Chapter 16 - Lipid Metabolism

- **Triacylglycerols** (TGs) and **glycogen** are the two major forms of stored energy in vertebrates
- Glycogen can supply ATP for muscle contraction for less than an hour
- Sustained work is fueled by metabolism of TGs which are very efficient energy stores because:
  (1) They are stored in an anhydrous form
  (2) Their fatty acids are more reduced than amino acids or monosaccharides

16.1 Adsorption and Mobilization of Fatty Acids

- Fatty acids (FA) and glycerol for metabolic fuels are obtained from triacylglycerols:

  (1) In the diet

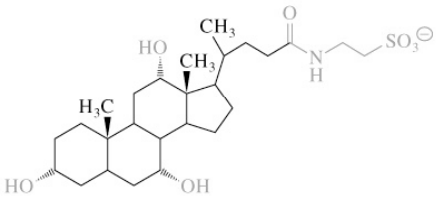
  (2) Stored in adipocytes (fat storage cells)
- Free fatty acids occur only in trace amounts in cells

A. Absorption of Dietary Lipids

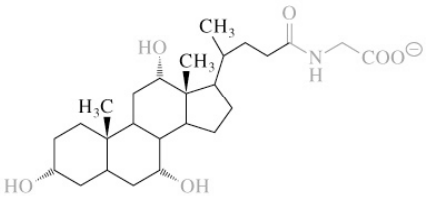
- Most diet lipids of mammals are TGs
- In the small intestine, fat particles are coated with bile salts and digested by pancreatic lipases
- Lipases degrade TGs to free fatty acids and a 2-monoacylglycerol
- Lipase catalyzes hydrolysis at the C-1 and C-3 positions of a TG

Fig 16.1 Bile salts

- Taurocholate and glycocholate (cholesterol derivatives) are the most abundant bile salts
- Amphipathic: hydrophilic (blue), hydrophobic (black)



Taurocholate



Glycocholate

Fig 16.2 Action of pancreatic lipase

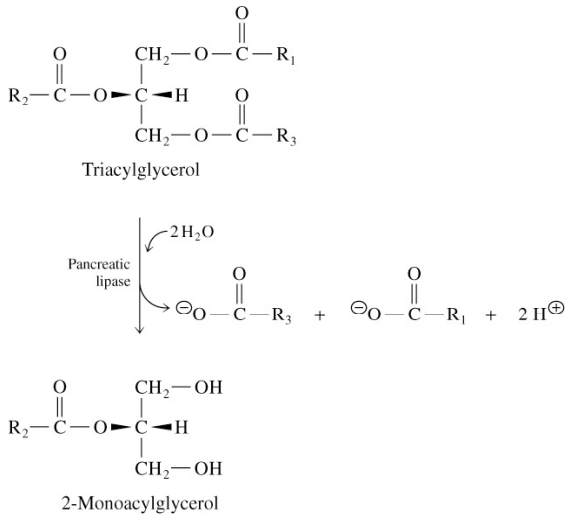


Fig 16.3 Dietary phospholipids are degraded by phospholipases

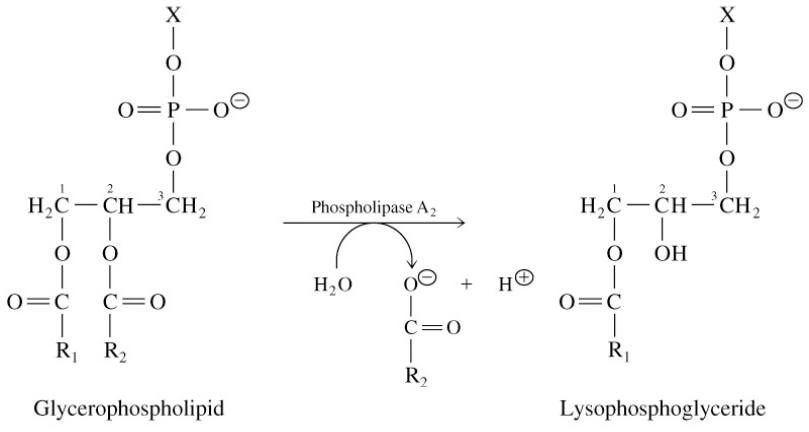
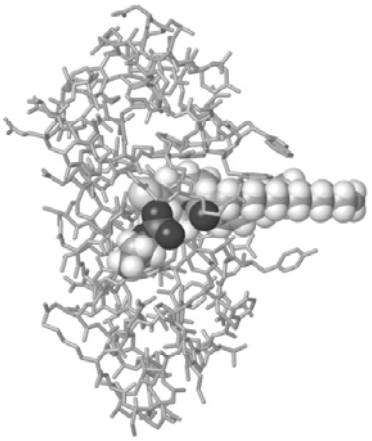


Fig 16.4 Structure of phospholipase A_2 from cobra venom

- Phospholipid substrate in the active site
- Calcium ion (purple) binds anionic head group



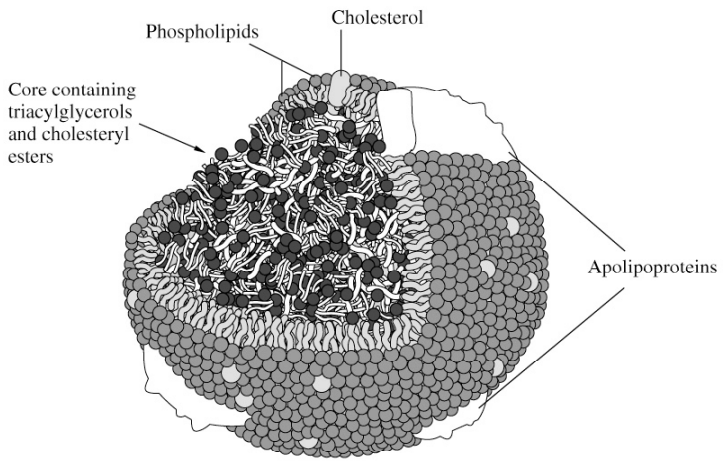
Dietary cholesterol

- Most dietary cholesterol is unesterified
- Cholesteryl esters are hydrolyzed by an intestinal esterase
- Free cholesterol is solublized by bile-salt micelles for adsorption
- Cholesteryl acyl CoA esters are formed in the intestinal cells

B. Lipoproteins

- TGs, cholesterol and cholesterol esters are insoluble in water and cannot be transported in blood or lymph as free molecules
- These lipids assemble with phospholipids and apoproteins (apolipoproteins) to form spherical particles called **lipoproteins** with:
  Hydrophobic cores: TGs, cholesteryl esters
  Hydrophilic surfaces: cholesterol, phospholipids, apolipoproteins

Fig 16.5 Structure of a lipoprotein



Chylomicrons

- Chylomicrons are the largest lipoproteins
- They deliver TGs from the intestine (via lymph and blood) to tissues (muscle for energy, adipose for storage)
- They are present in blood only after feeding
- Cholesterol-rich chylomicron remnants deliver cholesterol to the liver

Fig 16.6 Summary of lipoprotein metabolism

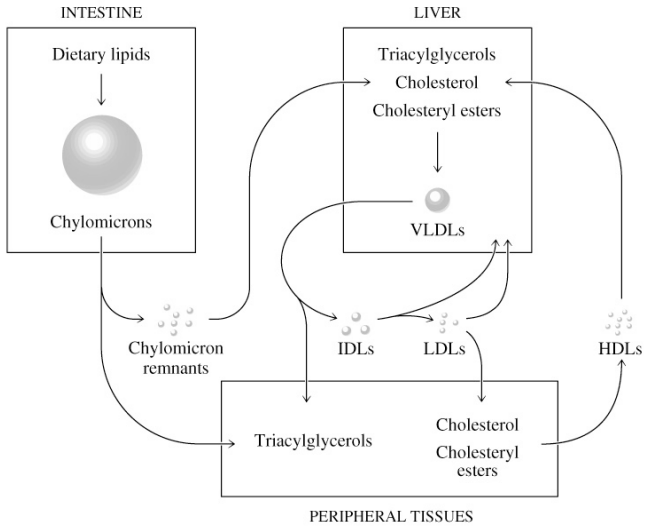


Table 16.1

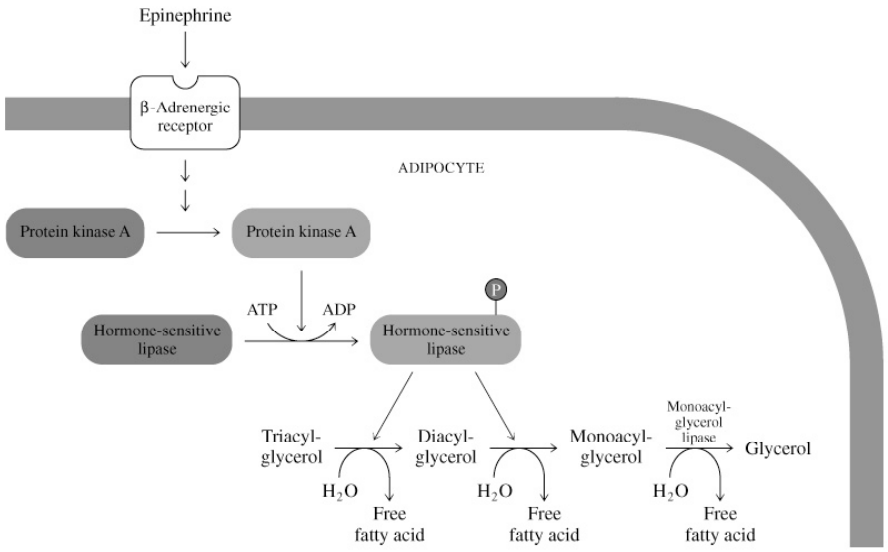
TABLE 16.1 Lipoproteins in human plasma

	Chylomicrons	VLDLs	IDLs	LDLs	HDLs
Molecular weight $\times 10^{-6}$	>400	10–80	5–10	2.3	0.18–0.36
Density ($g\,cm^{-3}$)	<0.95	0.95–1.006	1.006–1.019	1.019–1.063	1.063–1.210
Chemical composition (%)					
Protein	2	10	18	25	33
Triacylglycerol	85	50	31	10	8
Cholesterol	4	22	29	45	30
Phospholipid	9	18	22	20	29

