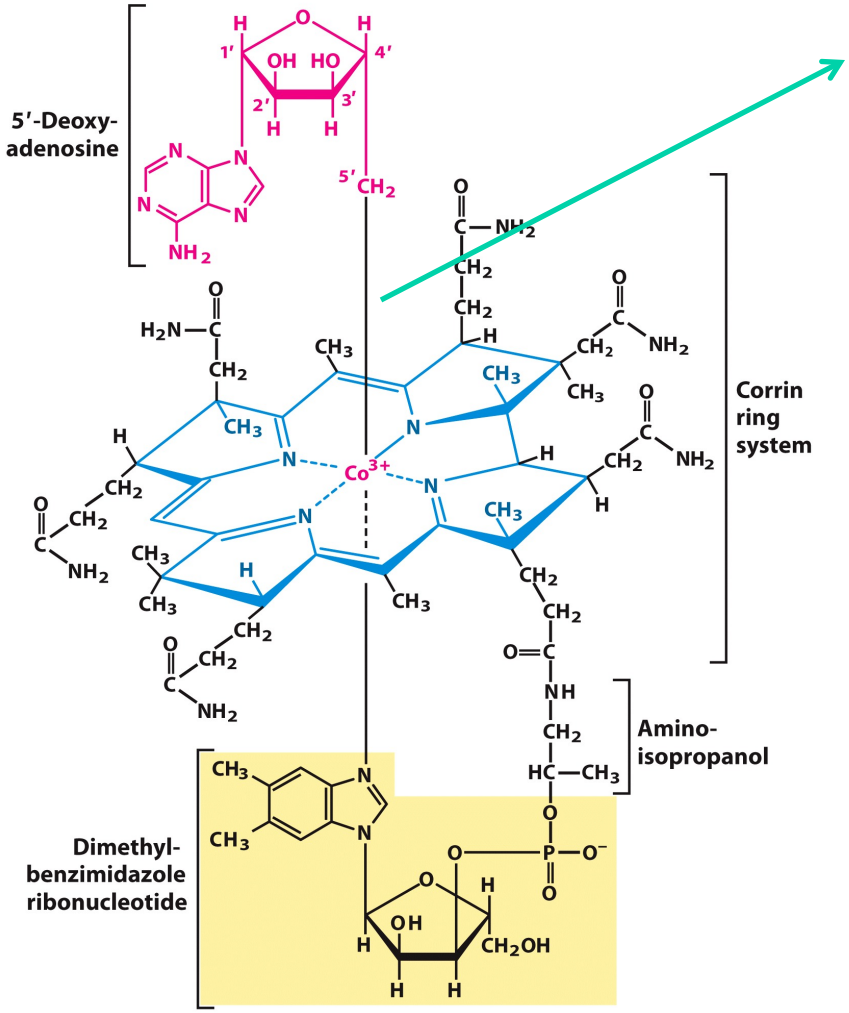
Isomerization in Propionate Oxidation Requires Coenzyme B_{12}



