# Lipid Metabolism

# Lipid: a major storage form of metabolic energy

Chapter 19 Opener Fundamentals of Biochemistry, 2/e

# Fatty acids

1. 지방산의 주요 생리적 기능
   (1) 인지질 (phospholipid)과 당지질 (glycolipid)들의 구성성분
   (2) 유도체들은 호르몬들이나 세포 내 전령 (intracellular messenger)로 작용
   (3) triacylglycerol과 같은 에너지 저장물질

2. 구조
   일반적인 구조식: $CH_3(CH_2)nCOOH$
   포화지방산: no C-C double bonds
   불포화지방산: double bonds

명명법; common name (http://www.cyberlipid.org/fa/acid0001.htm)
   systematic name: n-octadecan**oic** acid(stearic acid)
   octade**cenoic** acid (oleate)
   octadeca**dienoic** acid
   octadeca**trienoic** acid
   numbering: carboxyl 말단부터 시작

생물계에 존재하는 지방산들은 전형적으로는 14와 24개 사이의 짝수로 존재
그 중에서도 16과 18개의 탄소를 가진 것들이 가장 많다.

Fatty acids: carboxylic acids with long-chain hydrocarbon side groups
<14 or >20 are uncommon

**Table 9-1 The Common Biological Fatty Acids**

| Symbol[a] | Common Name | Systematic Name | Structure | mp (°C) |
|---|---|---|---|---|
| ***Saturated fatty acids*** | | | | |
| 12:0 | Lauric acid | Dodecanoic acid | $CH_3(CH_2)_{10}COOH$ | 44.2 |
| 14:0 | Myristic acid | Tetradecanoic acid | $CH_3(CH_2)_{12}COOH$ | 52 |
| 16:0 | Palmitic acid | Hexadecanoic acid | $CH_3(CH_2)_{14}COOH$ | 63.1 |
| 18:0 | Stearic acid | Octadecanoic acid | $CH_3(CH_2)_{16}COOH$ | 69.1 |
| 20:0 | Arachidic acid | Eicosanoic acid | $CH_3(CH_2)_{18}COOH$ | 75.4 |
| 22:0 | Behenic acid | Docosanoic acid | $CH_3(CH_2)_{20}COOH$ | 81 |
| 24:0 | Lignoceric acid | Tetracosanoic acid | $CH_3(CH_2)_{22}COOH$ | 84.2 |
| ***Unsaturated fatty acids (all double bonds are cis)*** | | | | |
| 16:1*n*−7 | Palmitoleic acid | 9-Hexadecenoic acid | $CH_3(CH_2)_5CH{=}CH(CH_2)_7COOH$ | −0.5 |
| 18:1*n*−9 | Oleic acid | 9-Octadecenoic acid | $CH_3(CH_2)_7CH{=}CH(CH_2)_7COOH$ | 13.2 |
| 18:2*n*−6 | Linoleic acid | 9,12-Octadecadienoic acid | $CH_3(CH_2)_4(CH{=}CHCH_2)_2(CH_2)_6COOH$ | −9 |
| 18:3*n*−3 | α-Linolenic acid | 9,12,15-Octadecatrienoic acid | $CH_3CH_2(CH{=}CHCH_2)_3(CH_2)_6COOH$ | −17 |
| 18:3*n*−6 | γ-Linolenic acid | 6,9,12-Octadecatrienoic acid | $CH_3(CH_2)_4(CH{=}CHCH_2)_3(CH_2)_3COOH$ | |
| 20:4*n*−6 | Arachidonic acid | 5,8,11,14-Eicosatetraenoic acid | $CH_3(CH_2)_4(CH{=}CHCH_2)_4(CH_2)_2COOH$ | −49.5 |
| 20:5*n*−3 | EPA | 5,8,11,14,17-Eicosapentaenoic acid | $CH_3CH_2(CH{=}CHCH_2)_5(CH_2)_2COOH$ | −54 |
| 22:6*n*−3 | DHA | 4,7,10,13,16,19-Docosohexenoic acid | $CH_3CH_2(CH{=}CHCH_2)_6CH_2COOH$ | |
| 24:1*n*−9 | Nervonic acid | 15-Tetracosenoic acid | $CH_3(CH_2)_7CH{=}CH(CH_2)_{13}COOH$ | 39 |

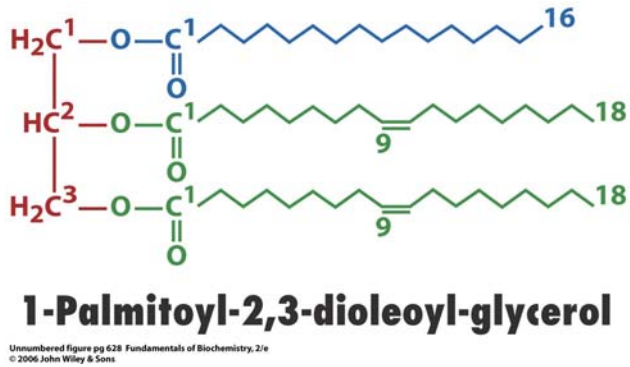
[a]Number of carbon atoms: Number of double bonds. For unsaturated fatty acids, the quantity "*n*−*x*" indicates the position of the last double bond in the fatty acid, where *n* is its number of C atoms, and *x* is the position of the last double-bonded C atom counting from the methyl terminal (ω) end.

*Source:* Dawson, R.M.C., Elliott, D.C., Elliott, W.H., and Jones, K.M., *Data for Biochemical Research* (3rd ed.), Chapter 8, Clarendon Press (1986).

**Table 9-1 Fundamentals of Biochemistry, 2/e**

# Lipid digestion, absorption, and transport

Triacylglycerol: long term *E* storage
reduced, nonpolar, anhydrous

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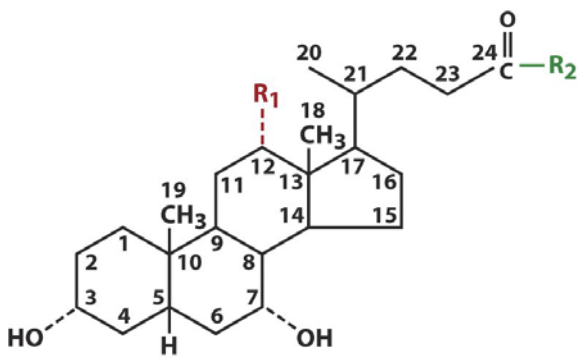
Digestion & absorption in small intestine
Bile acids (syn by liver, stored in gall bladder, secreted into small intestine)
Increase lipid-water interface



| | $R_1 = OH$ | $R_1 = H$ |
|---|---|---|
| $R_2 = OH$ | Cholic acid | Chenodeoxycholic acid |
| $R_2 = NH—CH_2—COOH$ | Glycocholic acid | Glycochenodeoxycholic acid |
| $R_2 = NH—CH_2—CH_2—SO_3H$ | Taurocholic acid | Taurochenodeoxycholic acid |

Figure 19-1 Fundamentals of Biochemistry, 2/e
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# Lipid transport

## in complex with proteins: lipoproteins

### nonpolar core of triacylglycerols and cholesteryl esters
### surrounded by an amphiphilic coating of protein, phospholipid, and cholesterol

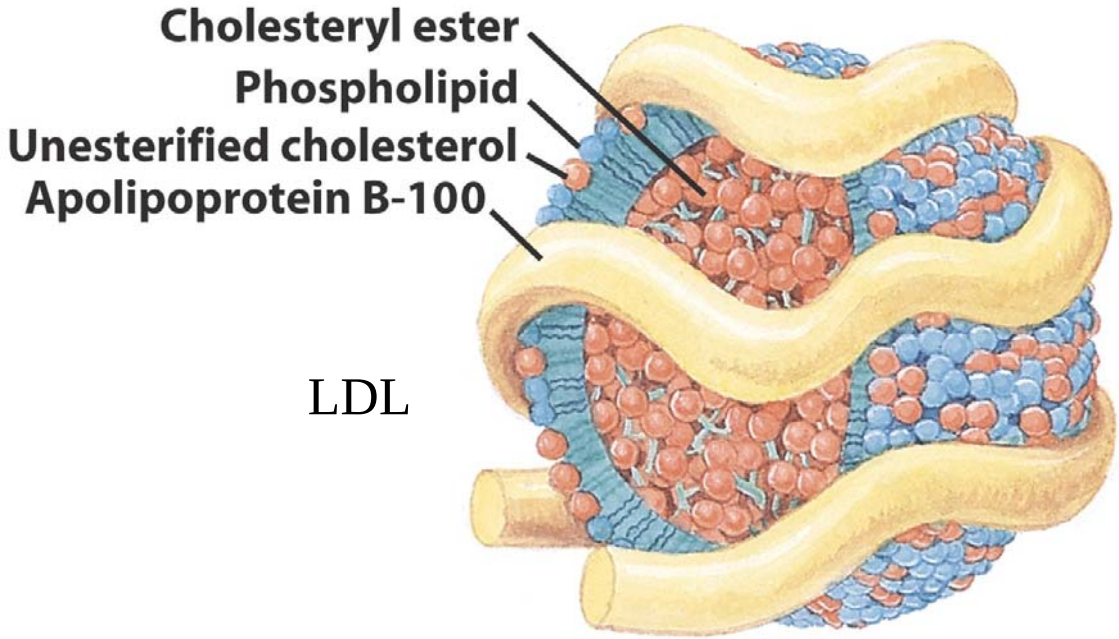
**Table 19-1 Characteristics of the Major Classes of Lipoproteins in Human Plasma.**

| | Chylomicrons | VLDL | IDL | LDL | HDL |
|---|---|---|---|---|---|
| Density ($g \cdot cm^{-3}$) | <0.95 | <1.006 | 1.006–1.019 | 1.019–1.063 | 1.063–1.210 |
| Particle diameter (Å) | 750–12,000 | 300–800 | 250–350 | 180–250 | 50–120 |
| Particle mass (kD) | 400,000 | 10,000–80,000 | 5000–10,000 | 2300 | 175–360 |
| % Protein[a] | 1.5–2.5 | 5–10 | 15–20 | 20–25 | 40–55 |
| % Phospholipids[a] | 7–9 | 15–20 | 22 | 15–20 | 20–35 |
| % Free cholesterol[a] | 1–3 | 5–10 | 8 | 7–10 | 3–4 |
| % Triacylglycerols[b] | 84–89 | 50–65 | 22 | 7–10 | 3–5 |
| % Cholesteryl esters[b] | 3–5 | 10–15 | 30 | 35–40 | 12 |
| Major apolipoproteins | A-I, A-II, B-48, C-I, C-II, C-III, E | B-100, C-I, C-II, C-III, E | B-100, C-I, C-II, C-III, E | B-100 | A-I, A-II, C-I, C-II, C-III, D, E |

[a]Surface components.

[b]Core lipids.

Apolipoproteins: at least nine are known




LDL

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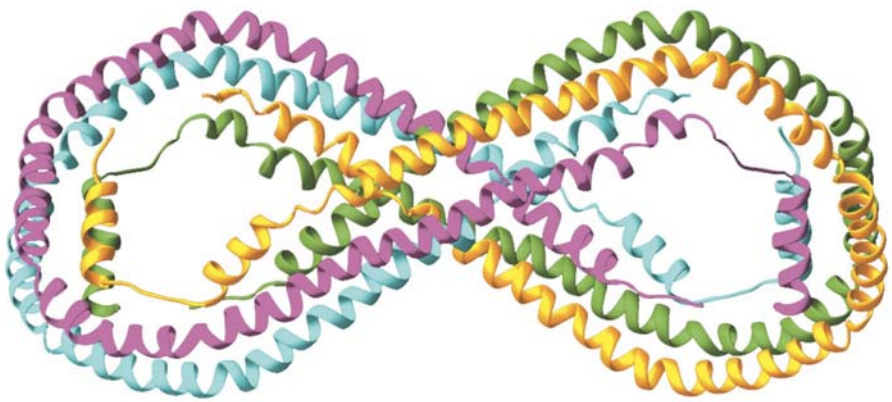
Human apoA-1



tetramer

Figure 19-6a Fundamentals of Biochemistry, 2/e
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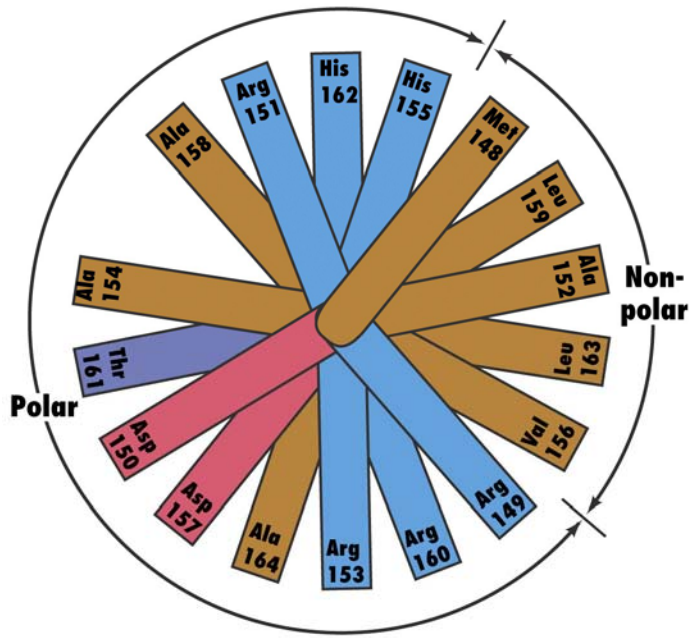


Figure 19-6b Fundamentals of Biochemistry, 2/e
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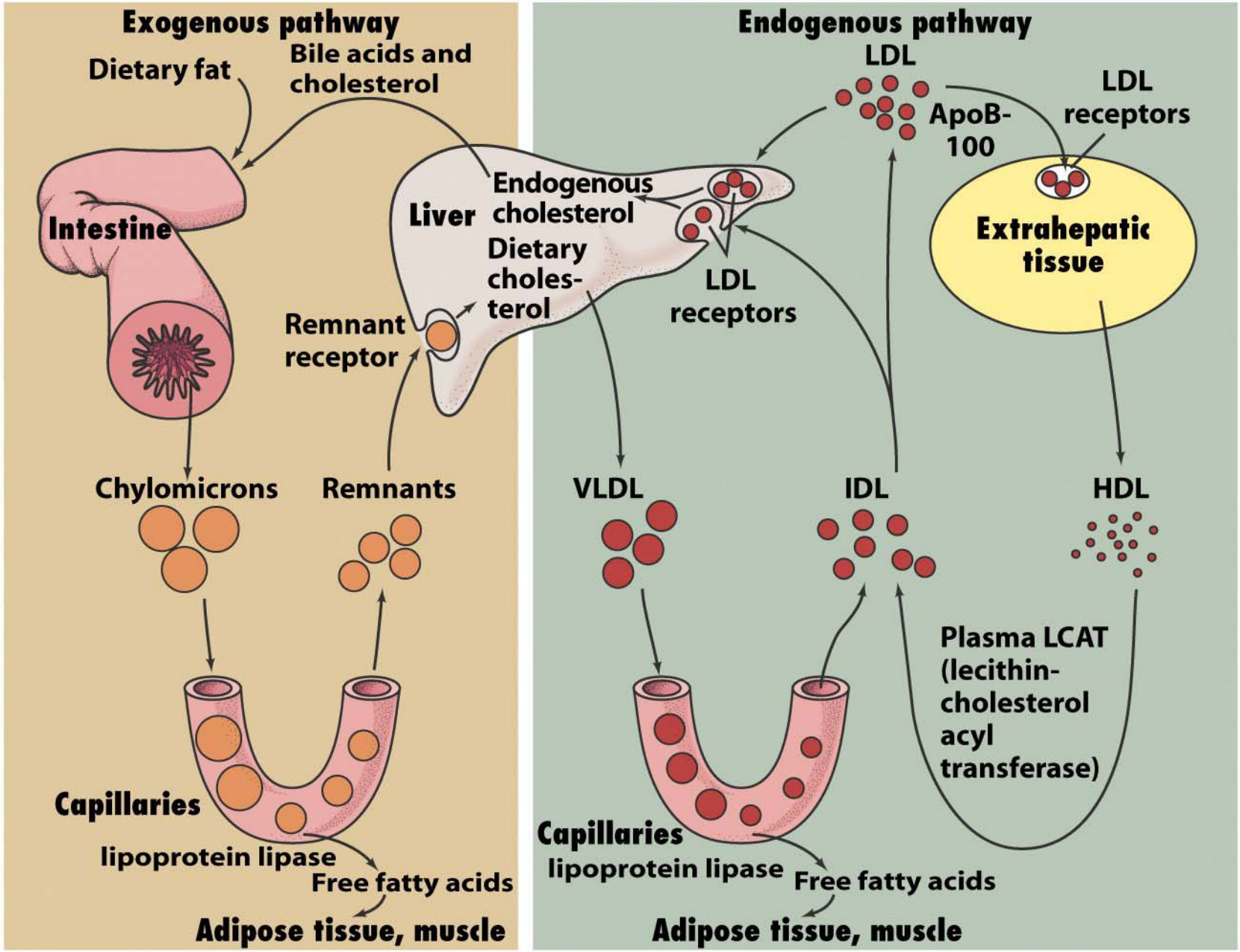



