Lippincott's Illustrated Reviews:

Pharmacology

You will have learned within, those are

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Chapter 21

Hyperlipidemias

I. Overview

Coronary heart disease (CHD) is the cause of about half of all deaths in the United States. The incidence of CHD is correlated with elevated levels of low-density lipoprotein (LDL) cholesterol and triacylglycerols and with low levels of high-density lipoprotein (HDL) cholesterol. Other risk factors for CHD include cigarette smoking, hypertension, obesity, and diabetes. Cholesterol levels may be elevated as a result of an individual's lifestyle (for example, by lack of exercise and consumption of a diet containing excess saturated fatty acids). Hyperlipidemias can also result from a single inherited gene defect in lipoprotein metabolism or, more commonly, from a combination of genetic and lifestyle factors. Appropriate lifestyle changes in combination with drug therapy can lead to a decline in the progression of coronary plaque, regression of preexisting lesions, and reduction in mortality due to CHD by 30 to 40 percent. Antihyperlipidemic drugs must be taken indefinitely; when therapy is terminated, plasma lipid levels return to pretreatment levels. The lipid-lowering drugs are listed in Figure 21.1. Figure 21.2 illustrates the normal metabolism of serum lipoproteins and the characteristics of the major genetic hyperlipidemias.

II. Treatment Goals

Plasma lipids consist mostly of lipoproteinsâ€”spherical macromolecular complexes of lipids and specific proteins (apolipoproteins). The clinically important lipoproteins, listed in decreasing order of atherogenicity, are LDL, very-low-density lipoprotein (VLDL) and chylomicrons, and HDL. The occurrence of CHD is positively associated with high total cholesterol, and even more strongly with elevated LDL cholesterol in the blood. In contrast to LDL cholesterol, high levels of HDL cholesterol have been associated with a decreased risk for heart disease (Figure 21.3). Reduction of the LDL level is the primary goal of cholesterol-lowering therapy. Figure 21.4 shows the current goals in the treatment of hyperlipidemia. Recommendations for the reduction of LDL cholesterol to specific target levels are influenced by the coexistence of CHD and the number of other cardiac risk factors. The higher the overall risk of heart disease, the more aggressive the recommended LDL-lowering therapy.

A. Treatment options for hypercholesterolemia

In patients with moderate hyperlipidemia, lifestyle changes, such as diet, exercise, and weight reduction, can lead to modest decreases in LDL levels and increases in HDL levels. However, most patients are

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unwilling to modify their lifestyle sufficiently to achieve LDL treatment goals, and drug therapy may be required. Patients with LDL levels higher than 160 mg/dL and with one other major risk factor, such as hypertension, diabetes, smoking, or a family history of early CHD, are candidates for drug therapy. Patients with two or more additional risk factors should be treated aggressively, with the aim of reducing their LDL level to less than 100 mg/dL and, in some patients, to as low as 70 mg/dL.

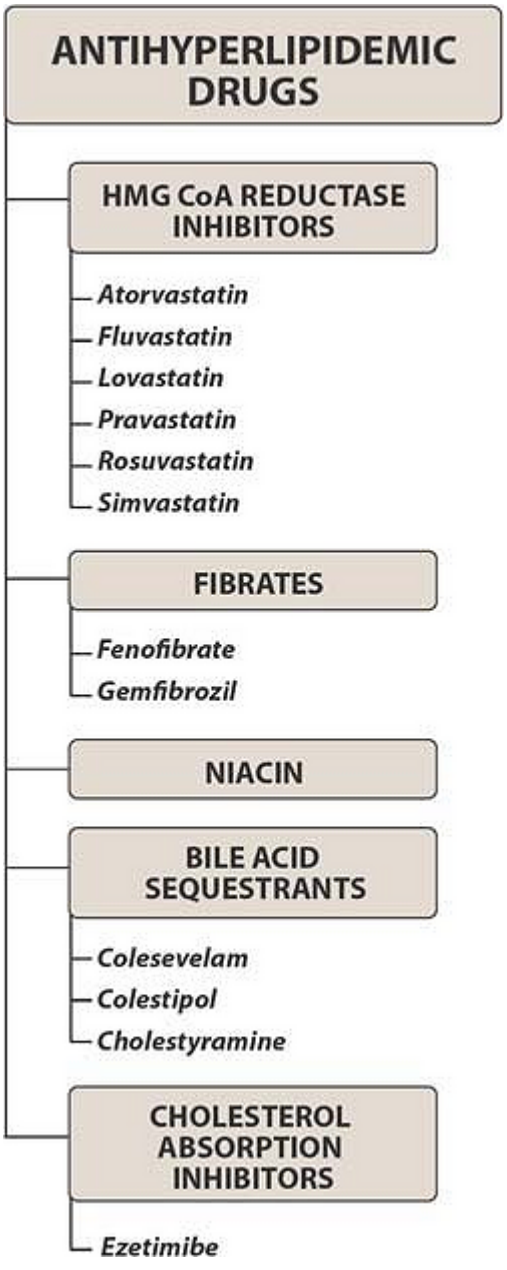
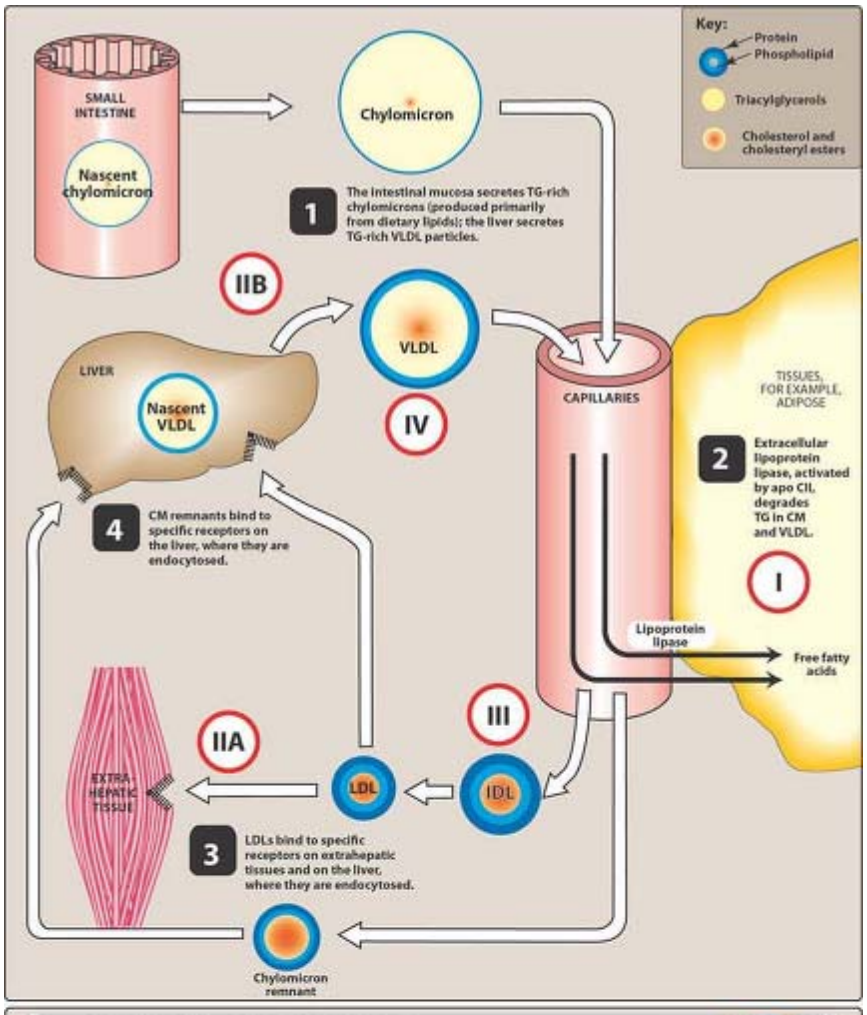


Figure 21.1 Summary of antihyperlipidemic drugs. HMG CoA = 3-hydroxy-3- methylglutaryl coenzyme A.



Type I [FAMILIAL HYPERCHYLOMICRONEMIA]

- Massive fasting hyperchylomicronemia, even following normal dietary fat intake, resulting in greatly elevated serum TG levels.
- Deficiency of lipoprotein lipase or deficiency of normal apolipoprotein CII (rare).
- Type I is not associated with an increase in coronary heart disease.
- Treatment: Low-fat diet. No drug therapy is effective for Type I hyperlipidemia.

Chylomicron

Type IIA [FAMILIAL HYPERCHOLESTEROLEMIA]

- Elevated LDL with normal VLDL levels due to a block in LDL degradation. This results in increased serum cholesterol but normal TG levels.
- Caused by defects in the synthesis or processing of LDL receptors.
- Ischemic heart disease is greatly accelerated.
- Treatment: Diet. Heterozygotes: *Cholestyramine* and *niacin*, or a statin.

LDL

Type IIB [FAMILIAL COMBINED (MIXED) HYPERLIPIDEMIA]

- Similar to Type IIA except that VLDL is also increased, resulting in elevated serum TG as well as cholesterol levels.
- Caused by overproduction of VLDL by the liver.
- Relatively common.
- Treatment: Diet. Drug therapy is similar to that for Type IIA .

VLDL LDL

Type III [FAMILIAL DYSBETALIPOPROTEINEMIA]

- Serum concentrations of IDL are increased, resulting in increased TG and cholesterol levels.
- Cause is either overproduction or underutilization of IDL due to mutant apolipoprotein E.
- Xanthomas and accelerated vascular disease develop in patients by middle age.
- Treatment: Diet. Drug therapy includes *niacin* and *fenofibrate*, or a statin.

IDL

Type IV [FAMILIAL HYPERTRIGLYCERIDEMIA]

- VLDL levels are increased, whereas LDL levels are normal or decreased, resulting in normal to elevated cholesterol, and greatly elevated circulating TG levels.
- Cause is overproduction and/or decreased removal of VLDL TG in serum.
- This is a relatively common disease. It has few clinical manifestations other than accelerated ischemic heart disease. Patients with this disorder are frequently obese, diabetic, and hyperuricemic.
- Treatment: Diet. If necessary, drug therapy includes *niacin* and/or *fenofibrate*.

VLDL

Type V [FAMILIAL MIXED HYPERTRIGLYCERIDEMIA]

- Serum VLDL and chylomicrons are elevated. LDL is normal or decreased.

Figure 21.2 Metabolism of plasma lipoproteins and related genetic diseases. Roman numerals in the white circles refer to specific genetic types of hyperlipidemias summarized on the facing page. CM = chylomicron, TG = triacylglycerol; VLDL = very-low density lipoprotein, LDL = low-density lipoprotein, IDL = intermediate-density lipoprotein, apo CII = apolipoprotein CII found in chylomicrons and VLDL.

B. Treatment options for hypertriacylglycerolemia

Elevated triacylglycerol (triglyceride) levels are independently associated with increased risk of CHD. Diet and exercise are the primary modes of treating hypertriacylglycerolemia. If indicated, *niacin* and *fibric acid* derivatives are the most efficacious in lowering triacylglycerol levels. Triacylglycerol reduction is a secondary benefit of the statin drugs (the primary benefit being LDL cholesterol reduction). [Note: The major lipid component of VLDL is composed of triacylglycerol.]

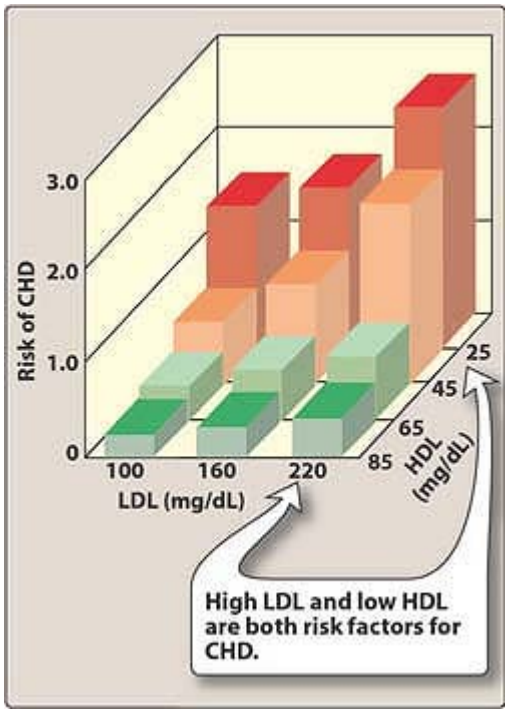


Figure 21.3 Effect of circulating LDL and HDL on the risk of coronary heart disease (CHD).

III. Drugs that Lower the Serum Lipoprotein Concentration

Antihyperlipidemic drugs target the problem of elevated serum lipids with complementary strategies. Some of these agents decrease production of the lipoprotein carriers of cholesterol and triglyceride, whereas others increase the degradation of lipoprotein. Still others decrease cholesterol absorption or directly increase cholesterol removal from the body. These drugs may be used singly or in combination. However, they are always accompanied by the requirement that dietary saturated and transfats[1] be low, and the caloric content of the diet must be closely monitored.

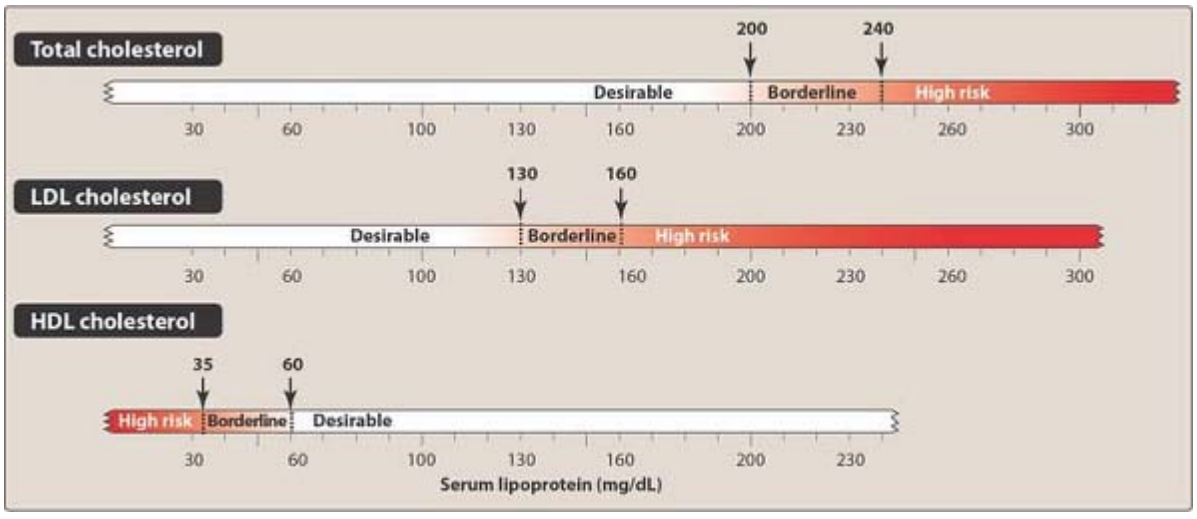


Figure 21.4 Goal lipoprotein levels achieved with dietary or drug therapy for the prevention of coronary heart disease. [Note: Lower goals for total and LDL cholesterol are recommended for patients with a history of heart disease.]

A. HMG CoA reductase inhibitors

3-Hydroxy-3-methylglutaryl (HMG) coenzyme A (COA) reductase inhibitors (commonly known as statins) lower elevated LDL cholesterol levels, resulting in a substantial reduction in coronary events and death from CHD. This group of antihyperlipidemic agents inhibits the first committed enzymatic step of cholesterol synthesis, and they are the first-line and more effective treatment for patients with elevated LDL cholesterol. Therapeutic benefits include plaque stabilization, improvement of coronary endothelial function, inhibition of platelet thrombus formation, and anti-inflammatory activity. The value of lowering the level of cholesterol with statin drugs has now been demonstrated in 1) patients with CHD with or without hyperlipidemia, 2) men with hyperlipidemia but no known CHD, and 3) men and women with average total and LDL cholesterol levels and no known CHD.

1. **Mechanism of action:**

   a. **Inhibition of HMG CoA reductase:** *Lovastatin* [LOE-vah-stat-in] *simvastatin* [sim-vah-STAT-in], *pravastatin* [PRAH-vah-stat-in], *atorvastatin* (a-TOR-vah-stat-in), *fluvastatin* [FLOO-vah-stat-in], and *rosuvastatin* [roe-SOO-va-sta-tin] are analogs of HMG, the precursor of cholesterol. *Lovastatin* and *simvastatin* are lactones that are hydrolyzed to the active drug. *Pravastatin* and *fluvastatin* are active as such. Because of their strong affinity for the enzyme, all compete effectively to inhibit HMG CoA reductase, the rate-limiting step in cholesterol synthesis. By inhibiting de novo cholesterol synthesis, they deplete the intracellular supply of cholesterol (Figure 21.5). *Rosuvastatin* and *atorvastatin* are the most potent LDL cholesterolâ€"lowering statin drugs, followed by *simvastatin, pravastatin* and then *lovastatin* and *fluvastatin.*

   b. **Increase in LDL receptors:** Depletion of intracellular cholesterol causes the cell to increase the number of specific cell-surface LDL receptors that can bind and internalize circulating LDLs. Thus, the end result is a reduction in plasma cholesterol, both by lowered cholesterol synthesis and by increased catabolism of LDL. [Note: Because these agents undergo a marked first-pass extraction by the liver, their dominant effect is on that organ.] The HMG CoA reductase inhibitors, like the bile acid sequestrant *cholestyramine*, can increase plasma HDL levels in some patients, resulting in an additional lowering of risk for CHD. Decreases in

triglyceride also occur.

2. **Therapeutic uses:** These drugs are effective in lowering plasma cholesterol levels in all types of hyperlipidemias (Figure 21.6). However, patients who are homozygous for familial hypercholesterolemia lack LDL receptors and, therefore, benefit much less from treatment with these drugs. [Note: These drugs are often given in combination with other antihyperlipidemic drugs; see below.] It should be noted that in spite of the protection afforded by cholesterol lowering, about one-fourth of the patients treated with these drugs still present with coronary events. Thus, additional strategies, such as diet, exercise, or additional agents, may be warranted.

