LIPID METABOLISM

Fatty Acid Oxidation

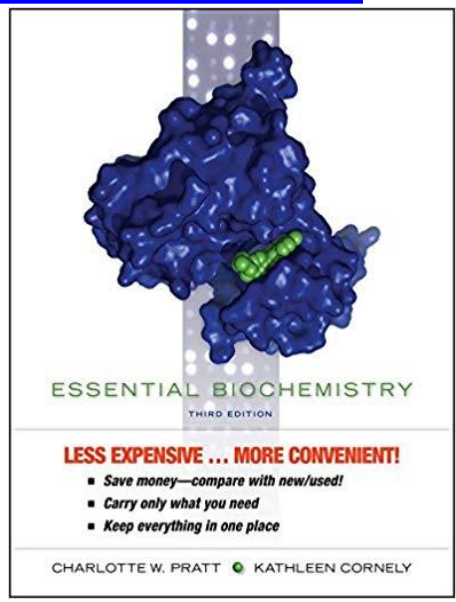
Fatty Acid Synthesis

Synthesis of Other Lipids

Part -2 and Part -3

For

Forth stage – Chemistry dept.



Professor

Dr. ABDULKADIR MOHAMMED NOORI

References :

1-Essential Biochemistry, Charlotte W. Pratt , Kathleen Cornely , , Third edition (2014).

Syllabus

Lipid Metabolism
General Concepts
Fatty Acid Oxidation
Fatty acids are activated before they are degraded
Each round of oxidation has four reactions
Degradation of unsaturated fatty acids requires isomerization and reduction
Oxidation of odd-chain fatty acids yields propionyl-CoA
Catabolism of propionyl-CoA.
Fatty Acid Synthesis
Acetyl-CoA can be converted to ketone bodies
Synthesis of Other Lipids
Triacylglycerols and phospholipids are built from acyl-CoA groups
Synthesis of phosphatidylethanolamine and phosphatidylcholine.
Phosphatidylinositol synthesis.
Cholesterol synthesis begins with acetyl-CoA
Conversion of squalene to cholesterol.
Some statins.
Cholesterol can be used in several ways

Part -2

KEY CONCEPTS:

- Fatty acid synthesis begins with the carboxylation of acetyl-CoA in the cytosol.

- Fatty acid synthase catalyzes seven separate reactions to extend a fatty acid by two carbons.

- Elongases and desaturases modify newly synthesized fatty acids.

- Various metabolites contribute to the regulation of fatty acid synthesis.

- Ketogenesis converts acetyl-CoA to small soluble ketone bodies.

Fatty Acid Synthesis

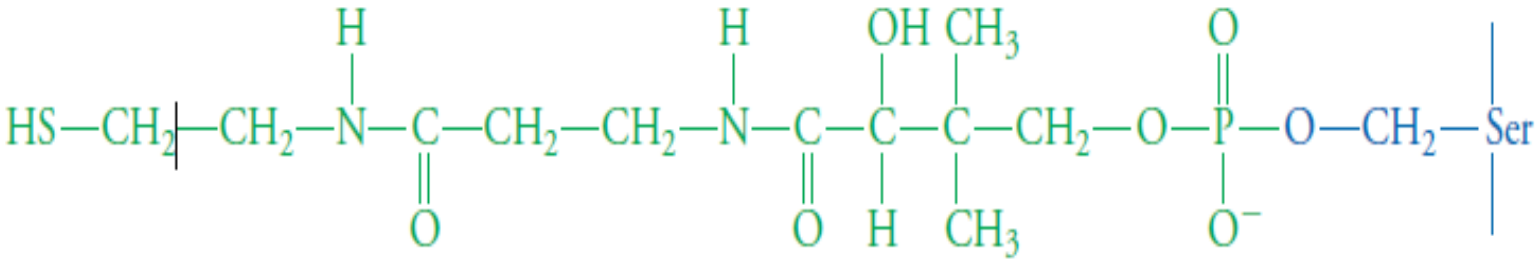
KEY CONCEPTS

- **Fatty acid synthesis begins with the carboxylation of acetyl-CoA in the cytosol.**
- **Fatty acid synthase catalyzes seven separate reactions to extend a fatty acid by two carbons.**
- **Elongases and desaturases modify newly synthesized fatty acids.**
- **Various metabolites contribute to the regulation of fatty acid synthesis.**
- **Ketogenesis converts acetyl-CoA to small soluble ketone bodies.**

At first glance, fatty acid synthesis appears to be the exact reverse of fatty acid oxidation. For example, fatty acyl groups are built and degraded two carbons at a time, and several of the reaction intermediates in the two pathways are similar or identical. However, ***the pathways for fatty acid synthesis and degradation must differ for thermodynamic reasons****, as we saw for glycolysis and gluconeogenesis.*

In mammalian cells, the opposing metabolic pathways of fatty acid synthesis and degradation are entirely separate. β Oxidation **takes place in the mitochondrial matrix**, and **synthesis occurs in the cytosol**. Furthermore, **the two pathways use different cofactors**. In β oxidation, **the acyl group is attached to coenzyme A**, but **a growing fatty acyl chain is bound by an acyl-carrier protein (ACP**; **Fig. 15).**

β Oxidation funnels electrons to ubiquinone and NAD1, but **in fatty acid synthesis, NADPH is the source of reducing power**. Finally, **β oxidation requires two ATP equivalents (two phosphoanhydride bonds) to "activate" the acyl group**, but **the biosynthetic pathway consumes one ATP for every two carbons incorporated into a fatty acid**. In this section, we focus on the reactions of fatty acid synthesis, comparing and contrasting them to β oxidation.



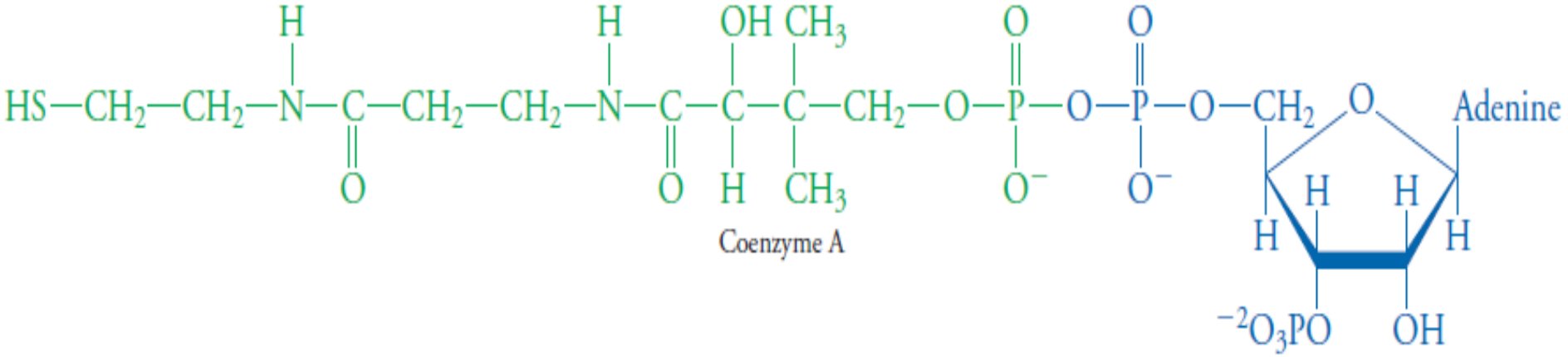


Figure 15. Acyl-carrier protein and coenzyme A. Both acyl-carrier protein (ACP) and coenzyme A (CoA) include a pantothenate (vitamin B5) derivative ending with a sulfhydryl group that forms a thioester with an acyl or acetyl group. In CoA, the pantothenate derivative is esterifi ed to an adenine nucleotide; in ACP, the group is esterifi ed to a Ser OH group of a polypeptide (in mammals, ACP is part of a larger multifunctional protein, fatty acid synthase).

Acetyl-CoA carboxylase catalyzes the first step of fatty acid synthesis

The starting material for fatty acid synthesis is acetyl-CoA, which may be generated in the mitochondria by the action of the pyruvate dehydrogenases complex. But just as cytosolic acyl-CoA cannot directly enter the mitochondria to be oxidized, mitochondrial acetyl-CoA cannot exit to the cytosol for biosynthetic reactions. ***The transport of acetyl groups to the cytosol involves citrate, which has a transport protein*** .Citrate synthase (the enzyme that catalyzes the first step of the citric acid cycle) combines acetyl-CoA with oxaloacetate to produce citrate, which then leaves the mitochondria. ATP-citrate lyase "undoes" the citrate synthase reaction to produce acetyl-CoA and oxaloacetate in the cytosol **(Fig. 15). Note** that ATP is consumed in the ATP-citrate lyase reaction to drive the formation of a thioester bond.

