LIPID METABOLISM

Fatty Acid Oxidation

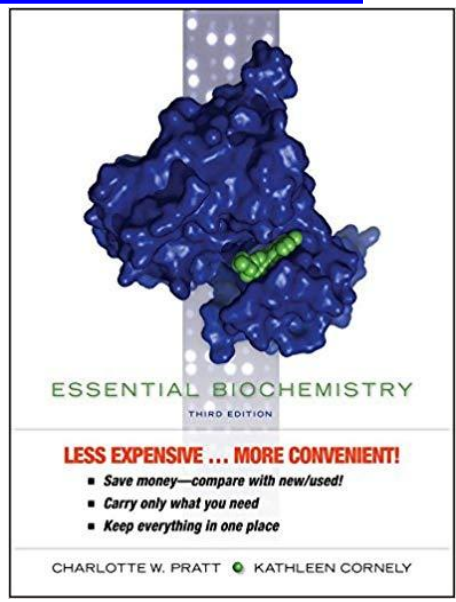
Fatty Acid Synthesis

Synthesis of Other Lipids

Part -1

For

Forth stage – Chemistry dept.



Professor

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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

Do You Remember?

- **Lipids are predominantly hydrophobic molecules that can be esterified but cannot form polymers.**
- **Cholesterol and other lipids that do not form bilayers have a variety of other functions.**
- **Metabolic fuels can be mobilized by breaking down glycogen, triacylglycerols, and proteins**

The molecules that fit the label of *lipid do not follow a single structural template* or share a common set of functional groups, as nucleotides and amino acids do. In fact, *lipids are defined primarily by the absence of functional groups*. *Because they* consist mainly of C and H atoms and have few if any N- or O-containing functional groups, they lack the ability to form hydrogen bonds and are therefore largely insoluble in water (most lipids are soluble in nonpolar organic solvents). Although some lipids do contain polar or charged groups, the bulk of their structure is hydrocarbon-like.

Fatty acids consist of a hydrocarbon chain with a carboxylic acid at one end.

A 16-C fatty acid: $CH_3(CH_2)_{14}$-COO^-

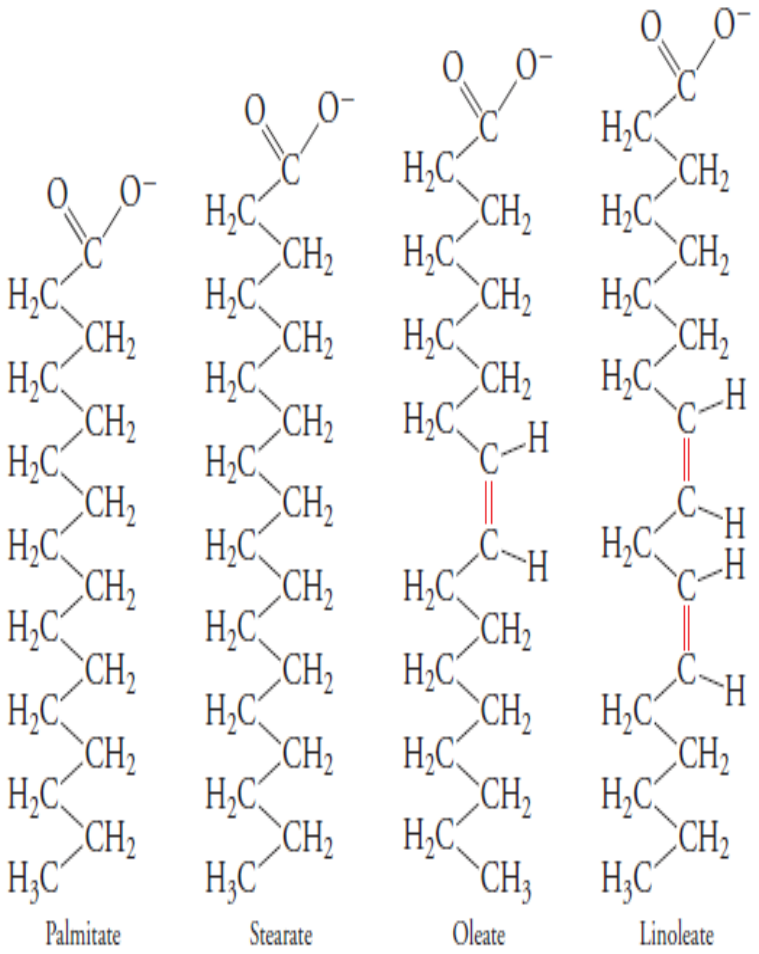
Non-polar polar

A 16-C fatty acid with one cis double bond between C atoms 9-10 may be represented as **16:1 cis Δ^9**.

Fatty acids contain long hydrocarbon chains

The simplest lipids are the **fatty acids, which are long-chain carboxylic acids** (at physiological pH, they are ionized to the carboxylate form). These molecules may contain up to 24 carbon atoms, but the most common fatty acids in plants and animals are the even-numbered C16 and C18 species such as palmitate and stearate:

Such molecules are called **saturated fatty acids** because all their tail carbons are "saturated" with hydrogen. **Unsaturated fatty acids** (which contain one or more double bonds) such as oleate and linoleate are also common in biological systems.



Some Common Fatty Acids

Number of Carbon Atoms	Common Name	Systematic Name[a]	Structure
Saturated fatty acids			
12	Lauric acid	Dodecanoic acid	$CH_3(CH_2)_{10}COOH$
14	Myristic acid	Tetradecanoic acid	$CH_3(CH_2)_{12}COOH$
16	Palmitic acid	Hexadecanoic acid	$CH_3(CH_2)_{14}COOH$
18	Stearic acid	Octadecanoic acid	$CH_3(CH_2)_{16}COOH$
20	Arachidic acid	Eicosanoic acid	$CH_3(CH_2)_{18}COOH$
22	Behenic acid	Docosanoic acid	$CH_3(CH_2)_{20}COOH$
24	Lignoceric acid	Tetracosanoic acid	$CH_3(CH_2)_{22}COOH$
Unsaturated fatty acids			
16	Palmitoleic acid	9-Hexadecenoic acid	$CH_3(CH_2)_5CH{=}CH(CH_2)_7COOH$
18	Oleic acid	9-Octadecenoic acid	$CH_3(CH_2)_7CH{=}CH(CH_2)_7COOH$
18	Linoleic acid	9,12-Octadecadienoic acid	$CH_3(CH_2)_4(CH{=}CHCH_2)_2(CH_2)_6COOH$
18	α-Linolenic acid	9,12,15-Octadecatrienoic acid	$CH_3CH_2(CH{=}CHCH_2)_3(CH_2)_6COOH$
18	γ-Linolenic acid	6,9,12-Octadecatrienoic acid	$CH_3(CH_2)_4(CH{=}CHCH_2)_3(CH_2)_3COOH$
20	Arachidonic acid	5,8,11,14-Eicosatetraenoic acid	$CH_3(CH_2)_4(CH{=}CHCH_2)_4(CH_2)_2COOH$
20	EPA	5,8,11,14,17-Eicosapentaenoic acid	$CH_3CH_2(CH{=}CHCH_2)_5(CH_2)_2COOH$
22	DHA	4,7,10,13,16,19-Docosahexaenoic acid	$CH_3CH_2(CH{=}CHCH_2)_6CH_2COOH$

[a]Numbers indicate the starting position of the double bond; the carboxylate carbon is in position 1.

? Which of the unsaturated fatty acids listed here are omega-3 fatty acids?

An **omega-3 fatty acid has a double bond starting three carbons from its methyl end** (the last carbon in the fatty acid chain is called the omega carbon).

In vegetable oils are mostly omega-6 with the first C=C at C6.

linoleic acid $CH_3{-}(CH_2)_4{-}CH{=}CH{-}CH_2{-}CH{=}CH{-}(CH_2)_7{-}COOH$

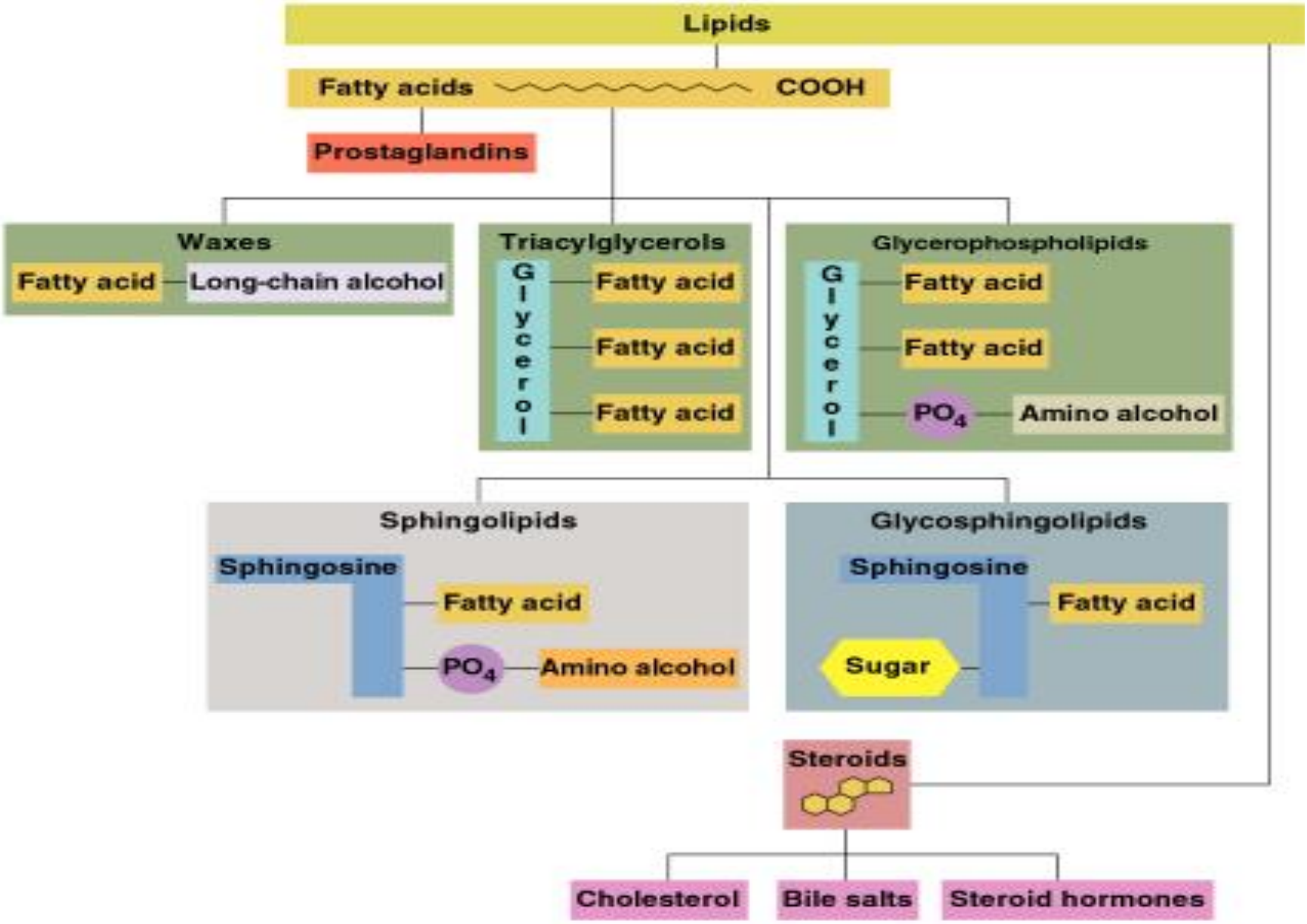
6

- In fish oils are mostly omega-3 with the first C=C at C3.