3. **Pharmacokinetics:** *Pravastatin* and *fluvastatin* are almost completely absorbed after oral administration; oral doses of *lovastatin* and *simvastatin* are from 30 to 50 percent absorbed. Similarly, *pravastatin*

and *fluvastatin* are active as such, whereas *lovastatin* and *simvastatin* must be hydrolyzed to their acid forms. Due to first-pass extraction, the primary action of these drugs is on the liver. All are biotransformed, with some of the products retaining activity. Excretion takes place principally through the bile and feces, but some urinary elimination also occurs. Their half-lives range from 1.5 to 2 hours. Some characteristics of the statins are summarized in Figure 21.7.

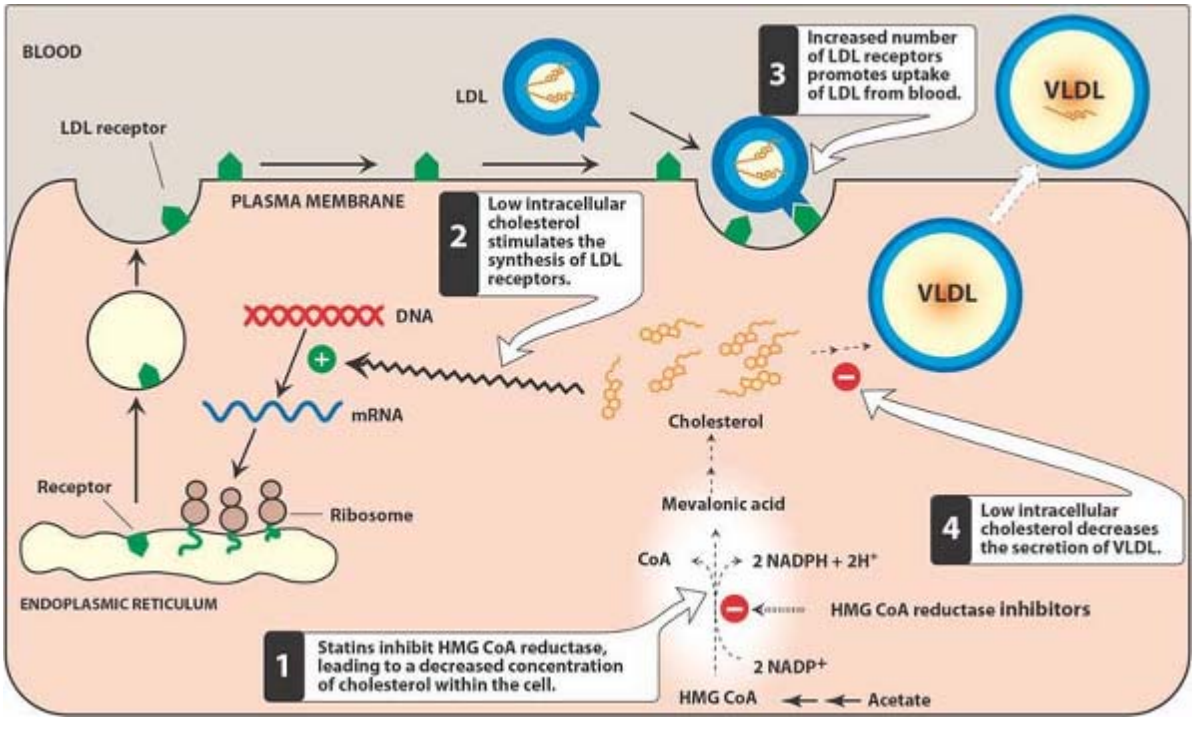


Figure 21.5 Inhibition of HMG CoA reductase by the statin drugs.

4. **Adverse effects:** It is noteworthy that during the 5-year trials of *simvastatin* and *lovastatin*, only a few adverse effects, related to liver and muscle function, were reported (Figure 21.8).

   a. **Liver:** Biochemical abnormalities in liver function have occurred with the HMG CoA reductase inhibitors. Therefore, it is prudent to evaluate liver function and measure serum transaminase levels periodically. These return to normal on suspension of the drug. [Note: Hepatic insufficiency can cause drug accumulation.]

   b. **Muscle:** Myopathy and rhabdomyolysis (disintegration or dissolution of muscle) have been reported only

rarely. In most of these cases, patients usually suffered from renal insufficiency or were taking drugs such as *cyclosporine, itraconazole, erythromycin, gemfibrozil*, or *niacin.* Plasma creatine kinase levels should be determined regularly.

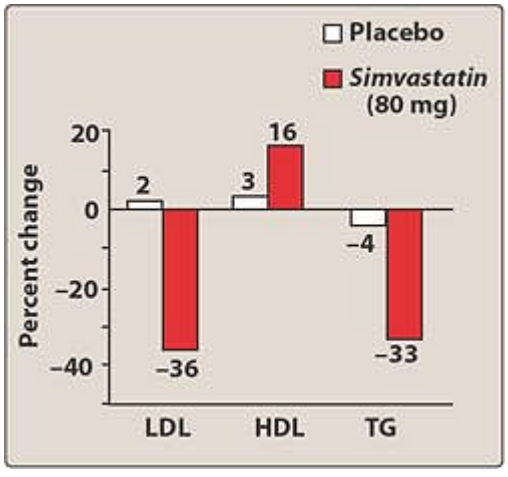


Figure 21.6 Effect of simvastatin on serum lipids of 130 patients with Type 2 diabetes treated for 6 weeks. HDL = high-density lipoprotein; LDL = low-density lipoprotein; TG = triacyglycerol.

Characteristic	*Atorvastatin*	*Fluvastatin*	*Lovastatin*	*Pravastatin*	*Rosuvastatin*	*Simvastatin*
Serum LDL cholesterol reduction produced (%)	50	24	34	34	50	41
Serum triacylglycerol reduction produced (%)	29	10	16	24	18	18
Serum HDL cholesterol increase produced (%)	6	8	9	12	8	12
Plasma half-life (hr)	14	1–2	2	1–2	19	1–2
Penetration of central nervous system	No	No	Yes	No	No	Yes
Renal excretion of absorbed dose (%)	2	<6	10	20	10	13

Figure 21.7 Summary of 3-hydroxy-3-methylglutaryl coenzyme (HMG CoA) reductase inhibitors.

c. **Drug interactions:** The HMG CoA reductase inhibitors may also increase *warfarin* levels. Thus, it is important to evaluate INR times frequently.

d. **Contraindications:** These drugs are contraindicated during pregnancy and in nursing mothers. They should not be used in children or teenagers.

B. Niacin (nicotinic acid)

Niacin[2] [NYE-a-sin] can reduce LDL (the â€œbadâ€ cholesterol carrier) levels by 10 to 20 percent and is the most effective agent for increasing HDL (the â€œgoodâ€ cholesterol carrier) levels. *Niacin* can be used in combination with statins, and a fixed-dose combination of *lovastatin* and long-acting *niacin* is available.

1. **Mechanism of action:** At gram doses, *niacin* strongly inhibits lipolysis in adipose tissueâ€”the primary producer of circulating free fatty acids. The liver normally utilizes these circulating fatty acids as a major precursor for triacylglycerol synthesis. Thus, *niacin* causes a decrease in liver triacylglycerol synthesis, which is required for VLDL production (Figure 21.9). LDL (the cholesterol-rich lipoprotein) is derived from VLDL in the plasma. Therefore, a reduction in the VLDL concentration also results in a decreased plasma LDL concentration. Thus, both plasma triacylglycerol (in VLDL) and cholesterol (in VLDL and LDL) are lowered (Figure 21.10). Furthermore, *niacin* treatment increases HDL cholesterol levels. Moreover, by boosting secretion of tissue plasminogen activator and lowering the level of plasma fibrinogen, *niacin* can reverse some of the endothelial cell dysfunction contributing to thrombosis associated with hypercholesterolemia and atherosclerosis.

Figure 21.8 Some adverse effects and precautions associated with 3-hydroxy-3-methylglutaryl coenzyme (HMG CoA) reductase inhibitors.

2. **Therapeutic uses:** *Niacin* lowers plasma levels of both cholesterol and triacylglycerol. Therefore, it is particularly useful in the treatment of familial hyperlipidemias. *Niacin* is also used to treat other severe hypercholesterolemias, often in combination with other antihyperlipidemic agents. In addition, it is the most potent antihyperlipidemic agent for raising plasma HDL levels, which is the most common indication for its clinical use.

3. **Pharmacokinetics:** *Niacin* is administered orally. It is converted in the body to nicotinamide, which is incorporated into the cofactor nicotinamide-adenine dinucleotide (NAD^+). *Niacin*, its nicotinamide derivative, and other metabolites are excreted in the urine. [Note: Nicotinamide alone does not decrease plasma lipid levels.]

4. **Adverse effects:** The most common side effects of *niacin* therapy are an intense cutaneous flush (accompanied by an uncomfortable feeling of warmth) and pruritus. Administration of *aspirin* prior to taking *niacin* decreases the flush, which is prostaglandin mediated. The sustained-release formulation of *niacin*, which is taken once daily at bedtime, reduces bothersome initial adverse effects. Some patients also experience nausea and abdominal pain. *Niacin* inhibits tubular secretion of uric acid and, thus, predisposes to hyperuricemia and gout. Impaired glucose tolerance and hepatotoxicity have also been reported.

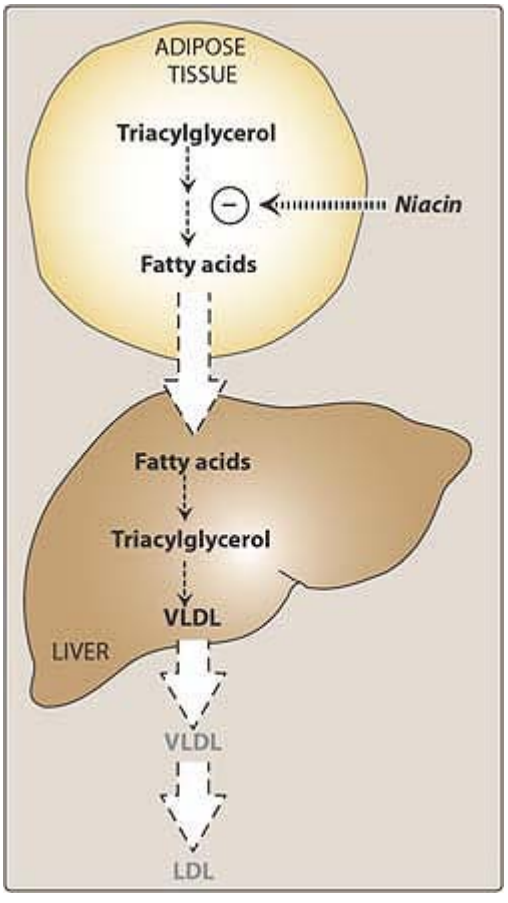


Figure 21.9 *Niacin* inhibits lipolysis in adipose tissue, resulting in decreased hepatic VLDL synthesis and production of LDLs in the plasma.

C. The fibrates: Fenofibrate and gemfibrozil

Fenofibrate [fen-oh-FIH-brate] and *gemfibrozil* [jem-FI-broh-zill] are derivatives of fibric acid that lower serum triacylglycerols and increase HDL levels. Both have the same mechanism of action. However, *fenofibrate* is more effective than *gemfibrozil* in lowering plasma LDL cholesterol and triglyceride levels.

1. **Mechanism of action:** The peroxisome proliferatorâ€“activated receptors (PPARs) are members of the nuclear receptor supergene family that regulates lipid metabolism. PPARs functions as a ligand-activated transcription factor. Upon binding to its natural ligand (fatty acids or eicosanoids) or hypolipidemic drugs, PPARs are activated. They then bind to peroxisome proliferator response elements, which are localized in numerous gene promoters. In particular, PPARs regulates the expression of genes encoding for proteins involved in lipoprotein structure and function. Fibrate-mediated gene expression ultimately leads to decreased triacylglycerol concentrations by increasing the expression of lipoprotein lipase (Figure 22.11) and decreasing apo CII

concentration. Fibrates also increase the level of HDL cholesterol by increasing the expression of apo AI and apo AII. *Fenofibrate* is a prodrug, producing an active metabolite, fenofibric acid, which is responsible for the primary effects of the drug.

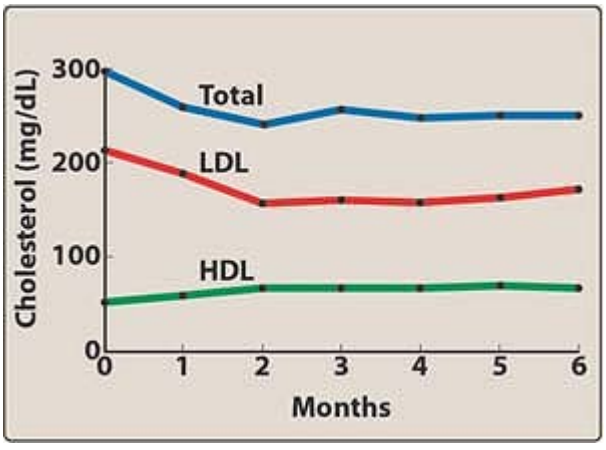


Figure 21.10 Plasma levels of cholesterol in hyperlipidemic patients during treatment with *niacin*.

2. **Therapeutic uses:** The fibrates are used in the treatment of hypertriacylglycerolemias, causing a significant decrease in plasma triacylglycerol levels. *Fenofibrate* and *gemfibrozil* are particularly useful in treating Type III hyperlipidemia (dysbetalipoproteinemia), in which

intermediate-density lipoprotein particles accumulate. Patients with hypertriacylglycerolemia [Type IV (elevated VLDL) or Type V (elevated VLDL plus chylomicron) disease] who do not respond to diet or other drugs may also benefit from treatment with these agents.

3. **Pharmacokinetics:** Both drugs are completely absorbed after an oral dose. *Gemfibrozil* and *fenofibrate* distribute widely, bound to albumin. Both drugs undergo extensive biotransformation and are excreted in the urine as their glucuronide conjugates.

4. **Adverse effects:**

   a. **Gastrointestinal effects:** The most common adverse effects are mild gastrointestinal disturbances. These lessen as the therapy progresses.

   b. **Lithiasis:** Because these drugs increase biliary cholesterol excretion, there is a predisposition to the formation of gallstones.

   c. **Muscle:** Myositis (inflammation of a voluntary muscle) can occur with both drugs; thus, muscle weakness or tenderness should be evaluated. Patients with renal insufficiency may be at risk. Myopathy and rhabdomyolysis have been reported in a few patients taking *gemfibrozil* and *lovastatin* together.

   d. **Drug interactions:** Both fibrates compete with the coumarin anticoagulants for binding sites on plasma proteins, thus transiently potentiating anticoagulant activity. INR times should therefore be monitored when a patient is taking both drugs. Similarly, these drugs may transiently elevate the levels of sulfonylureas.

   e. **Contraindications:** The safety of these agents in pregnant or lactating women has not been established. They should not be used in patients with severe hepatic and renal dysfunction or in patients with preexisting gallbladder disease.

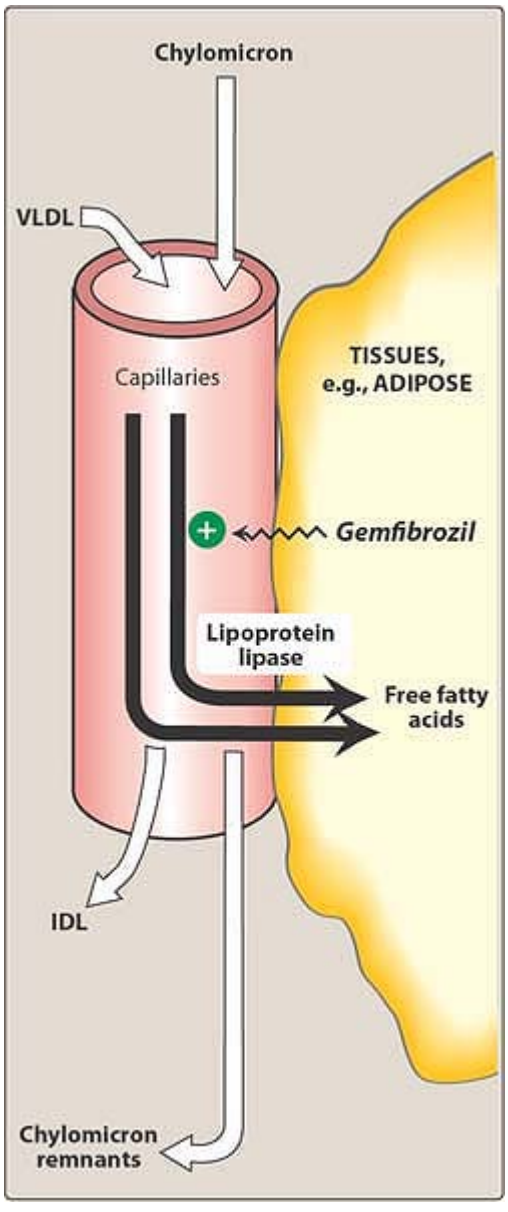


Figure 21.11 Activation of lipoprotein lipase by gemfibrozil.

D. Bile acidâ€“binding resins

Bile acid sequestrants (resins) have significant LDL cholesterolâ€“lowering effects, although the benefits are less than those observed with statins.

1. **Mechanism of action:** *Cholestyramine* [koe-LES-tir-a-meen], *colestipol* [koe-LES-tih-pole], and *colesevelam* [koh-le-SEV-e-lam] are anion-exchange resins that bind negatively charged bile acids and bile salts in the small intestine (Figure 21.12). The resin/bile acid complex is excreted in the feces, thus preventing the bile acids from returning to the liver by the enterohepatic circulation. Lowering the bile acid concentration causes hepatocytes to increase conversion of cholesterol to bile acids, resulting in a replenished supply of these compounds, which are essential components of the bile. Consequently, the intracellular cholesterol concentration decreases, which activates an increased hepatic uptake of cholesterol-containing LDL particles,

increased uptake is mediated by an up-regulation of cell-surface LDL receptors.] In some patients, a modest rise in plasma HDL levels is also observed. The final outcome of this sequence of events is a decreased total plasma cholesterol concentration.

2. **Therapeutic uses:** The bile acidâ€“binding resins are the drugs of choice (often in combination with diet or *niacin*) in treating Type IIa and Type IIb hyperlipidemias. [Note: In those rare individuals who are homozygous for Type IIaâ€”that is, for whom functional LDL receptors are totally lackingâ€”these drugs have little effect on plasma LDL levels.] *Cholestyramine* can also relieve pruritus caused by accumulation of bile acids in patients with biliary obstruction.