Figure 19-7 Fundamentals of Biochemistry, 2/e

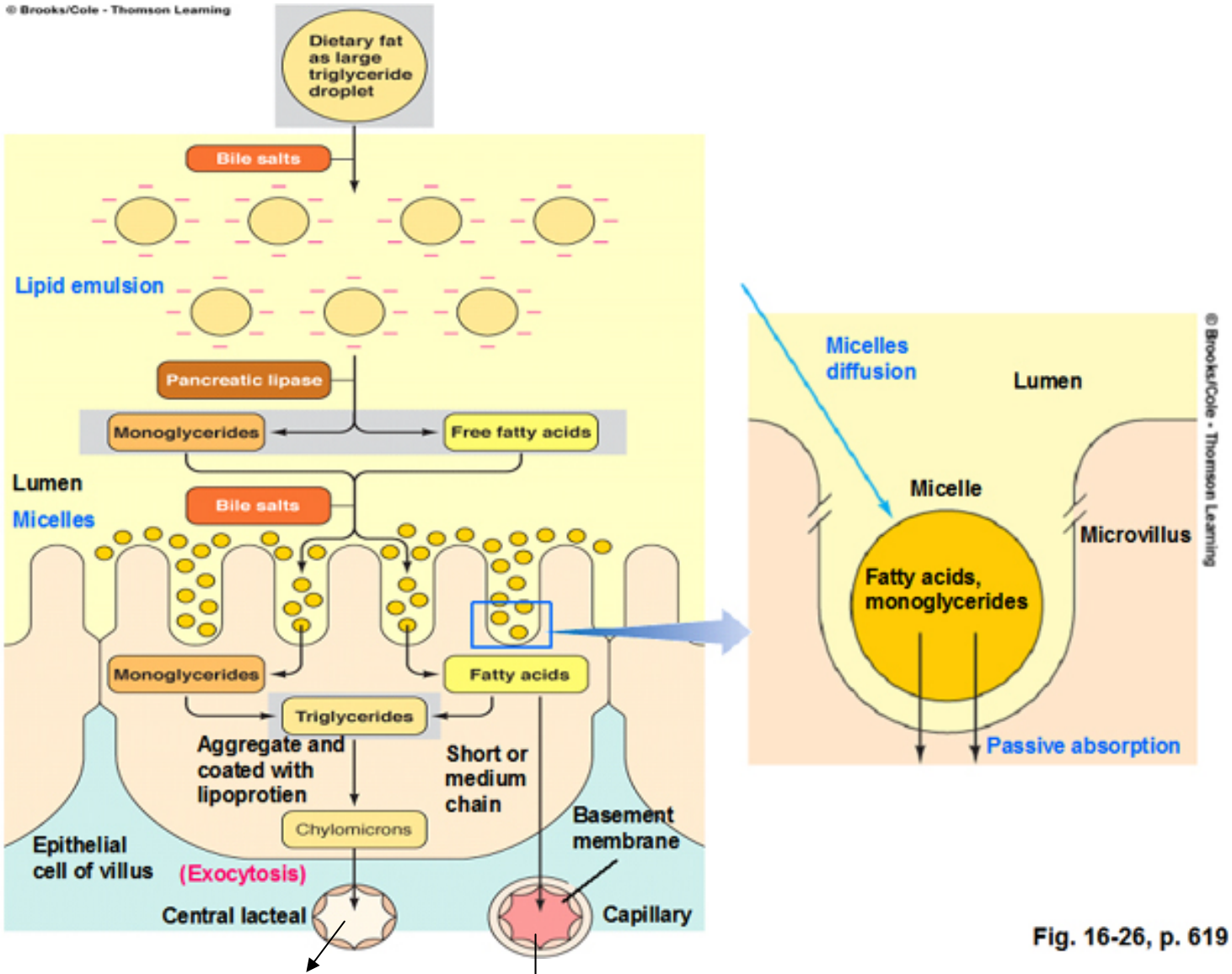
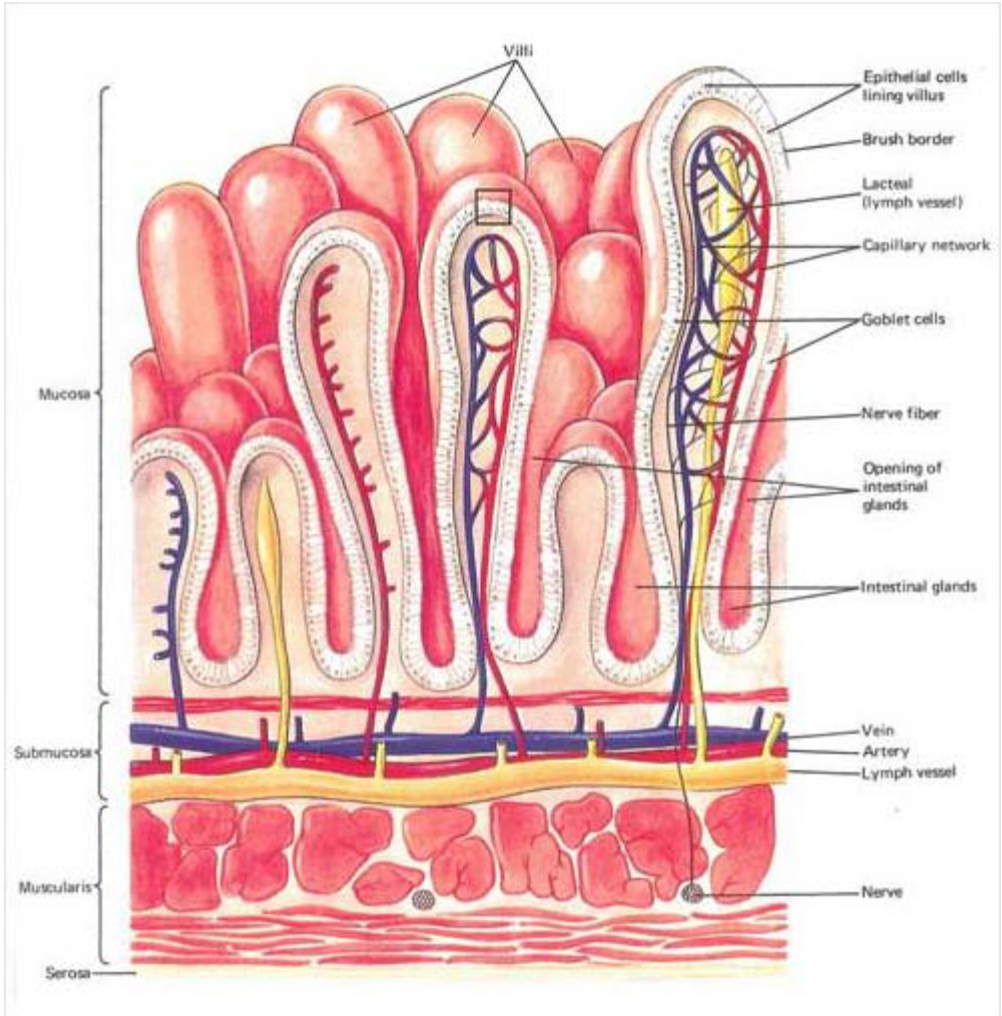


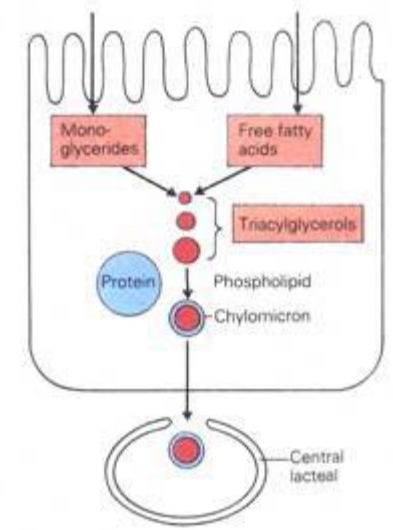

Fig. 16-26, p. 619

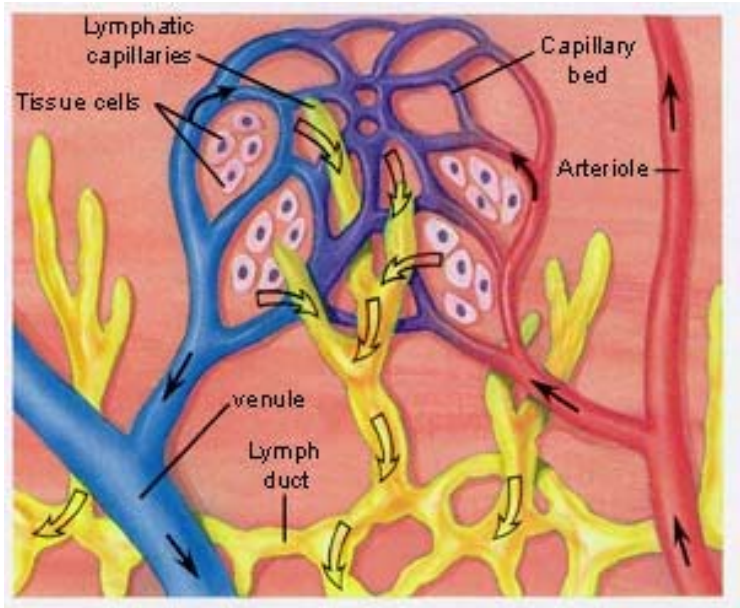
thoracic duct and left jugular vein

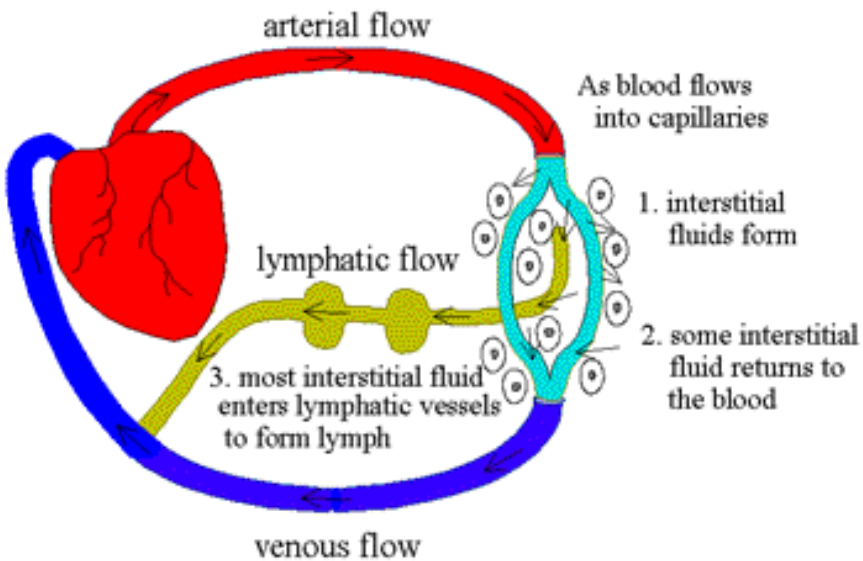
Portal vein to liver

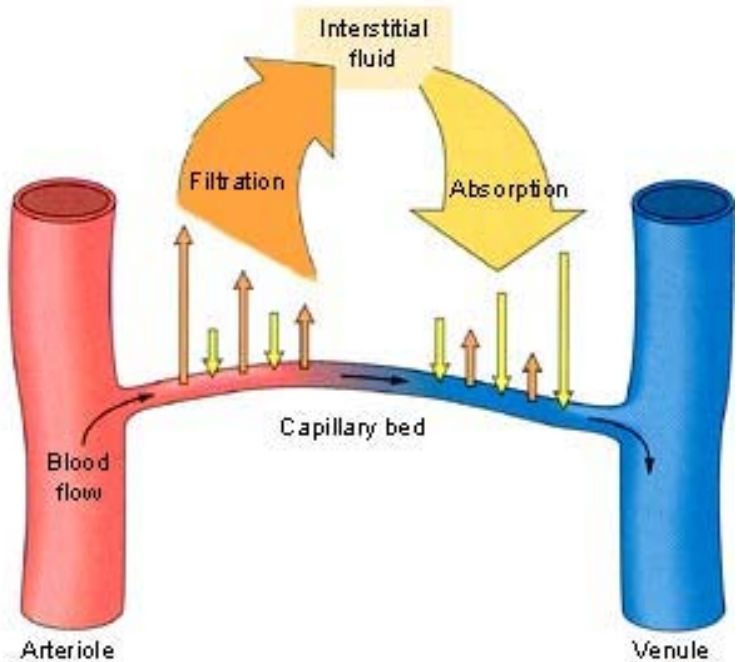


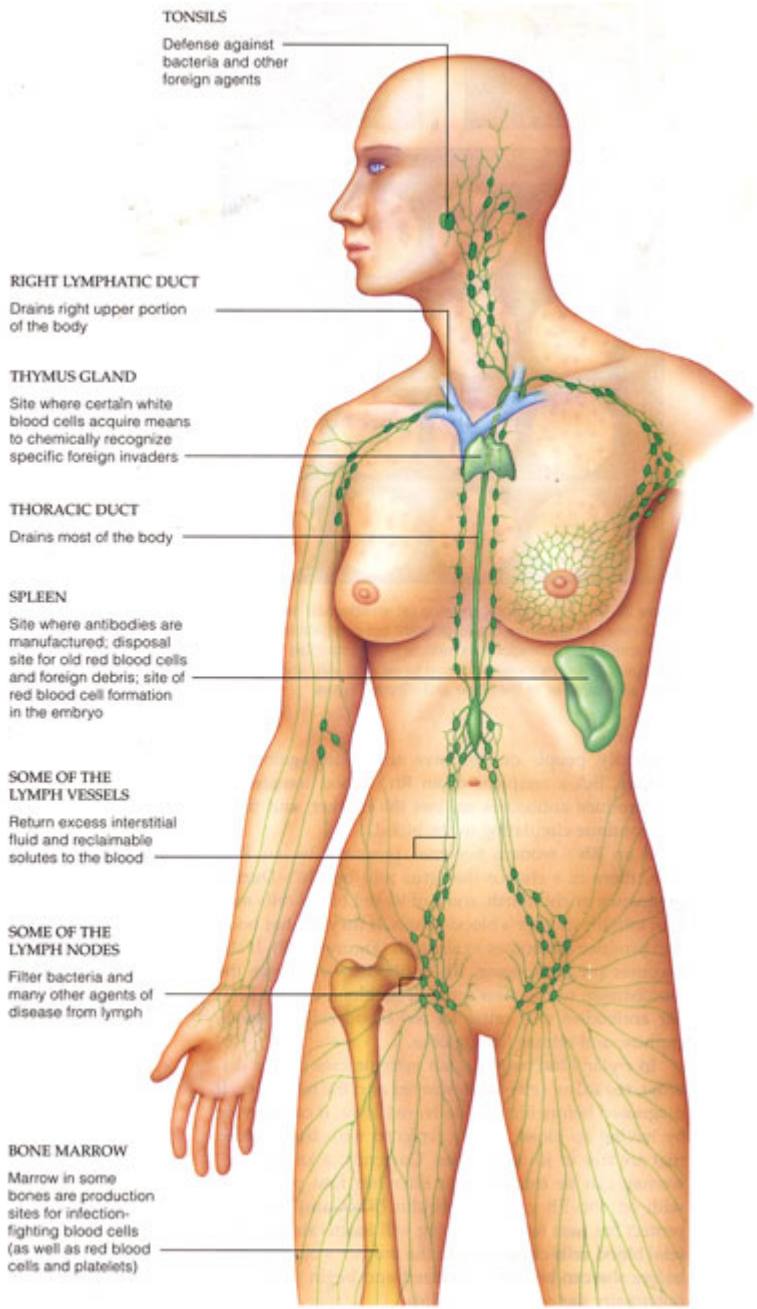

*3–31*
r phase of triacylglycerol absorption.

