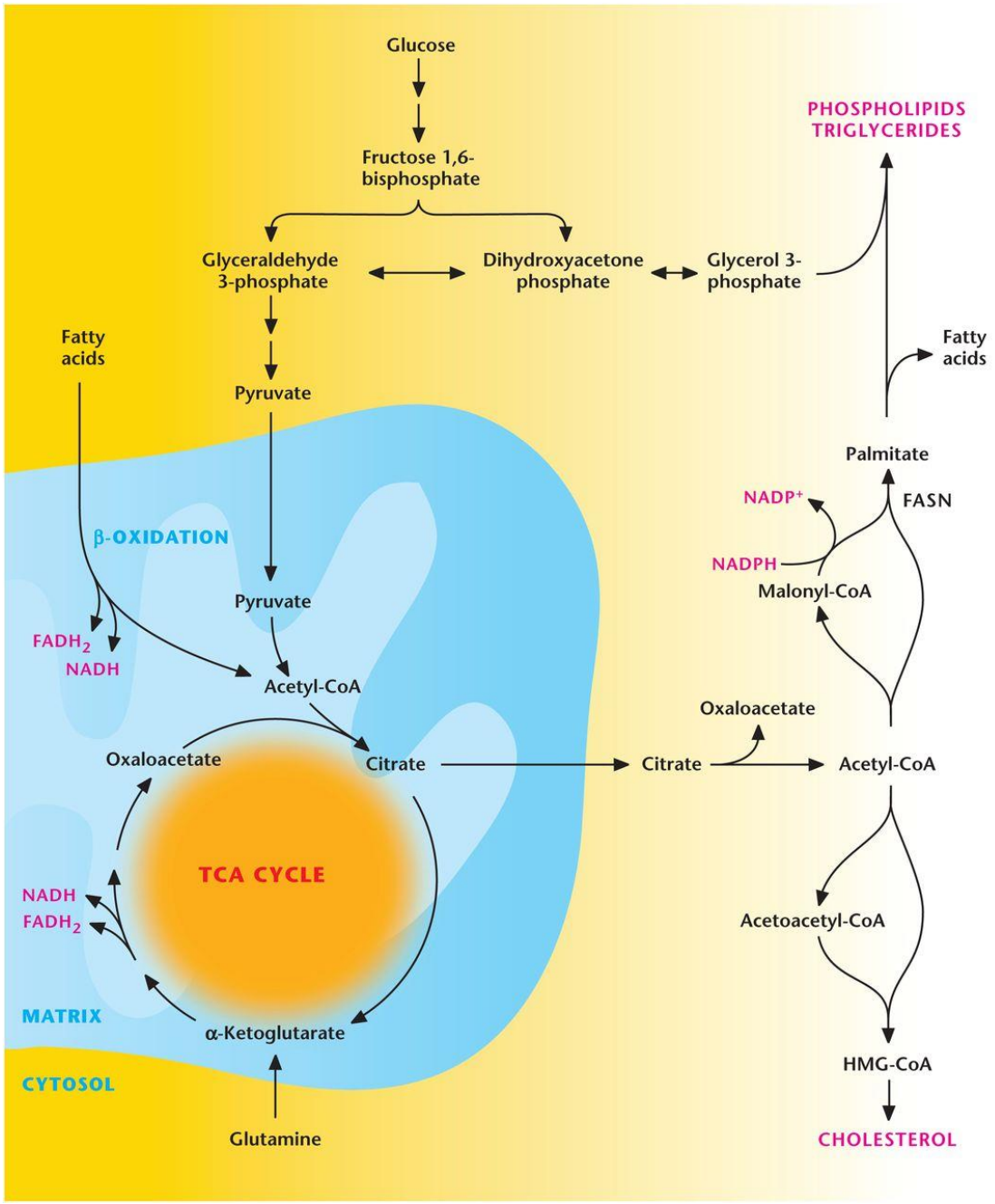
Overview of lipid metabolism



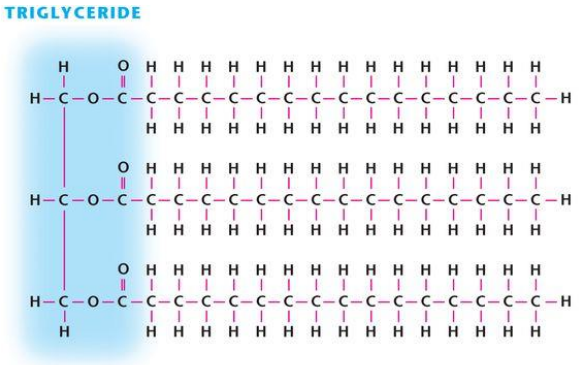
+

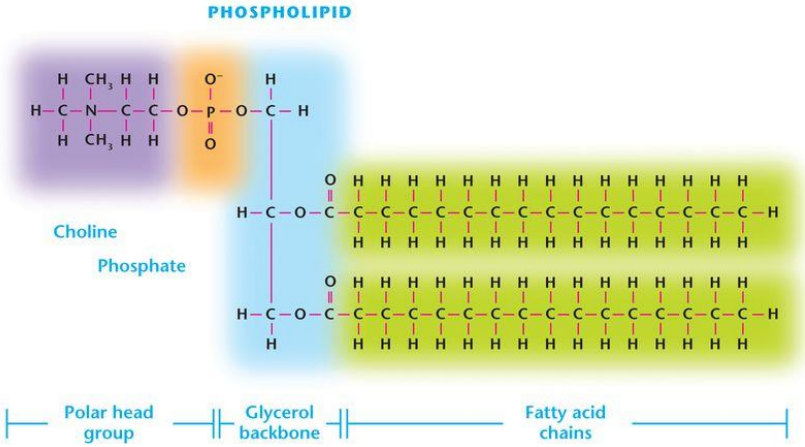
NADPH/NADP+

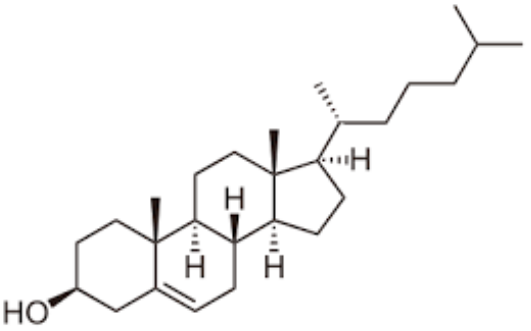
Overview of lipid metabolism lesson

- production of lipids,
- catabolism of lipids to generate ATP, and
- lipids as signaling molecules.

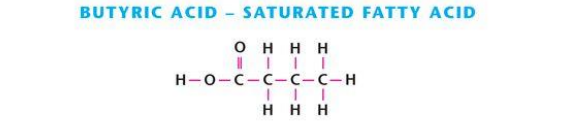
Structures of lipids: recap !