3. **Pharmacokinetics:** *Cholestyramine, colestipol*, and *colesevelam* are taken orally. Because they are insoluble in water and are very large (molecular weights are greater than 10^6), they are neither absorbed nor metabolically altered by the intestine. Instead, they are totally excreted in the feces.

4. **Adverse effects:**

    a. **Gastrointestinal effects:** The most common side effects are gastrointestinal disturbances, such as constipation, nausea, and flatulence. *Colesevelam* has fewer gastrointestinal side effects than other bile acid sequestrants.

    b. **Impaired absorptions:** At high doses, *cholestyramine* and *colestipol* (but not *colesevelam*) impair the absorption of the fat-soluble vitamins (A, D, E, and K).

    c. **Drug interactions:** *Cholestyramine* and *colestipol* interfere with the intestinal absorption of many drugsâ€”for example, *tetracycline, phenobarbital, digoxin, warfarin, pravastatin, fluvastatin, aspirin*, and thiazide diuretics. Therefore, drugs should be taken at least 1 to 2 hours before, or 4 to 6 hours after, the bile acidâ€“binding resins.

E. Cholesterol absorption inhibitors

Ezetimibe [eh-ZEH-teh-mib] selectively inhibits intestinal absorption of dietary and biliary cholesterol in the small intestine, leading to a decrease in the delivery of intestinal cholesterol to the liver. This causes a reduction of hepatic cholesterol stores and an increase in clearance of cholesterol from the blood. *Ezetimibe* lowers LDL cholesterol by 17 percent and triacylglycerols by 6 percent, and it increases HDL cholesterol by 1.3 percent. *Ezetimibe* is primarily metabolized in the small intestine and liver via glucuronide conjugation (a Phase II reaction), with subsequent biliary and renal excretion. Both *ezetimibe* and *ezetimibe*-glucuronide are slowly eliminated from plasma, with a half-life of approximately 22 hours. *Ezetimibe* has no clinically meaningful effect on the plasma concentrations of the fat-soluble vitamins A, D, and E. Patients with moderate to severe hepatic insufficiency should not be treated with *ezetimibe.* [Note: A formulation of *ezetimibe* and *simvastatin* has been shown to lower LDL levels more effectively than the statin alone.]

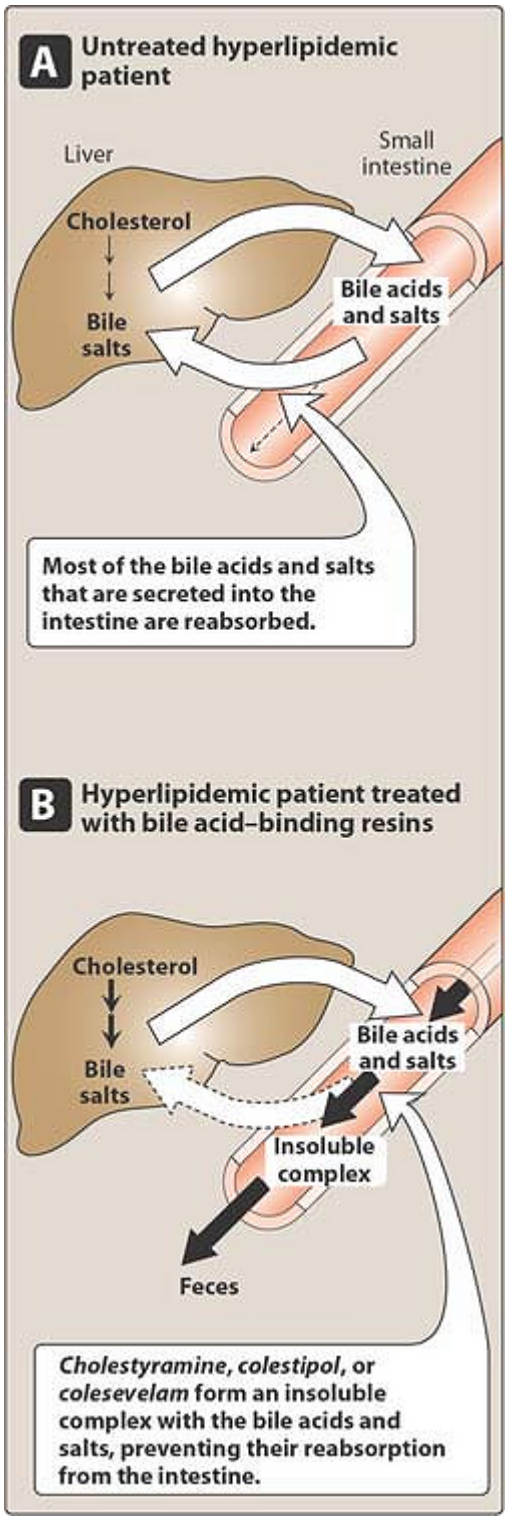


Figure 21.12 Mechanism of bile acidâ€“binding resins.

F. Combination drug therapy

It is often necessary to employ two antihyperlipidemic drugs to achieve treatment goals in plasma lipid levels. For

example, in Type II hyperlipidemias, patients are commonly treated with a combination of *niacin* plus a bile acidâ€“binding agent, such as *cholestyramine.* [Note: Remember that *cholestyramine* causes an increase in LDL receptors that clears the plasma of circulating LDL, whereas *niacin* decreases synthesis of VLDL and, therefore, also the synthesis of LDL.] The combination of an HMG CoA reductase inhibitor with a bile acidâ€“binding agent has also been shown to be very useful in lowering LDL cholesterol levels (Figure 21.13). A low dose statin in combination with *ezetimibe* achieves comparable or even greater LDL cholesterol reduction than a very-high-dose statin. *Simvastatin* and *ezetimibe* are currently available combined in one pill to treat elevated LDL cholesterol.

However, the clinical value of *ezetimibe* either alone or in combination with statins is uncertain. For example, in the ENHANCE study, patients with familial hypercholesterolemia were randomized to *simvastatin* plus either *ezetimibe* or placebo. At 2 years, patients who received *ezetimibe* had significantly greater reductions in LDL cholesterol, triglycerides, and C-reactive protein than did those on placebo. However, there were no significant differences between groups in HDL cholesterol, cardiovascular events, adverse events, or the primary endpointâ€”change in carotid-artery intimaâ€“media thickness

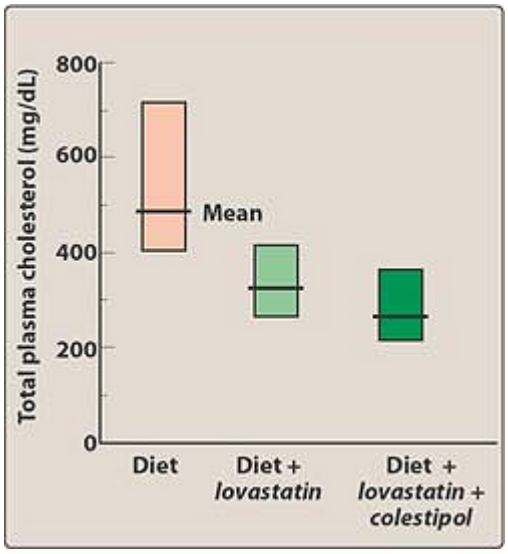


Figure 21.13 Response of total plasma cholesterol in patients with heterozygous familial hypercholesterolemia to a diet (low in cholesterol, low in saturated fat) and antihyperlipidemic drugs.

This study contradicts previous results in which clinical benefits correlated with the concurrent reduction in LDL cholesterol. Until this discrepancy is resolved, many experts recommend clinicians maximize statin dosages and use *niacin*, fibrates, and resins before considering *ezetimibe*,

Figure 21.14 summarizes some actions of the antihyperlipidemic drugs.

TYPE OF DRUG	EFFECT ON LDL	EFFECT ON HDL	EFFECT ON TRIACYLGLYCEROLS
HMG CoA reducatase inhibitors (statins)	↓↓↓↓	↑↑	↓↓
Fibrates	↓	↑↑↑	↓↓↓↓
Niacin	↓↓	↑↑↑↑	↓↓↓
Bile acid sequestrants	↓↓↓	↑	Minimal
Cholesterol absorption inhibitor	↓	↑	↓

Figure 21.14 Characteristics of antihyperlipidemic drug families. HDL = high-density lipoprotein; HMG-CoA = 3-hydroxy-3- methylglutaryl coenzyme A; LDL = low-density lipoprotein.

Study Questions

Choose the ONE best answer.

21.1 Which one of the following is the most common side effect of antihyperlipidemic drug therapy?

A. Elevated blood pressure.

B. Gastrointestinal disturbance.

C. Neurologic problems.

D. Heart palpitations.

E. Migraine headaches.

View Answer

21.2 Which one of the following hyperlipidemias is characterized by elevated plasma levels of chylomicrons and has no drug therapy available to lower the plasma lipoprotein levels?

A. Type I.

B. Type II.

C. Type III.

D. Type IV.

E. Type V.

View Answer

21.3 Which one of the following drugs decreases de novo cholesterol synthesis by inhibiting the enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase?

A. Fenofibrate.

B. Niacin.

C. Cholestyramine.

D. Lovastatin.

E. Gemfibrozil.

View Answer

21.4 Which one of the following drugs causes a decrease in liver triacylglycerol synthesis by limiting available free fatty acids needed as building blocks for this pathway?

A. Niacin.

B. Fenofibrate.

C. Cholestyramine.

D. Gemfibrozil.

E. Lovastatin.

View Answer

21.5 Which one of the following drugs binds bile acids in the intestine, thus preventing their return to the liver via the enterohepatic circulation?

A. Niacin.

B. Fenofibrate.

C. Cholestyramine.

D. Fluvastatin.

E. Lovastatin.

View Answer

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Chapter 22

Diuretics

I. Overview

Drugs inducing a state of increased urine flow are called diuretics. These agents are inhibitors of renal ion transporters that decrease the reabsorption of Na^+ at different sites in the nephron. As a result, Na^+ and other ions, such as Cl^-, enter the urine in greater than normal amounts along with water, which is carried passively to maintain osmotic equilibrium. Diuretics thus increase the volume of urine and often change its pH as well as the ionic composition of the urine and blood. The efficacy of the different classes of diuretics varies considerably, with the increase in Na^+ secretion varying from less than two percent for the weak, potassium-sparing diuretics to over 20 percent for the potent loop diuretics. In addition to these ion-transport inhibitors, there are osmotic diuretics that prevent water reabsorption, as well as aldosterone antagonists and a carbonic anhydrase inhibitor. The major clinical uses of diuretics are in managing disorders involving abnormal fluid retention (edema) or treating hypertension in which their diuretic action causes a decreased blood volume, leading to reduced blood pressure. In this chapter, the diuretic drugs (Figure 22.1) are discussed according to the frequency of their use.

II. Normal Regulation of Fluid and Electrolytes by the Kidneys

Approximately 16 to 20 percent of the blood plasma entering the kidneys is filtered from the glomerular capillaries into the Bowman's capsule. The filtrate, although normally free of proteins and blood cells, does contain most low-molecular-weight plasma components in approximately the same concentrations as are found in the plasma. These include glucose, sodium bicarbonate, amino acids, and other organic solutes as well as electrolytes, such as Na^+, K^+, and Cl^-. The kidney regulates the ionic composition and volume of urine by the active reabsorption or secretion of ions and/or the passive reabsorption of water at five functional zones along the nephronâ€”namely, the proximal convoluted tubule, the descending loop of Henle, the ascending loop of Henle, the distal convoluted tubule, and the collecting tubule and duct (Figure 22.2).

A. Proximal convoluted tubule

In the extensively convoluted proximal tubule located in the cortex of the kidney, almost all the glucose, bicarbonate, amino acids, and other metabolites are reabsorbed. Approximately two-thirds of the Na^+ is also reabsorbed. Chloride enters the lumen of the tubule in

exchange for a base anion, such as formate or oxalate, as well as paracellularly through the lumen. Water follows passively from the lumen to the blood to maintain osmolar equality. If not for the extensive reabsorption of solutes and water in the proximal tubule, the mammalian organism would rapidly become dehydrated and lose its normal osmolarity. The Na^+ that is reabsorbed is pumped into the interstitium by Na^+/K^+â€“adenosine triphosphatase (ATPase), thereby maintaining normal levels of Na^+ and K^+ in the cell. Carbonic anhydrase in the luminal membrane and cell of the proximal tubule modulates the reabsorption of bicarbonate (see *acetazolamide* below). Water follows salt reabsorption; thus, the presence of substances like mannitol and glucose would tend to become concentrated. This condition results in a higher osmolarity of the tubular fluid and prevents further water reabsorption, resulting in osmotic diuresis.

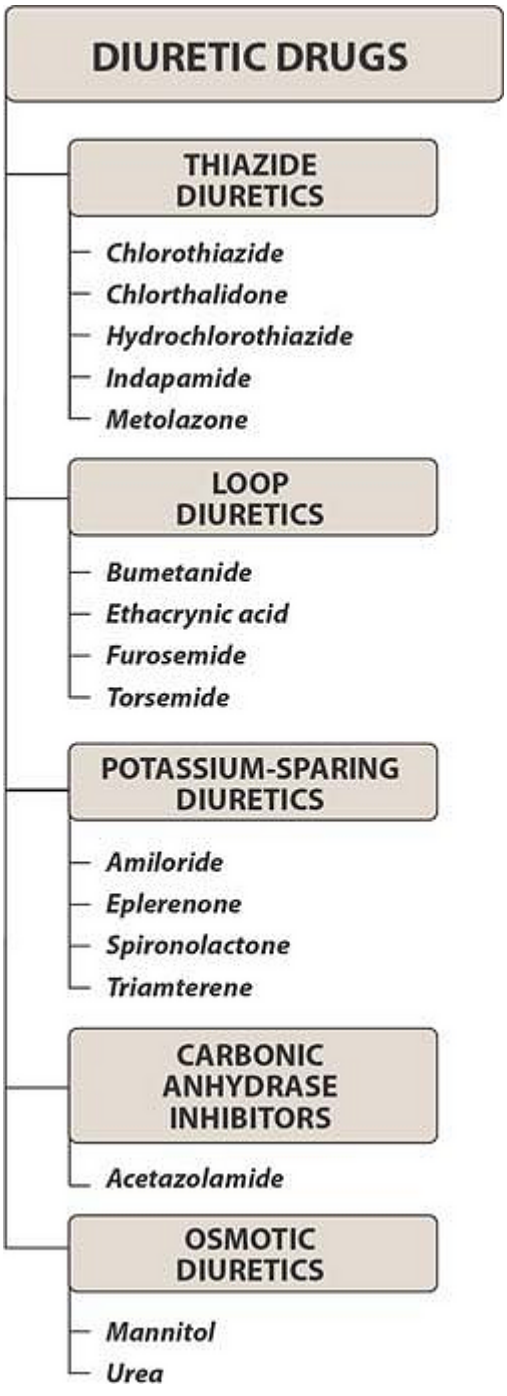

Figure 22.1 Summary of diuretic drugs.

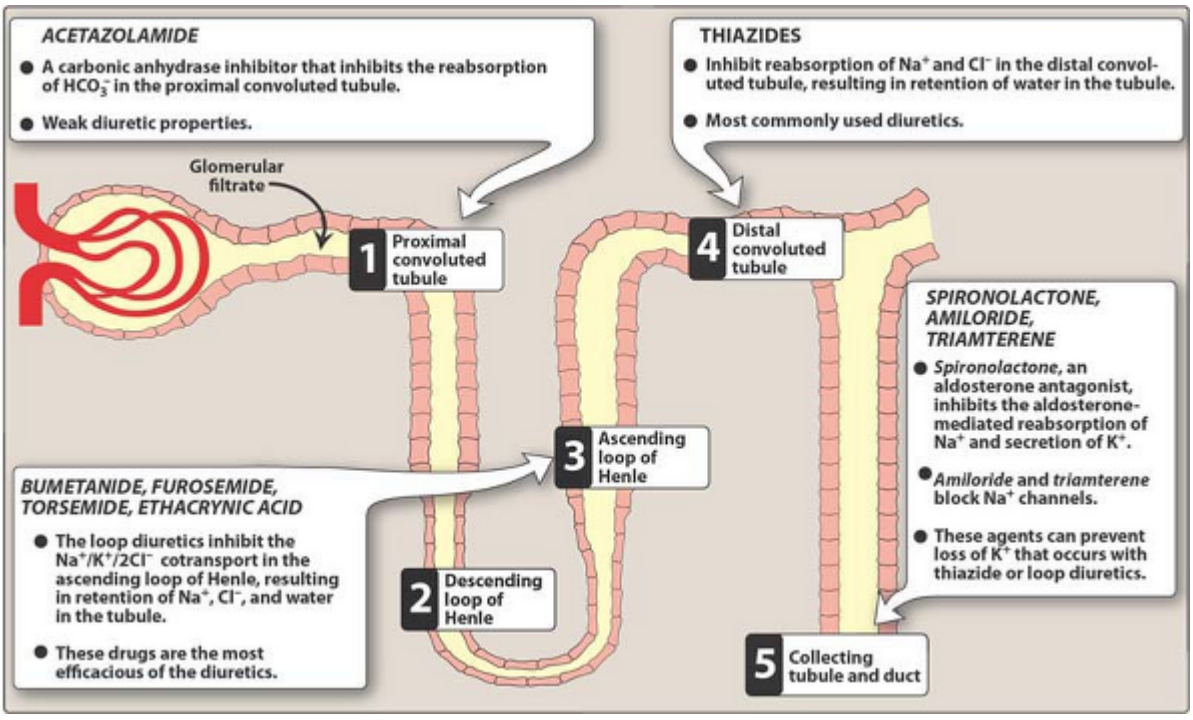

Figure 22.2 Major locations of ion and water exchange in the nephron, showing sites of action of the diuretic drugs.