linolenic acid $CH_3{-}CH_2{-}(CH{=}CH{-}CH_2)_3{-}(CH_2)_6{-}COOH$

3

Structures of Lipids



Adipocytes

- All cells can take up these materials to some extent to fulfill their immediate needs, but ***some tissues are specialized for the long-term storage of nutrients***. For example, fatty acids are used to build triacylglycerols, many of which travel in the form of lipoproteins to adipose tissue. Here, adipocytes take up the triacylglycerols and store them as intracellular fat globules. Because the mass of lipid is hydrophobic and does not interfere with activities in the aqueous cytoplasm, the fat globule can be enormous, occupying most of the volume of the adipocyte **(Fig.4).**

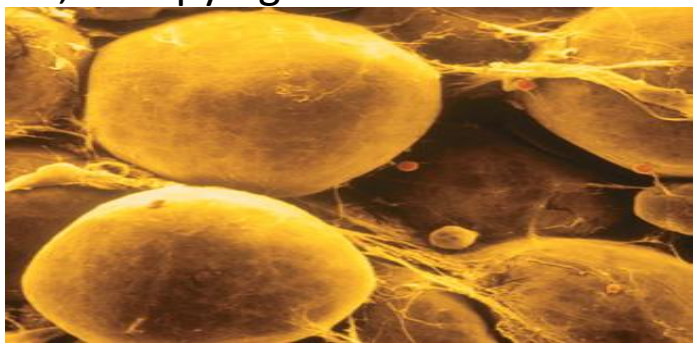


Figure 4. Adipocytes. These cells, which make up adipose tissue, contain a small amount of cytoplasm surrounding a large globule of triacylglycerols (fat).

Approximately half of all deaths in the United States are linked to the vascular disease **atherosclerosis (a term derived from the Greek *athero, "paste," and sclerosis,* "hardness"**). Atherosclerosis is a slow progressive disease that begins with the accumulation of lipids in the walls of large blood vessels. The damaged vessel wall forms a plaque with a core of cholesterol, cholesteryl esters, and remnants of dead macrophages, surrounded by proliferating smooth muscle cells that may undergo calcification, as occurs in bone formation. This accounts for the "hardening" of the arteries, **(Fig. 5),** blood clot that can prevent circulation to the heart (a heart attack) or brain (a stroke).

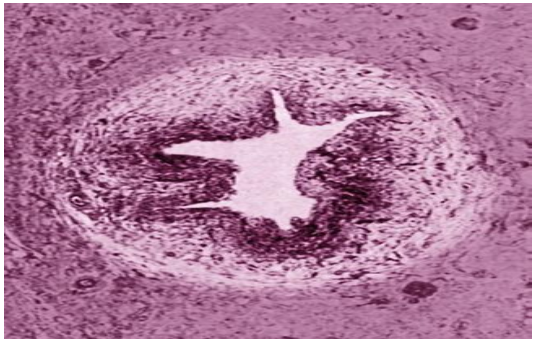


Figure 5. An atherosclerotic plaque in an artery. Note the thickening of the vessel wall.

Lipoproteins:

What is the source of the lipids that accumulate in vessel walls?

- They are deposited by lipoproteins known as LDL (low-density lipoproteins).
- Lipoproteins (particles consisting of lipids and specialized proteins) are the primary form of circulating lipid (Fig. 6a).
- Dietary lipids travel from the intestine to other tissues as chylomicrons (Fig. 6 b).. These lipoproteins are relatively large (1000 to 5000 Å in diameter) with a protein content of only 1% to 2%. Their primary function is to transport dietary triacylglycerols to adipose tissue and cholesterol to the liver. The liver repackages the cholesterol and other lipids—including triacylglycerols, phospholipids, and cholesteryl esters—into other lipoproteins known as VLDL (very-low-density lipoproteins). VLDL have a triacylglycerol content of about 50% and a diameter of about 500 Å. As they circulate in the bloodstream, VLDL give up triacylglycerols to the tissues, becoming smaller, denser, and richer in cholesterol and cholesteryl esters. After passing through an intermediate state (IDL, or intermediate-density lipoproteins), they become LDL, about 200 Å in diameter and about 45% cholesteryl ester (Table -1)

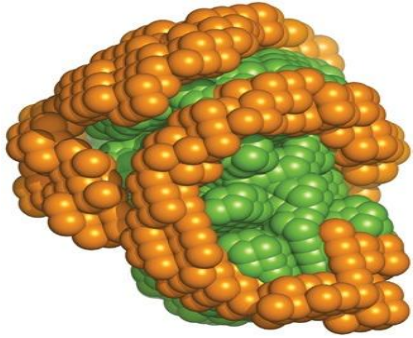


Figure 6 a. Structure of a lipoprotein. HDL particles. Three copies of apolipoprotein A1 (orange) wrap around a core containing phospholipids, cholesterol, and cholesteryl esters.

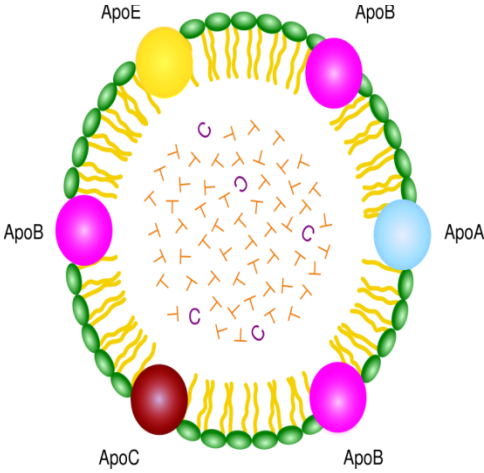


Figure 6 b. Chylomicron structure ApoA, ApoB, ApoC, ApoE (apolipoproteins); T (triacylglycerol); C (cholesterol); green (phospholipids)

- High concentrations of circulating LDL, measured as serum cholesterol (popularlycalled “bad cholesterol”), are a major factor in atherosclerosis. The disease is less likely to occur in individuals who consume low-cholesterol diets and who have high levels of HDL (high-density lipoproteins, sometimes called “good” cholesterol). HDL particles are even smaller and denser than LDL (see Table -1). The roles of the various lipoproteins are summarized in **Figure 7.**

[TABLE -1] Characteristics of Lipoproteins

Lipoprotein	Diameter (Å)	Density ($g \cdot cm^{-3}$)	% Protein	% Triacylglycerol	% Cholesterol and Cholesteryl Ester
Chylomicrons	1000–5000	<0.95	1–2	85–90	4–8
VLDL	300–800	0.95–1.006	5–10	50–65	15–25
IDL	250–350	1.006–1.019	10–20	20–30	40–45
LDL	180–250	1.019–1.063	20–25	7–15	45–50
HDL	50–120	1.063–1.210	40–55	3–10	15–20

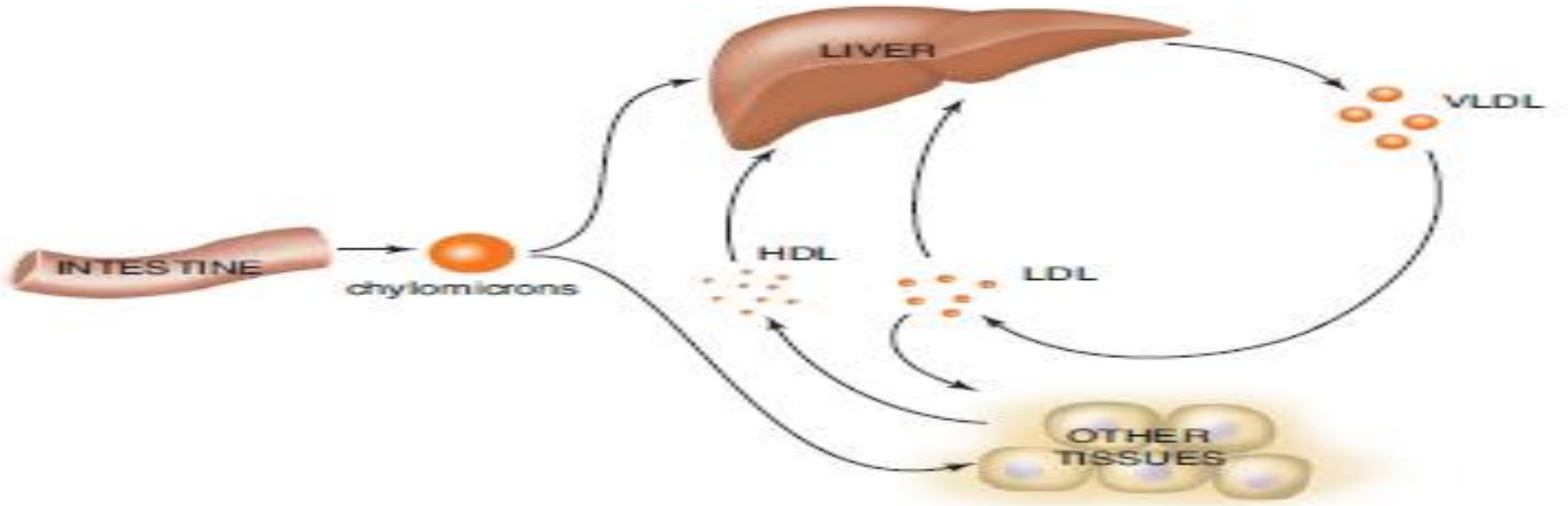


Figure 7. Lipoprotein function.

Large chylomicrons, which are mostly lipid, transport dietary lipids to the liver and other tissues. **The liver produces triacylglycerol-rich** verylow- density lipoproteins (**VLDL**). As they circulate in the tissues, **VLDL give up their triacylglycerols, becoming cholesterol-rich** low density lipoproteins (**LDL**), **which are taken up by tissues**. High-density lipoproteins (**HDL**), the **smallest and densest of the lipoproteins**, **transport cholesterol from the tissues back to the liver.**

The opposing actions of LDL and HDL are just one part of the body's efforts to regulate lipid metabolism, which consists of multiple pathways. For example, lipids are obtained by digesting food; they are synthesized from smaller precursors; they are used by cells as a source of free energy, as building materials, and as signaling molecules; they are stored in adipose tissue; and they are transported between tissues via lipoproteins

Lipids Metabolism

Triacylglycerols, the "polymeric" form of fatty acids, are hydrolyzed to release fatty acids (1) that are oxidatively degraded to the twocarbon intermediate acetyl-CoA (2).

Acetyl-CoA is also the starting material for the reductive biosynthesis of fatty acids (3), which can then be stored as triacylglycerols (4) or used in the synthesis of other lipids. Acetyl-CoA is also the precursor of lipids that are not built from fatty acids (these pathways are not shown here).

