Lipid metabolism and its regulation

From the Chemistry Exam to the Final Exam in Biochemistry

Dr. Lengyel Anna

TABLE 10–3 Eight Major Categories of Biological Lipids

Category	Category code	Examples
Fatty acids	FA	Oleate, stearoyl-CoA, palmitoylcarnitine
Glycerolipids	GL	Di- and triacylglycerols
Glycerophospholipids	GP	Phosphatidylcholine, phosphatidylserine, phosphatidylethanolamine
Sphingolipids	SP	Sphingomyelin, ganglioside GM2
Sterol lipids	ST	Cholesterol, progesterone, bile acids
Prenol lipids	PR	Farnesol, geraniol, retinol, ubiquinone
Saccharolipids	SL	Lipopolysaccharide
Polyketides	PK	Tetracycline, aflatoxin B_1

Table 10-3
Lehninger Principles of Biochemistry, Fifth Edition

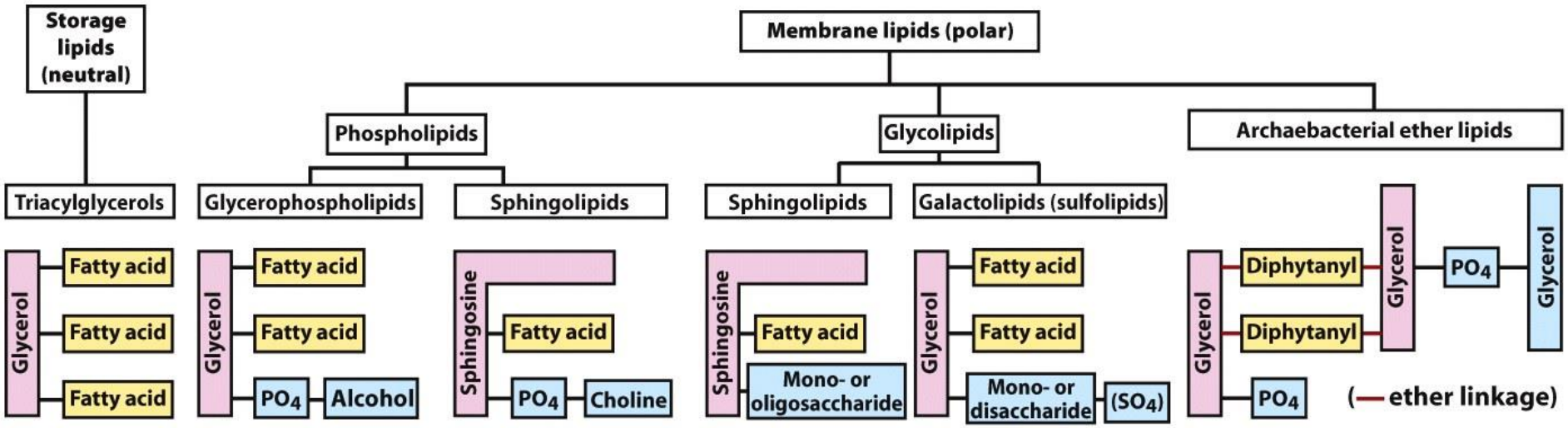

Figure 10-7
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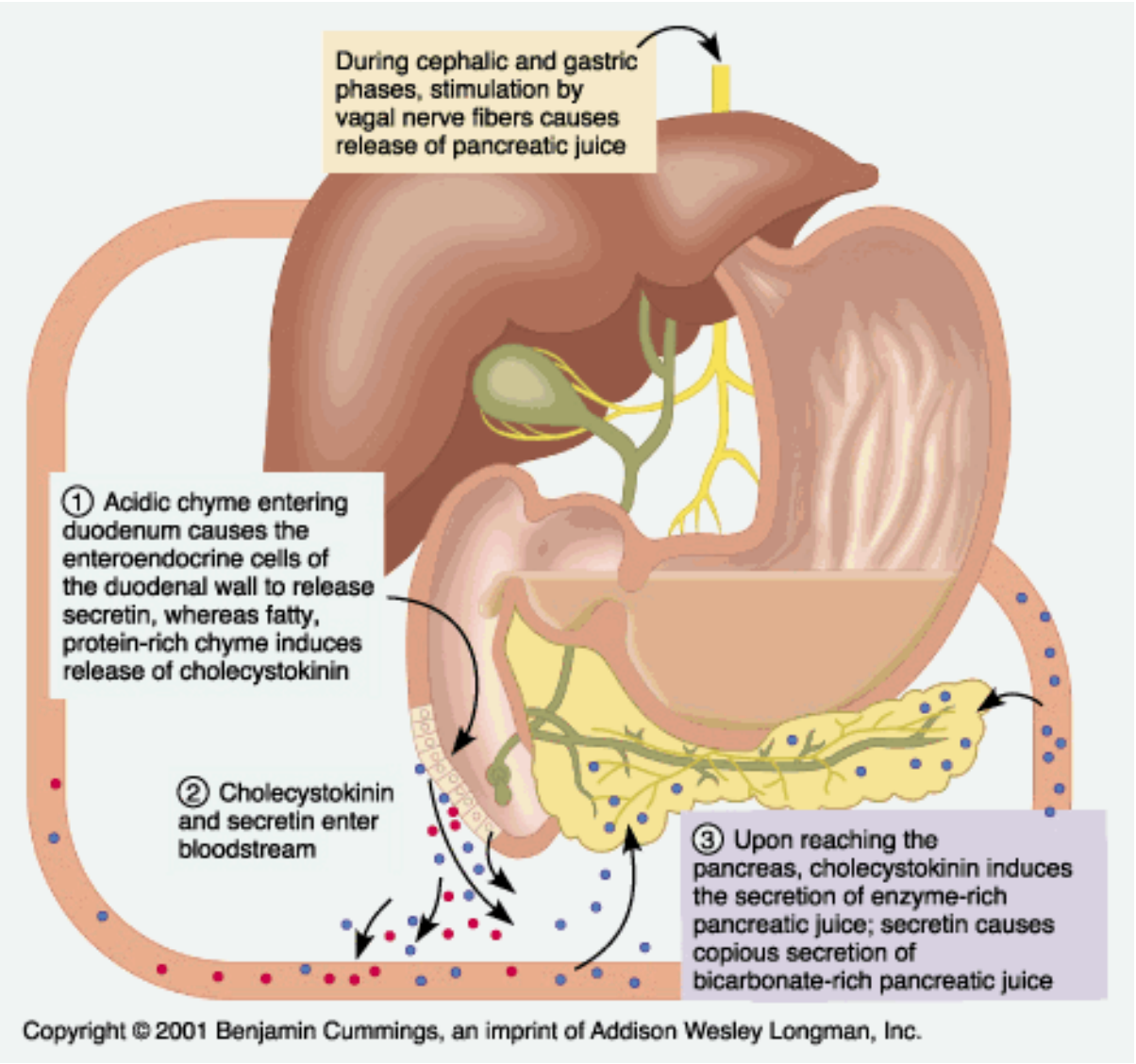
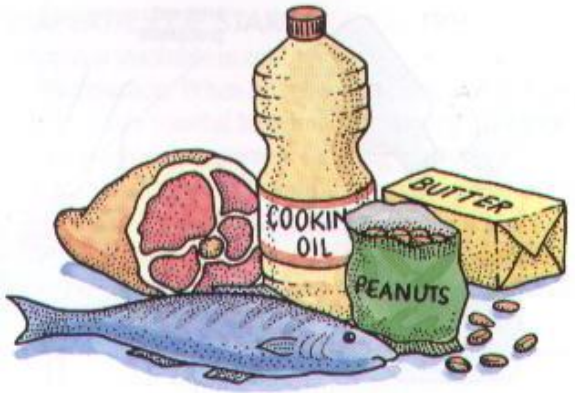




LIPID DIGESTION

Substrate	Extracellular enzymes	Intestinal mucosal enzymes	End Products
Triglycerides	*Lipase* / *Colipase*		β-mono-glyceride Fatty Acids
Phospholipids	*Phospholipase*	*Phosphatase*	Alcohols Fatty Acids Phosphate
Cholesterol Esters	*Cholesterol Esterase*		Cholestrol Fatty Acid
Waxes	*Lipase*		Monohydric Alcohol Fatty Acid

A gallstone that blocked the upper part of the bile duct would cause an increase in which of the following?

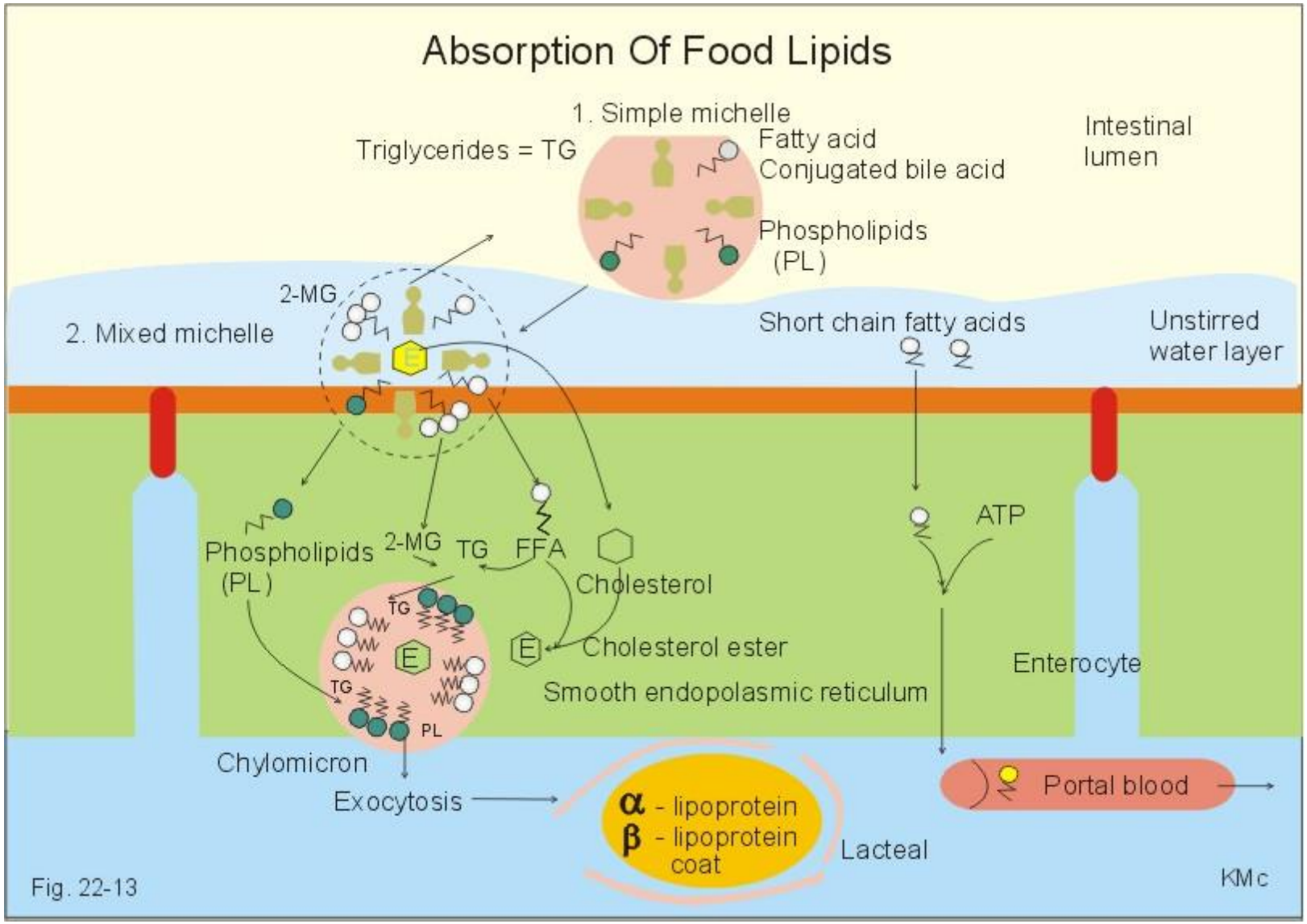
(A) The formation of chylomicrons

(B) The recycling of bile salts

(C) The excretion of bile salts

(D) Increased conjugation of bile salts

(E) The excretion of fat in the feces


Absorption Of Food Lipids
1. Simple michelle
Triglycerides = TG
Fatty acid
Conjugated bile acid
Phospholipids
(PL)
Intestinal
lumen
2-MG
2. Mixed michelle
Short chain fatty acids
Unstirred
water layer
ATP
Phospholipids
(PL)
2-MG
TG
FFA
Cholesterol
Cholesterol ester
Smooth endopolasmic reticulum
Enterocyte
Chylomicron
Exocytosis
α - lipoprotein
β - lipoprotein
coat
Lacteal
Portal blood
Fig. 22-13
KMc

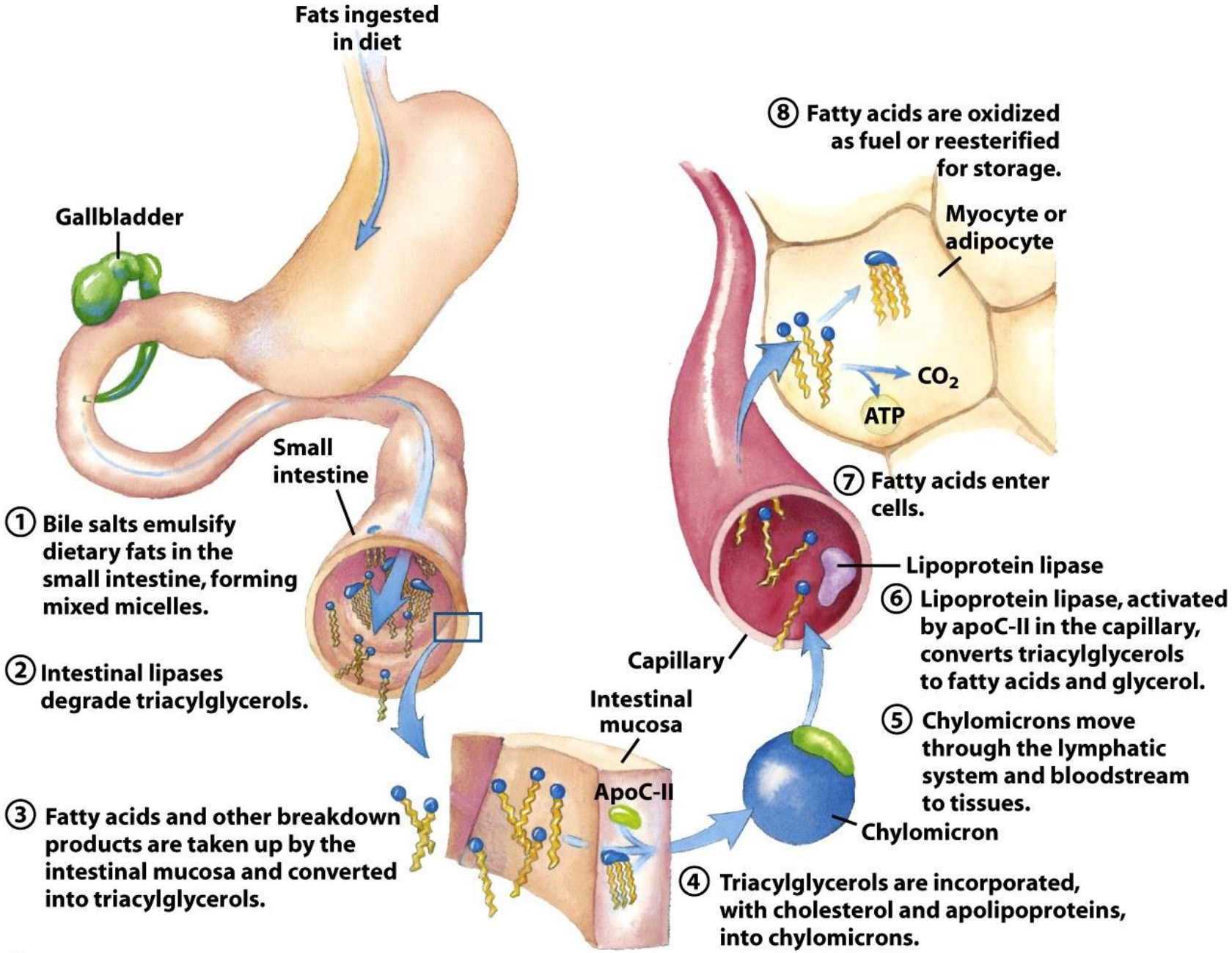


Figure 17-1

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Which of the following statements concerning the liver and the adipose cells is correct?

(A) Adipose cells contain glycerol kinase.

(B) Liver cells contain a hormone-sensitive lipase.

(C) Adipose cells have a transport system for glucose that is not regulated by insulin.

(D) Liver cells secrete lipoproteins when blood insulin levels are low.

(E) Adipose cells secrete lipoprotein lipase when blood insulin levels are high.

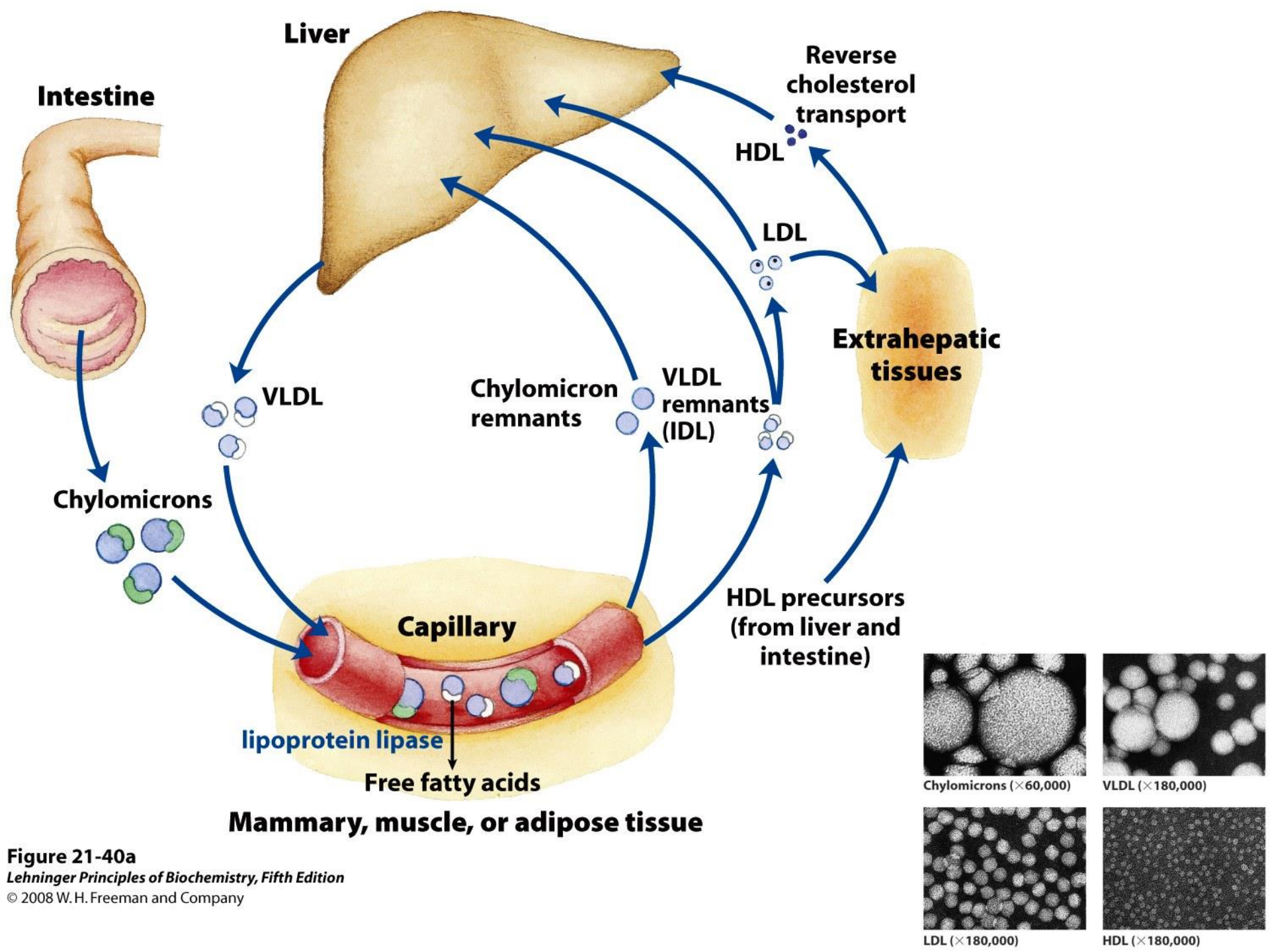

Figure 21-40a

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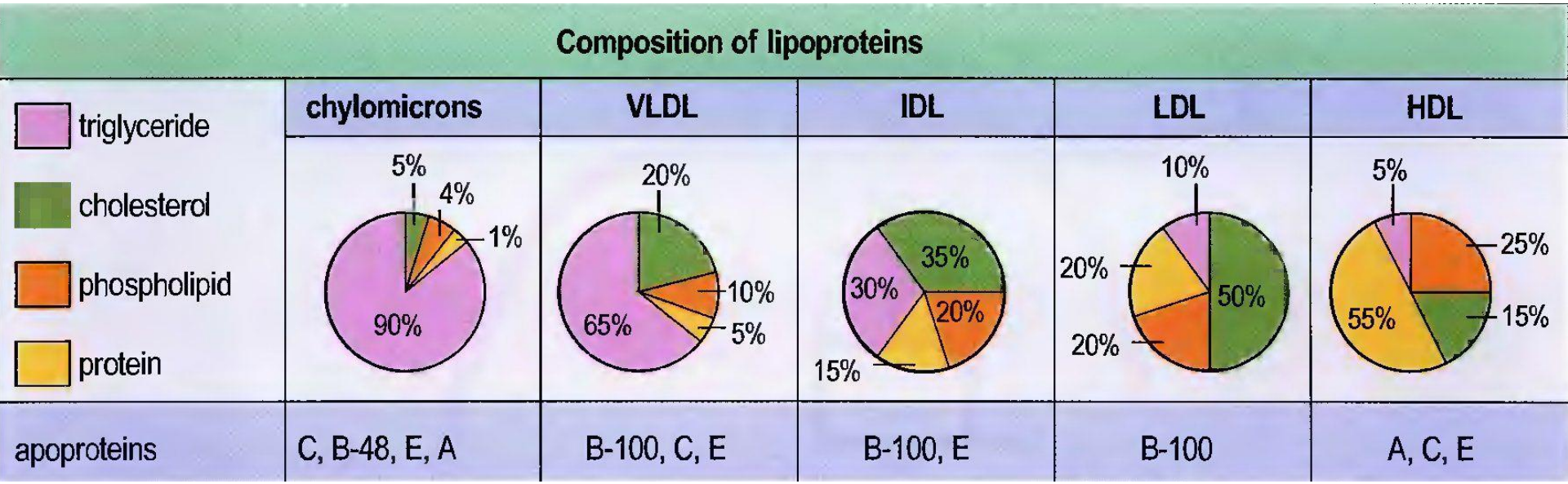


TABLE 21–1 Major Classes of Human Plasma Lipoproteins: Some Properties

Lipoprotein	Density (g/mL)	Composition (wt %)				
		Protein	Phospholipids	Free cholesterol	Cholesteryl esters	Triacylglycerols
Chylomicrons	<1.006	2	9	1	3	85
VLDL	0.95–1.006	10	18	7	12	50
LDL	1.006–1.063	23	20	8	37	10
HDL	1.063–1.210	55	24	2	15	4

Which of the following apoproteins is an activator of lipoprotein lipase?

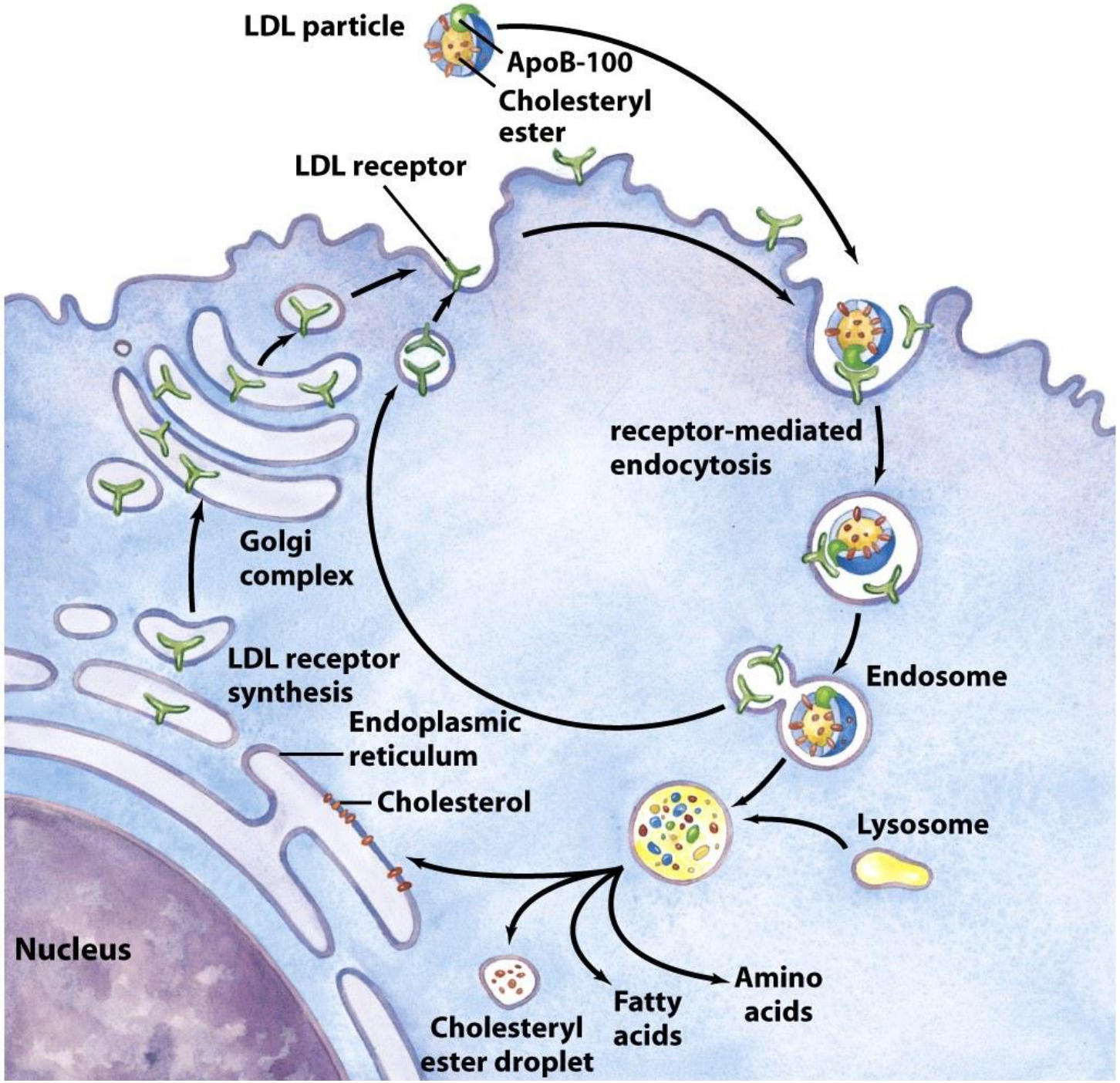
a) Apo A

b) Apo B

c) Apo C II

d) Apo D

e) Apo E


LDL particle
ApoB-100
Cholesteryl ester
LDL receptor
receptor-mediated endocytosis
Golgi complex
LDL receptor synthesis
Endosome
Endoplasmic reticulum
Cholesterol
Lysosome
Nucleus
Cholesteryl ester droplet
Fatty acids
Amino acids

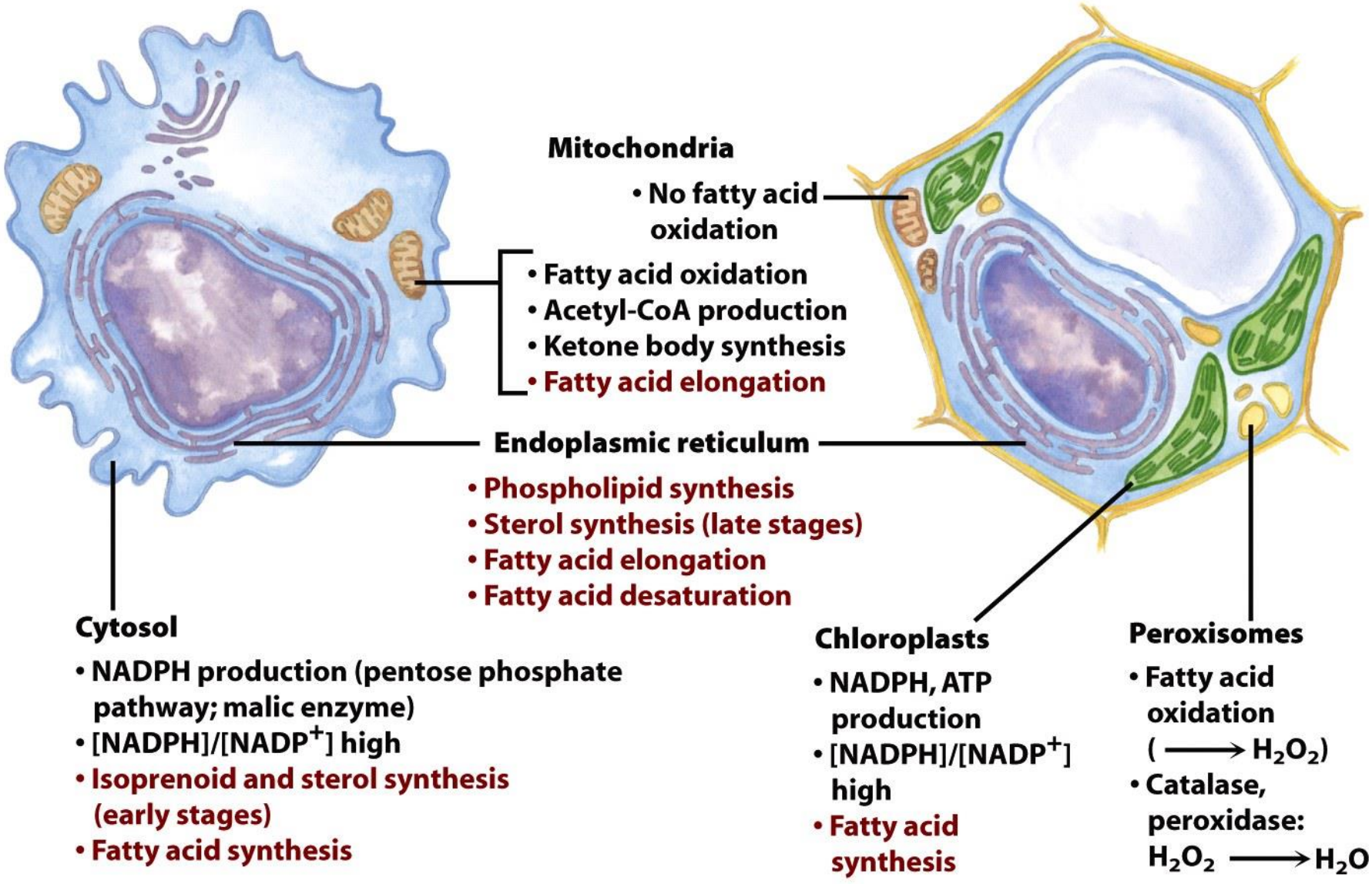


Figure 21-8
Lehninger Principles of Biochemistry, Fifth Edition

A 5-year-old boy presents with altered mental status, heart failure and muscle weakness. His serum levels of ketones and glucose are abnormally low. He is diagnosed with primary carnitine deficiency.
In which of the following is carnitine directly involved?