C. Storage and Mobilization of Fatty Acids (FA)

- TGs are stored in adipocytes, and fatty acids are released to supply energy demands
- A hormone-sensitive lipase converts TGs to free fatty acids and glycerol
- At low carbohydrate and insulin concentrations, TG hydrolysis is stimulated by increased epinephrine (binds to *b*-adrenergic receptors, and activates cAMP-dependent protein kinases)

Fig 16.7 Triacylglycerol degradation



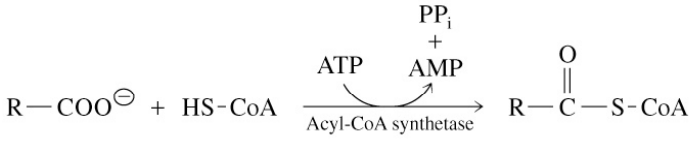
16.2 Fatty Acid Oxidation

- The **β-oxidation pathway** degrades fatty acids two carbons at a time
- Three stages:
  (1) Activation of fatty acids in the cytosol
  (2) Transport into the mitochondria
  (3) Degradation to two-carbon fragments (as acetyl CoA) in the mitochondrial matrix

A. Activation of Fatty Acids

- Fatty acids in the cytosol are activated by conversion to CoA thioesters by acyl-CoA synthetase (ATP dependent)
- The PP_i released is hydrolyzed by a pyrophosphatase to 2 P_i
- Net of <u>two</u> <u>ATP</u> <u>equivalents</u> are consumed to activate one fatty acid to a thioester

Activation of fatty acids: reaction



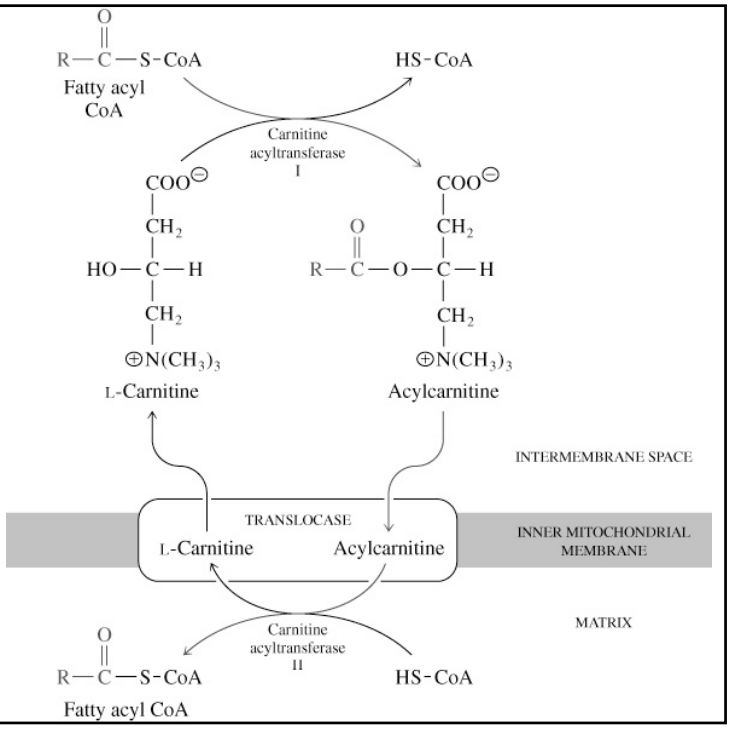
(16.1)

B. Transport of Fatty Acyl CoA into Mitochondria

- The **carnitine shuttle system** transfers long-chain fatty acyl CoA from the cytosol into the mitochondria
- Fatty acyl CoA is first converted to acylcarnitine (which can enter the mitochondria) and then back to fatty acyl CoA
- The β-oxidation cycle enzymes (mitochondrial) can then degrade the fatty acyl CoA

Fig 16.8

- Carnitine shuttle system
- Path of acyl group in red



C. The Reactions of β oxidation

- One round of β oxidation: 4 enzyme steps produce acetyl CoA from fatty acyl CoA
- Each round generates one molecule each of:

QH_2
NADH
Acetyl CoA
Fatty acyl CoA (2 carbons shorter each round)

Fig 16.9

β-Oxidation of saturated fatty acids

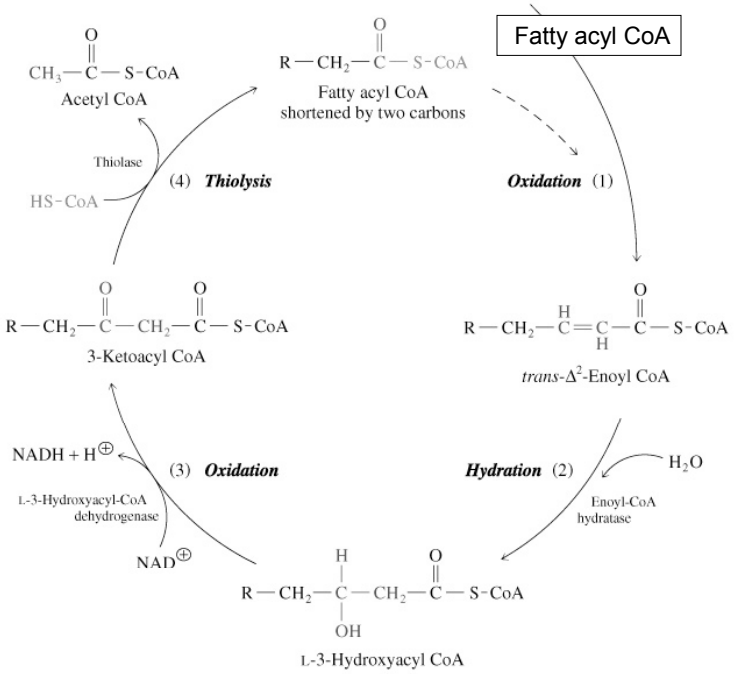
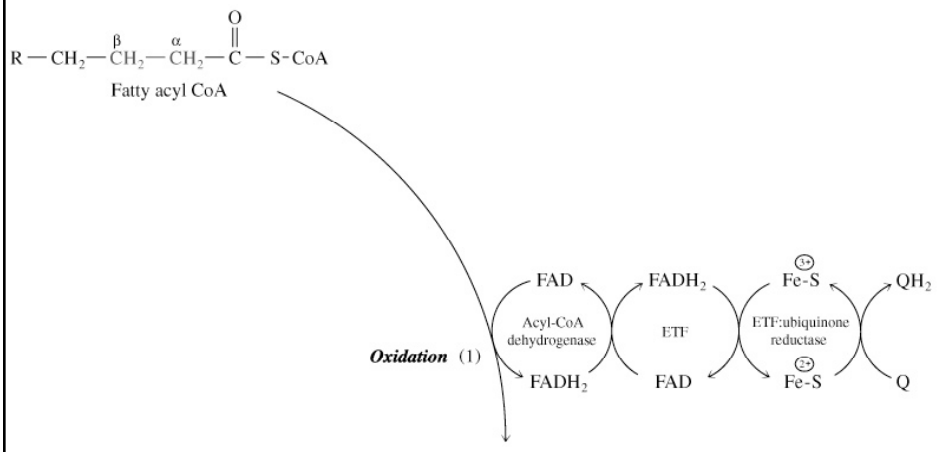


Fig 16.9 (continued)



D. ATP Generation from Fatty Acid Oxidation

- The balanced equation for oxidizing one palmitoyl CoA by seven cycles of β oxidation

Palmitoyl CoA + 7 HS-CoA + 7 Q + 7 NAD^+ + 7 H_2O

⟶ 8 Acetyl CoA + 7QH_2 + 7 NADH + 7 H^+

Net yield of ATP per palmitate oxidized to 16 CO_2

	ATP generated
8 acetyl CoA	80
7 QH_2	10.5
7 NADH	17.5
	108 ATP
ATP expended to activate palmitate	-2
Net yield:	**106 ATP**

16.3 β Oxidation of Odd-Chain and Unsaturated Fatty Acids

- Odd-chain fatty acids occur in bacteria and microorganisms
- Final cleavage product is propionyl CoA rather than acetyl CoA
- Three enzymes convert propionyl CoA to succinyl CoA (citric acid cycle intermediate)

Fig 16.10

Conversion of propionyl CoA to succinyl CoA

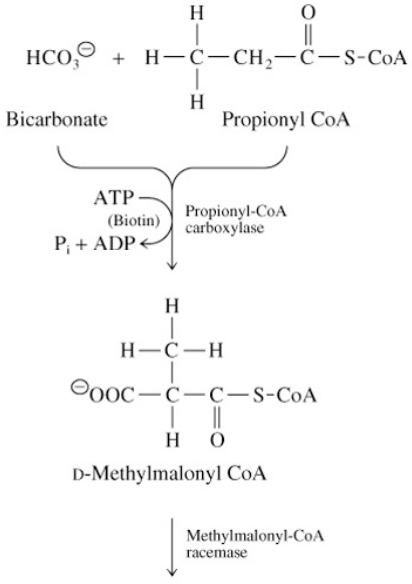
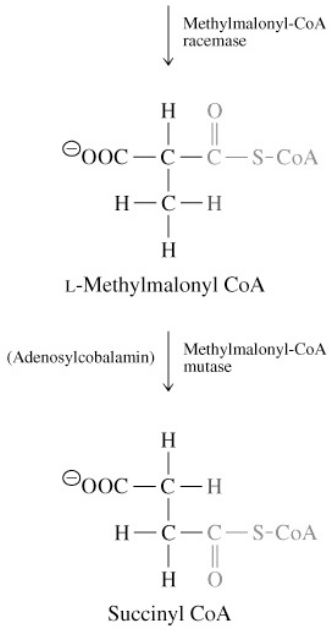


Fig 16.10 (cont)