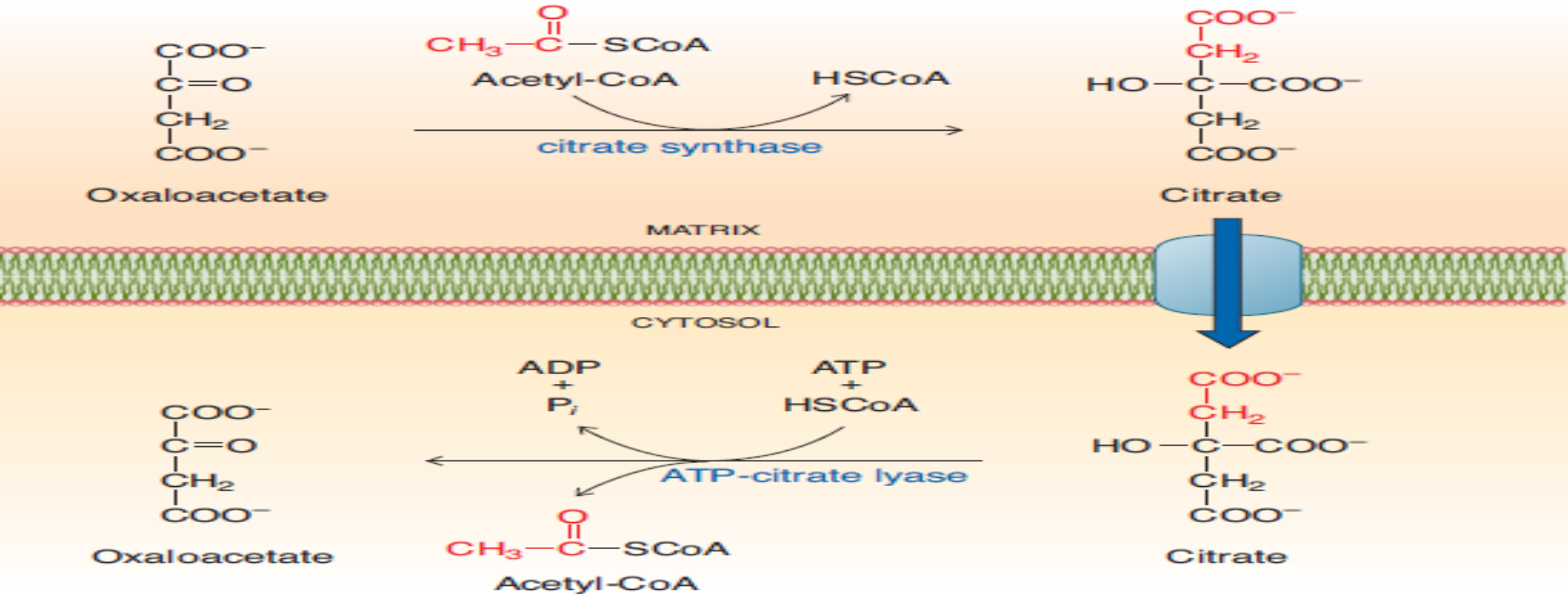
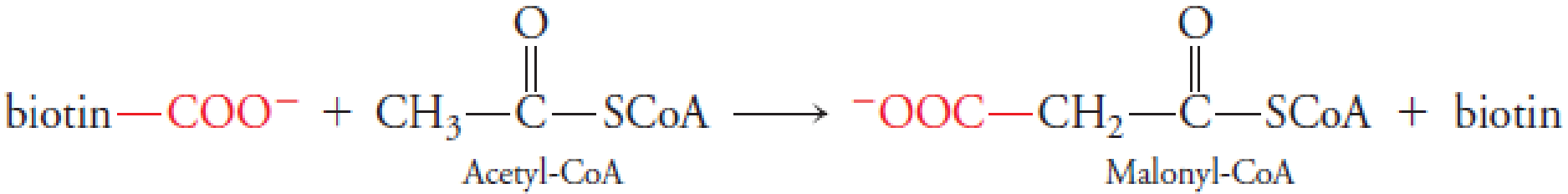


Figure 15. The citrate transport system. The citrate transport protein, along with mitochondrial citrate synthase and cytoplasmic ATP-citrate lyase, provides a route for transporting acetyl units from the mitochondrial matrix to the cytosol.

The first step of fatty acid synthesis is the carboxylation of acetyl-CoA, an ATP-dependent reaction carried out by acetyl-CoA carboxylase .The acetyl-CoA carboxylase mechanism is similar to that of propionyl-CoA carboxylase (step 1 in Fig. 12) and pyruvate carboxylase . First, CO2 (as bicarbonate, HCO3) Is "activated" by its attachment to a biotin prosthetic group in a reaction that converts ATP to ADP + Pi *:*

Next, the carboxybiotin prosthetic group transfers the carboxylate group to acetyl-CoA to form the three-carbon malonyl-CoA and regenerate the enzyme:



Malonyl-CoA is the donor of the two-carbon acetyl units that are used to build a fatty acid. Note that fatty acid synthesis requires a C3 intermediate, whereas β oxidation involves only two-carbon acetyl units.

Fatty acid synthase catalyzes seven reactions

The protein that carries out the main reactions of fatty acid synthesis in animals is a 540-kD multifunctional enzyme made of two identical polypeptides (Fig. 16).

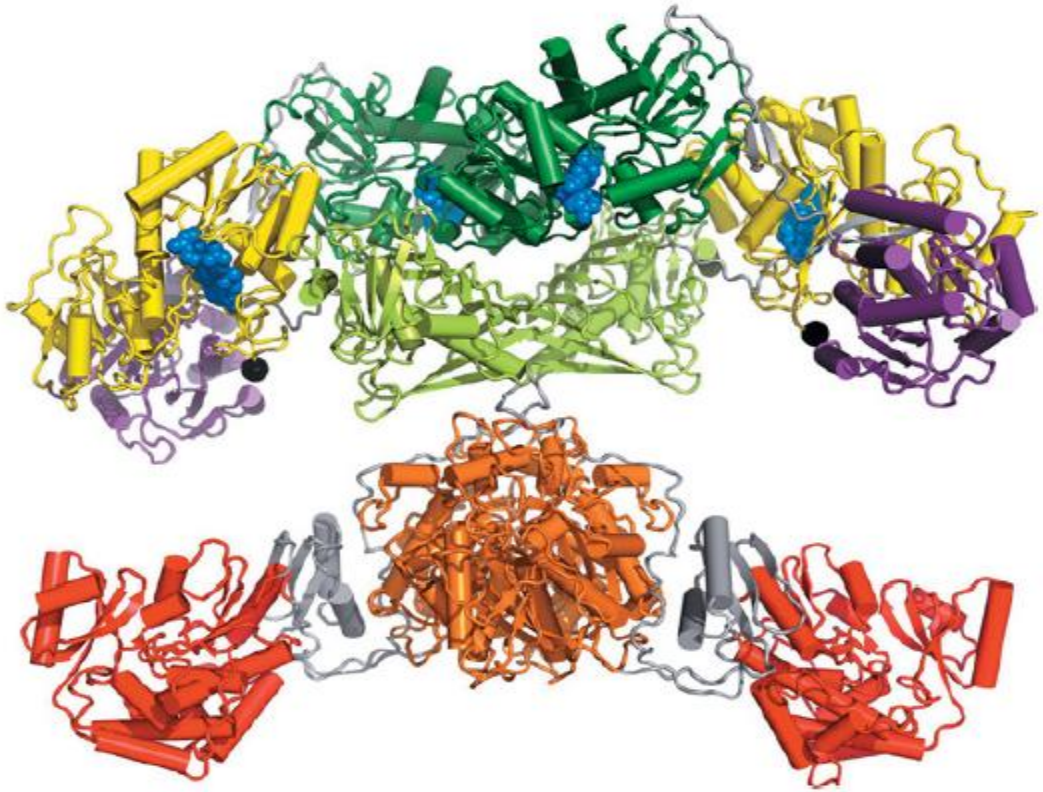
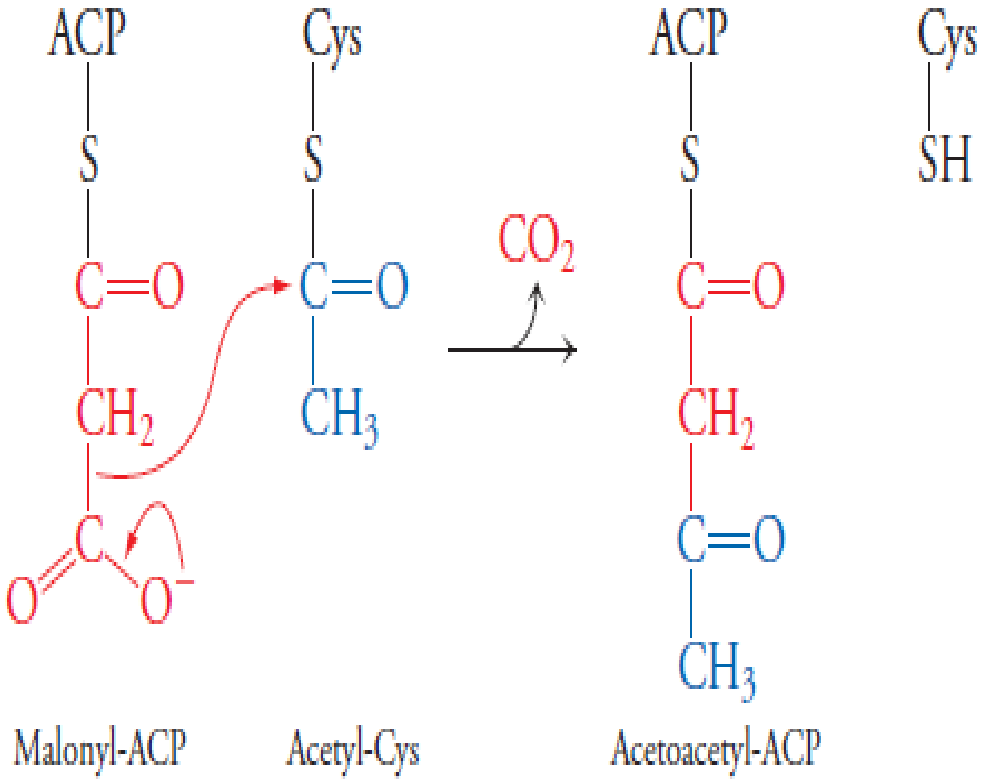


Figure 16. Mammalian fatty acid synthase. Three-dimensional structure of the fatty acid synthase dimer

The Figure 17. show the fatty acid synthesis. The steps show how fatty acid synthase carries out the synthesis of the C16 fatty acid palmitate starting from acetyl-CoA..

Reactions 1 and 2 are transacylation reactions that serve to prime or load the enzyme with the reactants for the condensation reaction (step 3). In the condensation reaction, decarboxylation of the malonyl group allows C2 to attack the acetyl thioester group to form acetoacetyl-ACP:

This chemistry explains the necessity for carboxylating an acetyl group to a malonyl group: C2 of an acetyl group would not be sufficiently reactive.



1.The two-carbon acetyl group that will be lengthened is transferred from CoA to a Cys side chain of fatty acid synthase.

2. The malonyl group that will donate an acetyl group to the growing fatty acyl chain is transferred from CoA to the ACP domain of the enzyme.

3. In this condensation reaction, the malonyl group is decarboxylated and the resulting two-carbon fragment attacks the acetyl group to form a four-carbon product.

4. The 3-ketoacyl product of step 3 is reduced.

5. A dehydration introduces a 2,3 double bond.

6. A second NADPH-dependent reduction completes the conversion of the condensation product to an acyl group.

7. The acyl group is transferred from ACP to the enzyme Cys group, and another malonyl group is loaded onto the free ACP, ready for another condensation reaction.