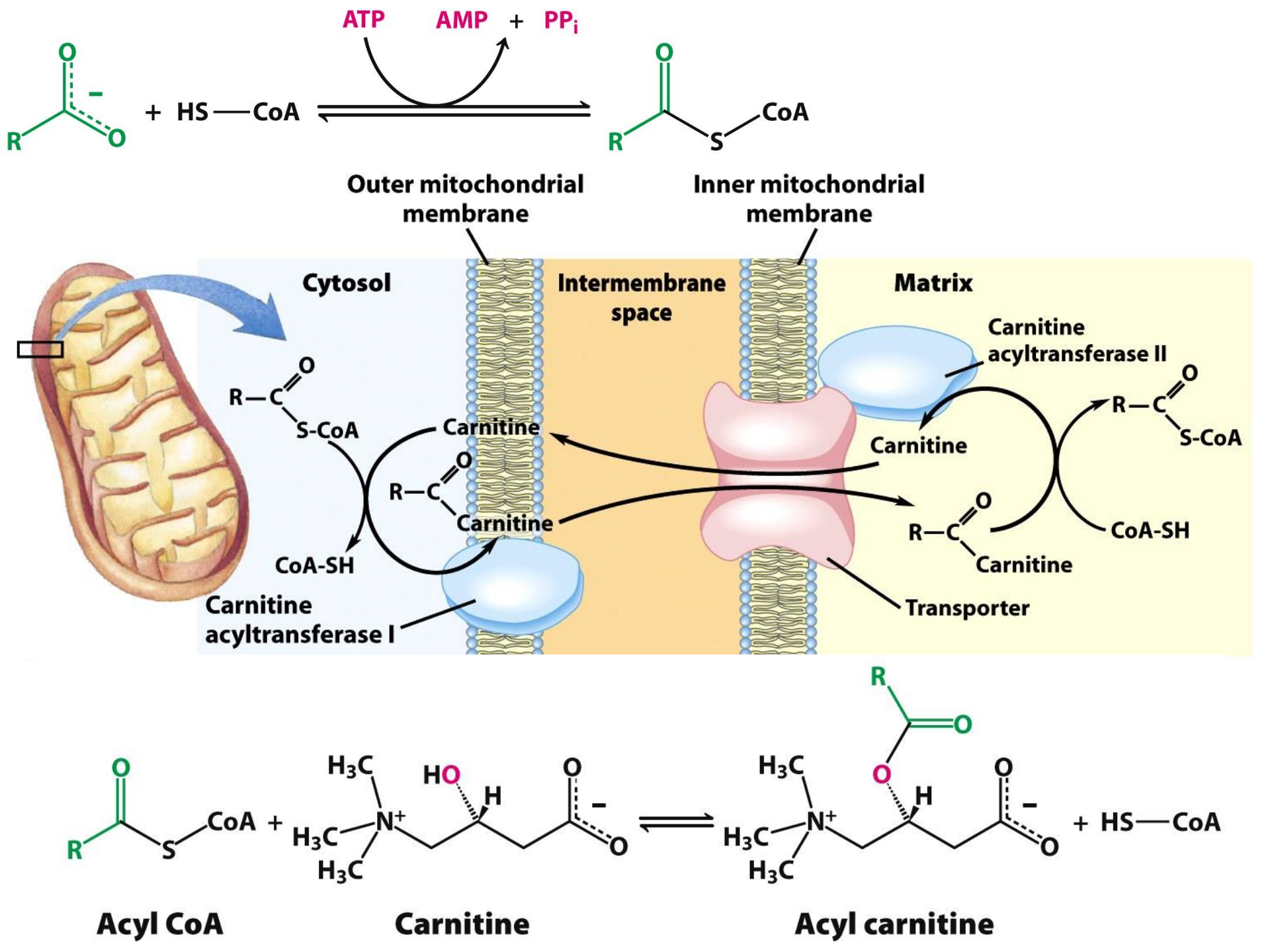
(A) Activation of fatty acids

(B) Transport of fatty acyl-CoA

(C) β-oxidation

(D) ω-oxidation

(E) α-oxidation


ATP
AMP + PPi
+ HS—CoA
CoA
Outer mitochondrial membrane
Inner mitochondrial membrane
Cytosol
Intermembrane space
Matrix
Carnitine acyltransferase II
S-CoA
Carnitine
CoA-SH
Carnitine acyltransferase I
Transporter
Acyl CoA
Carnitine
Acyl carnitine

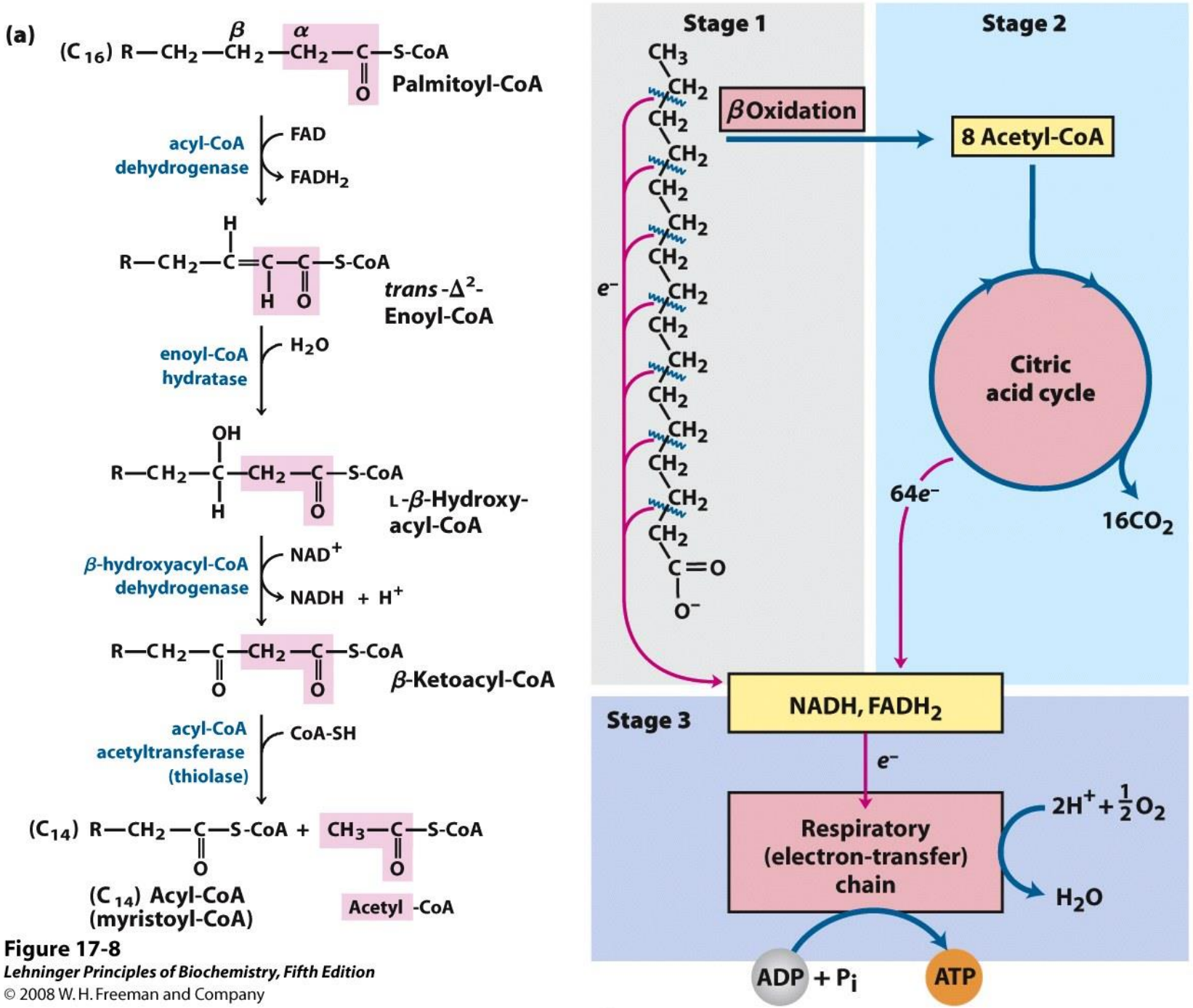


Figure 17-8

Lehninger Principles of Biochemistry, Fifth Edition

palmitoyl-CoA + 23 O_2 + 108 Pi + 108 ADP → CoA + 108 ATP + 16 CO_2 + 23 H_2O

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

Enzyme catalyzing the oxidation step	Number of NADH or $FADH_2$ formed	Number of ATP ultimately formed*
Acyl-CoA dehydrogenase	7 $FADH_2$	10.5
β-Hydroxyacyl-CoA dehydrogenase	7 NADH	17.5
Isocitrate dehydrogenase	8 NADH	20
α-Ketoglutarate dehydrogenase	8 NADH	20
Succinyl-CoA synthetase		8†
Succinate dehydrogenase	8 $FADH_2$	12
Malate dehydrogenase	8 NADH	20
Total		108

*These calculations assume that mitochondrial oxidative phosphorylation produces 1.5 ATP per $FADH_2$ oxidized and 2.5 ATP per NADH oxidized.

†GTP produced directly in this step yields ATP in the reaction catalyzed by nucleoside diphosphate kinase (p. 510).

The energetic cost of activating a fatty acid is equivalent to **2** ATP, and the net gain per molecule of **palmitate** is 106 ATP.

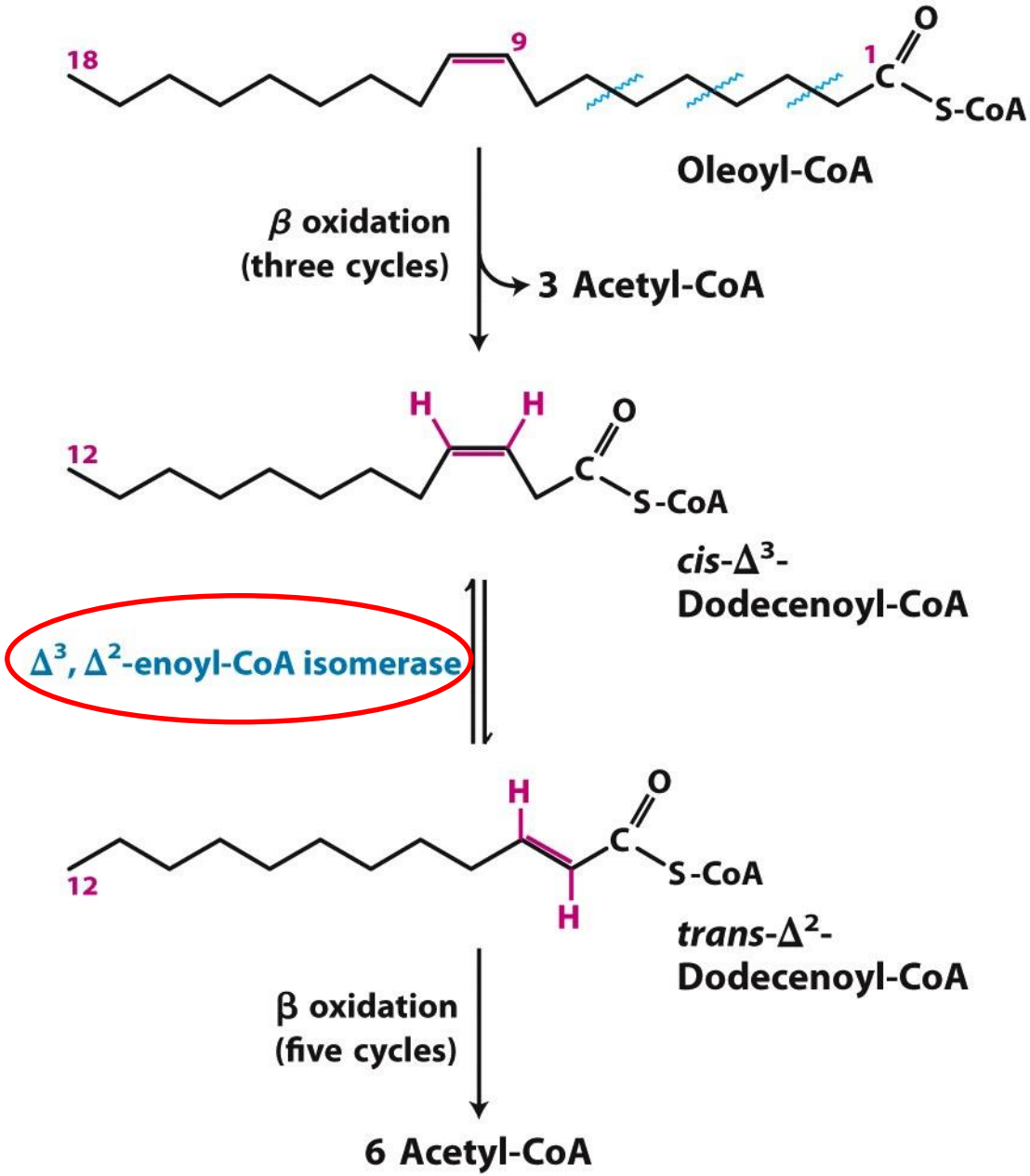


Figure 17-9
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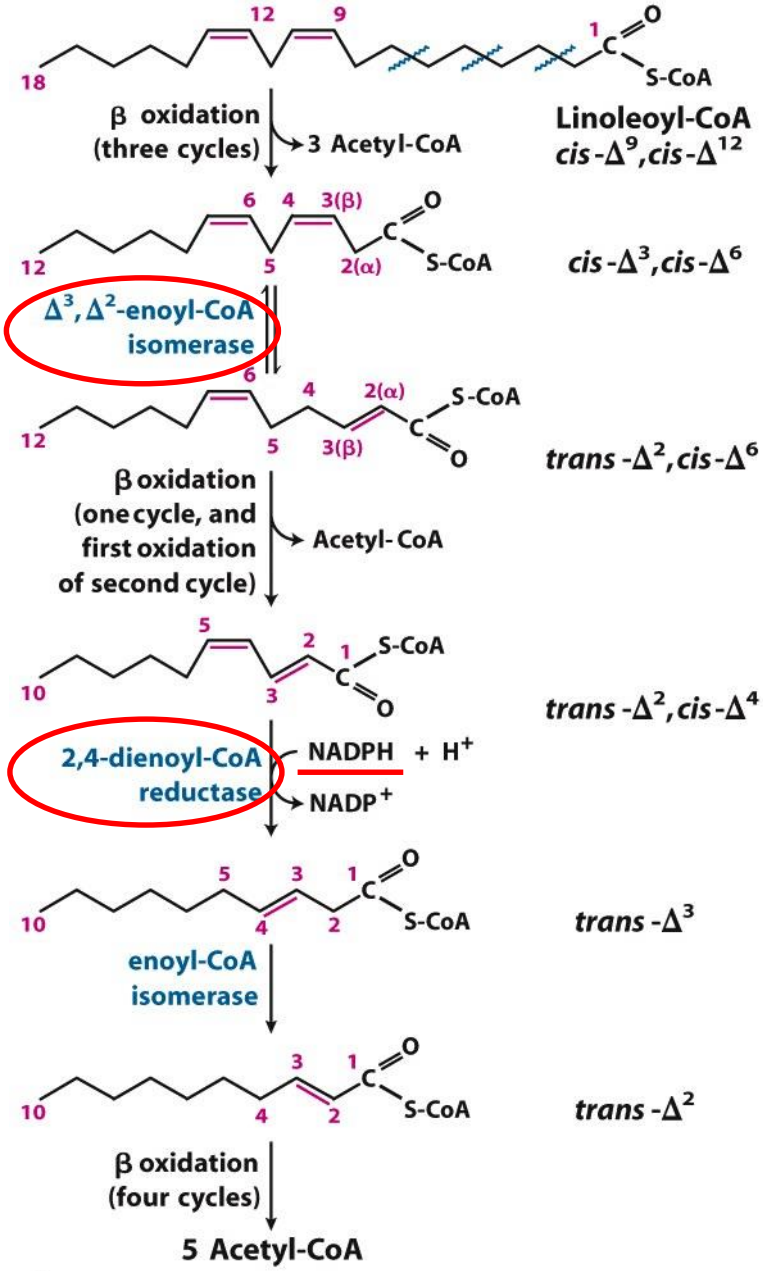

Figure 17-10

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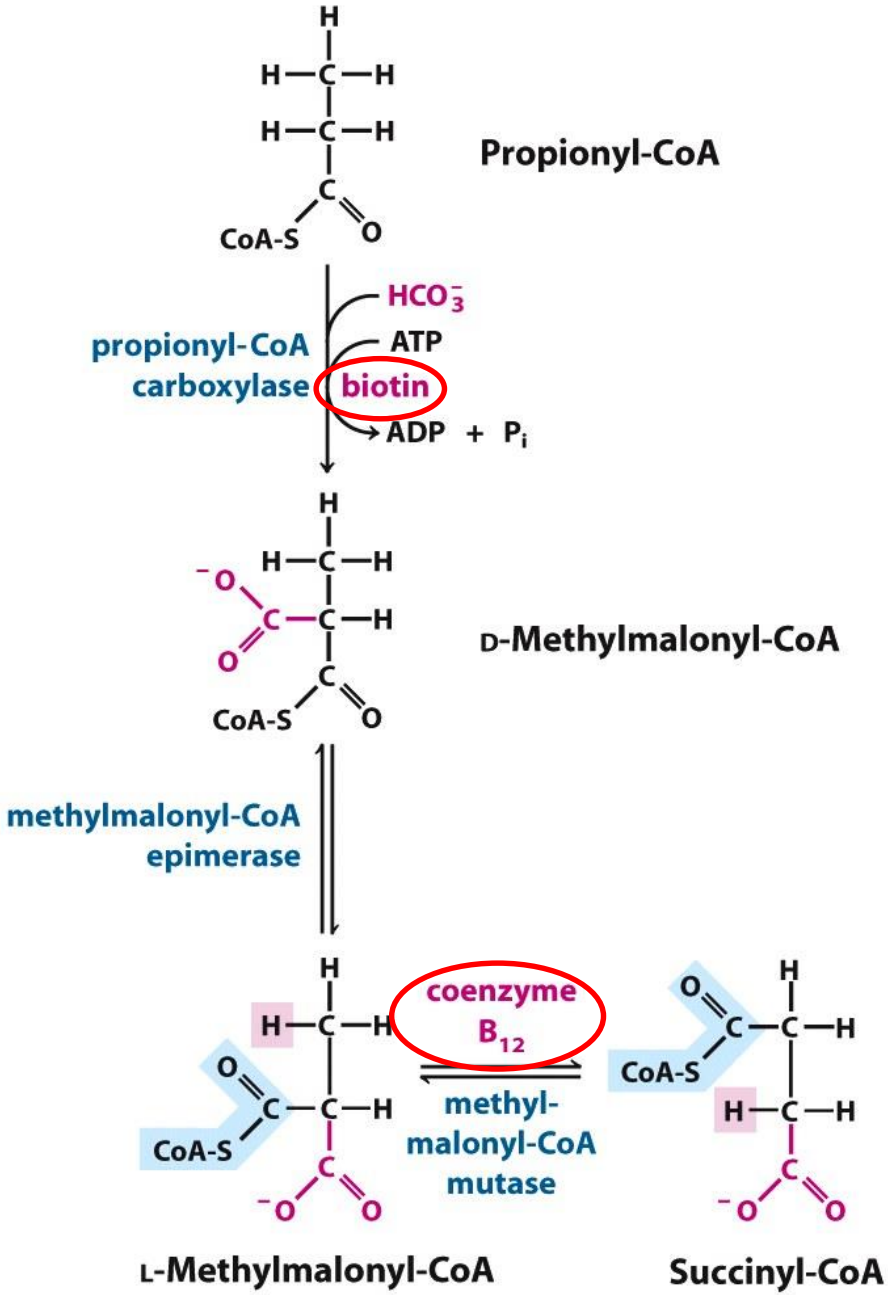

Figure 17-11

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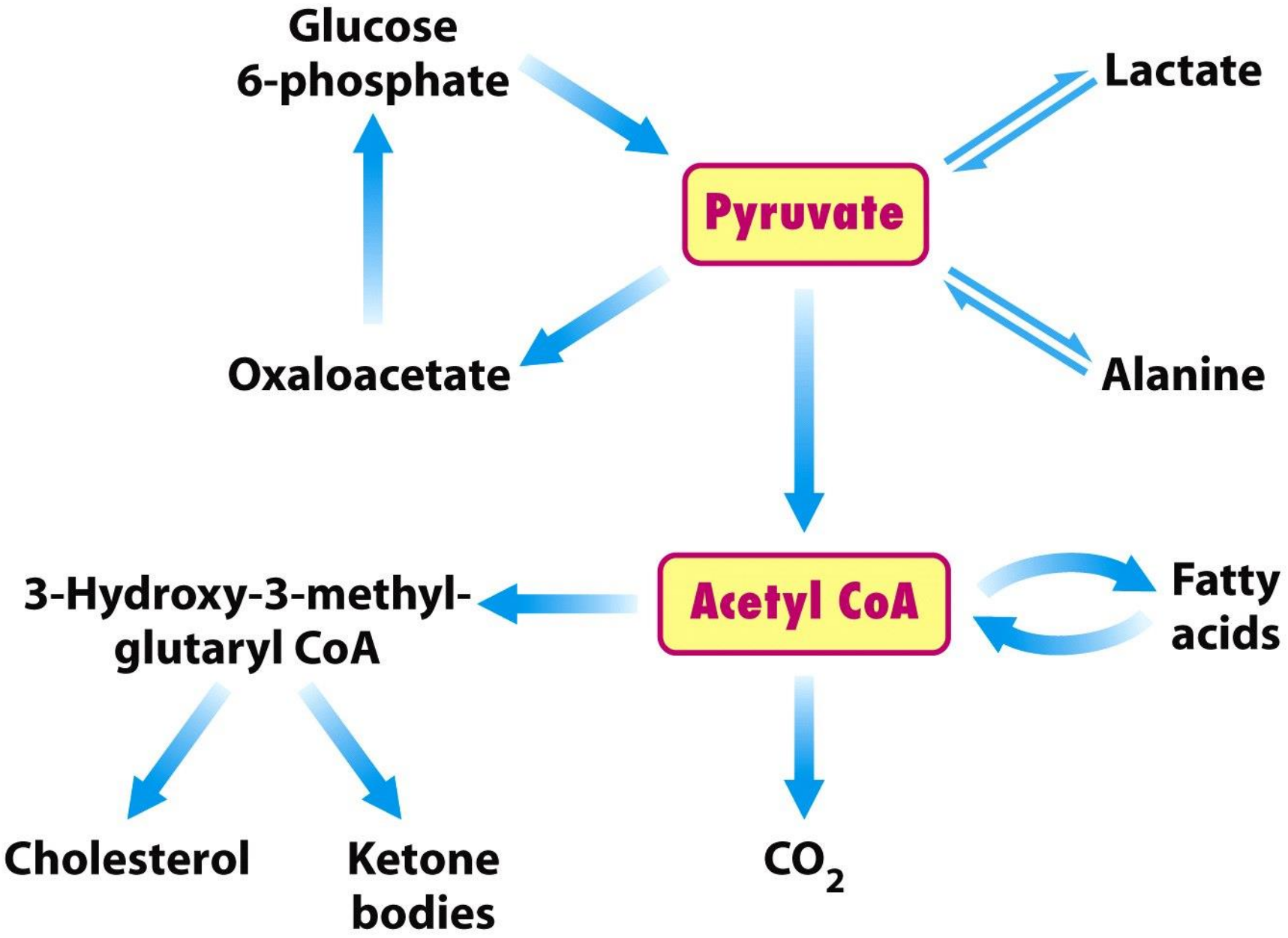

Glucose
6-phosphate
Lactate
Pyruvate
Oxaloacetate
Alanine
3-Hydroxy-3-methyl-
glutaryl CoA
Acetyl CoA
Fatty
acids
Cholesterol
Ketone
bodies
CO_2