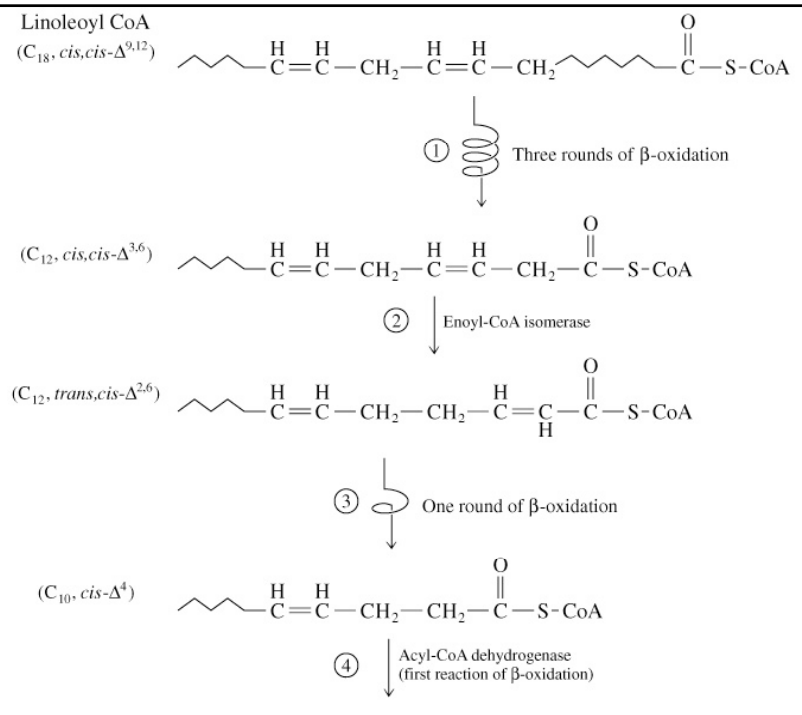
β Oxidation of Unsaturated Fatty Acids

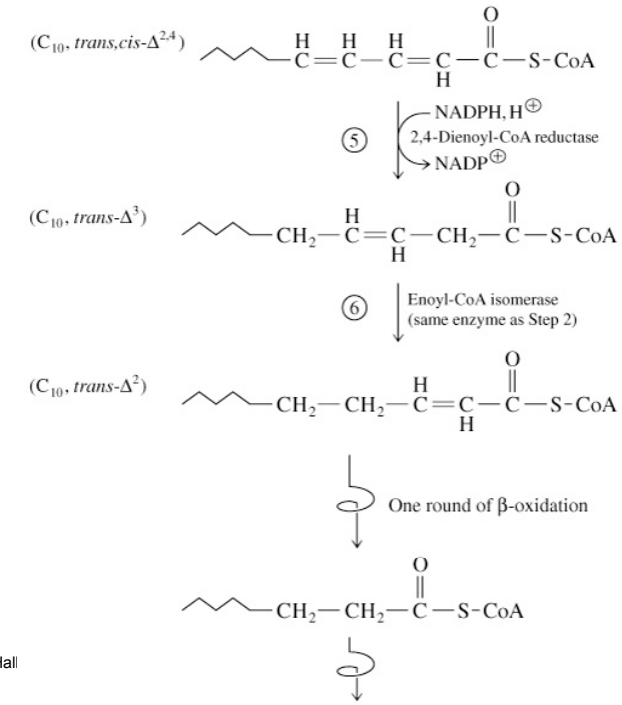
- Unsaturated FA are common in nature
- Degradation requires two other enzymes in addition to the β-oxidation pathway enzymes:

  (1) **Enoyl-CoA isomerase**

  (2) **2,4-Dienoyl-CoA-reductase**

(**Fig 16.11** - Pathway is on the next two slides)





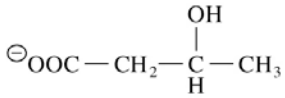
16.4 Ketone Bodies Are Fuel Molecules

- During fasting or starvation, glucose is decreased, and excess acetyl CoA from fat metabolism can be converted to **ketone bodies**:

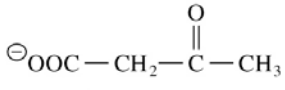
  β-Hydroxybutyrate
  Acetoacetate
  Acetone

- Ketone bodies can fuel brain cells during starvation

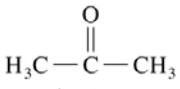
Fig 16.12 Ketone bodies



β-Hydroxybutyrate



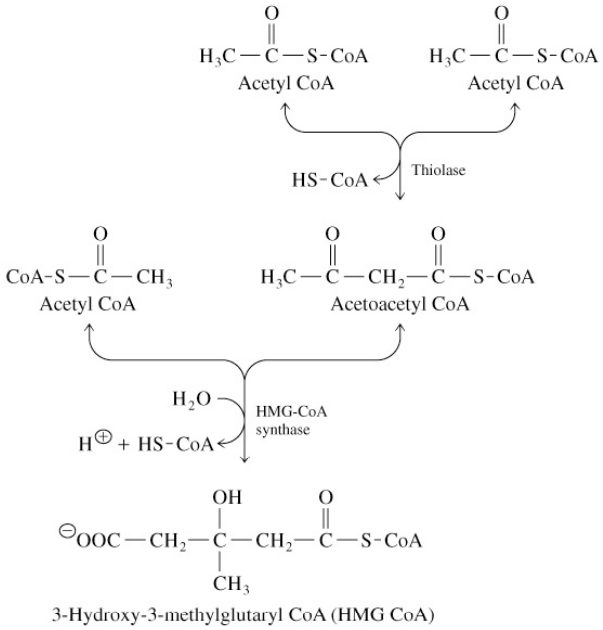
Acetoacetate



Acetone

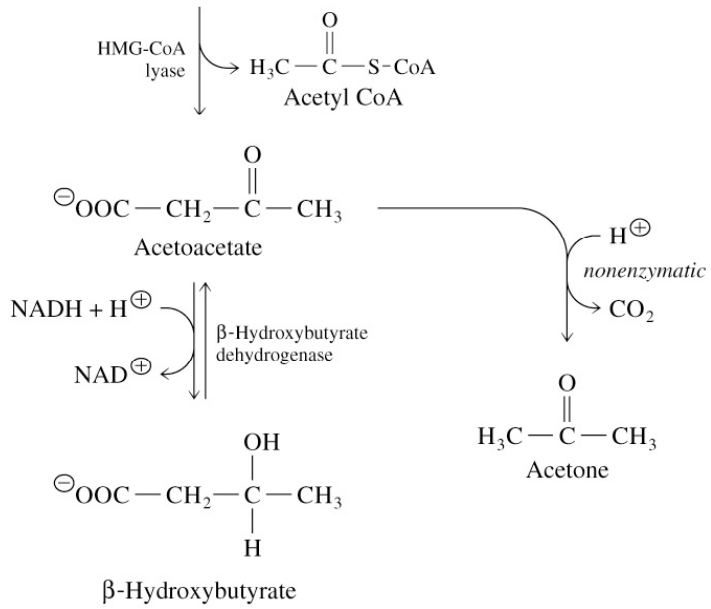
A. Ketone Bodies Are Synthesized in the Liver

Fig 16.13

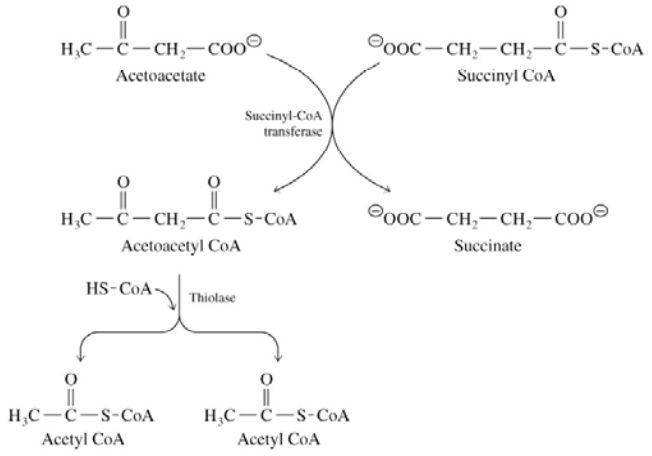


3-Hydroxy-3-methylglutaryl CoA (HMG CoA)

Fig 16.13 (cont)



B. Ketone Bodies Are Oxidized in Mitochondria



16.5 Fatty Acid Synthesis

- Occurs mainly in liver and adipocytes (mammals)
- FA synthesis and degradation occur by two completely separate pathways
- When glucose is plentiful, large amounts of acetyl CoA are produced by glycolysis and can be used for fatty acid synthesis
- Glucose oxidation in the pentose phosphate pathway provides NADPH for FA synthesis

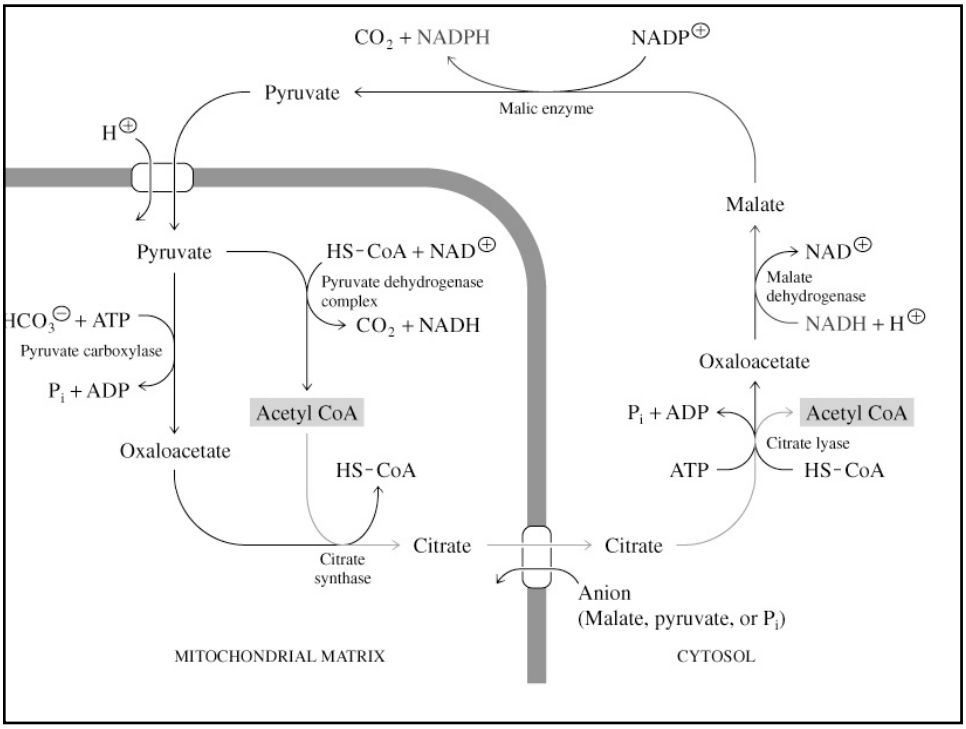
Table 16.2

TABLE 16.2 Comparison of fatty acid oxidation and synthesis in mammals

	Oxidation	Synthesis
Localization	Mitochondriand peroxisomes	Cytosol
Acyl carrier	CoA	Acyl carrier protein (ACP)
Carbonunits	C_2	C_2
Acceptor/donor	CoA(C_2)	Malonyl CoA(C_3, donor reaction evolves CO_2)
Mobile oxidation-reduction cofactors	$NAD^{\oplus}$, ETF, Q	NADPH
Organization of enzymes	Separate enzymes	