8. Steps 3 – 6 are repeated six times to build a C16 fatty acid.

9. A thioesterase hydrolyzes the thioester bond to release palmitate.

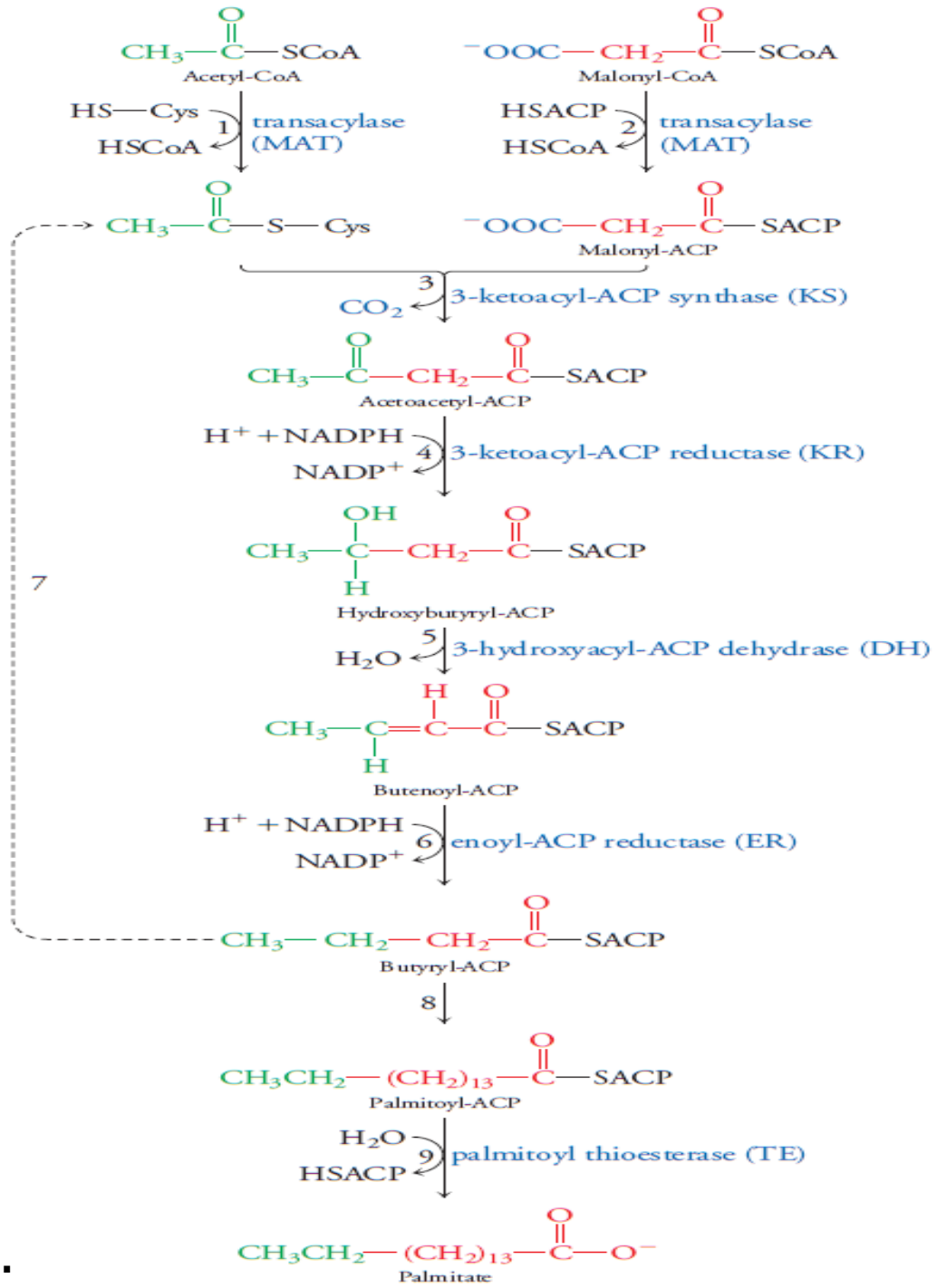
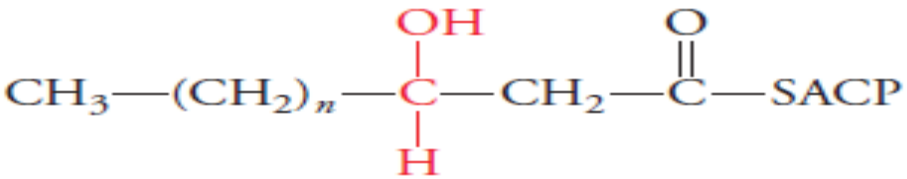
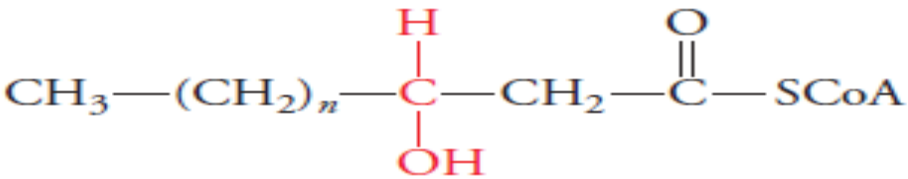


Figure 17. Fatty acid synthesis.

The hydroxyacyl product of Reaction 4 is chemically similar to the hydroxyacyl product of step 2 of b oxidation, but the intermediates of the two pathways have opposite confi gurations



3-Hydroxyacyl-ACP intermediate of fatty acid synthesis (D configuration)



3-Hydroxyacyl-ACP intermediate of β oxidation (L configuration)

The NADPH required for the two reduction steps of fatty acid synthesis (steps 4 and 6) is supplied mostly by the pentose phosphate pathway (see Section 13-4). The synthesis of one molecule of palmitate (the usual product of fatty acid synthase) requires the production of 7 malonyl-CoA, at a cost of 7 ATP. The seven rounds of fatty acid synthesis consume 14 NADPH, which is equivalent to 14x2.5, or 35, ATP, bringing the total cost to 42 ATP. Still, this energy investment is much less than the free energy yield of oxidizing palmitate. In mammals, fatty acid synthase produces mostly the 16-carbon saturated fatty acid palmitate.

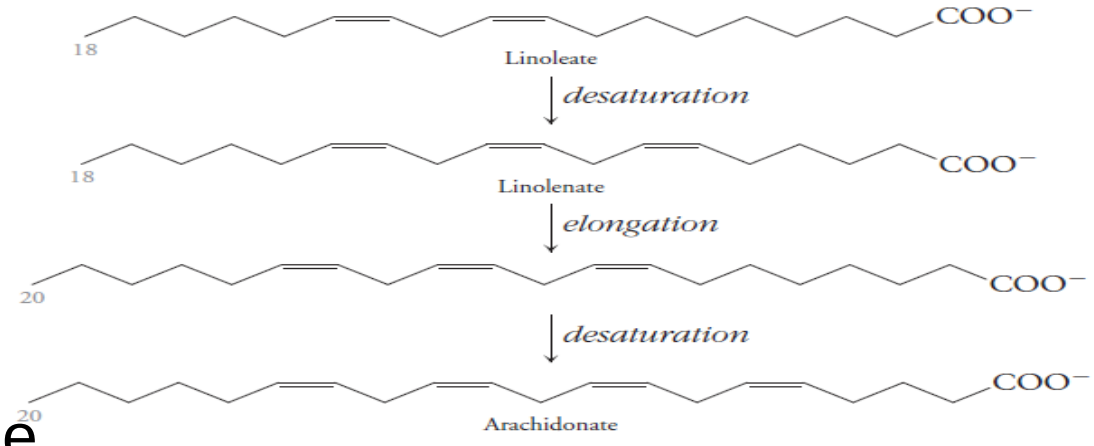
Other enzymes elongate and desaturate newly synthesized fatty acids

Some sphingolipids contain C22 and C24 fatty acyl groups. ***These and other longchain fatty acids are generated by enzymes known as elongases****, which extend the C16* fatty acid produced by fatty acid synthase. Elongation can occur in either the endoplasmic reticulum or mitochondria. The endoplasmic reticulum reactions use malonyl-CoA as the acetyl-group donor and are chemically similar to those of fatty acid synthase. In the mitochondria, fatty acids are elongated by reactions that more closely resemble the reversal of b oxidation but use NADPH.

Desaturases introduce double bonds into saturated fatty acids. These reactions take place in the endoplasmic reticulum, catalyzed by membrane-bound enzymes. The electrons removed in the dehydrogenation of the fatty acid are eventually transferred to molecular oxygen to produce H2O. The most common unsaturated fatty acids in animals are palmitoleate (a C16 molecule) and oleate (a C18 fatty acid; see Section 8-1), both with one *cis double bond at the 9,10 position. Trans fatty acids are relatively* rare in plants and animals, but they are abundant in some prepared foods.

Elongation can follow desaturation (and vice versa), so animals can synthesize a variety of fatty acids with different chain lengths and degrees of unsaturation. However, mammals cannot introduce double bonds at positions beyond C9 andtherefore cannot synthesize fatty acids such as linoleate and linolenate. These molecules are precursors of the C20 fatty acid arachidonate and other lipids with specialized biological activities **(Fig. 18).** ***Mammals must therefore obtain linoleate and linolenate from their diet*** *. These* ***essential fatty acids are abundant in fish and plant oils***. Unsaturated fatty acids with a double bond three carbons from the end, omega-3 fatty acids, may have health benefits (Box 8-A). A deficiency of essential fatty acids resulting from a very-low-fat diet may elicit symptoms such as slow growth and poor wound healing.

Figure 18. Synthesis of arachidonate. Linoleate (or linolenate) is elongated and desaturated to produce arachidonate, a C20 fatty acid with four double bonds



BIOCHEMISTRY NOTE :

Fats, Diet, and Heart Disease

Years of study have established a link between elevated LDL levels and atherosclerosis and indicate that certain diets contribute to the formation of fatty deposits that clog arteries and cause cardiovascular disease. Considerable research has been devoted to showing how dietary lipids influence serum lipid levels. For example, early studies showed that diets rich in saturated fats increased blood cholesterol (that is, LDL), whereas diets in which unsaturated vegetable oils replaced the saturated fats had the opposite effect. These and other findings led to recommendations that individuals at risk for atherosclerosis avoid butter, which is rich in saturated fat as well as cholesterol, and instead use margarine, which is prepared from cholesterol-free vegetable oils.

السمن النباتي أو المهدرج أو المارغرين Margarine وهي مادة غذائية بديلة للسمن الحيواني يتم تصنيعها من الزيوت النباتية أو من الشحوم الحيوانية بعمليةالهدرجة. لا يعد المارغرين غذاء صحيا وقد تسبب أمراض القلب. يطلق البعض اسم المارغرين على الزبدة نفسها.

The production of semisolid margarine from liquid plant oils (triacylglycerols containing unsaturated fatty acids) often includes a hydrogenation step to chemically saturate the carbons of the fatty acyl chains. In this process, some of the original *cis double* bonds are converted to *trans double bonds. In clinical studies, trans fatty acids are comparable* to saturated fatty acids in their tendency to increase LDL levels and decrease HDL levels. Dietary guidelines now warn against the excessive intake of *trans fatty acids* in the form of hydrogenated vegetable oils (small amounts of *trans fatty acids also occur* naturally in some animal fats). This would mean avoiding processed foods whose list of ingredients includes “partially hydrogenated vegetable oil.”