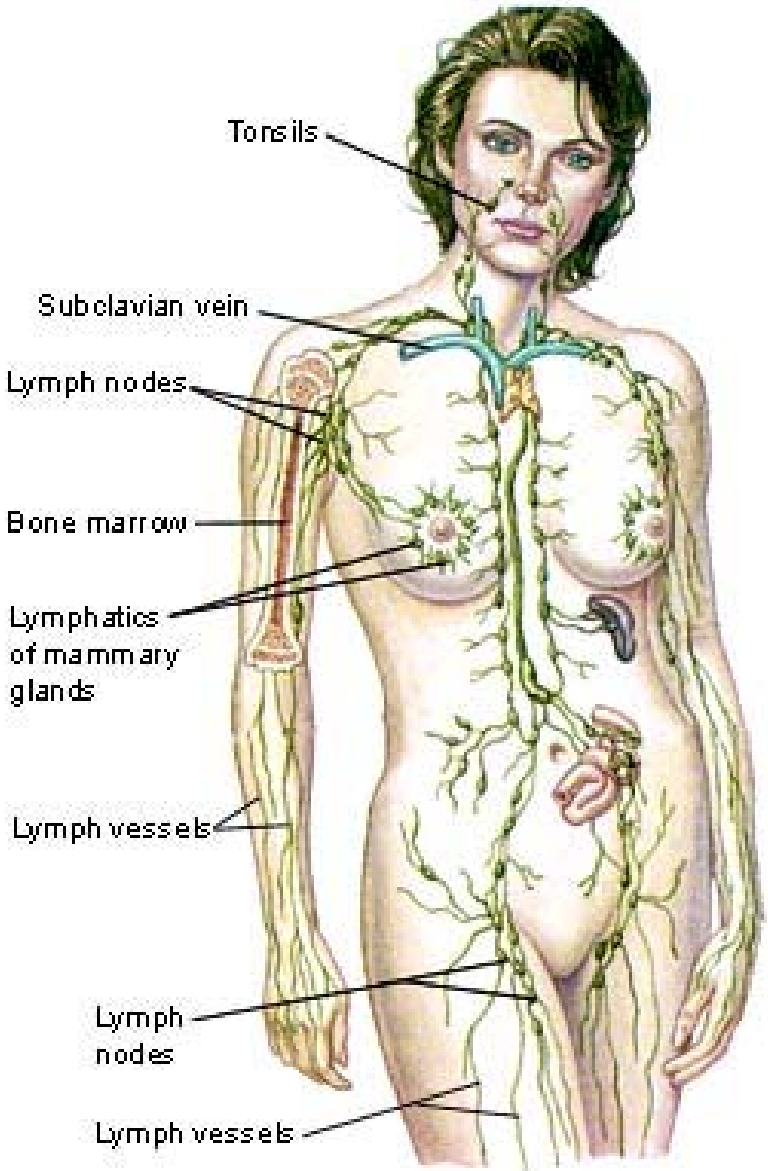



Lymphatic capillaries
Capillary bed
Tissue cells
Arteriole
venule
Lymph duct

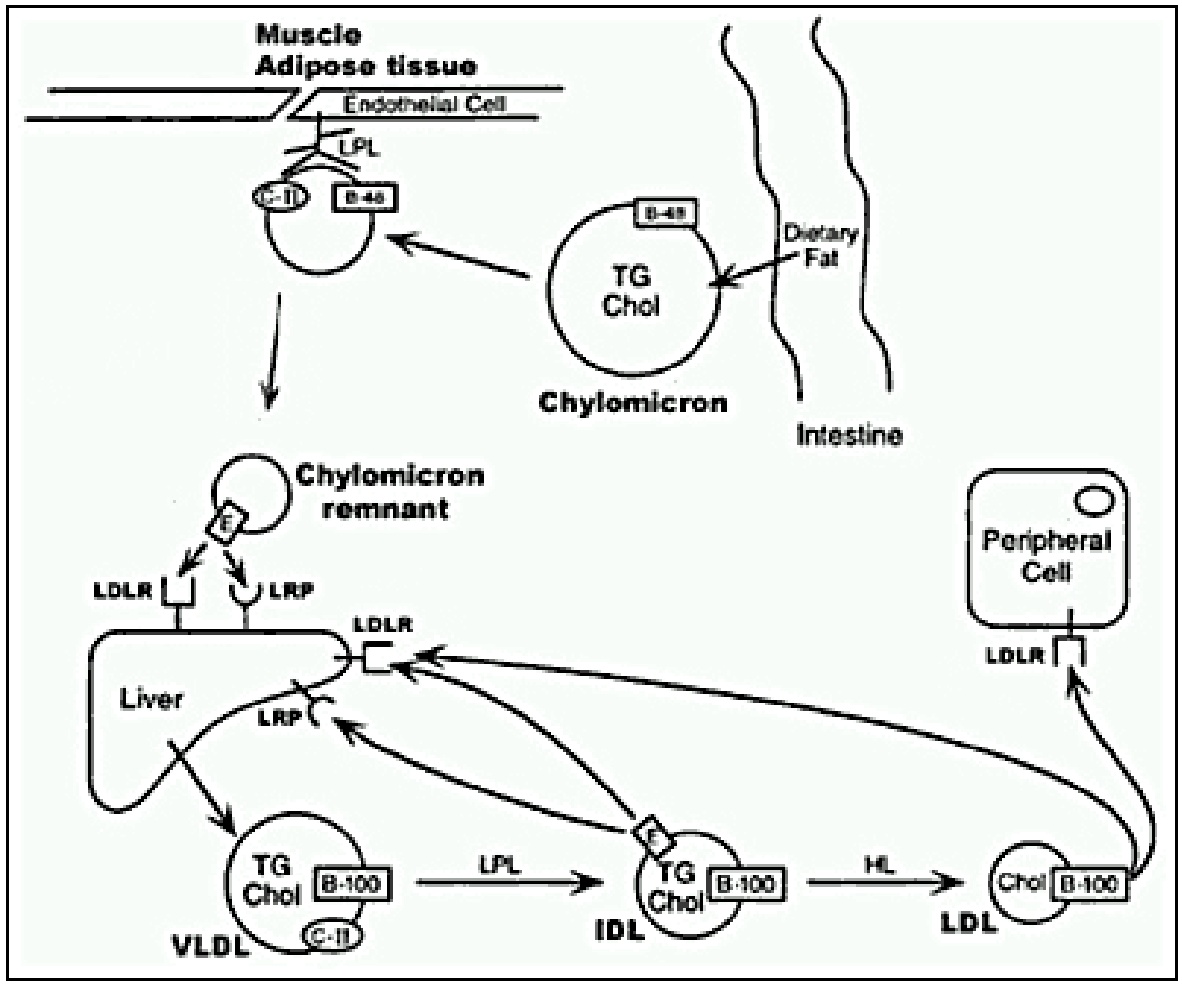

arterial flow
As blood flows into capillaries
1. interstitial fluids form
lymphatic flow
2. some interstitial fluid returns to the blood
3. most interstitial fluid enters lymphatic vessels to form lymph
venous flow


Interstitial fluid
Filtration
Absorption
Capillary bed
Blood flow
Arteriole
Venule

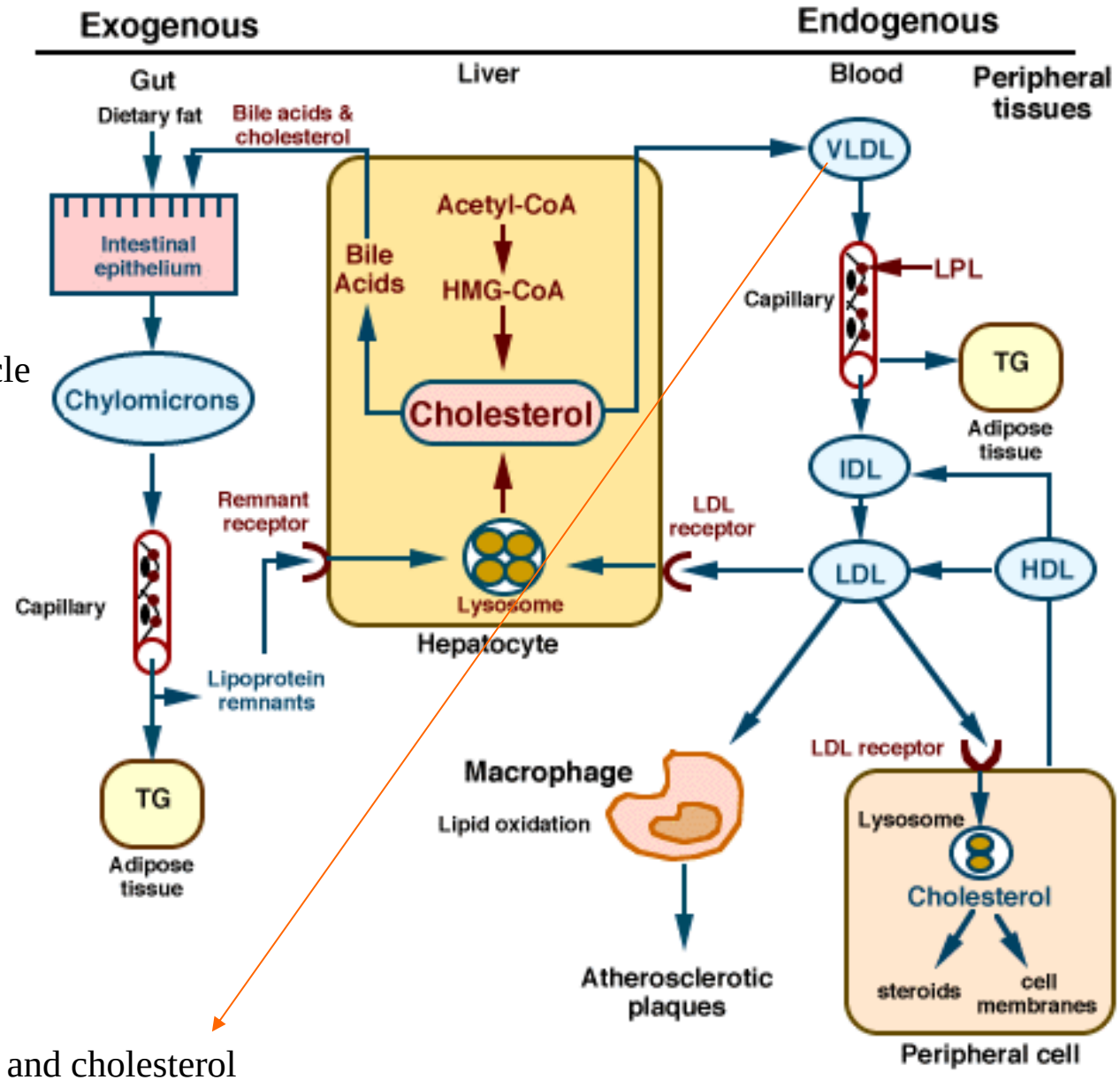

TONSILS
Defense against bacteria and other foreign agents
RIGHT LYMPHATIC DUCT
Drains right upper portion of the body
THYMUS GLAND
Site where certain white blood cells acquire means to chemically recognize specific foreign invaders
THORACIC DUCT
Drains most of the body
SPLEEN
Site where antibodies are manufactured; disposal site for old red blood cells and foreign debris; site of red blood cell formation in the embryo
SOME OF THE LYMPH VESSELS
Return excess interstitial fluid and reclaimable solutes to the blood
SOME OF THE LYMPH NODES
Filter bacteria and many other agents of disease from lymph
BONE MARROW
Marrow in some bones are production sites for infection-fighting blood cells (as well as red blood cells and platelets)


Tonsils
Subclavian vein
Lymph nodes
Bone marrow
Lymphatics of mammary glands
Lymph vessels
Lymph nodes
Lymph vessels

LPL: found in endothelial cells lining the capillaries



Deliver dietary TG to muscle and adipose tissue




Transport endogenous TG and cholesterol

# Receptor-mediated endocytosis of LDL

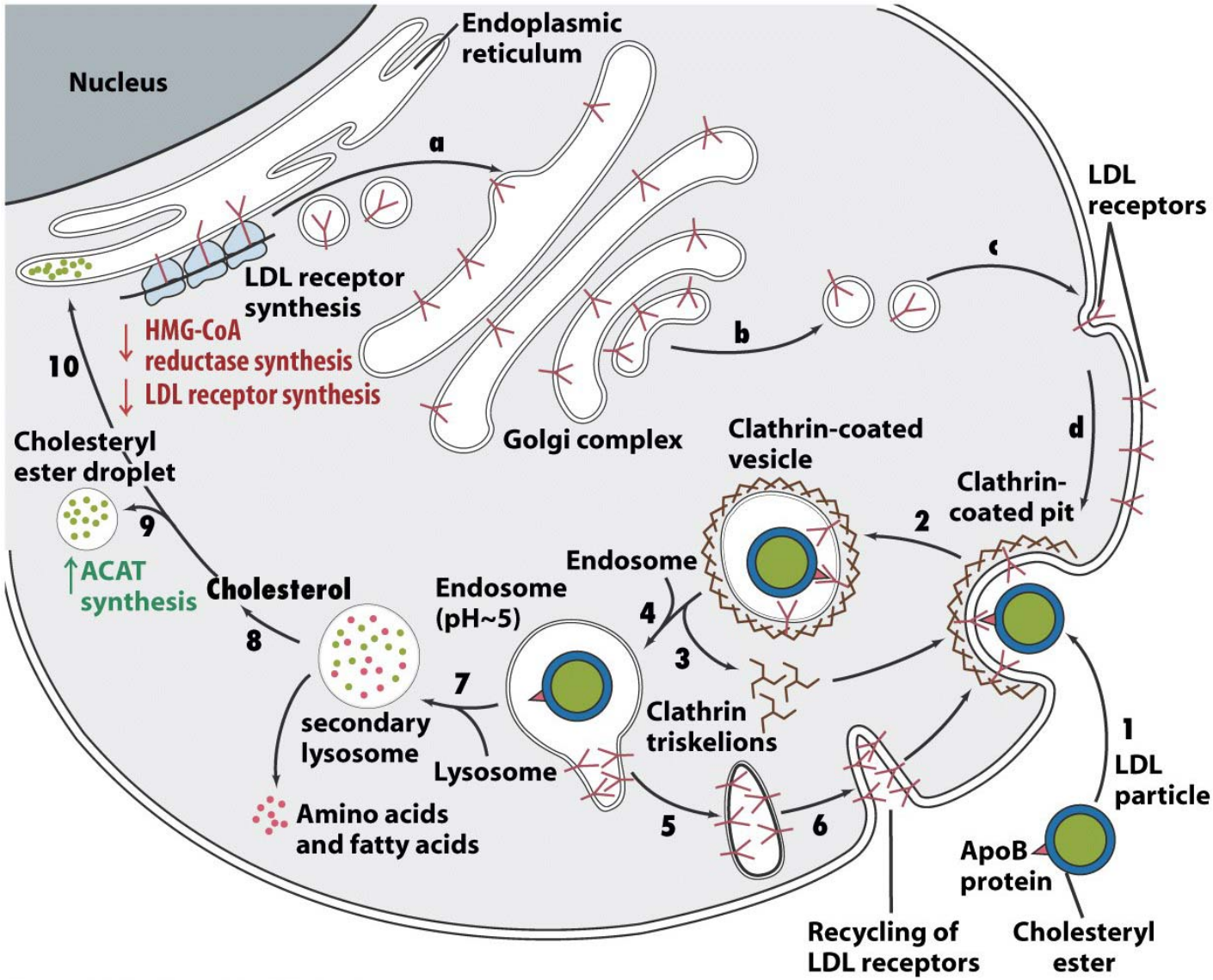



Figure 19-8 Fundamentals of Biochemistry, 2/e

# HDL transports cholesterol from the tissue to the liver

The liver is the only organ capable of disposing of
significant quantities of cholesterol (by its conversion to bile acids)

LDL: receptor-mediated endocytosis
HDL: SR-BI (cell-surface receptor)-mediated

# Fatty acid oxidation

occur in mitochondria

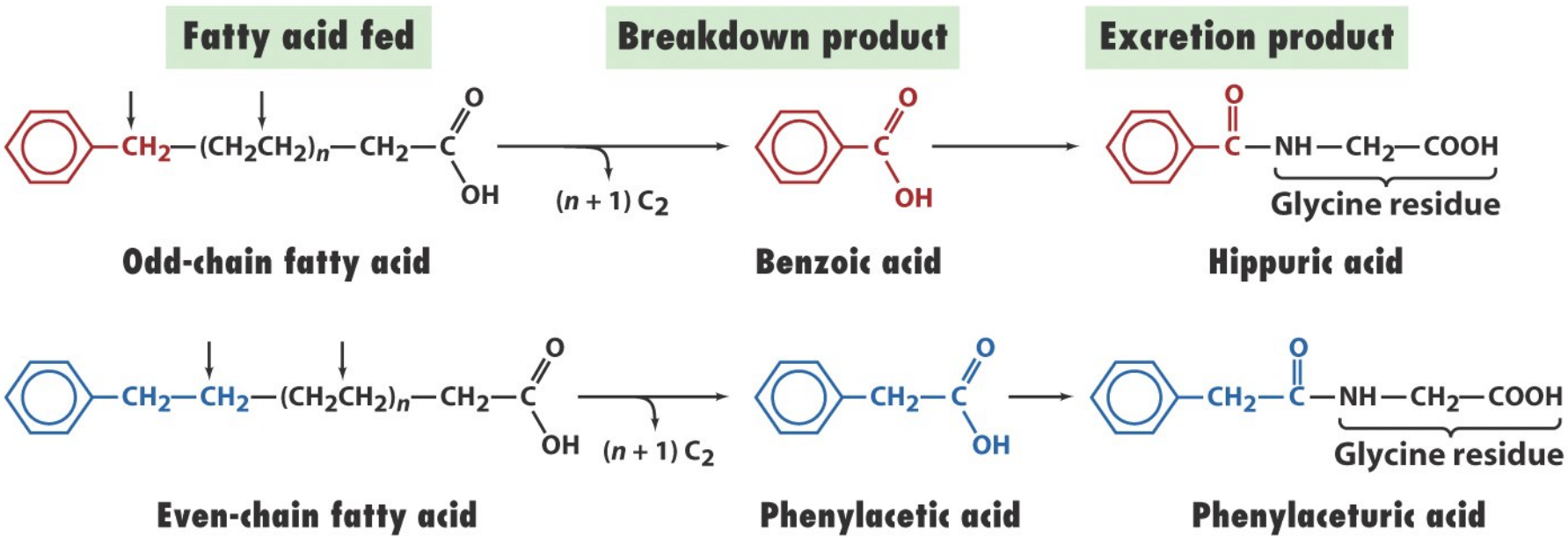



Figure 19-9 Fundamentals of Biochemistry, 2/e

# Fatty acid activation

long chain fatty acid

by Acyl-CoA synthetases (thiokinases)