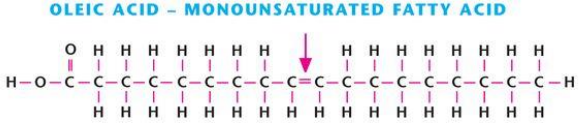


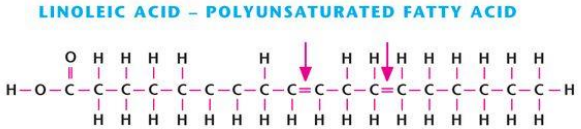




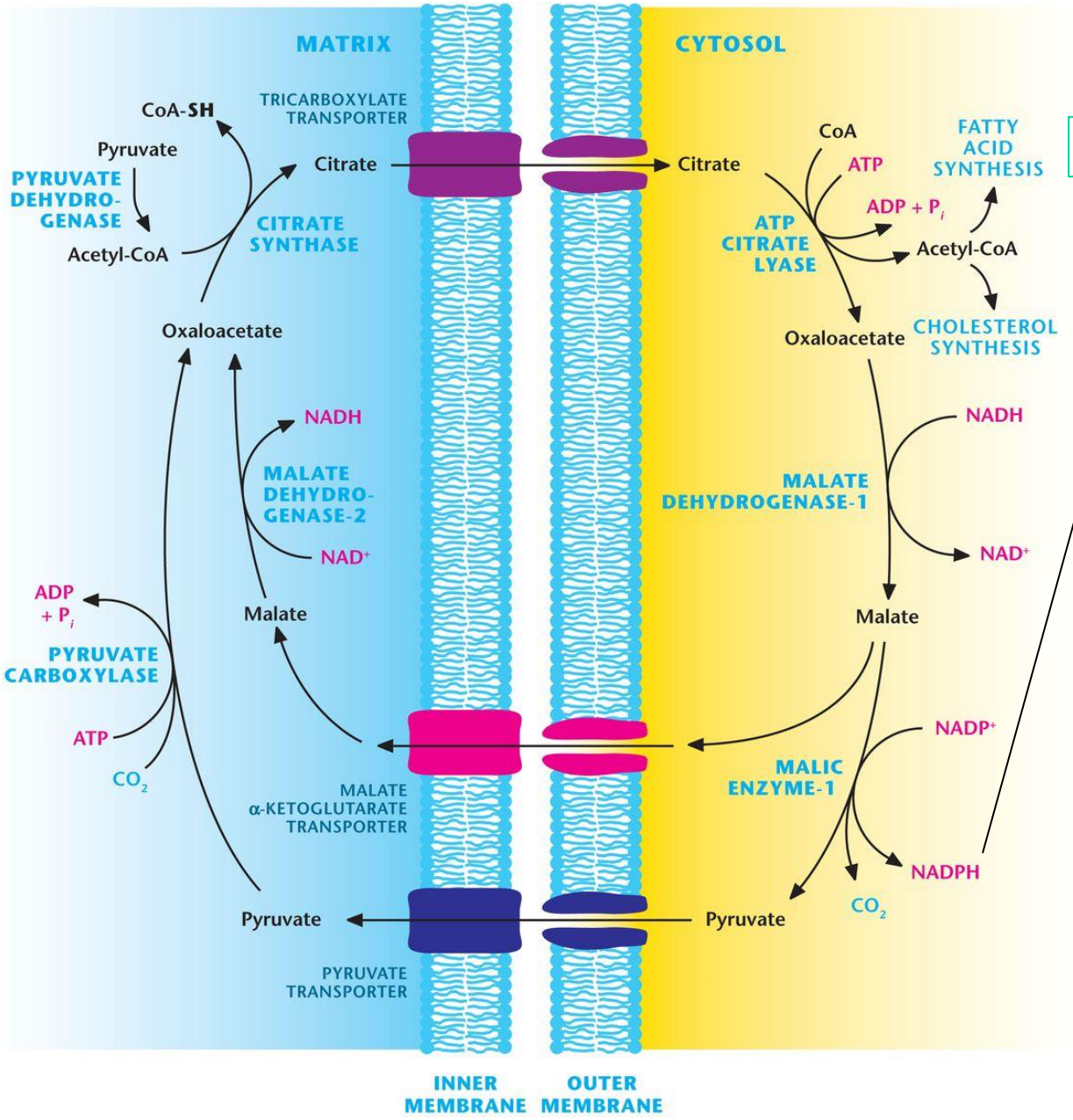
cholesterol







Mitochondrial citrate generates acetyl-CoA for fatty acid synthesis

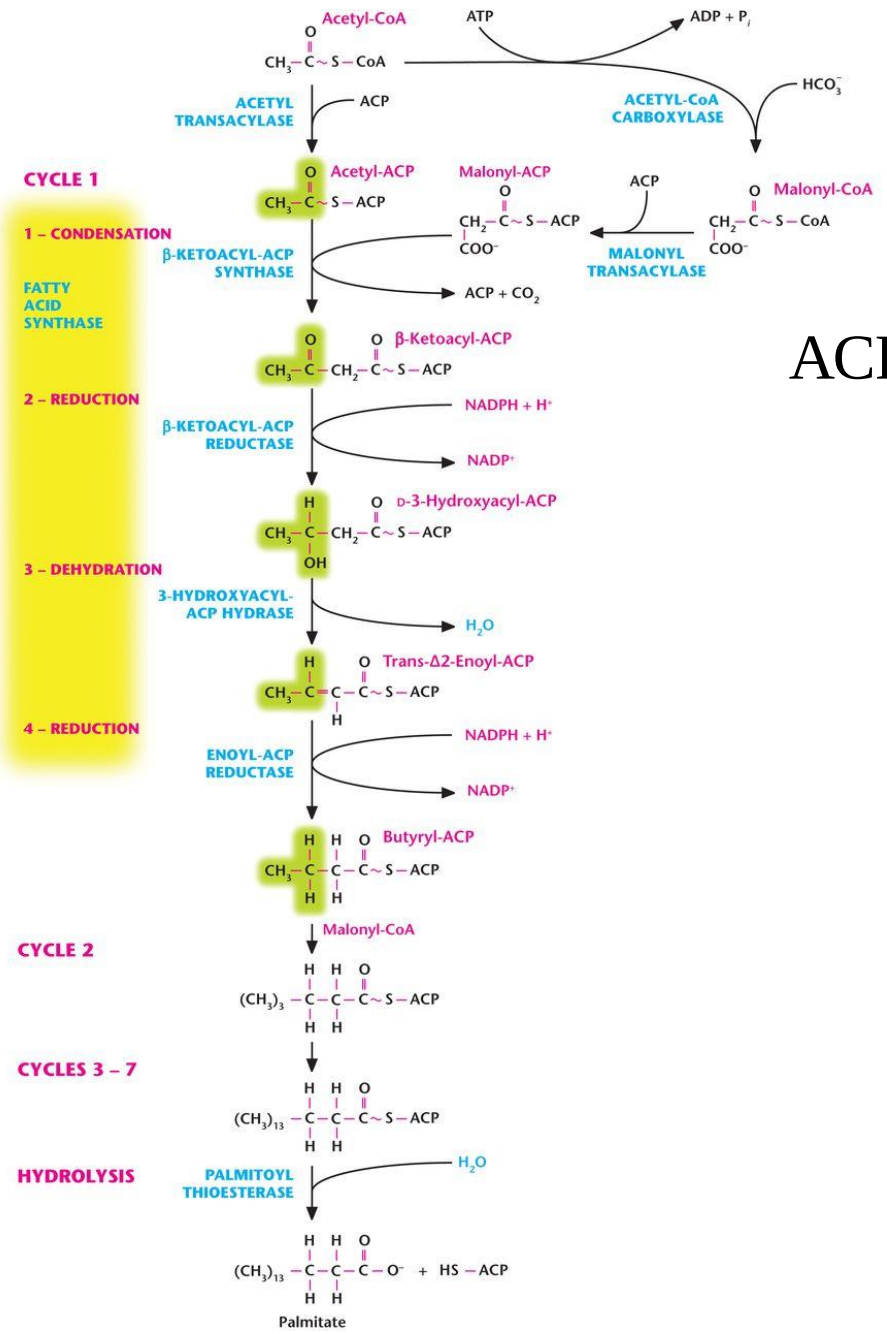


Fatty acid synthesis

NADPH

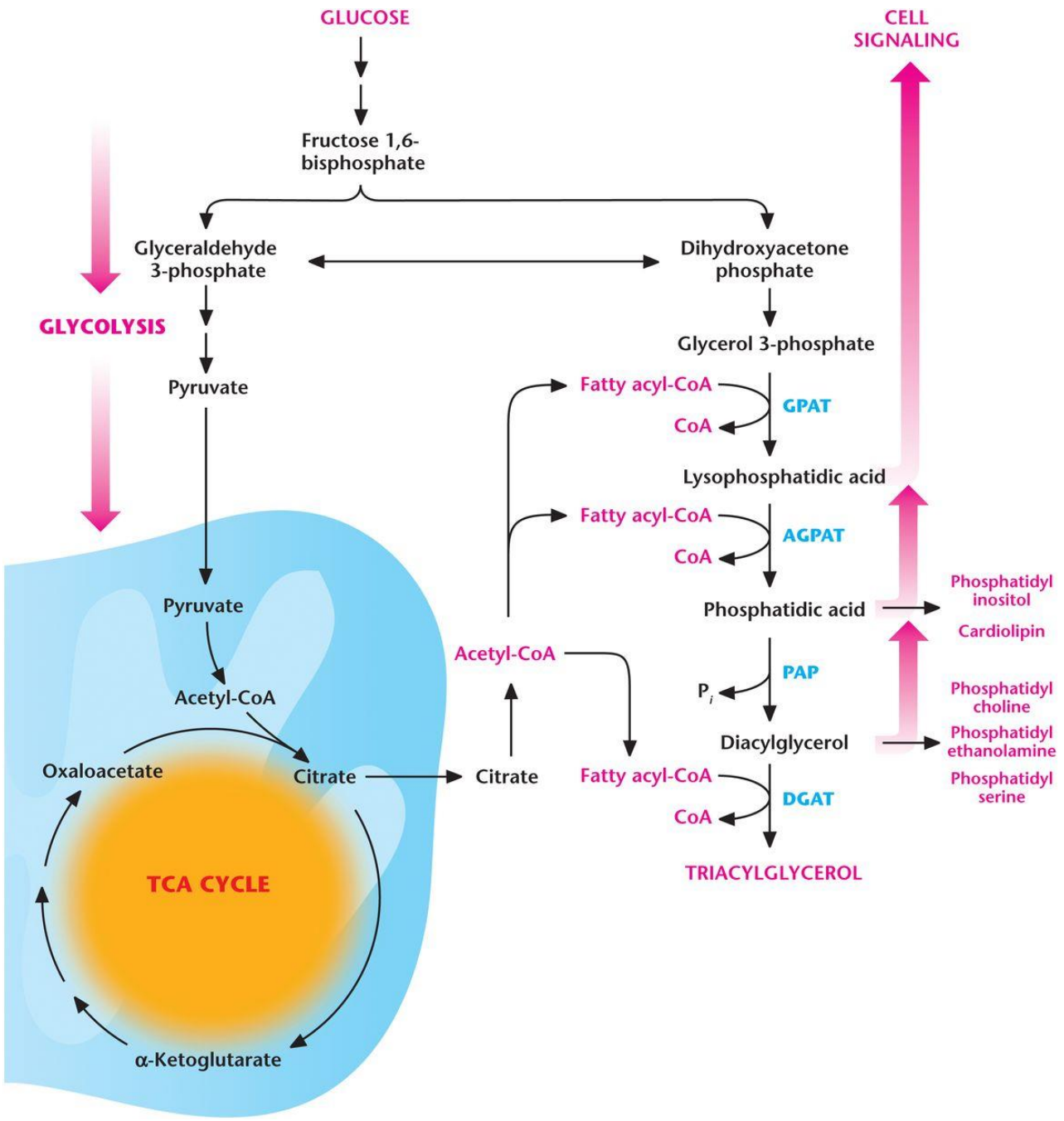