Fatty acid synthesis can be activated and inhibited

Under conditions of abundant metabolic fuel, the products of carbohydrate and amino acid catabolism are directed toward fatty acid synthesis, and the resulting fatty acids are stored as triacylglycerols. The rate of fatty acid synthesis is controlled by acetyl-CoA carboxylase, which catalyzes the first step of the pathway. This enzyme is inhibited by a pathway product (palmitoyl-CoA) and is allosterically activated by citrate (which signals abundant acetyl-CoA). Some of the mechanisms that regulate fatty acid metabolism are summarized in **Figure 19.**

There are both natural and synthetic inhibitors of fatty acid synthase, such as the widely used antibacterial agent triclosan and drugs that target pathogens more specifically. Fatty acid synthase inhibitors are of great scientific c and popular interest, given that excess body weight (due to fat) is a major health problem, affecting about two-thirds of the population of the United States. And because many tumors sustain high levels of fatty acid synthesis, fatty acid synthase inhibitors may also be useful for treating cancer.

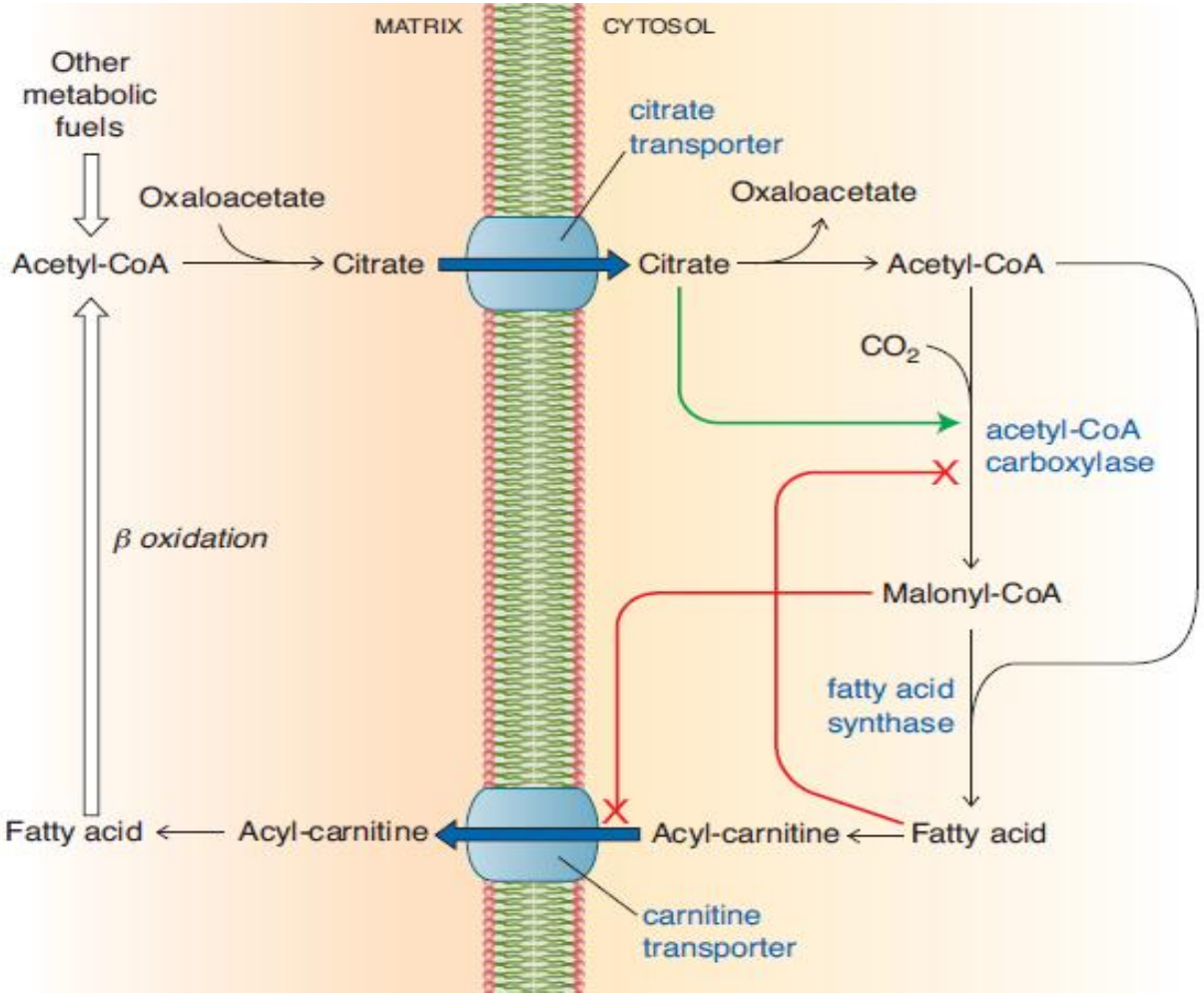


Figure 19.Some control mechanisms in fatty acid metabolism. Red symbols indicate inhibition, and the green symbol indicates activation.

Acetyl-CoA can be converted to ketone bodies

During a prolonged fast, when glucose is unavailable from the diet and liver glycogen has been depleted, many tissues depend on fatty acids released from stored triacylglycerols to meet their energy needs. However, the brain does not burn fatty acids because they pass poorly through the blood–brain barrier. Gluconeogenesis helps supply the brain's energy needs, but the liver also produces **ketone bodies to supplement** gluconeogenesis. The ketone bodies—acetoacetate and 3-hydroxybutyrate (also called b-hydroxybutyrate)—are synthesized from acetyl-CoA in liver mitochondria by a process called **ketogenesis (Figure 20).**

Because they are small and water-soluble, ketone bodies are transported in the bloodstream without specialized lipoproteins, and they can easily pass into the central nervous system. During periods of high ketogenic activity, **such as in diabetes**, ketone bodies may be produced faster than they are consumed. Some of the excess acetoacetate breaks down to acetone, which gives the breath a characteristic **sweet smell**. **Ketone bodies are also acids**, with a **p*K of about 3.5***. Their overproduction can lead to a drop in the pH of the blood, a condition called **ketoacidosis**. Mild symptoms may also develop in some individuals following a high-protein, low carbohydrate diet, when ketogenesis increases to offset the shortage of dietary carbohydrates.

Ketone bodies produced by the liver are used by other tissues as metabolic fuels after being converted back to acetyl-CoA**. The liver itself cannot catabolize** ketone bodies because **it lacks one of the required enzymes, 3-ketoacyl-CoA transferase.**

1. Two molecules of acetyl-CoA condense to form acetoacetyl-CoA. The reaction is catalyzed by a thiolase, which breaks a thioester bond.

2. The four-carbon acetoacetyl group condenses with a third molecule of acetyl-CoA to form the six-carbon 3-hydroxymethylglutaryl-CoA (HMG-CoA).

3. HMG-CoA is then degraded to the ketone body acetoacetate and acetyl-CoA.

4. Acetoacetate undergoes reduction to produce another ketone body, 3-hydroxybutyrate.

5. Some acetoacetate may also undergo nonenzymatic decarboxylation to acetone and CO2.

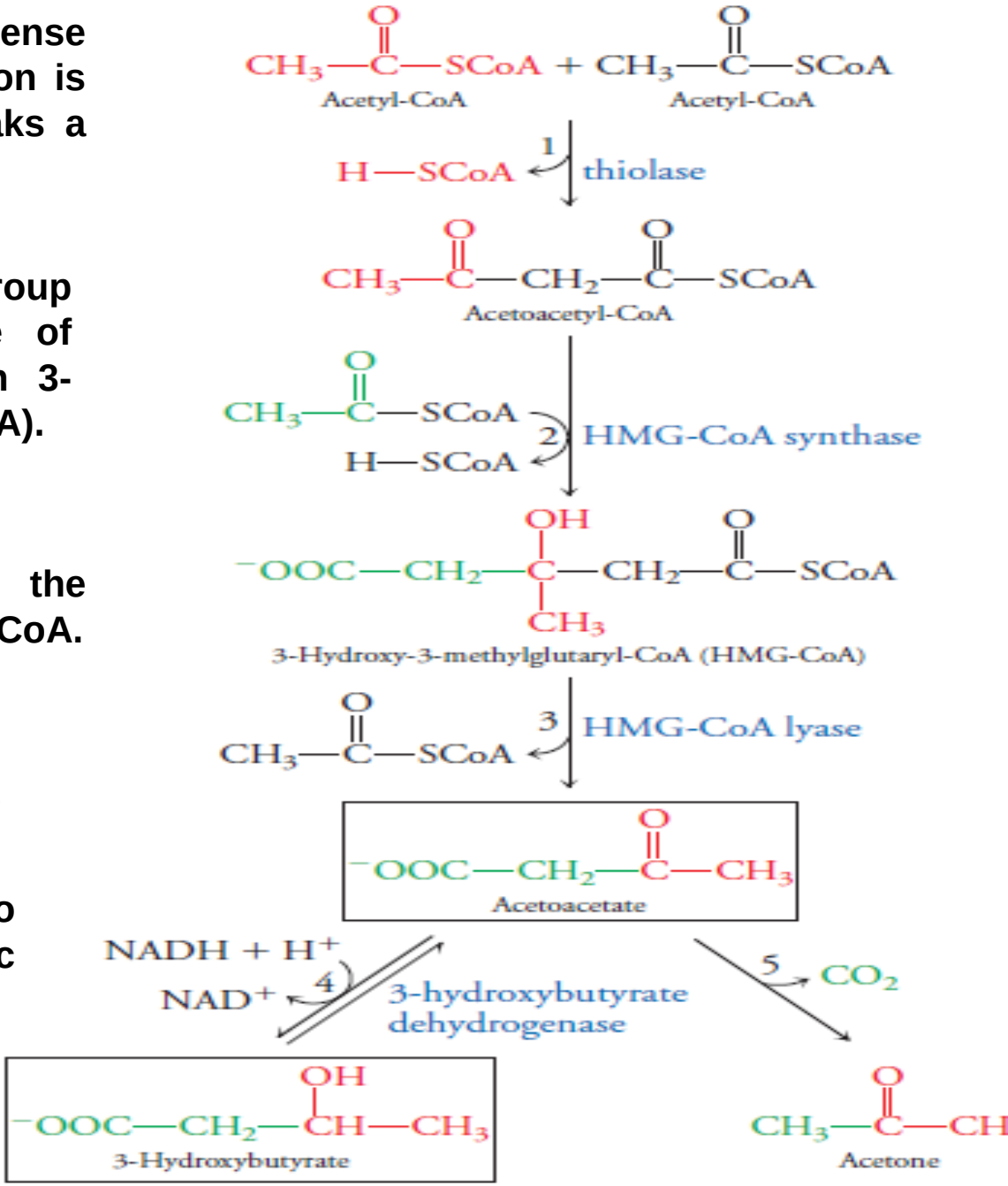


Figure 20. Ketogenesis. The ketone bodies are boxed.