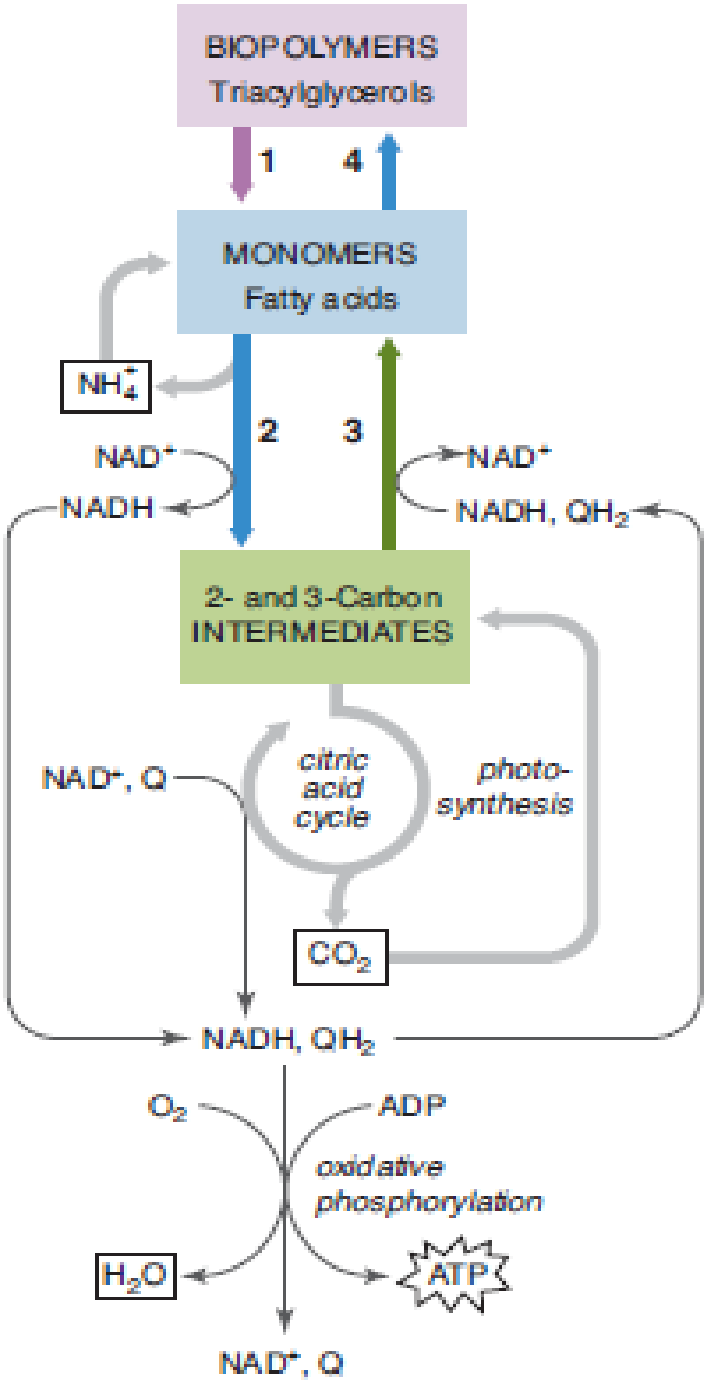
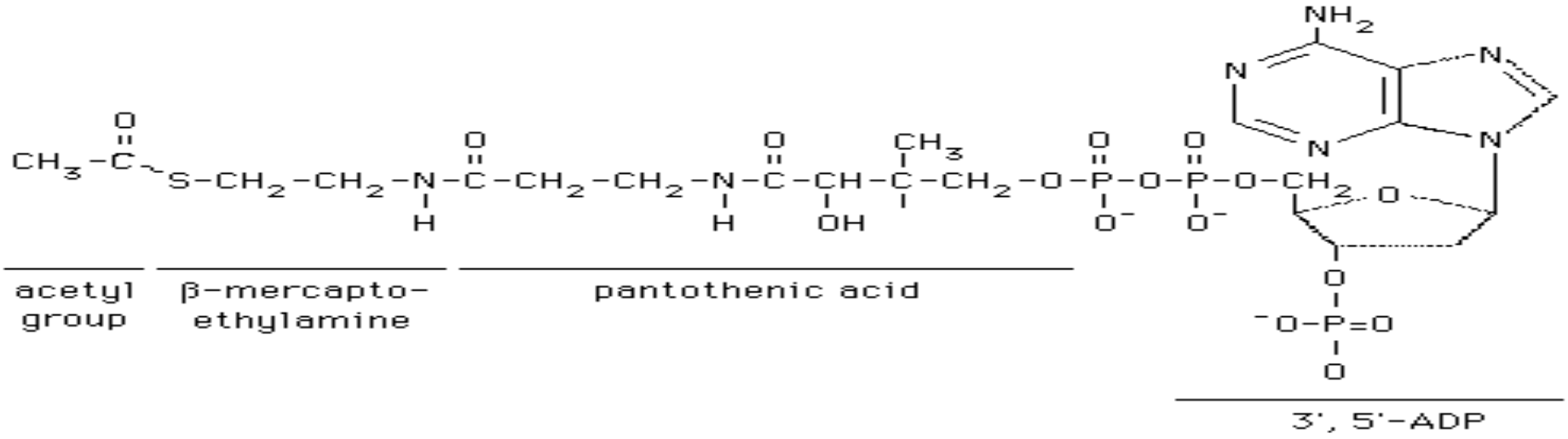


Figure 8. Lipid metabolism

Part -1

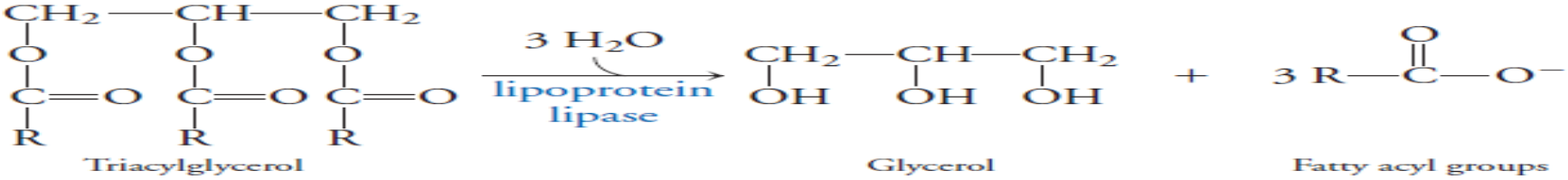
KEY CONCEPTS :

- Fatty acids to be degraded are linked to coenzyme A and then transported into mitochondria.
- The four reactions of each cycle of β oxidation produce acetyl-CoA, ubiquinone QH2, and NADH.
- Additional enzymes are required to break down unsaturated fatty acids.
- Fatty acids with an odd number of carbons yield propionyl-CoA that is ultimately converted to acetyl-CoA.
- Peroxisomes oxidize long-chain and branched fatty acids, producing H_2O_2.



Acetyl coenzyme A, showing its constituents

The degradation (oxidation) of fatty acids is a source of metabolic free energy. In this section we describe how cells obtain, activate, and oxidize fatty acids. In humans, *dietary triacylglycerols are the primary source of fatty acids used as metabolic fuel*. *The* triacylglycerols are carried by lipoproteins to tissues, where hydrolysis releases their fatty acids from the glycerol backbone. Hydrolysis occurs extracellularly, catalyzed by lipoprotein lipase, an enzyme associated with the outer surface of cells.



Triacylglycerols that are stored in adipose tissue are mobilized (their fatty acids are released to be used as fuel) by an intracellular hormone-sensitive lipase. The mobilized fatty acids travel through the bloodstream, not as part of lipoproteins, but bound to albumin, a 66-kD protein that accounts for about half of the serum protein (it also binds metal ions and hormones, serving as an all-purpose transport protein). *The concentration of free fatty acids in the body is very low because these molecules are detergents (which form micelles; see* FIG.9*) and can disrupt cell membranes.* After they enter cells, probably with the assistance of proteins, the fatty acids are either broken down for energy or re-esterified to form triacylglycerols or other complex lipids (as described in FIG.7). Many free fatty acids are deployed to the liver and muscle cells, especially heart muscle, which prefers to burn fatty acids even when carbohydrate fuels are available.

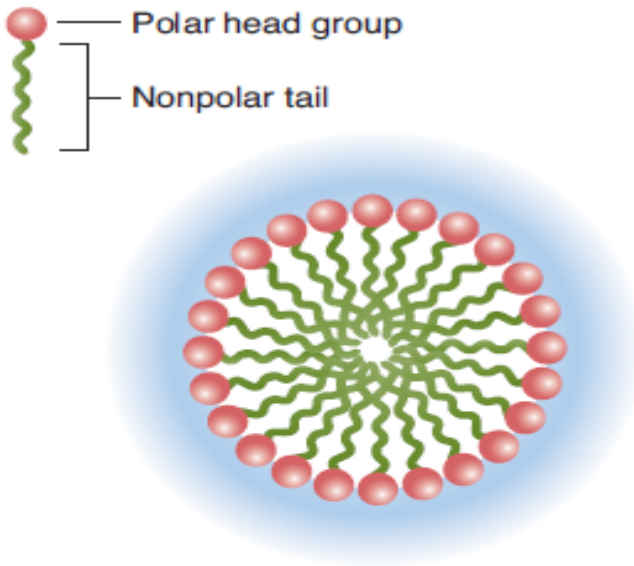
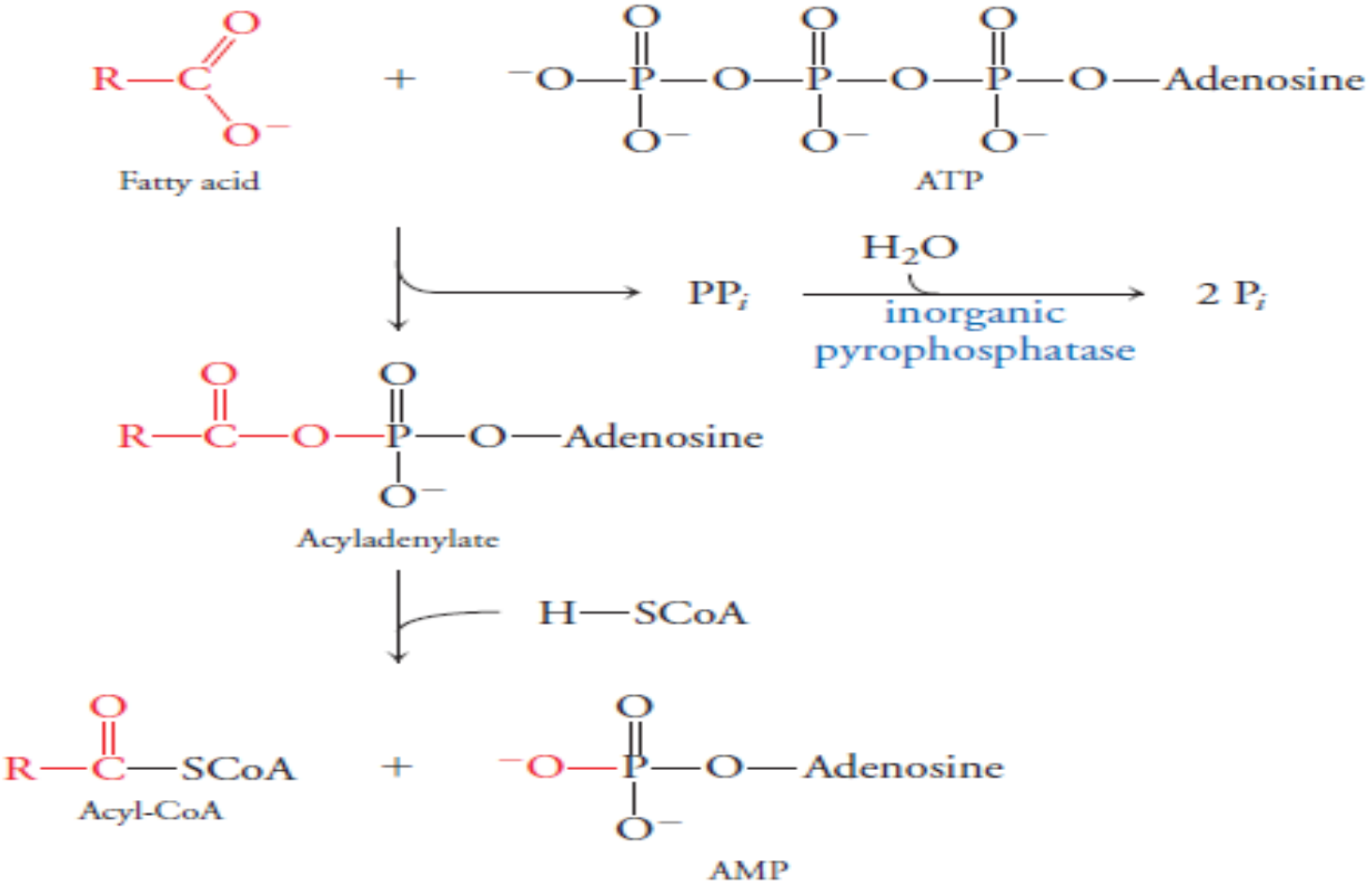


Figure -9 A micelle formed by amphiphilic molecules. The hydrophobic tails of the molecules aggregate, out of contact with water, due to the hydrophobic effect. The polar head groups are exposed to and can interact with the solvent water molecules.