Box 17-2 Figure 1
Lehninger Principles of Biochemistry, Seventh Edition

Complex Cobalt-Containing Compound: Coenzyme B_{12}

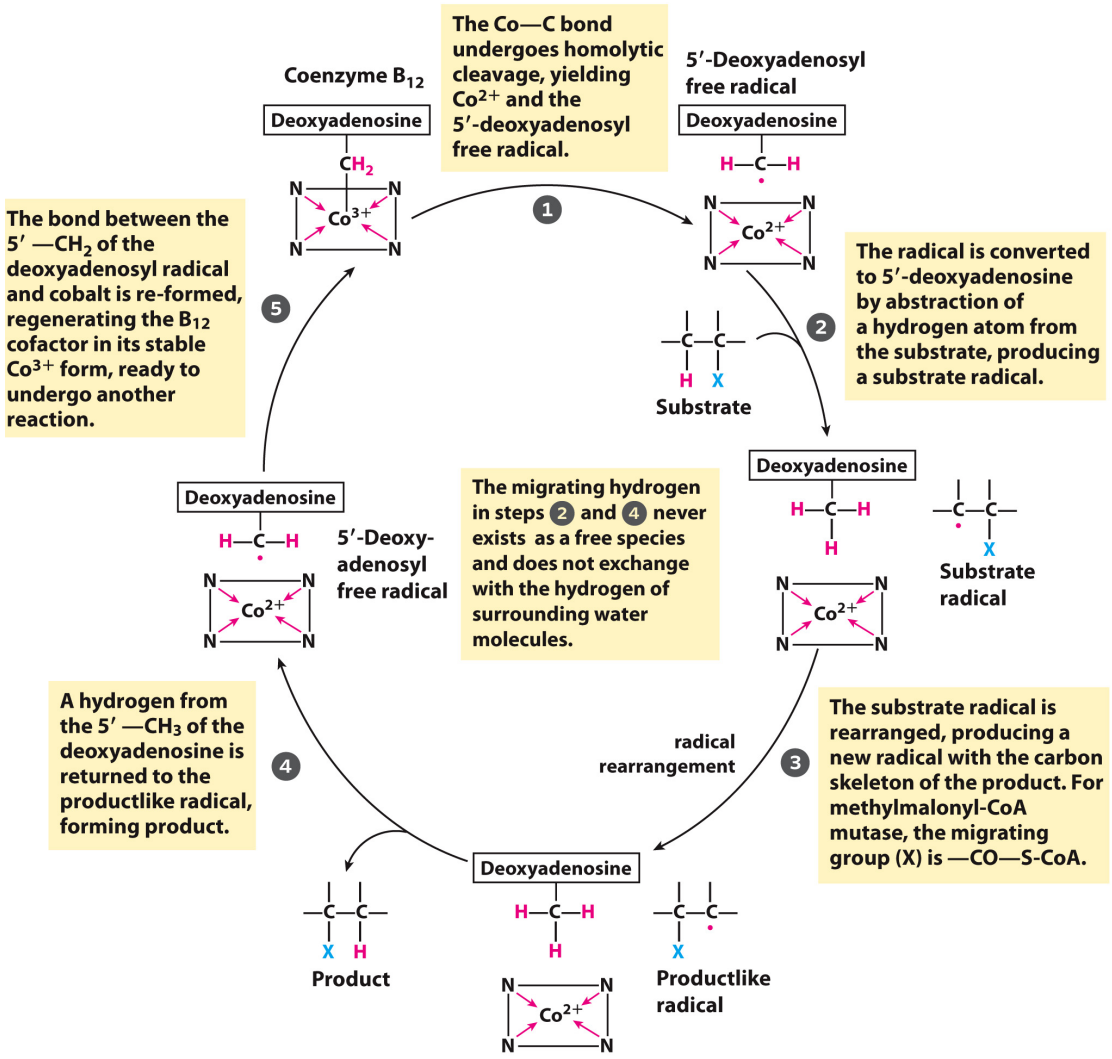


Box 17-2 figure 2
Lehninger Principles of Biochemistry, Sixth Edition

- Very unstable bond
- Breaks to yield $-CH_2^{\bullet}$ and Co^{3+}
- Used to transfer the hydrogen atom to a different C in the molecule (isomerization)
- No mixing of the transferred H atom with the hydrogen of the solvent (H_2O)

- *The formation of this complex cofactor occurs in one of two known reactions that cleaves a triphosphate from ATP*