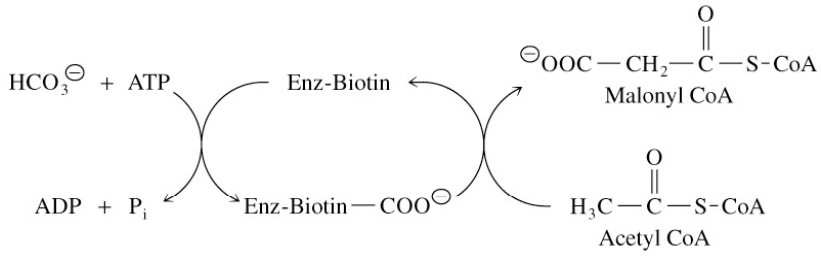
A. Transport of Acetyl CoA to the Cytosol

- Acetyl CoA from catabolism of carbohydrates and amino acids is exported from mitochondria via the **citrate transport system** (**Fig 16.15,** next slide)
- Cytosolic NADH also converted to NADPH
- Two molecules of ATP are expended for each round of this cyclic pathway



B. Carboxylation of Acetyl CoA

Fig 16.16 Acetyl CoA carboxylase catalyzes:

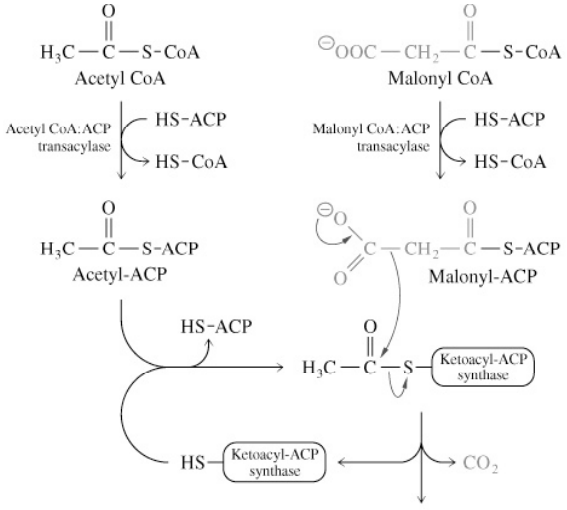


C. The Reactions of Fatty Acid Synthesis

- FA are synthesized by the repetitive condensation of two-carbon units derived from malonyl CoA
- Five separate stages:
  (1) *Loading* of precursors via thioester derivatives
  (2) *Condensation* of the precursors
  (3) *Reduction*
  (4) *Dehydration*
  (5) *Reduction*

Fig 16.17 Biosynthesis of FA from acetyl CoA and malonyl CoA in *E. coli*

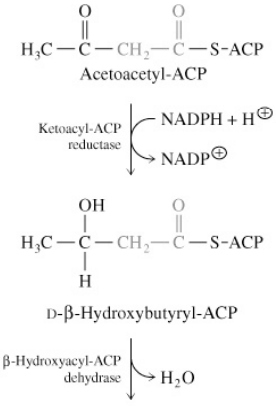
Loading. Two enzyme activities, acetyl CoA:ACP transacylase and malonyl CoA:ACP transacylase, are required for the loading steps, in which acetyl CoA and malonyl CoA are transesterified to ACP molecules.



Condensation. Ketoacyl-ACP synthase (also called the condensing enzyme) accepts an acetyl group from acetyl-ACP, releasing HS-ACP. Ketoacetyl-ACP synthase then catalyzes transfer of the acetyl group to malonyl-ACP, forming acetoacetyl-ACP and CO_2.

Fig 16.17 (continued)

Reduction. In the first reduction, the ketone of acetoacetyl-ACP is converted to an alcohol, forming D-β-hydroxybutyryl-ACP, in an NADPH-dependent reaction catalyzed by ketoacyl-ACP reductase.



Dehydration. A dehydrase catalyzes the removal of water with the formation of a double bond, producing *trans*-butenoyl-ACP.

Fig. 16.17 (continued)

Reduction. trans-Butenoyl-ACP is reduced to form butyryl-ACP in a reaction catalyzed by NADPH-dependent enoyl-ACP reductase. Synthesis continues by repeating Steps 2 through 5, with the four-carbon butyryl-ACP substituting for acetyl-ACP in the next condensation stage.

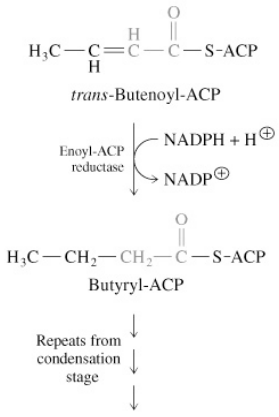
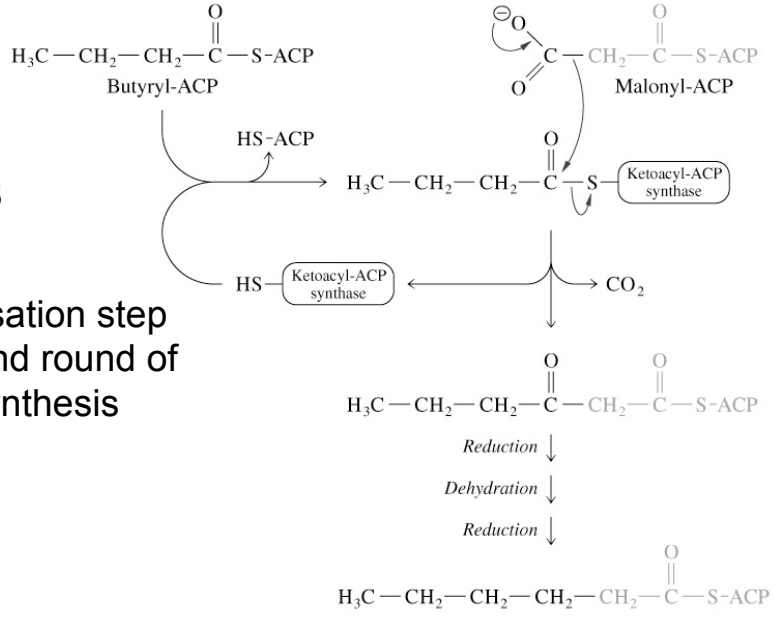


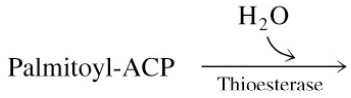
Fig 16.18

Condensation step for second round of FA biosynthesis



Final reaction of FA synthesis

- Rounds of synthesis continue until a C_{16} palmitoyl group is formed
- Palmitoyl-ACP is hydrolyzed by a thiolesterase



(16.3)

Overall stoichiometry of palmitate synthesis from acetyl CoA and malonyl CoA

Acetyl CoA + 7 Malonyl CoA + 14 NADPH + 14 H^+

↓

Palmitate + 7 CO_2 + 14 $NADP^+$ + 8 HS-CoA + 6 H_2O

Fig 16.19

- Organization of subunits in animal FA synthase

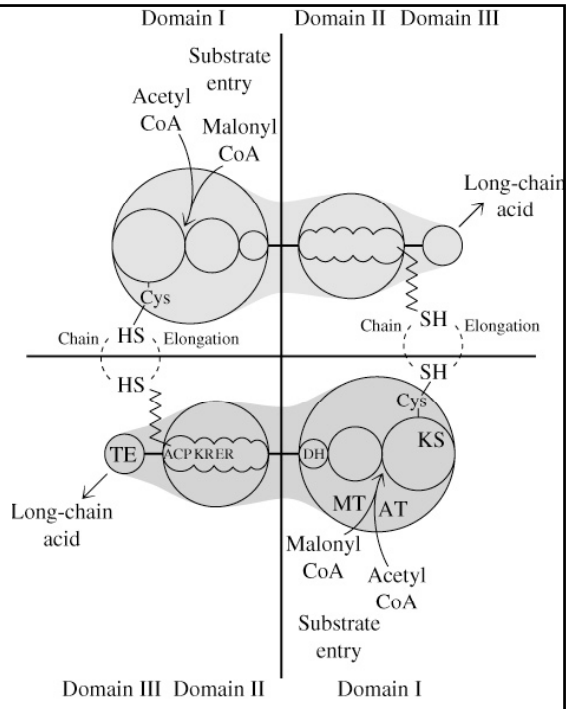


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Fig 16.20 Early steps in reactions of animal FA synthase (2 slides)