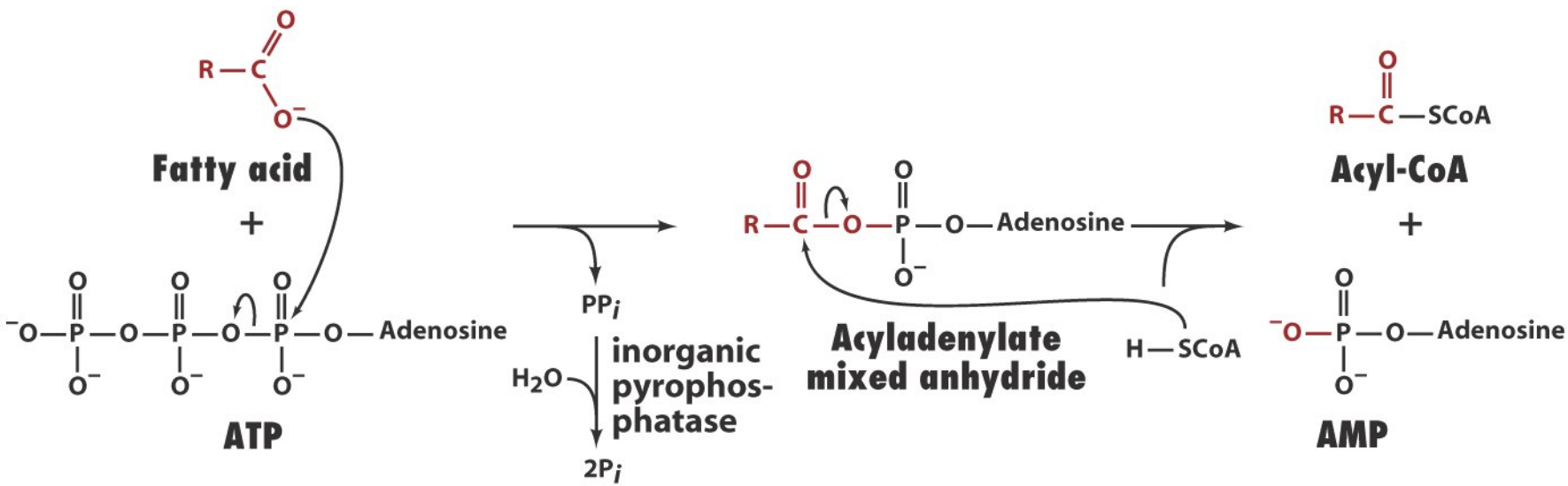
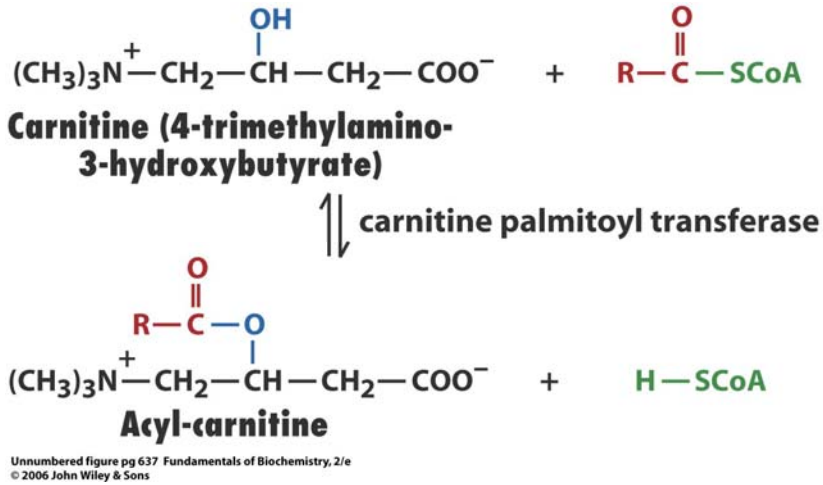
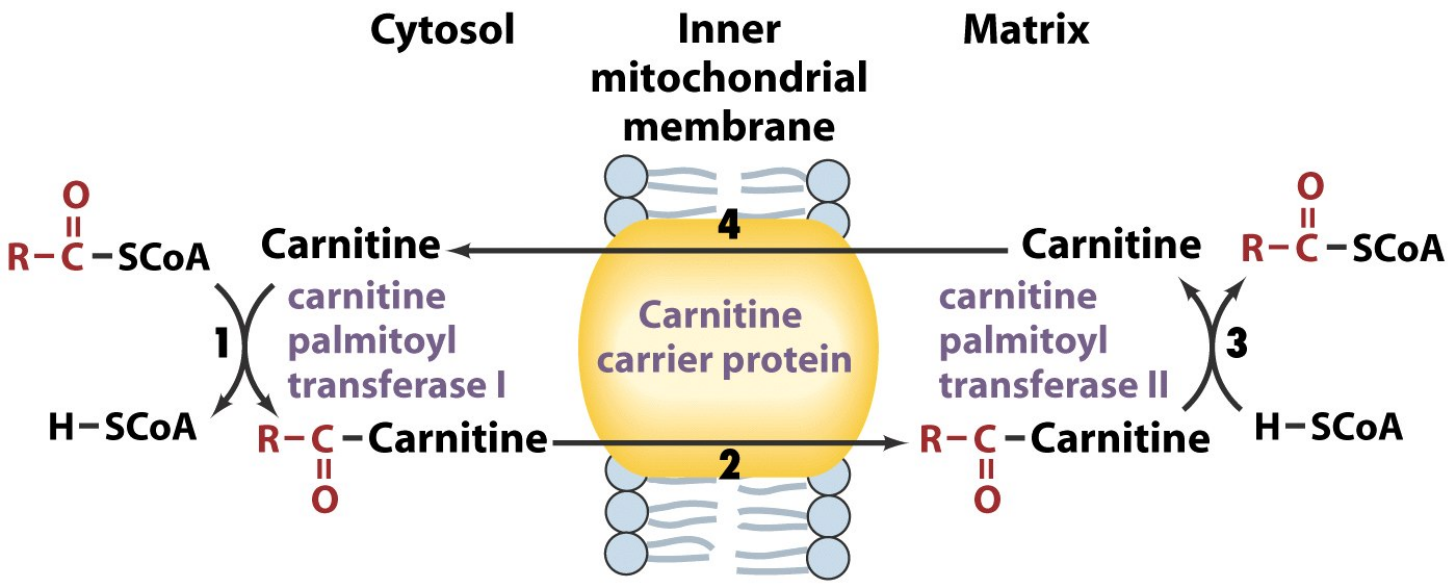



Figure 19-10 Fundamentals of Biochemistry, 2/e

# Transport across mito membrane

Medium chain: direct transfer & activation to acyl-CoA
Long chain: carnitine mediated

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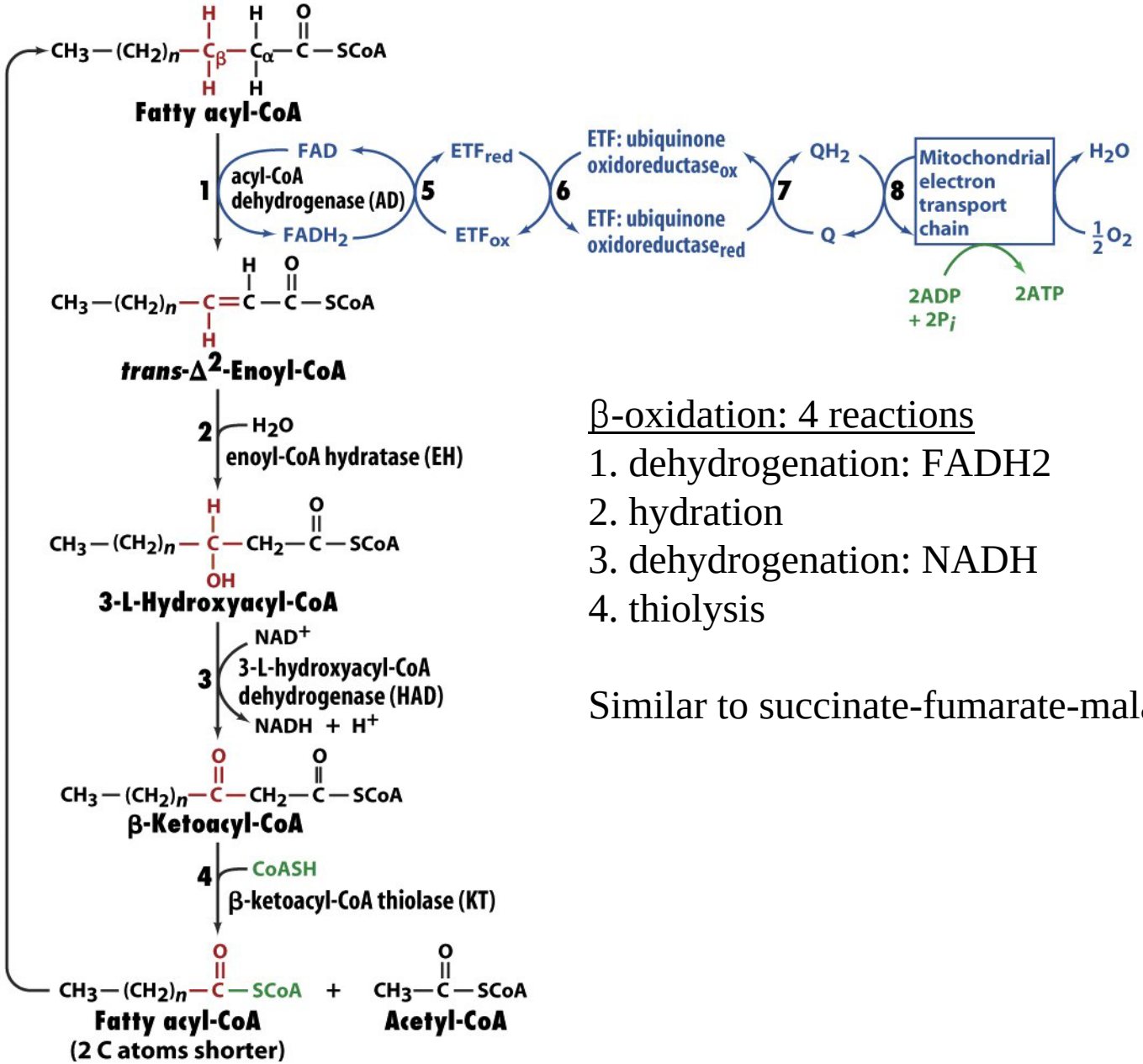



Figure 19-12 Fundamentals of Biochemistry, 2/e


β-oxidation: 4 reactions

1. dehydrogenation: FADH2
2. hydration
3. dehydrogenation: NADH
4. thiolysis

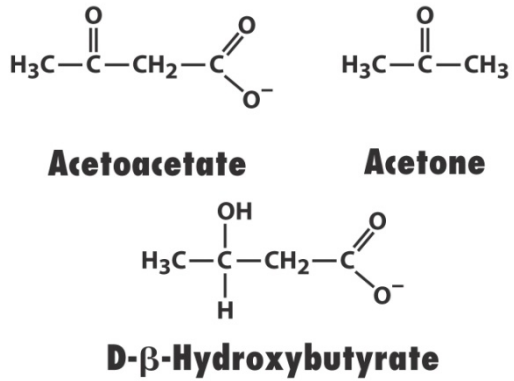
Similar to succinate-fumarate-malate-oxaloacetate

# Ketone bodies

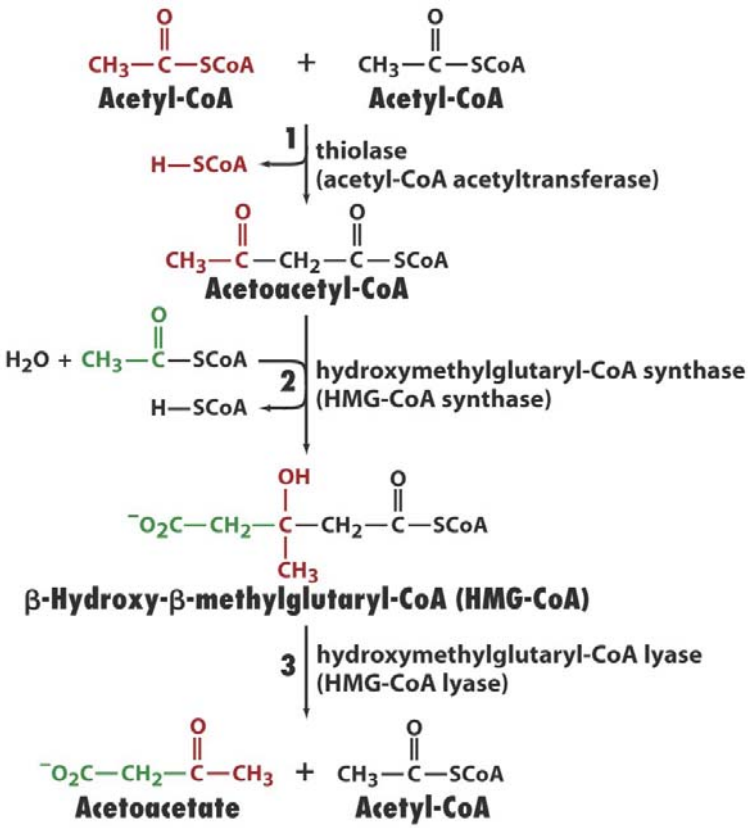
Ketogenesis: acetyl-CoA to acetoacetate or D-β-hydroxybutyrate

Important metabolic fuels for heart & skeletal muscle

During starvation the brain depends on ketone bodies



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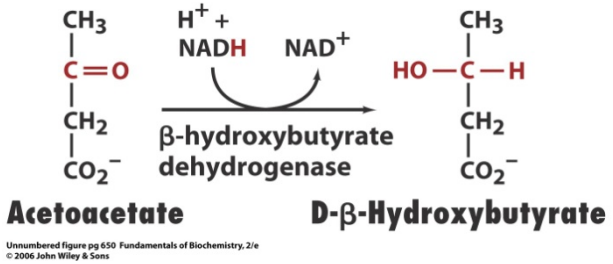
Acetoacetate formation

# Ketone bodies to acetyl-CoA

ketosis

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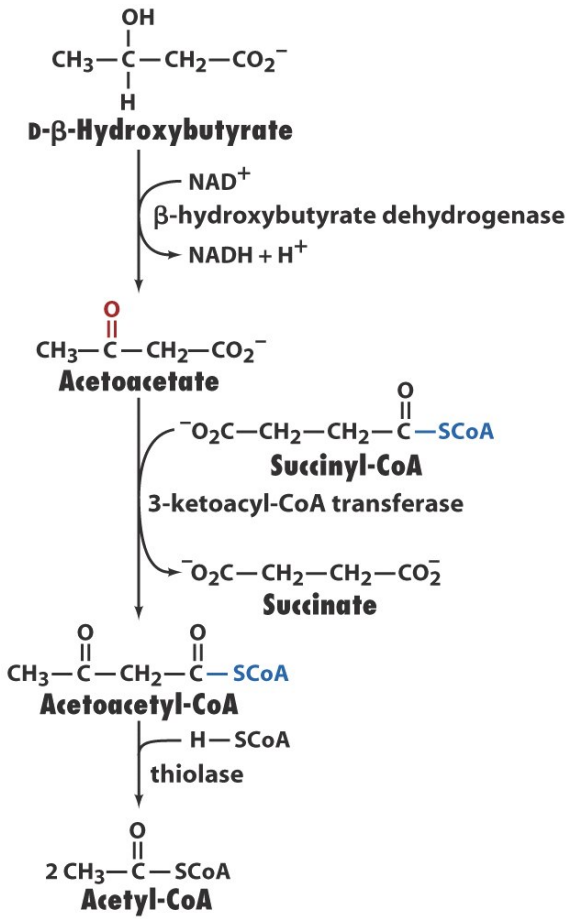