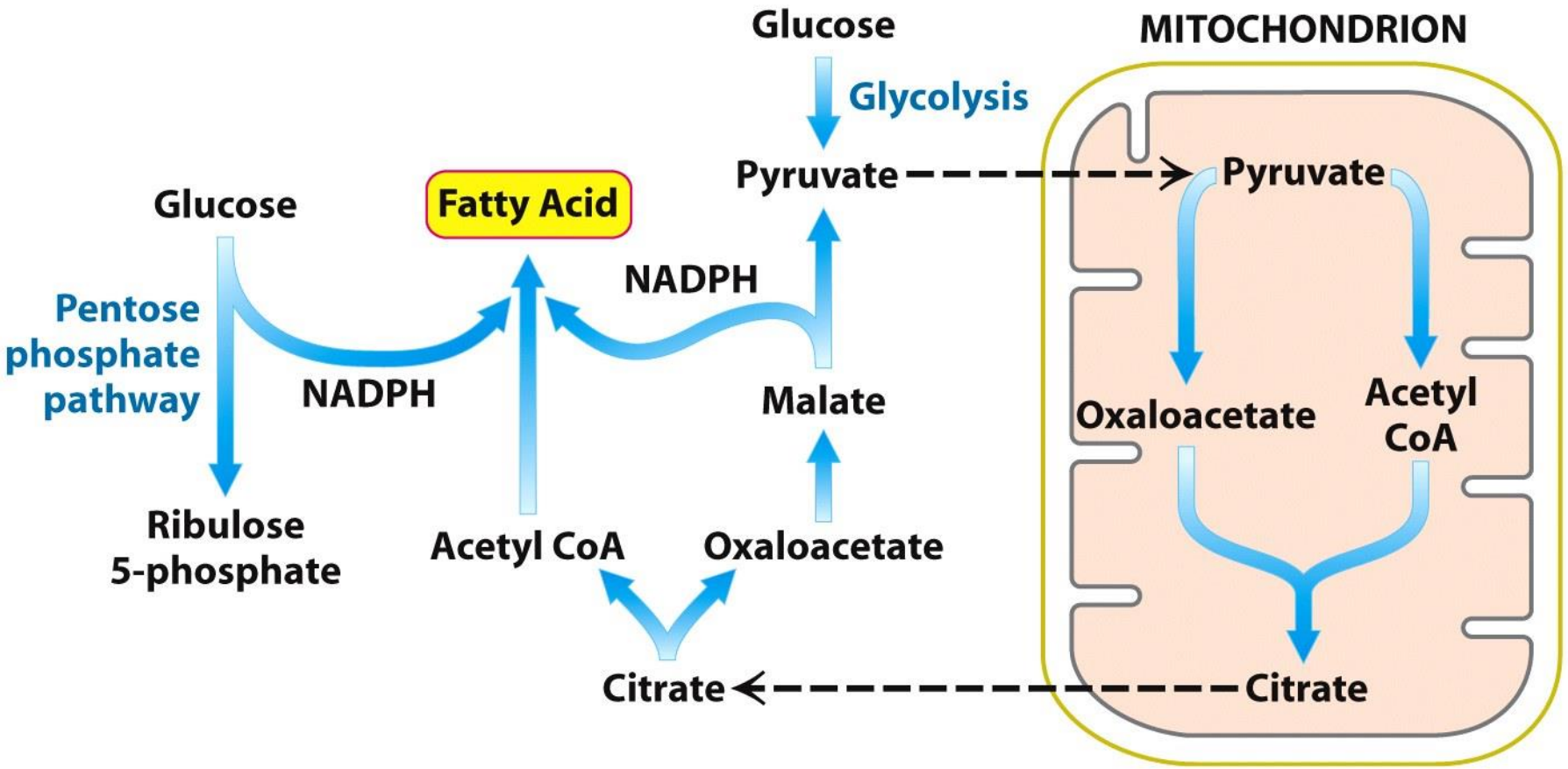
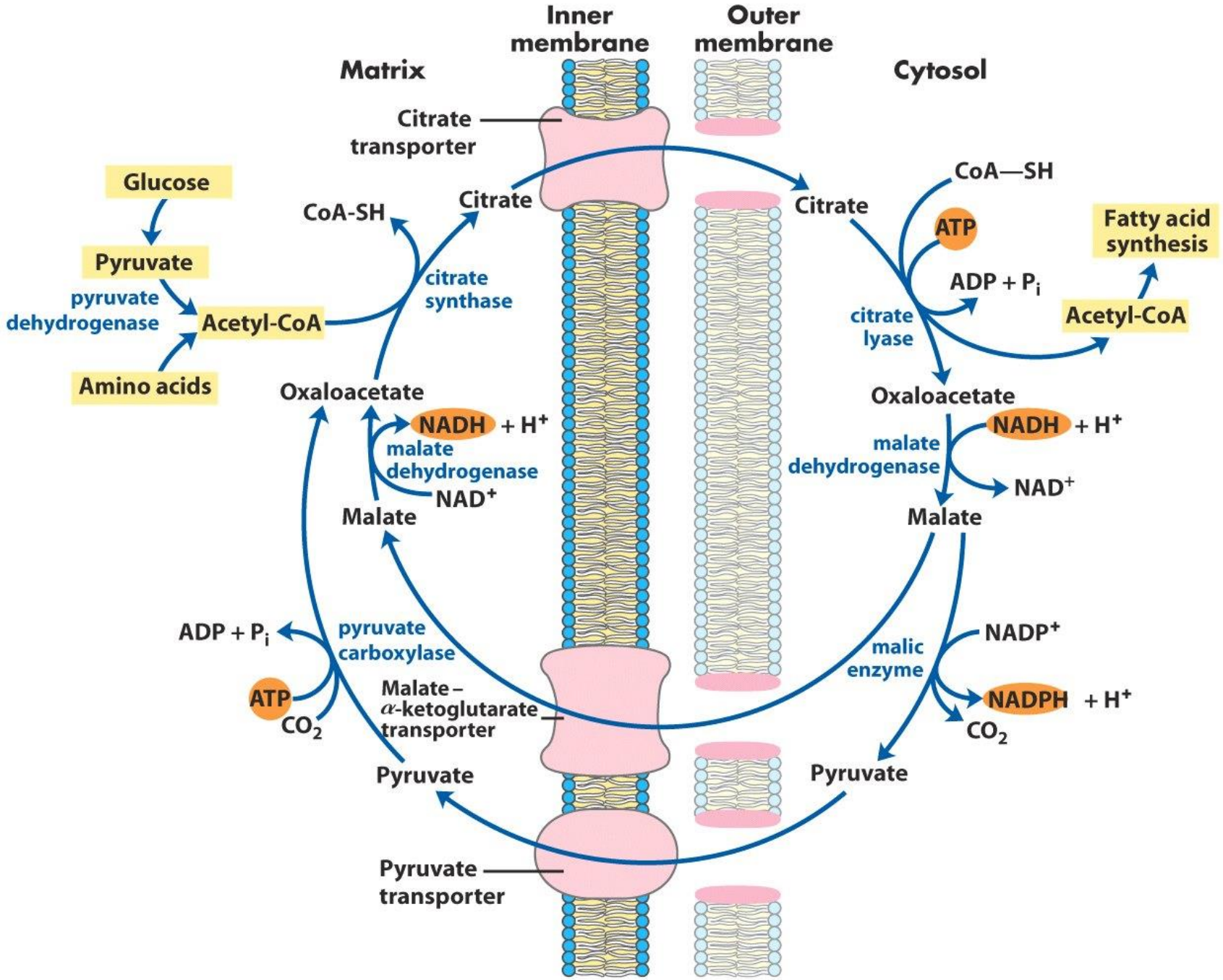
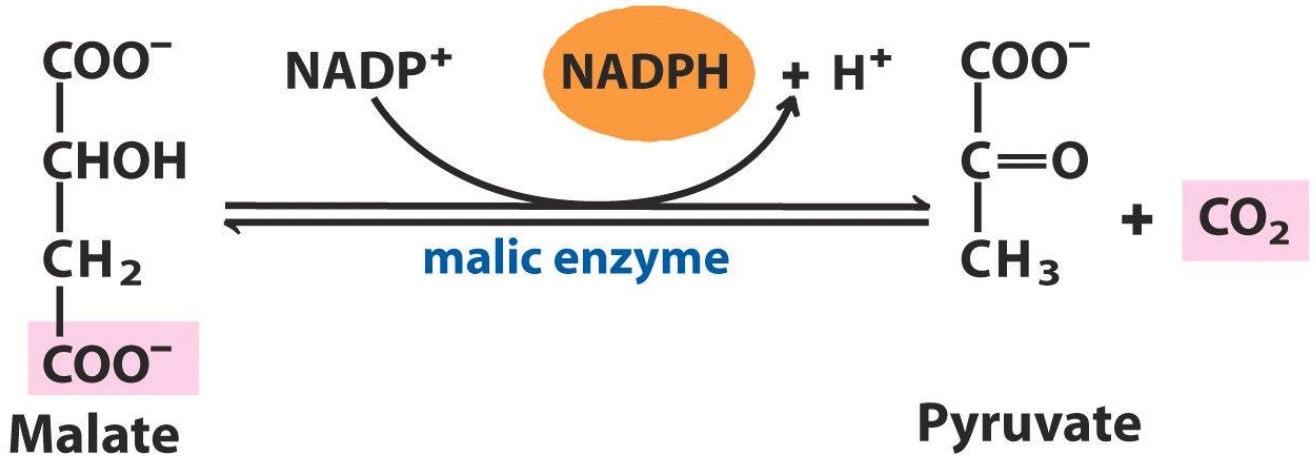
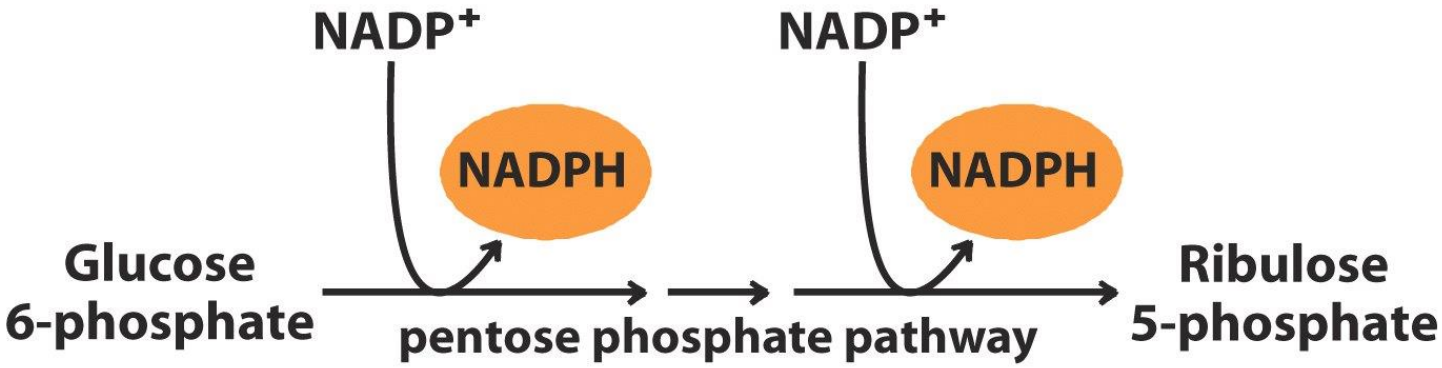


Figure 22.30
***Biochemistry*, Seventh Edition**


Inner membrane
Outer membrane
Matrix
Cytosol
Citrate transporter
Glucose
Pyruvate
pyruvate dehydrogenase
Acetyl-CoA
Amino acids
CoA-SH
Citrate
citrate synthase
Oxaloacetate
NADH + H+
malate dehydrogenase
NAD+
Malate
ADP + Pi
pyruvate carboxylase
ATP
CO2
Malate – α-ketoglutarate transporter
Pyruvate
Pyruvate transporter
Citrate
CoA—SH
ATP
ADP + Pi
citrate lyase
Fatty acid synthesis
Acetyl-CoA
Oxaloacetate
NADH + H+
malate dehydrogenase
NAD+
Malate
NADP+
malic enzyme
NADPH + H+
CO2
Pyruvate

Source of cytosolic NADPH

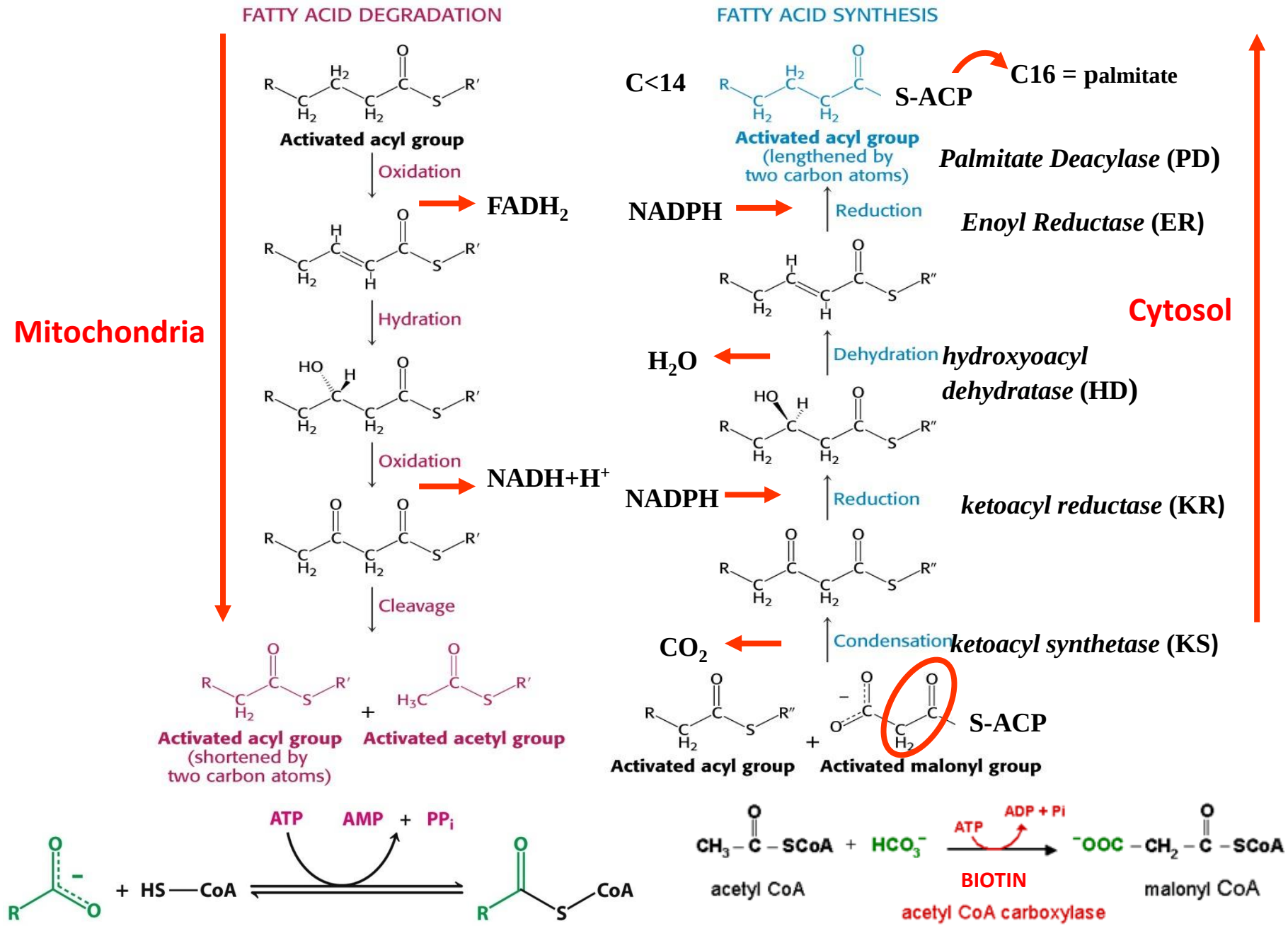




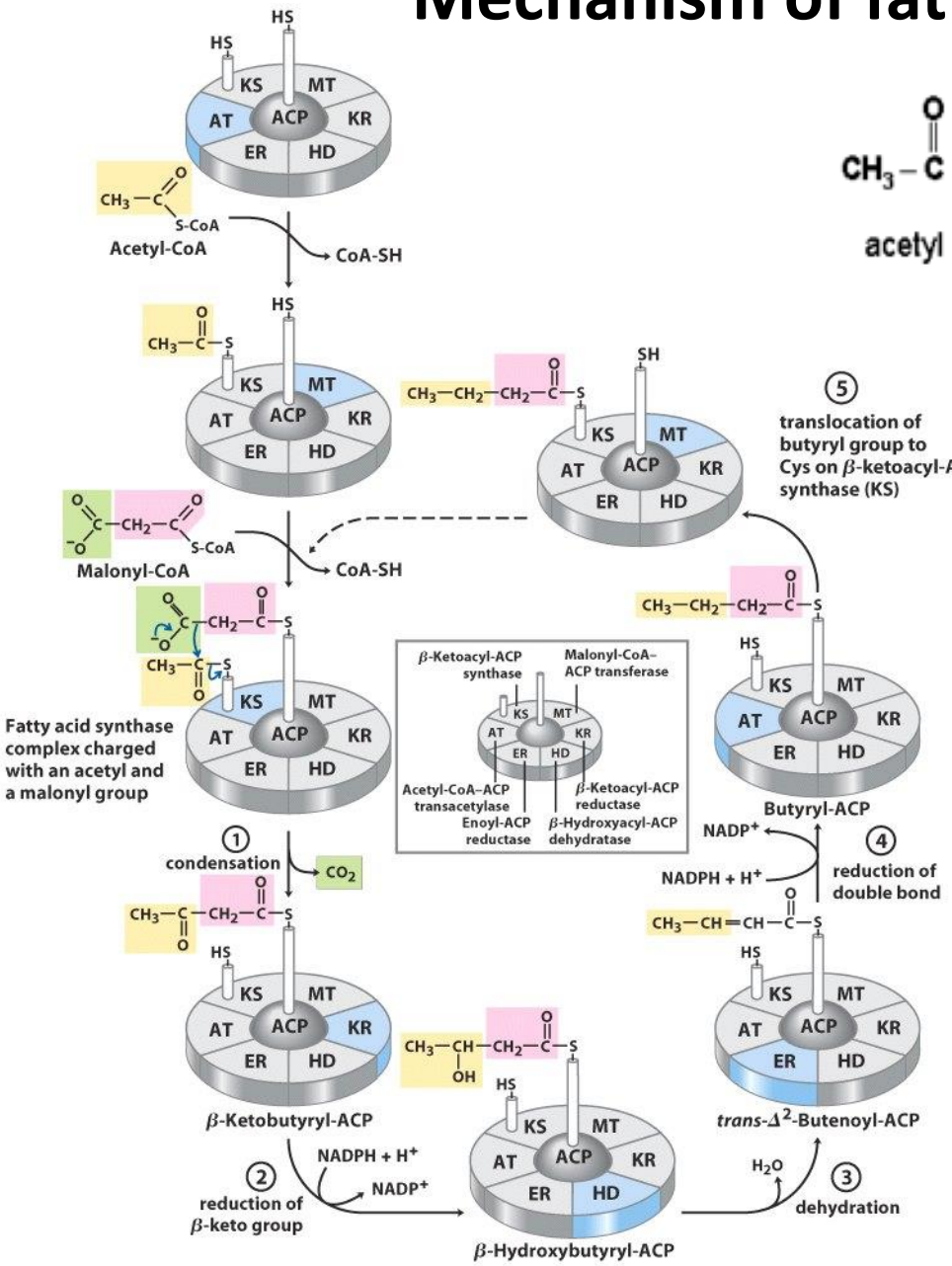
Cytosolic coenzyme	$NADPH/NADP^+$ ~75
levels in hepatocytes:	$NADH/NAD^+$ ~8×10^{-4}

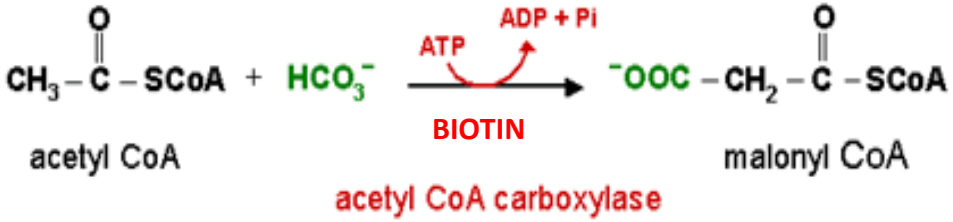
A 30- year-old pregnant woman has a sugar craving and consumes a hot fudge sundae. Her serum glucose level increases, which causes release of insulin. Insulin is known to increase the activity of acetyl-CoA carboxylase, the rate limiting enzyme of fatty acid biosynthesis. Which of the following best describes this regulatory enzyme?

a) It is activated by carboxylation
b) It catalyzes a reaction that condenses an acetyl group with malonyl group
c) It catalyzes a reaction that requires biotin and ATP
d) It converts Malonyl-CoA to Acetyl-CoA
e) It is activated by Malonyl-CoA.


FATTY ACID DEGRADATION
FATTY ACID SYNTHESIS
Mitochondria
Cytosol
Activated acyl group
Oxidation
FADH2
Hydration
Oxidation
NADH+H+
Cleavage
Activated acyl group
(shortened by
two carbon atoms)
Activated acetyl group
C<14
S-ACP
C16 = palmitate
Activated acyl group
(lengthened by
two carbon atoms)
Palmitate Deacylase (PD)
NADPH
Reduction
Enoyl Reductase (ER)
H2O
Dehydration
hydroxyoacyl
dehydratase (HD)
NADPH
Reduction
ketoacyl reductase (KR)
CO2
Condensation
ketoacyl synthetase (KS)
S-ACP
Activated acyl group
Activated malonyl group
ATP
AMP + PPi
+ HS—CoA
CoA
acetyl CoA
ATP
ADP + Pi
BIOTIN
acetyl CoA carboxylase
malonyl CoA

Mechanism of fatty acid synthesis





Ketoacyl Synthase (KS)

Ketoacyl Reductase (KR)

Hydroxyoacyl Dehydratase (HD)

Enoyl Reductase (ER)

} **four "basic"**

Acyl Carrier Protein (ACP)

Malonyl-CoA-ACP acyltransferase (MAT)

Acetyl-CoA-ACP-acyltransferase (AT)

Palmitate Deacylase (PD)
(*Thioesterase* TE)

} **other four**

Overall reactions for palmitate synthesis

$$7 \text{ malonyl-CoA} + 1 \text{ acetyl-CoA} + 14 \text{ NADPH} + 14 \text{ H}^+ = \text{palmitate} + 7 \text{ CO}_2 + 14 \text{ NADP}^+ + 6 \text{ H}_2\text{O} + 8 \text{ CoASH}$$

$$8 \text{ acetyl-CoA} + 7 \text{ ATP} + 14 \text{ NADPH} + 14 \text{ H}^+ = \text{palmitate} + 7 \text{ ADP} + 7 \text{ P}_i + 14 \text{ NADP}^+ + 6 \text{ H}_2\text{O} + 8 \text{ CoASH}$$

Notes

- Since fatty acids are elongated with C2 units, most fatty acids are even chain
- Fatty acid synthase of the cytosol produces max 16 C long saturated fatty acids.
- Longer and/or unsaturated fatty acids are produced by enzyme systems of ER and mitochondria.
- Odd chain fatty acids are produced when AT enzyme accepts propionyl-CoA as a substrate by mistake.

Newly synthesized fatty acids are not immediately degraded because of which of the following reasons?

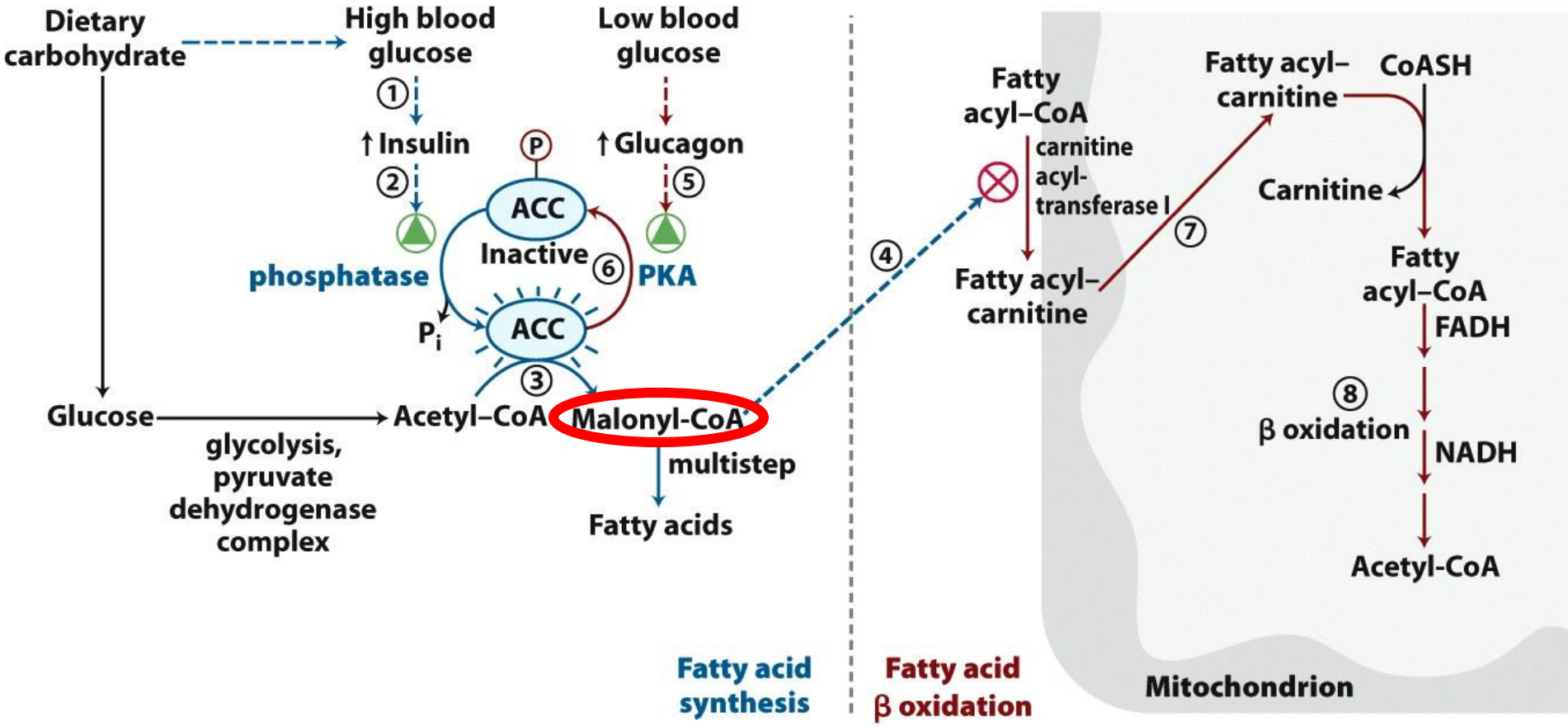
(A) Fatty acid synthesis occurs in tissues that do not contain the enzymes that degrade fatty acids.

(B) High NAD^+ levels inhibit fatty acid breakdown.

(C) Transport of fatty acids into mitochondia is inhibited under fatty acid synthesis.

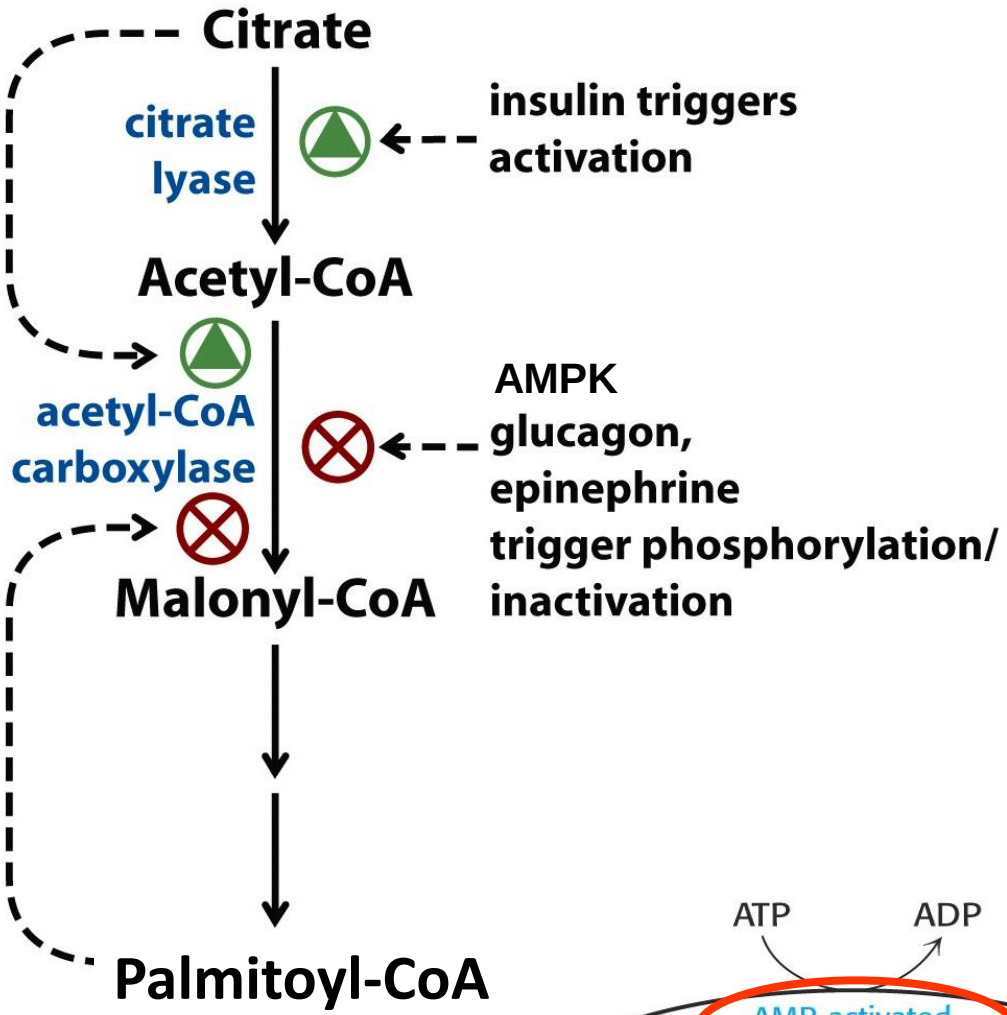
(D) Fatty acid synthesis occurs in the mitochondria, while fatty acid β-oxidation occurs in the cytosol.