Fatty acids are activated before they are degraded:

To be oxidatively degraded, a fatty acid must first be activated. Activation is a two-step reaction **catalyzed by acyl-CoA synthetase**. First, the fatty acid displaces the diphosphate group of ATP, then coenzyme A (HSCoA) displaces the AMP group to form an acyl-CoA:



ويعتبر أدينوسين ثلاثي (تراي) فوسفات ATP (الفصل الثامن) العملة الأساسية للطاقة الخلوية. وان متوسط القيمة لـ ΔG العائدة لتحلله هي (-7.3 kcal / مول). وغالباً مايعتبر هذا مركب فوسفات ذا طاقة عالية. وان ادينوسين ثنائي فوسفات (ADP) له متوسط القيمة نفسها ($\Delta G = -7.3$ kcal / مول) وأدينوسين احادي (مونو) فوسفات (AMP) يختلف، فهو مركب فوسفات ذو طاقة واطئة ($\Delta G^{0} = -4.4$ kcal / مول)

$$\underset{\text{ادينوسين تراي فوسفات}}{ATP} + H_2O \rightleftharpoons \underset{\text{ادينوسين داي فوسفات}}{ADP} + P_1 \qquad \Delta G = -7.3 \text{ Kcal / مول}$$

$$\underset{\text{ادينوسين داي فوسفات}}{ADP} + H_2O \rightleftharpoons \underset{\text{ادينوسين مونوفوسفات}}{AMP} + P_1 \qquad \Delta G = -7.3 \text{ Kcal / مول}$$

$$AMP + H_2O \rightleftharpoons \text{adenosine} + P_i \qquad \Delta G^{0} = -4.4 \text{ Kcal / مول}$$

ان تحلل بايروفوسفات لل ATP يعطي طاقة اكثر من تلك التي تنتج بإزاحة فوسفات فقط. وإن طاقة 10.0 كيلوسعرة/مول المتحررة من التحلل هذا تقوم بدفع تلك التفاعلات التي تحتاج الى طاقة اكثر من 7.3 كيلوسعرة/مول المتحررة من تحلل ATP الى ADP و Pi.

ولمزيد من «الدفع» لتفاعلات معينة، يقوم انزيم بايروفوسفاتيس Pyrophos phatase بشطر $P-P$ ليحرر 4.6 كيلوسعرة/مول.

$$P_i - P_i + H_2O \rightleftharpoons 2p_i \qquad \Delta G^{0} = -4.6 \text{kcal/ /مول}$$

The acyladenylate product of the first step has a large free energy of hydrolysis (in other words, its cleavage would release a large amount of free energy), so it conserves the free energy of the cleaved phosphoanhydride bond in ATP. The second step, transfer of the acyl group to CoA (the same molecule that carries acetyl groups as acetyl-CoA), likewise conserves free energy in the formation of a thioester bond. Consequently, the overall reaction:

fatty acid + CoA + ATP $\rightleftharpoons$ **acyl-CoA + AMP + PP*i***

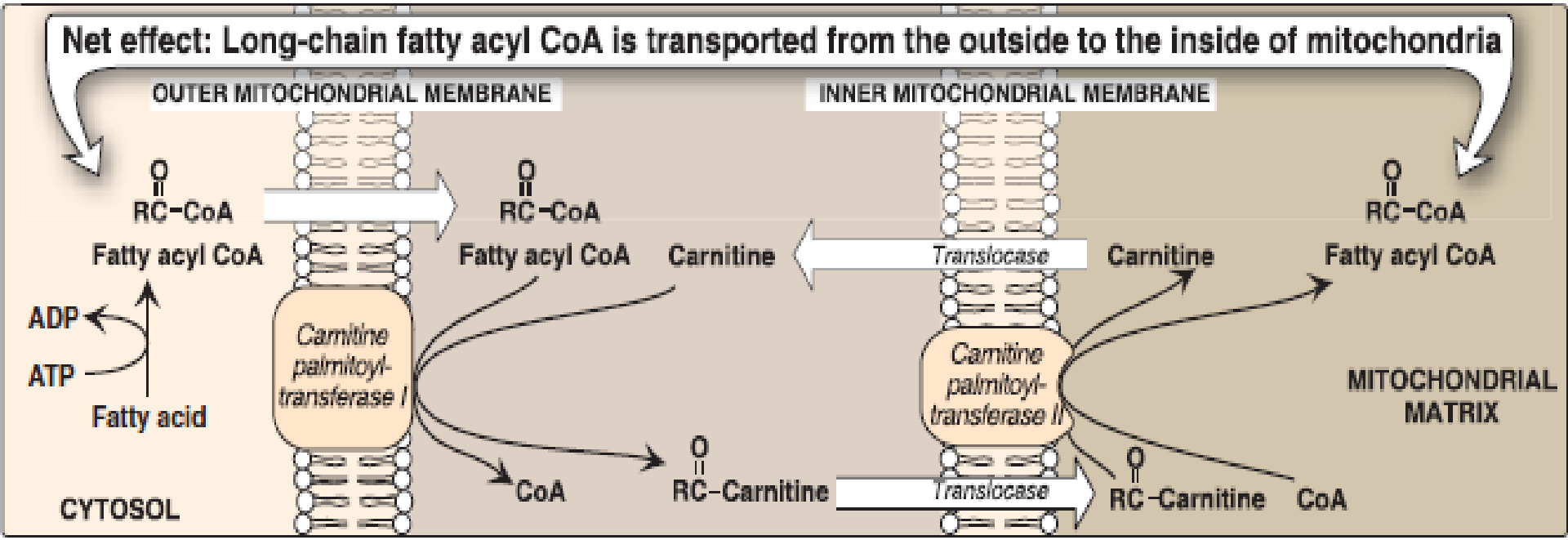
has a free energy change near zero. However, subsequent hydrolysis of the product PP*i (by the ubiquitous enzyme inorganic pyrophosphatase) is highly exergonic* مطلق للطاقة, and this reaction makes the formation of acyl-CoA spontaneous and irreversible. Most cells contain a set of acyl-CoA synthetases specific for fatty acids that are short (C2-C3), medium (C4-C12), long (≥C12), or very long (≥C22).

The enzymes that are specific for the longest acyl chains may function in cooperation with a membrane transport protein so that the fatty acid is activated as it enters the cell. Once the **large and polar coenzyme A is attached**, the **fatty acid is unable to diffuse back across the membrane and remains inside the cell to be metabolized.**

Fatty acids are **activated in the cytosol**, **but** the rest of the **oxidation pathway occurs in the mitochondria**. Because there is no transport protein for CoA adducts, acyl groups must enter the mitochondria via a shuttle system involving the small molecule carnitine **(Fig. 10). The acyl group is now ready to be oxidized.**

Transport of long-chain fatty acids (LCFA) into the mitochondria:

After a LCFA enters a cell, it is converted in the cytosol to its CoAderivative by long-chain fatty acyl CoA synthetase (thiokinase), anenzyme of the outer mitochondrial membrane. Because β-oxidation occurs in the mitochondrial matrix, the fatty acid must be transported across the inner mitochondrial membrane that is impermeable to CoA. Therefore, a specialized carrier transports the long-chain acyl group from the cytosol into the mitochondrial matrix. This carrier is carnitine, and this rate-limiting transport process is called the carnitine shuttle .



Entry of short- and medium-chain fatty acids into the mitochondria:

Fatty acids shorter than 12 carbons can cross the inner mitochondrial membrane without the aid of carnitine. Once inside the mitochondria, they are activated to their CoA derivatives by matrix enzymes, and are oxidized.

The carnitine shuttle system

Figure 10. The carnitine shuttle system.

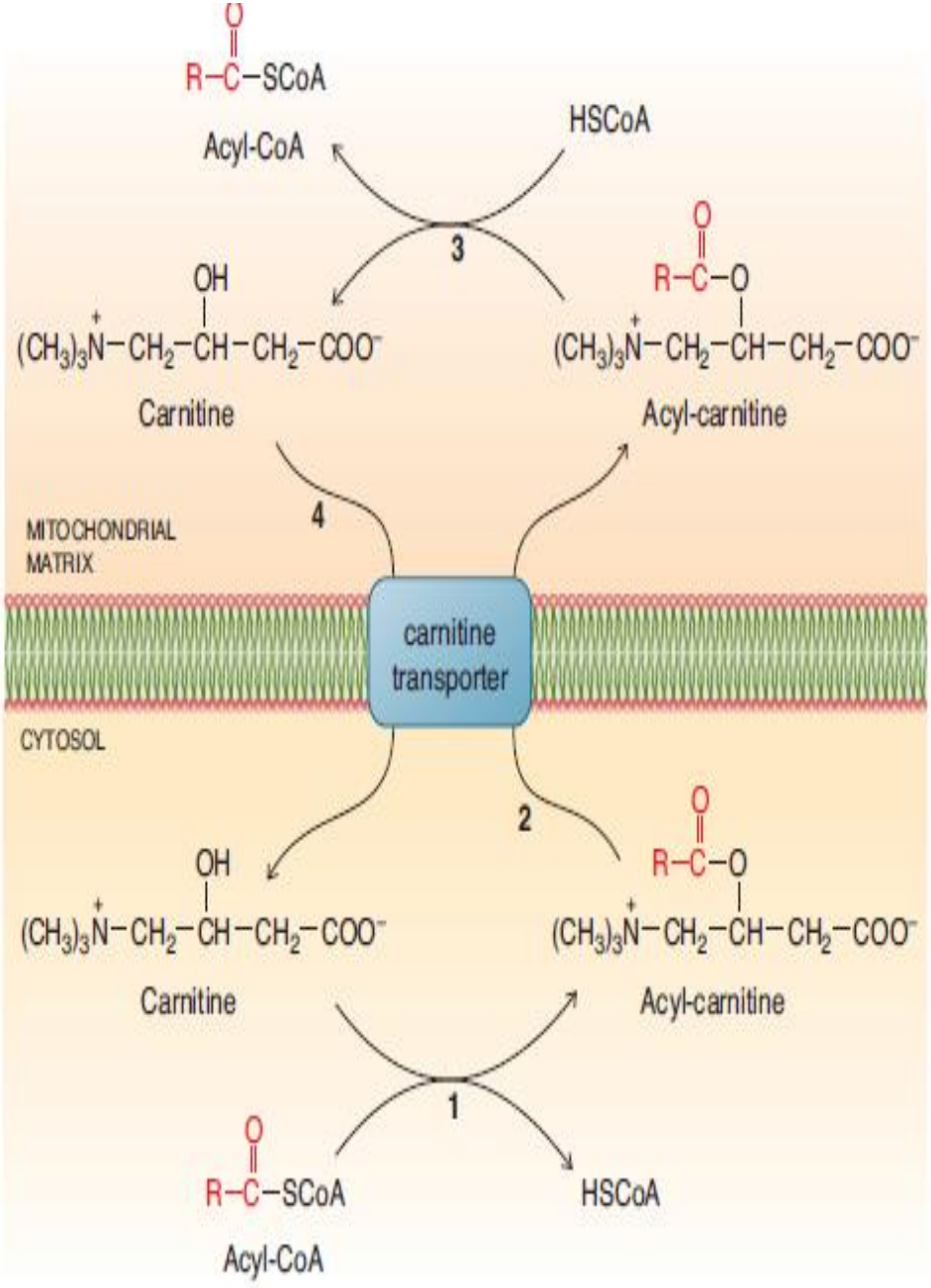
(1) A cytosolic carnitine acyltransferase transfers an acyl group from CoA to carnitine.