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# Fatty acid biosynthesis

Reverse of β-oxidation process

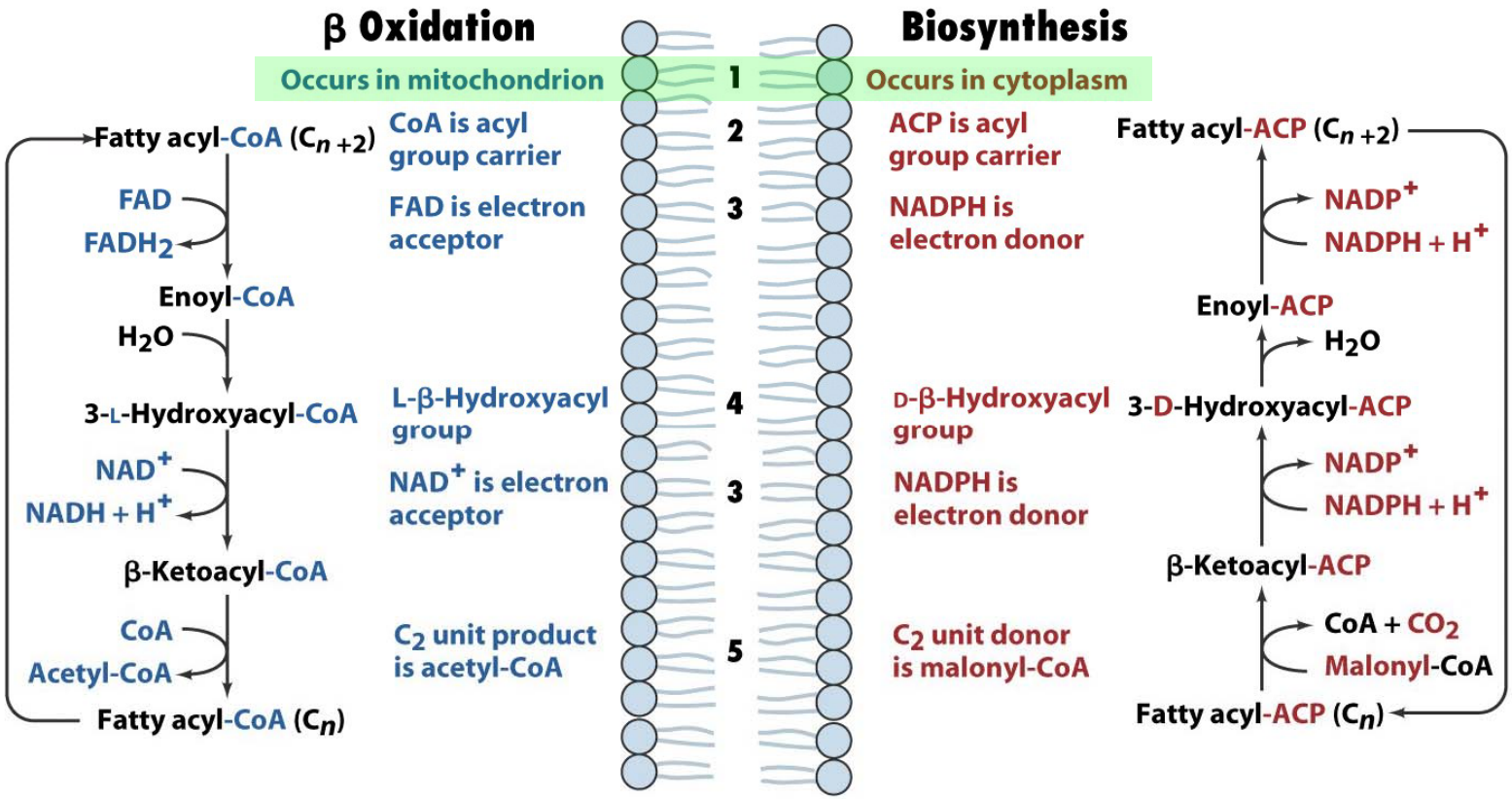



Figure 19-23 Fundamentals of Biochemistry, 2/e

# Acetyl group transfer from mito to cytosol

tricarboxylate transport system
ATP-citrate lyase

Citrate + CoA + ATP →
acetyl-CoA + oxaloacetate + ADP + Pi

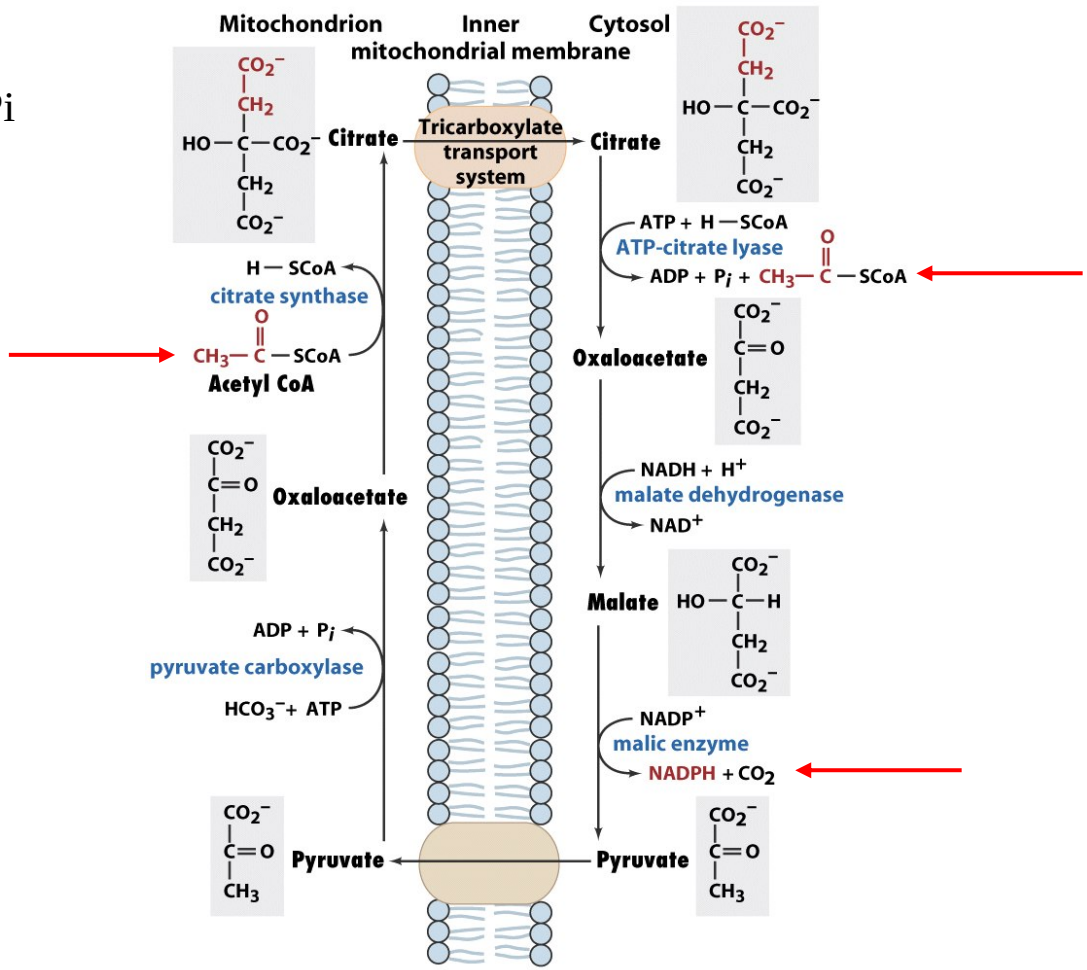


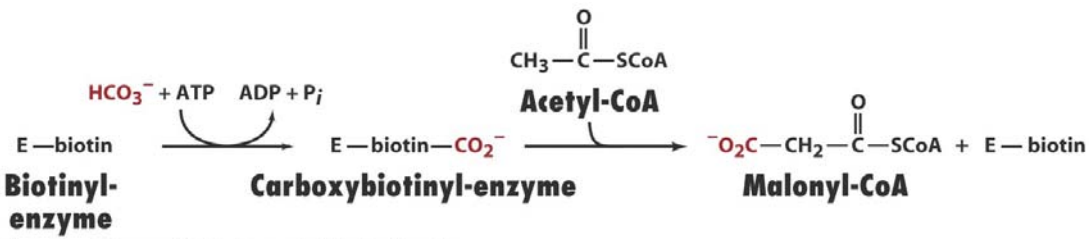

Figure 19-24 Fundamentals of Biochemistry, 2/e

# Acetyl-CoA carboxylase (ACC)

The first committed step of fatty acid synthesis & r.d.s.

Allosteric and covalent regulation

$CO_2$ activation and carboxylation

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# Mammalian ACC: two isoforms

adipose tissue, α-ACC; heart muscle, β-ACC; liver, both

Heart muscle does not synthesize fatty acids

What is the function of β-ACC?

Malonyl-CoA strongly inhibits the mito import of fatty acyl-CoA

*E. coli* ACC

regulated by guanine nucleotides

why? Fatty acid synthesis is coordinated with cell growth

# Fatty acid synthase

E. coli by individual enzymes
Plant: in chloroplast by individual enzymes
Yeast: cytosolic 2500-kD multifunctional enzyme α6β6
Animal: 534-kD consisting of two identical polypeptide chains

Acyl-carrier protein (ACP)
in *E. coli* 10-kD polypeptide
in animal a part of the multifunctional complex

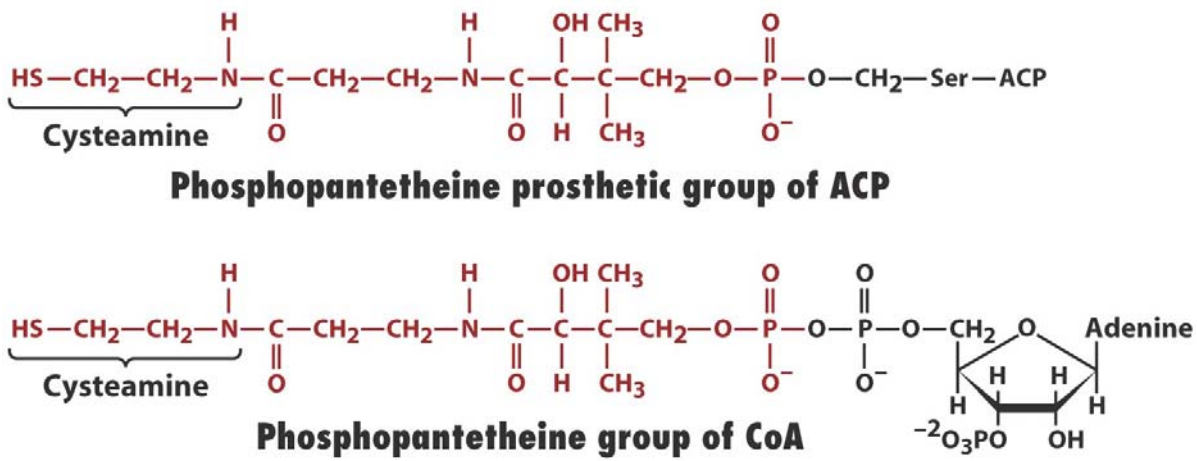


Figure 19-25 Fundamentals of Biochemistry, 2/e

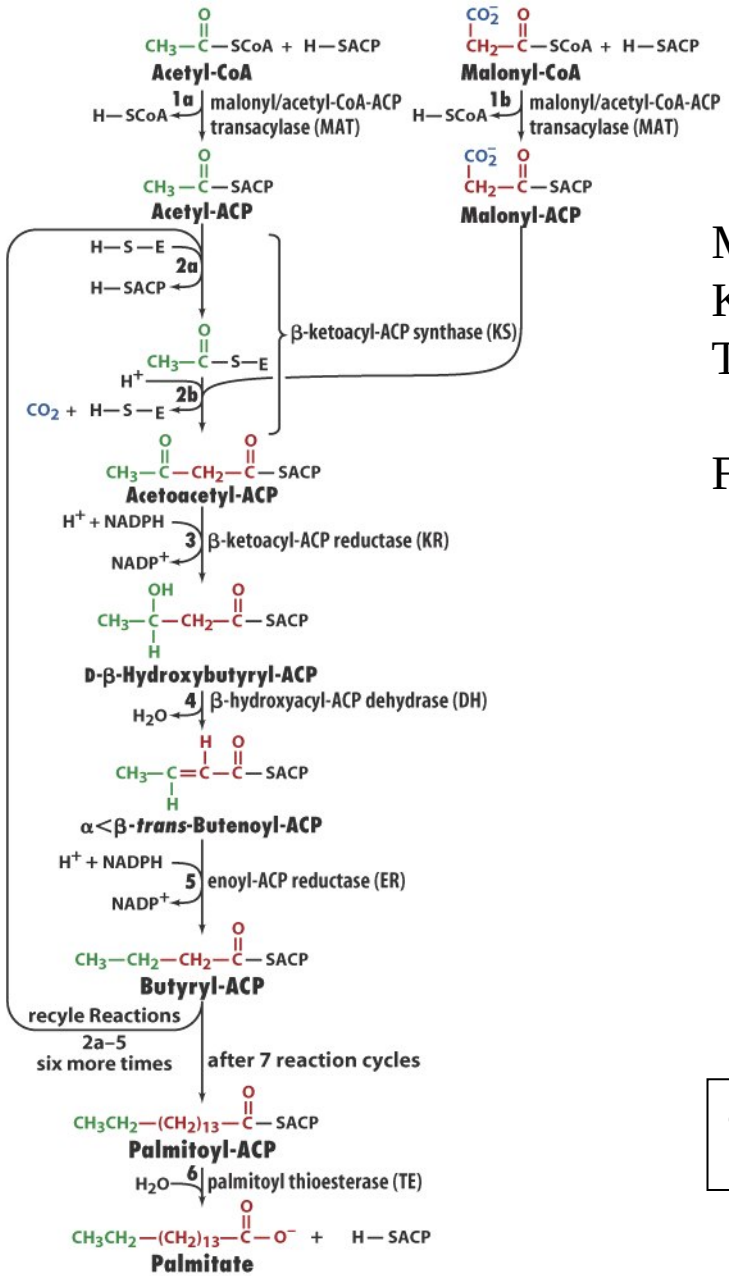


**Figure 19-26 Fundamentals of Biochemistry, 2/e**
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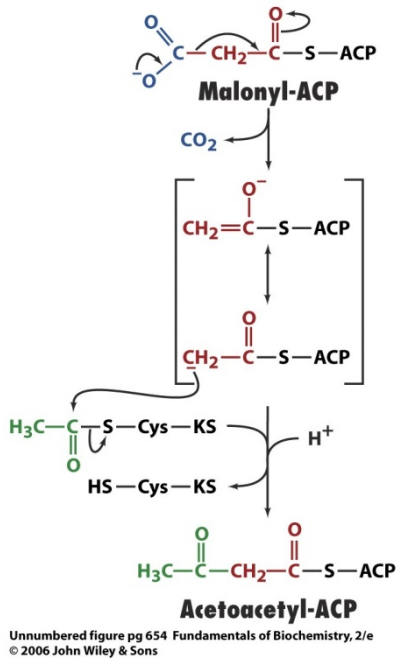
MAT: acetyl or malonyl group transfer to ACP
KS (condensing enzyme)
Two reductions & a dehydration
require two NADPH
Further elongation

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8 acetyl-CoA + 14 NADPH + 7 ATP →
palmitate + 14 $NADP^+$ + 8 CoA + 6 $H_2O$ + 7 ADP + 7 Pi

# Animal fatty acid synthase

Dimers operate in concert: head to tail
7 reactions by 6 discrete active sites (two by MAT)

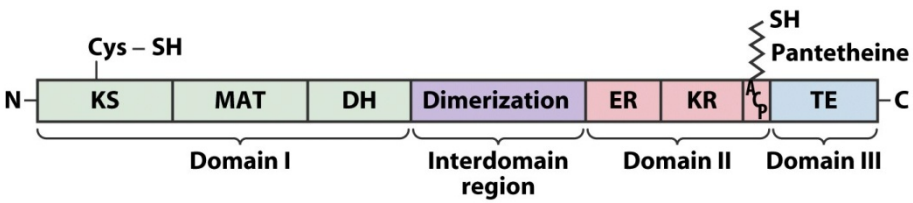


Figure 19-27 Fundamentals of Biochemistry, 2/e
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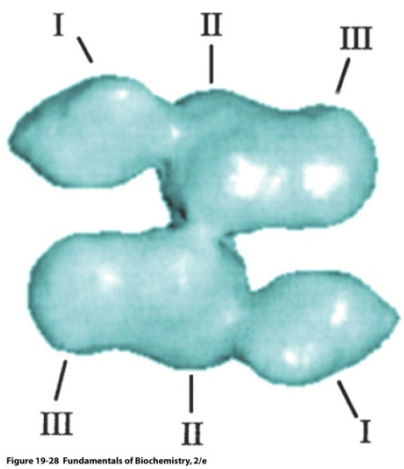
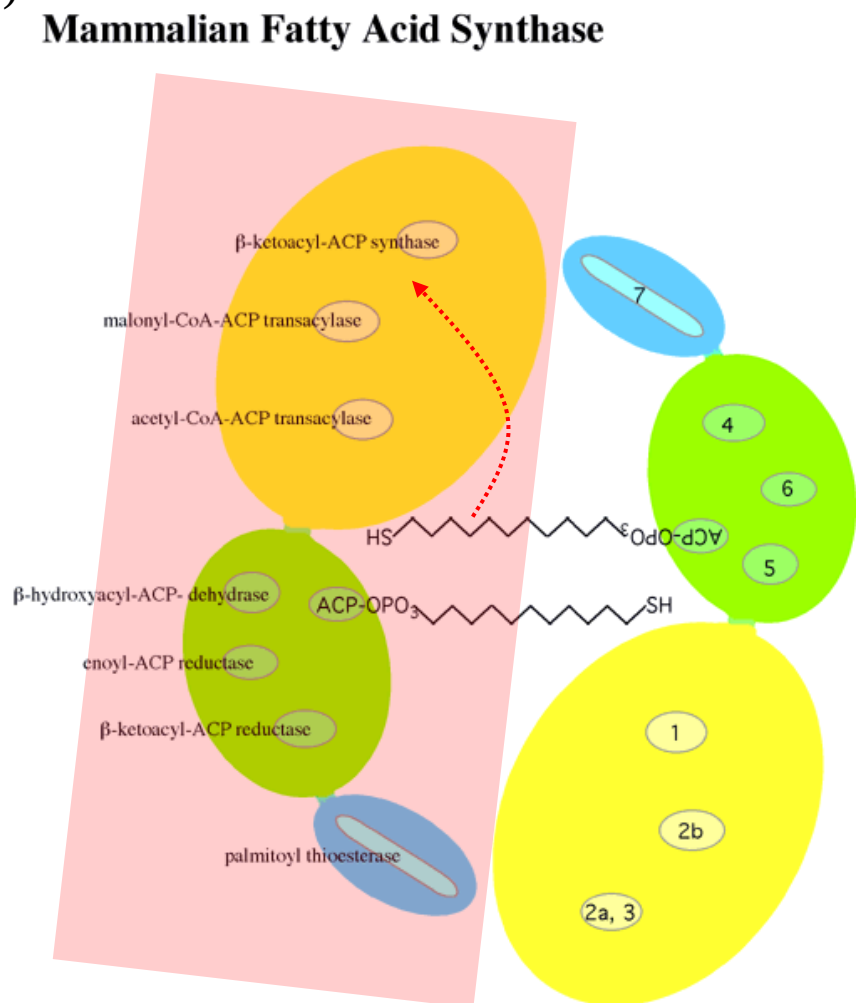



Figure 19-28 Fundamentals of Biochemistry, 2/e

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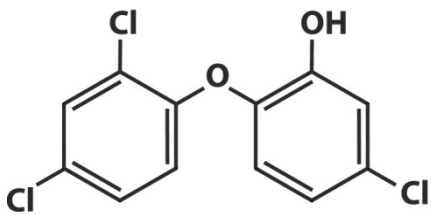
Malignant tissues: high levels of fatty acid synthase
An inhibitor of fatty acid synthesis: possible anticancer agent

Triclosan (5-chloro-2-(2,4-dichlorophenoxy)phenol)
- antibacterial agent
- inhibits enoyl-ACP reductase
- emergence of resistant strains