Coenzyme B_{12} Facillitates Functional Group Exchange

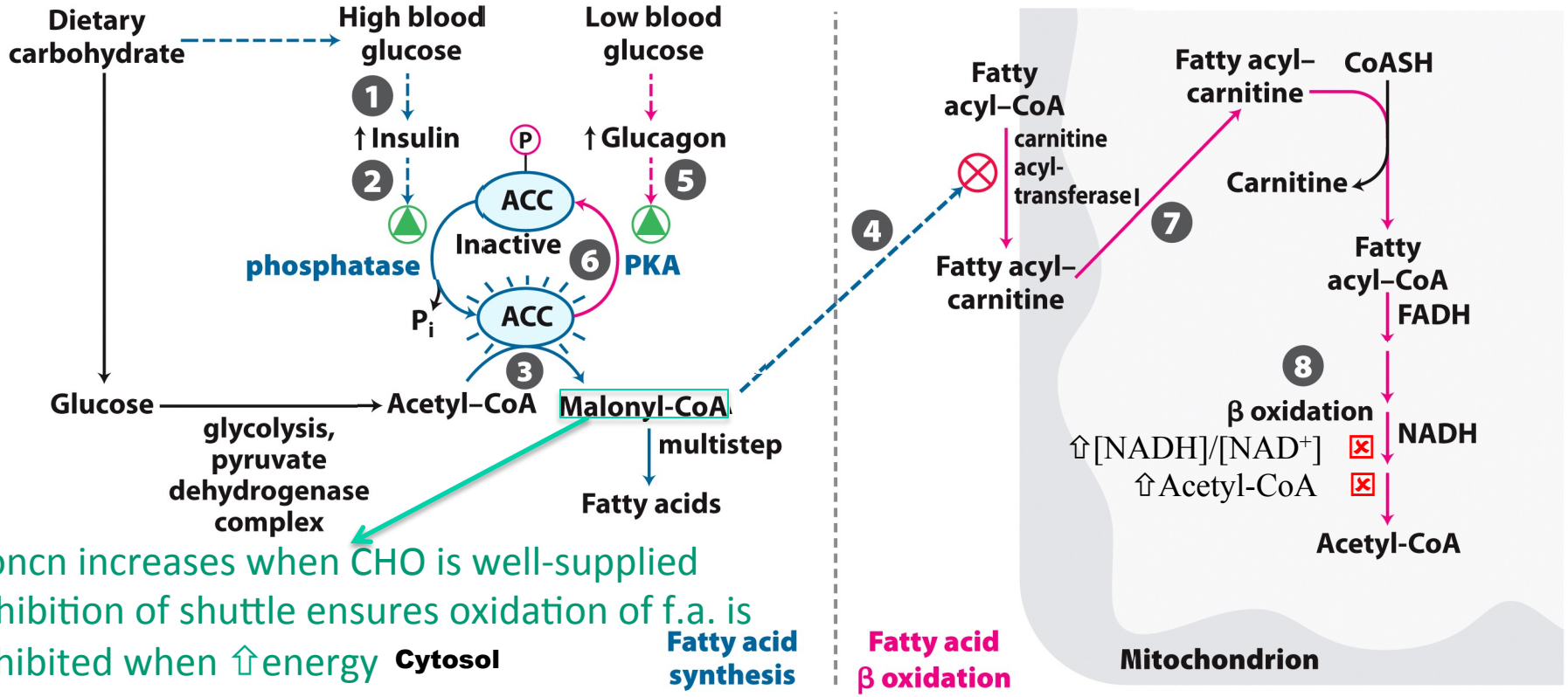


Box 17-2 Figure 4

Lehninger Principles of Biochemistry, Seventh Edition

Regulation of Fatty Acid Synthesis and Breakdown

- Occurs only when need for energy requires it
- *When the diet provides a ready source of carbohydrate as fuel, β oxidation of fatty acids is unnecessary and is therefore downregulated*
- *2 pathways for f.a.CoA in liver:* TAG synthesis in cytosol or f.a. oxidation in mito
- Transfer into mito is rate limiting, once f.a. are in mito they WILL undergo oxidation



Genetic defects in fatty acyl-CoA dehydrogenases

- Inability to oxidize fats for energy has serious effects on health
- More than 20 human genetic defects in f.a. transport and metabolism occur
- **MCAD** (medium chain acyl-CoA dehydrogenase) deficiency is the most common syndrome in European populations
    - Unable to oxidize f.a. of 6 – 12 Cs
    - If diagnosed after birth, the infant can be treated with low fat, high carbohydrate diet

β Oxidation in Plants Occurs Mainly in Peroxisomes

- Mitochondrial acyl-CoA dehydrogenase passes electrons into respiratory chain via electron-transferring flavoprotein.
  - energy captured as ATP
- Peroxisomal/glyoxysomal acyl-CoA dehydrogenase passes electrons directly to molecular oxygen.
  - A peroxisome is also a glyoxysome when enzymes for glyoxylate cycle are present
  - energy released as heat
  - hydrogen peroxide eliminated by catalase

β-Oxidation in Mitochondria vs. Peroxisomes

- Differ in the first step:

  - passes e^-s directly to O_2 forming H_2O_2 which is quickly removed by the action of **catalase**