1. **Acid and base secretory systems:** The proximal tubule is the site of the organic acid and base secretory systems (Figure 22.3). The organic acid secretory system, located in the middle-third segment, secretes a variety of organic acids, such as uric acid, some antibiotics, and diuretics, from the bloodstream into the proximal tubule's lumen. Most diuretic drugs are delivered to the tubular fluid via this system. The organic acid secretory system is saturable, and diuretic drugs in the bloodstream compete for transfer with endogenous organic acids, such as uric acid. This explains the hyperuricemia seen with certain of the diuretic drugs, such as *furosemide* or *hydrochlorothiazide*. A number of other interactions can also occur; for example,

probenecid interferes with *penicillin* secretion. The organic base secretory system is responsible for the secretion of creatinine, choline, and so on, and it is found in the upper and middle segments of the proximal tubule.

B. Descending loop of Henle

The remaining filtrate, which is isotonic, next enters the descending limb of the loop of Henle and passes into the medulla of the kidney. The osmolarity increases along the descending portion of the loop of Henle because of the countercurrent mechanism that is responsible for water reabsorption. This results in a tubular fluid with a three-fold increase in salt concentration. Osmotic diuretics exert part of their action in this region (see Figure 22.2).

C. Ascending loop of Henle

The cells of the ascending tubular epithelium are unique in being impermeable to water. Active reabsorption of Na^+, K^+, and Cl^- is mediated by a $Na^+/K^+/2Cl^-$ cotransporter. Both Mg^{2+} and Ca^{2+} enter the interstitial fluid via the paracellular pathway. The ascending loop is thus a diluting region of the nephron. Approximately 25 to 30 percent of the tubular sodium chloride returns to the interstitial fluid, thus helping to maintain the fluid's high osmolarity.

Because the ascending loop of Henle is a major site for salt reabsorption, drugs affecting this site, such as loop diuretics (see Figure 22.2), are the most efficacious of all the diuretic classes.

D. Distal convoluted tubule

The cells of the distal convoluted tubule are also impermeable to water. About 10 percent of the filtered sodium chloride is reabsorbed via a Na^+/Cl^- transporter that is sensitive to thiazide diuretics. Calcium reabsorption is mediated by passage through a channel and then transported by a Na^+/Ca^{2+}-exchanger into the interstitial fluid. The mechanism thus differs from that in the loop of Henle. Additionally, Ca^{2+} excretion is regulated by parathyroid hormone in this portion of the tubule.

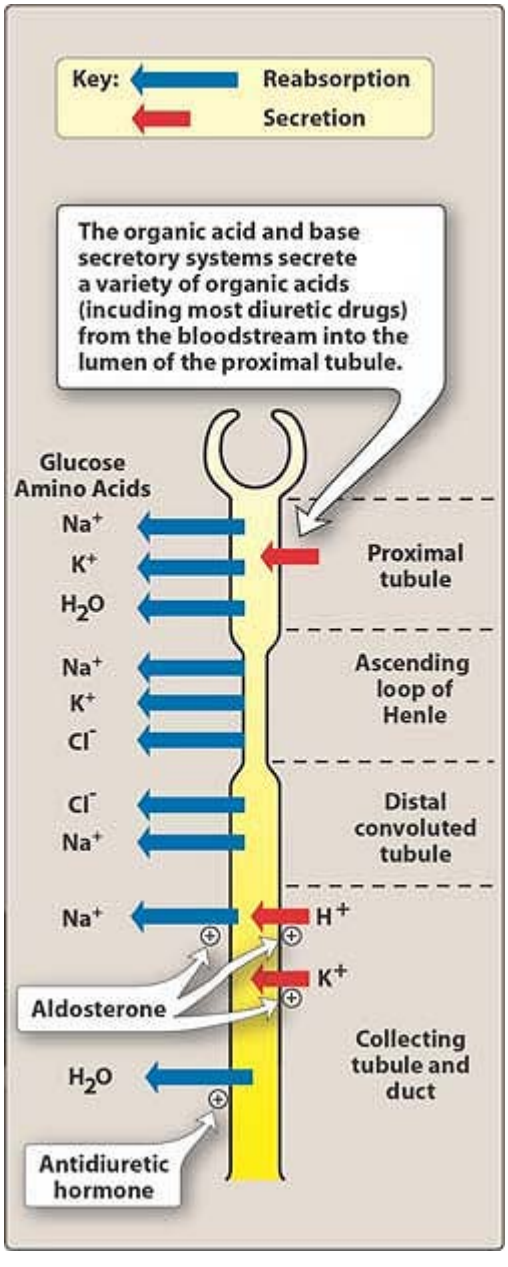

Figure 22.3 Sites of transport of solutes and water along the nephron.

E. Collecting tubule and duct

The principal cells of the collecting tubule and duct are responsible for Na^+, K^+, and water transport, whereas the intercalated cells affect H^+ secretion. The sodium enters the principal cells through channels but relies on a Na^+/K^+-ATPase to be transported into the blood. Aldosterone receptors in the principal cells influence Na^+ reabsorption and K^+ secretion. Antidiuretic hormone (ADH; vasopressin) receptors promote the reabsorption of water from the collecting tubules and ducts (see Figure 22.3). This action is mediated by cyclic adenosine monophosphate.

III. Kidney Function in Disease

A. Edematous states

In many diseases, the amount of sodium chloride reabsorbed by the kidney tubules is abnormally high. This leads to the retention of water, an increase in blood volume, and expansion of the extravascular fluid compartment, resulting in edema of the tissues. Several commonly encountered causes of edema include the following.

1. **Heart failure:** The decreased ability of the failing heart to sustain adequate cardiac output causes the kidney to respond as if there were a decrease in blood volume (hypovolemia). The kidney, as part of the normal compensatory mechanism, retains more salt and water as a means of raising blood volume and increasing the amount of blood that is returned to the heart. However, the diseased heart cannot increase its output, and the increased vascular volume results in edema (see p. 183 for causes and treatment of heart failure). Loop diuretics are commonly used.
2. **Hepatic ascites:** Ascites, the accumulation of fluid in the abdominal cavity, is a common complication of cirrhosis of the liver.
    a. **Increased portal blood pressure:** Blood flow in the portal system is often obstructed in cirrhosis, resulting in an increased portal blood pressure. Furthermore, the colloidal osmotic pressure of the blood is decreased as a result of impaired synthesis of plasma proteins by the diseased liver. Increased portal blood pressure and low osmolarity of the blood cause fluid to escape from the portal vascular system and collect in the abdomen.
    b. **Secondary hyperaldosteronism:** Fluid retention is also promoted by elevated levels of circulating aldosterone due to decreased blood volume. This secondary hyperaldosteronism results from the decreased ability of the liver to inactivate the steroid hormone and leads to increased Na^+ and water reabsorption, increased vascular volume, and exacerbation of fluid accumulation (see Figure 22.3). The potassium-sparing diuretic *spironolactone* is effective in this condition, but the loop diuretics are usually not.
3. **Nephrotic syndrome:** When damaged by disease, the glomerular membranes allow plasma proteins to enter the glomerular ultrafiltrate. The loss of protein from the plasma reduces the colloidal osmotic pressure, resulting in edema. The low plasma volume stimulates aldosterone secretion through the renin-angiotensin-aldosterone system. This leads to retention of Na^+ and fluid, further aggravating the edema.
4. **Premenstrual edema:** Edema associated with menstruation is the result of imbalances in hormones, such as estrogen excess, which facilitates the loss of fluid into the extracellular space. Diuretics can reduce the edema.

B. Nonedematous states

Diuretics also find wide usage in the treatment of nonedematous diseases.

1. **Hypertension:** Thiazides have been widely used in the treatment of hypertension, because of their ability not only to reduce blood volume but also to dilate arterioles (see p. 219).

2. **Hypercalcemia:** The seriousness of this condition requires a fast response. Usually, loop diuretics are employed, because they promote calcium excretion. However, it is important to understand that hypovolemia may counteract the desired effect; therefore, normal saline must also be infused to maintain blood volume.

3. **Diabetes insipidus:** When patients suffer from polyuria and polydipsia associated with this condition, they usually respond to thiazide diuretics. This seemingly paradoxic treatment depends on the ability of the thiazide to reduce plasma volume, thus causing a drop in glomerular filtration rate and promoting the reabsorption of Na^+ and water. The volume of urine entering the diluting segment and the subsequent urine flow are both decreased.

IV. Thiazides and Related Agents

The thiazides are the most widely used of the diuretic drugs. They are sulfonamide derivatives and, as such, are related in structure to the carbonic anhydrase inhibitors. However, the thiazides have significantly greater diuretic activity than *acetazolamide* (see below), and they act on the kidney by different mechanisms. All thiazides affect the distal tubule, and all have equal maximum diuretic effects, differing only in potency (expressed on a per milligram basis). [Note: They are sometimes called â€œceiling diuretics,â€ because increasing the dose above normal does not promote a further diuretic response.] Like the actions of the loop diuretics, the thiazides partly depend on renal prostaglandin synthesis by a mechanism that is not yet understood.

A. Thiazides

Chlorothiazide [klor-oh-THYE-ah-zide] was the first modern diuretic that was active orally, and was capable of affecting the severe edema of cirrhosis and heart failure with a minimum of side effects. Its properties are representative of the thiazide group, although newer derivatives, such as *hydrochlorothiazide* [hi-dro-klor-oh-THYE-ah-zide] or *chlorthalidone*, are now used more commonly. *Hydrochlorothiazide* has far less ability to inhibit carbonic anhydrase compared to *chlorothiazide.* It is also more potent, so that the required dose is considerably lower than that of *chlorothiazide*. On the other hand, the efficacy is exactly the same as that of the parent drug. In all other aspects it resembles *chlorothiazide*. [Note: *Chlorthalidone, indapamide*, and *metolazone* are referred to as thiazide-like diuretics, because they contain the sulfonamide residue in their chemical structures and their mechanism of action is similar. However, they are not truly thiazides.]

1. **Mechanism of action:** The thiazide derivatives act mainly in the distal tubule to decrease the reabsorption of Na^+â€”apparently by inhibition of a Na^+/Cl^- cotransporter on the luminal membrane of the distal convoluted tubule (see Figure 22.2). They have a lesser effect in the proximal tubule. As a result, these drugs increase the concentration of Na^+ and Cl^- in the tubular fluid. The acid-base balance is not usually affected. [Note: Because the site of action of the thiazide derivatives is on the luminal membrane, these drugs must be excreted into the tubular lumen to be effective. Therefore, with decreased renal function, thiazide diuretics lose efficacy.]

2. **Actions:**

   a. **Increased excretion of Na^+ and Cl^-:** *Chlorothiazide* causes diuresis with increased Na^+ and Cl^- excretion, which can result in the excretion of a very hyperosmolar urine. This latter effect is unique; the other diuretic classes are unlikely to produce a hyperosmolar urine. The diuretic action is not affected by the acid-base status of the body, nor does *chlorothiazide* change the

   acid-base status of the blood. The relative changes in the ionic composition of the urine during therapy with thiazide diuretics are given in Figure 22.4.

   b. **Loss of K^+:** Because thiazides increase the Na^+ in the filtrate arriving at the distal tubule, more K^+ is also exchanged for Na^+, resulting in a continual loss of K^+ from the body with prolonged use of these drugs. Therefore, it is imperative to measure serum K^+ often (more frequently at the beginning of therapy) to assure that hypokalemia does not develop.

c. **Loss of Mg^{2+}:** Magnesium deficiency requiring supplementation can occur with chronic use of thiazide diuretics, particularly in the elderly. The mechanism for the magnesuria is not understood.

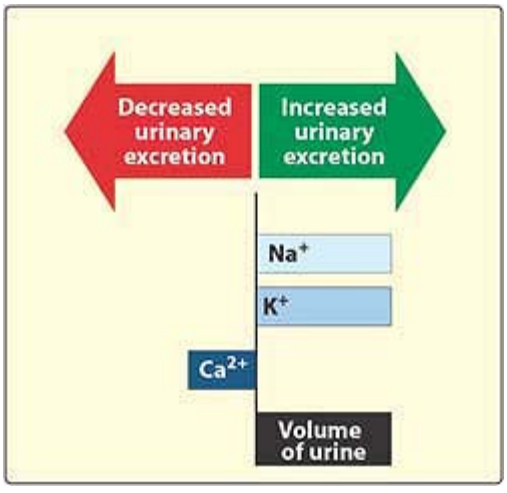

Figure 22.4 Relative changes in the composition of urine induced by thiazide diuretics.

d. **Decreased urinary calcium excretion:** Thiazide diuretics decrease the Ca^{2+} content of urine by promoting the reabsorption of Ca^{2+}. This contrasts with the loop diuretics, which increase the Ca^{2+} concentration of the urine. [Note: There is evidence from epidemiologic studies that use of thiazides preserves bone mineral density at the hip and spine and that the risk for hip fracture is reduced by a third.]

e. **Reduced peripheral vascular resistance:** An initial reduction in blood pressure results from a decrease in blood volume and, therefore, a decrease in cardiac output. With continued therapy, volume recovery occurs. However, there are continued hypotensive effects, resulting from reduced peripheral vascular resistance caused by relaxation of arteriolar smooth muscle.

3. **Therapeutic uses:**

a. **Hypertension:** Clinically, the thiazides have long been the mainstay of antihypertensive medication, because they are inexpensive, convenient to administer, and well tolerated. They are effective in reducing systolic and diastolic blood pressure for extended periods in the majority of patients with mild to moderate essential hypertension (see p. 215 for details on the treatment of hypertension). After 3 to 7 days of treatment, the blood pressure stabilizes at a lower level and can be maintained indefinitely by a daily-dosage level of the drug, which causes lower peripheral resistance without having a major diuretic effect. Many patients can be continued for years on the thiazides alone, although a small percentage of patients require additional medication, such as Î²-adrenergic blockers. [Note: The hypotensive actions of angiotensin-converting enzyme inhibitors are enhanced when given in combination with the thiazides.]

b. **Heart failure:** Thiazides can be the diuretic of choice in reducing extracellular volume in mild to moderate heart failure. If the thiazide fails, loop diuretics may be useful.

c. **Hypercalciuria:** The thiazides can be useful in treating idiopathic hypercalciuria, because they inhibit urinary Ca^{2+} excretion. This is particularly beneficial for patients with calcium oxalate stones in the urinary tract.

d. **Diabetes insipidus:** Thiazides have the unique ability to produce a hyperosmolar urine. Thiazides can

substitute for antidiuretic hormone in the treatment of nephrogenic diabetes insipidus. The urine volume of such individuals may drop from 11 L/day to about 3 L/day when treated with the drug.

4. **Pharmacokinetics:** The drugs are effective orally. Most thiazides take 1 to 3 weeks to produce a stable reduction in blood pressure, and they exhibit a prolonged biologic half-life (40 hours). All thiazides are secreted by the organic acid secretory system of the kidney (see Figure 22.3).

5. **Adverse effects:** Most of the adverse effects involve problems in fluid and electrolyte balance.

    a. **Potassium depletion:** Hypokalemia is the most frequent problem encountered with the thiazide diuretics, and it can predispose patients who are taking digitalis to ventricular arrhythmias (Figure 22.5). Often, K^+ can be supplemented by diet alone, such as by increasing the intake of citrus fruits, bananas, and prunes. In some cases, K^+ salt supplementation may be necessary. Activation of the renin-angiotensin-aldosterone system by the decrease in intravascular volume contributes significantly to urinary K^+ losses. Under these circumstances, the K^+ deficiency can be overcome by *spironolactone*, which interferes with aldosterone action, or by administering *triamterene*, which acts to retain K^+. Low-sodium diets blunt the potassium depletion caused by thiazide diuretics.

    b. **Hyponatremia:** This serious adverse effect may develop due to elevation of ADH as a result of hypovolemia, as well as diminished diluting capacity of the kidney and increased thirst. Limiting water intake and lowering the dose of diuretic can prevent this condition.

    c. **Hyperuricemia:** Thiazides increase serum uric acid by decreasing the amount of acid excreted by the organic acid secretory system. Being insoluble, the uric acid deposits in the joints, and a full-blown attack of gout may result in individuals who are predisposed to gouty attacks. It is important, therefore, to perform periodic blood tests for uric acid levels. [Note: *Probenecid*, a drug sometimes used in the treatment of gout, can interfere in the excretion of the thiazides and increase serum uric acid levels.]

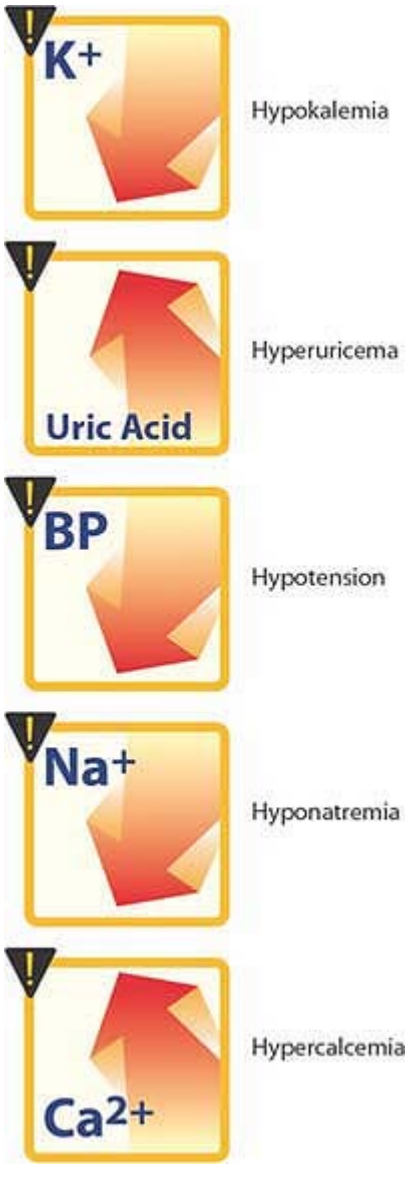

Figure 22.5 Summary of some adverse effects commonly observed with thiazide diuretics.

d. **Volume depletion:** This can cause orthostatic hypotension or light-headedness.

e. **Hypercalcemia:** The thiazides inhibit the secretion of Ca^{2+}, sometimes leading to elevated levels of Ca^{2+} in the blood.

f. **Hyperglycemia:** Patients with diabetes mellitus who are taking thiazides for hypertension may become hyperglycemic and have difficulty in maintaining appropriate blood sugar levels. This is due to impaired release of insulin and tissue uptake of glucose.

g. **Hyperlipidemia:** The thiazides can cause a 5- to 15-percent increase in serum cholesterol as well as increased serum low-density lipoproteins. Lipid levels, however, may return to normal with long-term therapy.

h. **Hypersensitivity:** Bone marrow suppression, dermatitis, necrotizing vasculitis, and interstitial nephritis are

very rare. Individuals who are hypersensitive to sulfa drugs may also be allergic to the thiazide diuretics.