(2) The carnitine transporter allows the acylcarnitine to enter the mitochondrial matrix.

(3) A mitochondrial carnitine acyltransferase transfers the acyl group to a mitochondrial CoA molecule.

(4) Free carnitine returns to the cytosol via the transport protein.

Q/ Why do acyl groups move into the mitochondrion, not out of it?



Each round of β oxidation has four reactions

- The pathway known as β **oxidation** degrades an acyl-CoA in a way that produces acetyl-CoA molecules for further oxidation and energy production by the citric acid cycle. In fact, in some tissues or under certain conditions, β oxidation supplies far more acetyl groups to the citric acid cycle than does glycolysis. β Oxidation also feeds electrons directly into the mitochondrial electron transport chain, which generates ATP by oxidative phosphorylation.
- β Oxidation is a spiral pathway. *Each round consists of four enzyme-catalyzed steps that yield one molecule of acetyl-CoA and an acyl-CoA* ***shortened by two carbons, which becomes the starting substrate for the next round. Seven rounds of*** **β** ***oxidation degrade*** **a C16 fatty acid to eight molecules of acetyl-CoA:**

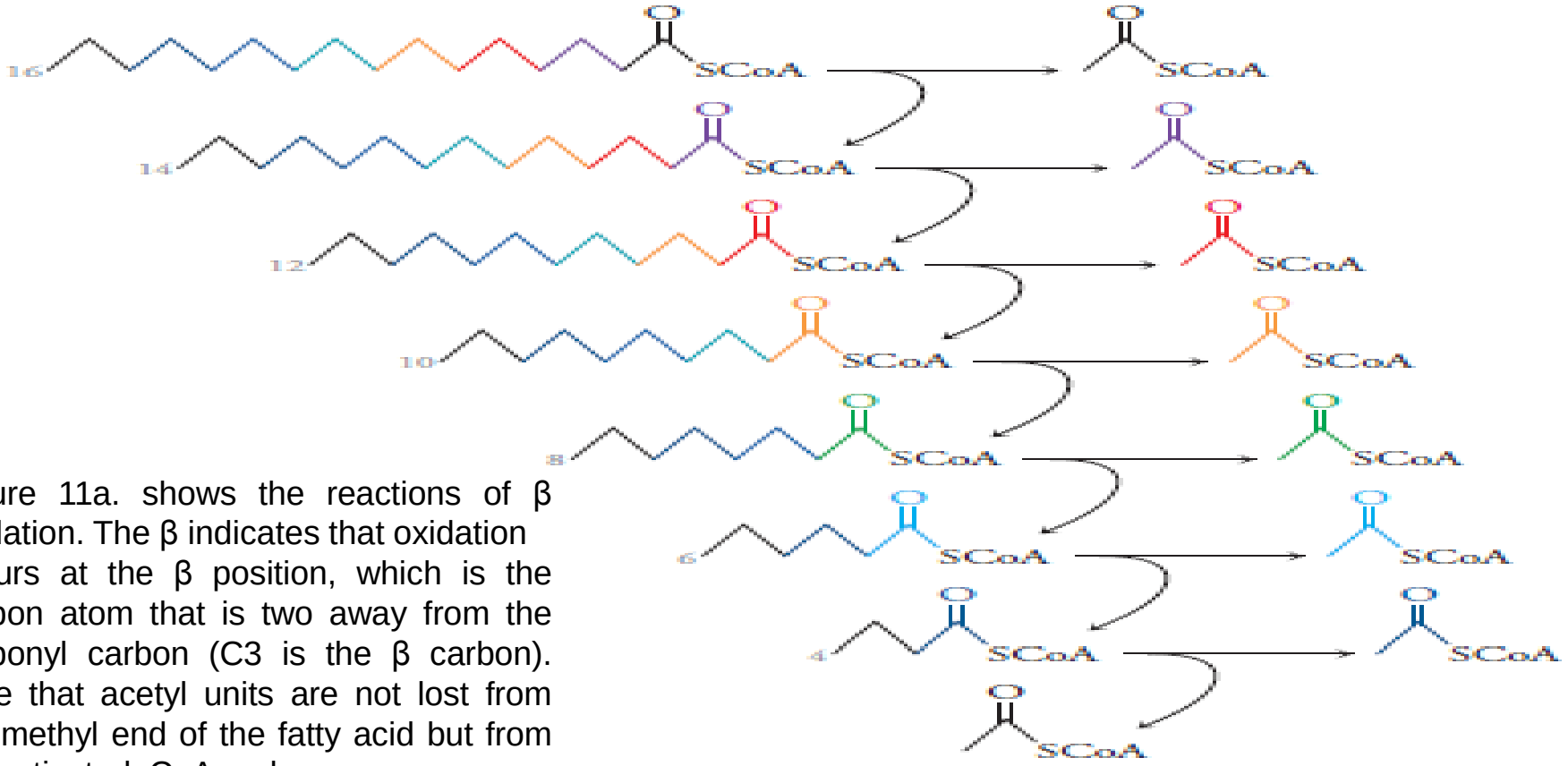
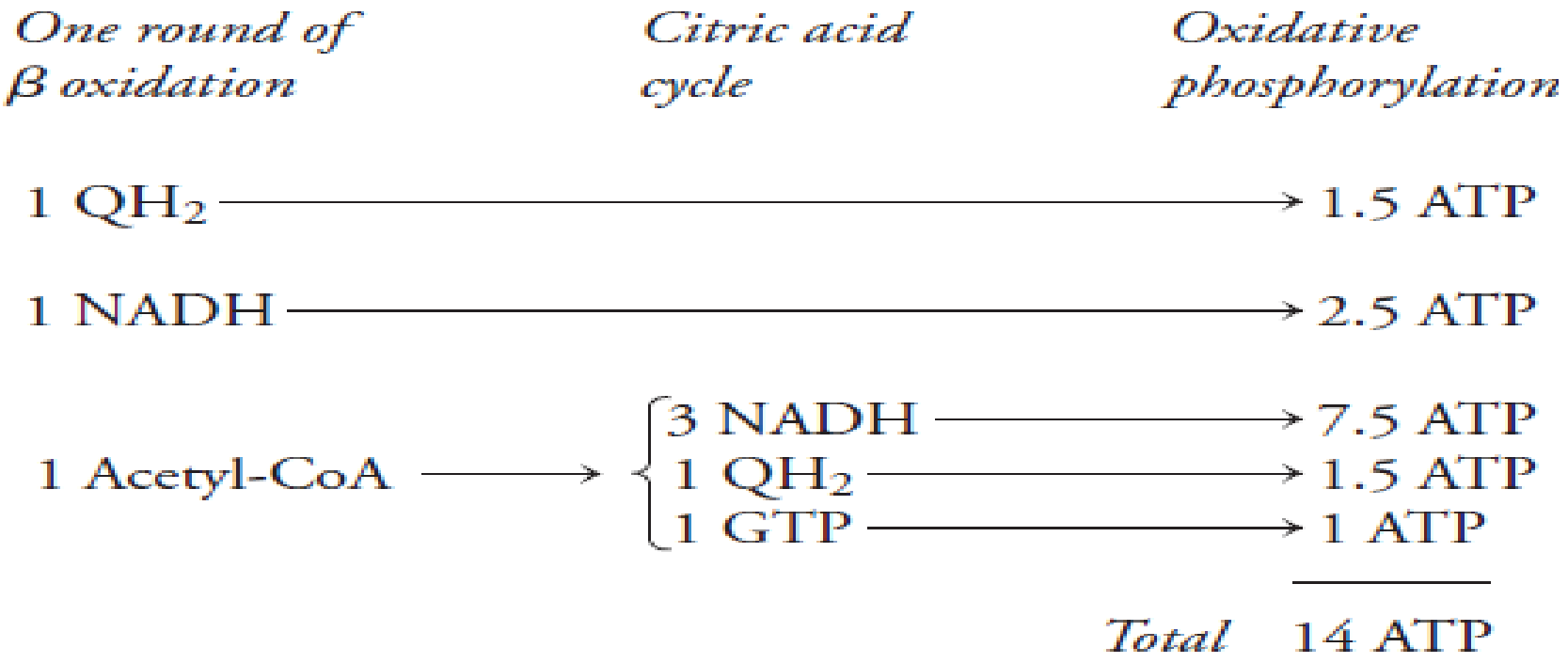


Figure 11a. shows the reactions of β oxidation. The β indicates that oxidation occurs at the β position, which is the carbon atom that is two away from the carbonyl carbon (C3 is the β carbon). Note that acetyl units are not lost from the methyl end of the fatty acid but from the activated, CoA end.

β Oxidation is a major source of cellular free energy, especially during a fast, when carbohydrates are not available. Each round of β oxidation produces one QH2, one NADH, and one acetyl-CoA. The citric acid cycle oxidizes the acetyl-CoA to produce an additional three NADH, one QH2, and one GTP. Oxidation of all the reduced cofactors yields approximately 13 ATP: 3 from the two QH2 and 10 from the four NADH A total of 14 ATP are generated from each round of β oxidation:

These four steps are repeated for saturated fatty acids of even-numbered carbon chains (n/2) – 1 times (where n is the number of carbons)



Each NADH yields approximately 2.5 ATP, and each QH2 yields approximately 1.5 ATP (we will see in Section 15-4 / page 412, why these values are not whole numbers) للاطلاع فقط

The P:O ratio describes the stoichiometry of oxidative phosphorylation:

Since the γ shaft of ATP synthase is attached to the c-subunit rotor, 3 ATP molecules are synthesized for every complete c-ring rotation. However, the number of protons translocated per ATP depends on the number of c subunits. **For mammalian ATP synthase, which has 8 c subunits, the stoichiometry is 8 H1 per 3 ATP, or 2.7 H1 per ATP.** Such non-integral values would be difficult to reconcile with most biochemical reactions, but they are consistent with the chemiosmotic theory: Chemical energy (from the respiratory oxidation–reduction reactions) is transduced to a proton motive force, then to the mechanical movement of a rotary engine (the c ring and its attached shaft), and fi nally back to chemical energy in the form of ATP.