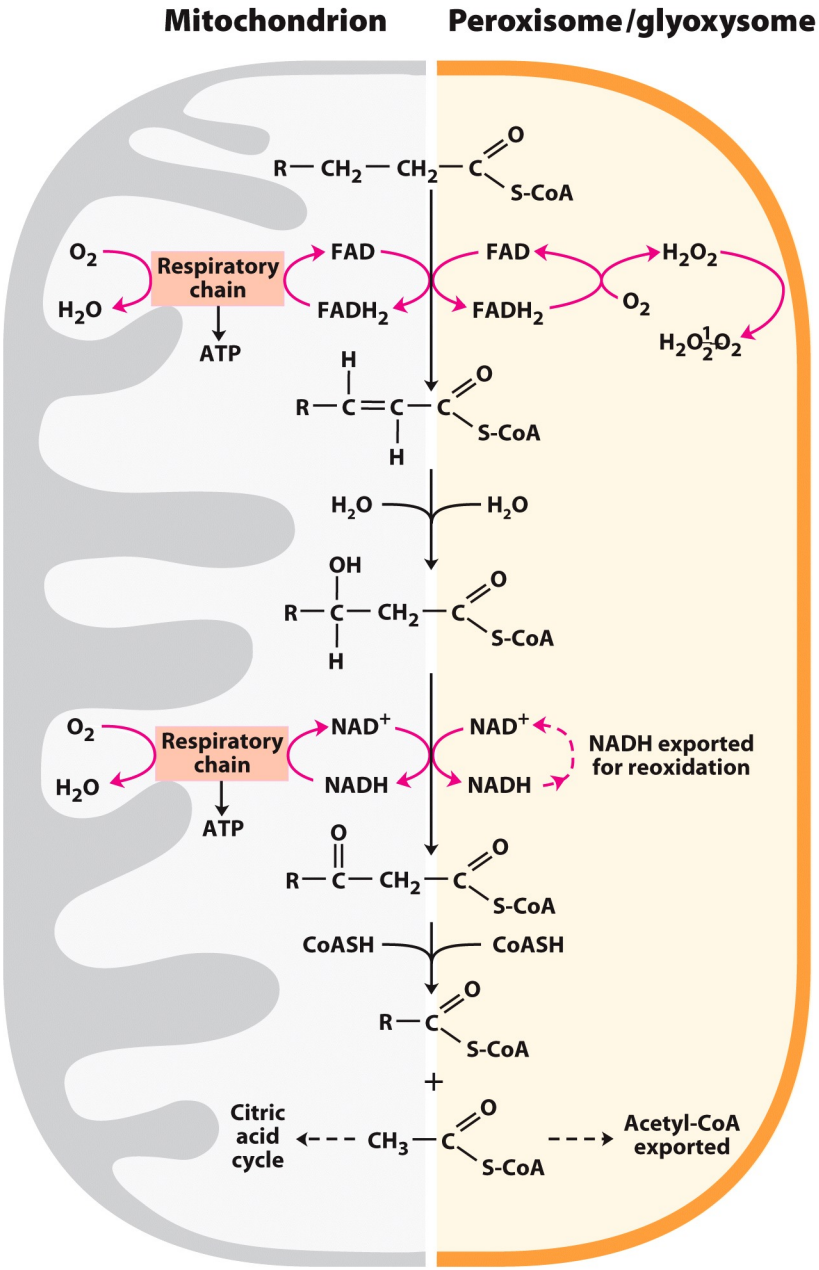
  - energy is lost as heat instead of producing ATP

- Differ in f.a. specificity:

  - more active on very long f.a. and branched f.a. (**α oxidation**)

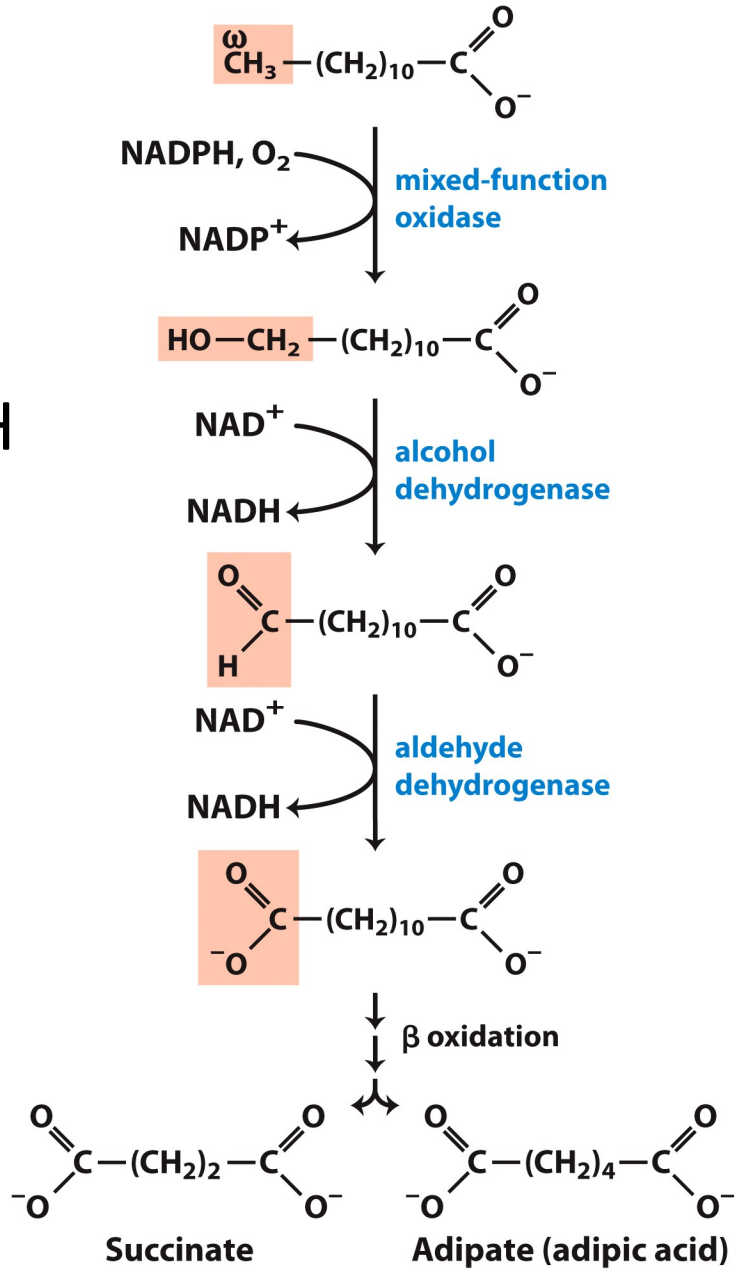
  - process long chain f.a. into shorter ones which are exported to mito to complete oxidation