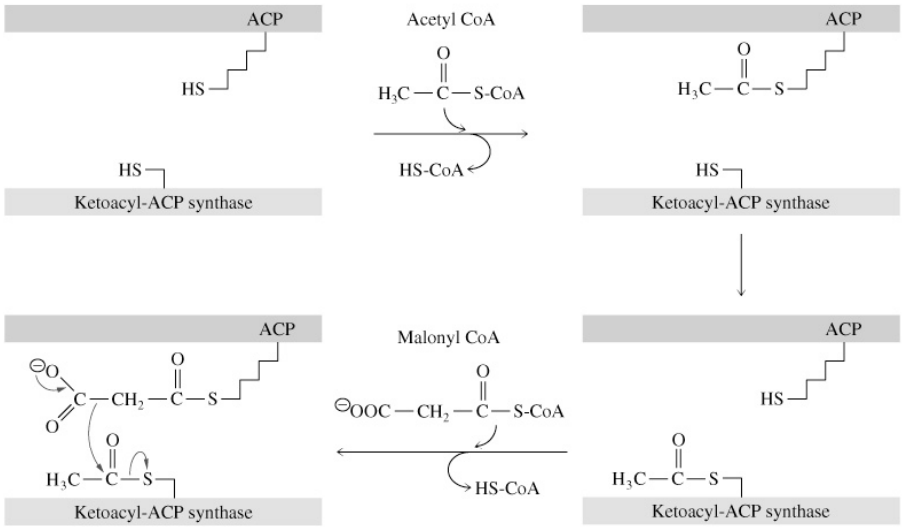
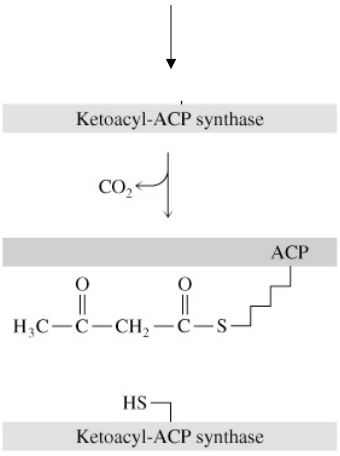


Fig 16.20 (continued)



(from previous slide)

16.6 Fatty Acid Elongation and Desaturation

Fig 16.21

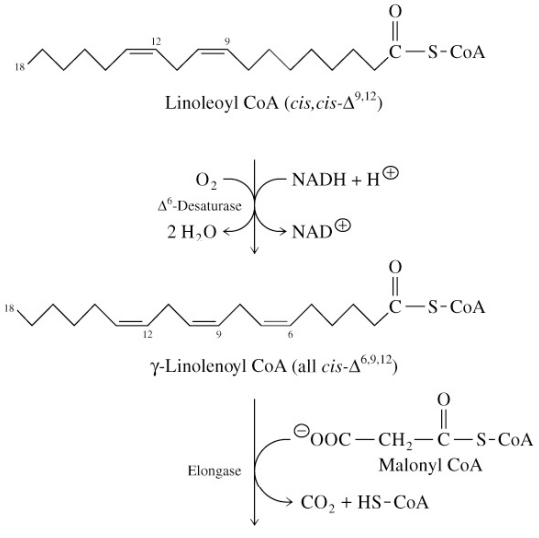
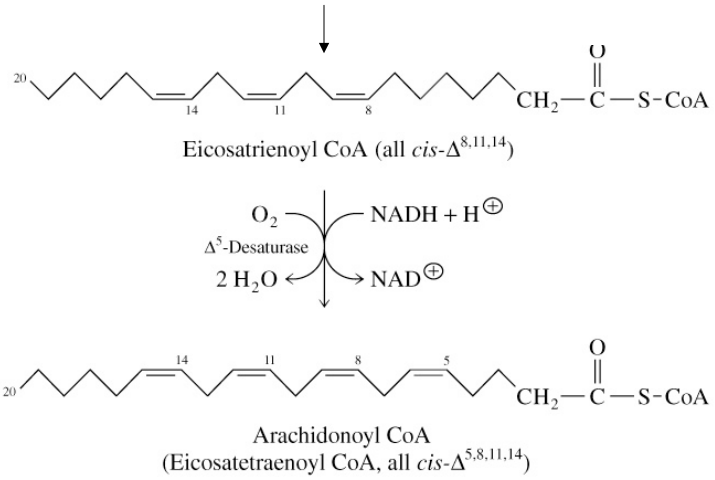


Fig 16.21 (cont)



16.7 Regulation of Fatty Acid Oxidation

- FA synthesis and oxidation are reciprocally regulated
- Fed state: Storage is favored (carbohydrates are used as fuel a precursors for FA synthesis)
- Fasting state: FA oxidation is favored as fats serve as fuel in place of glucose

Control points for FA oxidation

Fed state: **Insulin** (levels increase)

- Inhibits hydrolysis of stored TGs
- Stimulates formation of malonyl CoA, which inhibits CAT I
- FA remain in cytosol (FA oxidation enzymes are in the mitochondria)

Control points for FA oxidation (cont)

Fasted state: **Epinephrine** and **glucagon** increase (insulin decreases)

- Epinephrine activates lipase enzyme to produce more FA
- Glucagon inactivates malonyl CoA synthesis enzyme (leads to increased transport of FA into mitochondria and the β-oxidation pathway)

FA synthesis regulation via acetyl CoA carboxylase

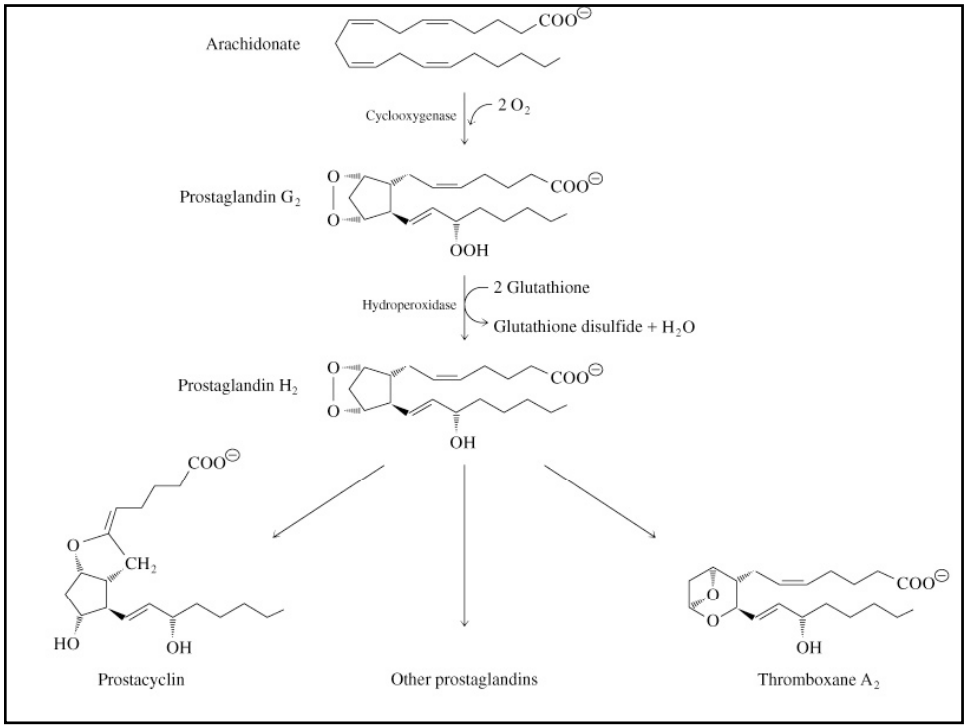
- Acetyl CoA carboxylase is inhibited by fatty acyl CoA (increased FA concentrations lead to decreased FA synthesis)
- Acetyl CoA carboxylase is under hormonal control: glucagon and epinephrine (fasted state) stimulate phosphorylation (inactivation) of the enzyme

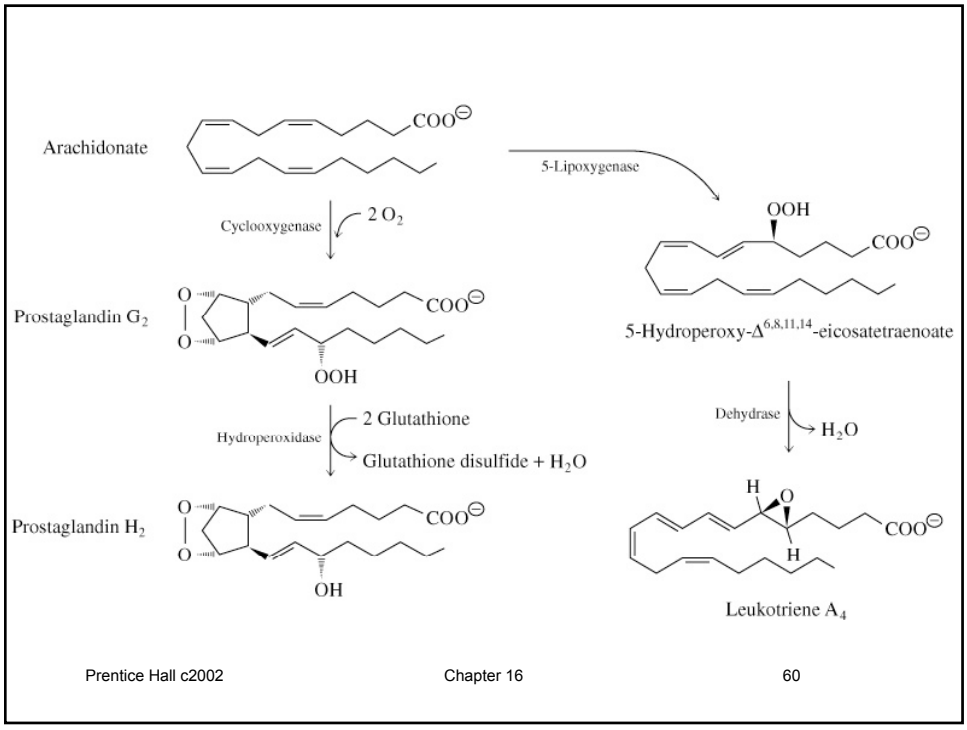
16.8 Synthesis of Eicosanoids

- Arachidonate is the precursor of **eicosanoids** (regulatory molecules) (**Fig 16.22**, next 2 slides)
- Eicosanoids

  (1) **Prostaglandins and thromboxanes** are local regulators (act at site of synthesis) and include: prostacyclin, thromboxane A_2