B. Thiazide-like analogs

These compounds lack the thiazide structure, but like the thiazides, they have the unsubstituted sulfonamide group and share their mechanism of action.

1. **Chlorthalidone:** *Chlorthalidone* [klor-THAL-i-done] is a nonthiazide derivative that behaves pharmacologically like *hydrochlorothiazide*. It has a very long duration of action and, therefore, is often used to treat hypertension. It is given once per day for this indication.
2. **Metolazone:** *Metolazone* [me-TOL-ah-zone] is more potent than the thiazides and, unlike the thiazides, causes Na^+ excretion in advanced renal failure.
3. **Indapamide:** *Indapamide* [in-DAP-a-mide] is a lipid-soluble, nonthiazide diuretic that has a long duration of action. At low doses, it shows significant antihypertensive action with minimal diuretic effects. *Indapamide* is metabolized and excreted by the gastrointestinal tract and the kidneys. It is therefore less likely to accumulate in patients with renal failure and may be useful in their treatment.

V. Loop or High-Ceiling Diuretics

Bumetanide [byoo-MET-ah-nide], *furosemide* [fu-RO-se-mide], *torsemide* [TOR-se-myde], and *ethacrynic* [eth-a-KRIN-ik] *acid* are four diuretics that have their major action on the ascending limb of the loop of Henle (see Figure 22.2). Compared to all other classes of diuretics, these drugs have the highest efficacy in mobilizing Na^+ and Cl^- from the body. They produce copious amounts of urine. *Furosemide* is the most commonly used of these drugs. *Ethacrynic acid* has a steeper dose-response curve than *furosemide*, but it shows greater side effects than those seen with the other loop diuretics and its use is therefore limited. *Bumetanide* is much more potent than *furosemide*, and its use is increasing. *Bumetanide* and *furosemide* are sulfonamide derivatives.

A. Bumetanide, furosemide, torsemide, and ethacrynic acid

1. **Mechanism of action:** Loop diuretics inhibit the cotransport of $Na^+/K^+/2Cl^-$ in the luminal membrane in the ascending limb of the loop of Henle. Therefore, reabsorption of these ions is decreased (Figure 22.6). The loop diuretics are the most efficacious of the diuretic drugs, because the ascending limb accounts for the reabsorption of 25 to 30 percent of filtered NaCl and downstream sites are not able to compensate for this increased Na^+ load.
2. **Actions:** The loop diuretics act promptly, even among patients who have poor renal function or have not responded to thiazides or other

diuretics. Changes in the composition of the urine induced by loop diuretics are shown in Figure 22.6. [Note: Loop diuretics increase the Ca^{2+} content of urine, whereas thiazide diuretics decrease the Ca^{2+} concentration of the urine. In patients with normal serum Ca^{2+} concentrations, hypocalcemia does not result, because Ca^{2+} is reabsorbed in the distal convoluted tubule. However, hypomagnesemia can occur due to loss of Mg^{2+}.] The loop diuretics cause decreased renal vascular resistance and increased renal blood flow. In addition, loop diuretics increase prostaglandin synthesis. The prostaglandins have a role in their diuretic action, and substances such as *indomethacin* that interfere in prostaglandin synthesis can reduce the diuretic action of these agents.

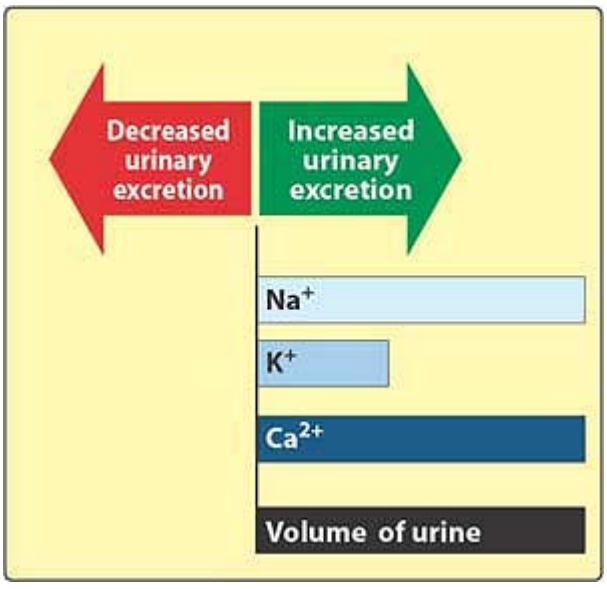

Figure 22.6 Relative changes in the composition of urine induced by loop diuretics.

3. **Therapeutic uses:** The loop diuretics are the drugs of choice for reducing the acute pulmonary edema of heart failure. Because of their rapid onset of action, particularly when given intravenously, the drugs are useful in emergency situations, such as acute pulmonary edema, which calls for a rapid, intense diuresis. Loop diuretics (along with hydration) are also useful in treating hypercalcemia, because they stimulate tubular Ca^{2+} excretion. They also are useful in the treatment of hyperkalemia.

4. **Pharmacokinetics:** Loop diuretics are administered orally or parenterally. Their duration of action is relatively briefâ€"2 to 4 hours. They are secreted into the urine.

5. **Adverse effects:** The adverse effects of the loop diuretics are summarized in Figure 22.7.

    a. **Ototoxicity:** Hearing can be affected adversely by the loop diuretics, particularly when used in conjunction with the aminoglycoside antibiotics. Permanent damage may result with continued treatment. *Ethacrynic acid* is the most likely to cause deafness. Vestibular function is less likely to be disturbed, but it, too, may be affected by combined treatment with the antibiotic.

    b. **Hyperuricemia:** *Furosemide* and *ethacrynic acid* compete with uric acid for the renal and biliary secretory systems, thus blocking its secretion and, thereby, causing or exacerbating gouty attacks.

    c. **Acute hypovolemia:** Loop diuretics can cause a severe and rapid reduction in blood volume, with the possibility of hypotension, shock, and cardiac arrhythmias. Hypercalcemia may occur under these conditions.

    d. **Potassium depletion:** The heavy load of Na^+ presented to the collecting tubule results in increased exchange of tubular Na^+ for K^+, with the possibility of inducing hypokalemia. The loss of K^+ from cells in exchange for H^+ leads to hypokalemic alkalosis. Potassium depletion can be averted by use of potassium-sparing diuretics or dietary supplementation with K^+.

    e. **Hypomagnesemia:** A combination of chronic use of loop diuretics and low dietary intake of Mg^{2+} can lead to hypomagnesemia, particularly in the elderly. This can be corrected by oral supplementation.

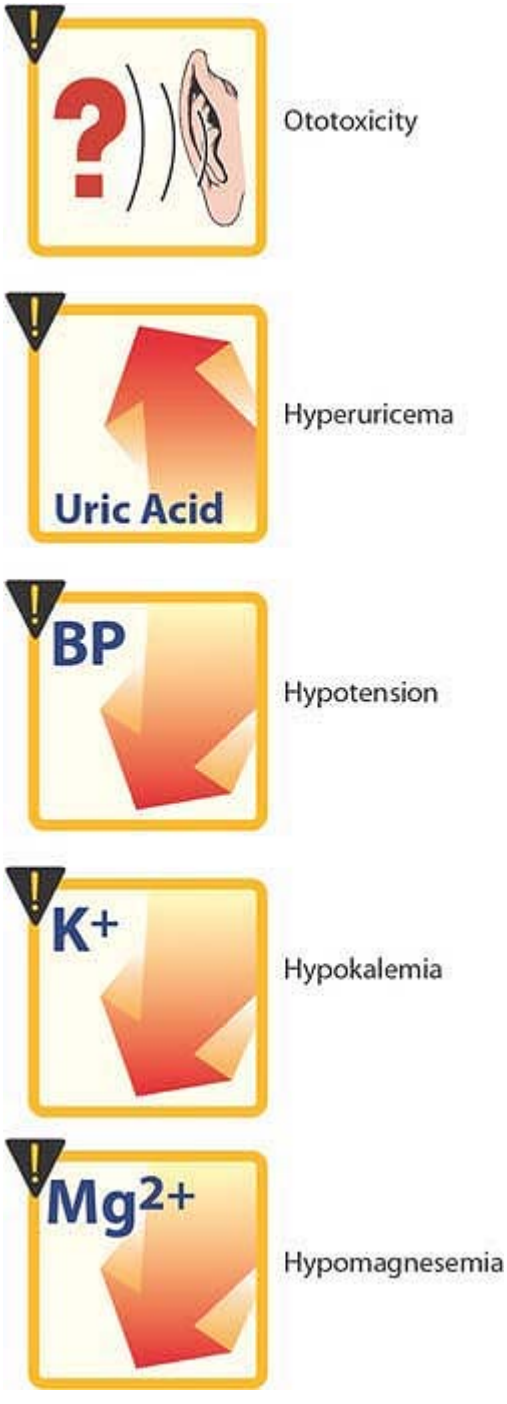

Figure 22.7 Summary of some adverse effects commonly observed with loop diuretics.

VI. Potassium-Sparing Diuretics

Potassium-sparing diuretics act in the collecting tubule to inhibit Na^+ reabsorption and K^+ excretion (Figure 22.8). Potassium-sparing diuretics are used alone primarily when aldosterone is present in excess. The major use of potassium-sparing agents is in the treatment of hypertension, most often in combination with a thiazide. It is

extremely important that patients who are treated with any potassium-sparing diuretic be closely monitored for potassium levels. Exogenous potassium supplementation is usually discontinued when potassium-sparing diuretic therapy is instituted.

A. Aldosterone antagonists: Spironolactone and eplerenone

1. **Mechanism of action:** *Spironolactone* [spear-oh-no-LAK-tone] is a synthetic steroid that antagonizes aldosterone at intracellular cytoplasmic receptor sites. The *spironolactone*-receptor complex is inactive. That is, it prevents translocation of the receptor complex into the nucleus of the target cell; thus, it cannot bind to DNA. This results in a failure to produce proteins that are normally synthesized in response to aldosterone. These mediator proteins normally stimulate the Na^+/K^+-exchange sites of the collecting tubule. Thus, a lack of mediator proteins prevents Na^+ reabsorption and, therefore, K^+ and H^+ secretion.

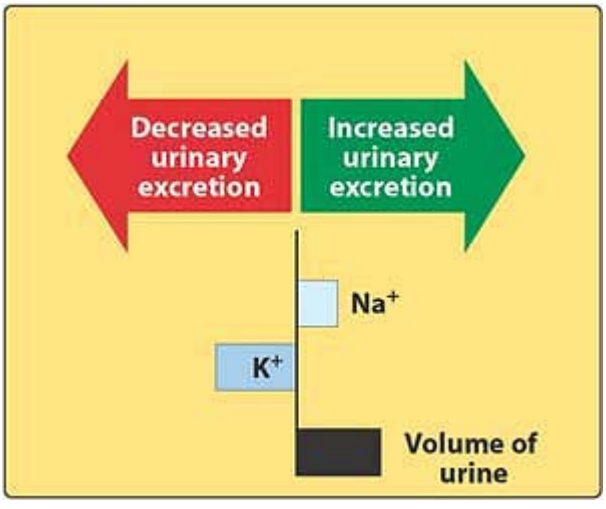

Figure 22.8 Relative changes in the composition of urine induced by potassiumsparing diuretics.

2. **Actions:** In most edematous states, blood levels of aldosterone are high, which is instrumental in retaining Na^+. When *spironolactone* is given to a patient with elevated circulating levels of aldosterone, the drug antagonizes the activity of the hormone, resulting in retention of K^+ and excretion of Na^+ (see Figure 22.8). In patients who have no significant circulating levels of aldosterone, such as those with Addison's disease (primary adrenal insufficiency), no diuretic effect of the drug occurs. In common with the thiazides and loop diuretics, the effect of *spironolactone* depends on renal prostaglandin synthesis. *Eplerenone* [eh-PLEH-reh-none] is a new aldosterone-receptor antagonist, with actions comparable to those of *spironolactone*. *Eplerenone* may have less endocrine effects than *spironolactone*.

3. **Therapeutic uses:**

   a. **Diuretic:** Although *spironolactone* has a low efficacy in mobilizing Na^+ from the body in comparison with the other drugs, it has the useful property of causing the retention of K^+. Because of this latter action, *spironolactone* is often given in conjunction with a thiazide or loop diuretic to prevent the K^+ excretion that would otherwise occur with these drugs. It is the diuretic of choice in patients with hepatic cirrhosis.

   b. **Secondary hyperaldosteronism:** *Spironolactone* is the only potassium-sparing diuretic that is routinely used alone to induce a net negative salt balance. It is particularly effective in clinical situations associated with secondary hyperaldosteronism.

c. **Heart failure:** *Spironolactone* prevents the remodeling that occurs as compensation for the progressive failure of the heart.

4. **Pharmacokinetics:** *Spironolactone* is completely absorbed orally and is strongly bound to proteins. It is rapidly converted to an active metabolite, canrenone. The action of *spironolactone* is largely due

to the effect of canrenone, which has mineralocorticoid-blocking activity. *Spironolactone* induces hepatic cytochrome P450.

5. **Adverse effects:** *Spironolactone* frequently causes gastric upsets and can cause peptic ulcers. Because it chemically resembles some of the sex steroids, *spironolactone* may act at receptors in other organs to induce gynecomastia in males and menstrual irregularities in females; therefore, the drug should not be given at high doses on a chronic basis. It is most effectively employed in mild edematous states, for which it is given for a few days at a time. At low doses, *spironolactone* can be used chronically with few side effects. Hyperkalemia, nausea, lethargy, and mental confusion can occur.

B. Triamterene and amiloride

Triamterene [trye-AM-ter-een] and *amiloride* [a-MIL-oh-ride] block Na^+ transport channels, resulting in a decrease in Na^+/K^+ exchange. Although they have a K^+-sparing diuretic action similar to that of *spironolactone*, their ability to block the Na^+/K^+-exchange site in the collecting tubule does not depend on the presence of aldosterone. Thus, they have diuretic activity even in individuals with Addison's disease. Like *spironolactone*, they are not very efficacious diuretics. Both *triamterene* and *amiloride* are frequently used in combination with other diuretics, usually for their potassium-sparing properties. For example, much like *spironolactone*, they prevent the loss of K^+ that occurs with thiazides and *furosemide*. The side effects of *triamterene* are leg cramps and the possibility of increased blood urea nitrogen as well as uric acid and K^+ retention.

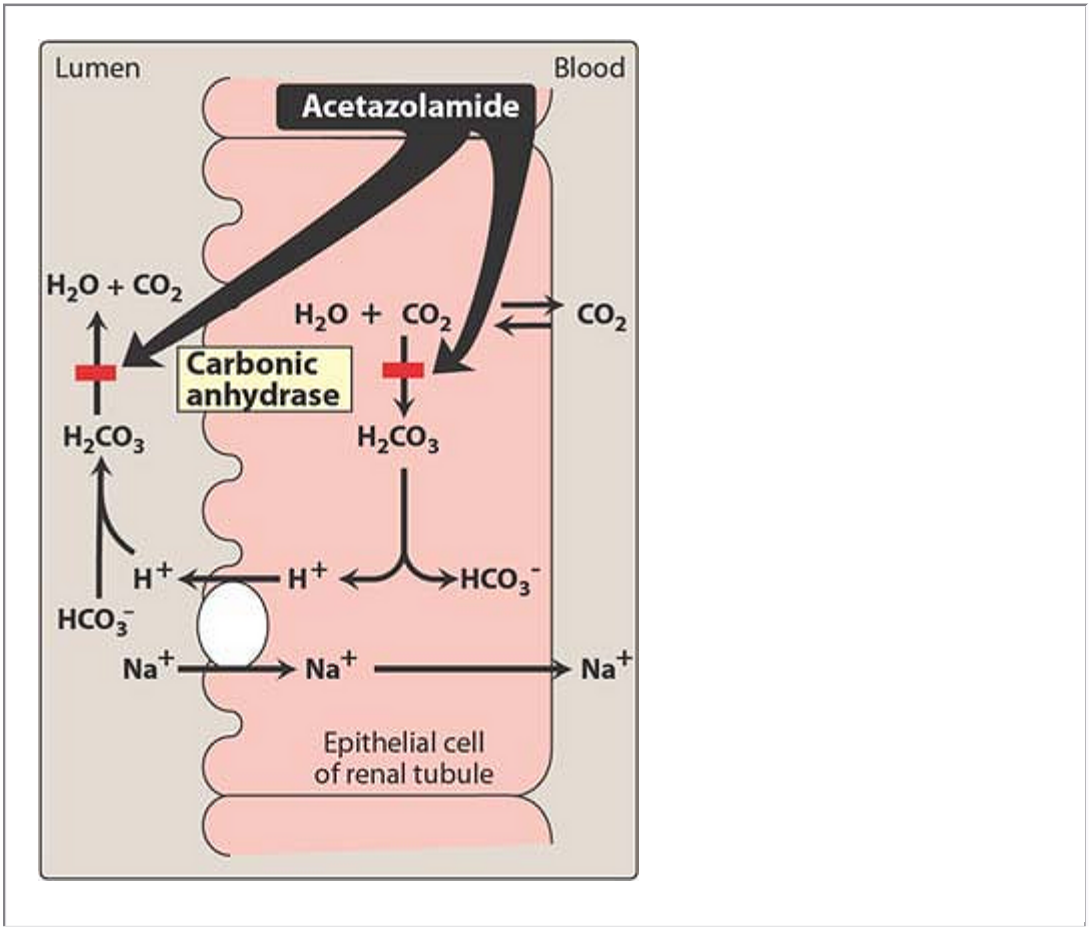

Figure 22.9 Role of carbonic anhydrase in sodium retention by epithelial cells of renal tubule.

VII. Carbonic Anhydrase Inhibitors

Acetazolamide [ah-set-a-ZOLE-a-mide] inhibits the enzyme carbonic anhydrase in the proximal tubular epithelial cells. Carbonic anhydrase inhibitors are more often used for their other pharmacologic actions rather than for their diuretic effect, because they are much less efficacious than the thiazides or loop diuretics.