PPP
1C metabolism
IDH

Fatty acid synthesis pathway

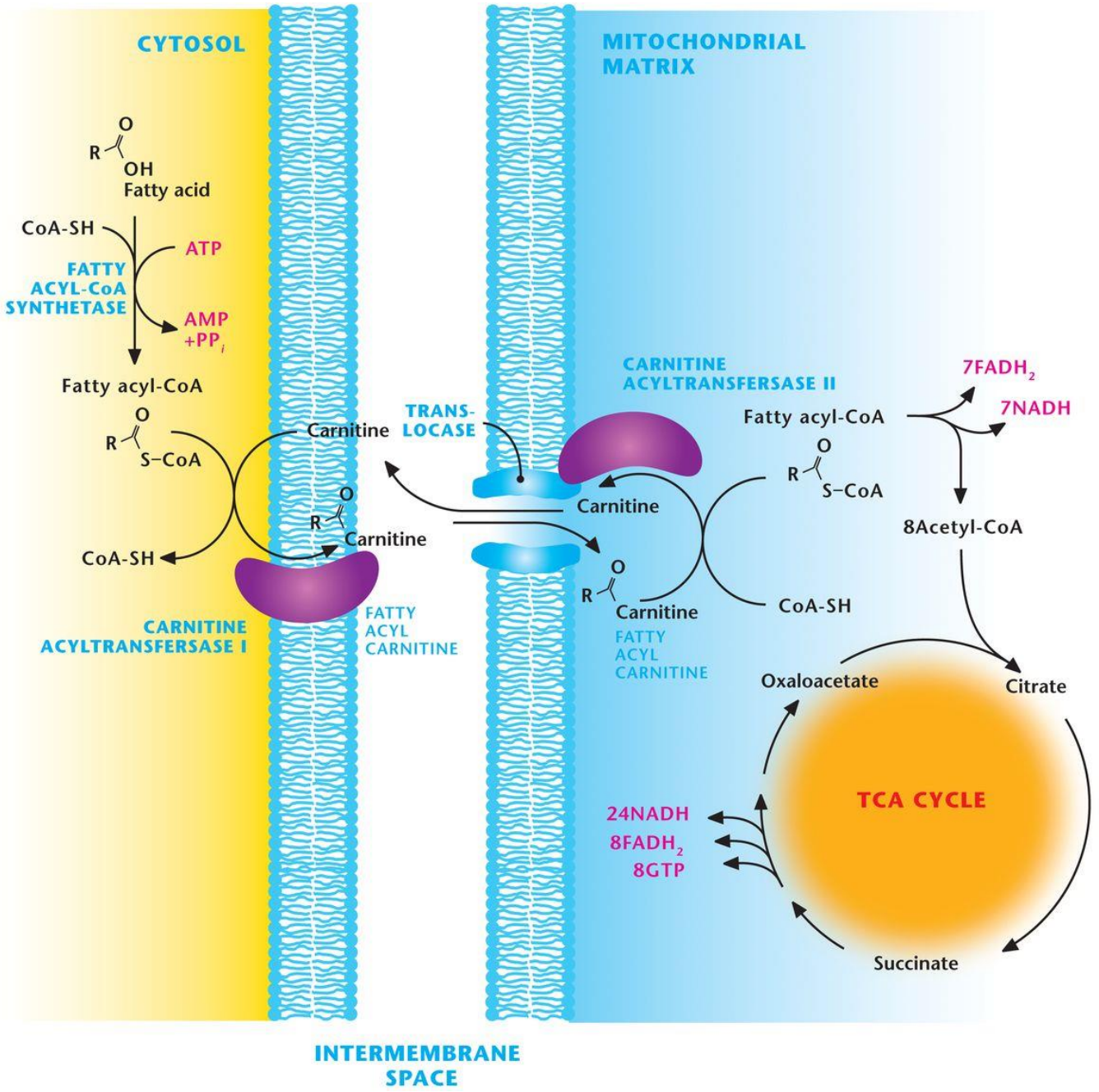


ACP= acetyl carrier protein

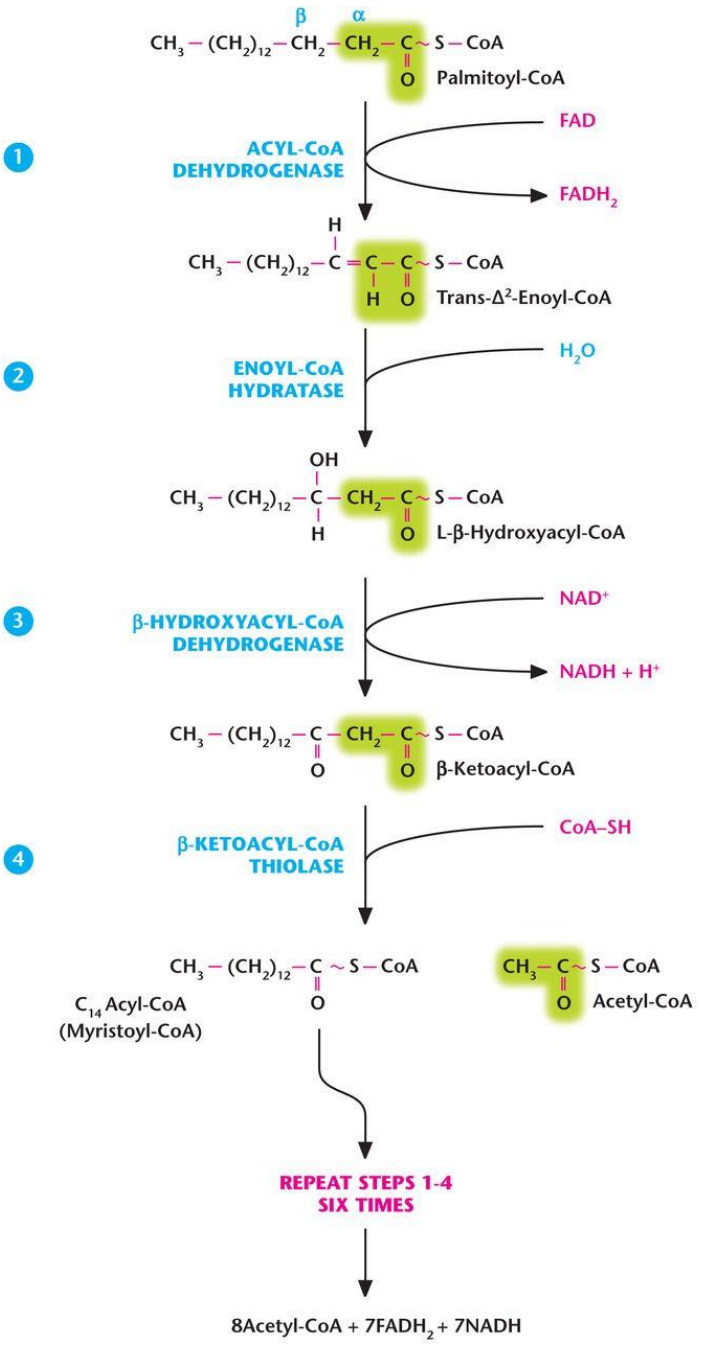
Synthesis of lipids (TAGs)



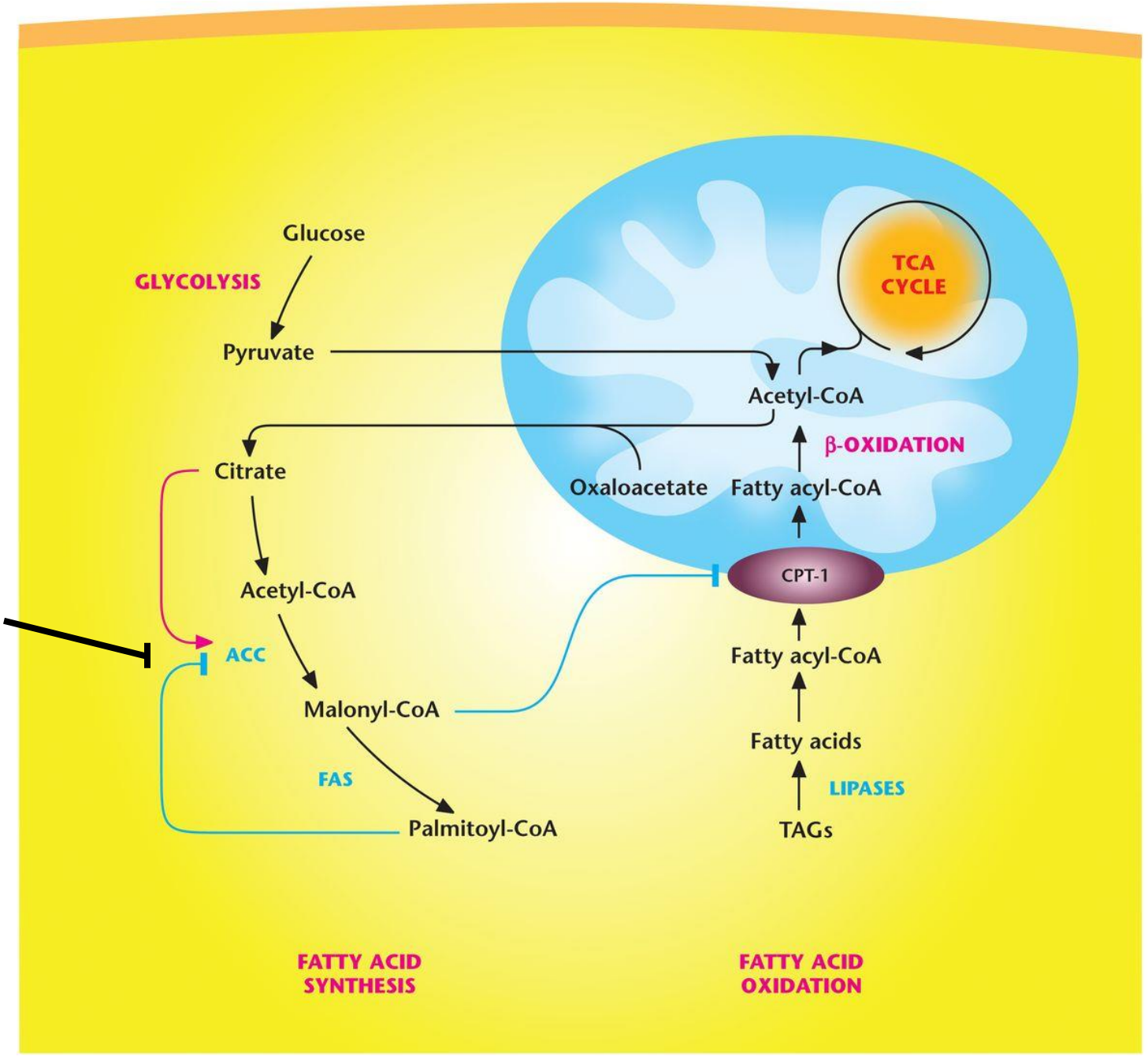
Carnitine shuttle to transport fatty acids into mitochondria