The relationship between respiration (the activity of the electron transport complexes) and ATP synthesis is traditionally expressed as a P:O ratio, that is, the number of phosphorylations of ADP relative to the number of oxygen atoms reduced. For example, the oxidation of NADH by O2 (carried out by the sequential activities of Complexes I, III, and IV) translocates 10 protons into the intermembrane space. The movement of these 10 protons back into the matrix via the F0 component would theoretically drive the synthesis of about 3.7 ATP since 1 ATP can be made for every 2.7 protons translocated, at least in mammalian mitochondria:

$$\frac{1\ \text{ATP}}{2.7\ \text{H}^+} \times 10\ \text{H}^+ = 3.7$$

Thus, the P:O ratio would be about 3.7 (3.7 ATP per 1/2 O_2 reduced). For an electronpair originating as QH2, only 6 protons would be translocated (by the activities of Complexes III and IV), and the P:O ratio would be approximately 2.2:

$$\frac{1\ \text{ATP}}{2.7\ \text{H}^+} \times 6\ \text{H}^+ = 2.2$$

In vivo, the P:O ratios are actually a bit lower than the theoretical values, because some of the protons translocated during electron transport do leak across the membrane or are consumed in other processes, such as the transport of Pi into the mitochondrial matrix (see Fig. 15-6). Consequently, **experimentally determined P:O ratios are closer to 2.5 when NADH is the source of electrons and 1.5 for ubiquinol**. These values are the basis for our tally of the ATP yield for the complete oxidation of glucose by glycolysis and the citric acid cycle (see Section 14-2).

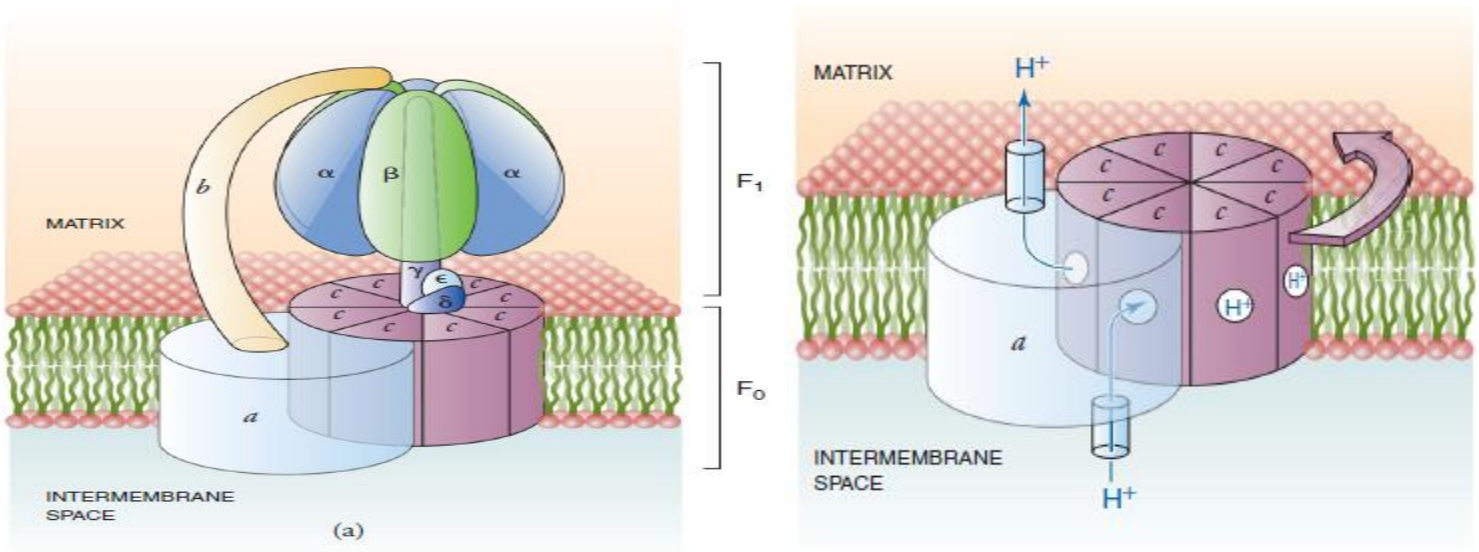
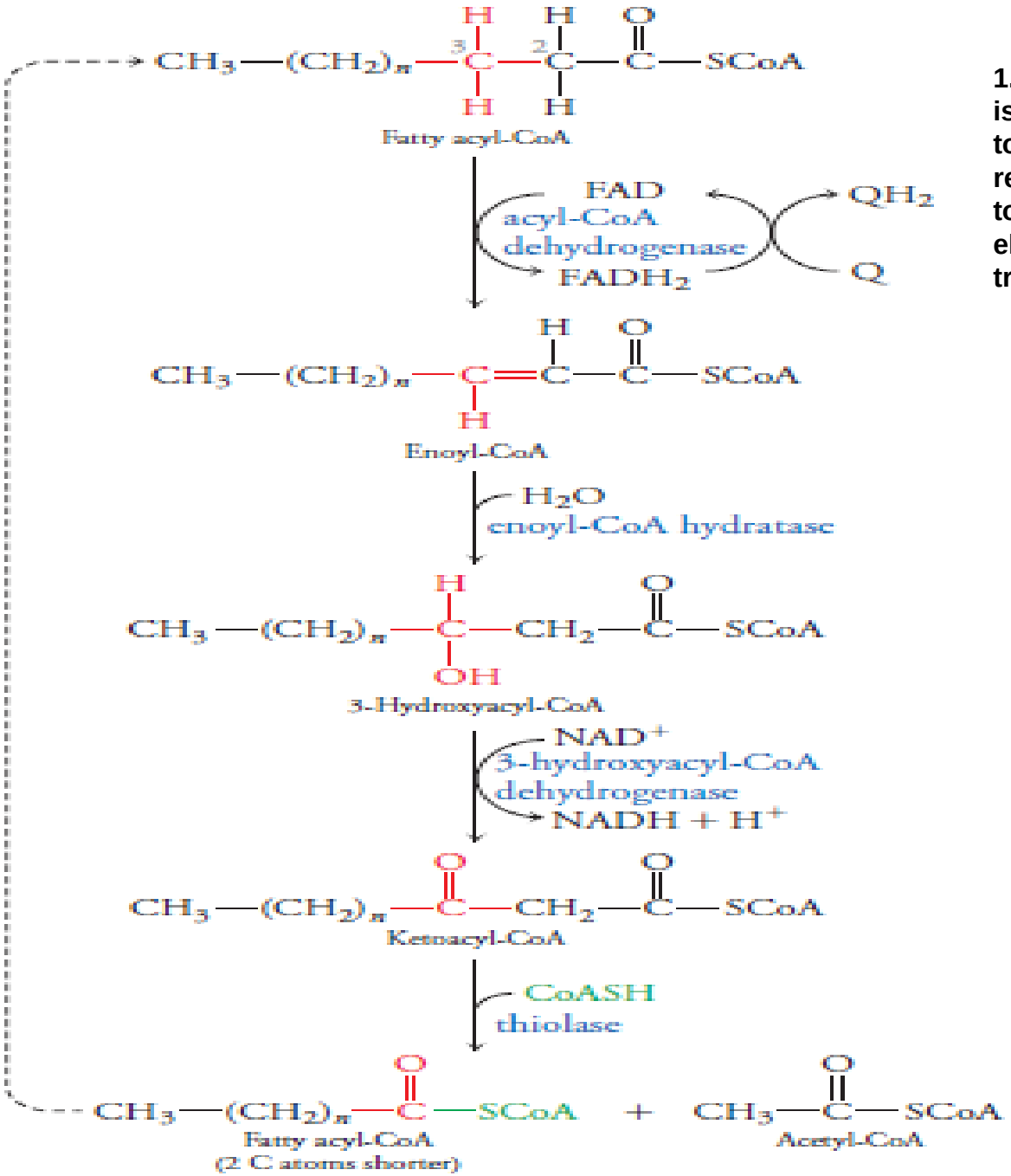


Figure 15-23 Mechanism of proton transport by ATP synthase.
للاطلاع فقط



1. Oxidation of acyl-CoA at the 2,3 position is catalyzed by an acyl-CoA dehydrogenase to yield a 2,3-enoyl-CoA. The two electrons removed from the acyl group are transferred to an FAD prosthetic group. A series of electrontransfer reactions eventually transfers the electrons to ubiquinone (Q).

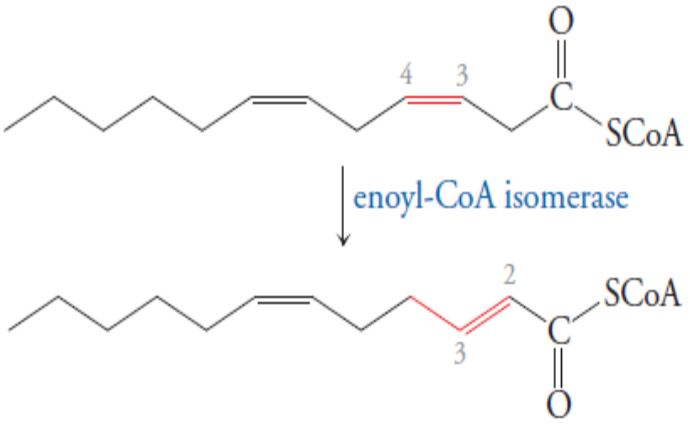
2. The second step is catalyzed by a hydratase, which adds the elements of water across the double bond produced in the first step.

3. The hydroxyacyl-CoA is oxidized by another dehydrogenase. In this case, NADis the cofactor.

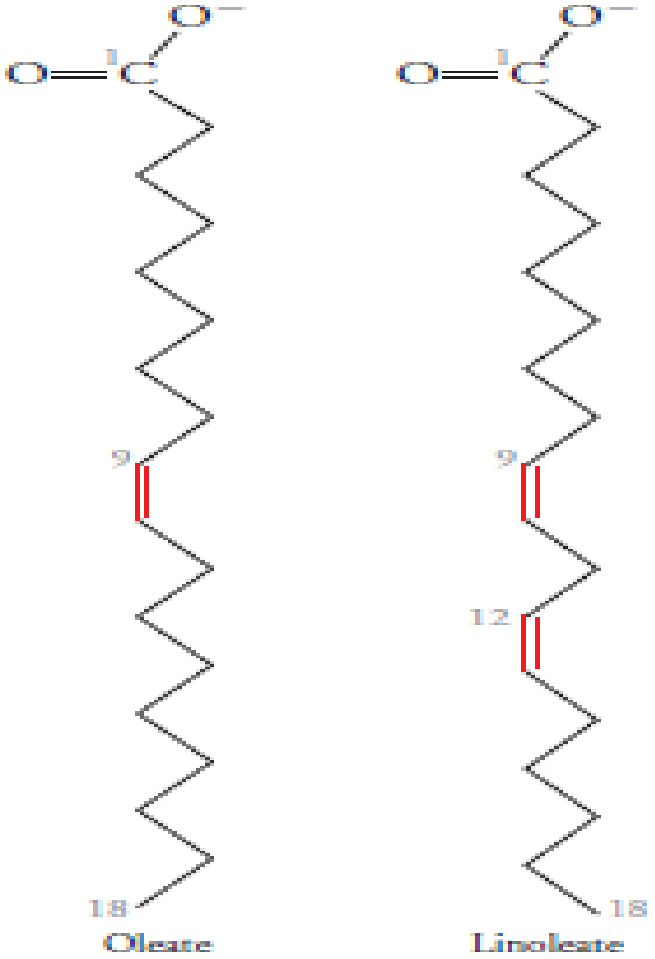
4. The final step, thiolysis, is catalyzed by a
thiolase and releases acetyl-CoA. The remaining acyl-CoA, two carbons shorter
than the starting substrate, undergoes another round of the four reactions (dotted line).