Triclosan



Box 19-3 figure 2 Fundamentals of Biochemistry, 2/e

# Synthesis of triacylglycerols

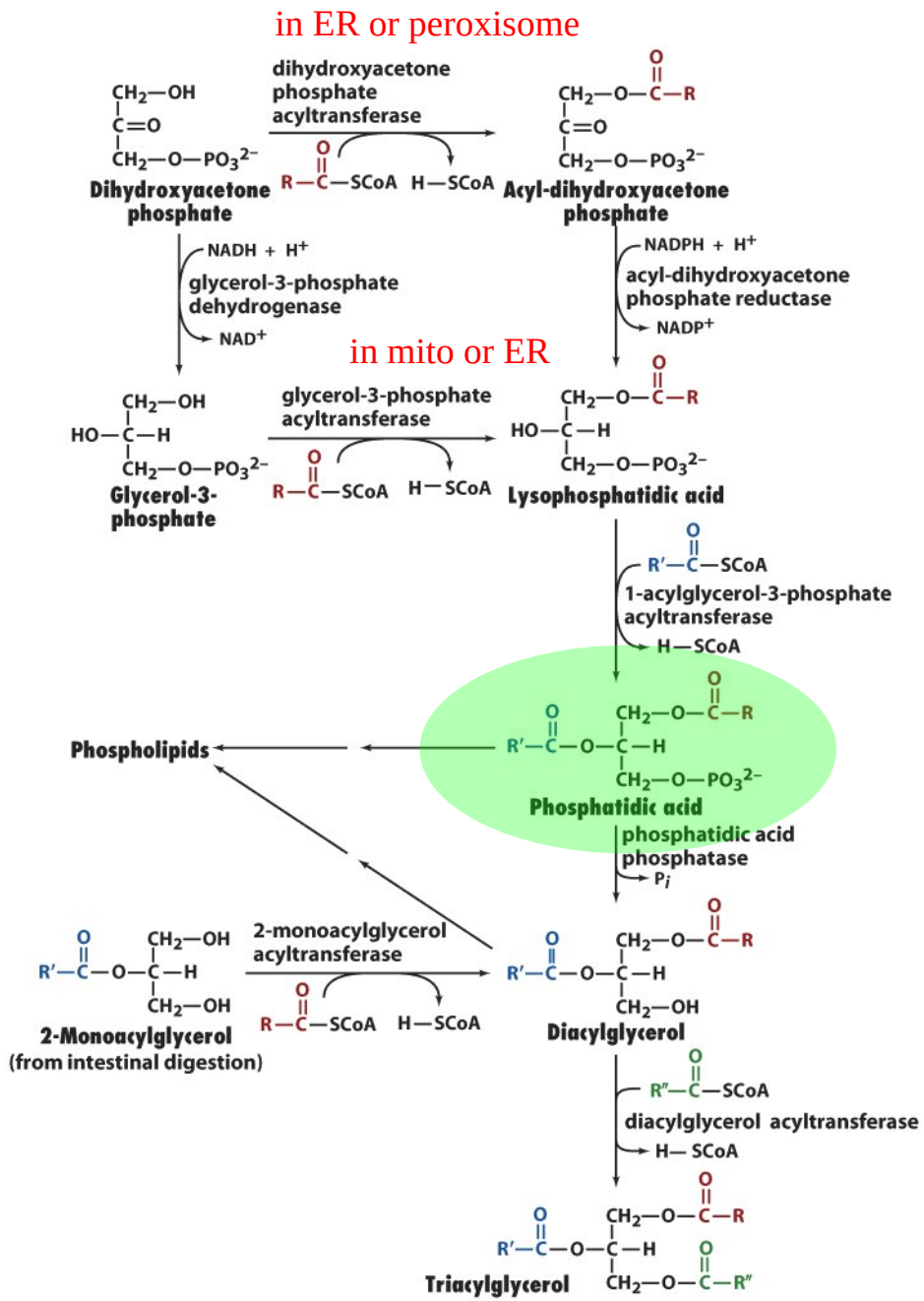



Figure 19-30 Fundamentals of Biochemistry, 2/e

## Glycerogenesis

important for triacylglycerol biosynthesis

dihydroxyacetone phosphate and glycerol-3-phosphate

from glycolysis or gluconeogenesis

A summary of lipid metabolism

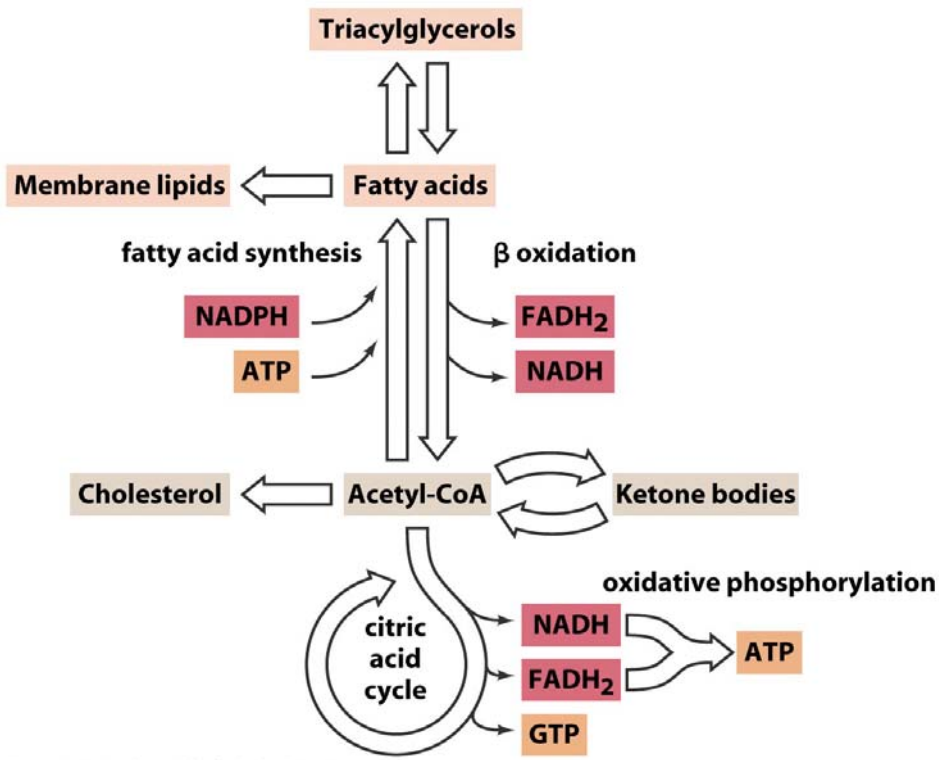



Figure 19-31 Fundamentals of Biochemistry, 2/e

# Regulation of Fatty acid metabolism

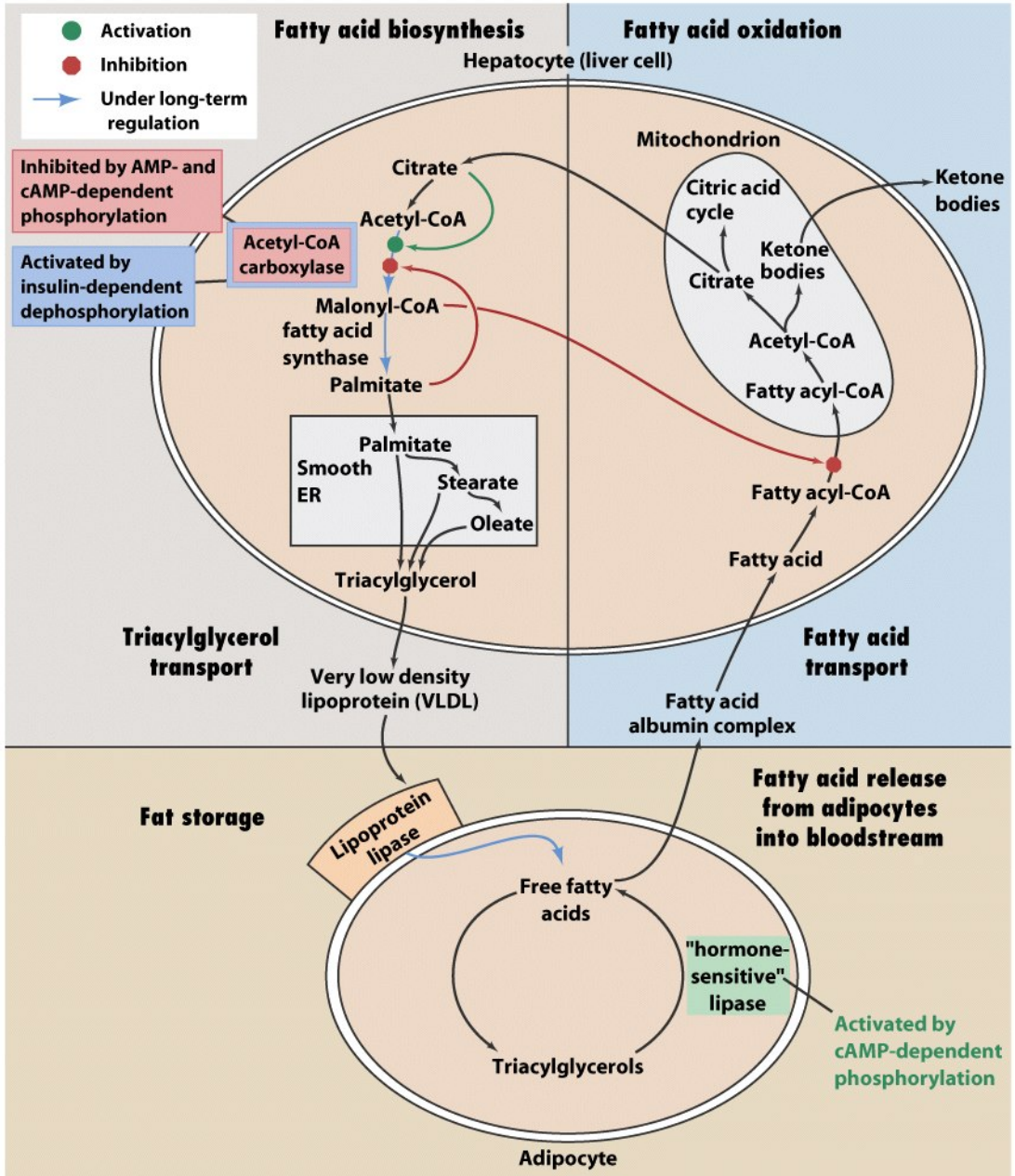



Figure 19-32 Fundamentals of Biochemistry, 2/e

## Lipase

### Lipoprotein lipase (LPL)

Lipoprotein lipase is found in vascular endothelium. It is activated by insulin, ACTH, TSH, glucagon and thyroid hormone. Its activity is enhanced by heparin. As discussed above, lipoprotein lipase hydrolyzes CM and VLDL to free fatty acids and glycerol and VLDL-remnants, respectively. Apolipoprotein C is essential for activation of LPL.

### Hepatic lipase

This enzyme hydrolyzes surface phospholipids on lipoproteins and is responsible for converting VLDL to LDL.

### Hormone sensitive lipase

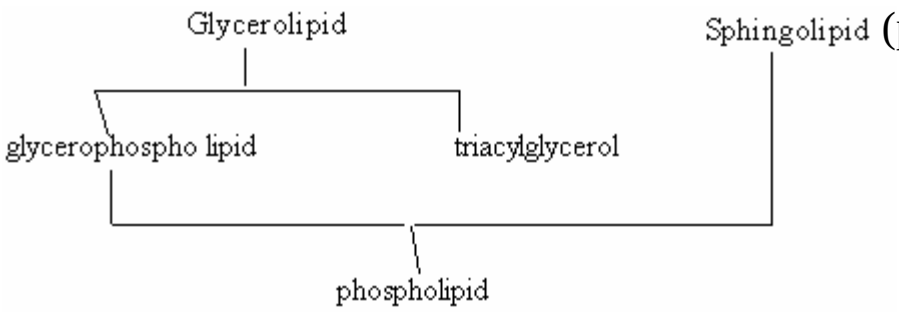
This enzyme is responsible for lipolysis (mobilization of triglycerides from adipose tissue to yield free fatty acids and glycerol). The enzyme is stimulated by catecholamines, growth hormone, thyroxine, corticosteroids and prostaglandins. It is inhibited by insulin. Fatty acids are transported to the liver (free or albumin-bound), where they are taken up and used for energy (beta oxidation), combined with triglycerides to form VLDL or incorporated into ketones. Therefore, lipolysis will increase VLDL production.

# Synthesis of other lipids

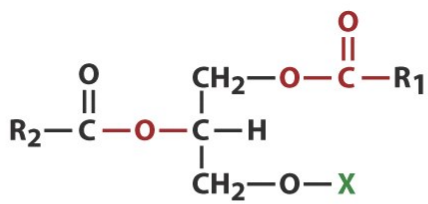
Membrane lipids and signal molecules

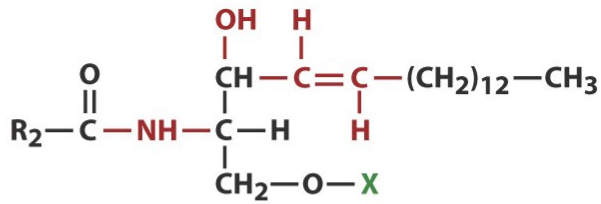
Synthesis in membranes of the cytosolic side of ER & then transport to their destinations

Gylcerolipids & sphingolipids




(phospholipid or glycolipid)



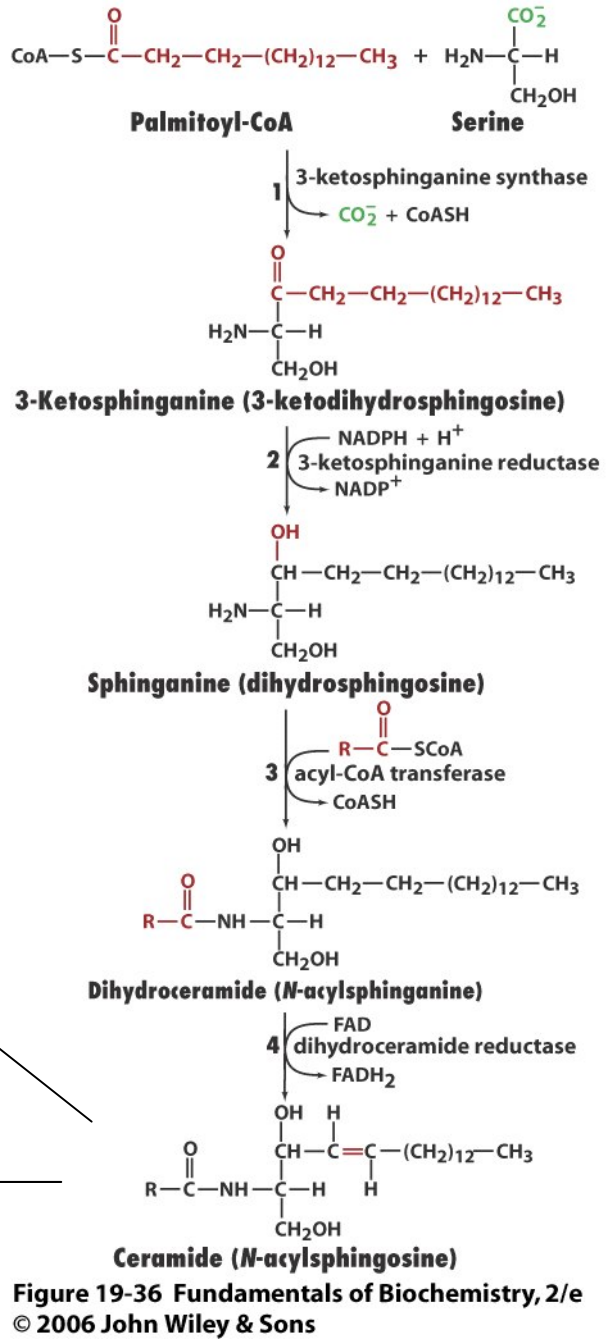




| | | |
|---|---|---|
| X = H | 1,2-Diacylglycerol | *N*-Acylsphingosine (ceramide) |
| X = Carbohydrate | Glyceroglycolipid | Sphingoglycolipid (glycosphingolipid) |
| X = Phosphate ester | Glycerophospholipid | Sphingophospholipid |

Figure 19-33 Fundamentals of Biochemistry, 2/e

# Biosynthesis of sphingolipids

Most are glycolipids: carbohydrate units to the C1-OH
Biosynthetic precursors: palmitoyl-CoA & serine




Galactoceramide
Glucoceramide
ganglioside

UDP-hexose

phosphocholine

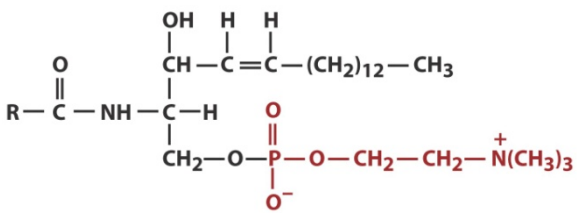
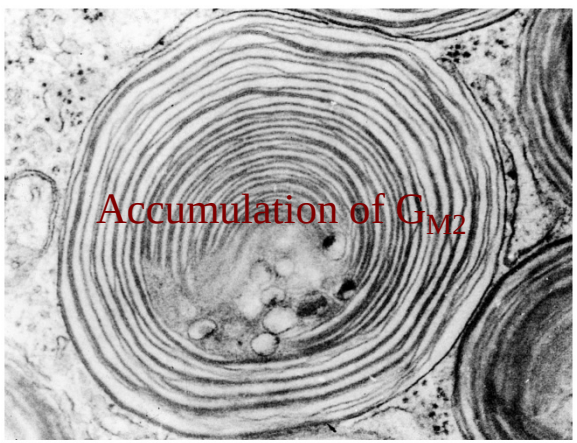
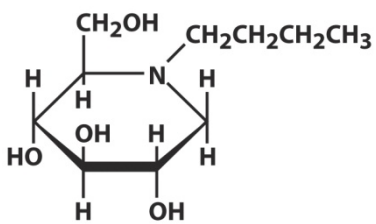