  (2) **Leukotrienes**


Arachidonate
COO⊖
Cyclooxygenase
2 O2
Prostaglandin G2
O
O
COO⊖
OOH
Hydroperoxidase
2 Glutathione
Glutathione disulfide + H2O
Prostaglandin H2
O
O
COO⊖
OH
COO⊖
O
CH2
HO
OH
Prostacyclin
Other prostaglandins
O
O
COO⊖
OH
Thromboxane A2


Arachidonate
COO⊖
5-Lipoxygenase
Cyclooxygenase
2 O2
OOH
COO⊖
Prostaglandin G2
O
O
COO⊖
OOH
5-Hydroperoxy-Δ6,8,11,14-eicosatetraenoate
Dehydrase
H2O
Hydroperoxidase
2 Glutathione
Glutathione disulfide + H2O
Prostaglandin H2
O
O
COO⊖
OH
H
O
COO⊖
H
Leukotriene A4

16.9 Synthesis of Triacylglycerols (TGs) and Glycerophospholipids (GPLs)

- Most fatty acids in cells are found in esterified forms as TGs or GPLs
- Phosphatidic acid (phosphatidate) is an intermediate in the synthesis of TGs and GPLs
- Glycerol 3-phosphate is acylated by fatty acyl CoA molecules

Fig 16.23 Formation of phosphatidate

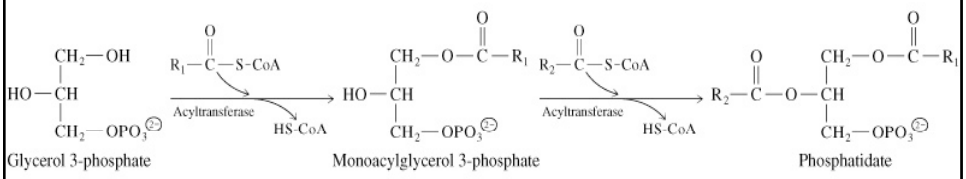
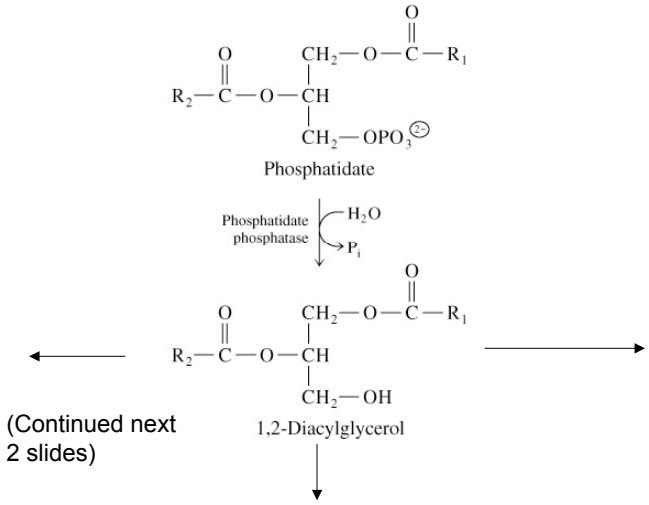


Fig 16.24 Synthesis of TGs and neutral phospholipids



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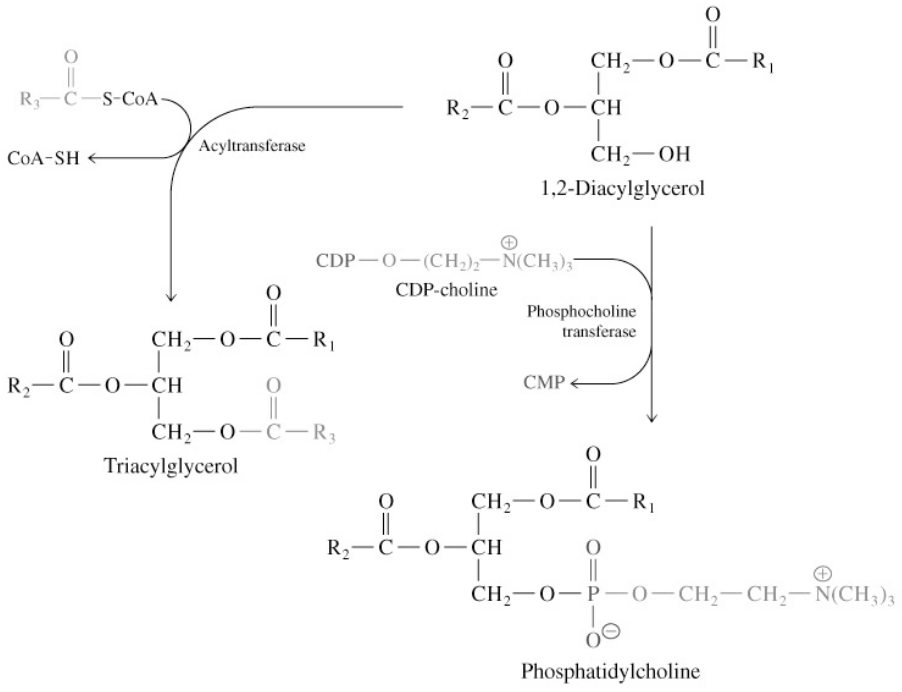

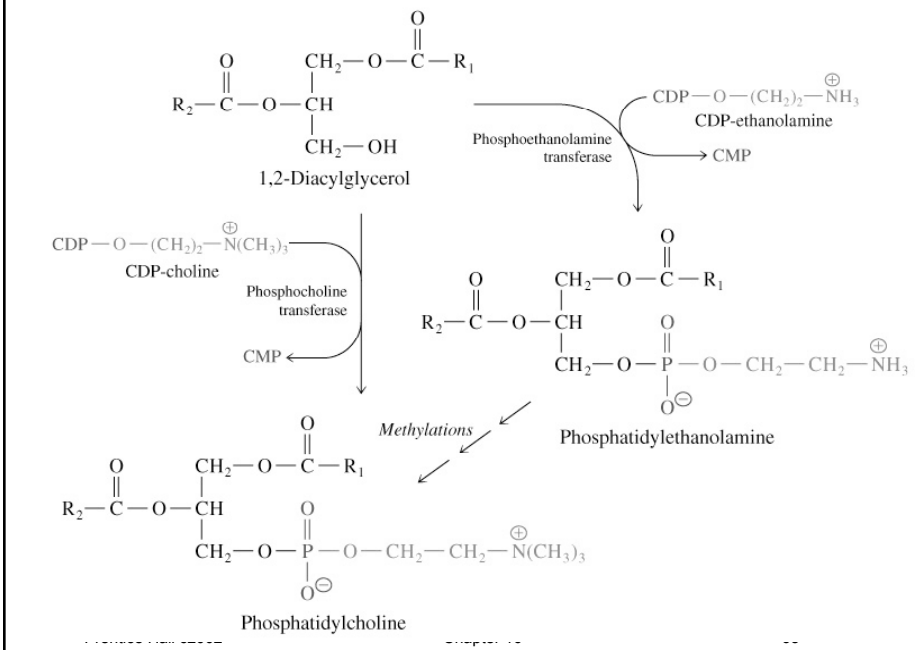

Fig16.25 Synthesis of acidic phospholipids

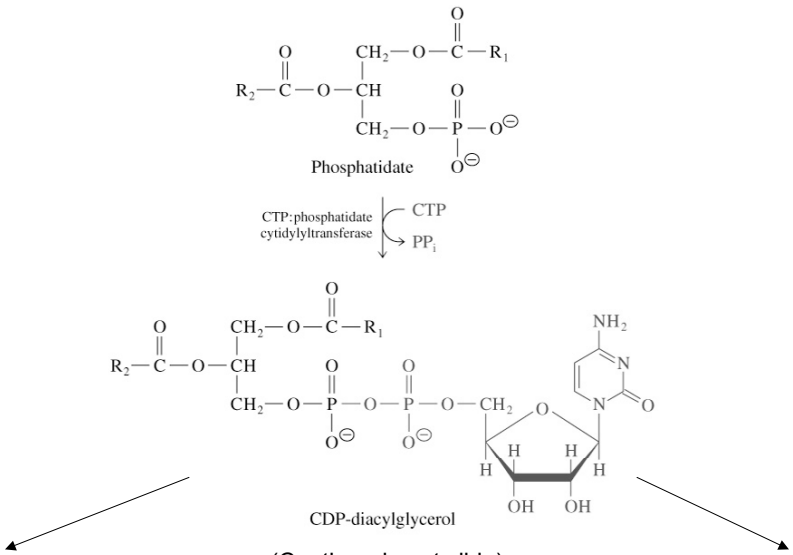

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Fig 16.25 (continued)

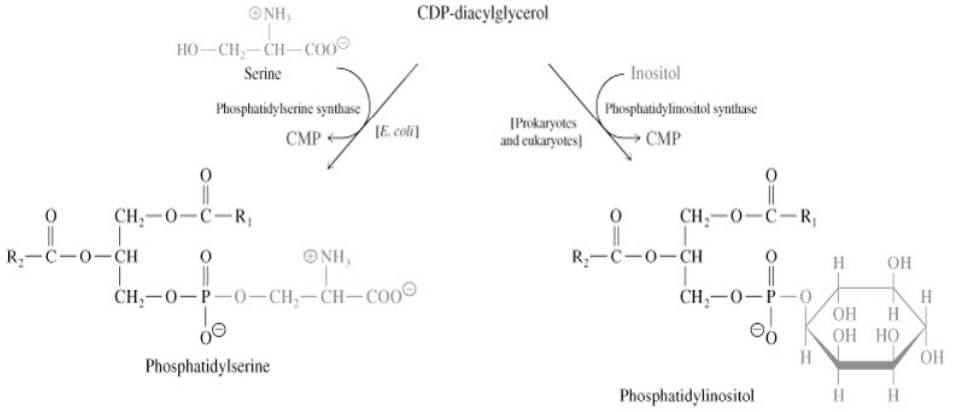
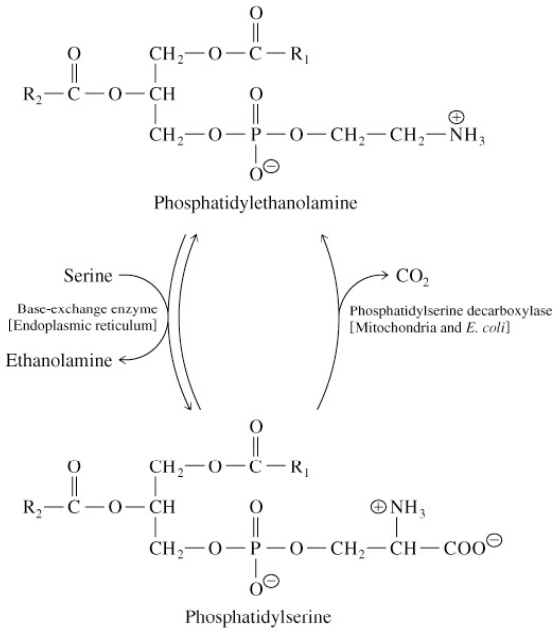