Figure 11b. The reactions of β oxidation.

Degradation of unsaturated fatty acids requires isomerization and reduction

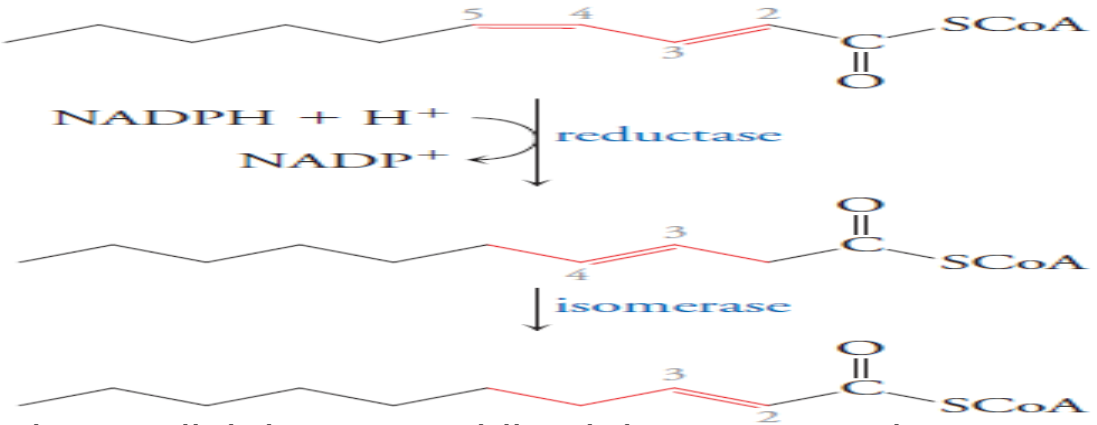


Degradation of unsaturated fatty acids requires isomerization and reduction Common fatty acids such as oleate and linoleate (*right) contain cis double bonds* that present obstacles عقبات to the enzymes that catalyze β oxidation. For linoleate, the first three rounds of β oxidation proceed as usual. But the acyl-CoA that begins the fourth round has a 3,4 double bond (originally the 9,10 double bond). Furthermore, this molecule is a *cis enoyl-CoA, but enoyl-CoA hydratase (the enzyme that catalyzes step 2* of β oxidation) recognizes only the *trans configuration. This metabolic* obstacle is removed by the enzyme enoyl-CoA isomerase, which converts the *cis 3,4 double bond to a trans 2,3 double bond so that* β *oxidation can continue.*



A second obstacle arises after the first reaction of the fifth round of β oxidation. Acyl-CoA dehydrogenase introduces a 2,3 double bond as usual, but the original 12,13 double bond of linoleate is now at the 4,5 position. The resulting dienoyl- CoA is not a good substrate for the next enzyme, enoyl-CoA hydratase. The dienoyl- CoA must undergo an NADPH-dependent reduction to convert its two double bonds to a single *trans 3,4 double bond. This product must then be isomerized to* produce the *trans 2,3 double bond that is recognized by enoyl-CoA hydratase.*

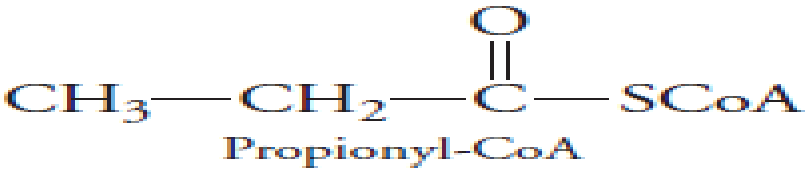
WHY are unsaturated fatty acids less fattening?



Carbon compounds with double bonds are slightly more oxidized than saturated compounds, so less energy is released in converting them to CO 2 . Accordingly, a diet rich in unsaturated fatty acids contains fewer calories than a diet rich in saturated fatty acids. The bypass reactions (التفاعلات الجانبية) described above provide the molecular explanation why *unsaturated fatty acids yield less free energy than saturated fatty acids. First, the enoyl-CoA isomerase reaction bypasses the QH2-producing* acyl-CoA dehydrogenase step, so 1.5 fewer ATP are produced. Second, the NADPH dependent reductase consumes 2.5 ATP equivalents because NADPH is energetically equivalent to NADH.

Oxidation of odd-chain fatty acids yields propionyl-CoA

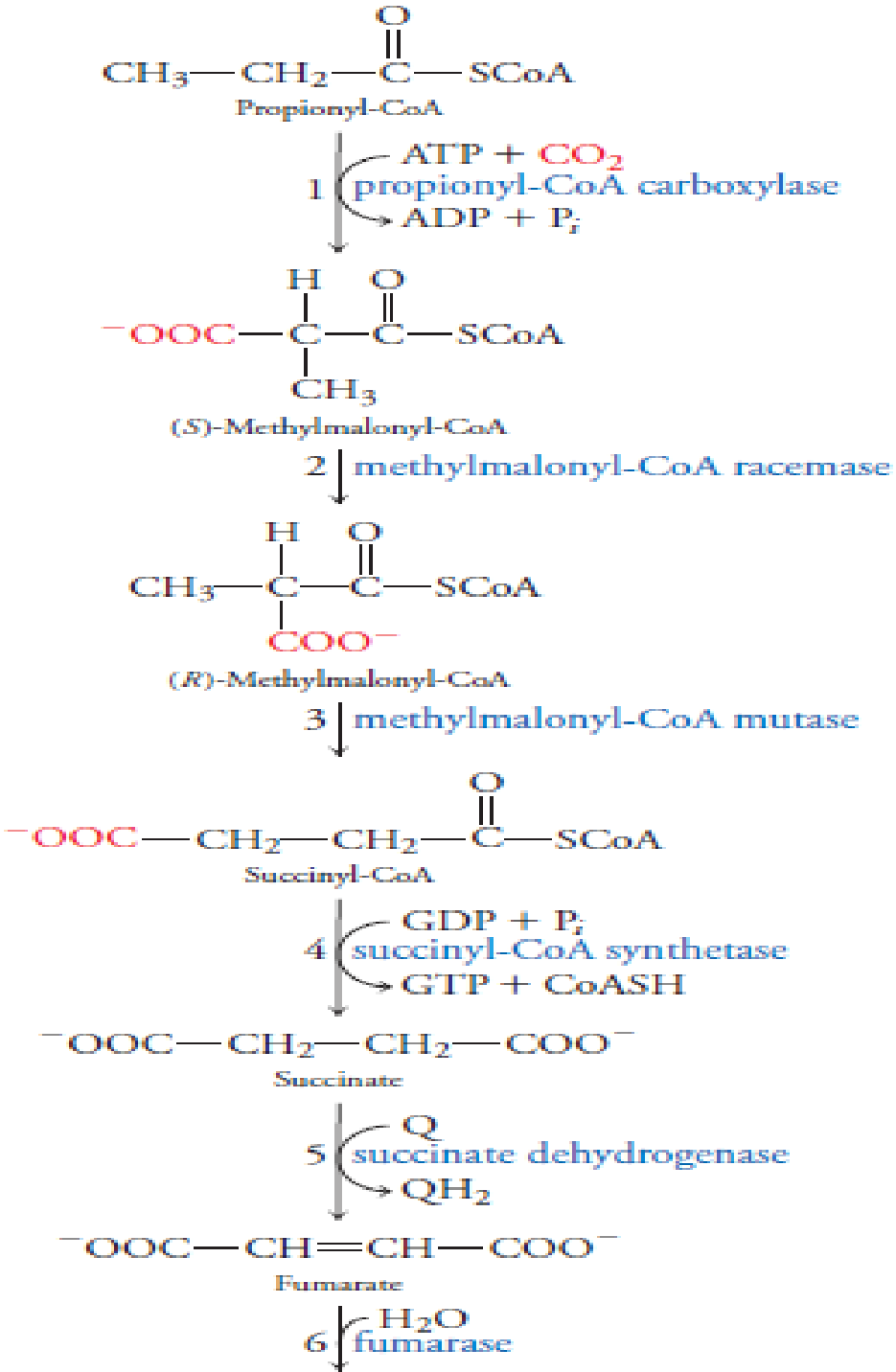
Most fatty acids have an even number of carbon atoms (this is because they are synthesized by the **addition of two-carbon acetyl units**, as we will see later in this chapter). However, some **plant and bacterial fatty acids that make their way into the human system have an odd number of carbon atoms**. *The final round of β oxidation of these molecules leaves a three-carbon fragment,* ***propionyl-CoA****, rather than the usual acetyl-CoA.*



Propionyl-CoA

This intermediate can be further metabolized by the sequence of steps outlined in **Figure 12. At first, this pathway seems longer than necessary**. For example, **adding a carbon to C3** of the propionyl group would immediately **generate succinyl-CoA**. However, such a reaction is **not chemically favored**, **because C3 is too far from the electron-delocalizing effects of the CoA thioester**. Consequently, propionyl-CoA carboxylase must add a carbon to C2, and then methylmalonyl-CoA mutase must rearrange the carbon skeleton to produce succinyl-CoA. Note that succinyl-CoA is not the end point of the pathway. Because it is a citric acid cycle intermediate, it acts catalytically and is not consumed by the cycle. ***The complete catabolism of the carbons derived from propionyl-CoA requires that the succinyl-CoA be converted to pyruvate and then to acetyl-CoA, which enters the citric acid cycle as a substrate.***

Catabolism of propionyl-CoA

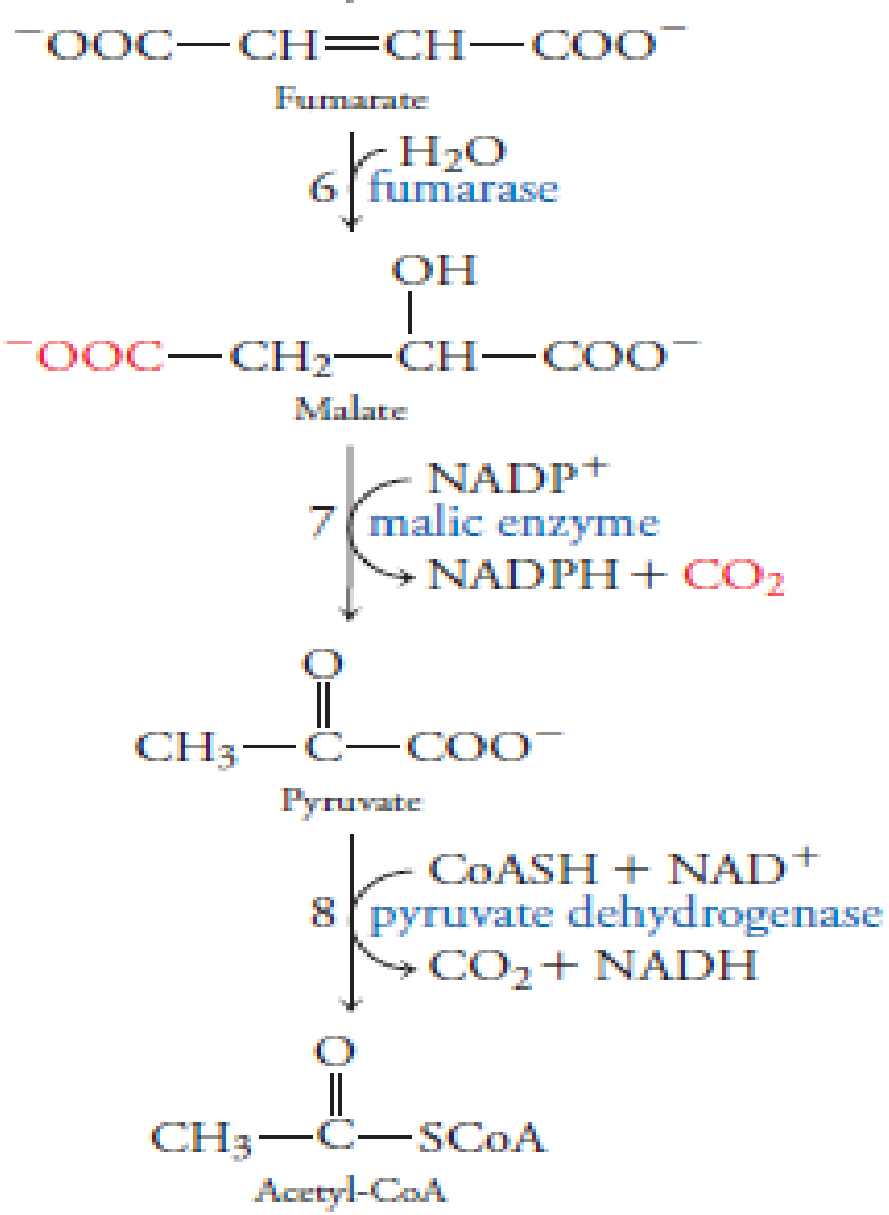


1.Propionyl-CoA carboxylase adds a carboxyl group at C2 of the propionyl group to form a four-carbon methylmalonyl group.