SUMMARY (Fatty Acid Synthesis)

• Fatty acids are synthesized by a pathway that resembles the reverse of β oxidation. In the first step of fatty acid synthesis, acetyl-CoA carboxylase catalyzes an ATP-dependent reaction that converts acetyl-CoA to malonyl-CoA, which becomes the donor of two carbon groups.

• Mammalian fatty acid synthase is a multifunctional enzyme in which the growing fatty acyl chain is attached to acyl-carrier protein rather than CoA. Elongases and desaturases may modify newly synthesized fatty acids.

• The liver can convert acetyl-CoA to ketone bodies to be used as metabolic fuels in other tissues.

Part -3

KEY CONCEPTS:

- Acyl groups are transferred from CoA to a glycerol backbone to generate triacylglycerols and phospholipids.

- Cholesterol is synthesized from acetyl-CoA.

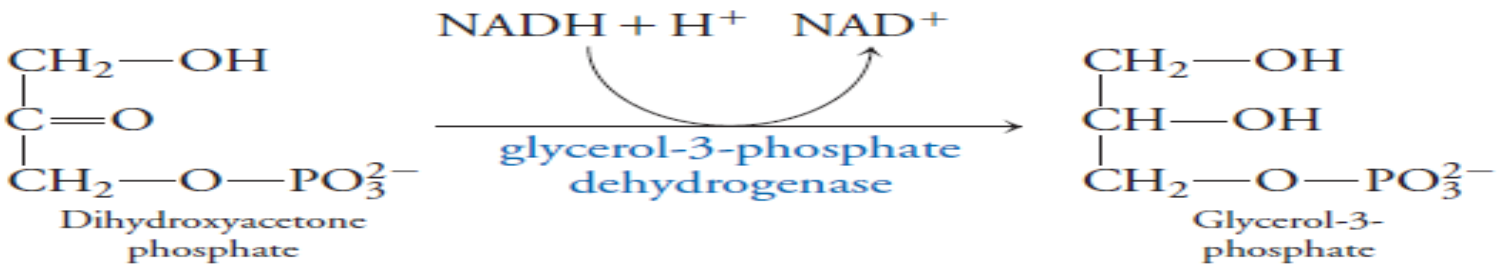
- Cholesterol can be used both inside and outside the cell.

Synthesis of Other Lipids

Lipid metabolism encompasses many chemical reactions involving fatty acids, which are structural components of other lipids such as triacylglycerols, glycerophospholipids, and sphingolipids. This section covers the biosynthesis of some of the major types of lipids, including the synthesis of cholesterolfrom acetyl-CoA.

Triacylglycerols and phospholipids are built from acyl-CoA groups

Triacylglycerols are synthesized by attaching fatty acyl groups to a glycerol backbone derived from phosphorylated glycerol or from glycolytic intermediates, for example, dihydroxyacetone phosphate:



The fatty acyl groups are first activated to CoA thioesters in an ATP-dependent manner:

$$\text{fatty acid} + \text{CoA} + \text{ATP} \rightleftharpoons \text{acyl-CoA} + \text{AMP} + \text{PP}_i$$

This reaction is catalyzed by acyl-CoA synthetase, the same enzyme that activates fatty acids for oxidation. Triacylglycerols are assembled as shown in **Figure 21.** The acyl transferases that add fatty acids to the glycerol backbone are not highly specific with respect to chain length or degree of unsaturation of the fatty acyl group, but human triacylglycerols usually contain palmitate at C1 and unsaturated oleate at C2.

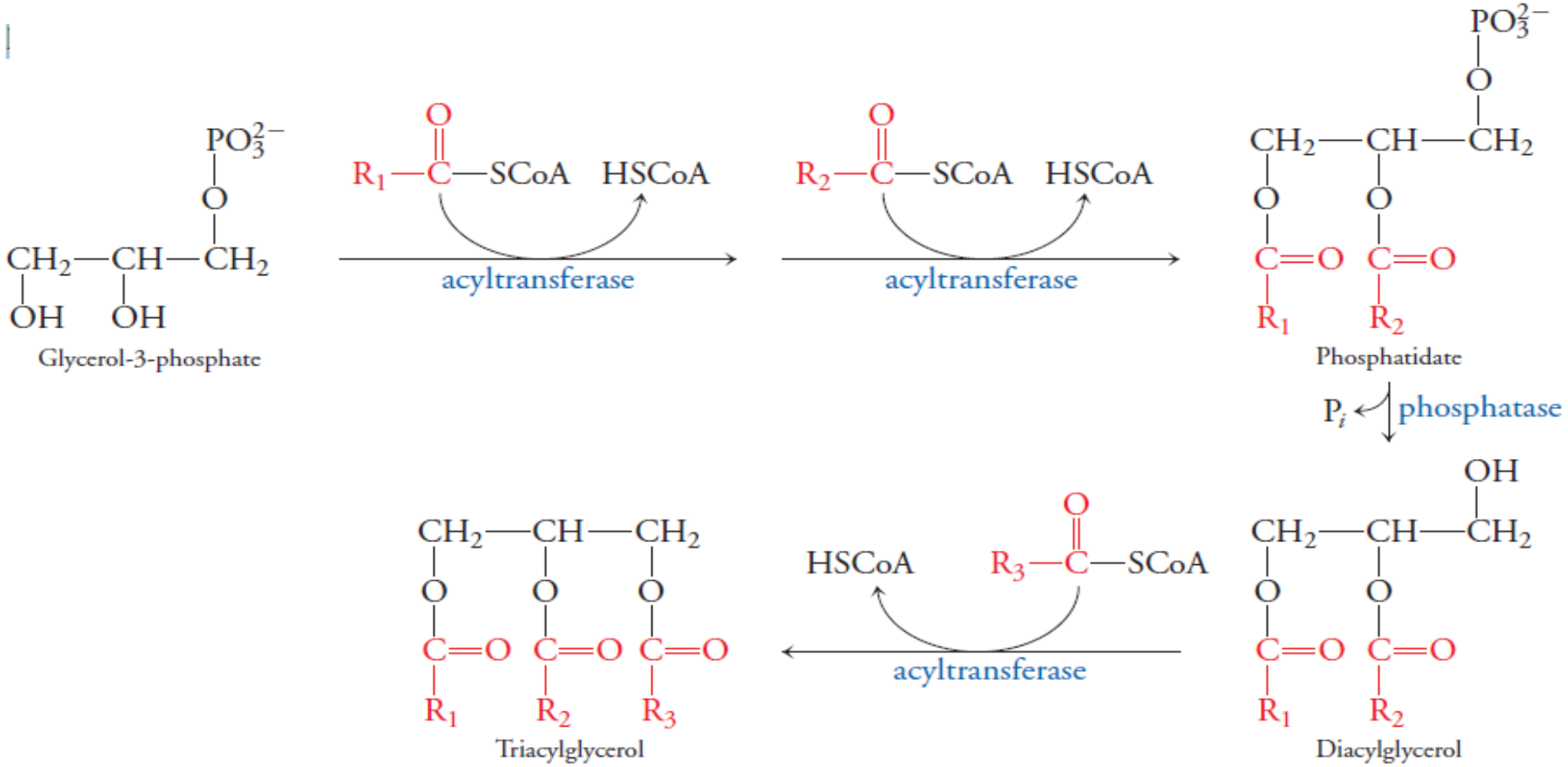


Figure 21. Triacylglycerol synthesis. An acyltransferase appends a fatty acyl group to C1 of glycerol-3-phosphate. A second acyltransferase reaction adds an acyl group to C2, yielding phosphatidate. A phosphatase removes P*i* *to produce* diacylglycerol. The addition of a third acyl group yields a triacylglycerol.

Synthesis of phosphatidylethanolamine and phosphatidylcholine

1. ATP phosphorylates the OH group of ethanolamine or choline (X is H in ethanolamine, and CH3 in choline).

2. The phosphoryl group then attacks CTP to form CDP–ethanolamine or CDP–choline. The PPi product is subsequently hydrolyzed.