Figure 19-36 Fundamentals of Biochemistry, 2/e

# Sphingolipid degradation and Lipid storage diseases

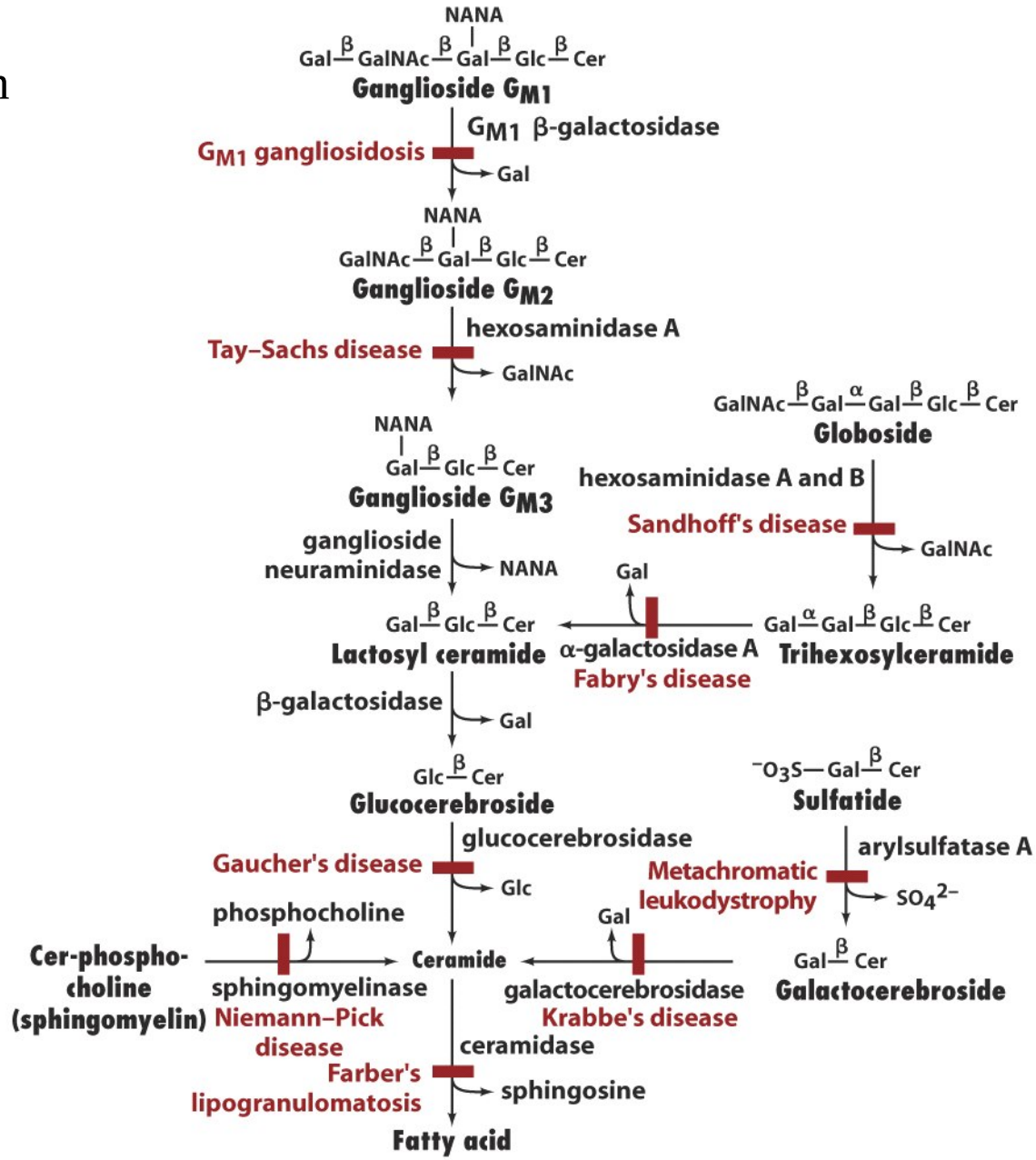



Box 19-4 figure 2 Fundamentals of Biochemistry, 2/e




***N*-Butyldeoxynojirimycin**






Box 19-4 figure 1 Fundamentals of Biochemistry, 2/e

Eicosanoids from arachidonic acid (p 247, Fig. 9-12)

Act at very low conc and locally
Tissue dependent products
Varity of function
- pain and fever
- blood pressure
- blood coagulation
- reproduction

Opposite actions
- thromboxane & prostacyclin

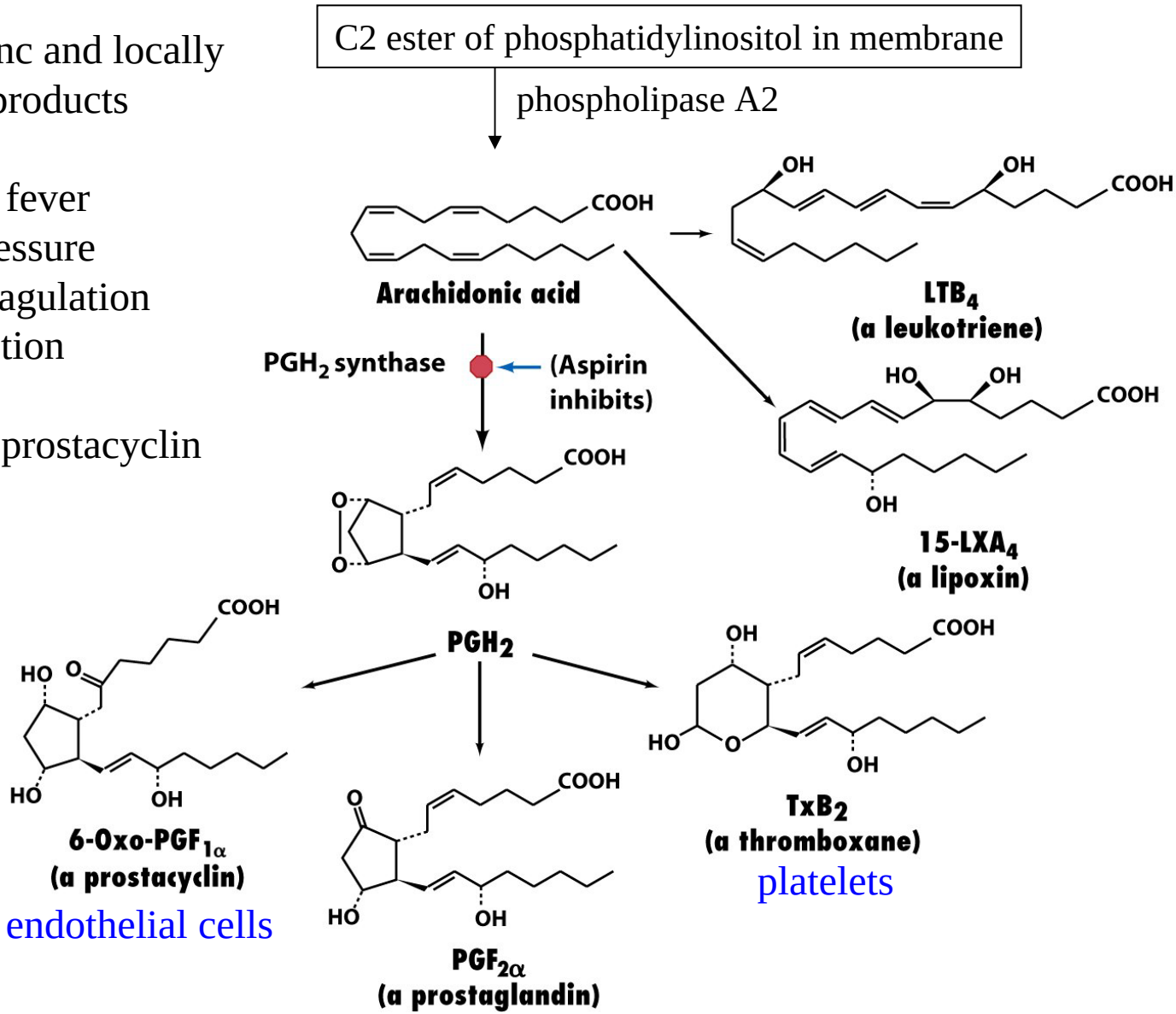



Figure 9-12 Fundamentals of Biochemistry, 2/e

# Prostaglandins

Prostaglandin H2 synthase (COX)

Cyclooxygenase & peroxidase

Two isoforms: COX-1 & COX-2

COX-1: constitutive expression in most tissue

COX-2: certain tissue in response to inflammatory stimuli

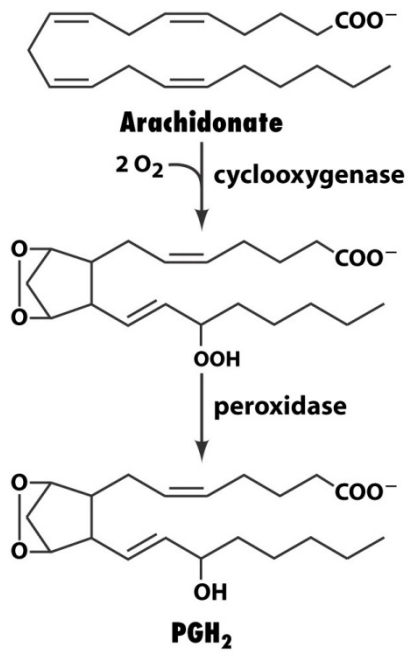



Figure 19-37 Fundamentals of Biochemistry, 2/e
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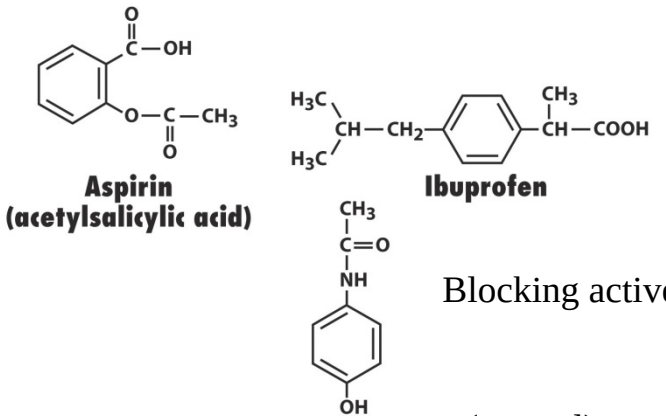
Acetylation of a Ser residue




Blocking active site

(tyrenol)

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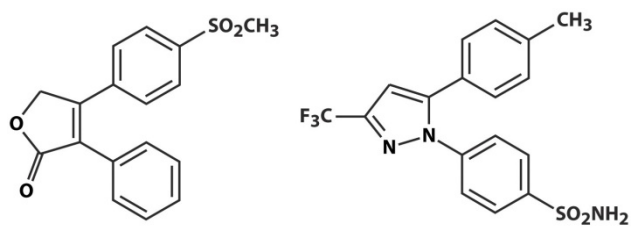
COX-2 specific

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Finding of COX-3: a target of acetaminophen?

Poor binding of acetaminophen to COX-1 & -2

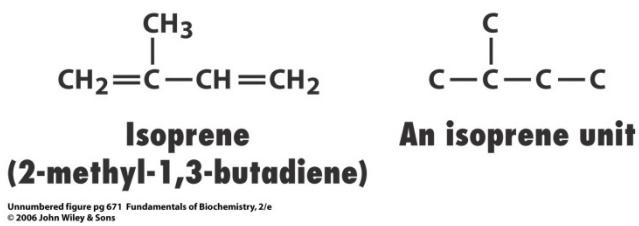
# Cholesterol metabolism

<u>Biosynthesis</u>

HMG-CoA synthesis in cytosol: thiolase & HMG-CoA synthase
(in mitochondria for ketone bodies)

Mevalonate (C6): by HMG-CoA reductase
the rate limiting step

Isopentenyl pyrophosphate (C5)

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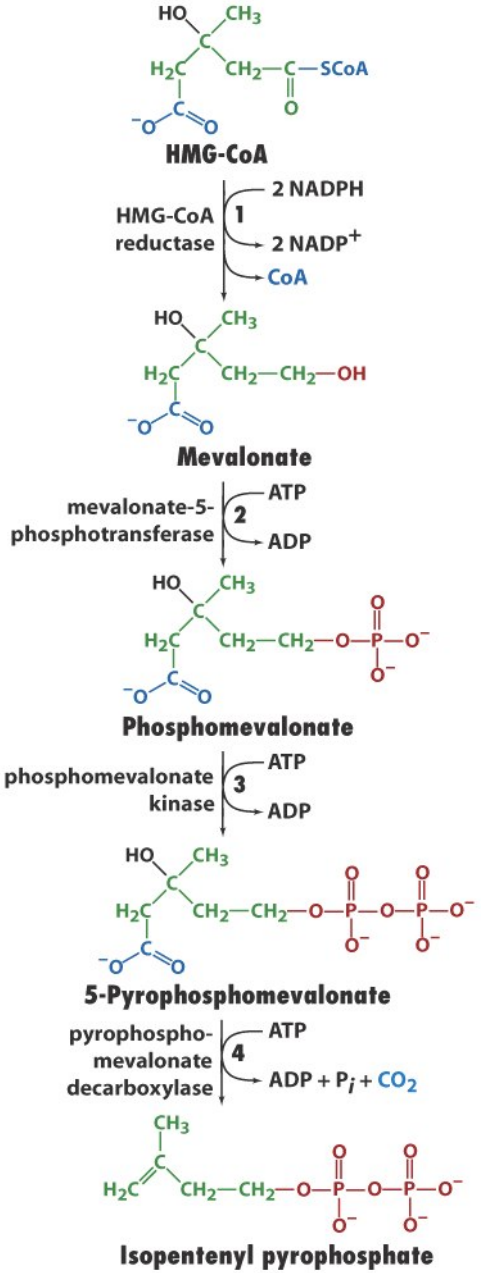


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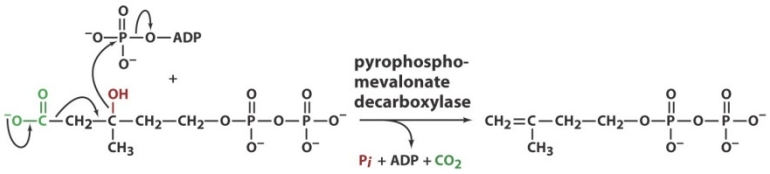


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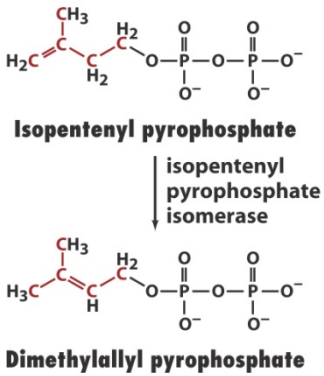


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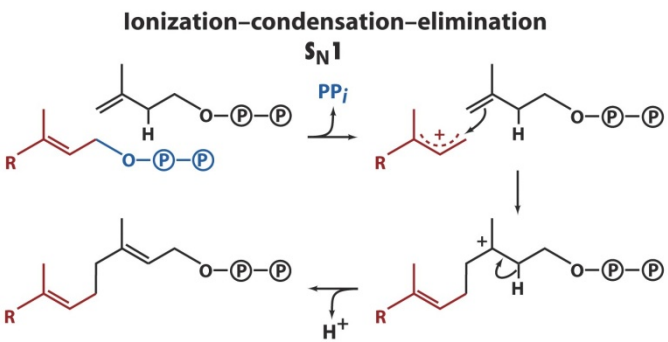


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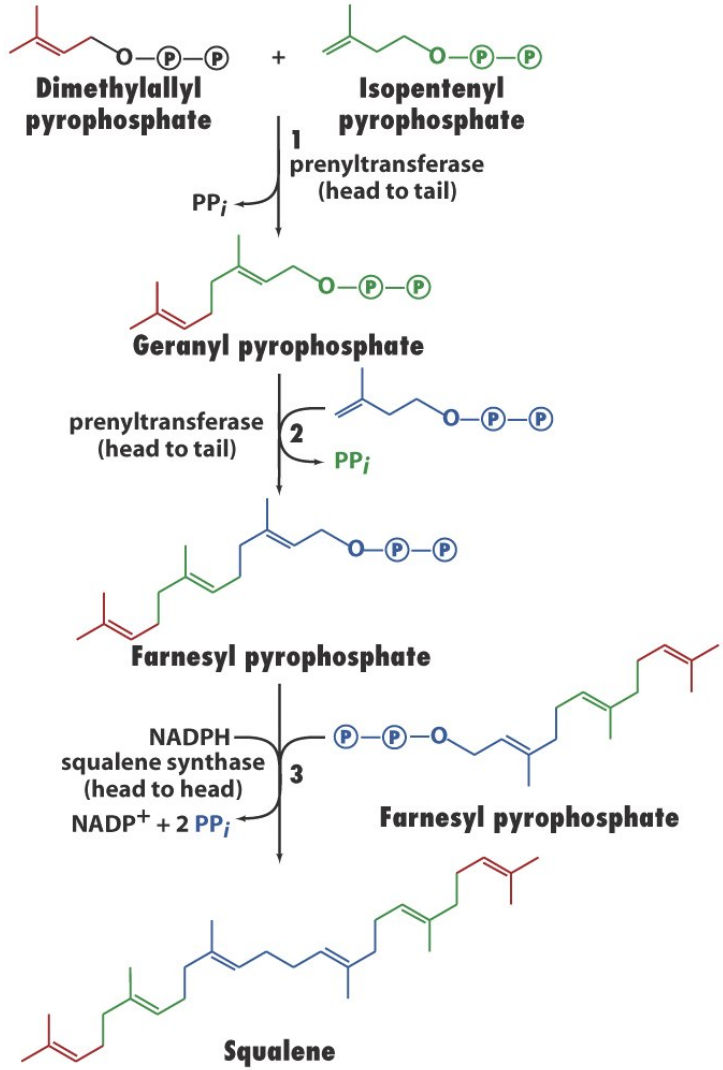