Example of mitochondrial β-oxidation: the palmitoyl-CoA case

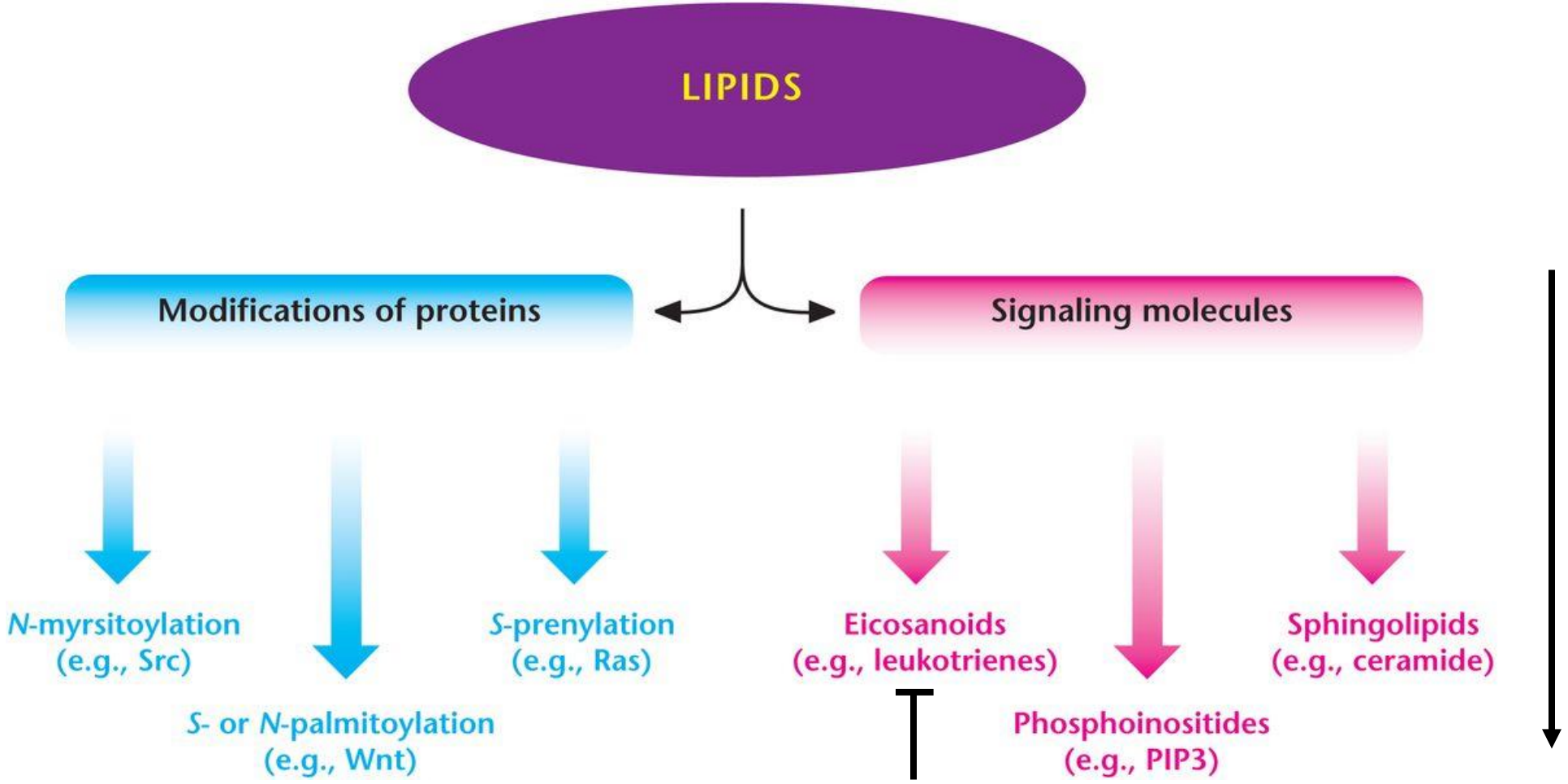


Metabolic regulation of fatty acid synthesis and oxidation



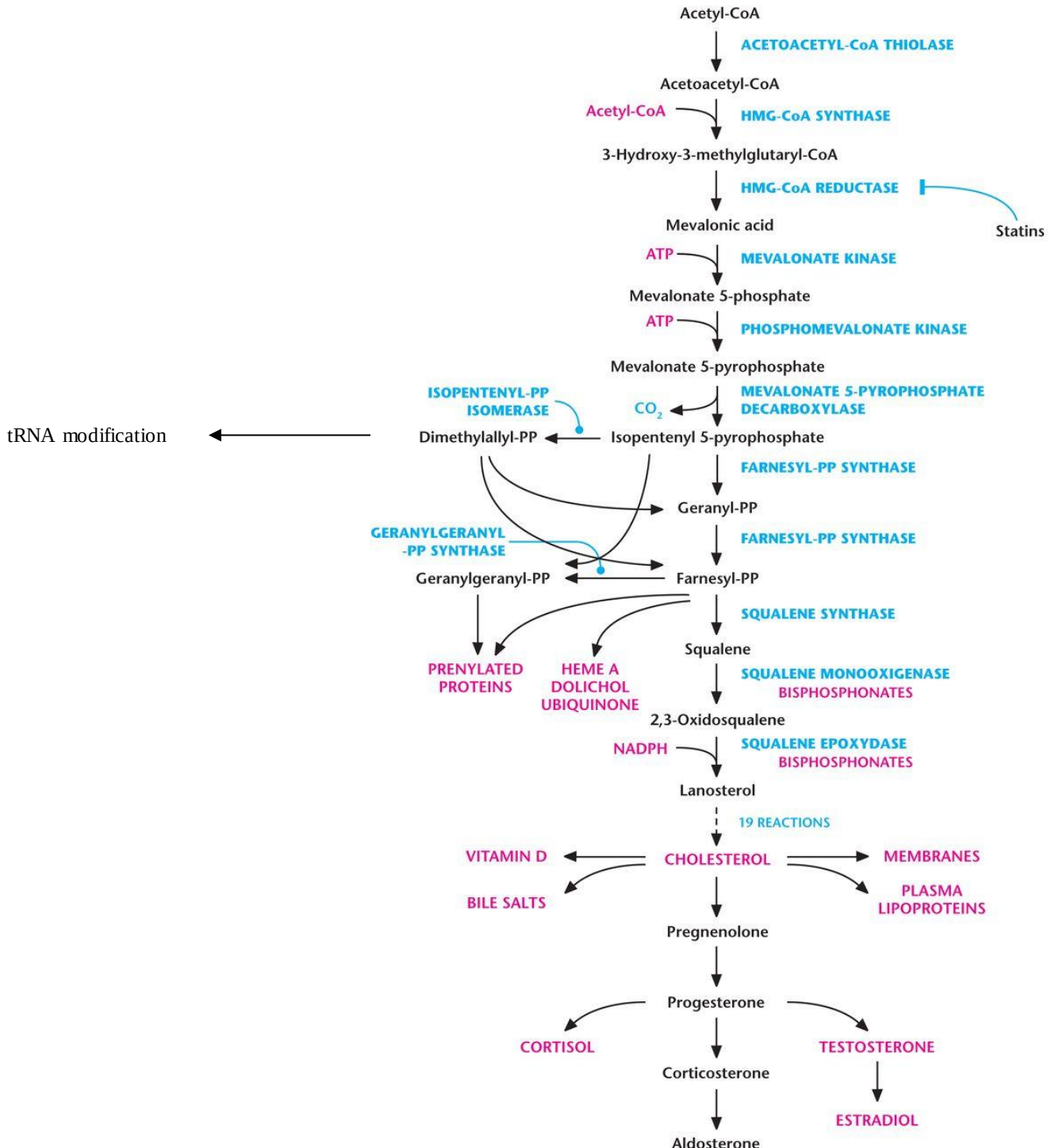
AMPK

Lipids modulate cell signaling and activates biological signals



attachment of lipids to proteins is to allow water-soluble proteins to interact with hydrophobic membranes.

Mevalonate pathway and cholesterol biosynthesis



Fates of body Cholesterol

- Cholesterol **is not an energy producing lipid**.
- Cholesterol in human body is **component of various biomembranes of cells.**
- **Cholesterol helps in nerve impulse conduction**
- Cholesterol is a **precursor for:**

Bile acids

Vitamin D

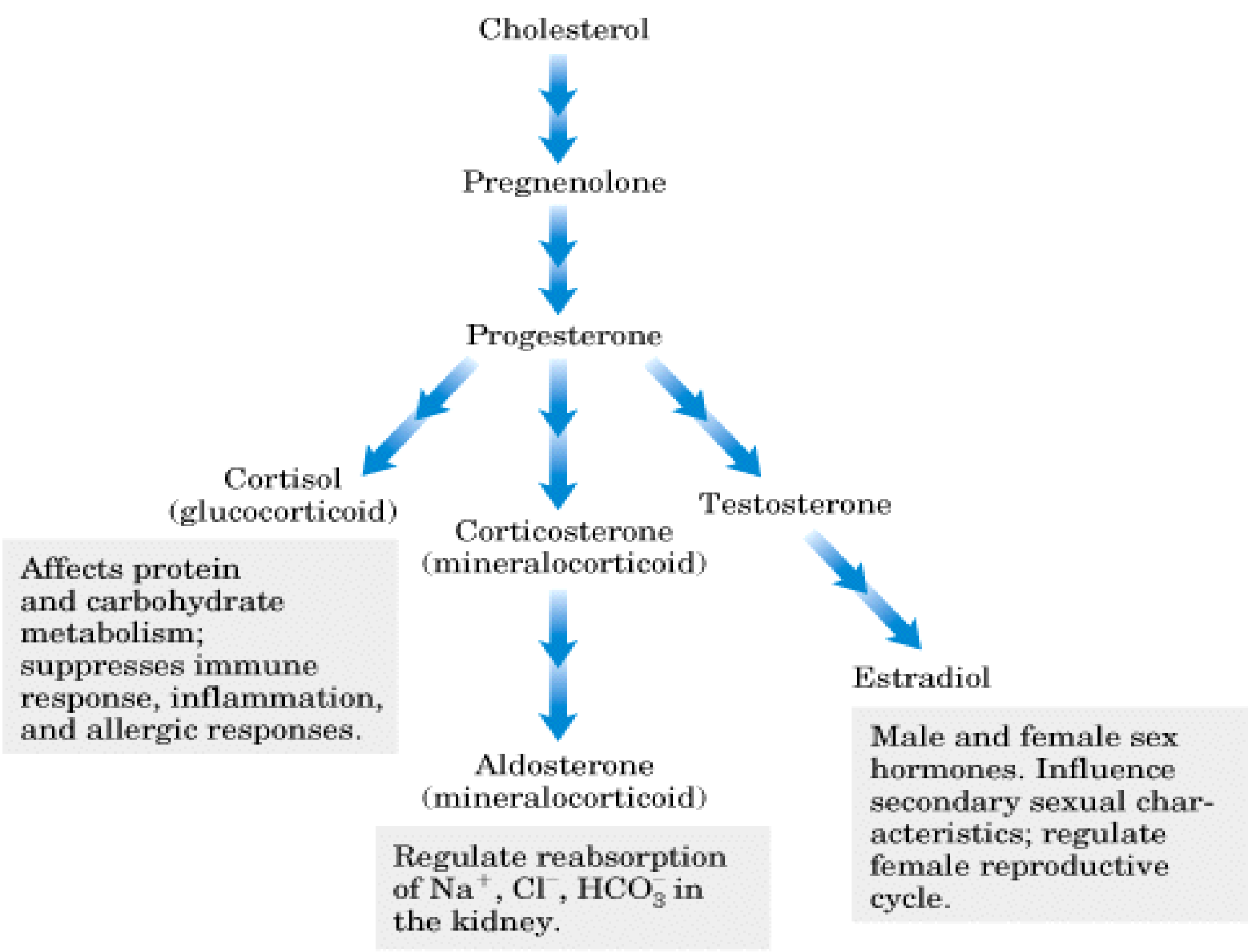
Steroidal Hormones such as:

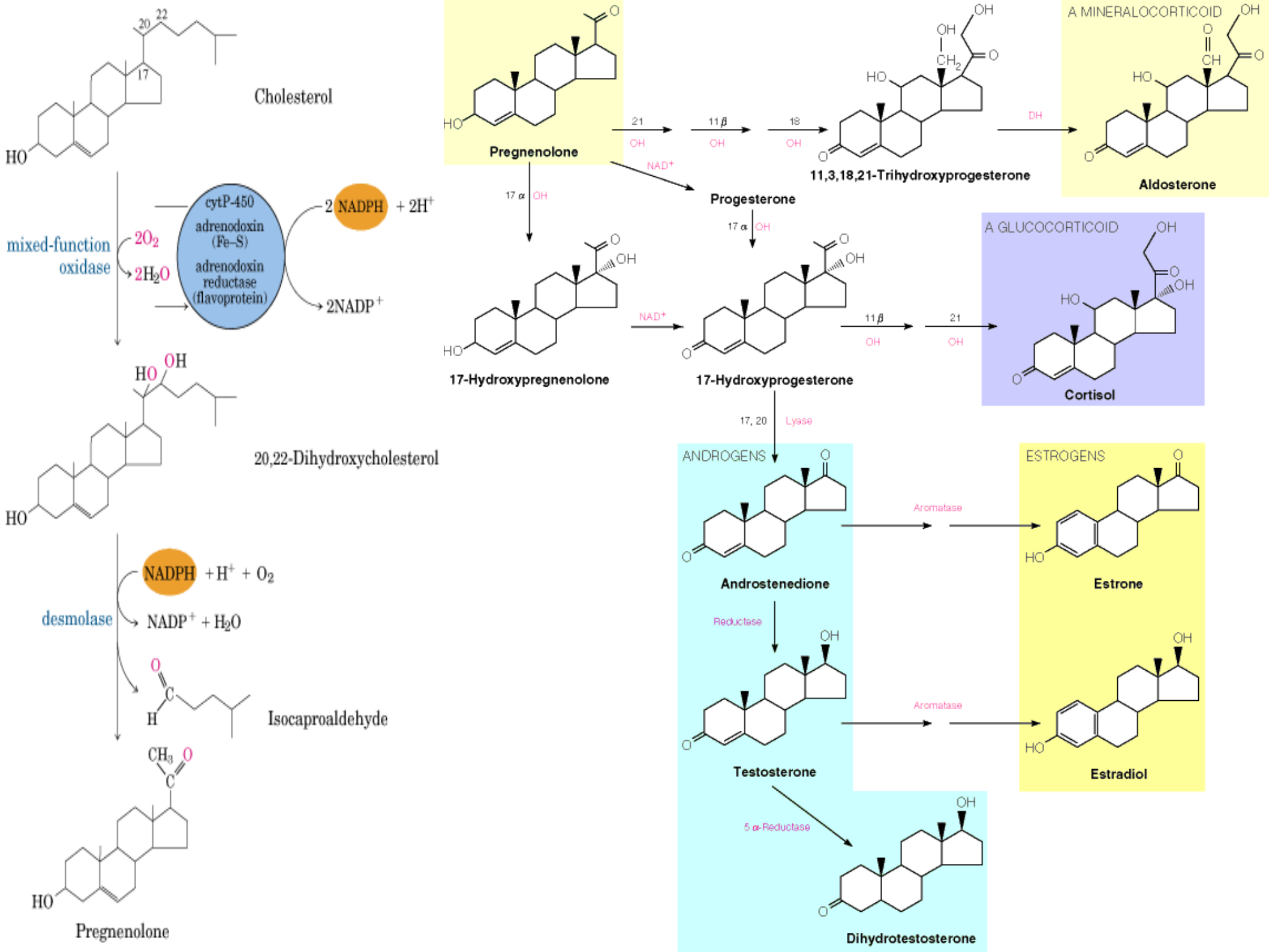
Aldosterone

Estrogen

Progesterone

Testosterone


Cholesterol
Pregnenolone
Progesterone
Cortisol
(glucocorticoid)
Affects protein and carbohydrate metabolism; suppresses immune response, inflammation, and allergic responses.
Corticosterone
(mineralocorticoid)
Aldosterone
(mineralocorticoid)
Regulate reabsorption of Na^+, Cl^-, HCO_3^- in the kidney.
Testosterone
Estradiol
Male and female sex hormones. Influence secondary sexual characteristics; regulate female reproductive cycle.


Cholesterol
mixed-function oxidase
$2O_2$
$2H_2O$
cytP-450
adrenodoxin (Fe–S)
adrenodoxin reductase (flavoprotein)
2 NADPH + $2H^+$
$2NADP^+$
20,22-Dihydroxycholesterol
NADPH $+H^+ + O_2$
desmolase
$NADP^+ + H_2O$
Isocaproaldehyde
Pregnenolone
Pregnenolone
21 OH
11β OH
18 OH
DH
NAD+
11,3,18,21-Trihydroxyprogesterone
A MINERALOCORTICOID
Aldosterone
Progesterone
17α OH
17-Hydroxypregnenolone
NAD+
17α OH
17-Hydroxyprogesterone
11β OH
21 OH
A GLUCOCORTICOID
Cortisol
17, 20 Lyase
ANDROGENS
Androstenedione
Aromatase
ESTROGENS
Estrone
Reductase
Testosterone
Aromatase
Estradiol
5α-Reductase
Dihydrotestosterone

Cholesterol metabolism

1) To identify the structure of cholesterol
2) To outline the synthesis of cholesterol
3) To describe the regulation of cholesterol synthesis
4) To illustrate the role of bile in lipid metabolism

A) Cholesterol – cell membrane, precursor of bile salts and acids, steroid hormones

B) Sources of cholesterol *(Fig. 18.1)*

1) *Influx*

a) diet

b) extrahepatic synthesis

c) hepatic synthesis

2) *Efflux*

a) free cholesterol in bile

b) bile salts/ acids

c) VLDL

C) Influx is not precisely balanced by efflux, leading to coronary artery disease (CAD)

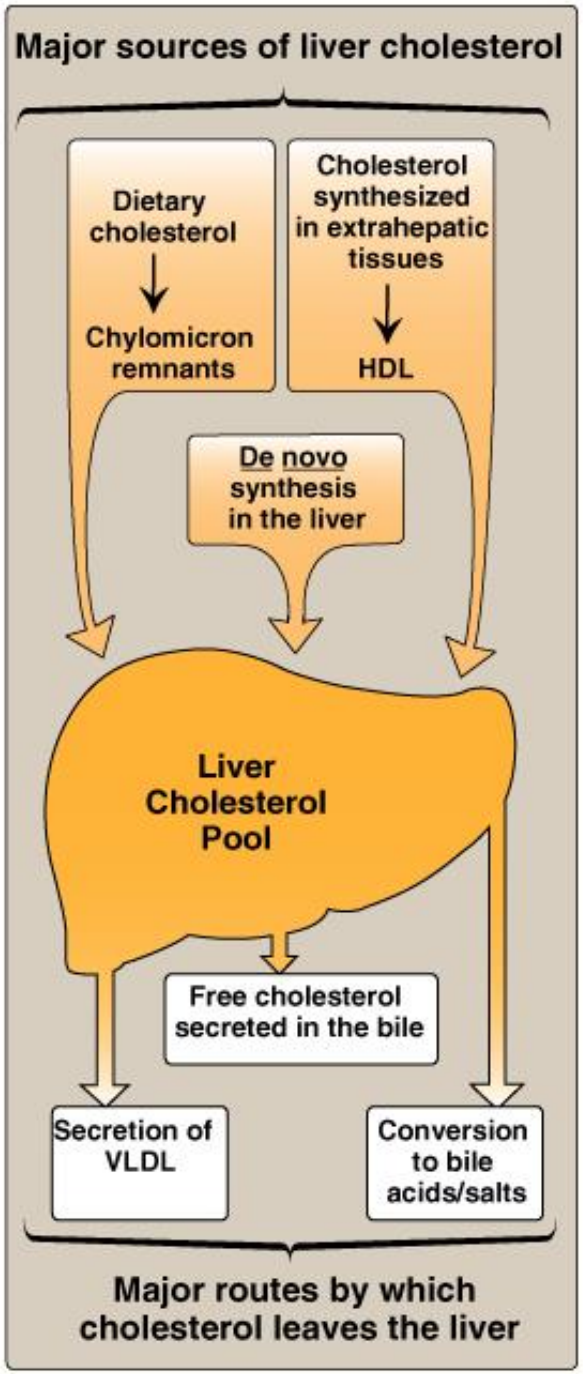


Figure 18.1

Sources of liver cholesterol (influx) and routes by which cholesterol leaves the liver (efflux).

Cholesterol structure

A) General *(Fig. 18.2)*
   1) hydrophobic
   2) has 4 fused rings, A, B, C, D ("steroid nucleus")
   3) 8C, branched hydrocarbon chain attached at C-17 on D ring
   4) ring A has a C-3 hydroxyl group
   5) Ring B has double bound between C-5 and C-6

B) Sterols
   1) steroids with 8-10 carbons at C-17
   2) hydroxyl group at C-3

C) Cholesteryl esters
   1) fatty acid esterified and C-3
   2) more hydrophobic than free cholesterol
   3) not found in membranes
   4) most abundant form in plasma
   5) most be transported in lipoprotein particle in blood

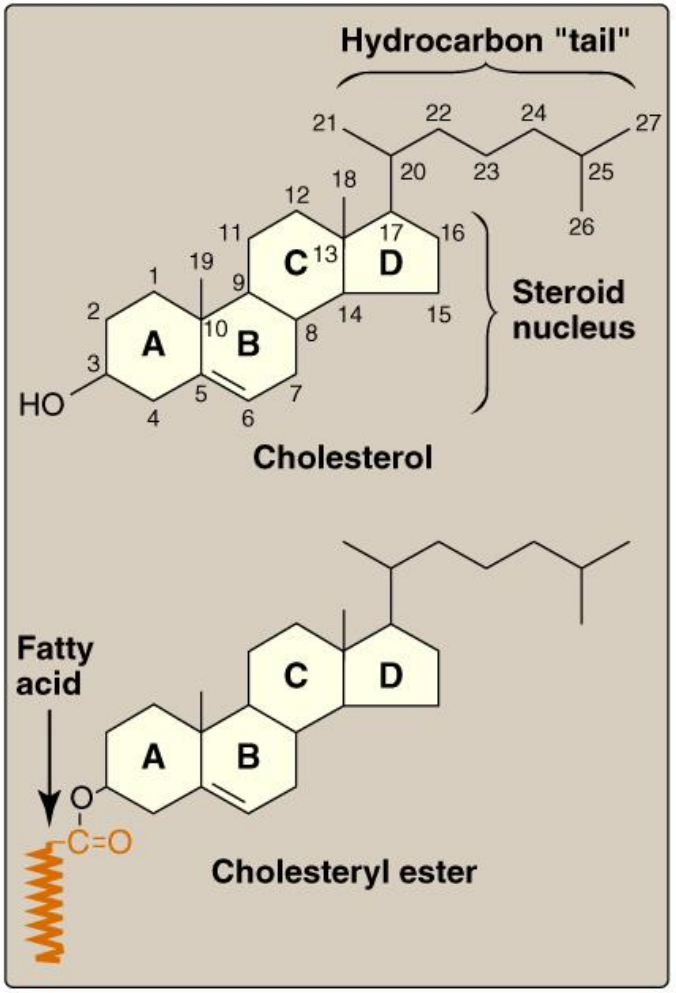


Figure 18.2
Structure of cholesterol.