- **Zellweger syndrome** – inability to make peroxisomes



ω oxidation

- In the ER of liver and kidney
- For f.a. with 10 – 12 Cs
- Addition of OH by a **mixed function oxidase** (cytochrome P450)
- **Alcohol dehydrogenase** oxidizes OH to aldehyde
- **Aldehyde dehydrogenase** oxidizes aldehyde to acid
- CoA can attach to either end and β oxidation resumes

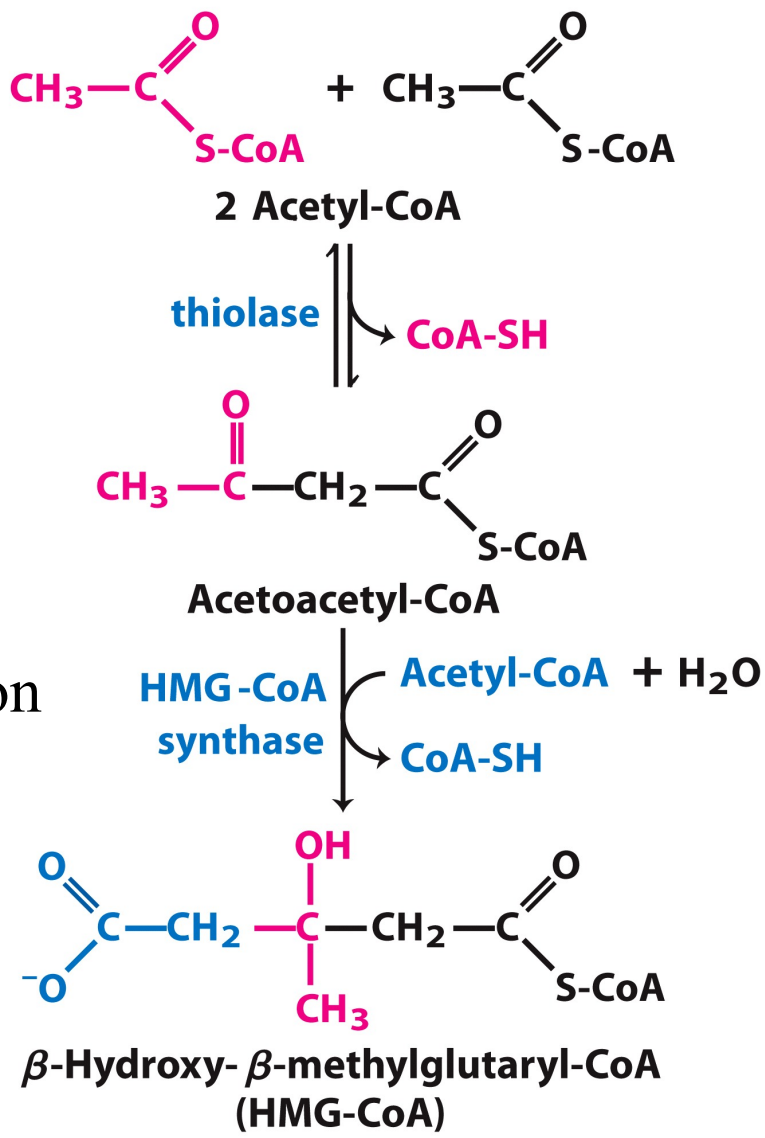


Ketone Bodies

- Entry of acetyl-CoA into citric acid cycle requires oxaloacetate
- When oxaloacetate is depleted, acetyl-CoA is converted into ketone bodies (acetone, acetoacetate and D-β-hydroxybutyrate)
  - Frees Coenzyme A for continued β-oxidation
  - Acetone is exhaled
  - Acetoacetate and β-HB are transported in the blood
- Under starvation conditions, the brain can use ketone bodies for energy
- The first step is reverse of the last step in the β-oxidation: ***thiolase*** reaction joins two acetate units