A. Acetazolamide

1. **Mechanism of action:** *Acetazolamide* inhibits carbonic anhydrase located intracellularly (cytoplasm) and on the apical membrane of the proximal tubular epithelium (Figure 22.9). [Note: Carbonic anhydrase catalyzes the reaction of CO_2 and H_2O, leading to H_2CO_3, which spontaneously ionizes to H^+ and HCO_3^- (bicarbonate)]. The decreased ability to exchange Na^+ for H^+ in the presence of *acetazolamide* results in a mild diuresis. Additionally, HCO_3^- is retained in the lumen, with marked elevation in urinary pH. The loss of HCO_3^- causes a hyperchloremic metabolic acidosis and decreased diuretic efficacy following several days of therapy. Changes in the composition of urinary electrolytes induced by *acetazolamide* are summarized in Figure 22.10. Phosphate excretion is increased by an unknown mechanism.

2. **Therapeutic uses:**

   a. **Treatment of glaucoma:** The most common use of *acetazolamide* is to reduce the elevated intraocular pressure of open-angle glaucoma. *Acetazolamide* decreases the production of aqueous humor, probably by blocking carbonic anhydrase in the ciliary

   body of the eye. It is useful in the chronic treatment of glaucoma but should not be used for an acute attack; *pilocarpine* is preferred for an acute attack because of its immediate action. Topical carbonic anhydrase inhibitors, such as *dorzolamide* and *brinzolamide*, have the advantage of not causing any systemic effects.

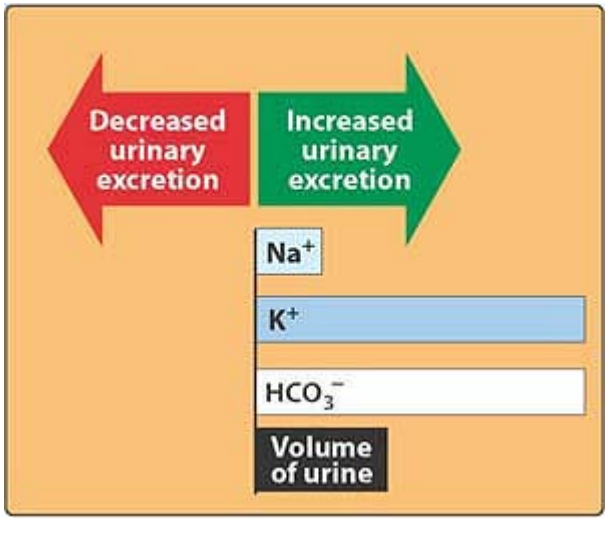

Figure 22.10 Relative changes in the composition of urine induced by *acetazolamide*.

b. **Mountain sickness:** Less commonly, *acetazolamide* can be used in the prophylaxis of acute mountain sickness among healthy, physically active individuals who rapidly ascend above 10,000 feet. *Acetazolamide* given nightly for 5 days before the ascent prevents the weakness, breathlessness, dizziness, nausea, and cerebral as well as pulmonary edema characteristic of the syndrome.

3. **Pharmacokinetics:** *Acetazolamide* is given orally once to four times daily. It is secreted by the proximal tubule.

4. **Adverse effects:** Metabolic acidosis (mild), potassium depletion, renal stone formation, drowsiness, and paresthesia may occur. The drug should be avoided in patients with hepatic cirrhosis, because it could lead to a decreased excretion of NH_4^+.

VIII. Osmotic Diuretics

A number of simple, hydrophilic chemical substances that are filtered through the glomerulus, such as *mannitol* [MAN-i-tol] and *urea* [yu-REE-ah], result in some degree of diuresis. This is due to their ability to carry water with them into the tubular fluid. If the substance that is filtered subsequently undergoes little or no reabsorption, then the filtered substance will cause an increase in urinary output. Only a small amount of additional salt may also be excreted. Because osmotic diuretics are used to effect increased water excretion rather than Na^+ excretion, they are not useful for treating conditions in which Na^+ retention occurs. They are used to maintain urine flow following acute toxic ingestion of substances capable of producing acute renal failure. Osmotic diuretics are a mainstay of treatment for patients with increased intracranial pressure or acute renal failure due to shock, drug toxicities, and trauma. Maintaining urine flow preserves long-term kidney function and may save the patient from dialysis. [Note: *Mannitol* is not absorbed when given orally and should only be given intravenously.] Adverse effects include extracellular water expansion and dehydration as well as hypo- or hypernatremia. The expansion of extracellular water results because the presence of *mannitol* in the extracellular fluid extracts water from the cells and causes hyponatremia until diuresis occurs. Dehydration, on the other hand, can occur if water is not replaced adequately.

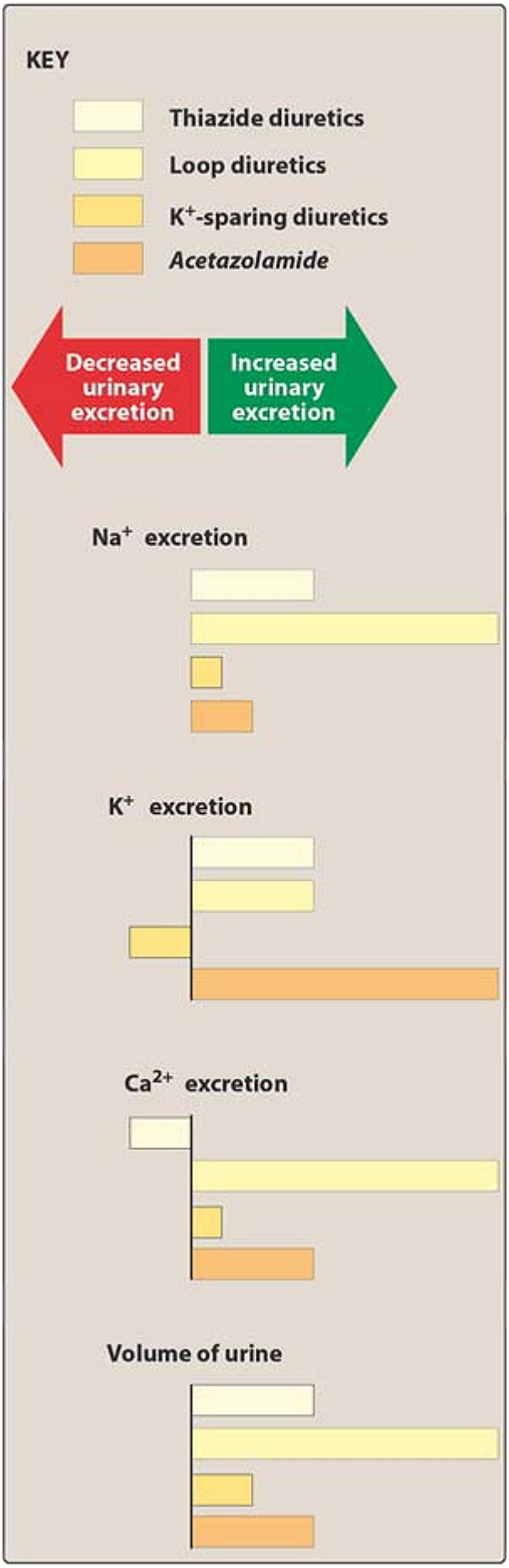
KEY
Thiazide diuretics
Loop diuretics
K+-sparing diuretics
Acetazolamide
Decreased urinary excretion
Increased urinary excretion
Na+ excretion
K+ excretion
Ca2+ excretion
Volume of urine

Figure 22.11 Summary of relative changes in urinary composition induced by diuretic drugs.

Figure 22.11 summarizes the relative changes in urinary composition induced by diuretic drugs.

Study Questions

Choose the ONE best answer.

22.1 An elderly patient with a history of heart disease and who is having difficulty breathing is brought into the emergency room. Examination reveals that she has pulmonary edema. Which of the following treatments is indicated?

A. Spironolactone.

B. Furosemide.

C. Acetazolamide.

D. Chlorthalidone.

E. Hydrochlorothiazide.

View Answer

22.2 A group of college students is planning a mountain climbing trip to the Andes. Which of the following drugs would be appropriate for them to take to prevent mountain sickness?

A. A thiazide diuretic.

B. An anticholinergic.

C. A carbonic anhydrase inhibitor.

D. A loop diuretic.

E. A Î²-blocker.

View Answer

22.3 An alcoholic male has developed hepatic cirrhosis. To control the ascites and edema, he is prescribed which one of the following?

A. Hydrochlorothiazide.

B. Acetazolamide.

C. Spironolactone.

D. Furosemide.

E. Chlorthalidone.

View Answer

22.4 A 55-year-old male with kidney stones has been placed on a diuretic to decrease calcium excretion. However, after a few weeks, he develops an attack of gout. Which diuretic was he taking?

A. Furosemide.

B. Hydrochlorothiazide.

C. Spironolactone.

D. Triamterene.

View Answer

22.5 A 75-year-old woman with hypertension is being treated with a thiazide. Her blood pressure responds and reads at 120/76 mm Hg. After several months on the medication, she complains of being tired and weak. An analysis of the blood indicates low values for which of the following ?

A. Calcium.

B. Uric acid.

C. Potassium.

D. Sodium.

E. Glucose

View Answer

22.6 Which of the following drugs is contraindicated in a patient with hyperkalemia?

A. Acetazolamide

B. Chlorothiazide

C. Ethacrynic acid

D. Chlorthalidone

E. Spironolactone

View Answer

22.7 Which would be the initial treatment choice to manage the hypertension in an African-American woman with a past medical history of gout and severe hypokalemia?

A. Hydrochlorothiazide

B. Spironolactone

C. alsartan

D. Atenolol

E. Enalapril

View Answer

Editors: **Finkel, Richard; Clark, Michelle A.; Cubeddu, Luigi X.**
Title: *Lippincott's Illustrated Reviews: Pharmacology, 4th Edition*

Chapter 23

Pituitary and Thyroid

I. Overview

The neuroendocrine system, which is controlled by the pituitary and hypothalamus, coordinates body functions by transmitting messages between individual cells and tissues. This contrasts with the nervous system which communicates locally by electrical impulses and neurotransmitters directed through neurons to other neurons or to specific target organs, such as muscle or glands. Nerve impulses generally act within milliseconds. The endocrine system releases hormones into the bloodstream, which carries these chemical messengers to target cells throughout the body. Hormones have a much broader range of response time than do nerve impulses, requiring from seconds to days, or longer, to cause a response that may last for weeks or months. The two regulatory systems are closely interrelated. For example, in several instances, the release of hormones is stimulated or inhibited by the nervous system, and some hormones can stimulate or inhibit nerve impulses. Chapters 24 to 26 focus on drugs that affect the synthesis and/or secretion of specific hormones and their actions. In this chapter, the central role of the hypothalamic and pituitary hormones in regulating body functions is briefly presented (Figure 23.1). In addition, drugs affecting thyroid hormone synthesis and/or secretion are discussed.

II. Hypothalamic and Anterior Pituitary Hormones

The hormones secreted by the hypothalamus and the pituitary are all peptides or low-molecular-weight proteins that act by binding to specific receptor sites on their target tissues. The hormones of the anterior pituitary are regulated by neuropeptides that are called either â€œreleasingâ€ or â€œinhibitingâ€ factors or hormones. These are produced in cell bodies in the hypothalamus, and they reach the cells of the pituitary by the hypophysial portal system (Figure 23.2). The interaction of the releasing hormones with their receptors results in the activation of genes that promote the synthesis of protein precursors. These are then processed posttranslationally to the hormones and are released into the circulation. [Note: Unlike those of the posterior pituitary, the hormones of the anterior pituitary are not stored in granules prior to release.] Each hypothalamic regulatory hormone controls the release of a specific hormone

from the anterior pituitary. The hypothalamic-releasing hormones are primarily used for diagnostic purposes (that is, to determine pituitary insufficiency). [Note: The hypothalamus also synthesizes the precursor proteins of the hormones vasopressin and oxytocin, which are transported to the posterior pituitary, where they are stored until released.] Although a number of pituitary hormone preparations are currently used therapeutically for specific hormonal deficiencies (examples of which follow), most of these agents have limited therapeutic applications. Hormones of the anterior and posterior pituitary are administered either intramuscularly (IM), subcutaneously, or intranasally, but not orally, because their peptidyl nature makes them susceptible to destruction by the proteolytic enzymes of the digestive tract.

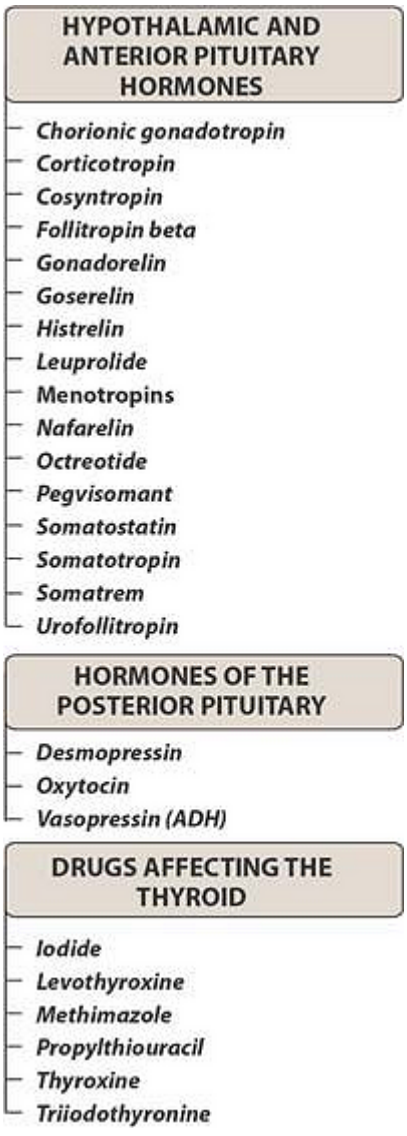

Figure 23.1 Some of the hormones and drugs affecting the hypothalamus, pituitary, and thyroid.

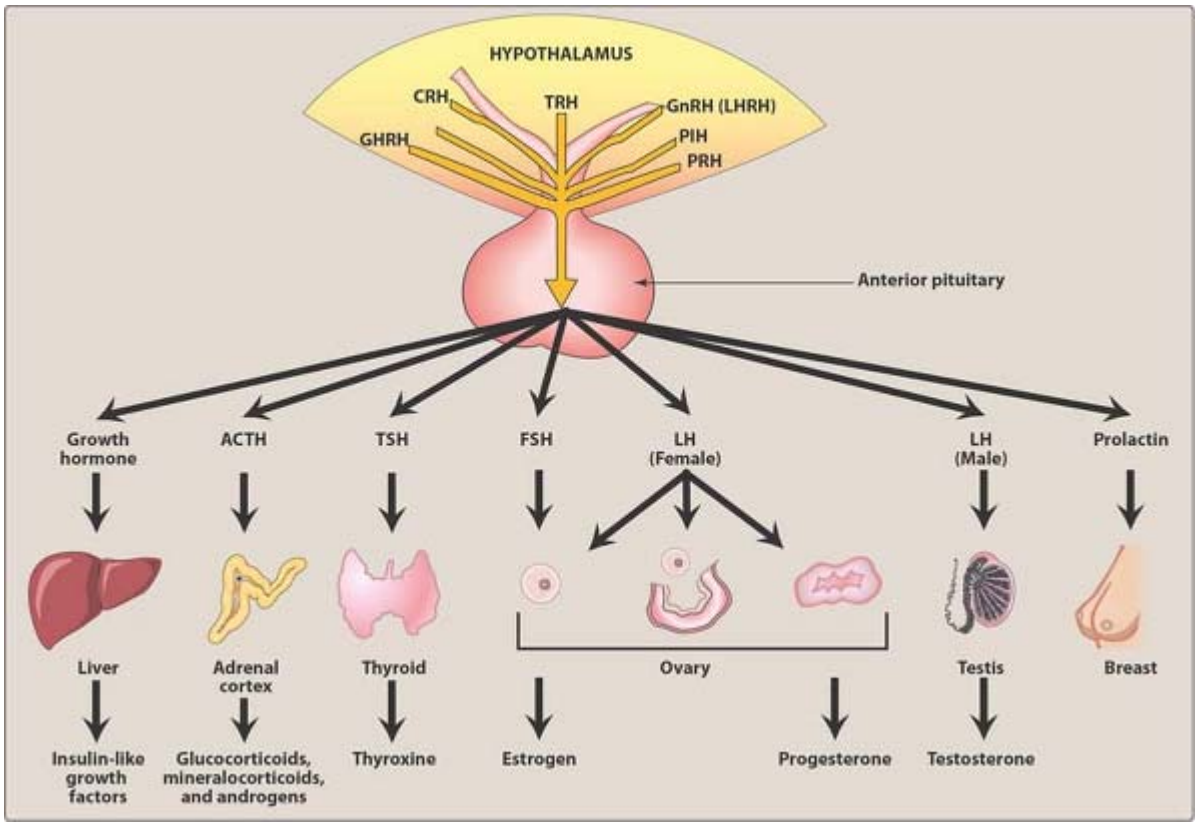

Figure 23.2 Hypothalamic-releasing hormones and actions of anterior pituitary hormones. GHRH = growth hormone-releasing hormone; TRH = thyrotropin-releasing hormone; CRH= corticotropin-releasing hormone; GnRH (LHRH) = gonadotropinreleasing hormone (luteinizing hormone-releasing hormone); PIH = prolactin-inhibiting hormone (dopamine); and PRH = prolactin-releasing hormone; ACTH = adrenocorticotropic hormone; TSH = thyrotropin-stimulating hormone; FSH = follicle-stimulating hormone; LH = luteinizing hormone

A. Adrenocorticotropic hormone (corticotropin)

Corticotropin-releasing hormone (CRH) is responsible for the synthesis and release of the peptide proopiomelanocortin by the hypothalamus (Figure 23.3). Adrenocorticotropic hormone (ACTH), or *corticotropin*

[kor-ti-koe-TROE-pin] is a product of the posttranslational processing of this precursor polypeptide. [Note: CRH is used diagnostically to differentiate between Cushing's syndrome and ectopic ACTH-producing cells.] Other products of proopiomelanocortin are Î³-melanocyte stimulating hormone and Î²-lipotropin, the latter being the precursor of the endorphins. Normally, ACTH is released from the pituitary in pulses with an overriding diurnal rhythm, with the highest concentration occurring at approximately 6 AM and the lowest in the evening. Stress stimulates its secretion, whereas cortisol acting via negative feedback suppresses its release.