Cholesterol synthesis

A) Occurs in virtually all tissues
B) Highest in liver, intestine, adrenal cortex, and reproductive tissues
C) Basic building block is acetate
D) Reductant is NADPH
E) Driven by hydrolysis of thioester bond of acetyl CoA and of terminal phosphate of ATP
F) Enzymes are in cytoplasm and ER
G) Regulated by cholesterol levels
H) Synthesis of HMG CoA *(Fig. 18.3)*
   1) first 2 reactions – similar to those seen in ketone body synthesis
   2) the *HMG-CoA synthase* is <u>cytosolic</u>

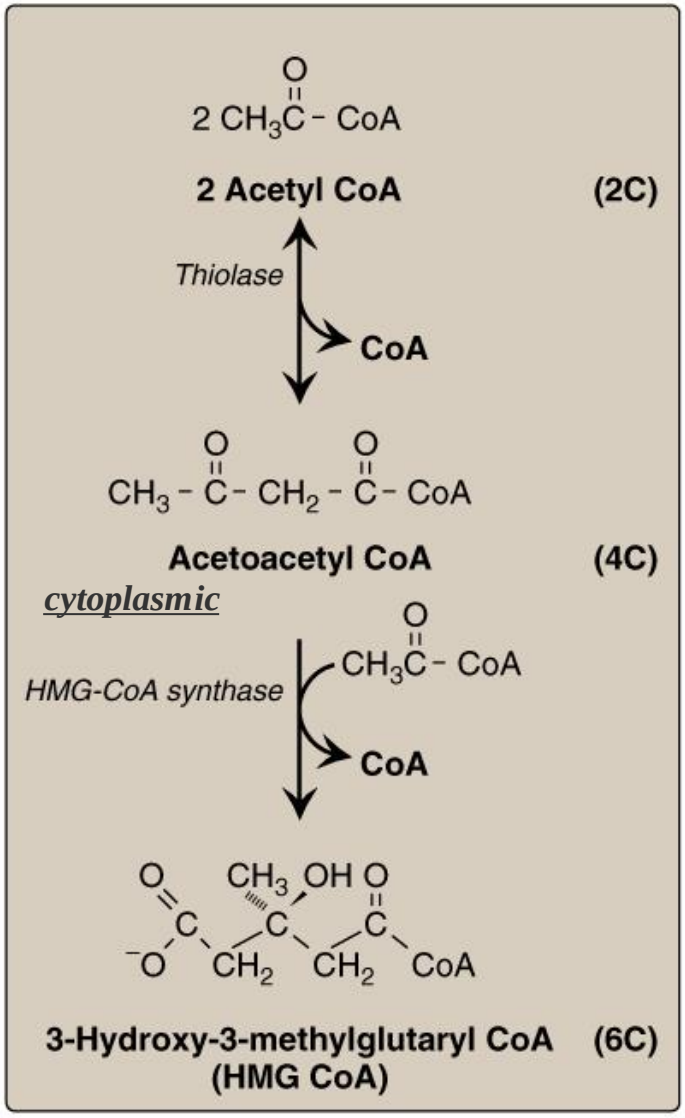


Figure 18.3
Synthesis of 3-hydroxy-3-methylglutaryl CoA (HMG CoA).

I) Committed, rate-limited step is catalyzed by *HMG CoA reductase*
   1) HMG CoA converted to mevalonic acid
   2) CoA released
   3) NADPH used for the biosynthetic reductant
   4) enzyme is highly regulated
   5) ER-associated enzyme facing the cytoplasm
   6) the target of statin drugs

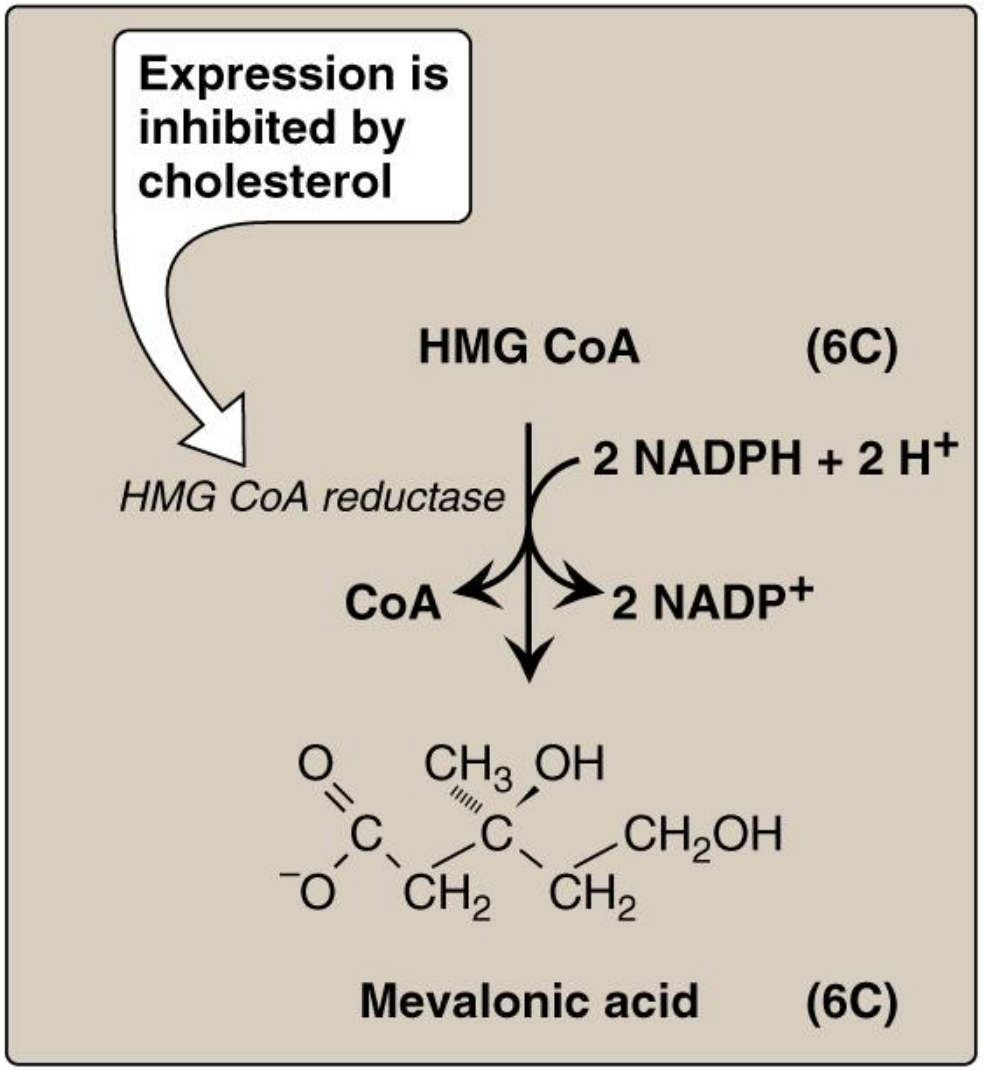


Figure 18.4
Synthesis of mevalonic acid.

J) Mevalonate is phosphorylated twice using ATP to yield 5-pyrophosphomevalonate

K) Decarboxylation (ATP-dependent) results in 5C isopentenyl pyrophosphate (IPP)

L) Isomerization of IPP results in 3,3 dimethylallyl pyrophosphate (DPP)

M) DPP + IPP yields geranyl pyrophosphate (GPP). Released PPi is hydrolyzed to 2 Pi by ubiquitous pyrophosphatase

N) GPP + IPP yields farnesyl pyrophosphate (FPP)

O) FPP + FPP, followed by reduction by NADPH yields squalene

P) series of oxidation and reduction reactions yield lanosterol

Q) multistep, complicated reactions convert lanosterol to cholesterol

R) note the use of 5C building blocks

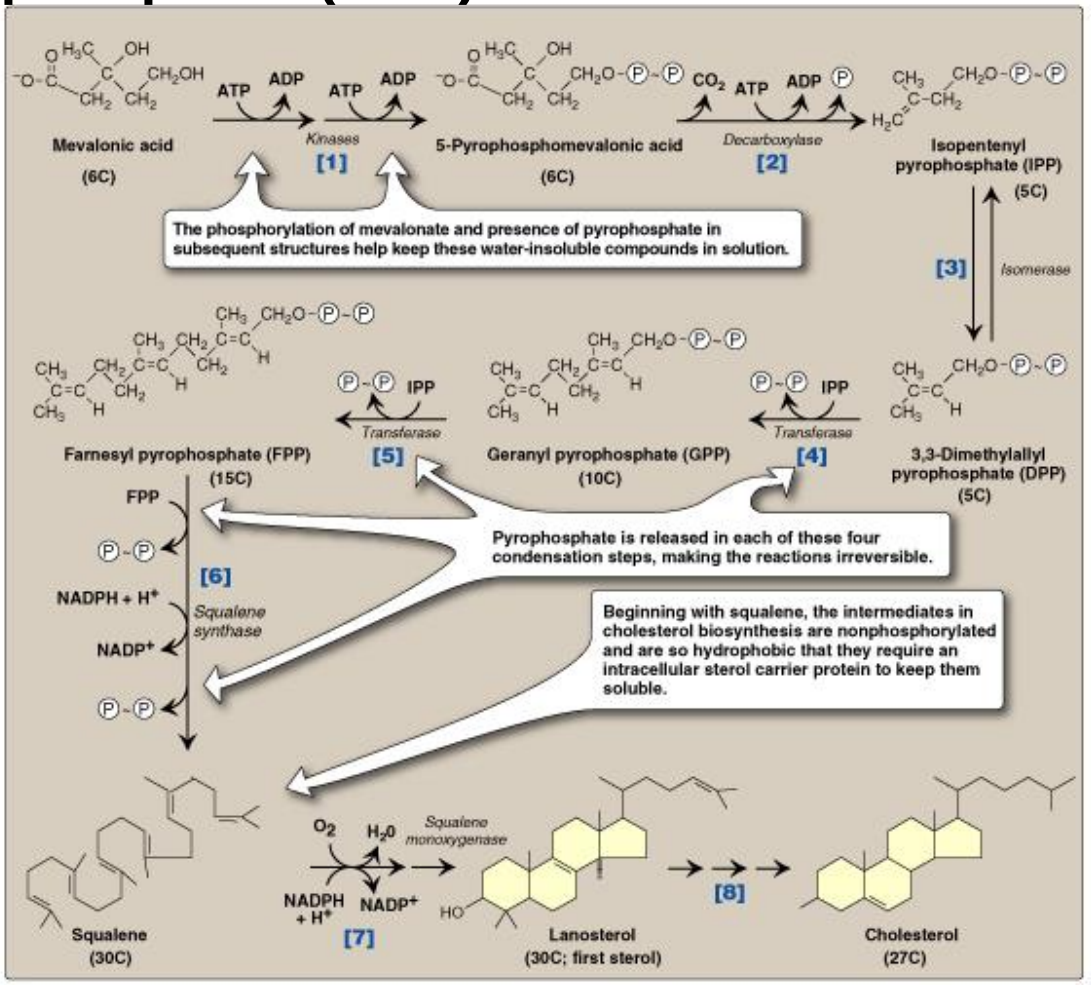


Figure 18.5
Synthesis of cholesterol from mevalonic acid.