Release of Free Coenzyme A

The reactions of ketone body formation occur in the ***matrix of liver mitochondria***



Another condensation with acetyl-CoA yields HMG-CoA

This frees 2 CoA molecules from 3 acetyl CoA

Figure 17-19 part 1
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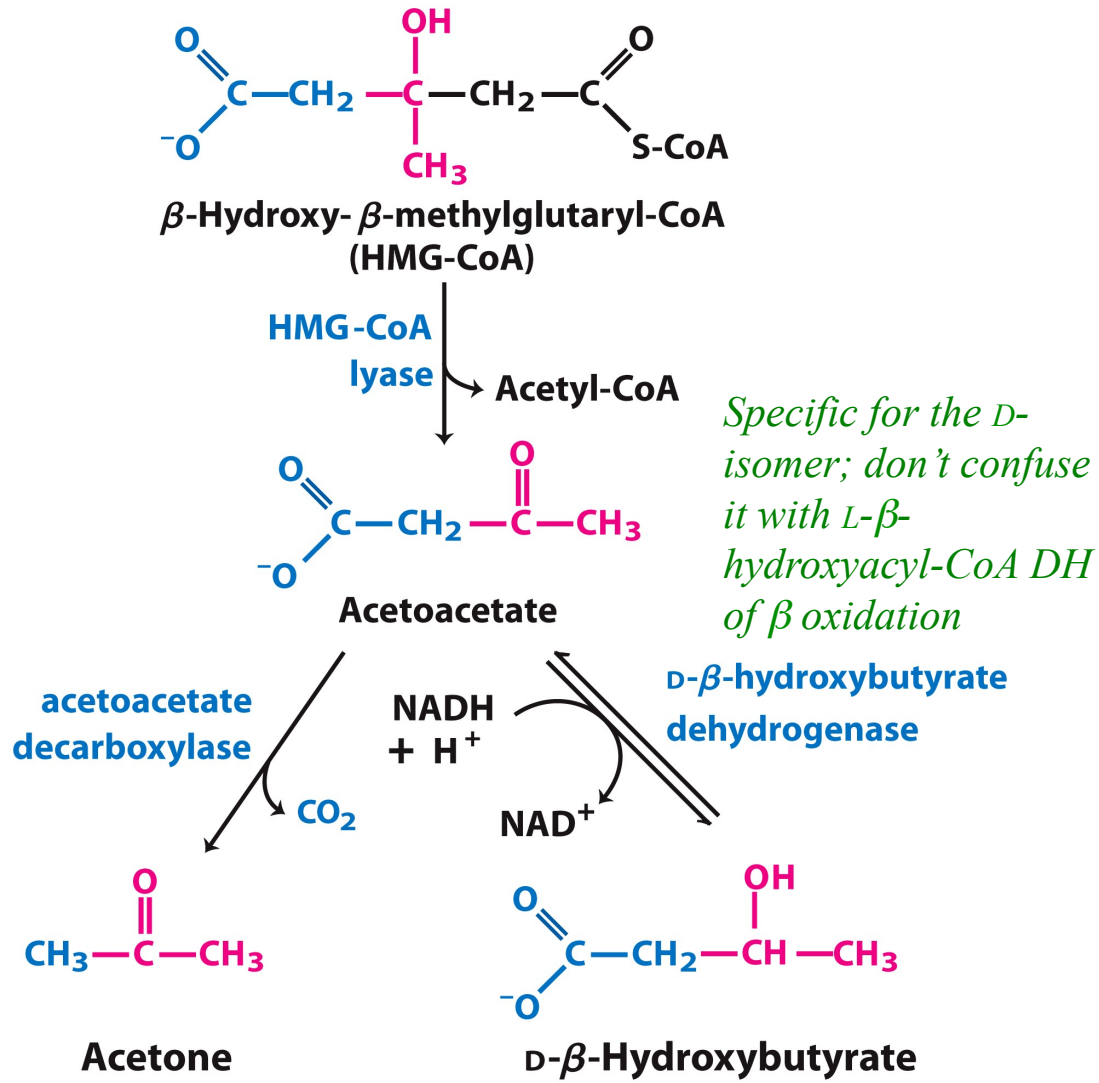
Formation of Ketone Bodies: Degradation of HMG-CoA