(E) Newly synthesized fatty acids cannot be converted to their coenzyme A (CoA) derivatives.



NADH inhibits hydroxy-acyl-CoA dehydrogenase

Ac-CoA inhibits thiolase



Muscle work or fasting:

ATP ↓ AMP↑

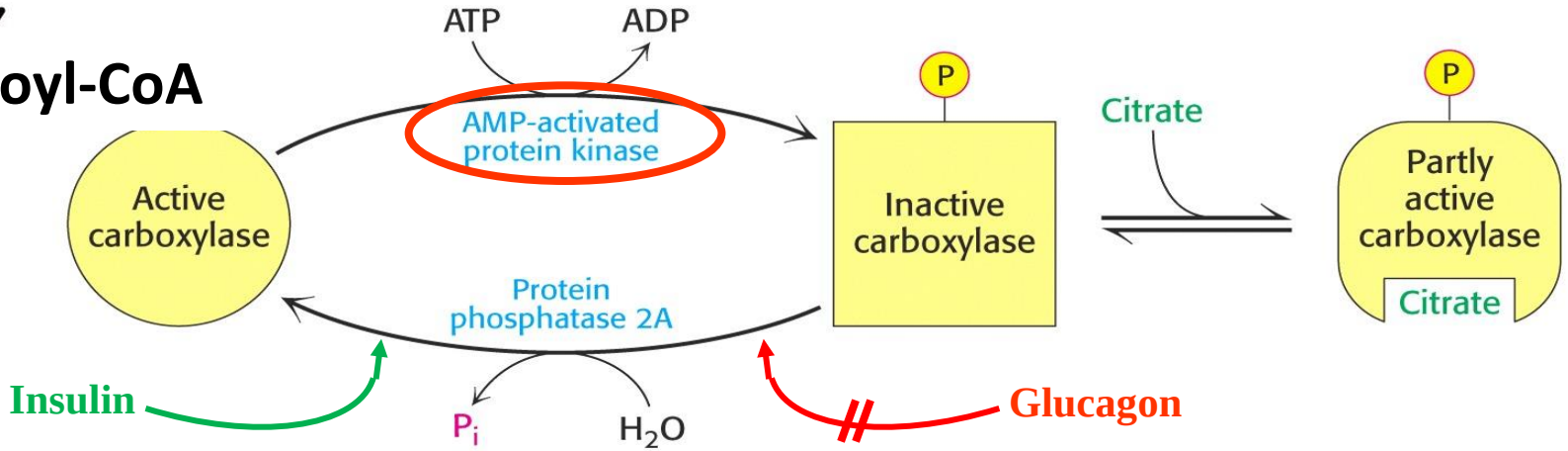
AMPK activated by high AMP levels

ACC phosphorylated = inhibited

Malonyl-CoA level ↓

β-oxidation ↑

ATP ↑



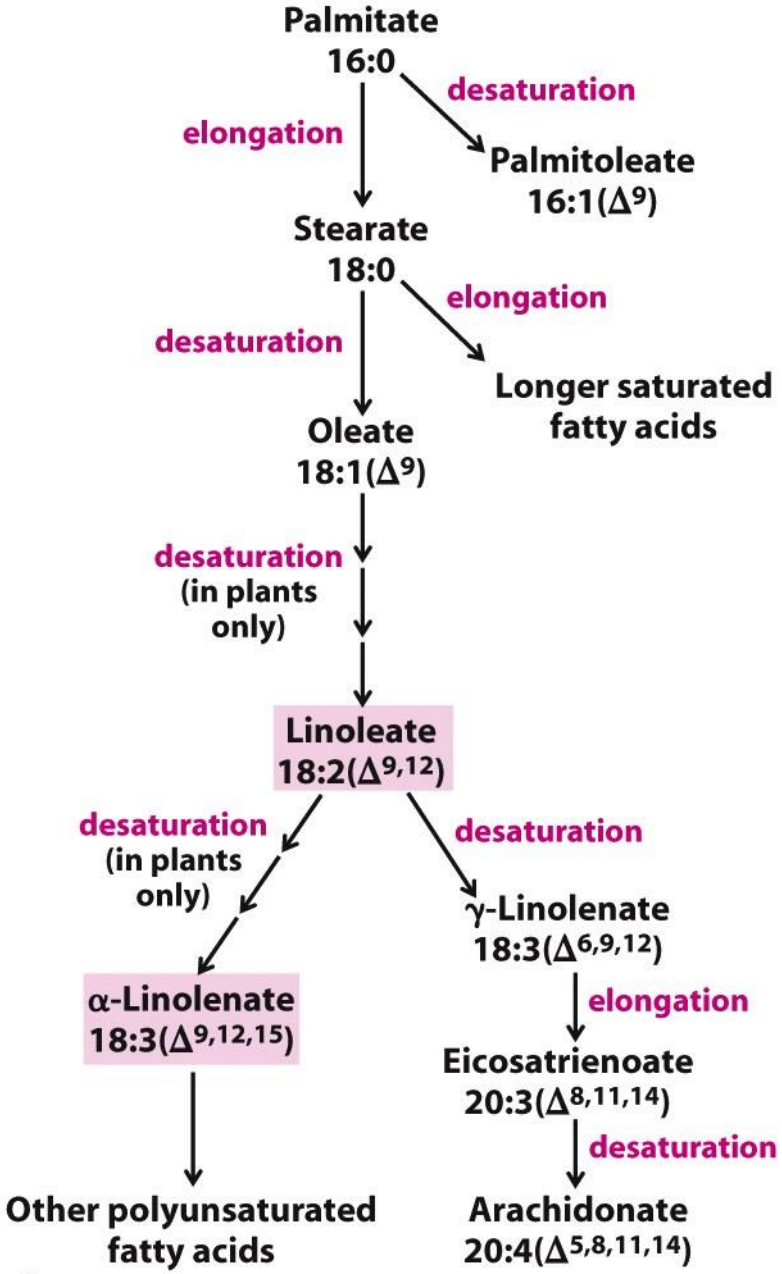


Figure 21-12

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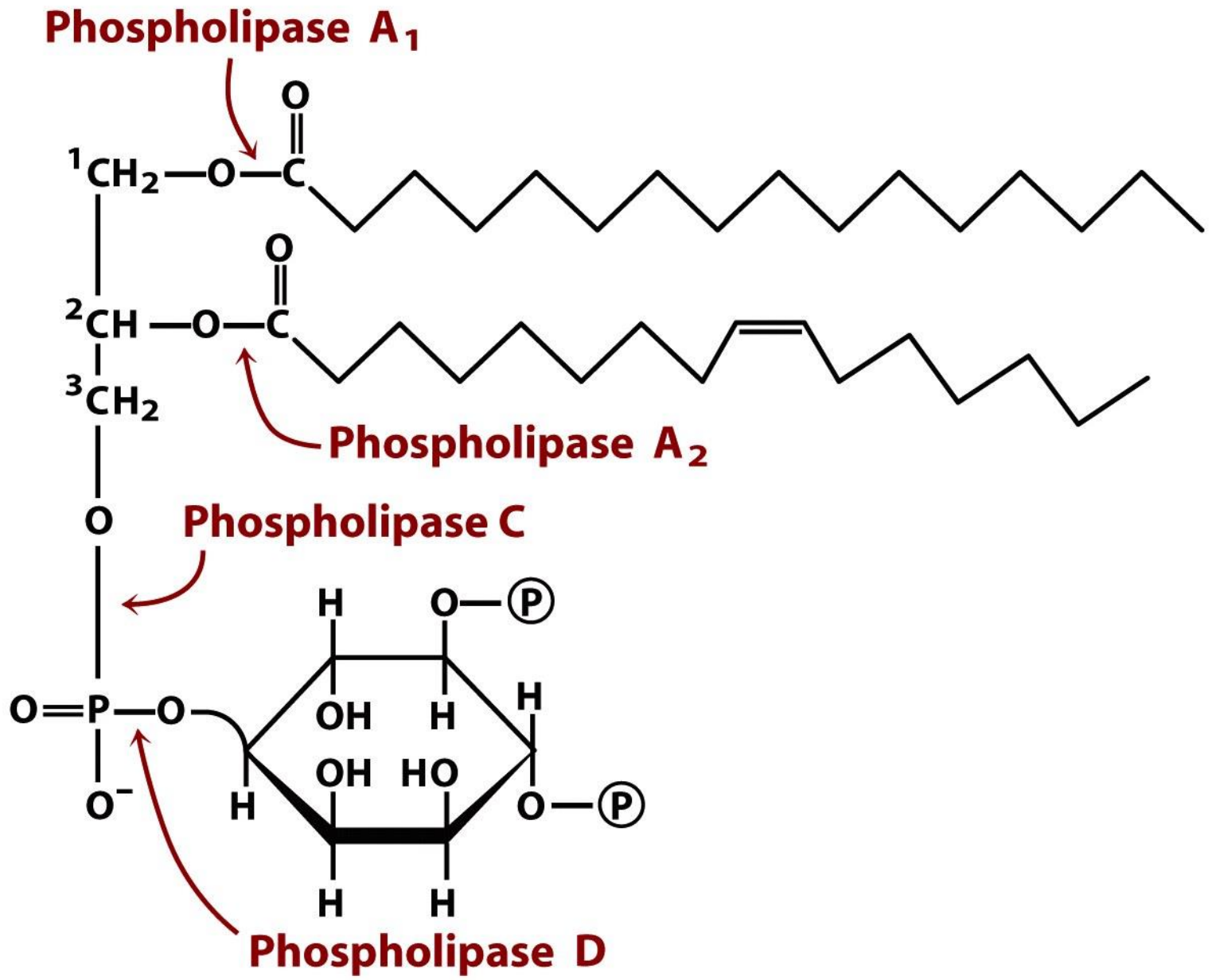


Figure 10-16
Lehninger Principles of Biochemistry, Fifth Edition

A 40-year-old woman has rheumatoid arthritis, a crippling disease causing severe pain and deformation in the joints of the fingers. She is prescribed prednisone, a steroidal anti-inflammatory drug. What is the mechanism of steroidal anti-inflammatory agents?

a) Prevent conversion of arachidonic acid to epoxides
b) Inhibit phospholipase A_2
c) Promote activation of prostacyclins
d) Degrade thromboxanes
e) Promote leukotriene formation from HPETEs

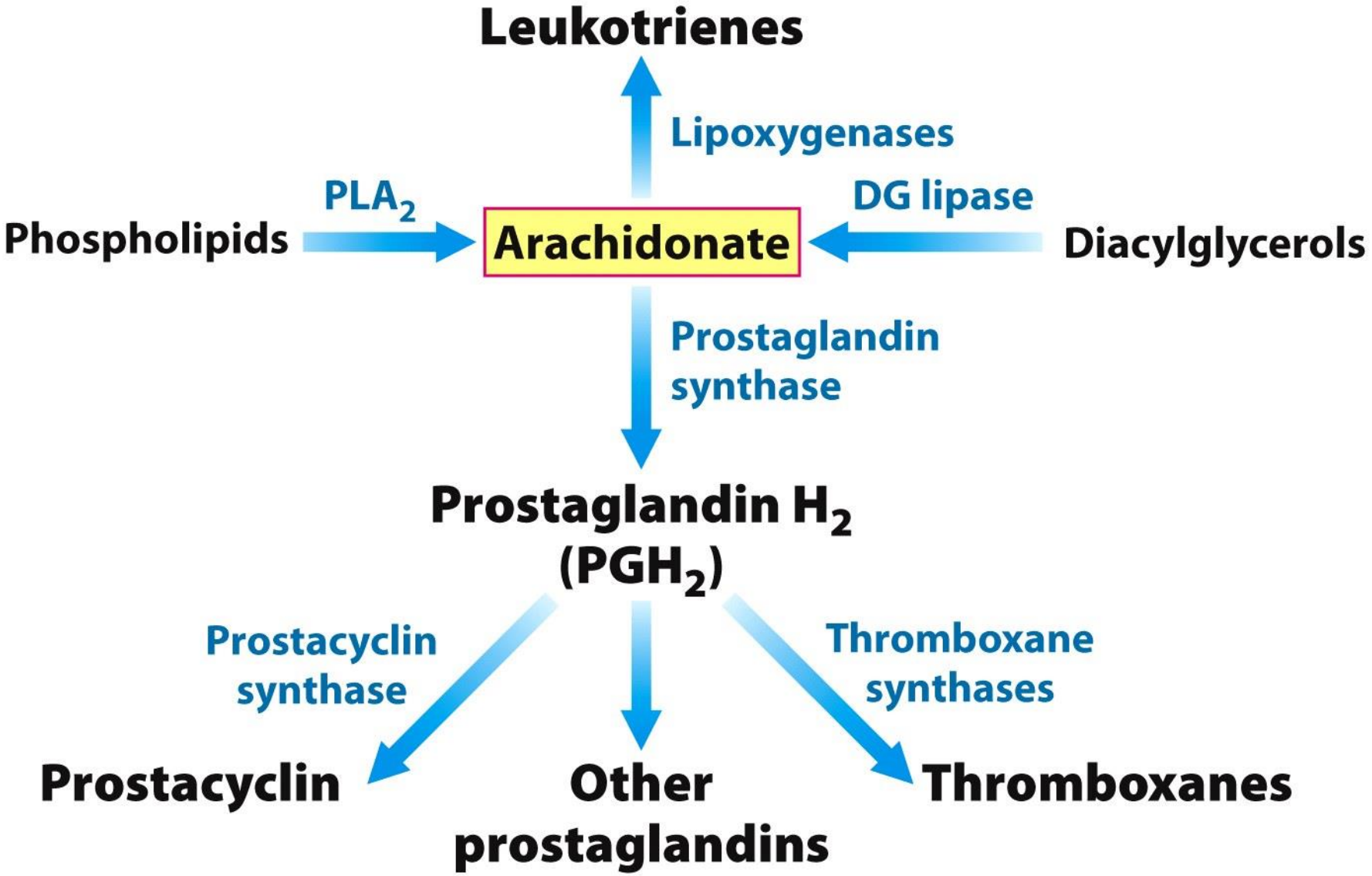


Figure 22.32
***Biochemistry*, Seventh Edition**

What is the mechanism of non-steroid anti-inflammatory agents (NSAIDs)?

a) Promote leukotriene formation from HPETEs
b) Inhibit phospholipase A2
c) Promote activation of prostacyclins
d) Degrade thromboxanes
e) Inhibit cyclooxigenase (COX) enzyme

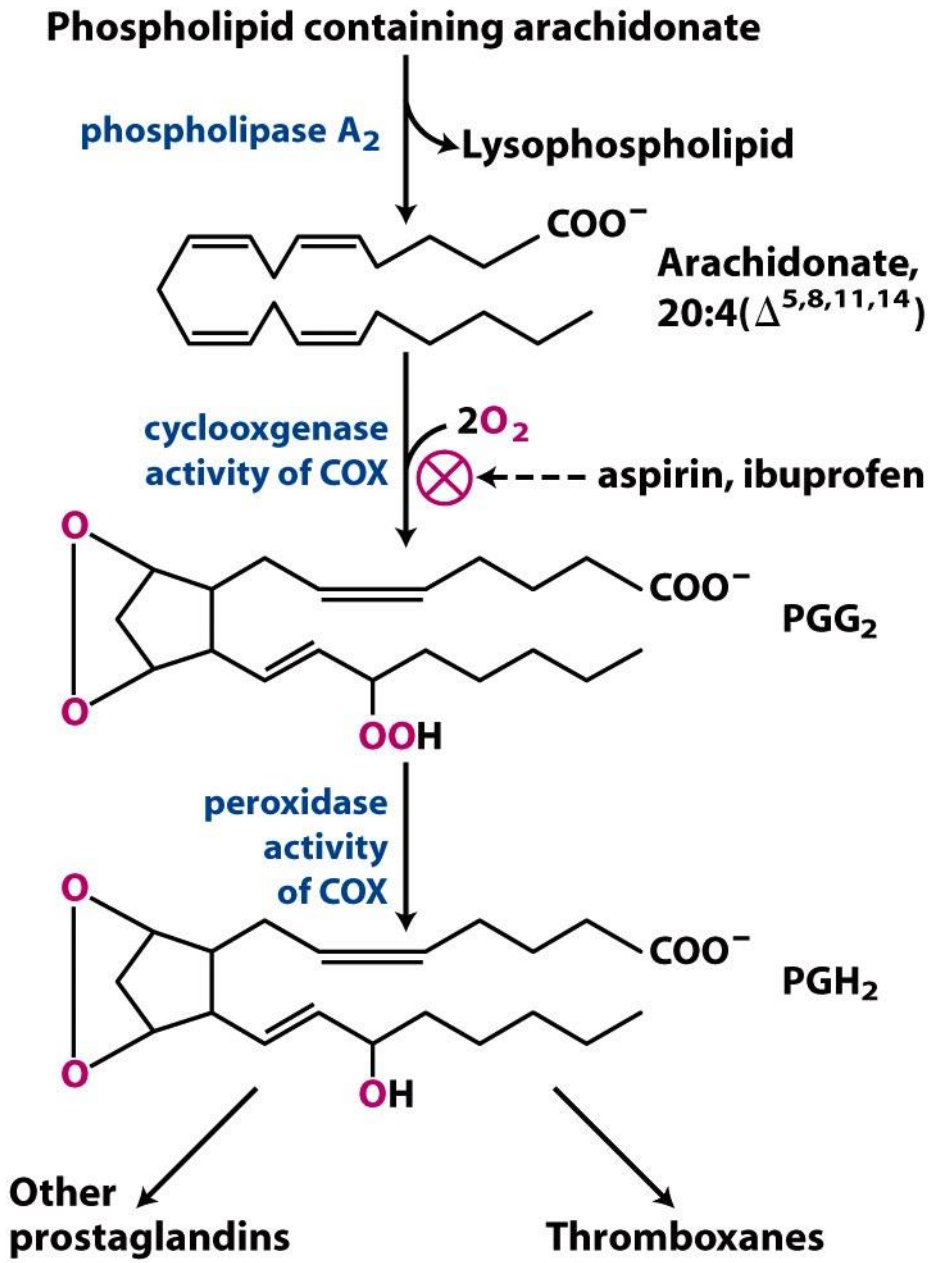
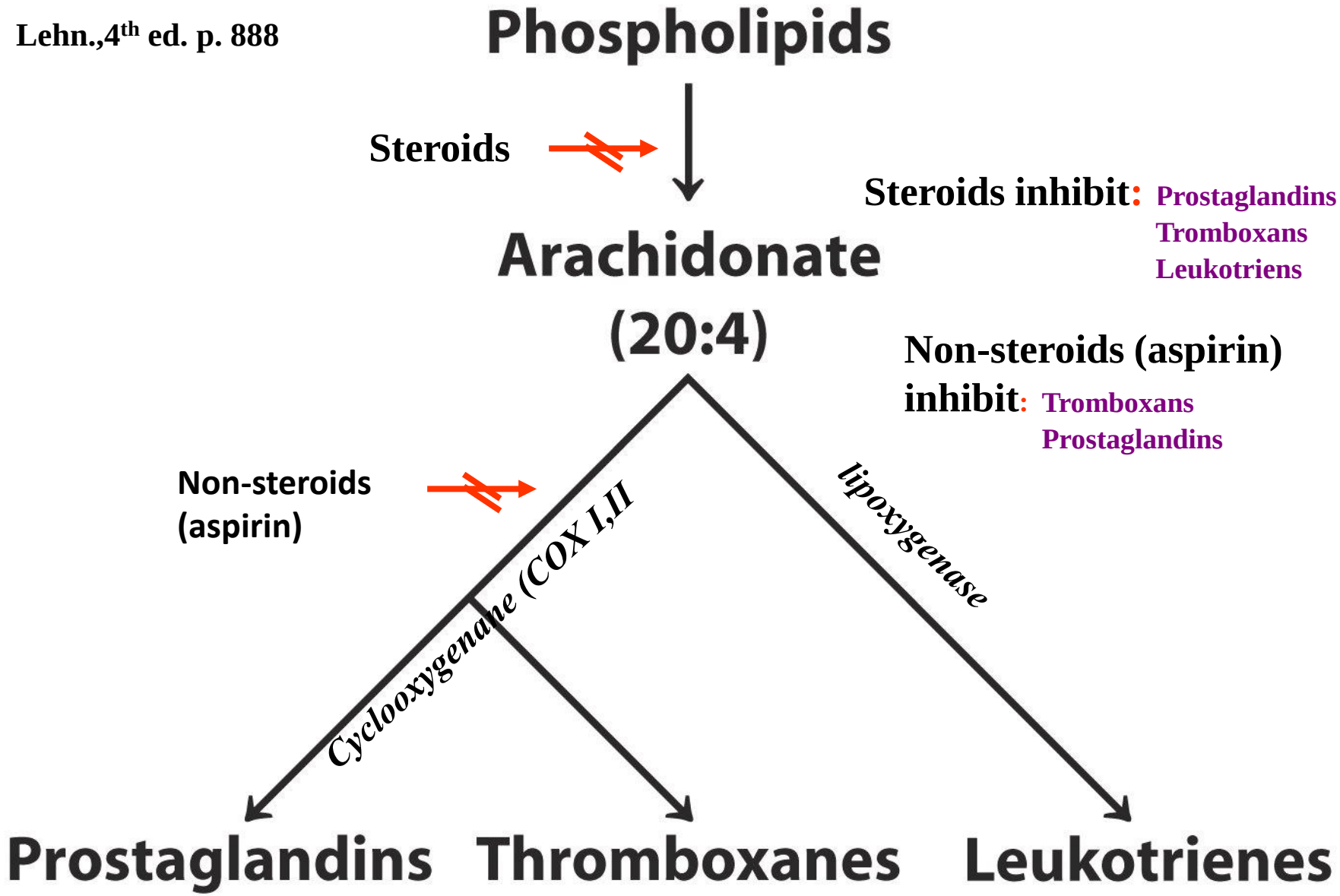
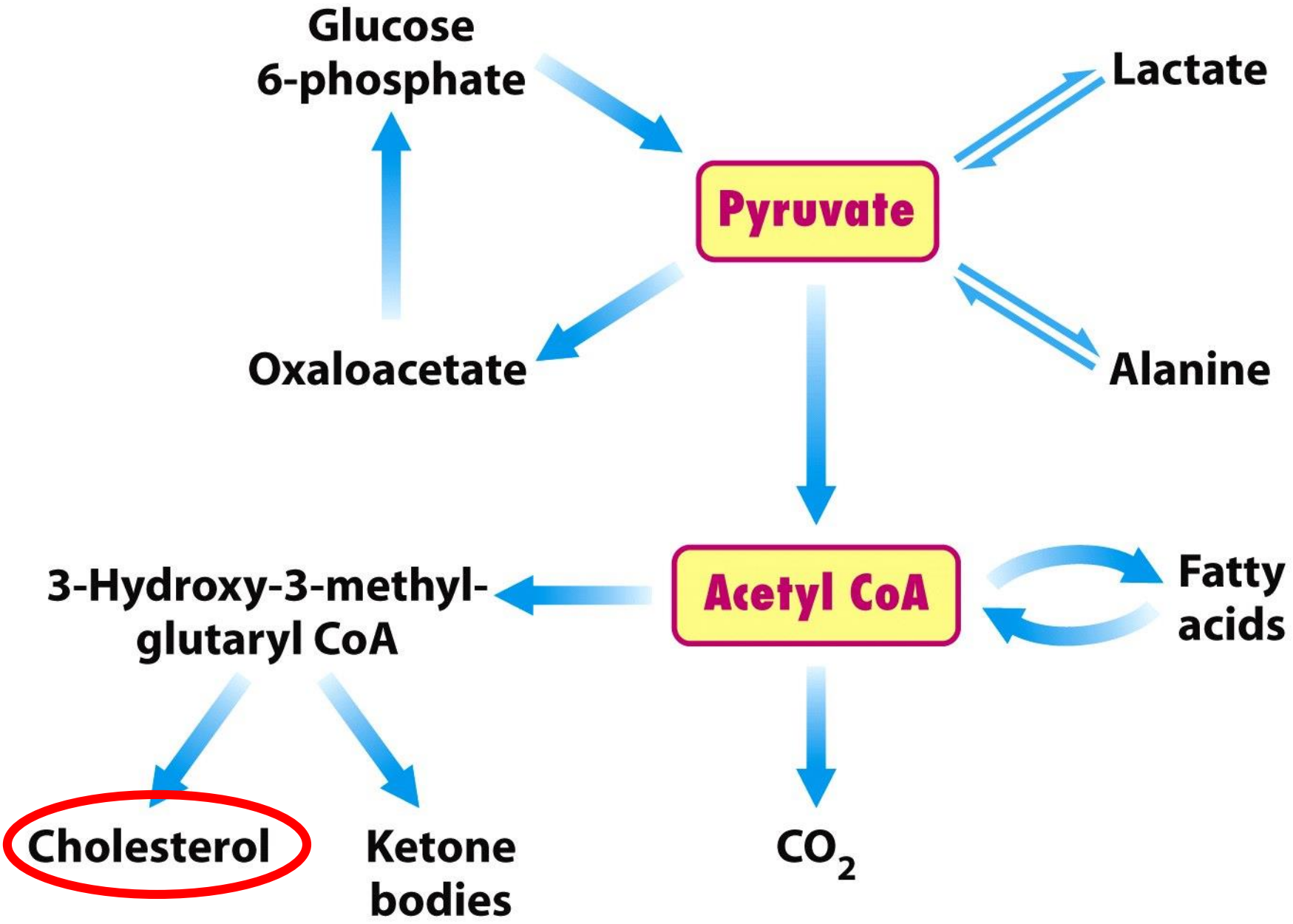


Figure 21-15a

Lehninger Principles of Biochemistry, Fifth Edition

Lehn.,4th ed. p. 888




Glucose
6-phosphate
Lactate
Pyruvate
Oxaloacetate
Alanine
Acetyl CoA
3-Hydroxy-3-methyl-
glutaryl CoA
Fatty
acids
Cholesterol
Ketone
bodies
CO_2