Regulation of cholesterol synthesis

A) Major regulatory point is *HMG CoA reductase (Fig. 18.6)*
B) Expression of the *HMG CoA reductase* gene is stimulated by sterol-regulatory element binding protein, SREBP, binding to SRE in the promoter – high cholesterol blocks SREBP cleavage from the ER. SREBP stays in the cytoplasm and *HMG CoA reductase* gene transcription is reduced (negative feedback)
C) Sterol-independent phosphorylation/dephosphorylation – Phospho form is inactive. High AMP (low ATP levels) – low cholesterol synthesis. Dephospho form (high ATP) is active.
D) High insulin levels – the expression of the *HMG CoA reductase* gene is increased. Glucagon lowers transcription of the *HMG CoA reductase* gene.

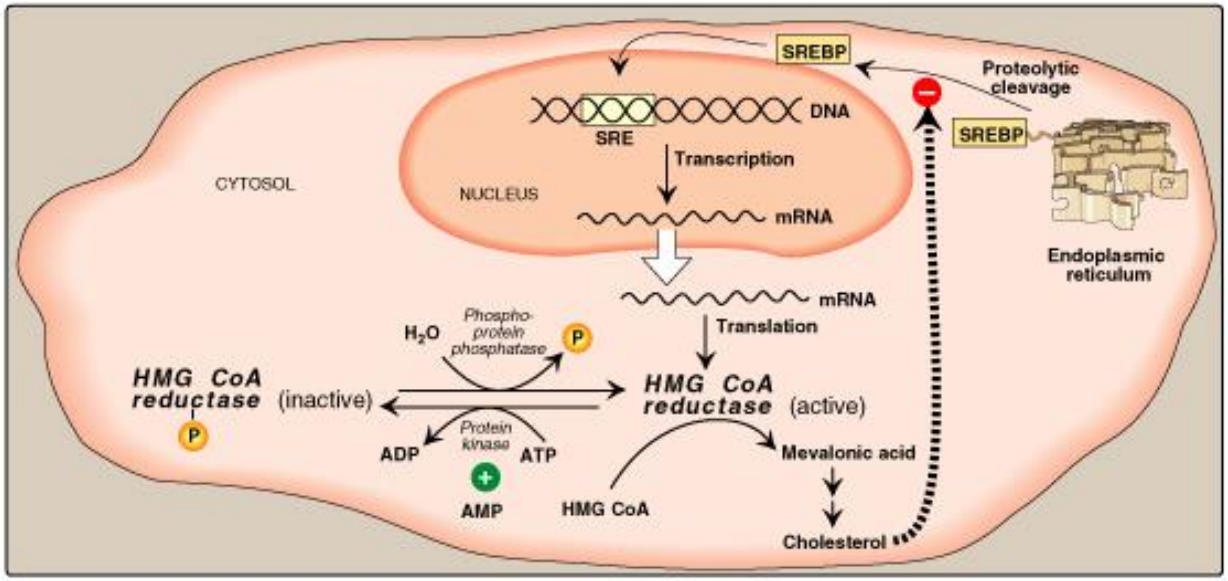


Figure 18.6

Regulation of *HMG CoA reductase*. SRE = sterol regulatory element; SREBP = sterol regulatory element-binding protein.

F) Statin drugs are, reversible, competitive inhibitors of *HMG CoA reductase (Fig. 18.7)*

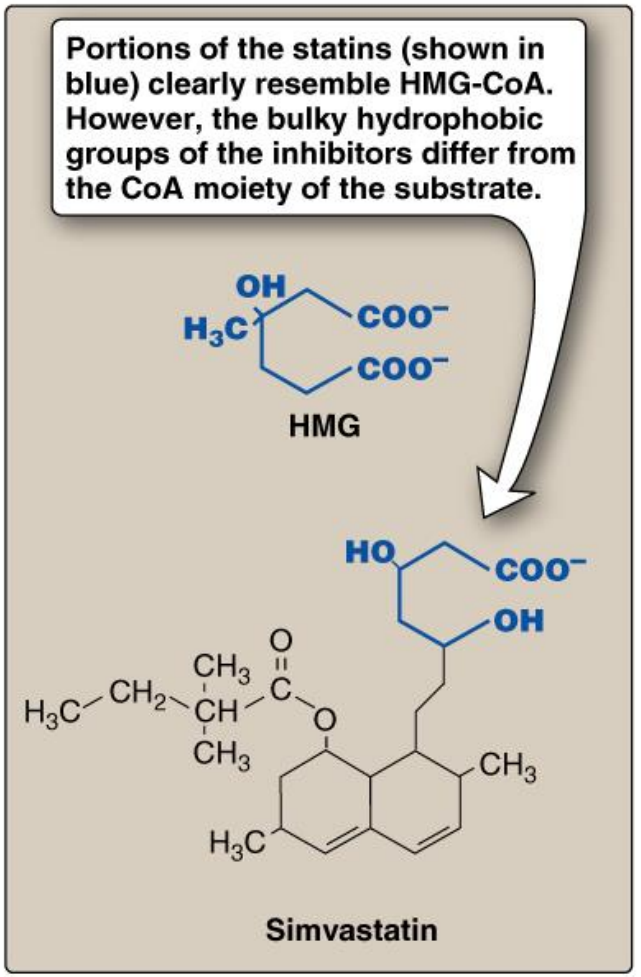


Figure 18.7
Structural similarity of HMG and simvastatin, a clinically useful cholesterol-lowering drug of the "statin" family.

Competitive inhibitors of cholesterol biosynthesis

- **Drugs like Statins- Lovastatin ,Simvastatin**
- **Competitive inhibitors** of key Enzyme **HMG CoA Reductase** of Cholesterol biosynthesis.
- **Decreases Endogenous Cholesterol Biosynthesis**

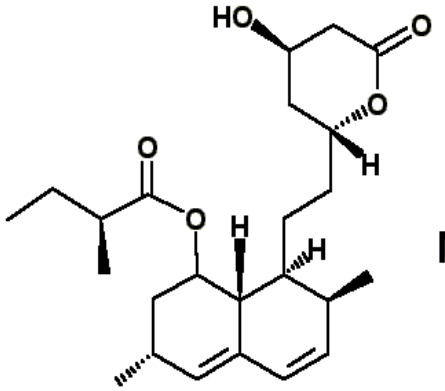
Lovastatin Inhibits Cholesterol Biosynthesis

- **Lovastatin (Mevinolin) blocks HMG-CoA Reductase activity and prevents biosynthesis of Cholesterol.**
- **Lovastatin is an (inactive) Lactone**
- **In body, Lactone is hydrolyzed to Mevanolinic acid, which is a competitive inhibitor of HMG CoA reductase.**

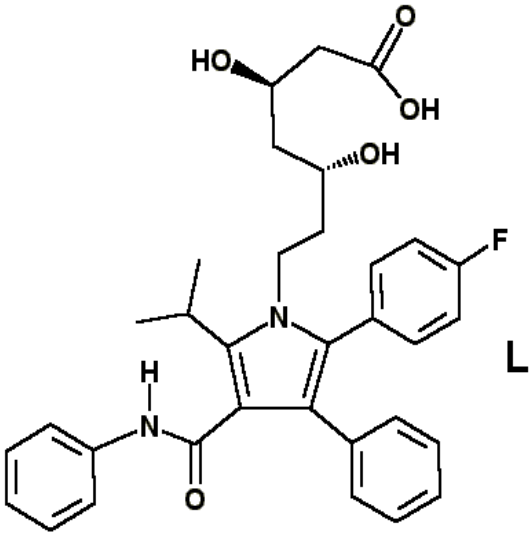
Drugs Lowering Cholesterol

- **Statins** – decrease HMG CoA Reductase activity

Statins



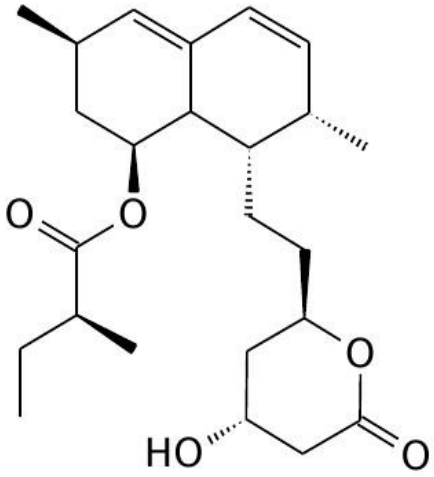
Mevacor (lovastatin)



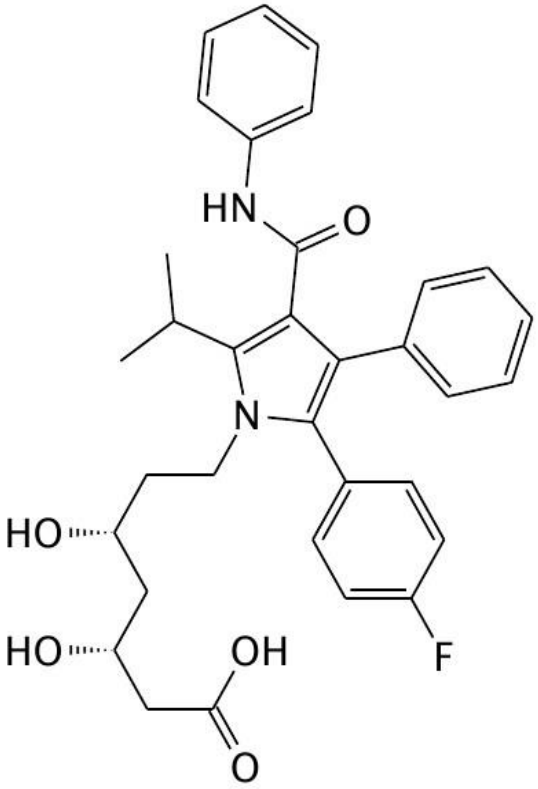
Lipitor

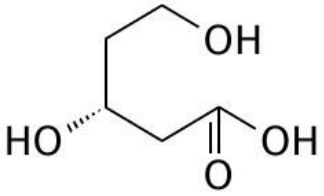
“Statins” Competitively Inhibit HMG-CoA Reductase