3. The C3 OH group of diacylglycerol displaces CMP to generate the glycerophospholipid.

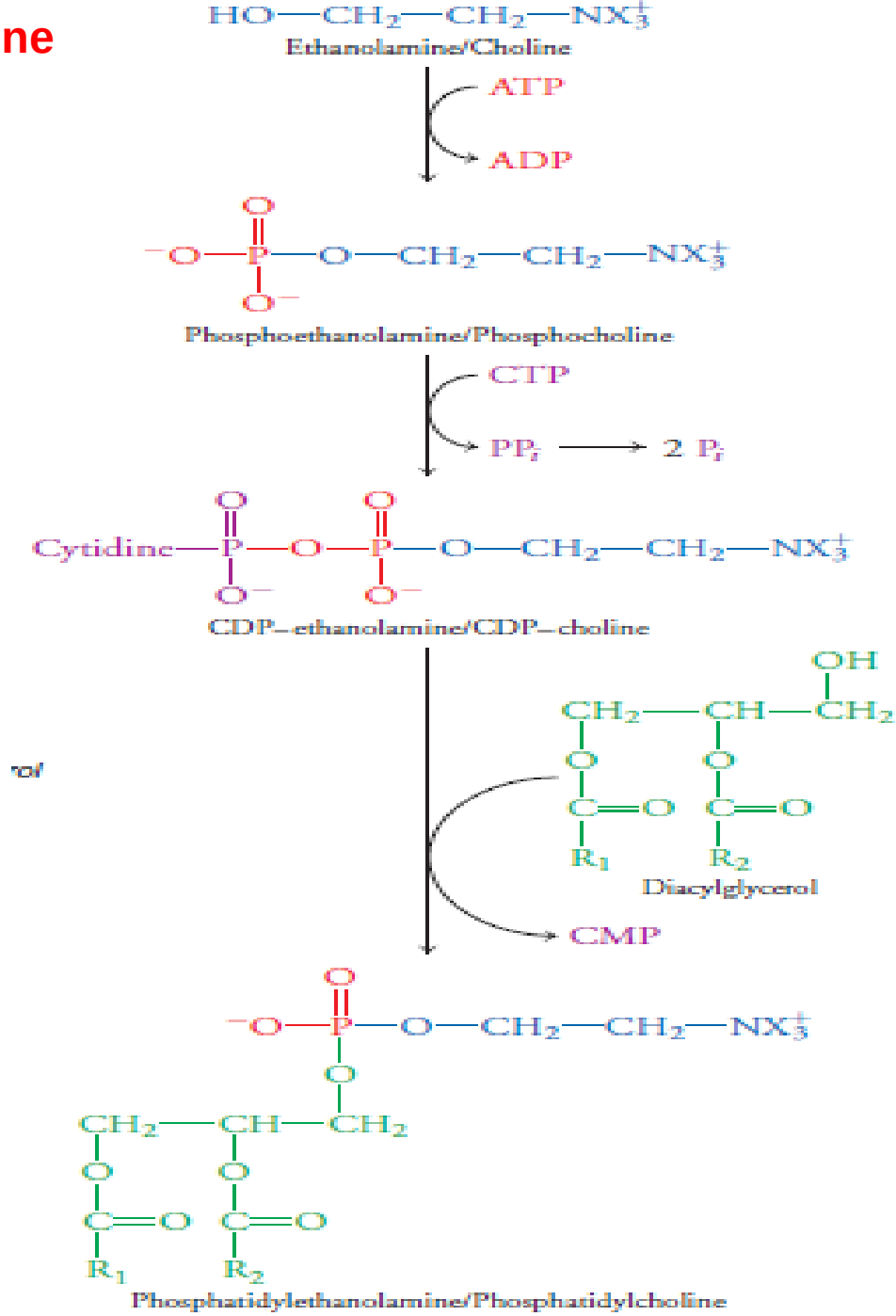
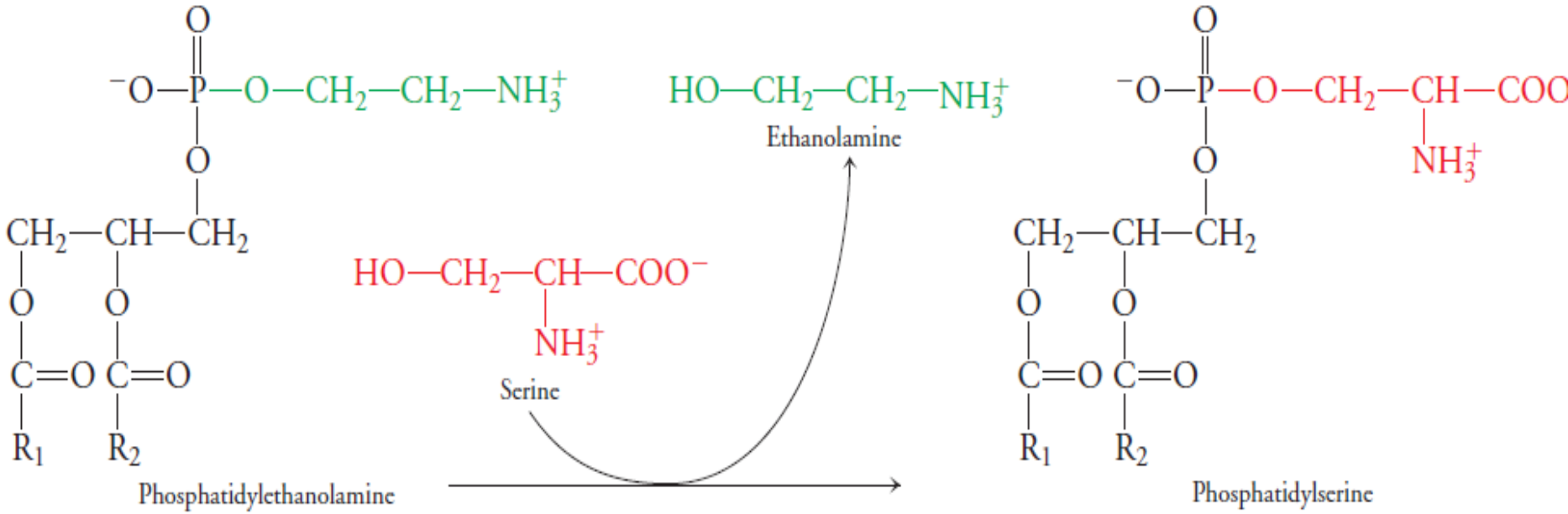


Figure 22. Synthesis of phosphatidylethanolamine and phosphatidylcholine.

The triacylglycerol biosynthetic pathway also provides the precursors for glycerophospholipids. *These amphipathic phospholipids are synthesized from phosphatidate or diacylglycerol by pathways that include an activating step in which the nucleotide cytidine triphosphate (CTP) is cleaved. In some cases, the phospholipid head group is* activated; in other cases, the lipid tail portion is activated. **Figure 22 shows how the head groups ethanolamine and choline are activated** before being added to diacylglycerol to produce phosphatidylethanolamine and phosphatidylcholine.

Phosphatidylserine is synthesized from hosphatidylethanolamine by a head group exchange reaction in which serine displaces the ethanolamine head group:



Phosphatidylinositol synthesis

In the synthesis of phosphatidylinositol, the diacylglycerol component is activated, rather than the head group, so that the inositol head group adds to CDP– diacylglycerol (Figure 23).

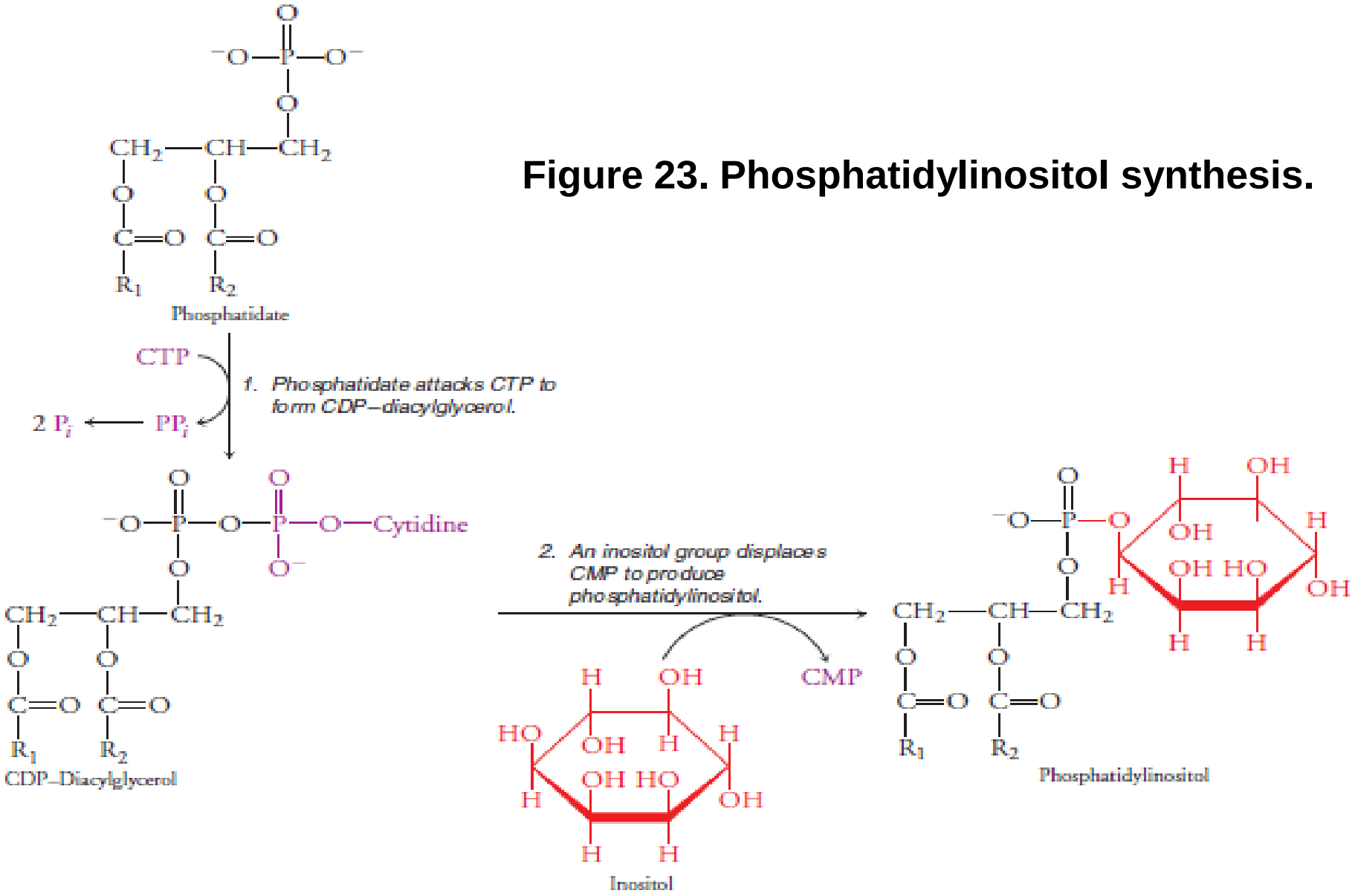


Figure 23. Phosphatidylinositol synthesis.

Cholesterol synthesis begins with acetyl-CoA

Cholesterol molecules, like fatty acids, are built from two-carbon acetyl units. In fact, *the fi rst steps of cholesterol synthesis resemble those of ketogenesis. However,* ketone bodies are synthesized in the mitochondria (and only in the liver), and cholesterol is synthesized in the cytosol. The reactions of cholesterol biosynthesis and ketogenesis diverge after the production of HMG-CoA. In ketogenesis, this compound is cleaved to produce acetoacetate (**see Fig. 20**). In cholesterol synthesis, the thioester group of HMG-CoA is reduced to an alcohol, releasing the six-carbon compound mevalonate **(Fig. 24).**