The key regulatory enzyme of cholesterol synthesis is:

a) HMG- Co A synthase

b) HMG Co A lyase

c) HMG Co A reductase

d) Mevalonate kinase

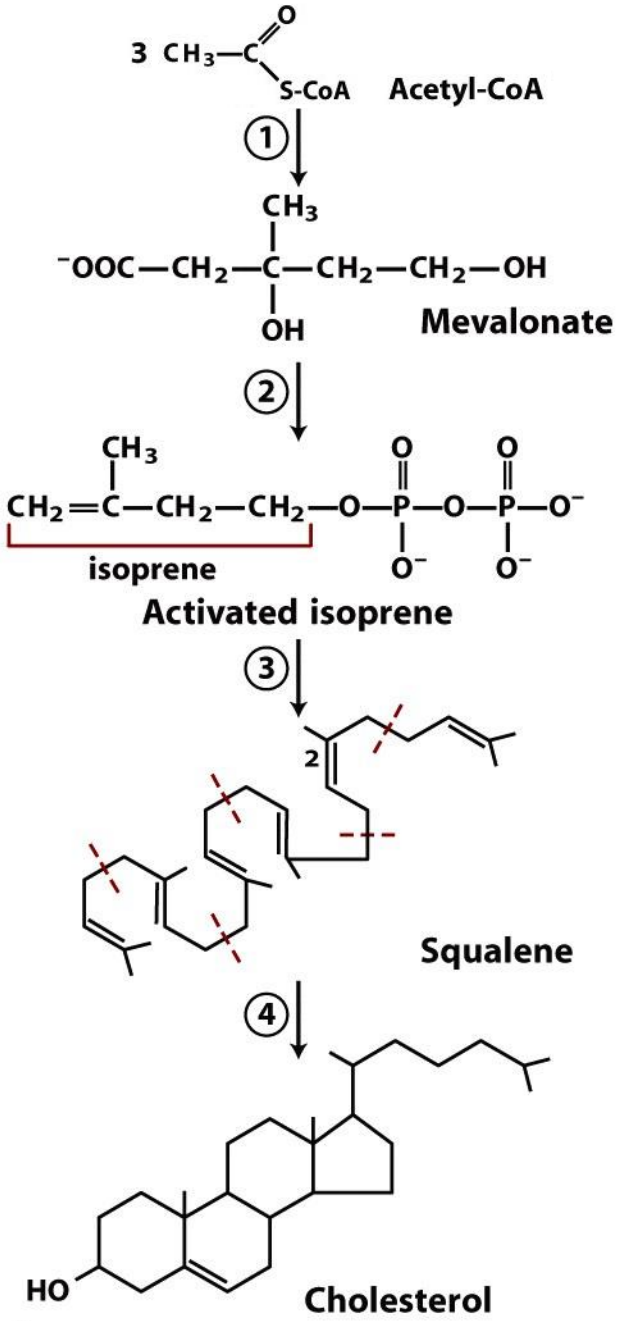


Figure 21-33

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Synthesis of mevalonate

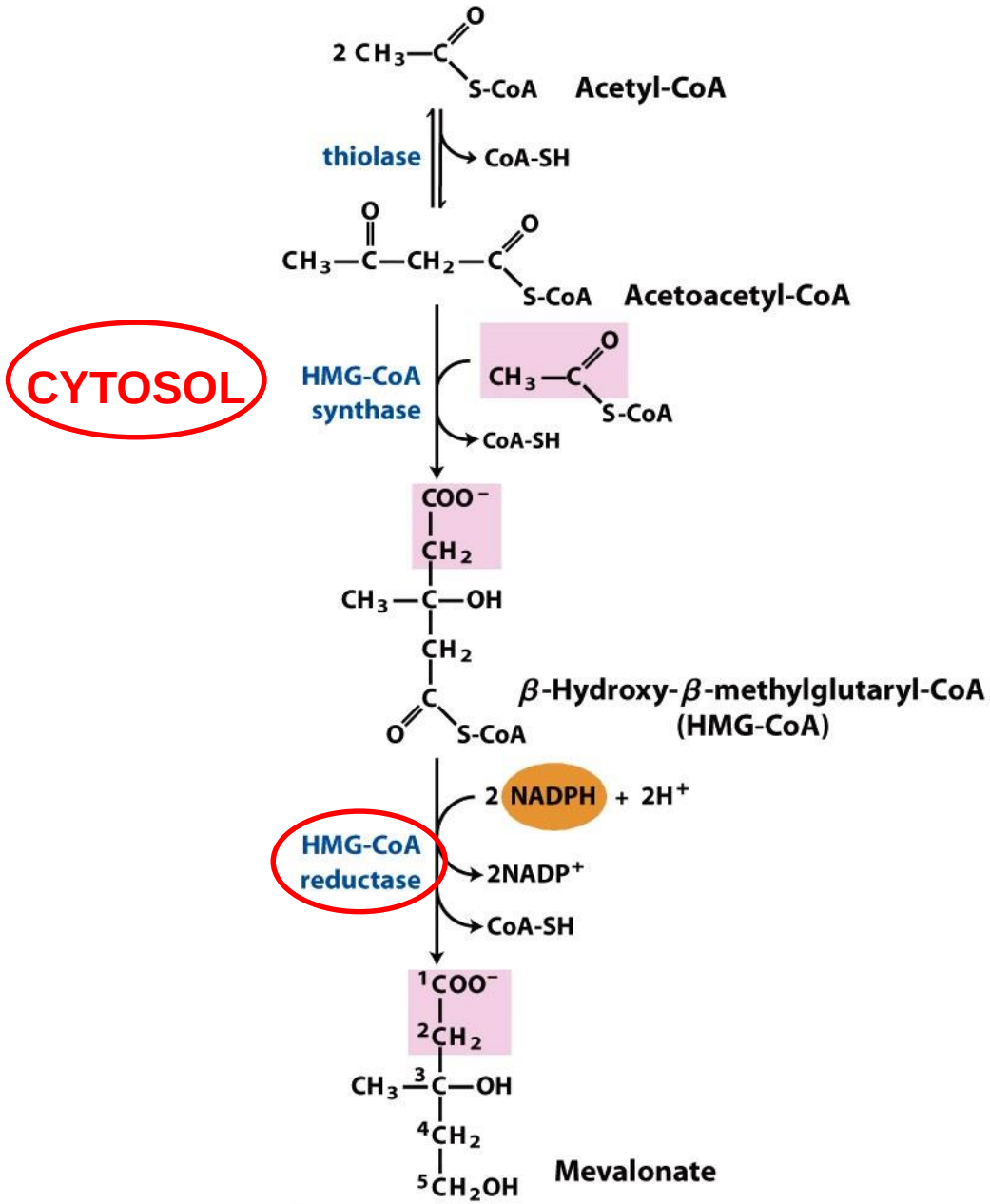

Figure 21-34

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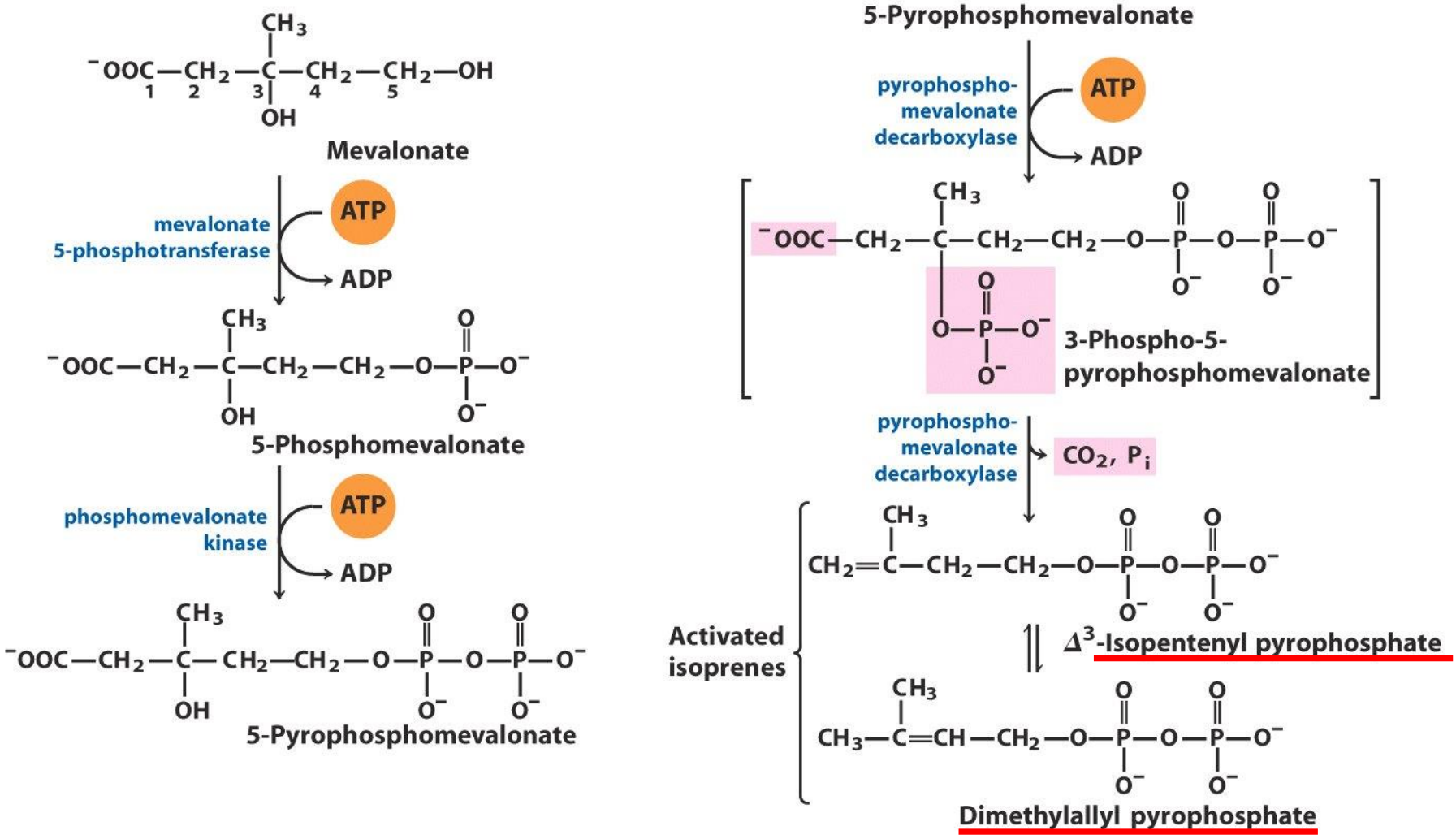
Synthesis of activated isoprenes



Synthesis of squalene

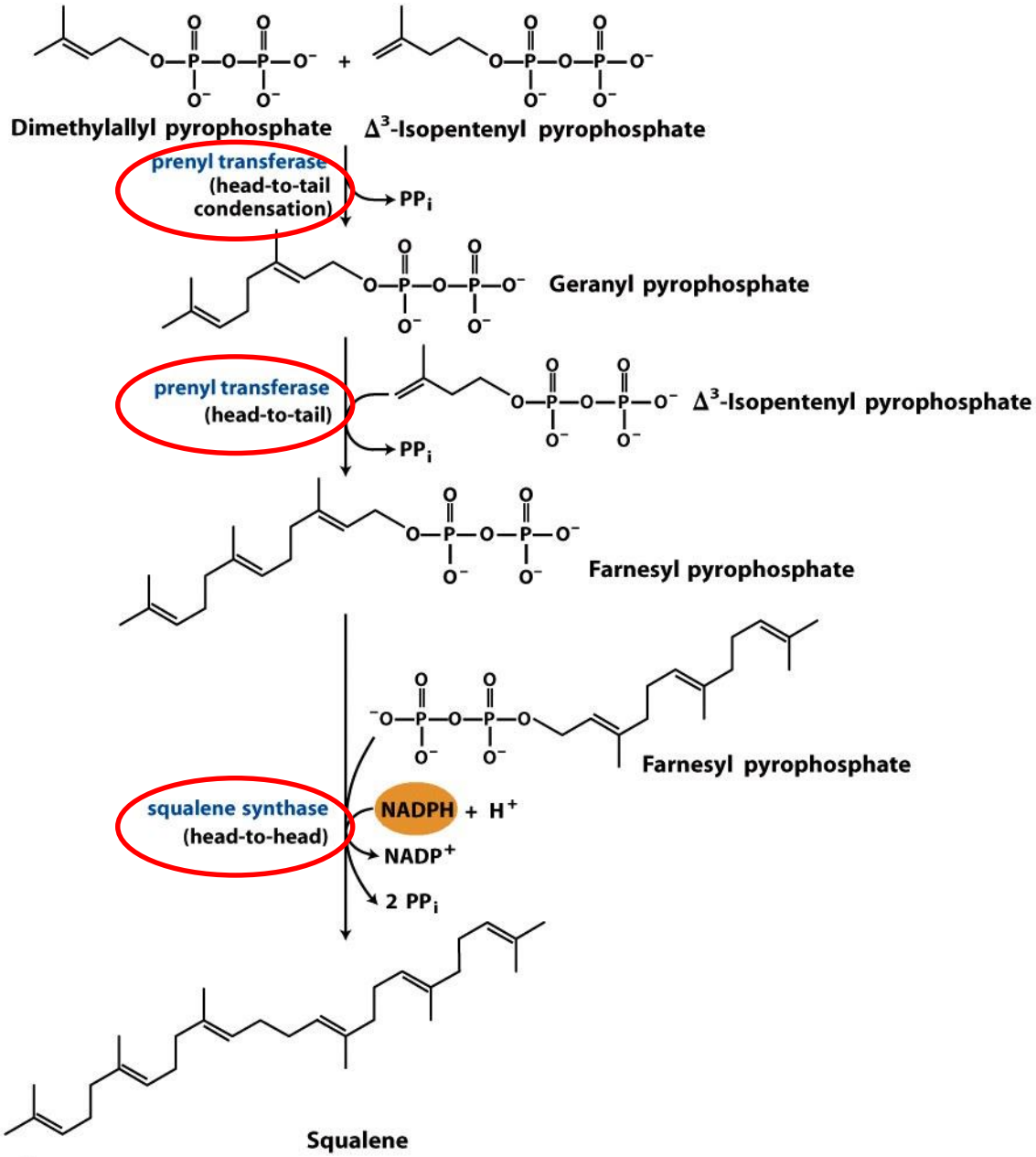


Figure 21-36

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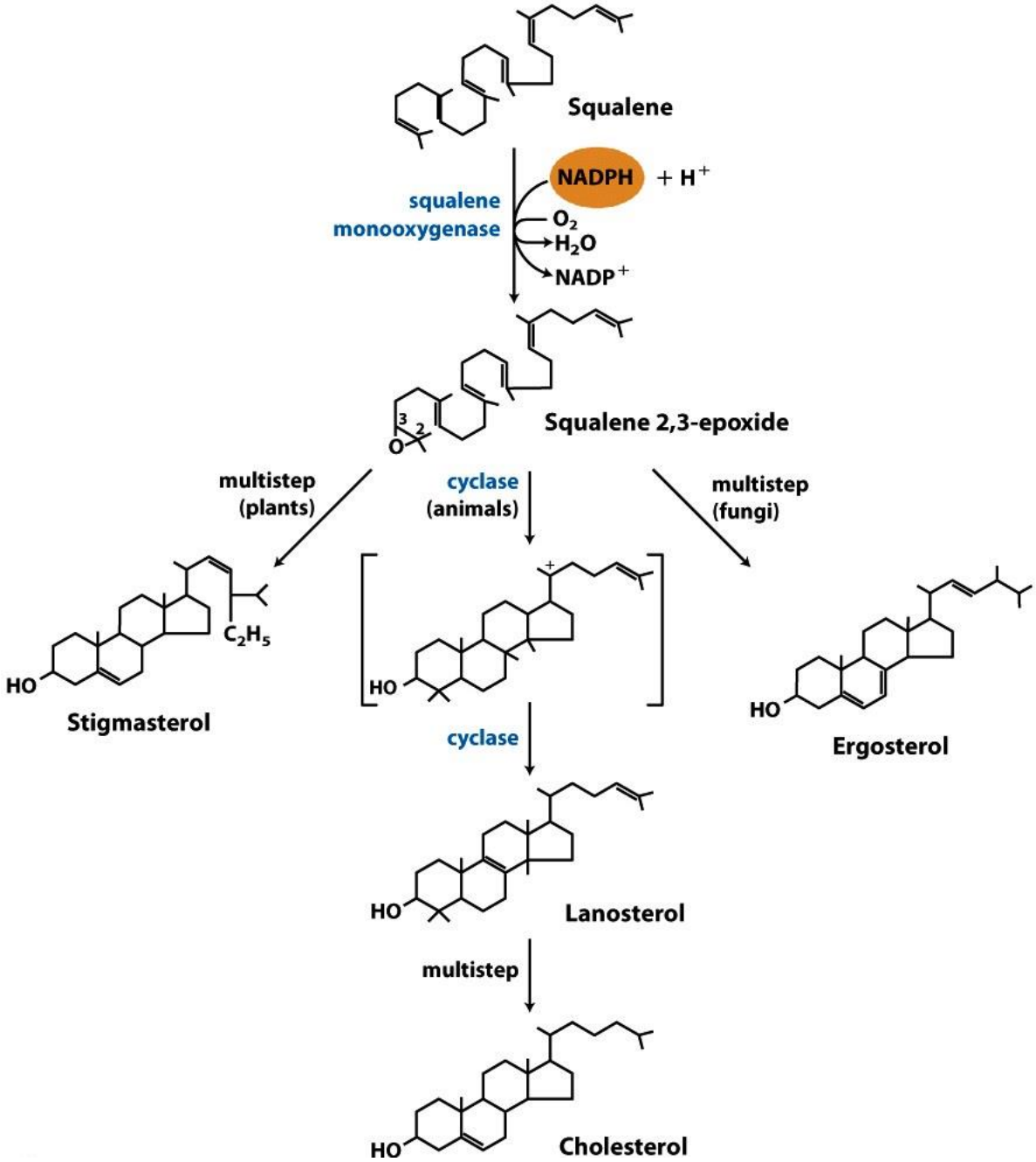
Synthesis of cholesterol



Synthesis of cholesteryl esters

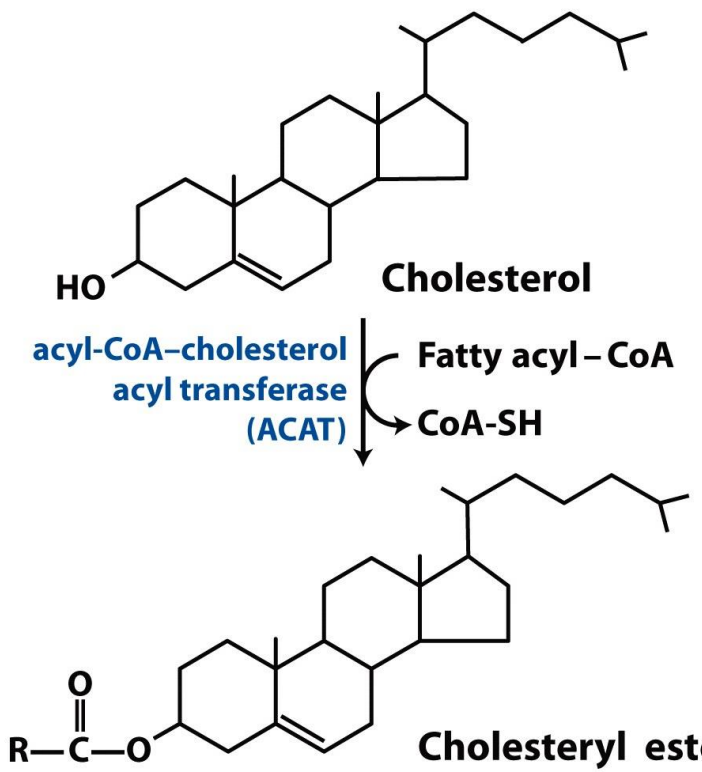


Figure 21-38
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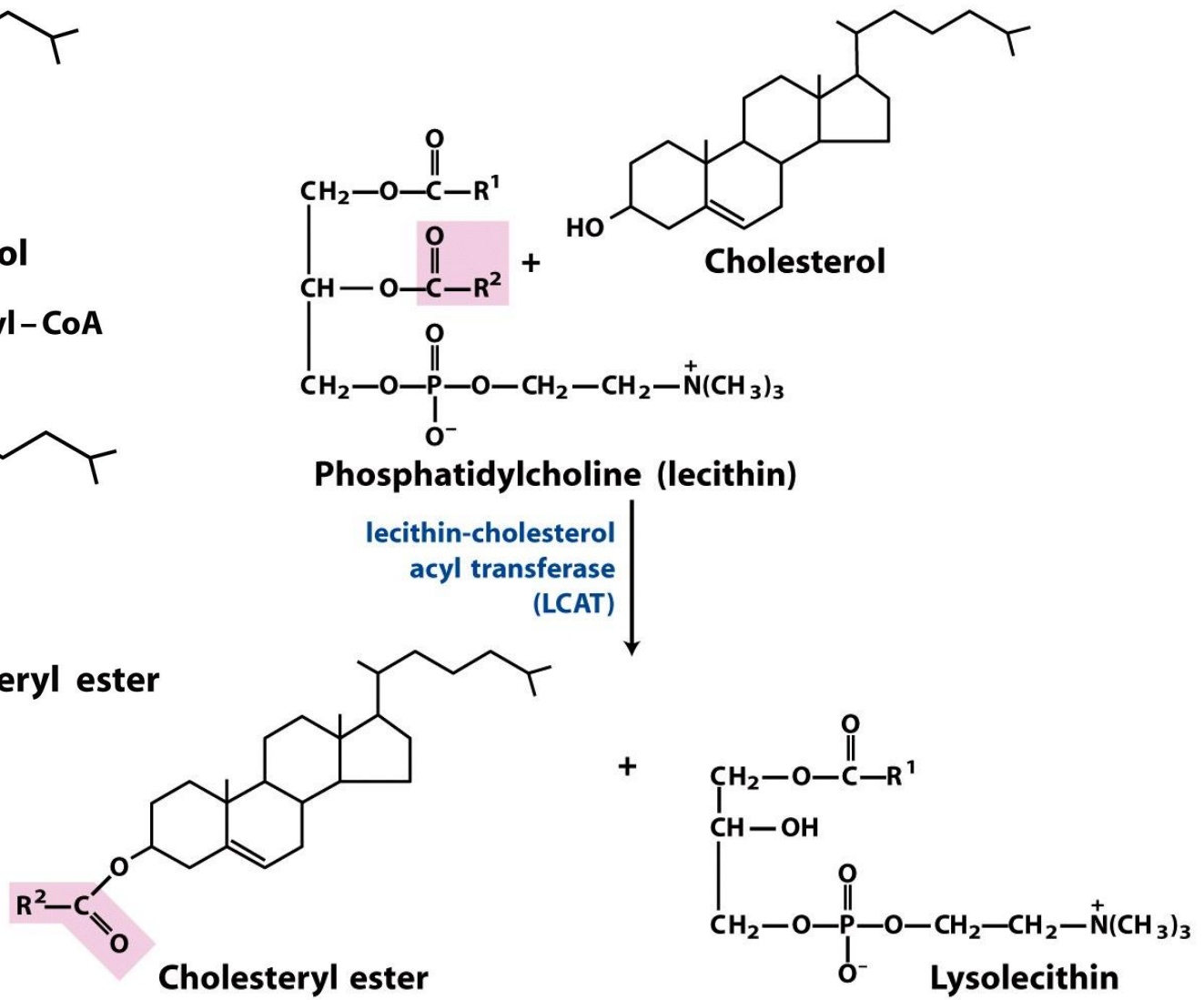

Figure 21-41
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A 40-year-old man presents with chest pain that radiates to his left jaw and shoulder. He is diagnosed with a myocardial infarct (heart attack) and is prescribed a statin medication. Statins are competitive inhibitors of HMG-CoA reductase, which converts HMG-CoA to which of the following?

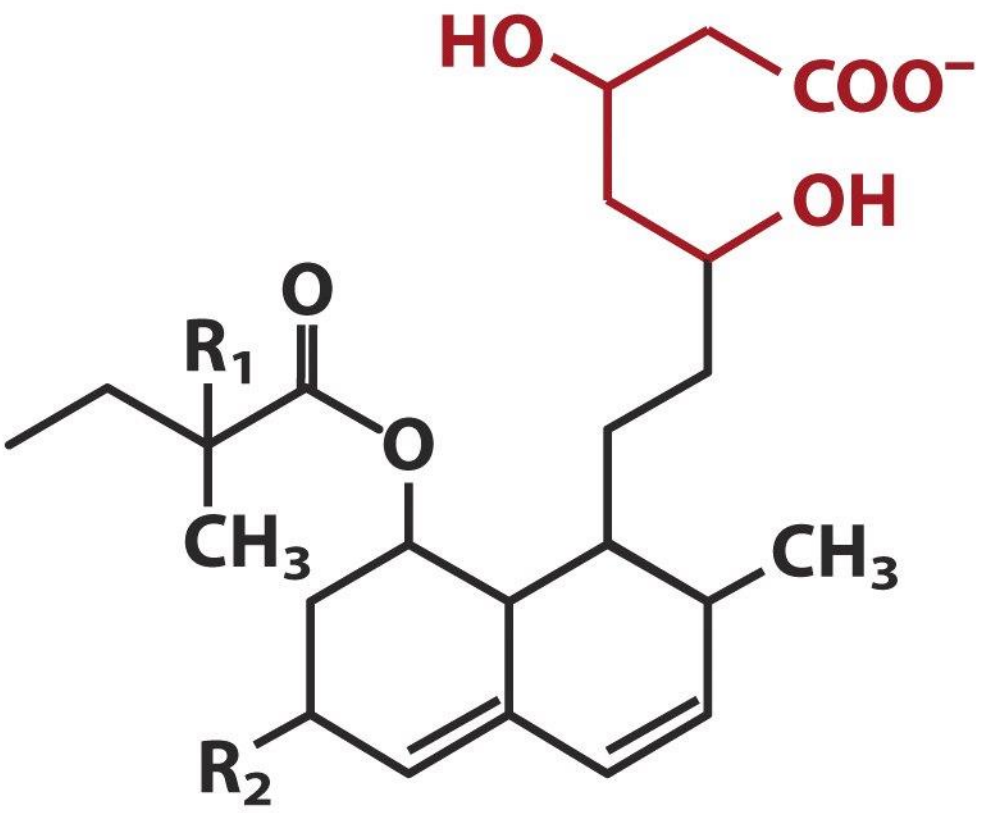
a) Mevalonate

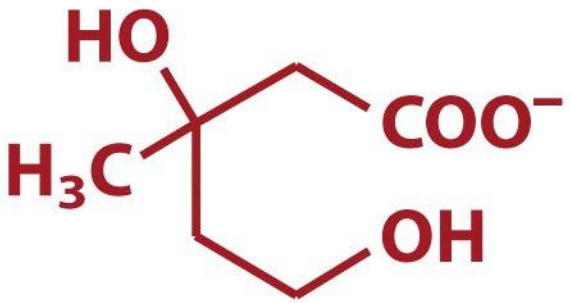
b) Isopentenyl pyrophosphate

c) Geranyl pyrophosphate

d) Farnesyl pyrophosphate

e) Cholesterol

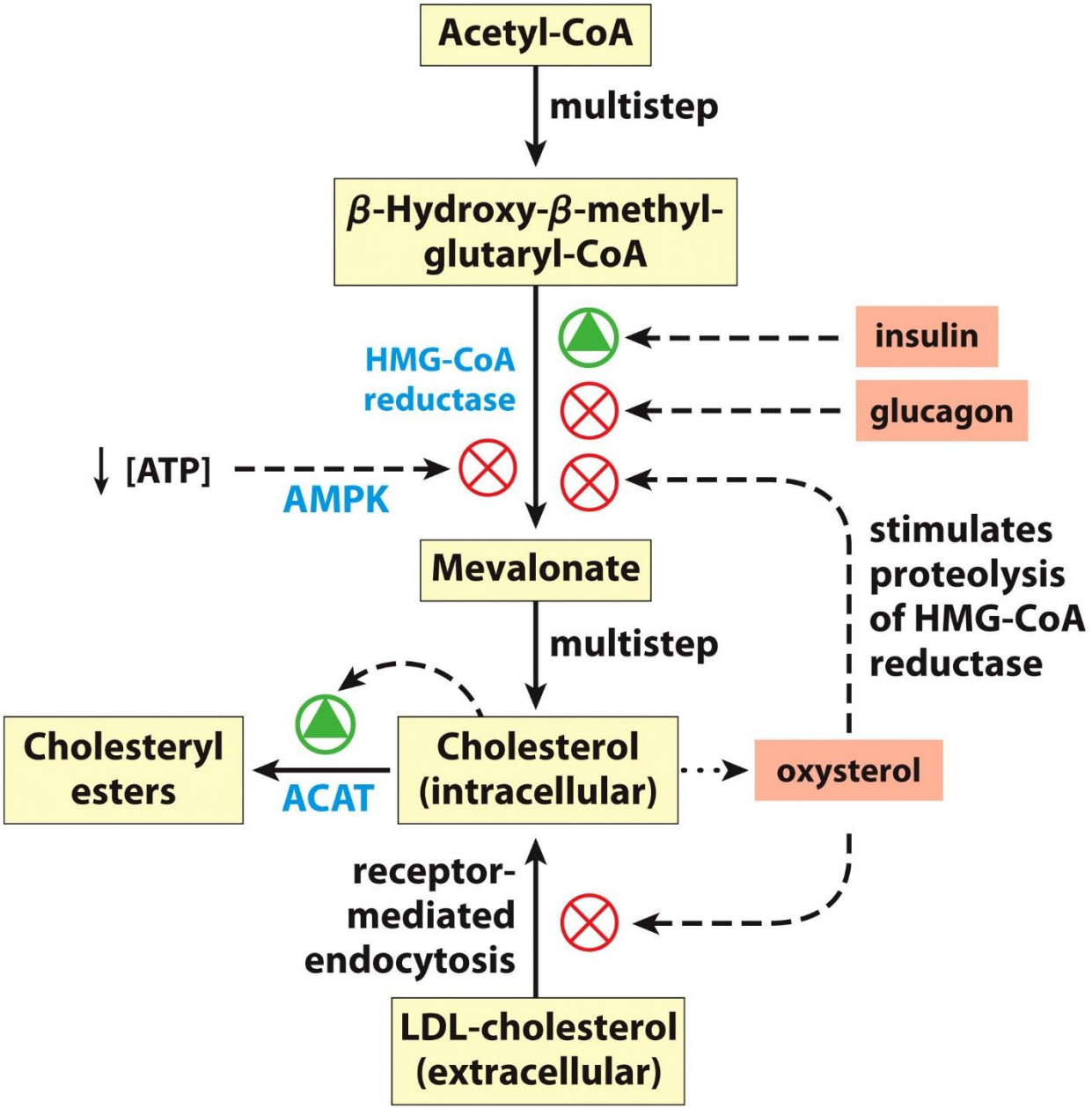




Mevalonate

$R_1 = H$	$R_2 = H$	Compactin
$R_1 = CH_3$	$R_2 = CH_3$	Simvastatin (Zocor)
$R_1 = H$	$R_2 = OH$	Pravastatin (Pravachol)
$R_1 = H$	$R_2 = CH_3$	Lovastatin (Mevacor)

Regulation of cholesterol synthesis



How does inhibition of HMG-CoA reductase cause lowering of cholesterol and LDL levels?

a) It increases serum level of HDL
b) It decreases serum level of LDL by promoting catabolism
c) It inhibits the formation of LDL from IDL
d) It inhibits the rate limiting step in cholesterol biosynthesis
e) It inhibits synthesis of LDL receptors.