Fig 16.26

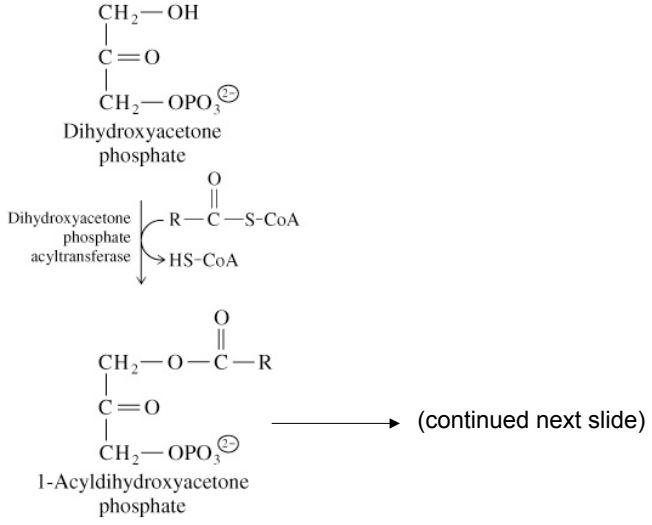
- Interconversions of phosphatidyl-ethanolamine (PE), phosphatidylserine (PS)



16.10 Synthesis of Ether Lipids

- These lipids have an ether linkage in place of one ester linkage of phospholipids
- Dihydroxyacetone is the starting point for synthesis of the ether lipids

Fig 16.27 Synthesis of ether lipids



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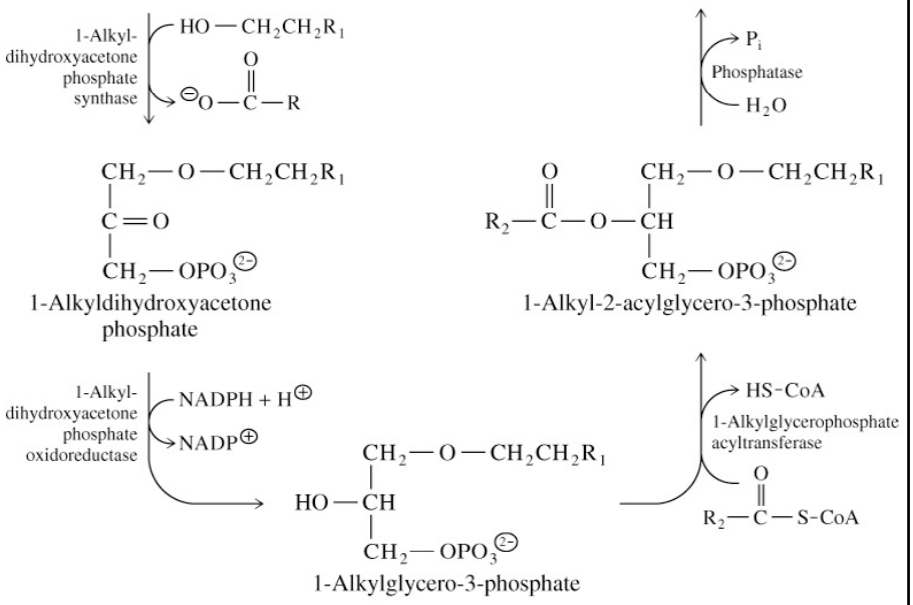
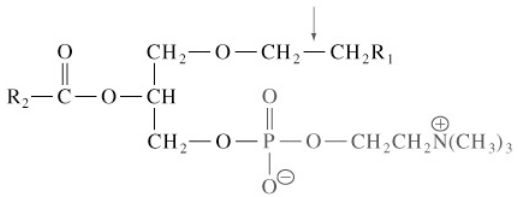
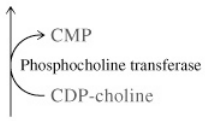


Fig 16.27 (cont)





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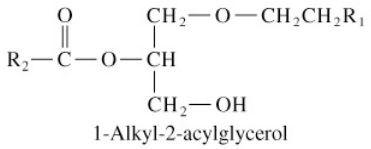
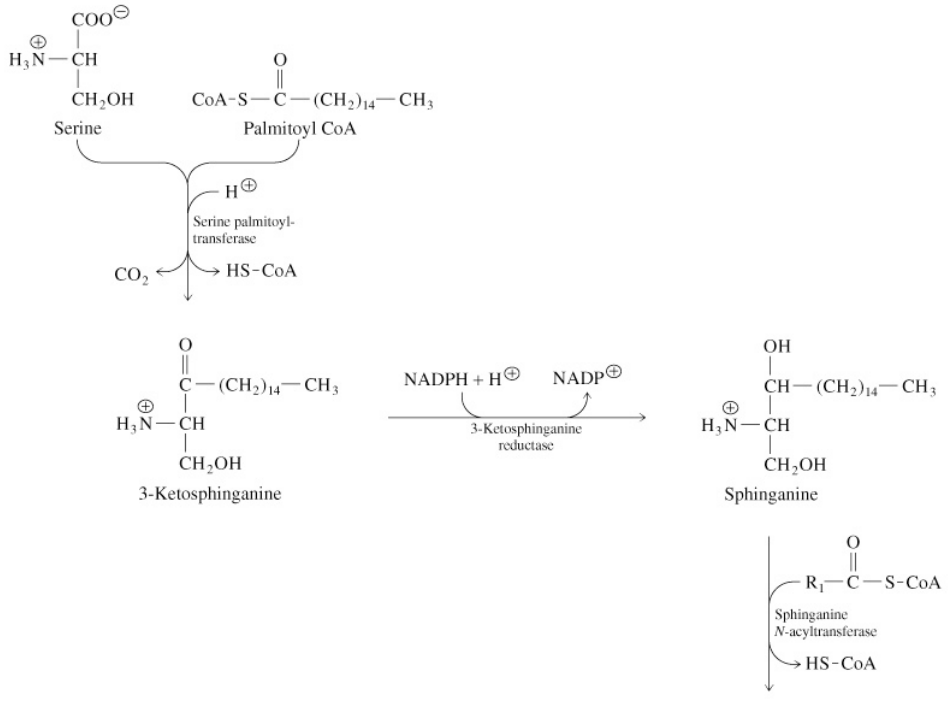
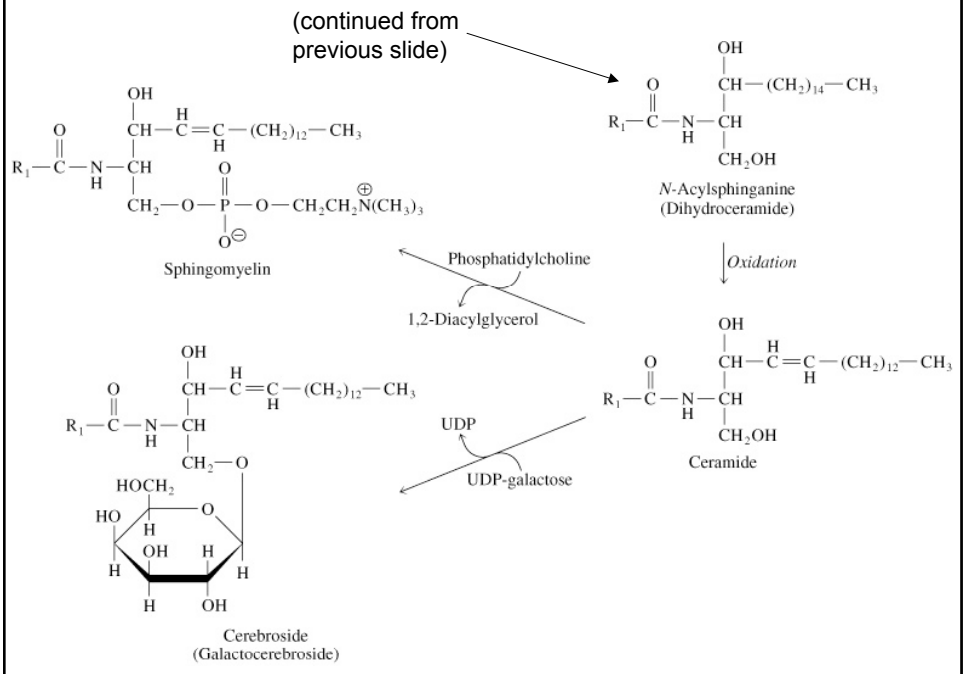


16. 11 Synthesis of Sphingolipids

- Sphingolipids are membrane lipids that have **sphingosine** (a C_{18} unsaturated alcohol) as the structural backbone
- Sphingolipids include sphingomyelins and cerebrosides
- Condensation of serine and palmitoyl CoA produces 3-ketosphinganine to start the pathway (**Figure 16.28**, next two slides)





16.12 Synthesis of Cholesterol

- Cholesterol is a precursor of steroid hormones and bile acids, and an important component of many mammalian membranes
- Most cholesterol is synthesized in the liver
- Liver-derived and dietary cholesterol are both delivered to body cells by lipoproteins
- Cholesterol biosynthesis is regulated by hormones and blood cholesterol levels

Summary: stages of cholesterol biosynthesis

Acetate (C_2) → Isoprenoid (C_5) →

Squalene (C_{30}) → Cholesterol (C_{27})