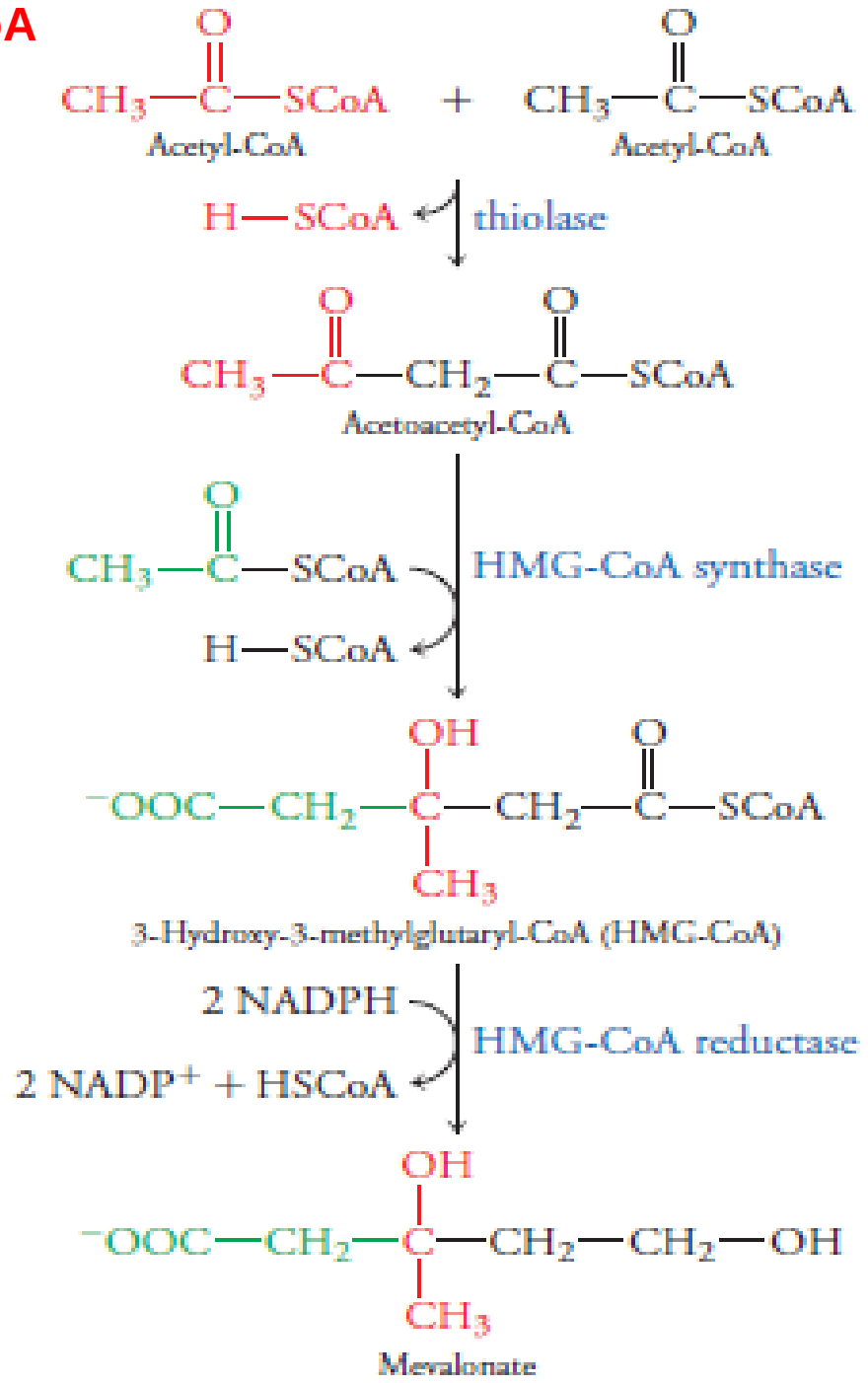
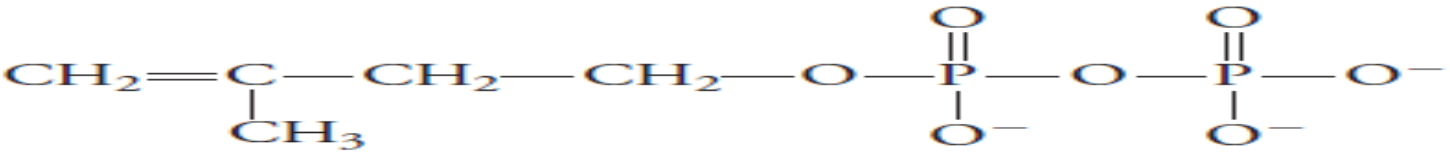


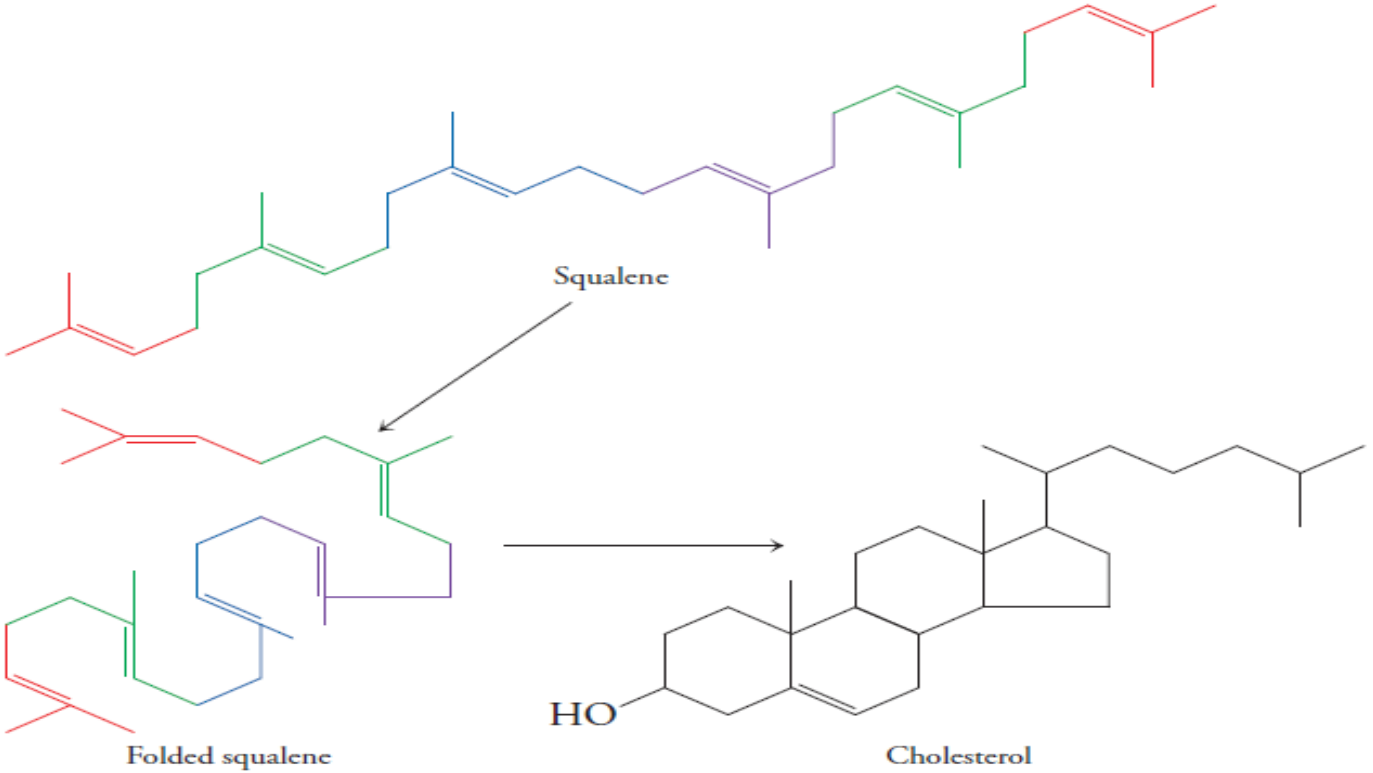
Figure 24. The first steps of cholesterol biosynthesis. Note the resemblance of this pathway to ketogenesis (Fig. 20) through the production of HMG-CoA. HMG-CoA reductase then catalyzes a four-electron reductive deacylation to yield mevalonate.

In the next four steps of cholesterol synthesis, mevalonate acquires two phosphoryl groups and is decarboxylated to produce the fi ve-carbon compound isopentenyl pyrophosphate:



Isopentenyl pyrophosphate

Conversion of squalene to cholesterol. The six isoprene units of squalene are shown in different colors. The molecule folds and undergoes cyclization. Additional reactions convert the C 30 squalene to cholesterol, a C27 molecule.



Some Statins Inhibitors

Synthetic inhibitors known as statins bind extremely tightly to HMG-CoA reductase All the statins have an HMG-like group that acts as a competitive inhibitor of HMG-CoA binding to the enzyme **(Fig. 25).** Their rigid hydrophobic groups also prevent the enzyme from forming a structure that would accommodate the pantothenate moiety of CoA. The physiological effect of the statins is to lower serum cholesterol levels by blocking mevalonate synthesis. Cells must then obtain cholesterol from circulating lipoproteins. But since mevalonate is also the precursor of other isoprenoids such as ubiquinone, the long-term use of statins can have negative side effects.

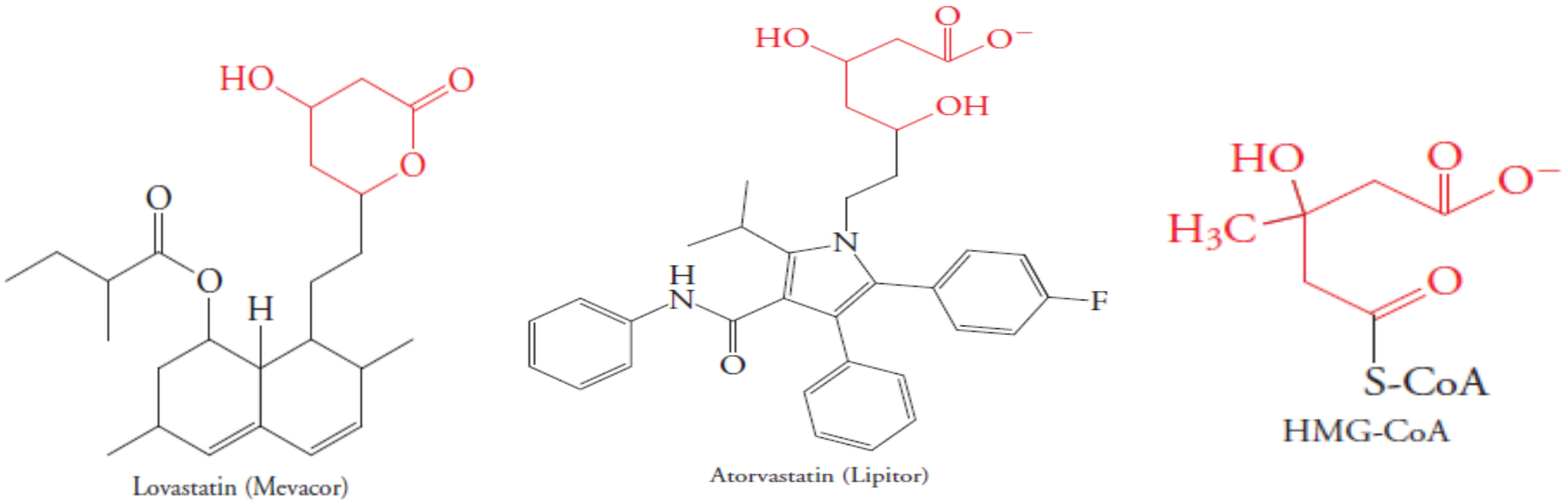
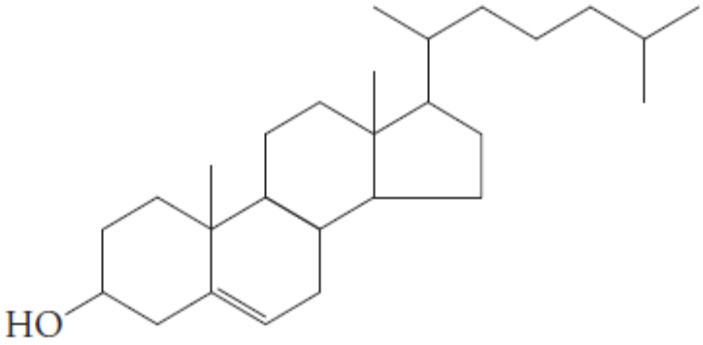


Figure 25. Some statins. These inhibitors of HMG-CoA reductase have a bulky hydrophobic group plus an HMG-like group (colored red).