2.A racemase interconverts the two different methylmalonyl-CoA stereoisomers (the two configurations are indicated by the R and S symbols).

3.Methylmalonyl-CoA mutase rearranges the carbon skeleton to generate succinyl-CoA.

4-6.Succinyl-CoA, a citric acid cycle intermediate, is converted to malate by reactions 5–7 of the citric acid cycle .



7. After being exported from the mitochondria, malate is decarboxylated by malic enzyme to produce pyruvate in the cytosol.

8. Pyruvate, imported back into the mitochondria, can then be converted to acetyl-CoA by the pyruvate dehydrogenase complex.

Figure 12. Catabolism of propionyl-CoA.

Methylmalonyl-CoA mutase, which catalyzes step 3 of Figure 12., is an unusual enzyme because it mediates a rearrangement of carbon atoms and requires a prosthetic group derived from the vitamin cobalamin (vitamin B12; Fig. 13)

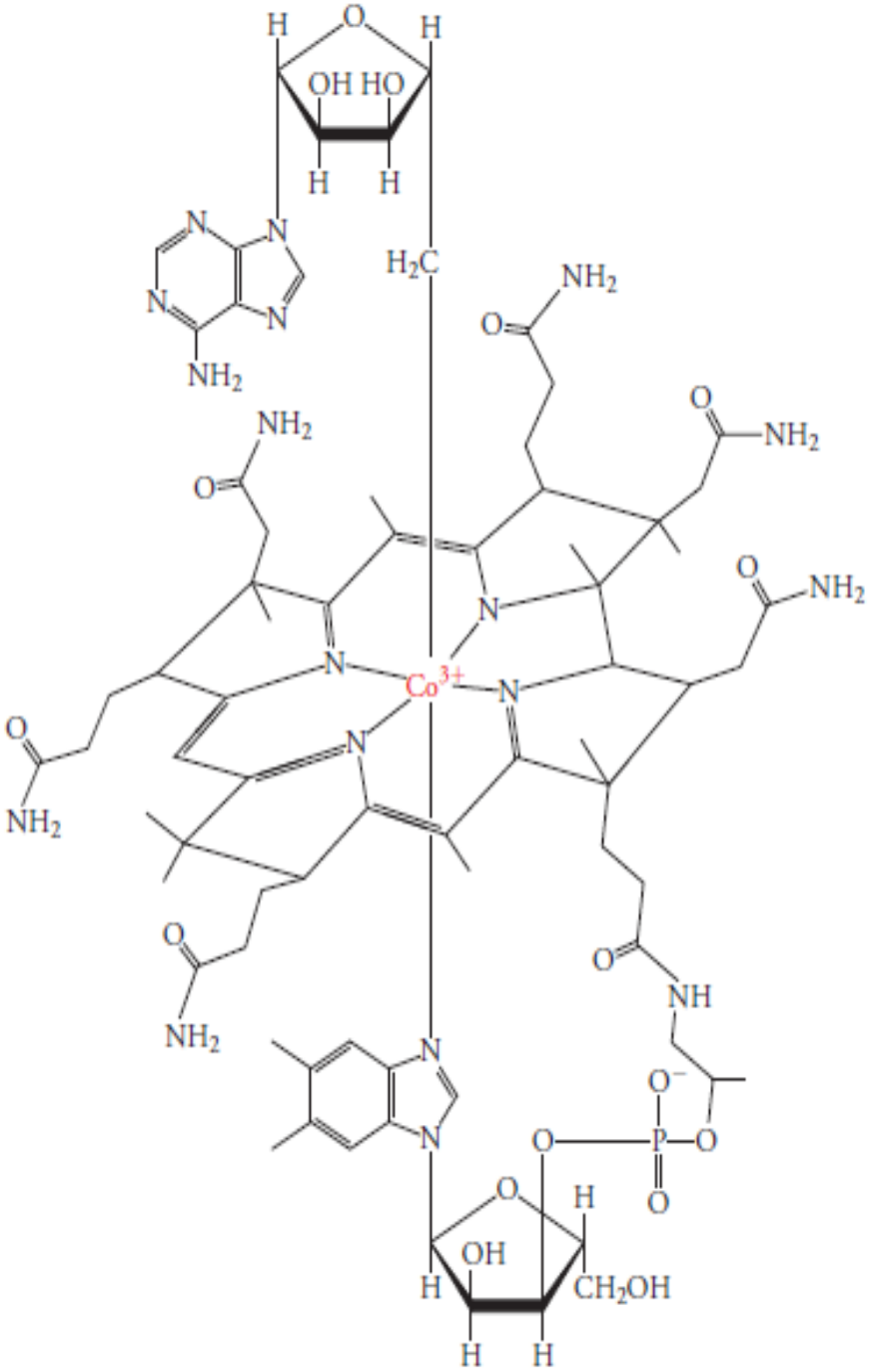


Figure 13.The cobalamin-derived cofactor. The prosthetic group of methylmalonyl-CoA mutase is a derivative of the vitamin cobalamin. The structure includes a hemelike ring structure with a central cobalt ion. Note that one of the Co ligands is a carbon atom, an extremely rare instance of a carbon–metal bond in a biological system.

Some fatty acid oxidation occurs in peroxisomes

The majority of a mammalian cell's fatty acid oxidation occurs in mitochondria, but a small percentage is carried out in organelles known as **peroxisomes (Fig.14).** In plants, all fatty acid oxidation occurs in peroxisomes and glyoxysomes. Peroxisomes are enclosed by a single membrane and contain a variety of degradative and biosynthetic enzymes. The peroxisomal b oxidation pathway differs from the mitochondrial pathway in the first step. An **acyl-CoA oxidase** catalyzes the reaction (in mitochondria **is catalyzed by an acyl-CoA dehydrogenase**).

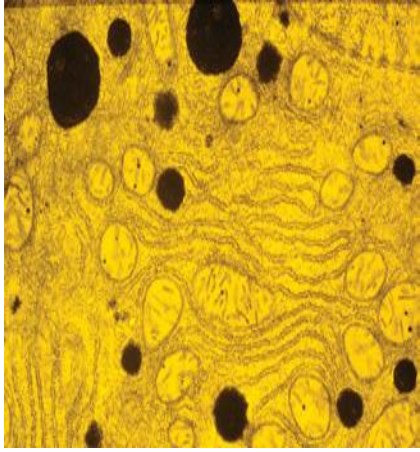
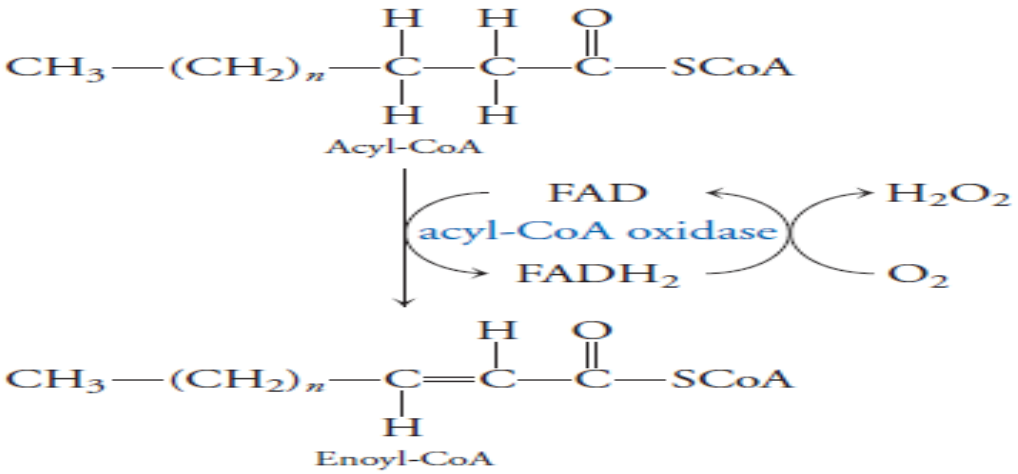


Figure 14. Peroxisomes. Nearly all eukaryotic cells contain these single membrane- bound organelles (dark structures), which are similar to plant glyoxysome.



The enoyl-CoA product of the reaction is identical to the product of the mitochondrial acyl-CoA dehydrogenase reaction (see Fig. 11b), but the electrons removed from the acyl-CoA are transferred not to ubiquinone but directly to molecular oxygen to produce hydrogen peroxide, H_2O_2. This reaction product, which gives the peroxisome its name, is subsequently broken down by the peroxisomal enzyme catalase:

$$2\ H_2O_2 \rightarrow 2\ H_2O + O_2$$

Because the peroxisomal oxidation enzymes are specific for very-long-chain fatty acids (such as those containing over 20 carbons) and bind short-chain fatty acids with low affinity, ***the peroxisome serves as a chain-shortening system***. The partially degraded fatty acyl-CoAs then make their way to the mitochondria for complete oxidation.

The peroxisome is also responsible for **degrading some branched-chain fatty acids**, which are **not recognized by the mitochondrial enzymes**. One such nonstandard fatty acid is phytanate, which is derived from the side chain of chlorophyll molecules and is present in all plant-containing diets. Phytanate must be degraded by peroxisoma lenzymes because the methyl group at C3 prevents dehydrogenation by 3- hydroxyacyl-CoA dehydrogenase (step 3 of the standard β oxidation pathway).

SUMMARY (Fatty Acid Oxidation)

• Lipoproteins transport lipids, including cholesterol, in the bloodstream. High levels of LDL are associated with the development of atherosclerosis.

• Fatty acids released from triacylglycerols by the action of lipases are activated by their attachment to CoA in an ATP-dependent reaction.

• In the process of b oxidation, a series of four enzymatic reactions degrades a fatty acyl-CoA two carbons at a time, producing one QH2, one NADH, and one acetyl-CoA, which can be further oxidized by the citric acid cycle. Reoxidation of the reduced cofactors generates considerable ATP.

• Oxidation of unsaturated and odd-chain fatty acids requires additional enzymes. Very-long-chain and branched fatty acids are oxidized in peroxisomes.