Which of the following compounds directly inhibits the expression of the HMG-CoA reductase gene?

a) Squalene

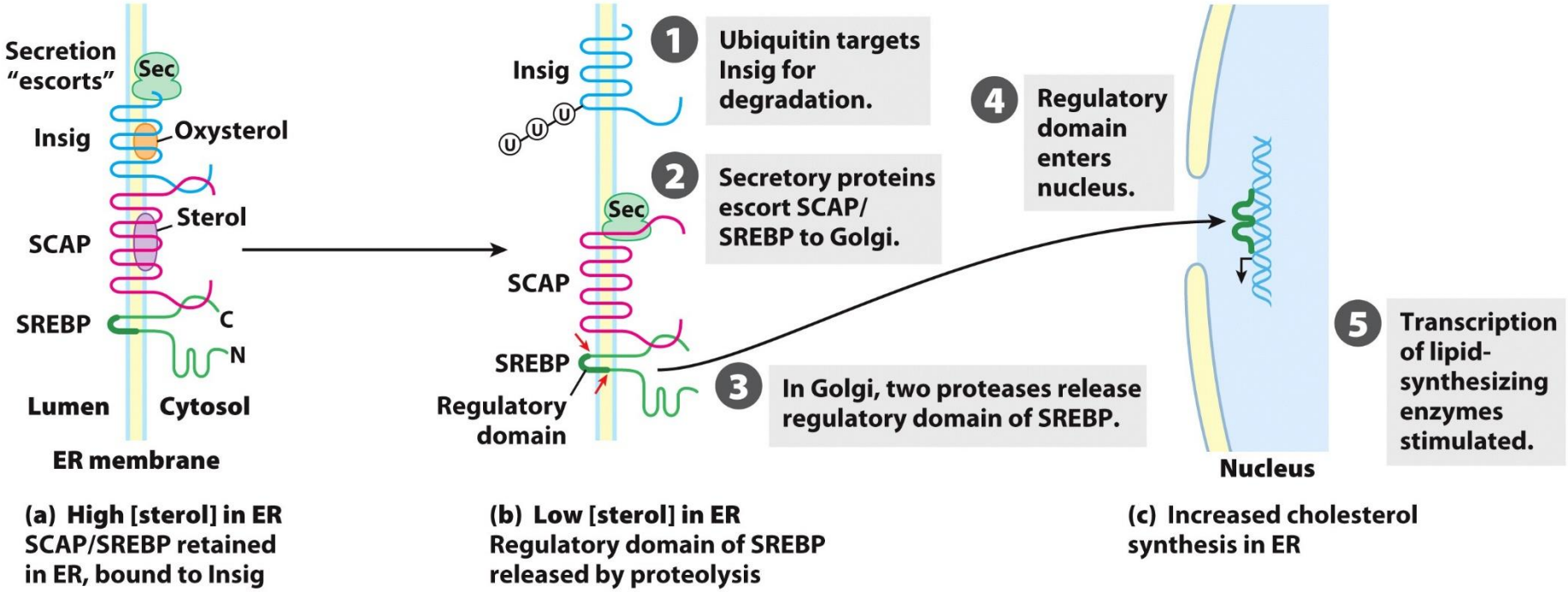
b) HMG-CoA

c) Lanosterol

d) Isopentenyl pyrophosphate

e) Cholesterol

Transcriptional regulation of cholesterol synthesis

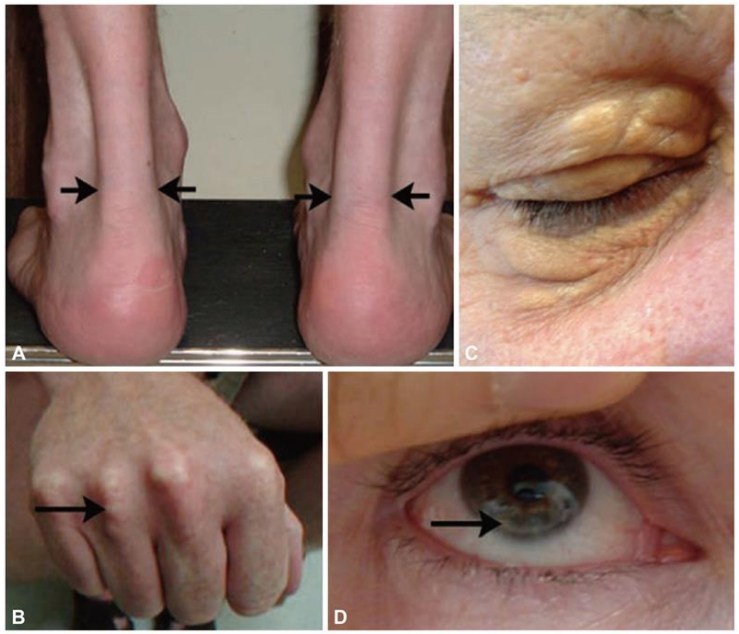


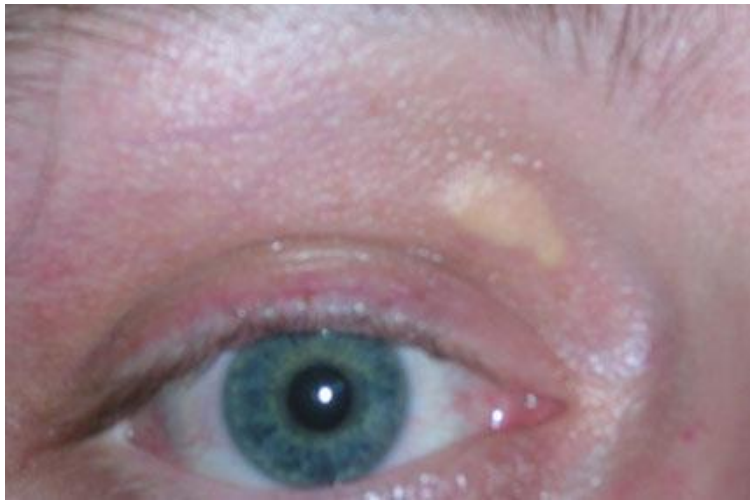
Familial hypercholesterolemia

Autosomal dominant disorder, incidence of heterozygous form 1:500, incidence of homozygous form 1:1.000.000
Elevated blood cholesterol and LDL levels (VLDL, Triglycerid levels usually within the normal range)
Pathophysiology: Missing/nonfunctional LDL-receptors or mutation in ApoB100
Instead of liver cells macrophages take up cholesterol → foam cells

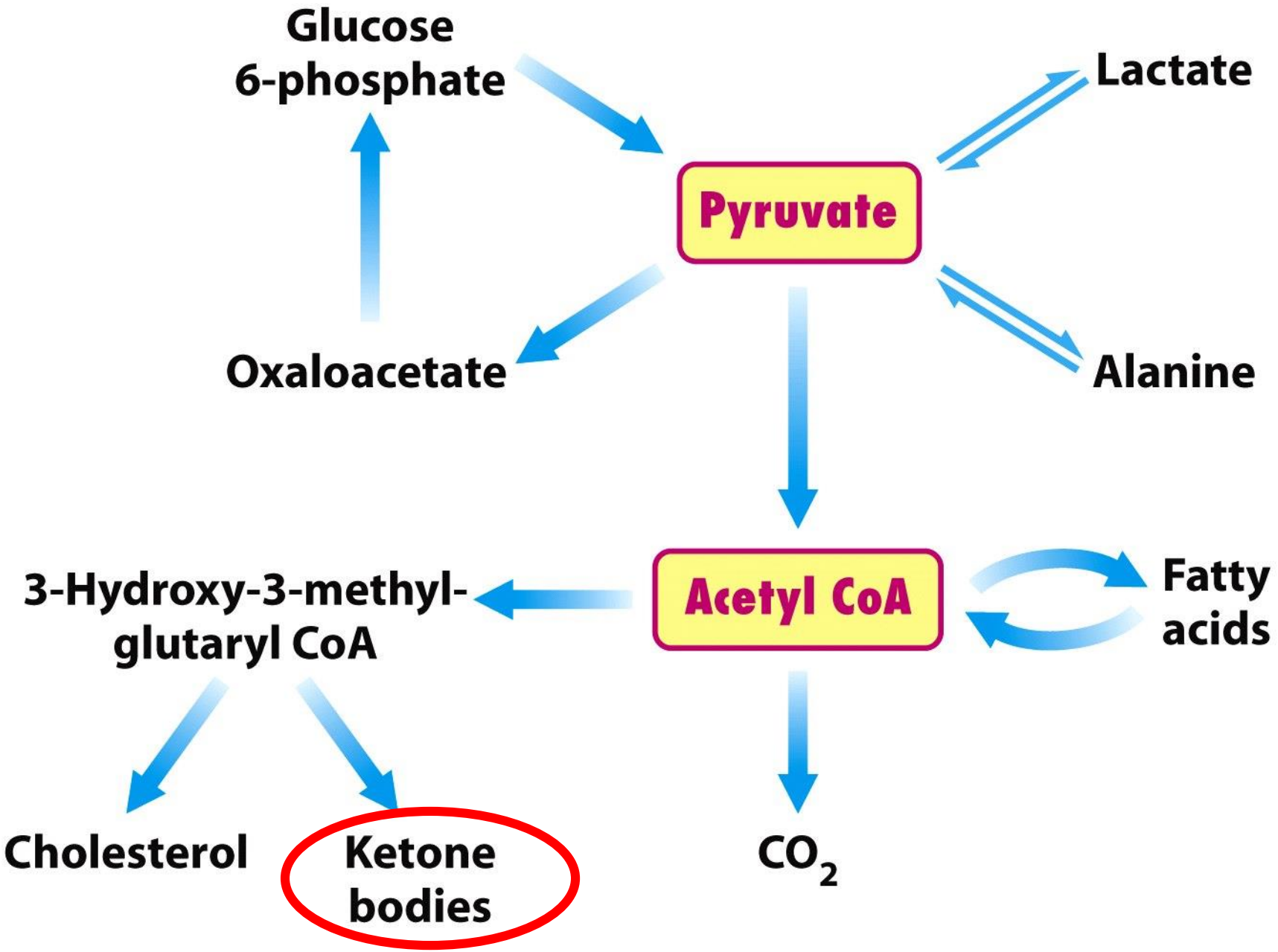
Symptoms:

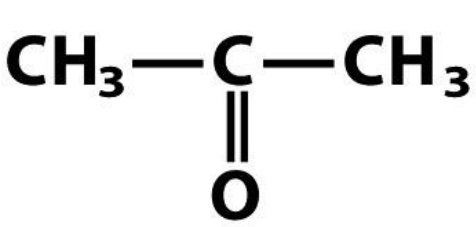
- Obesity
- Atherosclerosis
- Early onset of cardiovascular diseases
- Early onset atherosclerosis in the family history
- Xanthoma, xanthelasma palpebrum
- Brown pigmentation on the face
- Early death (2nd-3rd decade to 50s with therapy)



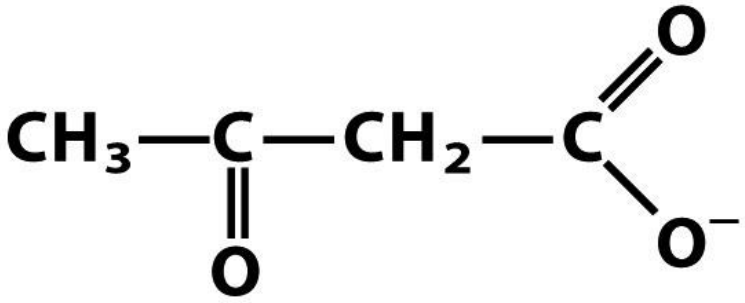


Xanthelasma

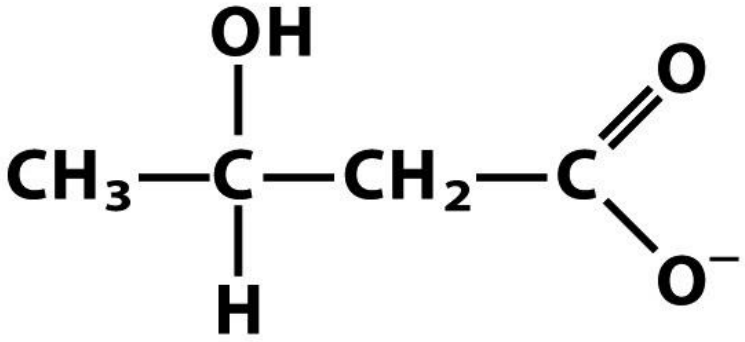

Glucose
6-phosphate
Lactate
Pyruvate
Oxaloacetate
Alanine
3-Hydroxy-3-methyl-
glutaryl CoA
Acetyl CoA
Fatty
acids
Cholesterol
Ketone
bodies
CO_2



Acetone



Acetoacetate



D-β-Hydroxybutyrate

Formation of ketone bodies

MITOCHONDRION

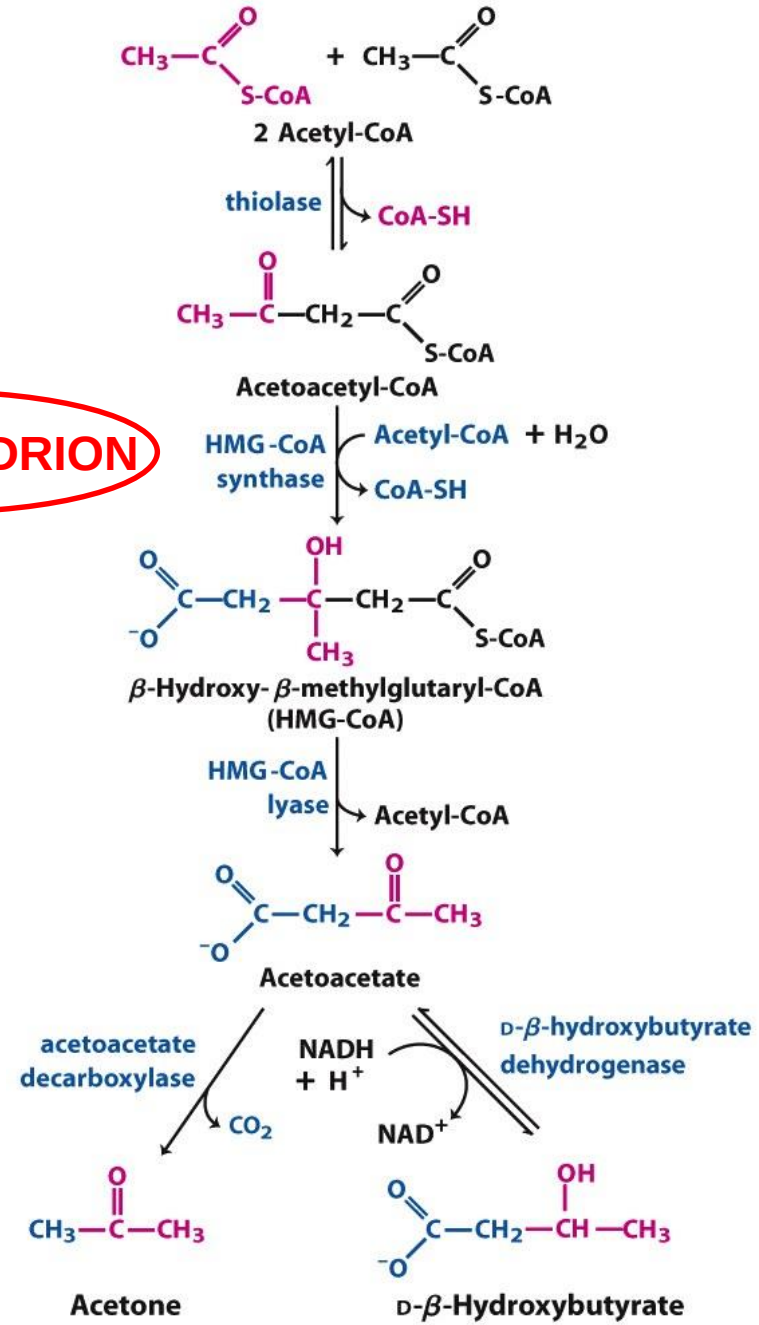


Figure 17-18

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The use of ketone bodies as fuel

Ketone bodies are used as fuels in all tissues except liver, which lacks this enzyme.

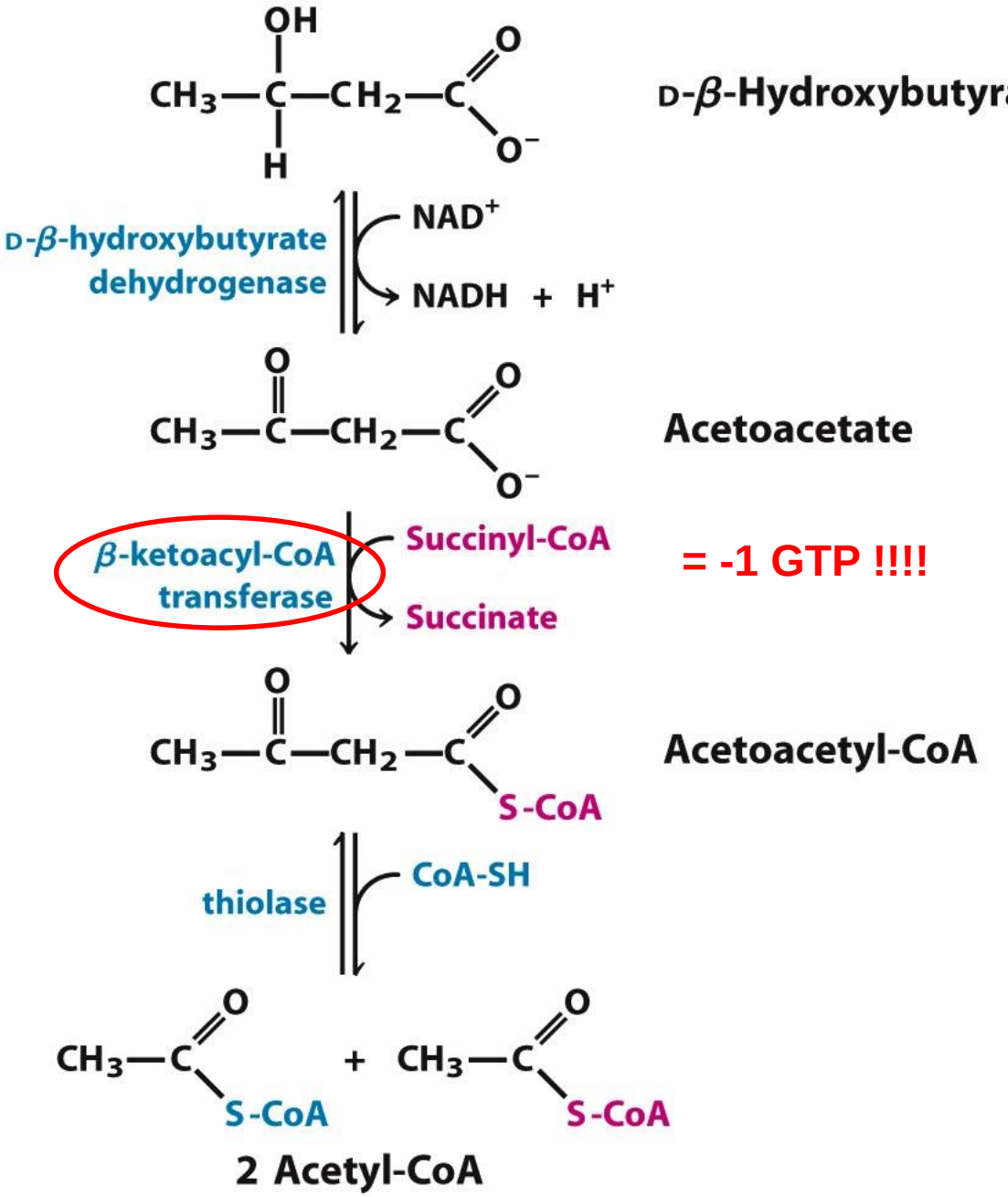

Figure 17-19
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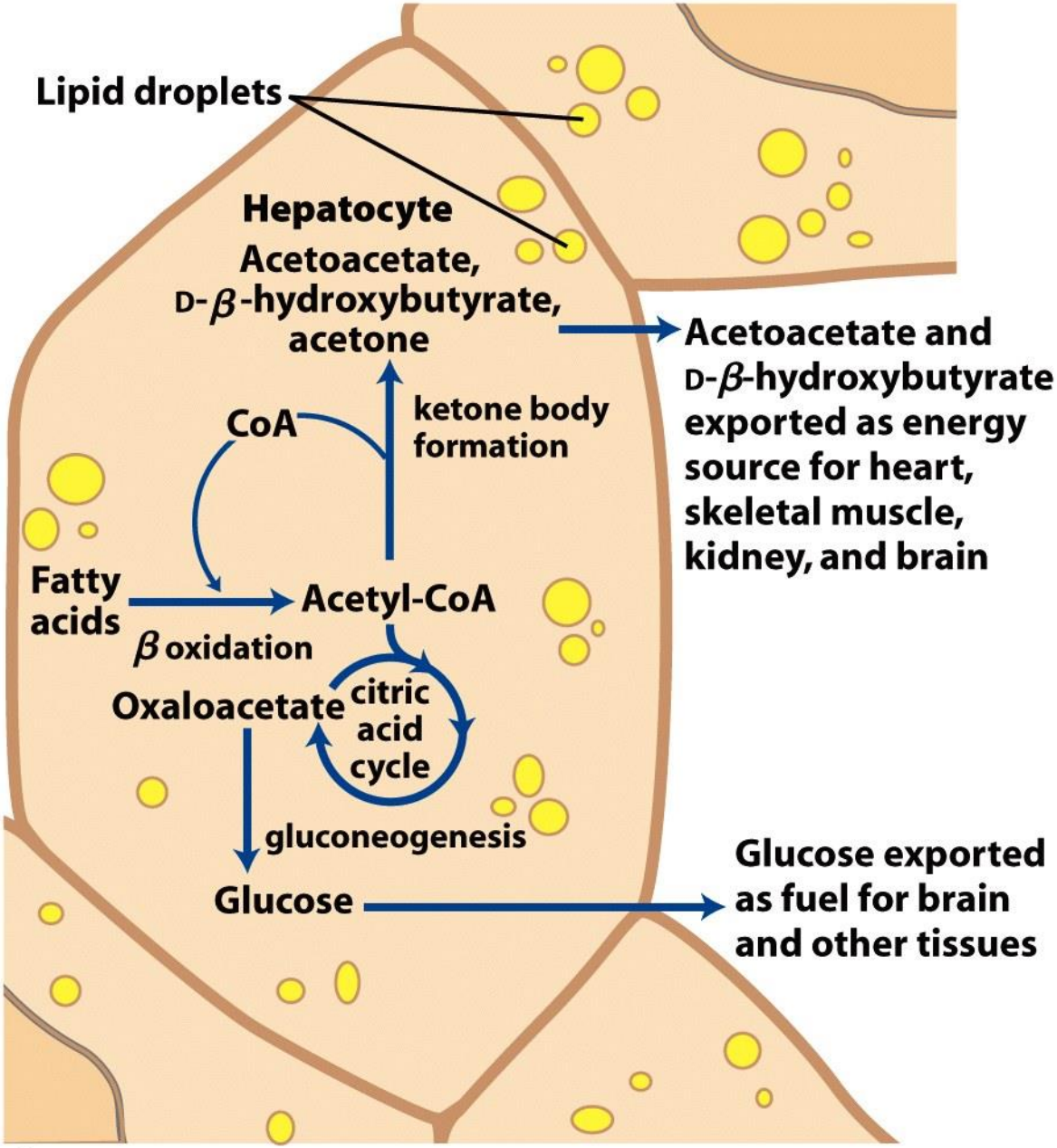