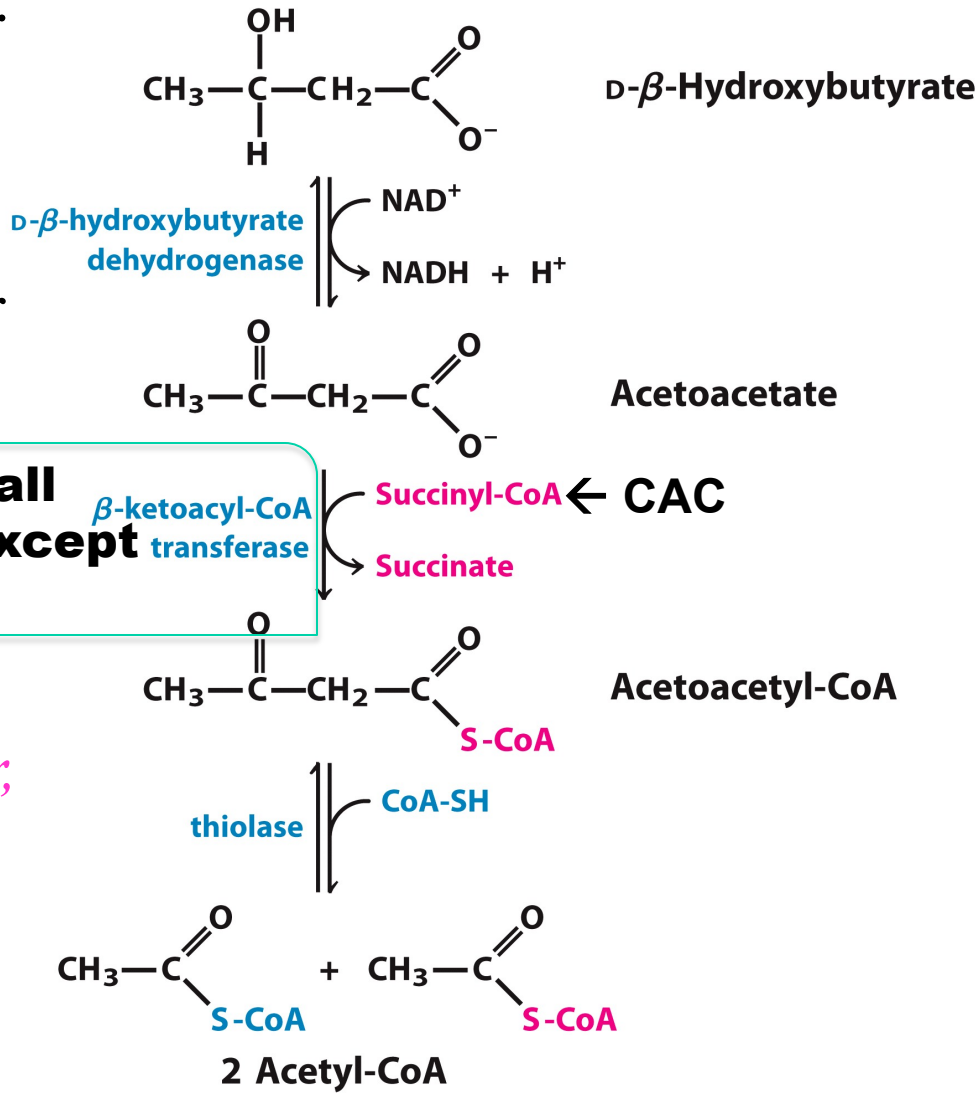
Specific for the D-isomer; don't confuse it with L-β-hydroxyacyl-CoA DH of β oxidation

- In order to traffic to other tissues, CoA must be removed. Acetone, acetoacetate, and β-hydroxybutyrate can then travel through the blood.
- Acetone is removed as a gas and exhaled, but acetoacetate and β-hydroxybutyrate can traffic to the brain for use in energy production.
- Untreated diabetes → [acetoacetate] is high → more acetone produced → exhaled (odor)

Ketone Bodies as fuel

In extrahepatic tissues:

Ketone bodies can be used as fuels in all tissues except the liver



The liver is a producer, not a consumer, of ketone bodies

Figure 17-20
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Liver is the source of ketone bodies

- Production of ketone bodies increases during starvation (and diabetes)
- Ketone bodies are released by liver to bloodstream
- Organs other than liver can use ketone bodies as fuels
- High levels of acetoacetate and β-hydroxybutyrate lower blood pH dangerously (acidosis)
- Acidosis due to ketone bodies - ketoacidosis