Figure 19-39 Fundamentals of Biochemistry, 2/e

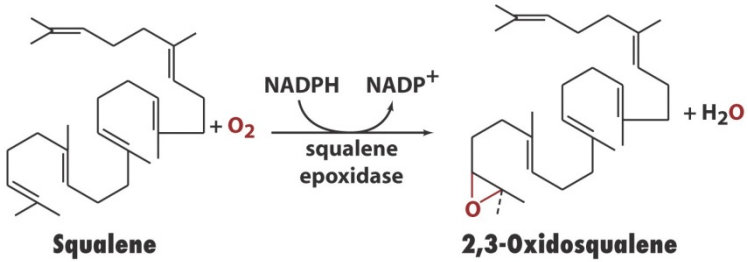


Figure 19-40 Fundamentals of Biochemistry, 2/e
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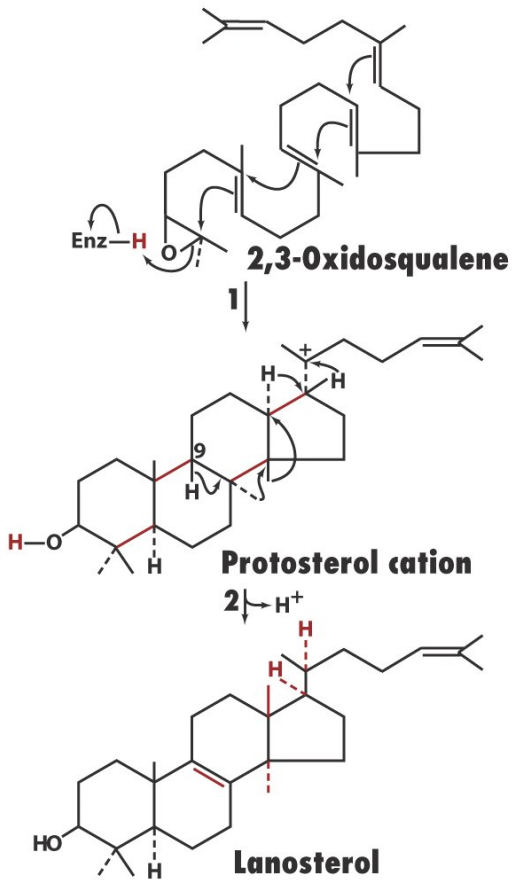


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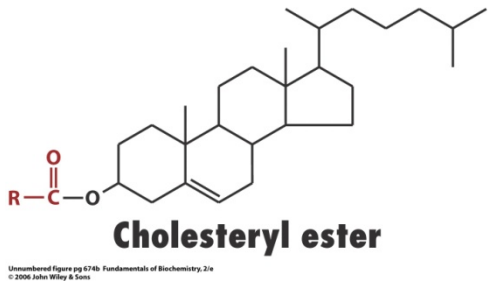


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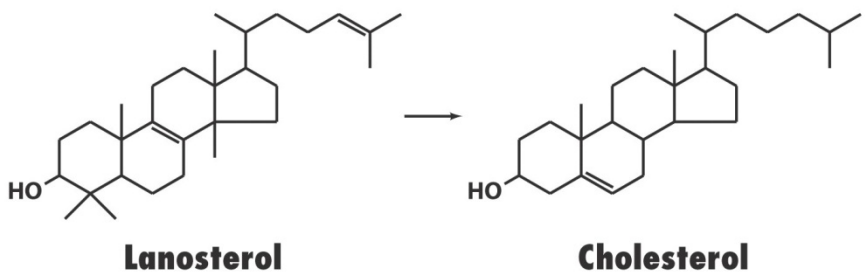


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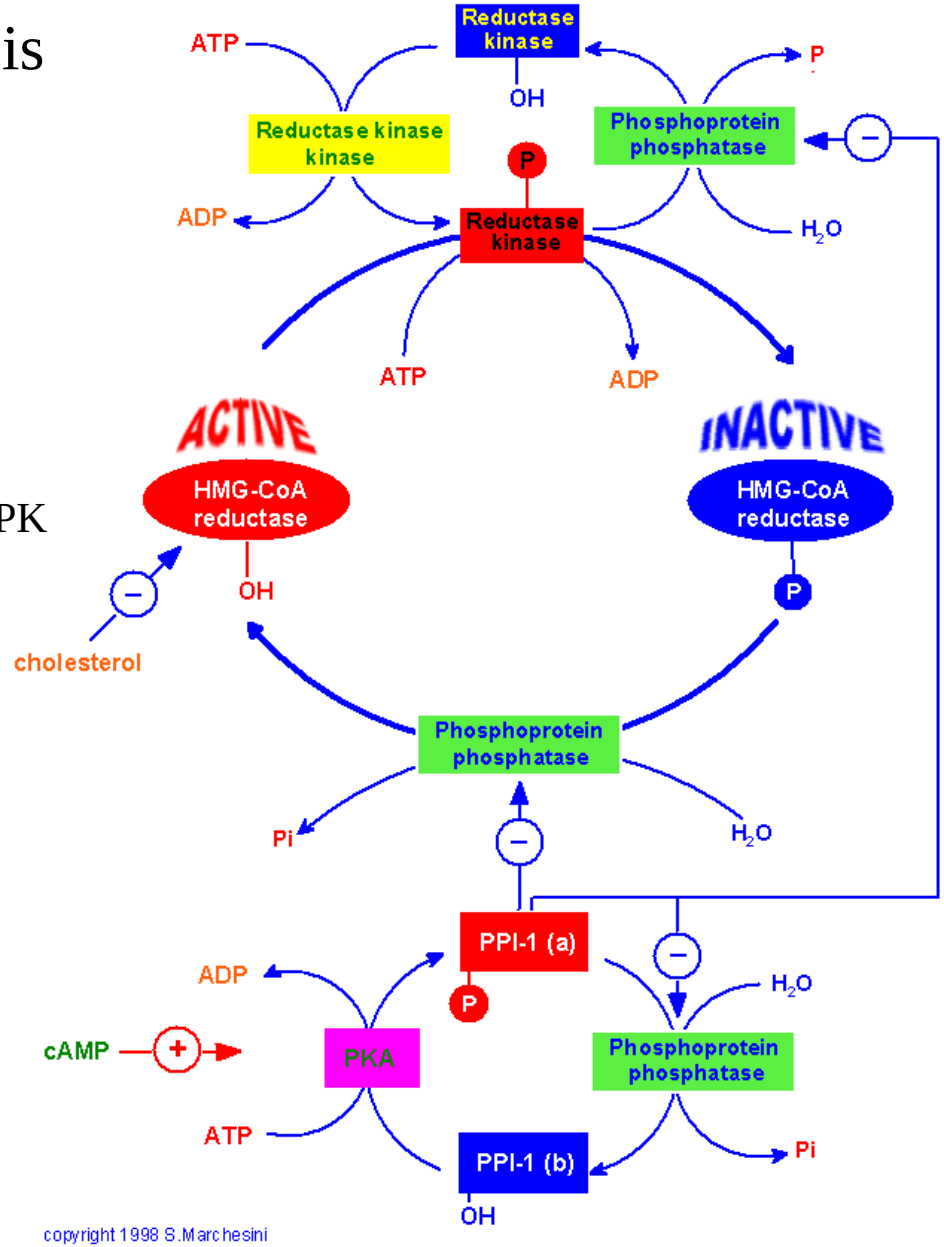
# Regulation of cholesterol synthesis

The main regulation: HMG-CoA reductase

<u>Short-term regulation</u>
Competitive inhibition
Allosteric effects
Covalent modification: phosphorylation by AMPK

AMPK
http://www.indstate.edu/thcme/mwking/ampk.html




http://www.med.unibs.it/~marchesi/cholest.html

Long-term control: gene expression

the primary regulation

Increased as much as 200-fold along with >20 other genes for synthesis and uptake

Sterol regulatory element (SRE)

SREBP: regulatory & bHLH domains

SCAP: SREBP cleavage-activating protein

sterol-sensing domain & WD repeat

Activation procedure

- Low cholesterol in ER
- SCAP conformation change
- Transport to golgi apparatus via membranous vesicles
- Site-1 protease
- Site-2 protease
- bHLH binding to SRE

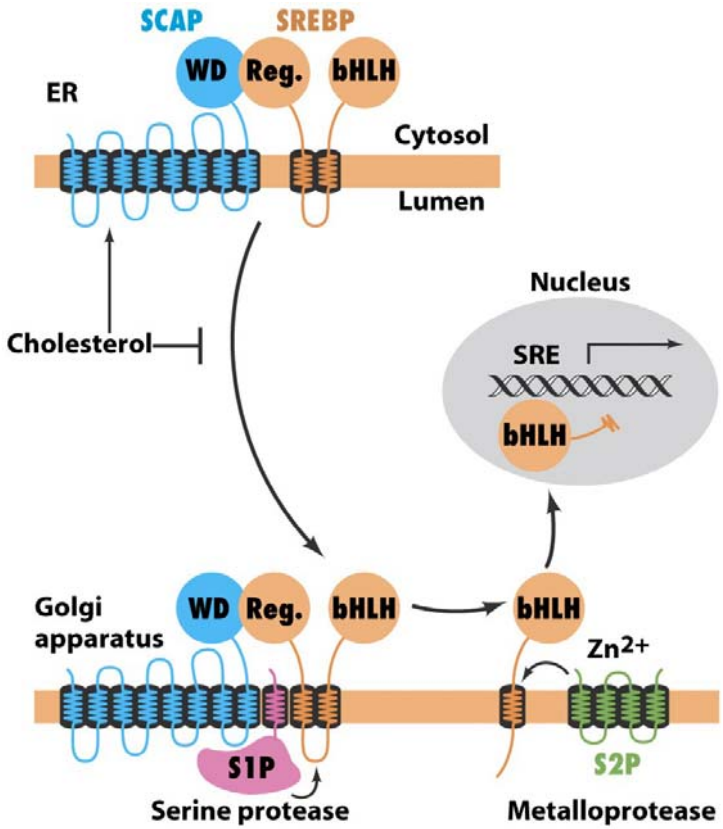



Figure 19-42 Fundamentals of Biochemistry, 2/e

# HMG-CoA reductase inhibitors: statins

Hypercholesterolemia
Competitive inhibitor of HMG-CoA reductase

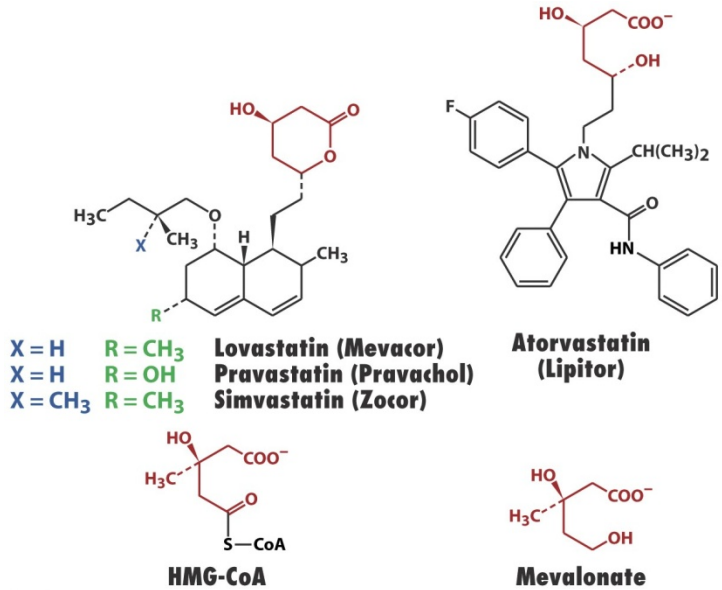
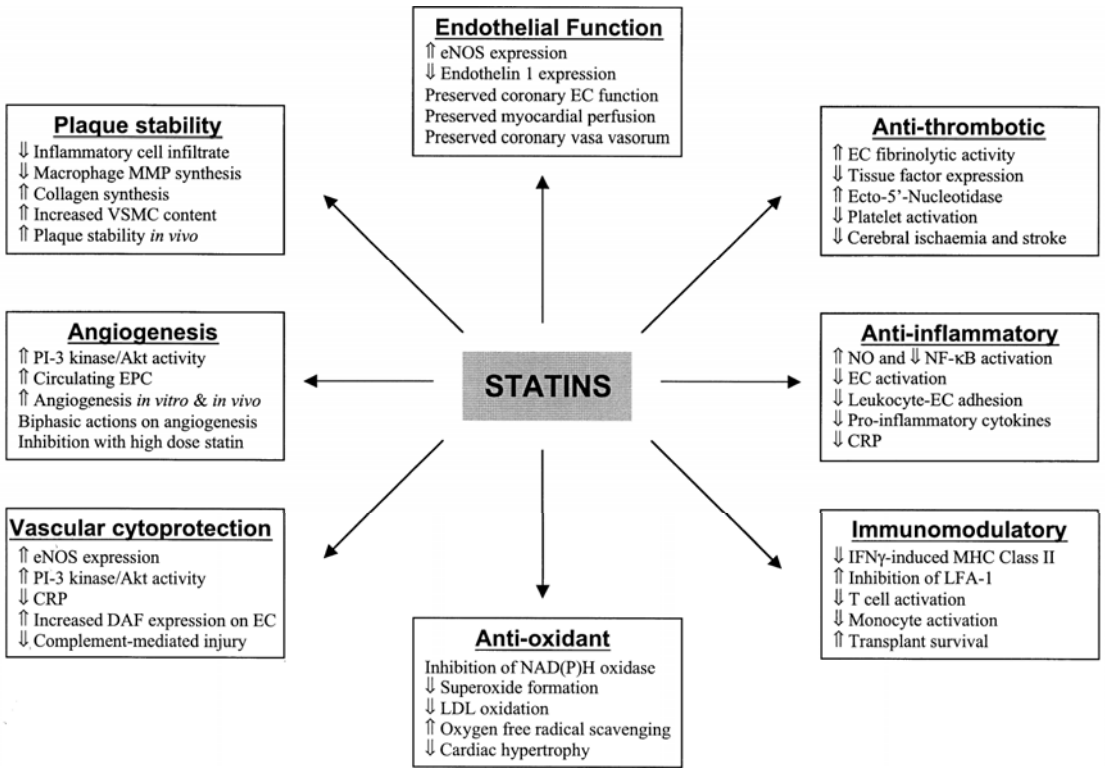



Figure 19-43 Fundamentals of Biochemistry, 2/e


http://www.clinsci.org/cs/105/0251/cs1050251f03.htm?resolution=HIGH

# Cholesterol transport and atherosclerosis

Cellular cholesterol concentration depends on
- the rate of cholesterol synthesis
- the ability of cell to absorb cholesterol from circulating lipoproteins

High LDL is a strong risk factor for cardiovascular disease
Accumulation of lipid in vessel walls: Atherosclerosis
- Myocardial infarction (heart attack)
- Stroke (brain)

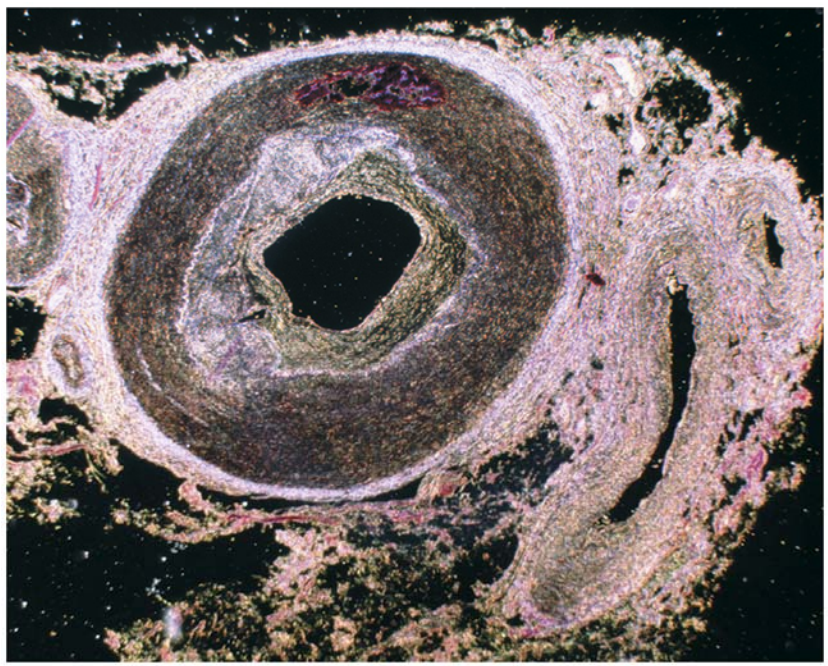


Figure 19-44 Fundamentals of Biochemistry, 2/e

## Role of the LDL receptors

familial hypercholesterolemia (FH)

Long-term ingestion of a high-fat/high-cholesterol diet

## Cholesterol efflux from cells

LDL receptor: FH

ABCA1 (ATP-cassette binding protein A1): Tangier disease

- no HDL synthesis
- accumulation of cholesteryl ester in macrophages
- develop atherosclerosis

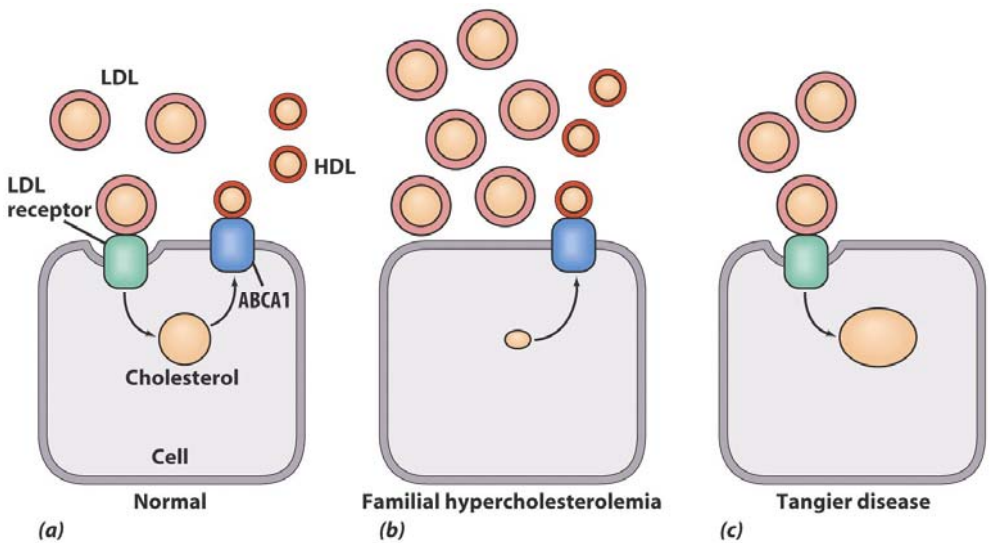



Figure 19-45 Fundamentals of Biochemistry, 2/e