1. **Mechanism of action:** The target organ of ACTH is the adrenal cortex, where it binds to specific receptors on the cell surfaces. The occupied receptors activate G proteinâ€“coupled processes to increase cyclic adenosine monophosphate (cAMP), which in turn stimulates the rate-limiting step in the adrenocorticosteroid synthetic pathway (cholesterol to pregnenolone). This pathway ends with the synthesis and release of the adrenocorticosteroids and the adrenal androgens (see Figure 23.3).
2. **Therapeutic uses:** The availability of synthetic adrenocorticosteroids with specific properties has limited the

use of *corticotropin* mainly to serving as a diagnostic tool for differentiating between primary adrenal insufficiency (Addison's disease, associated with adrenal atrophy) and secondary adrenal insufficiency (caused by the inadequate secretion of ACTH by the pituitary). Therapeutic *corticotropin* preparations are extracts from the anterior pituitaries of domestic animals or synthetic human ACTH. The latter, *cosyntropin* [ko-sin-TROE-pin], which consists of the amino-terminal 24 amino acids of the hormone, is preferred for the diagnosis of adrenal insufficiency. ACTH is used in the treatment of infantile spasm (West Syndrome).

3. **Adverse effects:** Toxicities are similar to those of glucocorticoids. Antibodies can form against ACTH derived from animal sources.

B. Growth hormone (somatotropin)

Somatotropin [soe-mah-toe-TROE pin] is a large polypeptide that is released by the anterior pituitary in response to growth hormone (GH)â€“releasing hormone produced by the hypothalamus (see Figure 23.2). Secretion of GH is inhibited by another pituitary hormone, *somatostatin* (see below). GH is released in a pulsatile manner, with the highest levels occurring during sleep. With increasing age, GH secretion decreases, being accompanied by a decrease in lean muscle mass. Human GH is produced synthetically by recombinant DNA technology. GH from animal sources is ineffective in humans. *Somatotropin* influences a wide variety of biochemical processes; for example, through stimulation of protein synthetic processes, cell proliferation and bone growth are promoted. Increased formation of hydroxyproline from proline boosts cartilage synthesis.

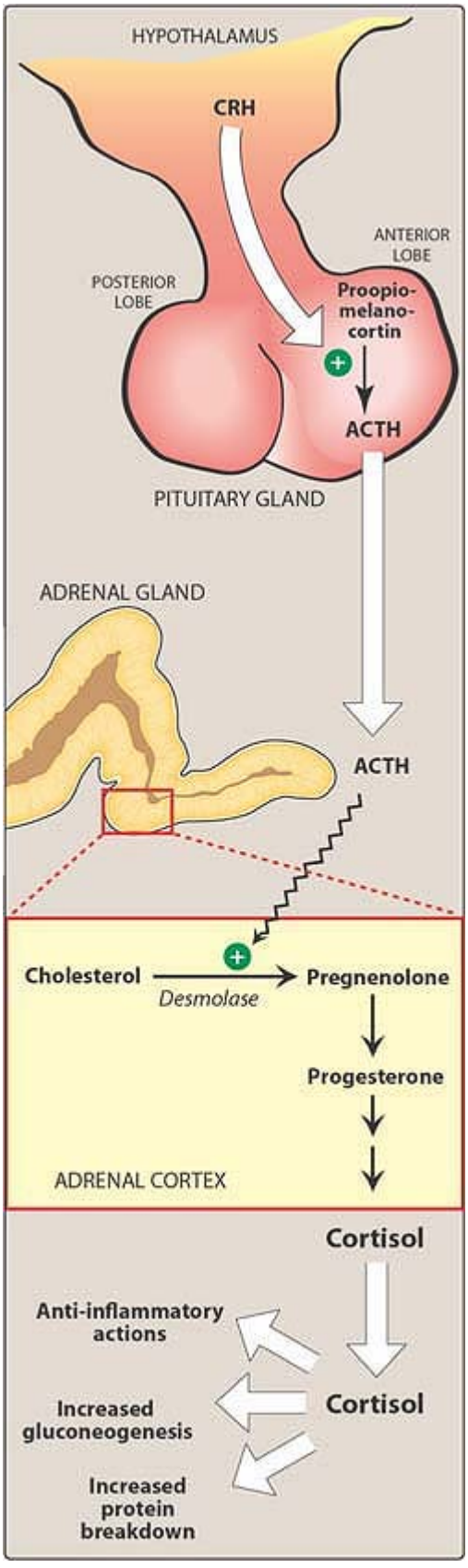

Figure 23.3 Secretion and actions of adrenocorticotropic hormone (ACTH). CRH = corticotropin-releasing

hormone.

1. **Mechanism of action:** Although many physiologic effects of GH are exerted directly at its targets, others are mediated through the somatomedinsâ€"insulin-like growth factors I and II (IGF-I and IGF-II). [Note: In acromegaly, IGF-I levels are consistently high, reflecting elevated GH.]

2. **Therapeutic uses:** *Somatotropin* is used in the treatment of GH deficiency in children. It is important to establish whether the GH deficit is actually due to hypopituitarism, because other factors, such as normal thyroid status, are essential for successful *somatotropin* therapy. [Note: After a study published in 1990 indicated that GH administered to men over 60 years of age for 6 months increased their lean body mass, bone density, and skin thickness, whereas adipose tissue mass decreased, many started to call GH the antiaging hormone. This has led to abuse by some athletes seeking to enhance their performance. GH is not approved for this purpose, and some who have taken it have developed diabetes.] A therapeutically equivalent drug, *somatrem* [SOE-ma-trem], contains an extra terminal methionyl residue not found in *somatotropin*. Although the half-lives of these drugs are short (approximately 25 minutes), they induce the release from the liver of IGF-I (formerly somatomedin C), which is responsible for subsequent GH-like actions. *Somatotropin* and *somatrem* should not be used in individuals with closed epiphyses or an enlarging intracranial mass.

C. Growth hormoneâ€"inhibiting hormone (somatostatin)

In the pituitary, *somatostatin* [soe-ma-toe-STAT in] binds to distinct receptors, SSTR2 and SSTR5, which suppress GH and thyroid-stimulating hormone release. Originally isolated from the hypothalamus, *somatostatin* is a small polypeptide that is also found in neurons throughout the body as well as in the intestine and pancreas. *Somatostatin* therefore has a number of actions. For example, it not only inhibits the release of GH but, also, that of insulin, glucagon, and gastrin. *Octreotide* [ok-TREE-oh-tide] is a synthetic octapeptide analog of *somatostatin*. Its half-life is longer than that of the natural compound, and a depot form is also available. The two forms suppress GH and IGF-I for 12 hours and 6 weeks, respectively. They have found use in the treatment of acromegaly caused by hormone-secreting tumors and in secretory diarrhea associated with tumors producing vasoactive intestinal peptide (VIPomas). Adverse effects of *octreotide* treatment are flatulence, nausea, and steatorrhea. Gallbladder emptying is delayed, and asymptomatic cholesterol gallstones can occur with long-term treatment. [Note: An analog of human GH that has polyethylene glycol polymers attached, *pegvisomant* [peg-VI-soe-mant], is being employed in the treatment of acromegaly that is refractory to other modes of surgical, radiologic, or pharmacologic intervention. It acts as an antagonist at one of the GH receptors and results in the normalization of IGF-I levels.

D. Gonadotropin-releasing hormone/luteinizing hormoneâ€"releasing hormone

Gonadotropin-releasing hormone (GnRH), also called *gonadorelin* [go-nad-oh-RELL-in], is a decapeptide obtained from the hypothalamus. Pulsatile secretion of GnRH is essential for the release of *follicle-stimulating hormone* (*FSH*) and *luteinizing hormone* (*LH*) from the pituitary, whereas continuous administration inhibits gonadotropin release. GnRH is employed to stimulate gonadal hormone production in hypogonadism. A number of synthetic analogs, such as *leuprolide* [loo-PROE-lide], *goserelin* [GOE-se-rel-in], *nafarelin* [naf-A-rel-in], and *histrelin* [his-TREL-in], act as agonists at GnRH receptors (Figure 23.4). These are effective in suppressing production of the gonadal hormones and, thus, are effective in the treatment of prostatic cancer,

endometriosis, and precocious puberty. Adverse effects of *gonadorelin* include hypersensitivity, dermatitis, and headache. In women, the analogs may cause hot flushes and sweating as well as diminished libido, depression, and ovarian cysts. They are contraindicated in pregnancy and breast-feeding. In men, they initially cause a rise in testosterone that can result in bone pain; hot flushes, edema, gynecomastia, and diminished libido also occur.

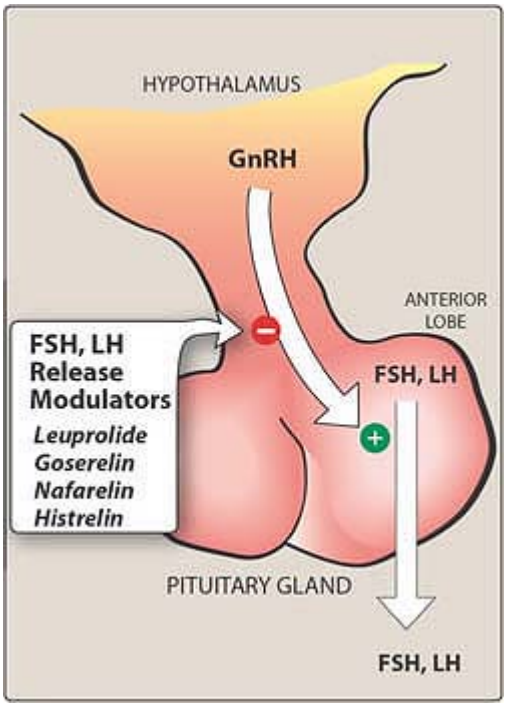

Figure 23.4 Secretion of follicle-stimulating hormone (FSH) and lutenizing hormone (LH). GnRH = gonadotropin-releasing hormone.

E. Gonadotropins: Human menopausal gonadotropin, follicle-stimulating hormone, and human chorionic gonadotropin

The gonadotropins are glycoproteins that are produced in the anterior pituitary. The regulation of gonadal steroid hormones depends on these agents. They find use in the treatment of infertility in men and women. *Menotropins* [men-oh-TROE-pin] (*human menopausal gonadotropins*, or *hMG*) are obtained from the urine of menopausal women and contain *FSH* and *luteinizing hormone LH*. *Chorionic gonadotropin* (*hCG*) is a placental hormone and an *LH* agonist, to which it is structurally related. It is also excreted in the urine. *Urofollitropin* [yoor-oh-fol-li-TROE-pin] is *FSH* obtained from menopausal women and is devoid of *LH*. *Follitropin beta* [fol-ih-TROE-pin] is human *FSH* manufactured by recombinant DNA technology. All of these hormones are injected IM. Injection of *hMG* or *FSH* over a period of 5 to 12 days causes ovarian follicular growth and maturation, and with subsequent injection of *hCG*, ovulation occurs. In men who are lacking gonadotropins, treatment with *hCG* causes external sexual maturation, and with the subsequent injection of *hMG*, spermatogenesis occurs. Adverse effects include ovarian enlargement and possible hypovolemia. Multiple births are not uncommon. Men may develop gynecomastia.

F. Prolactin

Prolactin is a peptide hormone similar in structure to GH, and is also secreted by the anterior pituitary. Its secretion is inhibited by dopamine acting at D_2 receptors. Its primary function is to stimulate and maintain lactation. In addition, it decreases sexual drive and reproductive function. The hormone enters a cell, where it activates a tyrosine kinase to promote tyrosine phosphorylation and gene activation. There is no preparation available for hypoprolactinemic conditions. On the other hand, hyperprolactinemia, which is associated with galactorrhea and hypogonadism, is usually treated with D_2-receptor agonists, such as *bromocriptine* and *cabergoline*. Both of these agents also find use in the treatment of microadenomas and macroprolactinomas. They not only act at the D_2 receptor to inhibit prolactin secretion but also cause increased hypothalamic dopamine by decreasing its turnover.

Among their adverse effects are nausea, headache, and sometimes, psychiatric problems.

III. Hormones of the Posterior Pituitary

In contrast to the hormones of the anterior lobe of the pituitary, those of the posterior lobe, *vasopressin* and *oxytocin*, are not regulated by releasing hormones. Instead, they are synthesized in the hypothalamus, transported to the posterior pituitary, and released in response to specific physiologic signals, such as high plasma osmolarity or parturition. Each is a nonapeptide with a circular structure due to a disulfide bridge. Reduction of the disulfide inactivates these hormones. They are susceptible to proteolytic

cleavage and, thus, are given parenterally. Both hormones have very short half-lives. Their actions are summarized in Figure 23.5.

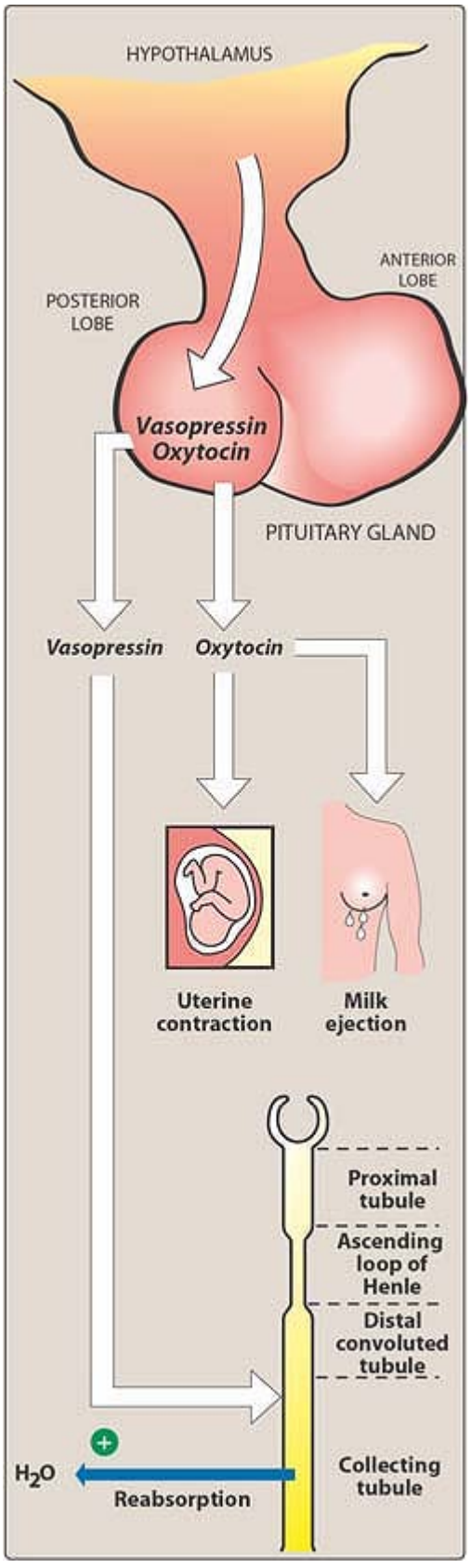

Figure 23.5 Actions of oxytocin and vasopressin. ACTH = adrenocorticotropic hormone.

A. Oxytocin

Oxytocin [ok-se-TOE-sin], originally extracted from animal posterior pituitaries, is now chemically synthesized. Its only use is in obstetrics, where it is employed to stimulate uterine contraction to induce or reinforce labor or to promote ejection of breast milk. [Note: The sensitivity of the uterus to *oxytocin* increases with the duration of pregnancy when it is under estrogenic dominance.] To induce labor, the drug is administered intravenously. However, when used to induce â€œmilk let-down,â€ it is given as a nasal spray. *Oxytocin* causes milk ejection by contracting the myoepithelial cells around the mammary alveoli. Although toxicities are uncommon when the drug is used properly, hypertensive crises, uterine rupture, water retention, and fetal death have been reported. Its antidiuretic and pressor activities are very much lower than those of *vasopressin*. [Note: *Oxytocin* is contraindicated in abnormal fetal presentation, fetal distress, and premature births.]

B. Vasopressin

Vasopressin [vas-oh-PRESS-in] (antidiuretic hormone), is structurally related to *oxytocin*. The chemically synthesized nonapeptide has replaced that extracted from animal posterior pituitaries. *Vasopressin* has both antidiuretic and vasopressor effects (see Figure 23.5). In the kidney, it binds to the V_2 receptor to increase water permeability and resorption in the collecting tubules. Thus, the major use of *vasopressin* is to treat diabetes insipidus. It also finds use in controlling bleeding due to esophageal varices or colonic diverticula. Other effects of *vasopressin* are mediated by the V_1 receptor, which is found in liver, vascular smooth muscle (where it causes constriction), and other tissues. As might be expected, the major toxicities are water intoxication and hyponatremia. Headache, bronchoconstriction, and tremor can also occur. Caution must be used when treating patients with coronary artery disease, epilepsy, and asthma.

C. Desmopressin

Because of its pressor properties, *vasopressin* has been modified to *desmopressin* [des-moe-PRESS-in] (1-desamino-8-d-arginine vasopressin), which has minimal activity at the V_1 receptor, making it largely free of pressor effects. This analog is now preferred for diabetes insipidus and nocturnal enuresis and is longer-acting than *vasopressin*. *Desmopressin* is conveniently administered intranasally. However, local irritation may occur.

IV. Thyroid Hormones

The thyroid gland facilitates normal growth and maturation by maintaining a level of metabolism in the tissues that is optimal for their normal function. The two major thyroid hormones are *triiodothyronine* (*T3*; the most active form) and *thyroxine* (*T4*). Although the thyroid gland is not essential for life, inadequate secretion of thyroid hormone (hypothyroidism) results in bradycardia, poor resistance to cold, and mental and physical slowing (in children, this can cause mental retardation and dwarfism). If, however, an excess of thyroid hormones is secreted (hyperthyroidism), then tachycardia and cardiac arrhythmias, body wasting, nervousness, tremor, and excess

heat production can occur. [Note: The thyroid gland also secretes the hormone calcitoninâ€”a serum calcium-lowering hormone.]