Figure 17-20

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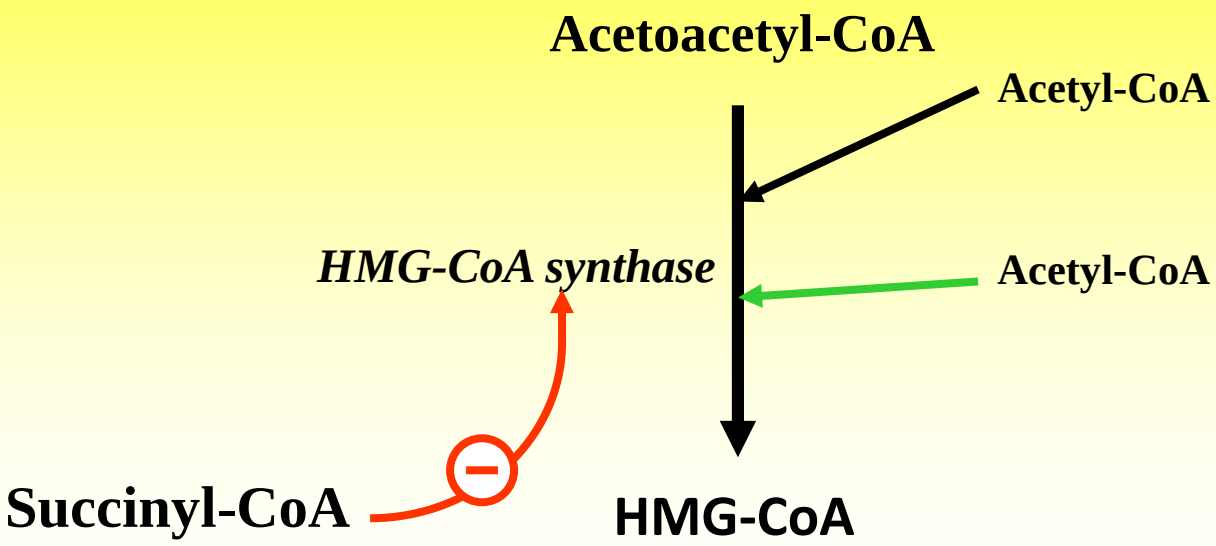
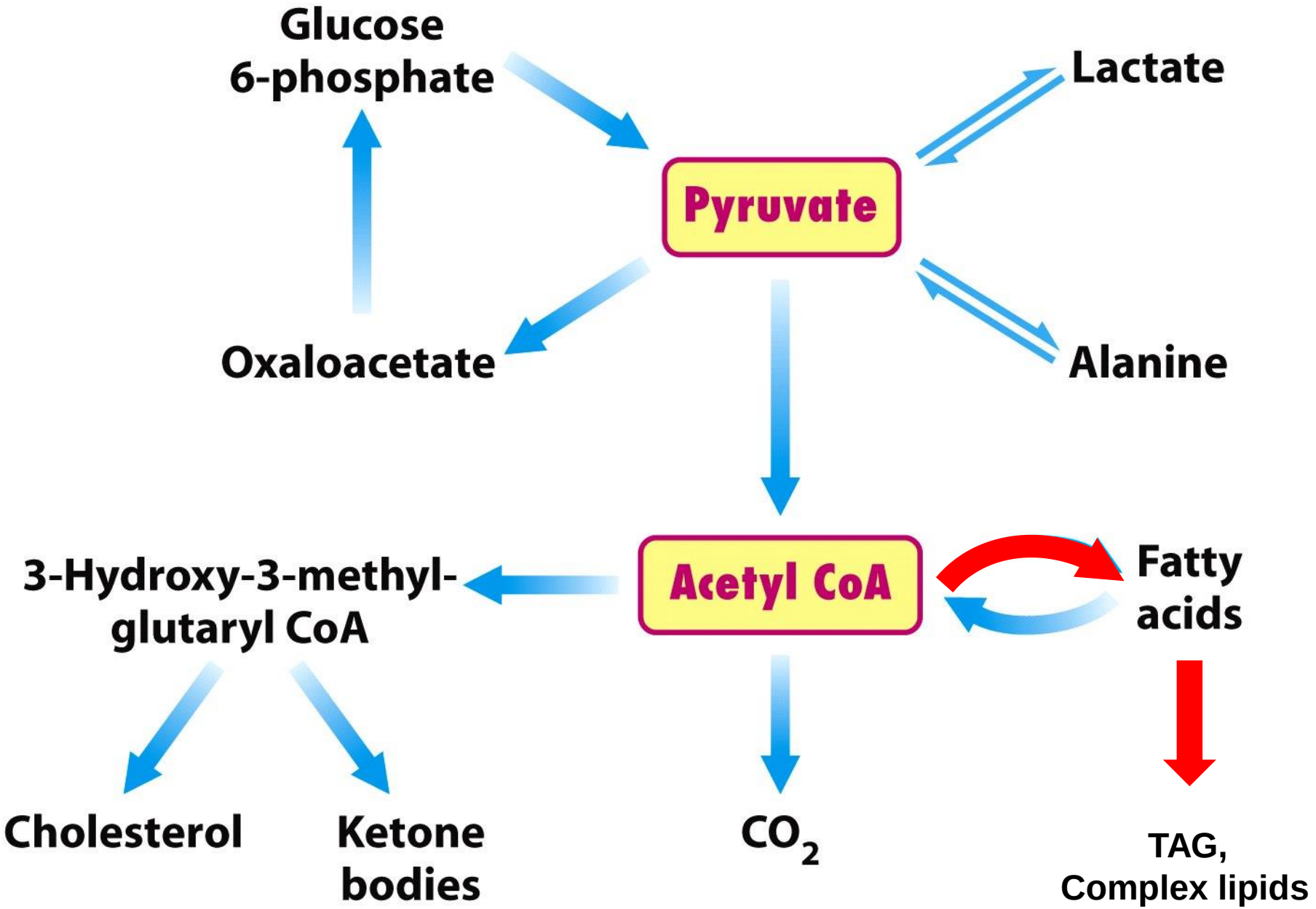
Regulation of ketone body synthesis via HMG-CoA synthase




Glucose
6-phosphate
Lactate
Pyruvate
Oxaloacetate
Alanine
3-Hydroxy-3-methyl-
glutaryl CoA
Acetyl CoA
Fatty
acids
Cholesterol
Ketone
bodies
CO_2
TAG,
Complex lipids

The triacylglycerol cycle

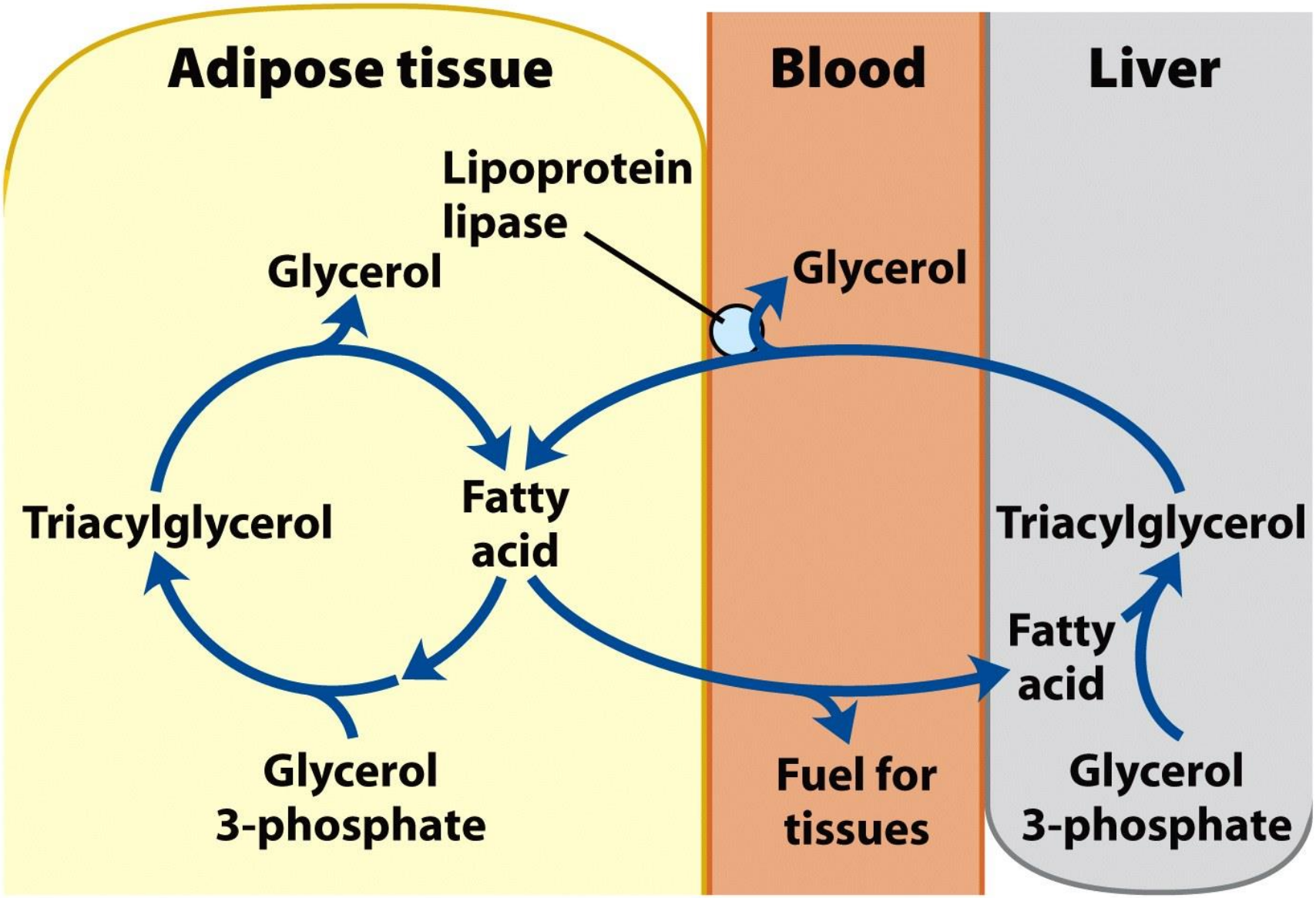


Figure 21-20
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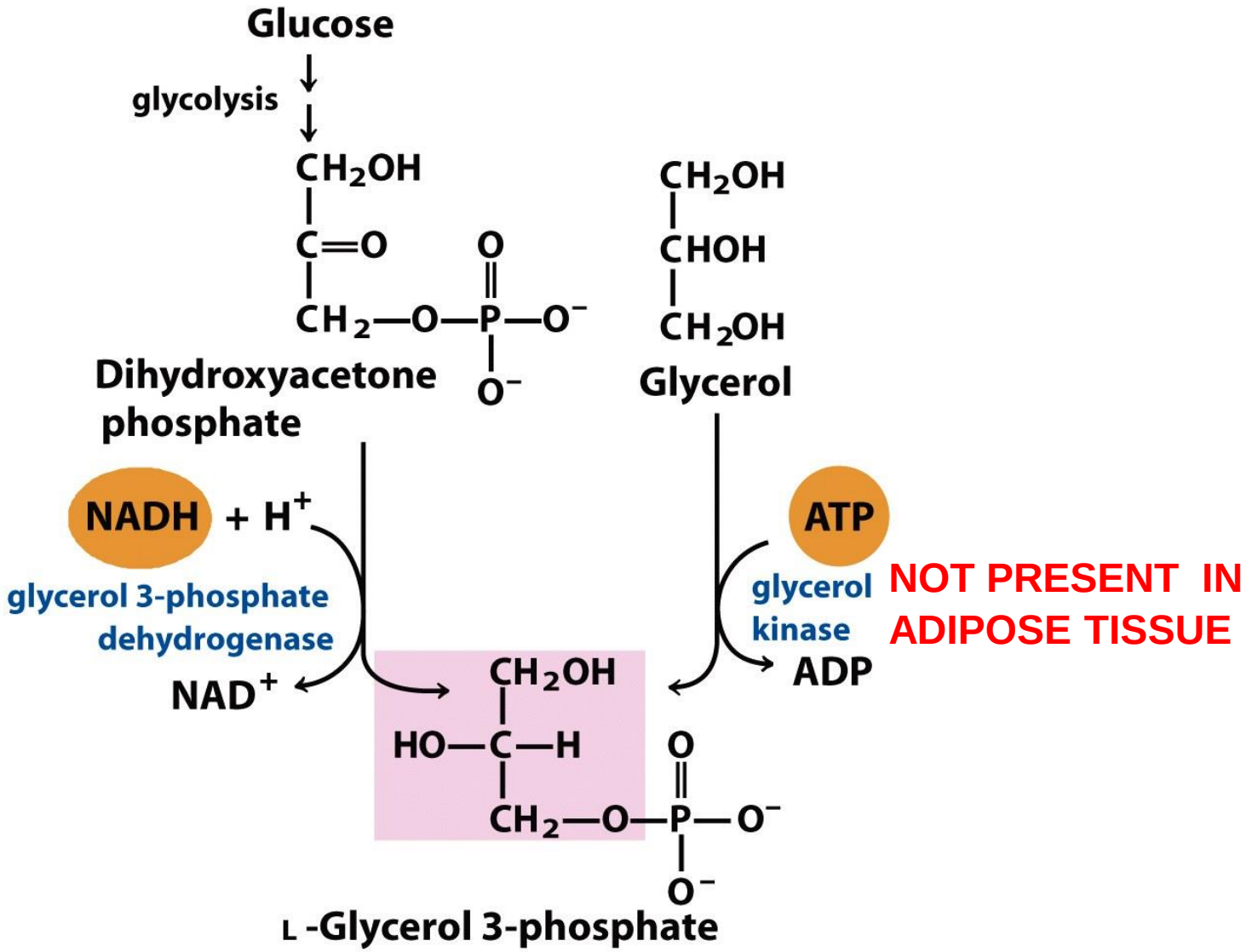
Production of glycerol-phosphate for lipid synthesis



Glyceroneogenesis

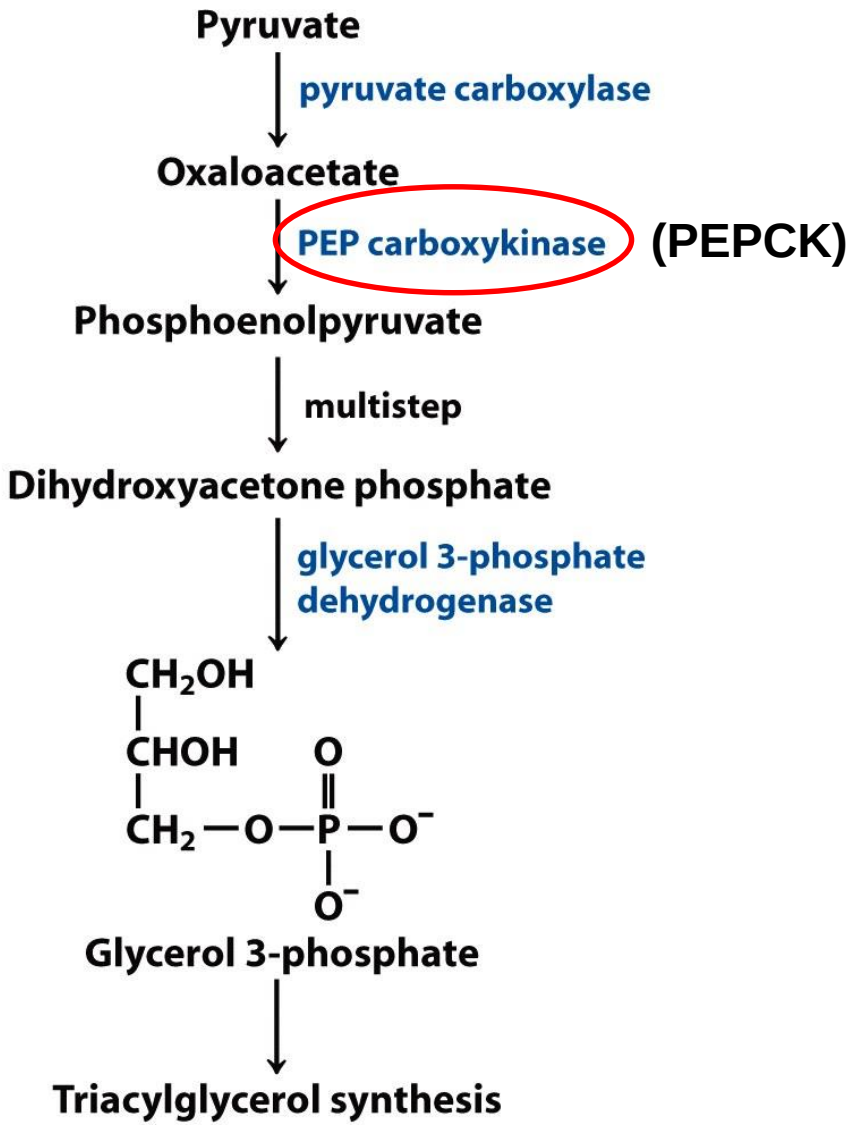


Figure 21-21
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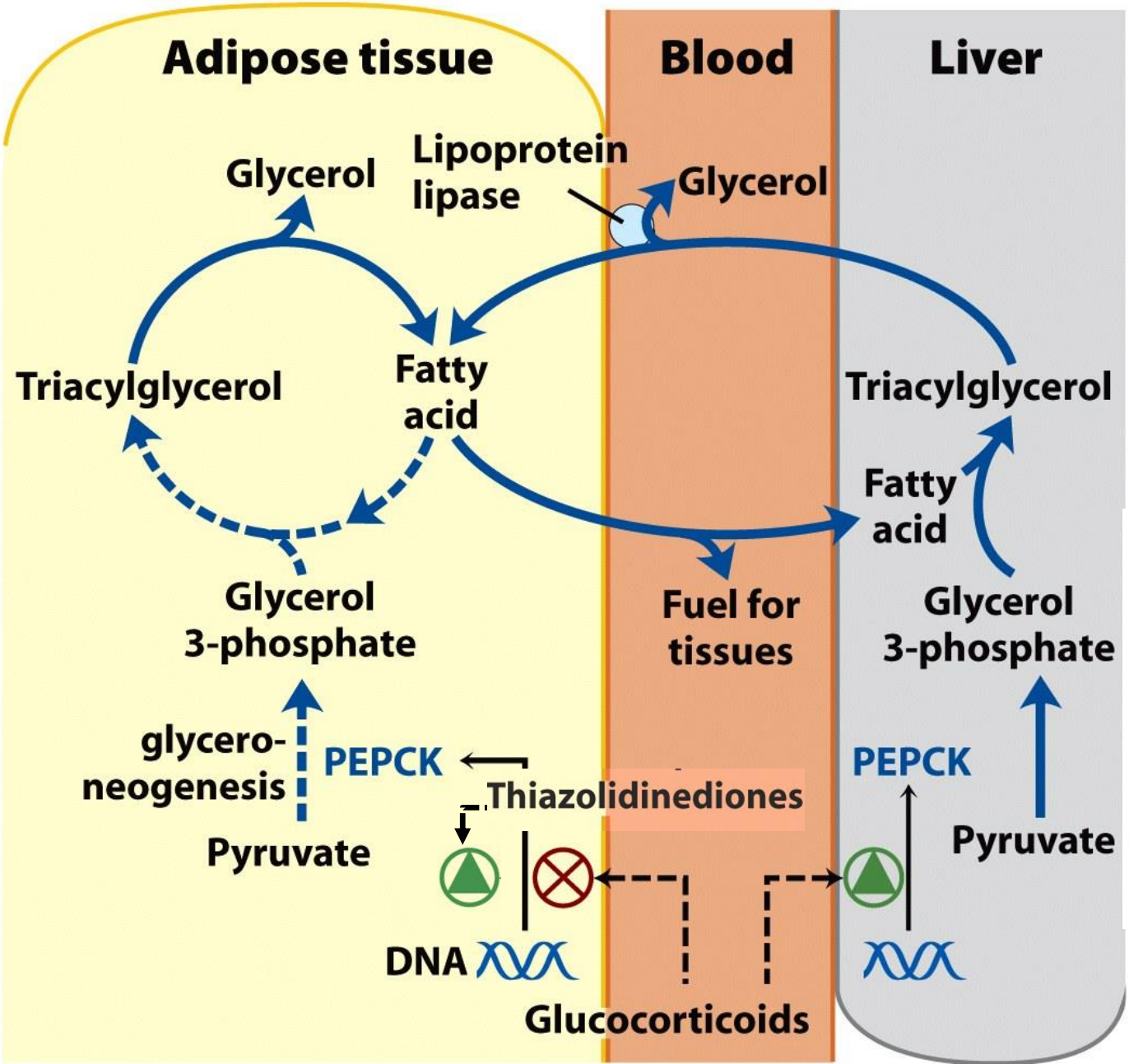
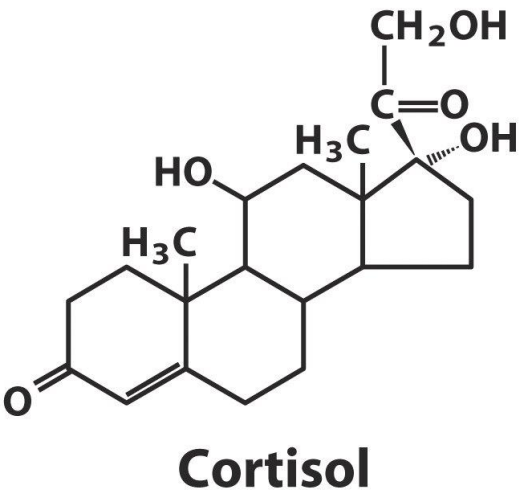
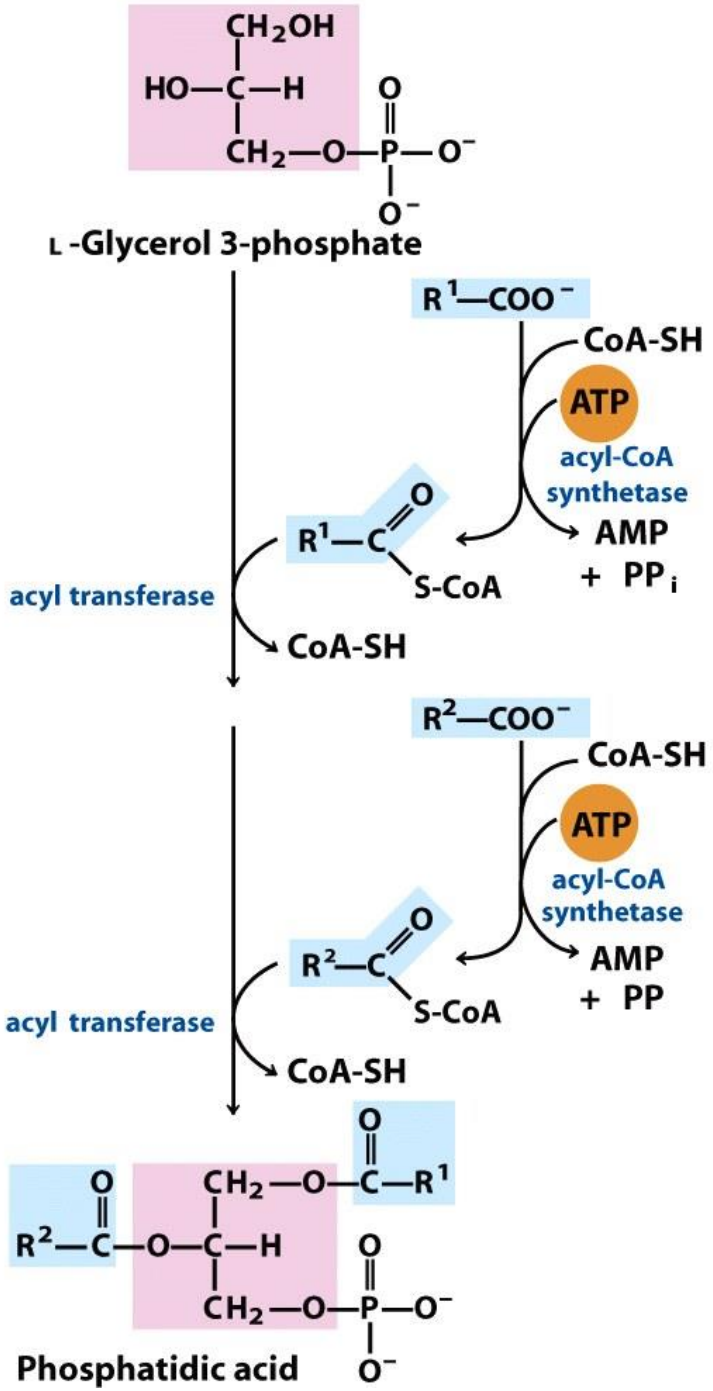
Regulation of the glyceroneogenesis