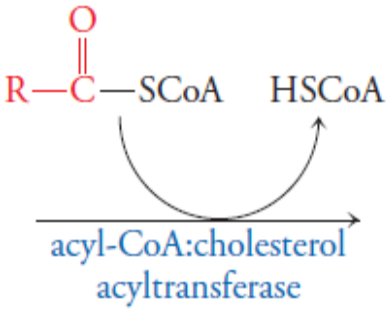
Cholesterol can be used in several ways

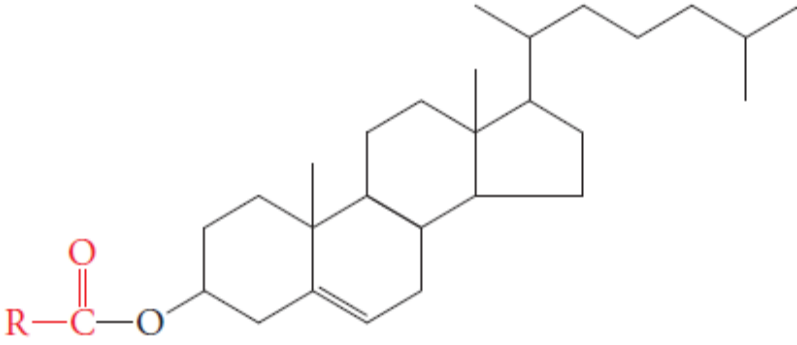
Newly synthesized cholesterol has several fates:

1. It can be incorporated into a cell membrane.
2. It may be acylated to form a cholesteryl ester for storage or, in liver, for packaging in VLDL.



Cholesterol

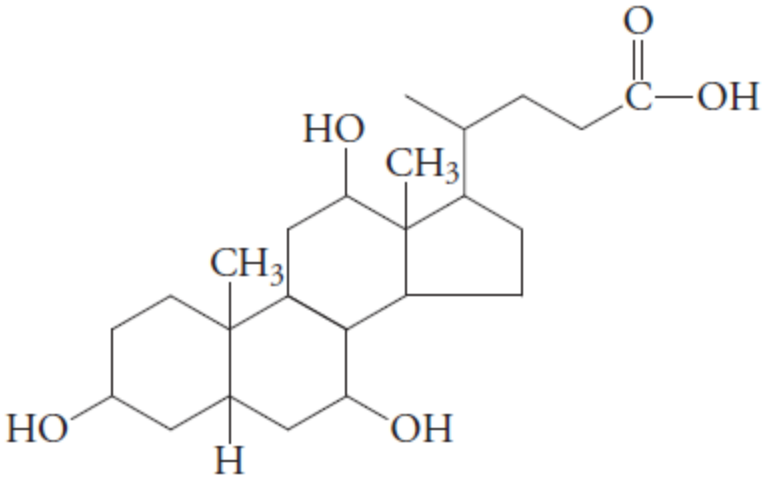




Cholesteryl ester

3. It is a precursor of steroid hormones such as testosterone and estrogen in the appropriate tissues.

4. It is a precursor of bile acids such as cholate:



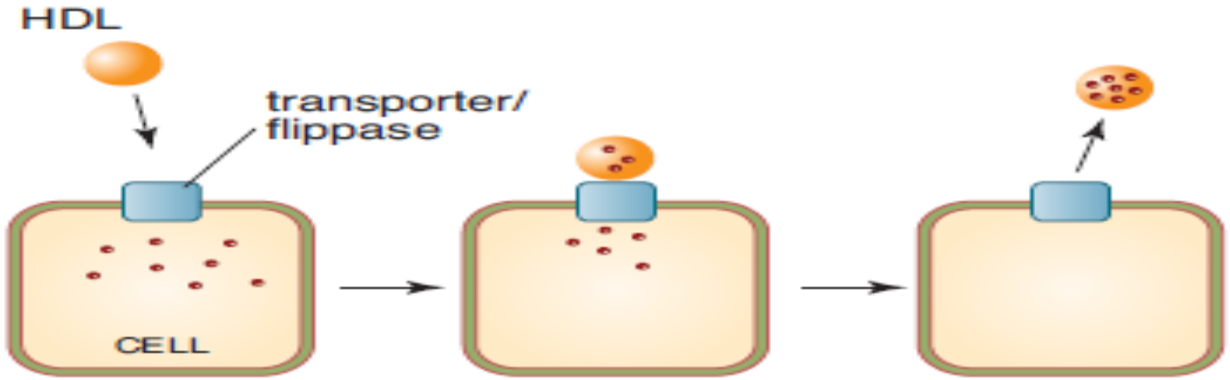
Cholate

Bile acids and cholesterol

Bile acids are synthesized in the liver, stored in the gallbladder, and secreted into the small intestine. There, they aid digestion by acting as detergents to solubilize dietary fats and make them more susceptible to lipases. Although bile acids are mostly reabsorbed and recycled through the liver for reuse, some are excreted from the body. ***This is virtually the only route for cholesterol disposal.***

Cells can synthesize cholesterol as well as obtain it from circulating LDL. When LDL proteins dock with the LDL receptor on the cell surface, the lipoprotein–receptor complex undergoes endocytosis. Inside the cell, the lipoprotein is degraded and cholesterol enters the cytosol.

High-density lipoproteins (HDL) are essential for removing excess cholesterol from cells. The efflux of cholesterol requires the close juxtaposition موقع متجاور of the cell membrane and an HDL particle as well as specific cell-surface proteins. One of these is an ABC transporter that acts as a flippase to move cholesterol from the cytosolic leaflet to the extracellular leaflet, from which it can diffuse into the HDL particle



A summary of lipid metabolism

The processes of breaking down and synthesizing lipids illustrate some general principles related to how the cell carries out opposing metabolic pathways. The diagram in Figure 26. includes the major lipid metabolic pathways covered in this chapter.

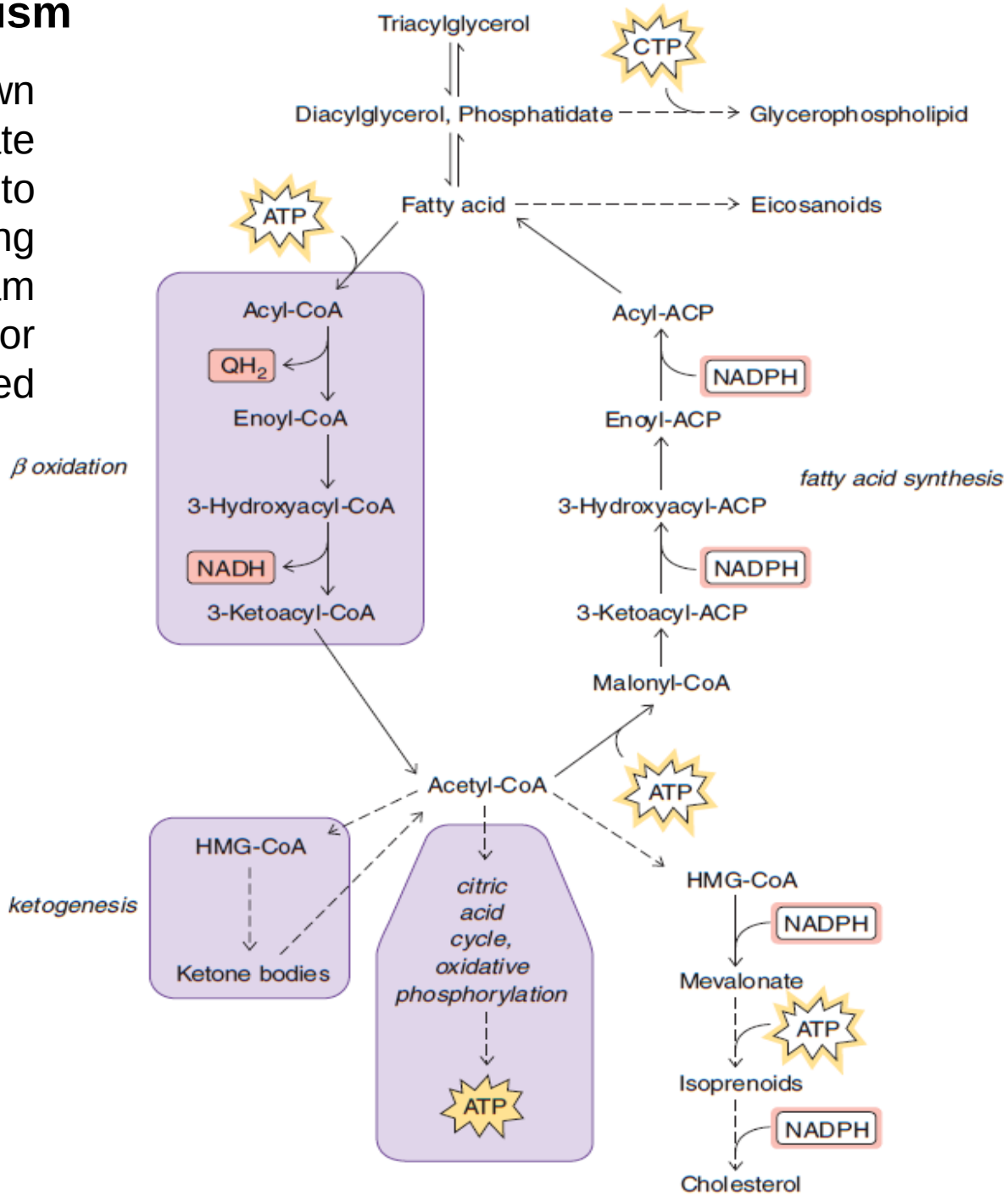


Figure 17-24 Summary of lipid metabolism. Only the major pathways covered in this chapter are included. Open gold symbols indicate ATP consumption; filled gold symbols indicate ATP production. Open and filled red symbols represent the consumption and production of reduced cofactors (NADH, NADPH, and QH2). The shaded portions of the diagram indicate reactions that occur in mitochondria.