A. Stage 1: Acetyl CoA to Isopentenyl Pyrophosphate

- The carbons of cholesterol come from cytosolic acetyl CoA (transported from mitochondria via citrate transport system)
- First step is a sequential condensation of three molecules of acetyl CoA
- Isopentenyl pyrophosphate is an important donor of isoprenyl groups for many synthetic reactions

Fig 16.29

- Stage I of Cholesterol Biosynthesis

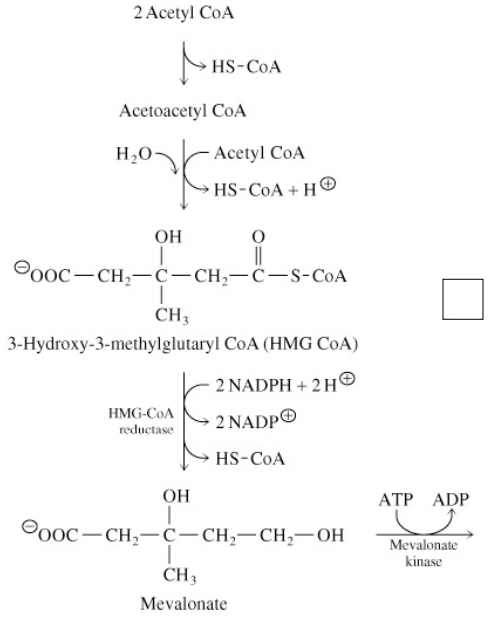
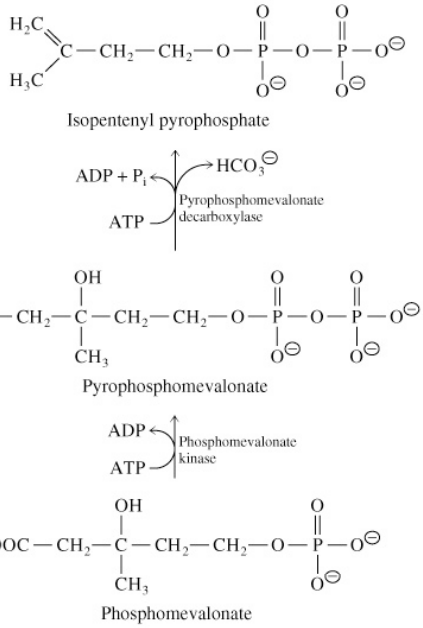


Fig 16.29 (continued)



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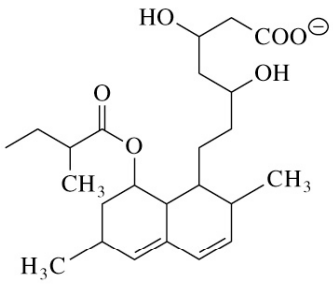
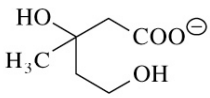
HMG-CoA reductase

- Catalyzes first committed step in pathway
- Primary site for regulating cholesterol synthesis
- Three regulatory mechanisms:
  - Covalent modification
  - Repression of transcription
  - Control of degradation
- Cholesterol-lowering statin drugs (e.g. Lovastatin) inhibit HMG-CoA reductase

Fig 16.30 Lovastatin resembles mevalonate



Lovastatin



Mevalonate

B. Stage 2

- **Fig 16.31** Isopentenyl Pyrophosphate to Squalene

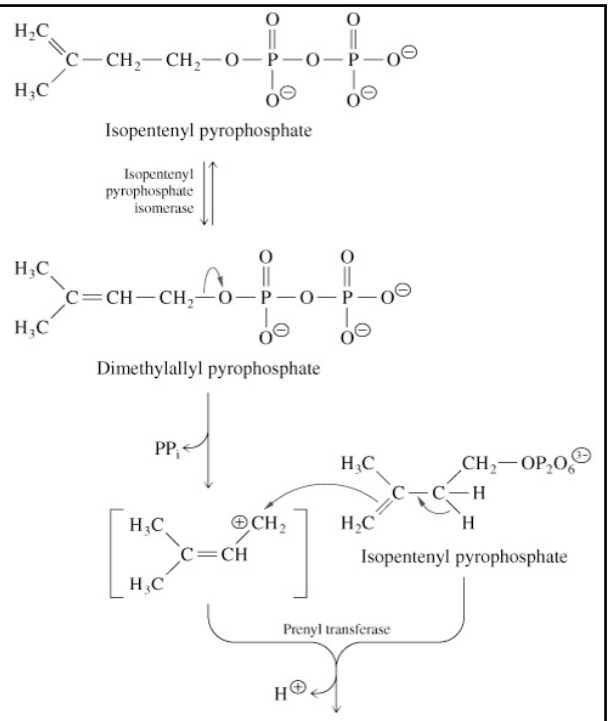
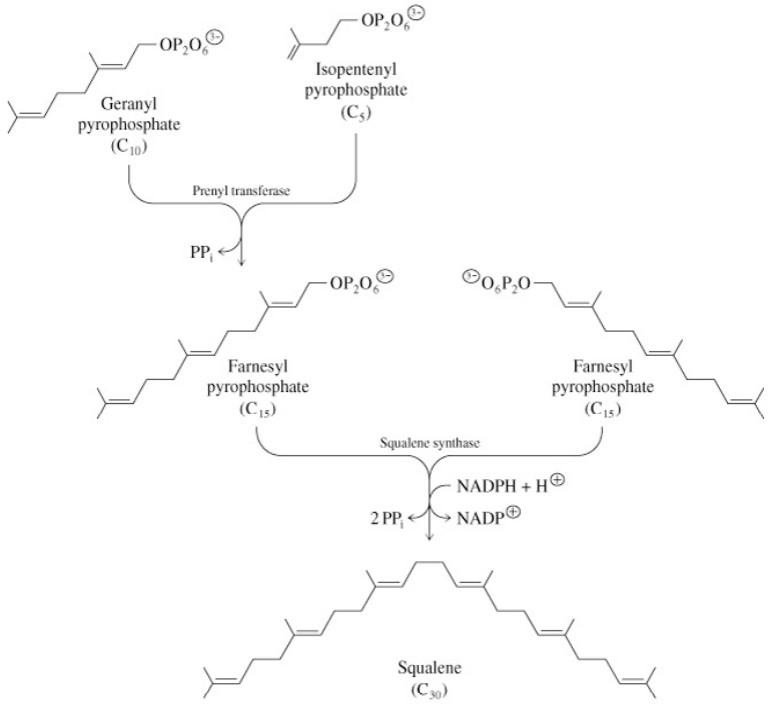
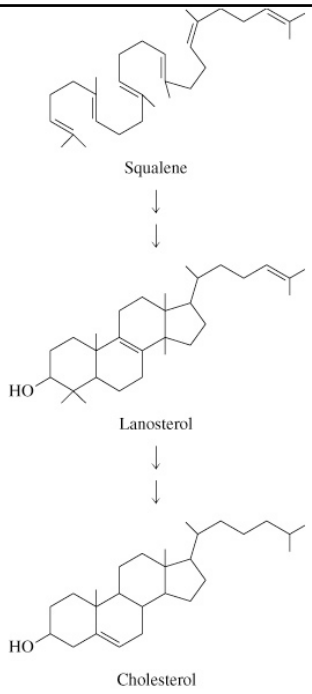


Fig 16.3 (cont)



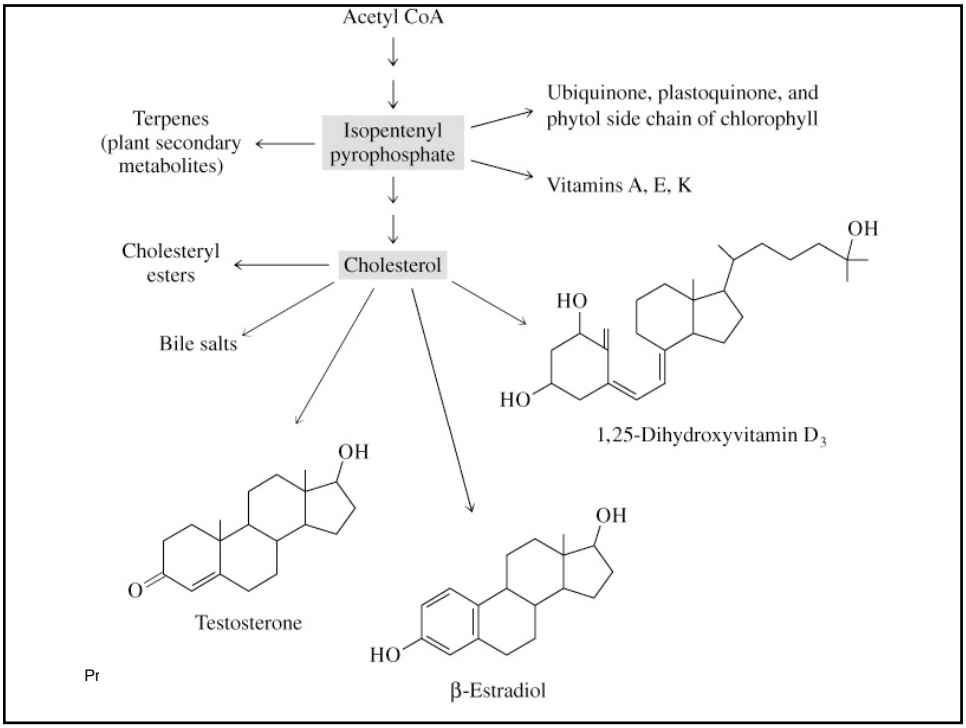
C. Stage 3:

- Squalene to Cholesterol



D. Other Products of Cholesterol Metabolism

- Many isoprenoids are synthesized from cholesterol or its precursors
- Isopentenyl pyrophosphate (C_5) is a precursor of a large number of products
- **Figure 16.33** (next slide) summarizes the products of cholesterol metabolism



16.13 Lipids Are Made at a Variety of Sites

- Most lipid biosynthesis in eukaryotic cells occurs in the endoplasmic reticulum (PC, PE, PI, PS)
- Enzymes of lipid synthesis are membrane-bound with active sites facing the cytosol
- Other lipid synthesis locations include: plasma membrane, mitochondria, lysosomes and peroxisomes