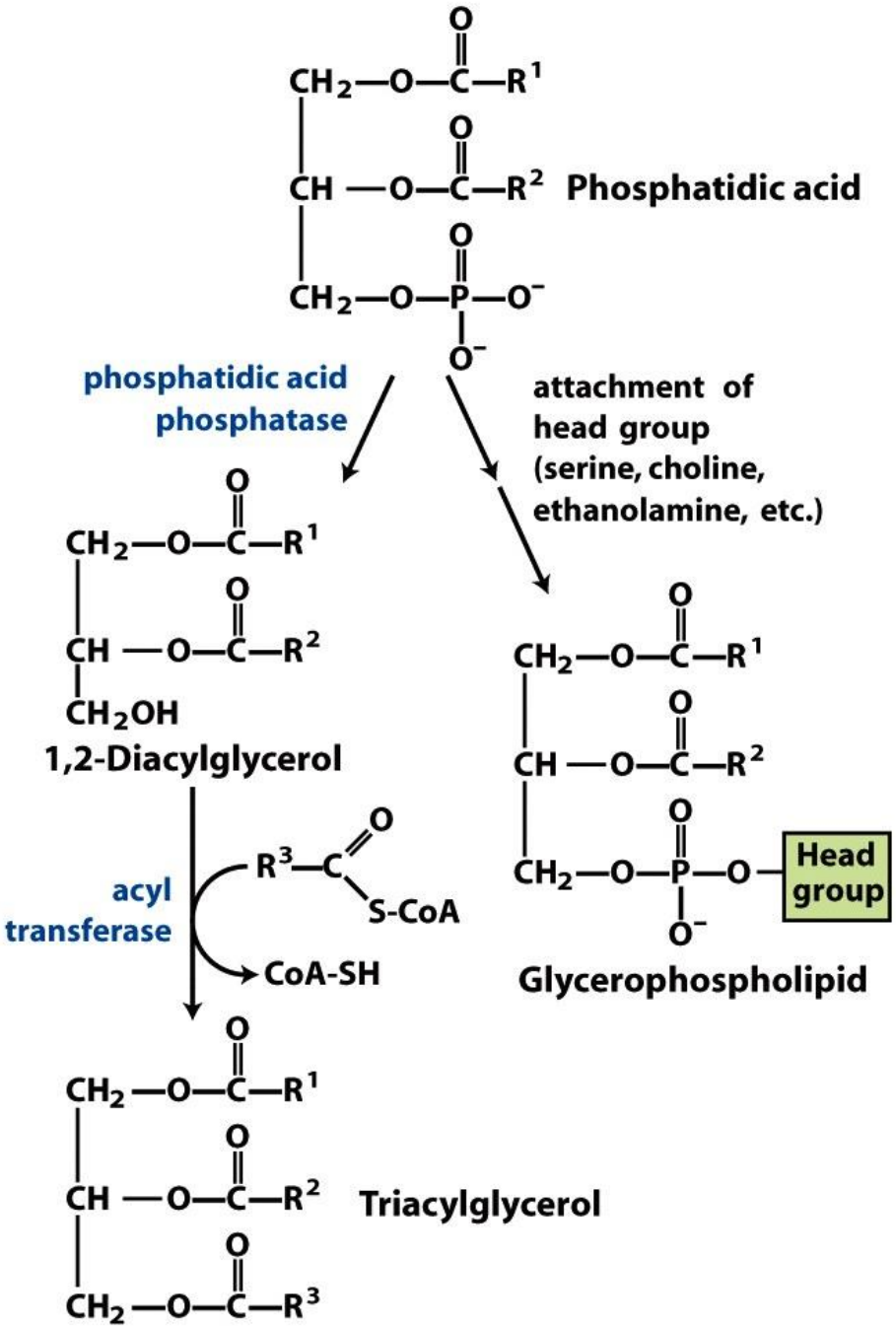


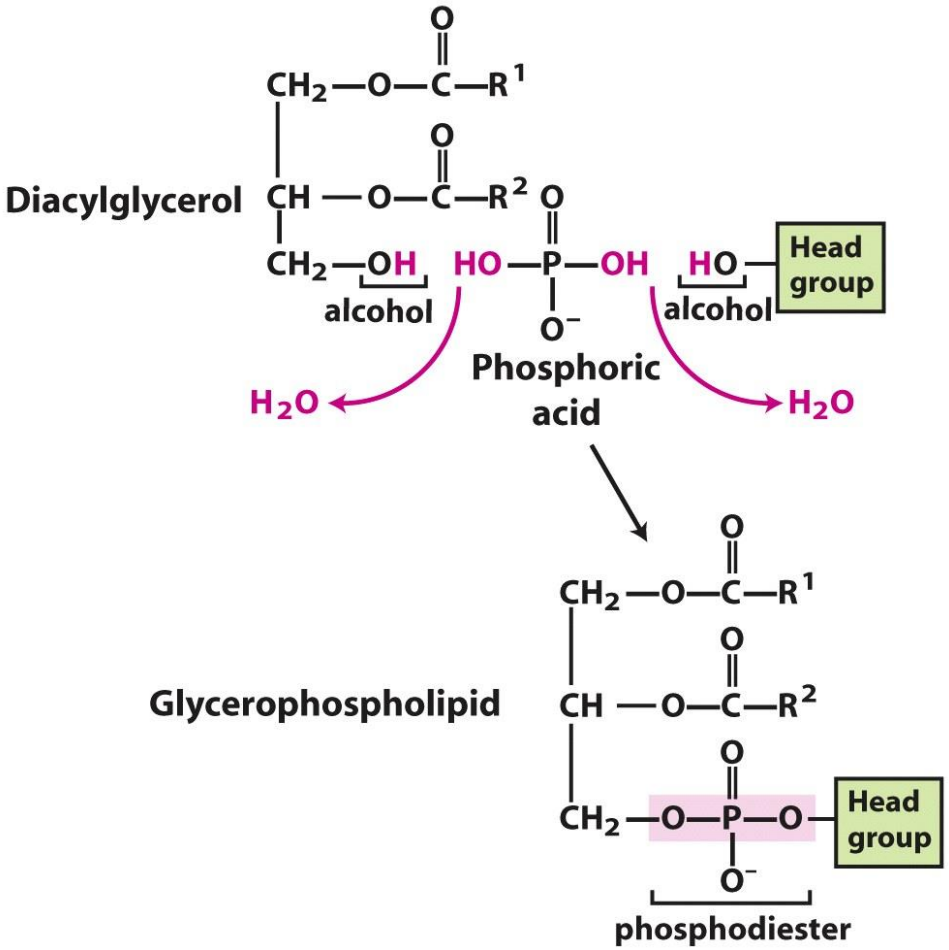
Cortisol

Production of triacylglycerols



Production of glycerophospholipids





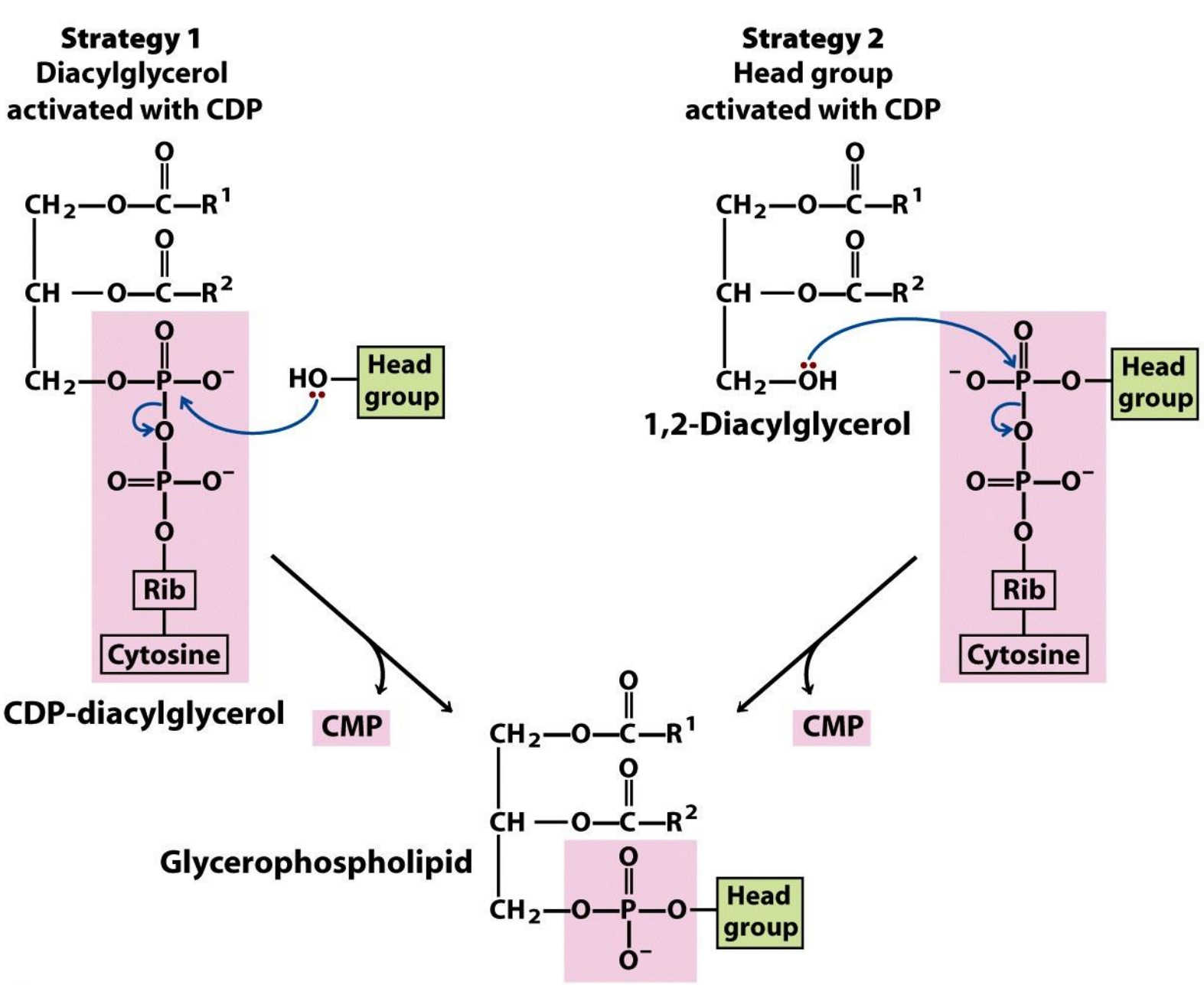


Figure 21-24

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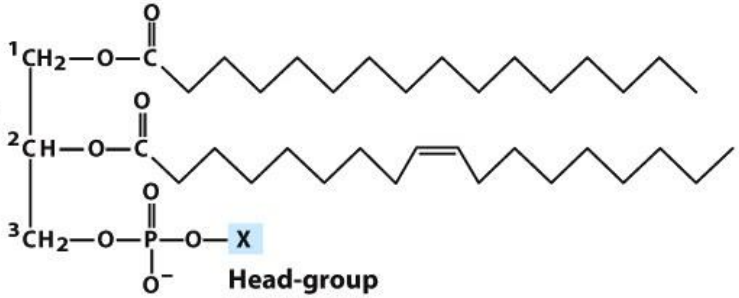
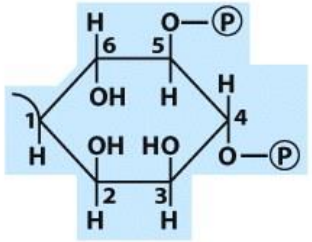
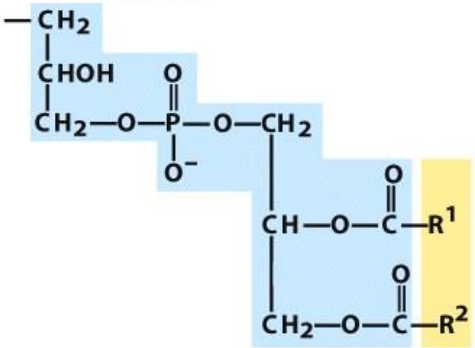
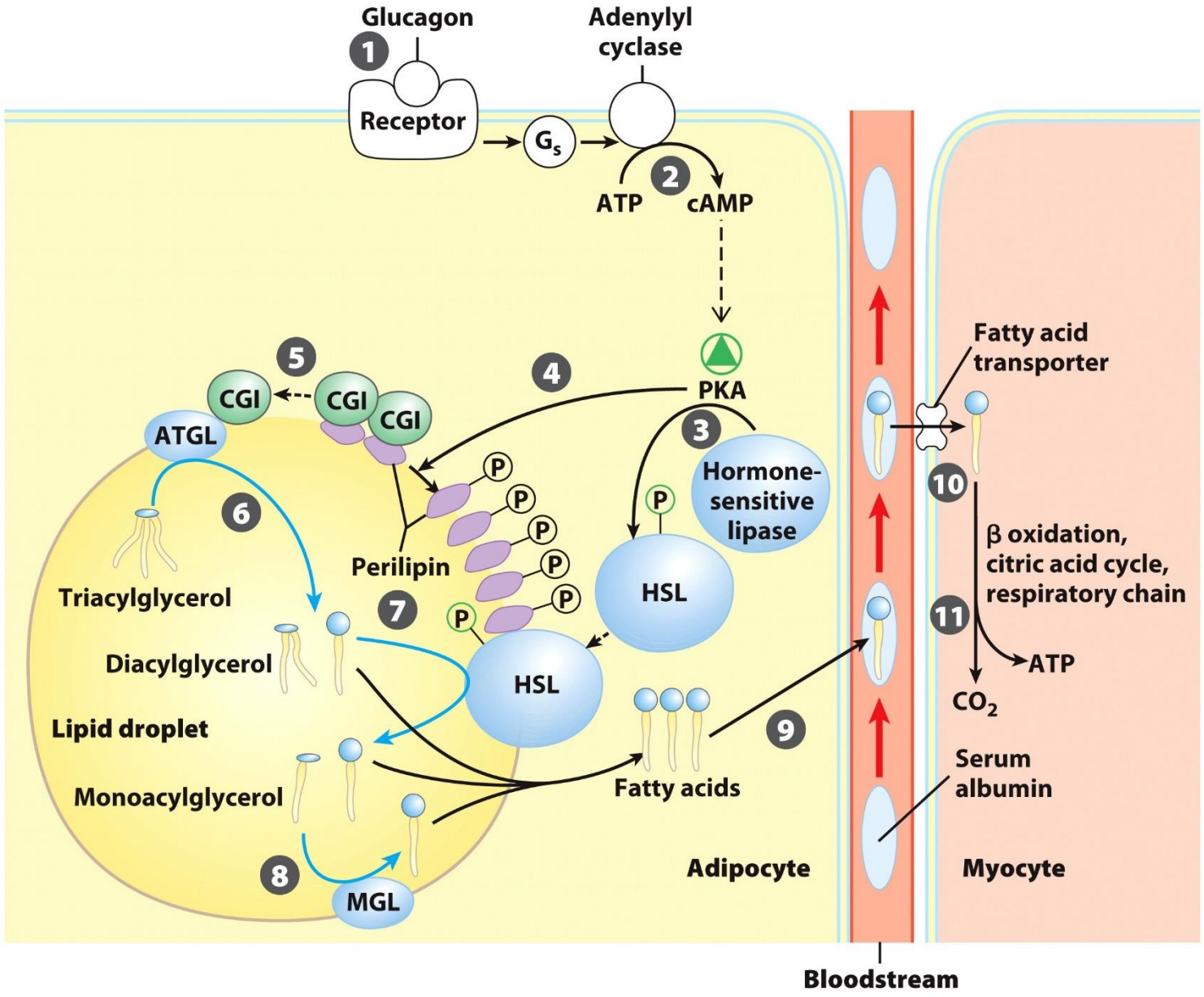
Glycerophospholipid (general structure)



Name of glycerophospholipid	Name of X	Formula of X	Net charge (at pH 7)
Phosphatidic acid	—	—H	−1
Phosphatidylethanolamine	Ethanolamine	—CH_2—CH_2—$\overset{+}{N}H_3$	0
Phosphatidylcholine	Choline	—CH_2—CH_2—$\overset{+}{N}(CH_3)_3$	0
Phosphatidylserine	Serine	—CH_2—$CH(\overset{+}{N}H_3)$—COO^-	−1
Phosphatidylglycerol	Glycerol	—CH_2—$CH(OH)$—CH_2—OH	−1
Phosphatidylinositol 4,5-bisphosphate	*myo*-Inositol 4,5-bisphosphate		−4
Cardiolipin	Phosphatidyl-glycerol		−2

Mobilization of triacylglycerols



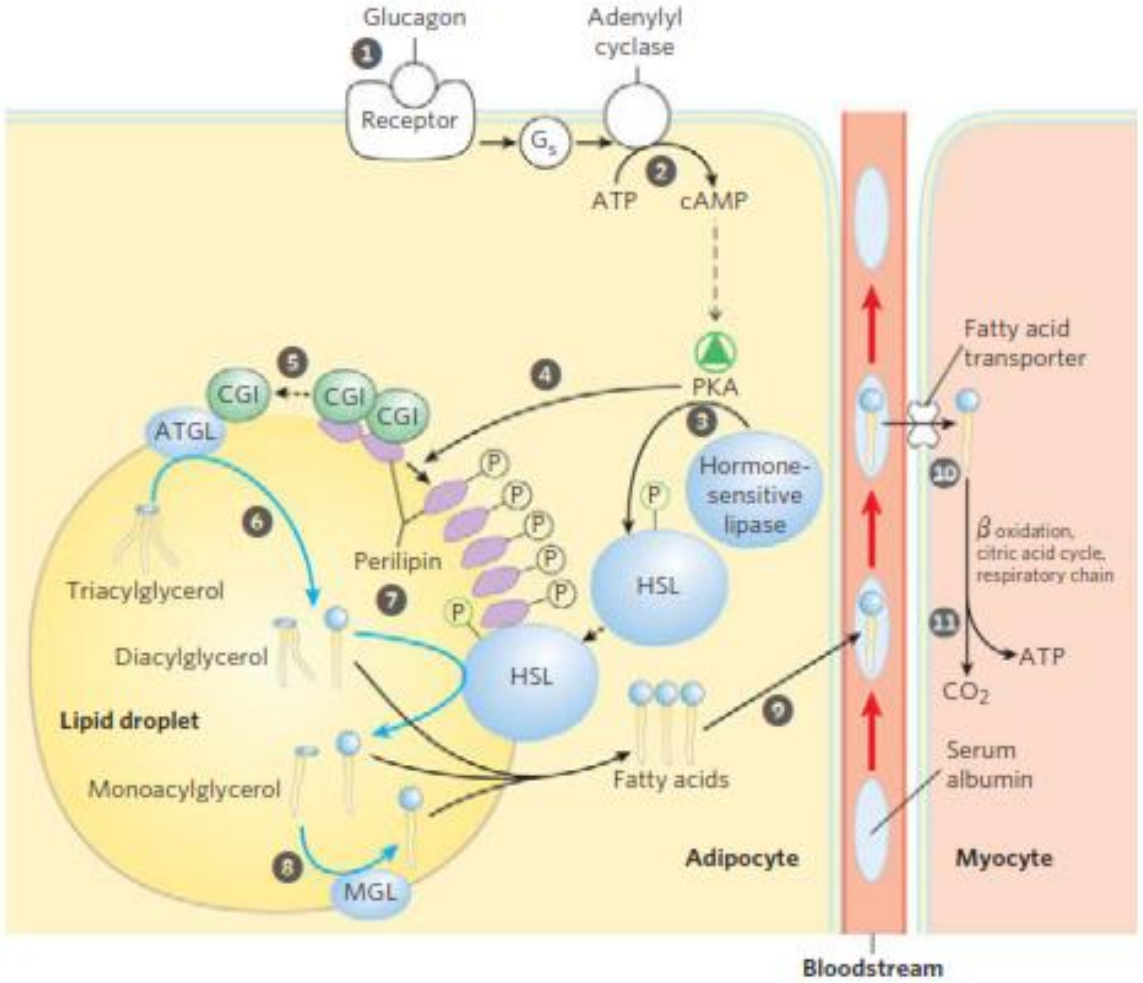
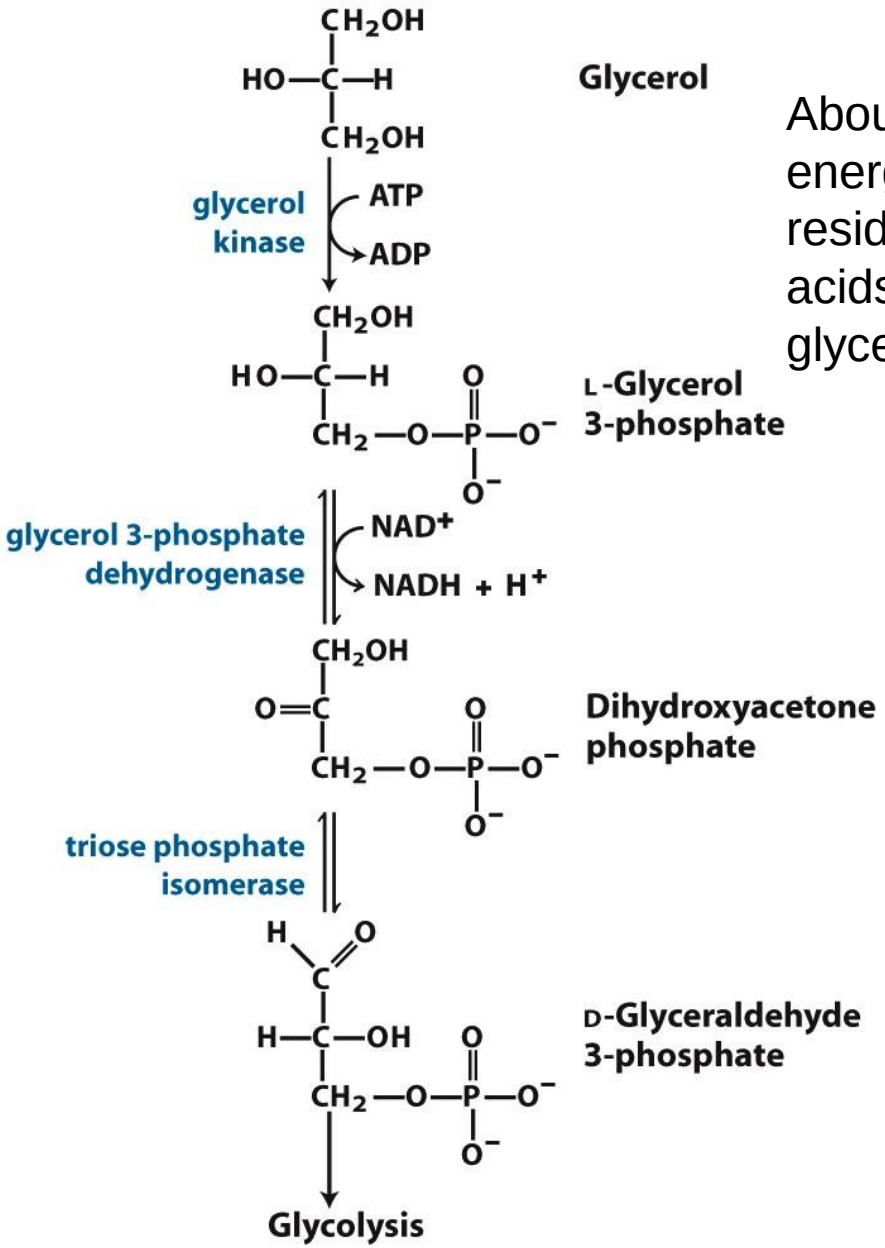
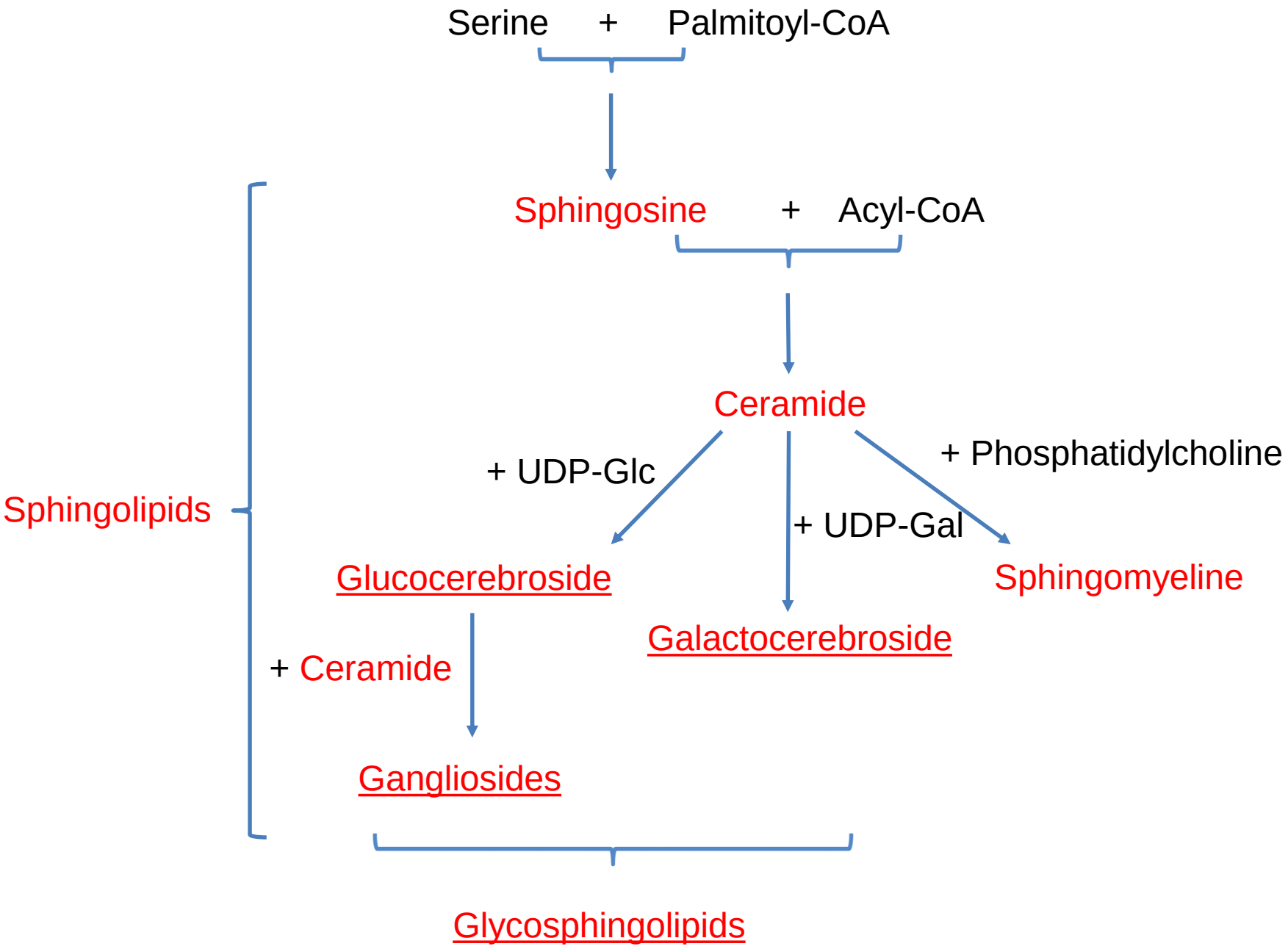


FIGURE 17–3 Mobilization of triacylglycerols stored in adipose tissue. When low levels of glucose in the blood trigger the release of glucagon, ❶ the hormone binds its receptor in the adipocyte membrane and thus ❷ stimulates adenylyl cyclase, via a G protein, to produce cAMP. This activates PKA, which phosphorylates ❸ the hormone-sensitive lipase (HSL) and ❹ perilipin molecules on the surface of the lipid droplet. Phosphorylation of perilipin causes ❺ dissociation of the protein CGI from perilipin. CGI then associates with the enzyme adipose triacylglycerol lipase (ATGL), activating it. Active ATGL ❻ converts triacylglycerols to diacylglycerols. The phosphorylated perilipin associates with phosphorylated HSL, allowing it access to the surface of the lipid droplet, where ❼ it converts diacylglycerols to monoacylglycerols. A third lipase, monoacylglycerol lipase (MGL) ❽, hydrolyzes monoacylglycerols. ❾ Fatty acids leave the adipocyte, bind serum albumin in the blood, and are carried in the blood; they are released from the albumin and ❿ enter a myocyte via a specific fatty acid transporter. ⓫ In the myocyte, fatty acids are oxidized to CO_2, and the energy of oxidation is conserved in ATP, which fuels muscle contraction and other energy-requiring metabolism in the myocyte.

Entry of glycerol into glycolysis

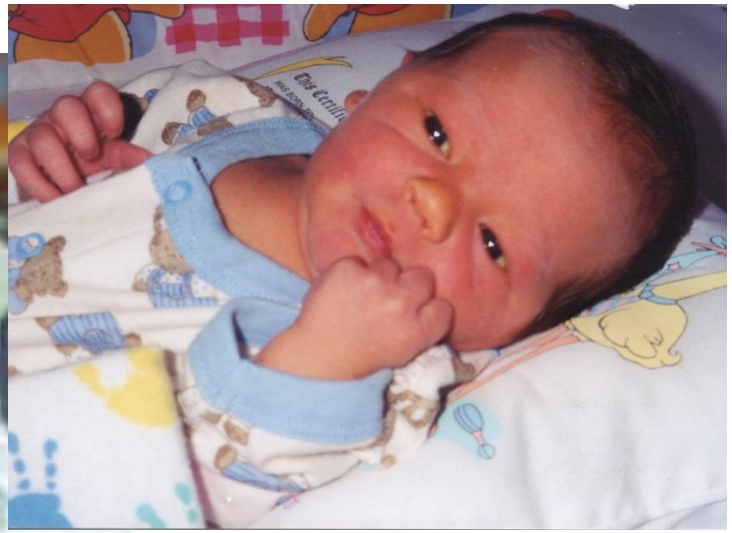


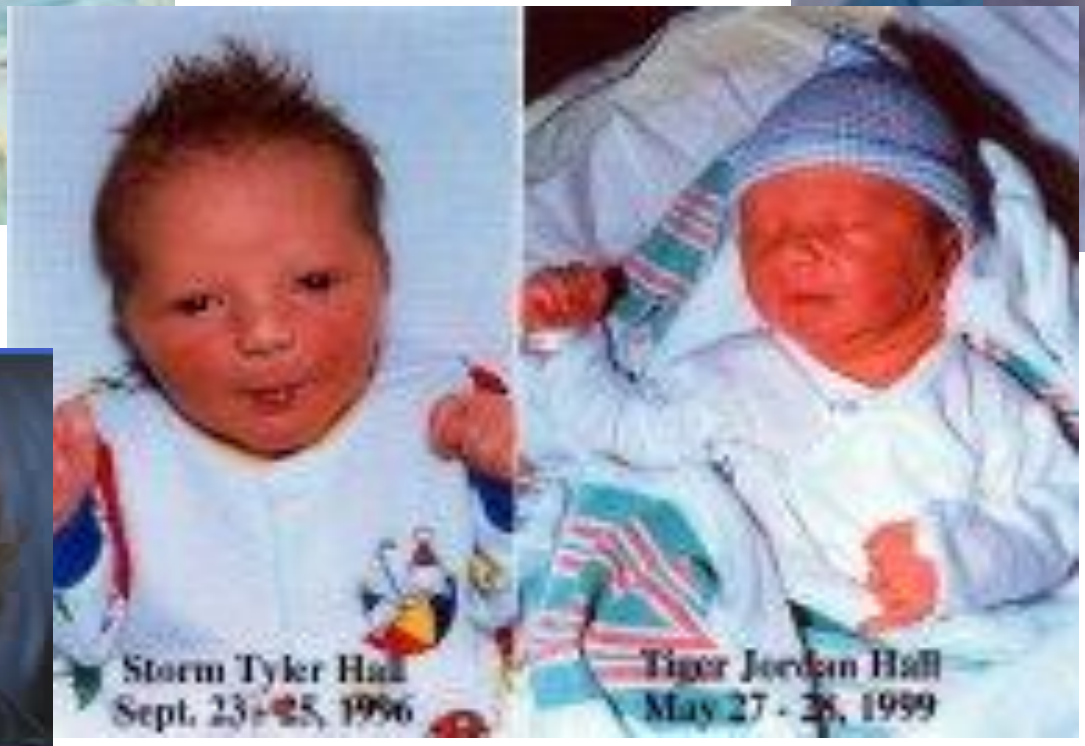
About 95% of the biologically available energy of triacylglycerols resides in their three long-chain fatty acids; only 5% is contributed by the glycerol moiety.


Serine + Palmitoyl-CoA
Sphingosine + Acyl-CoA
Ceramide
+ UDP-Glc
+ UDP-Gal
+ Phosphatidylcholine
Sphingolipids
Glucocerebroside
Galactocerebroside
Sphingomyeline
+ Ceramide
Gangliosides
Glycosphingolipids

A 4-month-old infant presents with a seizure. His mother reports that her infant has been irritable and lethargic over the past several days. The infant is found to have a profoundly low serum glucose level (hypoglycemia) and a profoundly low ketone body level. The infant is diagnosed with medium-chain acyl CoA dehydrogenase (MCAD) deficiency.
What is the etiology of this patient's symptoms?

(A) β -oxidation of fatty acids is blocked
(B) He is consuming a diet that is too low in protein.
(C) Triacylglycerols are being stored in adipose tissue.
(D) Glucose is being used up for fatty acid synthesis.
(E) Fatty acyl CoA cannot be transported into mitochondria.




Storm Tyler Hall
Sept. 23-25, 1996
Tiger Jordan Hall
May 27 - 28, 1999