Mevastatin

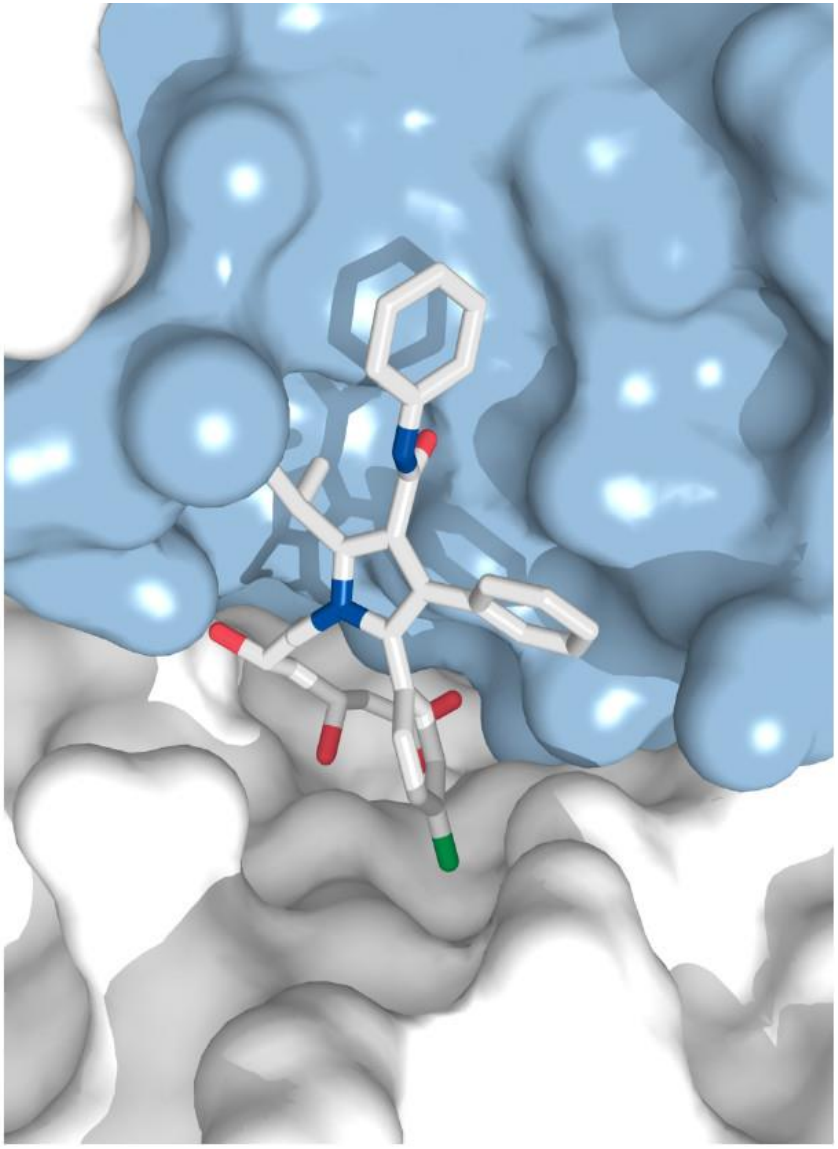


Atorvastatin





Mevalonate



Effects Of "Statins"
(HMG-CoA Reductase Inhibitors)

- **Action: Competitively inhibits HMG-CoA Reductase, key enzyme for *de novo* cholesterol biosynthesis.**

- **Effects Of Statins in Human body:**
- **Cells express more LDL receptors**
- **Decreases serum LDL levels**
- **Increased HDL levels**
- **Increased HDL/LDL ratio**
- **Suppresses production of VLDL in Liver**

- **Advantages: Specific; Effective; Well-tolerated.**

- **Disadvantages: Hepatotoxicity; myopathy; most expensive; contradicted in pregnant and nursing women.**

Degradation of cholesterol
conversion to bile acids and salts

BILE ACIDS AND SALTS

A) Structure of bile acids (*Fig. 18.8*)

1) 24 carbon atoms

2) 2 or 3 hydroxyl groups

3) side chain ends with a carboxyl group

4) pK_a of carboxyl is 6.0

5) amphipathic (hydroxyl groups in β configuration, above the rings and methyl groups are in the α configuration, below the rings) – this is why they act as emulsifying agents

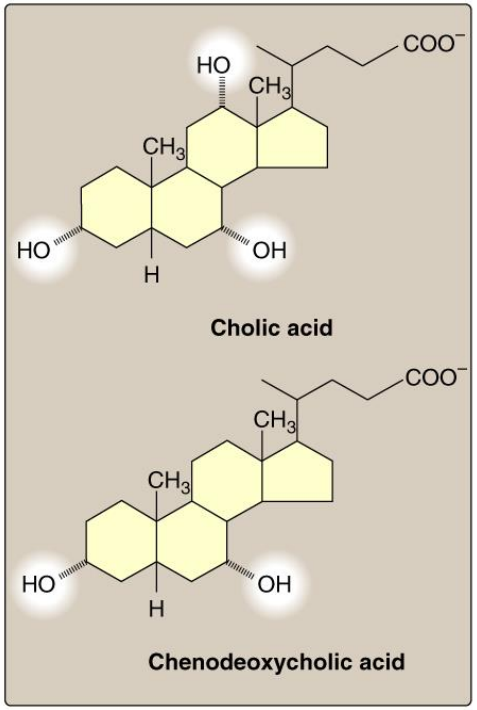


Figure 18.8
Bile acids.

B) Synthesis of bile acids *(Fig. 18.9)*

1) liver, multistep process starting with cholesterol
2) hydroxyl groups inserted, double bond in B ring reduced, hydrocarbon chain shortened by three carbons, carboxyl group added to end of chain
3) rate-limiting committed step catalyzed by *cholesterol 7-α hydroxylase* (feedback inhibited by cholic acid, stimulated by cholesterol)
4) most common products are "primary" bile acids – cholic acid and chenodeoxycholic acid (*Fig. 18.8*)

C) Synthesis of bile salts (*Fig. 18.10*) – conjugation of glycine or taurine on bile acids. Most common are glycocholic and glycochenodeoxycholic acids, and taurocholic and taurochenodeoxycholic acids. Bile salts are more acidic (lower pK_a) and better emulsifiers.

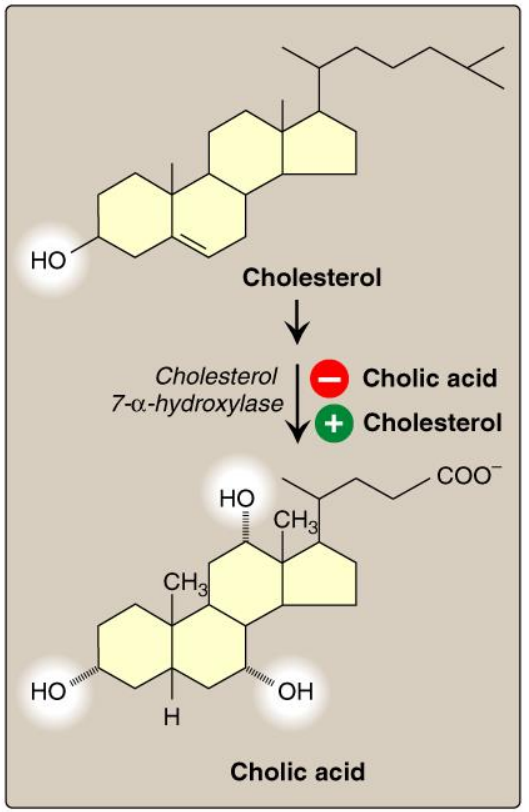


Figure 18.9
Synthesis of cholic acid.

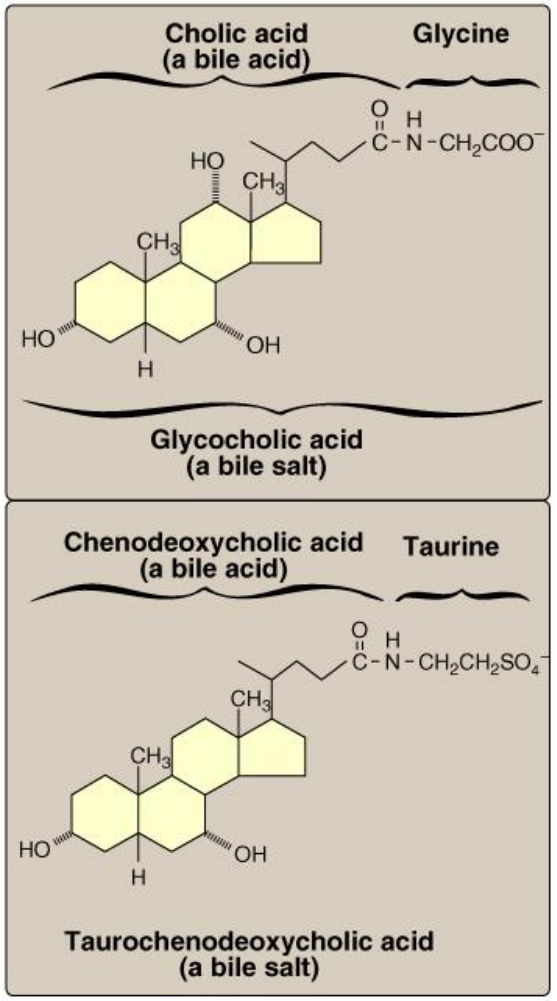


Figure 18.10
Bile salts.

D) Bacterial flora in the gut can remove glycine and taurine and regenerate bile acids. They can also convert some of the "primary" bile acids to "secondary" bile acids by removing a hydroxyl group to produce deoxycholic acid and lithocholic acid.

E) Cholesterol levels can be lowered by increasing the excretion of bile acids and salts. Cholestyramine and dietary fiber bind bile acids and salts and stimulate their excretion. This draws the biosynthetic pathway forward and lowers the serum level of the precursor, cholesterol. This helps lower the risk of coronary artery disease.

Take home message

• Lipids, such as triacylglycerol (TAG) and phospholipids, are generated from glucose-derived glycerol and mitochondrial-derived fatty acids (Fig. 1).
• Fatty acid synthesis takes place in the cytosol, where mitochondrial citrate serves as the precursor to eventually generate palmitate, which can be modified to other fatty acids.
• Fatty acid β-oxidation occurs in the mitochondrial matrix. Fatty acids are transported into the matrix through carnitine acyltransferase I (CPTI) located in the outer mitochondrial membrane, along with carnitine acyltransferase II (CPTII) and carnitine-acylcarnitine translocase, located in the inner mitochondrial membrane.
• Fatty acid synthesis is coupled to NADPH → NADP+, whereas fatty acid oxidation generates acetyl-CoA, NADH, and FADH2 to produce ATP through oxidative phosphorylation.
• Fatty acid synthesis is regulated by acetyl-CoA carboxylase (ACC), which is activated by citrate and inhibited by the fatty acid palmitate.
• Fatty acid β-oxidation is regulated by malonyl-CoA, which inhibits carnitine acyltransferase (CPTI) activity, thereby preventing fat-ty acid import into the mitochondrial matrix for β-oxidation.
• Lipids can modify proteins to alter their function. Notable modifications are N-myristoylation, S- or N-palmitoylation, and S-prenylation.
• Lipids, such as eicosanoids, phosphoinositides, and sphingolipids, serve as signaling molecules.
• The cholesterol biosynthetic pathway initiates in the cytosol and is controlled by the enzyme3-hydroxy-3-methylglutaryl CoA reductase(HMG-CoA reductase), the target of statins(class of cholesterol-lowering drugs).