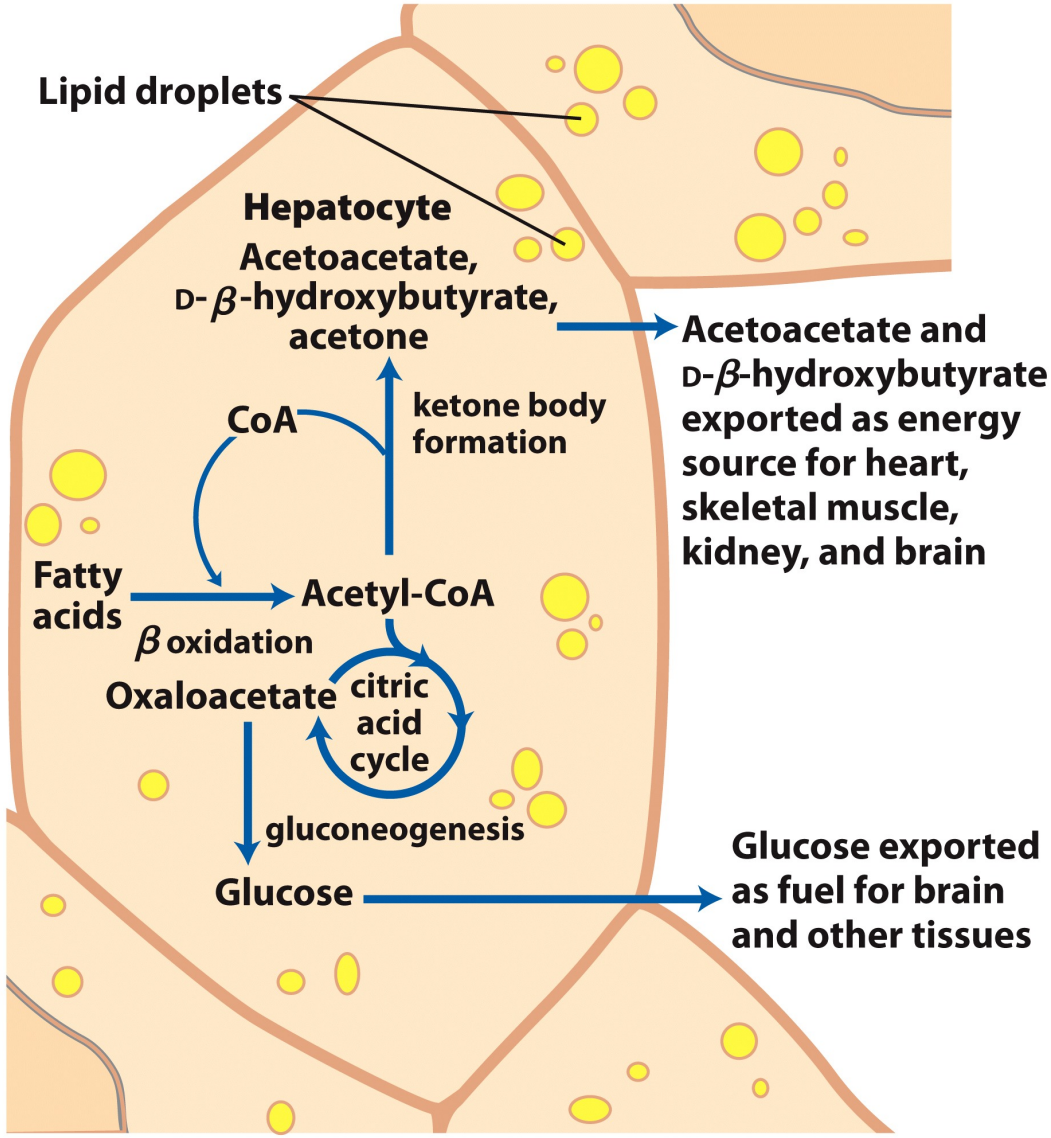

Figure 17-21
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Chapter 17: Summary

In this chapter, we learned that:

- fats are an important energy source in animals
- two-carbon units in fatty acids are oxidized in a four-step β oxidation process into acetyl-CoA
- in the process, a lot of NADH and $FADH_2$ forms; these can yield a lot of ATP in the electron-transport chain
- during peroxisomal oxidation, fats can be oxidized to generate heat
- acetyl-CoA formed in the liver can be either oxidized via the citric acid cycle or converted to ketone bodies that serve as fuels for other tissues