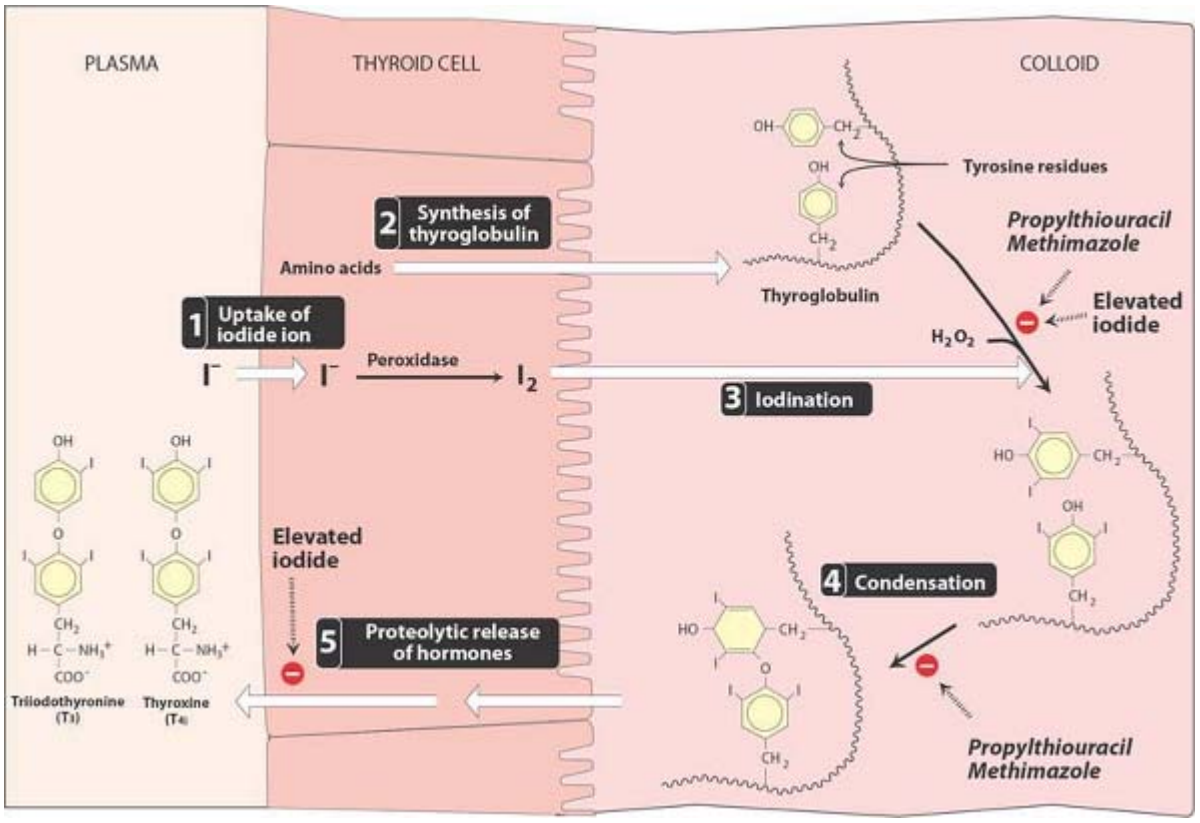

Figure 23.6 Biosynthesis of thyroid hormones.

A. Thyroid hormone synthesis and secretion

The thyroid gland is made up of multiple follicles that consist of a single layer of epithelial cells surrounding a lumen filled with colloid (thyroglobulin), which is the storage form of thyroid hormone. A summary of the steps in thyroid hormone synthesis and secretion is shown in Figure 23.6.

1. **Regulation of synthesis:** Thyroid function is controlled by a tropic hormone, thyroid-stimulating hormone (TSH; thyrotropin). TSH is a glycoprotein, structurally related to *LH* and *FSH*, which is synthesized by the anterior pituitary (see Figure 23.2). TSH generation is governed by the hypothalamic thyrotropin-releasing hormone (TRH). TSH action is mediated by cAMP and leads to stimulation of *iodide* (I^-) uptake. Oxidation to iodine (I_2) by a peroxidase is followed by iodination of tyrosines on thyroglobulin. [Note: Antibodies to thyroid peroxidase are diagnostic for Hashimoto's thyroiditis.] Condensation of two diiodotyrosine residues gives rise to *T4*, whereas condensation of a monoiodotyrosine residue with a diiodotyrosine residue generates *T3*, which is still bound to the

protein. The hormones are released following proteolytic cleavage of the thyroglobulin.

2. **Regulation of secretion:** Secretion of TSH by the anterior pituitary is stimulated by the hypothalamic TRH. Feedback inhibition of TRH occurs with high levels of circulating thyroid hormone. [Note: At pharmacologic doses, *dopamine, somatostatin*, or glucocorticoids can also suppress TSH secretion.] Most of the hormone (*T3* and *T4*) is bound to thyroxine-binding globulin in the plasma.

B. Mechanism of action

Both *T4* and *T3* must dissociate from thyroxine-binding plasma proteins prior to entry into cells, either by diffusion or by active transport. In the cell, *T4* is enzymatically deiodinated to *T3*, which enters the nucleus and attaches to specific receptors. The activation of these receptors promotes the formation of RNA and subsequent protein synthesis, which is responsible for the effects of T_4.

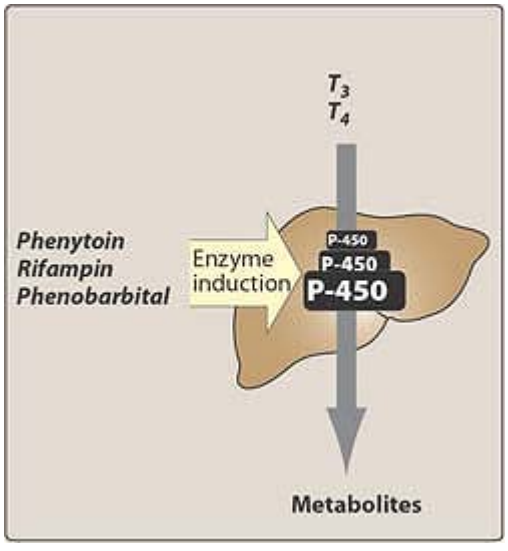

Figure 23.7 Enzyme induction can increase the metabolism of the thydroid hormones. *T3 = triiodothyronine; T4 = thyroxine.*

C. Pharmacokinetics

Both *T4* and *T3* are absorbed after oral administration. Food, calcium preparations, and aluminum-containing antacids can decrease the absorption of *T4* but not of *T3. T4* is converted to *T3* by one of two distinct deiodinases, depending on the tissue. The hormones are metabolized through the microsomal P450 system. Drugs that induce the P450 enzymes, such as *phenytoin, rifampin*, and *phenobarbital*, accelerate metabolism of the thyroid hormones (Figure 23.7).

D. Treatment of hypothyroidism

Hypothyroidism usually results from autoimmune destruction of the gland or the peroxidase and is diagnosed by elevated TSH. It is treated with *levothyroxine* (*T4*) [leh-vo-thye-ROK-sin]. The drug is given once daily because of its long half-life. Steady state is achieved in 6 to 8 weeks. Toxicity is directly related to *T4* levels and manifests itself as nervousness, heart palpitations and tachycardia, intolerance to heat, and unexplained weight loss.

E. Treatment of hyperthyroidism (thyrotoxicosis)

Excessive amounts of thyroid hormones in the circulation are associated with a number of disease states, including Graves' disease, toxic adenoma, and goiter. In these situations, TSH levels are reduced. The goal of therapy is to decrease synthesis and/or release of additional hormone. This can be accomplished by removing part or all of the thyroid gland, by inhibiting synthesis of the hormones, or by blocking release of the hormones from the follicle.

1. **Removal of part or all of the thyroid:** This can be accomplished either surgically or by destruction of the gland by beta particles emitted by radioactive iodine (^{131}I), which is selectively taken up by the thyroid follicular cells. Younger patients are treated with the isotope without prior pretreatment with *methimazole* (see below),

whereas the opposite is the case in elderly patients. Most patients become hypothyroid as a result of this drug and require treatment with *levothyroxine*.

2. **Inhibition of thyroid hormone synthesis:** The thioamides, *propylthiouracil* [proe-pil-thye-oh-YOOR-ah-sil] (*PTU*) and *methimazole* [meth-IM-ah-zole], are concentrated in the thyroid, where they inhibit both the oxidative processes required for iodination of tyrosyl groups and the coupling of iodotyrosines to form *T3* and *T4* (see Figure 23.6). *PTU* can also block the conversion of *T4* to *T3* [Note: These drugs have no effect on the thyroglobulin already stored in the gland; therefore, observation of any clinical effects of these drugs may be delayed until thyroglobulin stores are depleted.] The thioamides are well absorbed from the gastrointestinal tract, but they have short half-lives. Several doses of *PTU* are required per day, whereas a single dose of *methimazole* suffices due to the duration of its antithyroid effect. The effects of these drugs are slow in onset; thus, they are not effective in the treatment of thyroid storm (see below). Relapse may occur. Relatively rare adverse effects include agranulocytosis, rash, and edema.

3. **Thyroid storm:** Î²-Blockers that lack sympathomimetic activity, such as *propranolol*, are effective in blunting the widespread sympathetic stimulation that occurs in hyperthyroidism. Intravenous administration is effective in treating thyroid storm. An alternative in patients suffering from severe heart failure or asthma is the calcium-channel blocker, *diltiazem*. Other agents used in the treatment of thyroid storm include *PTU* (because it inhibits the peripheral conversion of T_4 to *T3* but *methimazole* does not), *iodides*, and glucocorticoids (to protect against shock).

4. **Blockade of hormone release:** A pharmacologic dose of *iodide* inhibits the iodination of tyrosines (the so-called â€œacute Wolff-Chaikoff effectâ€), but this effect lasts only a few days. What is more important, *iodide* inhibits the release of thyroid hormones from thyroglobulin by mechanisms not yet understood. Today, *iodide* is rarely used as the sole therapy. However, it is employed to treat potentially fatal thyrotoxic crisis (thyroid storm) or prior to surgery, because it decreases the vascularity of the thyroid gland. *Iodide* is not useful for long-term therapy, because the thyroid ceases to respond to the drug after a few weeks. *Iodide* is administered orally. Adverse effects are relatively minor and include sore mouth and throat, swelling of the tongue or larynx, rashes, ulcerations of mucous membranes, and a metallic taste in the mouth.

Study Questions

Choose the ONE best answer.

23.1 Symptoms of hyperthyroidism include all of following except:

A. Tachycardia.

B. Nervousness.

C. Poor resistance to cold.

D. Body wasting.

E. Tremor.

View Answer

23.2 Which of the following best describes the effect of propylthiouracil on thyroid hormone production?

A. It blocks the release of thyrotropin-releasing hormone.

B. It inhibits uptake of iodide by thyroid cells.

C. It prevents the release of thyroid hormone from thyroglobulin.

D. It blocks iodination and coupling of tyrosines in thyroglobulin to form thyroid hormones.

E. It blocks the release of hormones from the thyroid gland.

View Answer

23.3 Hyperthyroidism can be treated by all but which one of the following?

A. Triiodothyronine.

B. Surgical removal of the thyroid gland.

C. Iodide.

D. Propylthiouracil.

E. Methimazole.

View Answer

23.4 Which one of the following hormones is a non-peptide, allowing oral administration?

A. ACTH

B. Growth hormone

C. GnRH

D. Thyroxine

E. CRH

View Answer

23.5 Which one of the following agents is INCORRECTLY paired to a clinical use of the drug?

A. Desmopressin: treatment of diabetes insipidis

B. Octreotide: treatment of diarrhea associated with vasoactive intestinal peptide tumors

C. Oxytocin: induction of labor

D. hCG: treatment of infertility in men and women

E. Pegvisoment: treatment of short stature in men and women.

View Answer

Editors: **Finkel, Richard; Clark, Michelle A.; Cubeddu, Luigi X.**
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Chapter 24

Insulin and OralHypoglycemic Drugs

I. Overview

The pancreas is both an endocrine gland that produces the peptide hormones *insulin*, glucagon, and somatostatin and an exocrine gland that produces digestive enzymes. The peptide hormones are secreted from cells located in the islets of Langerhans (Î² cells produce *insulin*, Î± cells produce glucagon, and Î´ cells produce somatostatin). These hormones play an important role in regulating the metabolic activities of the body, particularly the homeostasis of blood glucose.[1] Hyperinsulinemia (due, for example, to an insulinoma) can cause severe hypoglycemia. More commonly, a relative or absolute lack of *insulin*, such as in diabetes mellitus, can cause serious hyperglycemia, which, if left untreated, can result in retinopathy, nephropathy, neuropathy, and cardiovascular complications. Administration of *insulin* preparations or oral hypoglycemic agents (Figure 24.1) can prevent morbidity and reduce mortality associated with diabetes.

II. Diabetes Mellitus

The incidence of diabetes is growing rapidly both in the United States and worldwide. For example, it is estimated that more than 180 million people worldwide are afflicted with diabetes, and the prevalence is expected to more than double by the year 2030. In the United States, approximately 21 million people are estimated to suffer from diabetes, and it is a major cause of morbidity and mortality. Diabetes is not a single disease. Rather, it is a heterogeneous group of syndromes characterized by an elevation of blood glucose caused by a relative or absolute deficiency of *insulin*. [Note: Frequently, the inadequate release of *insulin* is aggravated by an excess of glucagon.] The American Diabetes Association (ADA) recognizes four clinical classifications of diabetes: Type 1 diabetes (formerly *insulin*-dependent diabetes mellitus), Type 2 diabetes (formerly nonâ€“*insulin* dependent diabetes mellitus), gestational diabetes, and diabetes due to other causes (e.g., genetic defects or medication induced).[2] Figure 24.2 summarizes the characteristics of Type 1 and Type 2 diabetes. Gestational diabetes is defined as carbohydrate intolerance with onset or first recognition during pregnancy. It is important to maintain adequate glycemic control during pregnancy, because uncontrolled gestational diabetes

can lead to fetal macrosomia (overly large body) and shoulder dystocia (difficult delivery), as well as neonatal hypoglycemia. Diet, exercise, and/or *insulin* administration are effective in this condition. *Glyburide* may be a reasonably safe alternative to *insulin* therapy for gestational diabetes. However, larger randomized studies are needed to fully assess neonatal outcomes and optimal dosing regimens.

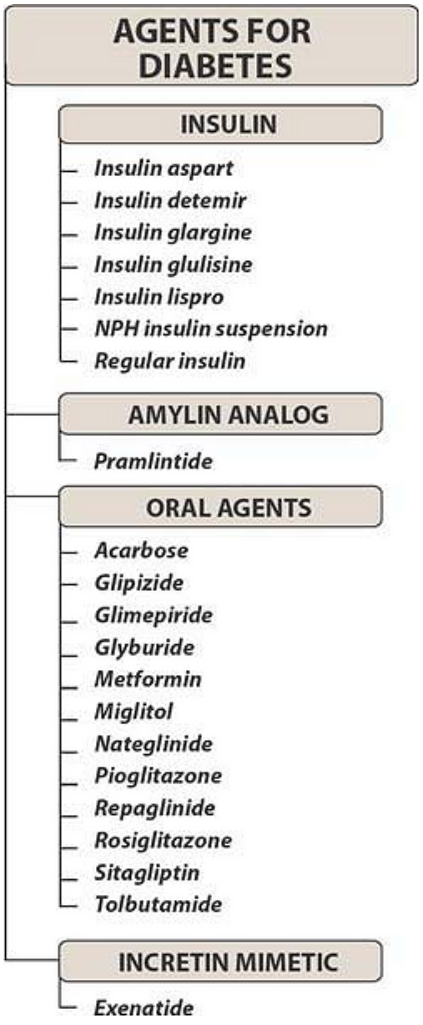
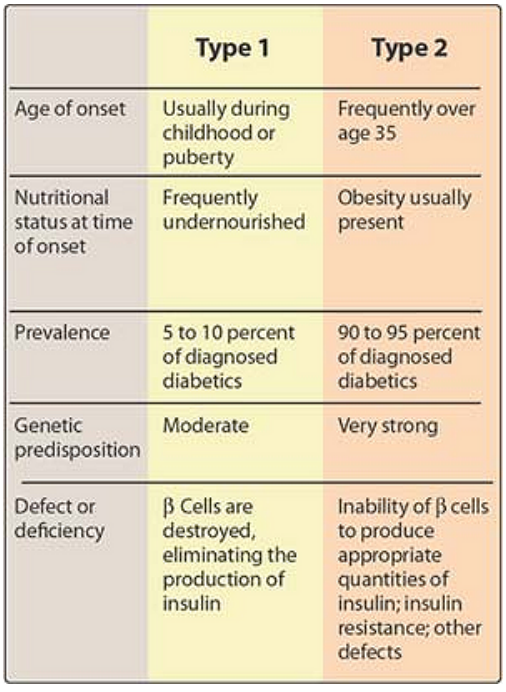


Figure 24.1 Summary of drugs used in the treatment of diabetes.



	Type 1	Type 2
Age of onset	Usually during childhood or puberty	Frequently over age 35
Nutritional status at time of onset	Frequently undernourished	Obesity usually present
Prevalence	5 to 10 percent of diagnosed diabetics	90 to 95 percent of diagnosed diabetics
Genetic predisposition	Moderate	Very strong
Defect or deficiency	β Cells are destroyed, eliminating the production of insulin	Inability of β cells to produce appropriate quantities of insulin; insulin resistance; other defects

Figure 24.2 Comparison of Type 1 and Type 2 diabetes.

A. Type 1 diabetes

Type 1 diabetes most commonly afflicts individuals in puberty or early adulthood, but some latent forms can occur later in life. The disease is characterized by an absolute deficiency of *insulin* caused by massive Î²-cell necrosis. Loss of Î²-cell function is usually ascribed to autoimmune-mediated processes directed against the Î² cell, and it may be triggered by an invasion of viruses or the action of chemical toxins. As a result of the destruction of these cells, the pancreas fails to respond to glucose, and the Type 1 diabetic shows classic symptoms of *insulin* deficiency (polydipsia, polyphagia, polyuria, and weight loss). Type 1 diabetics require exogenous *insulin* to avoid the catabolic state that results from and is characterized by hyperglycemia and life-threatening ketoacidosis.

1. **Cause of Type 1 diabetes:** In the postabsorptive period of a normal individual, low, basal levels of circulating *insulin* are maintained through constant Î²-cell secretion. This suppresses lipolysis, proteolysis, and glycogenolysis. A burst of *insulin* secretion occurs within 2 minutes after ingesting a meal, in response to transient increases in the levels of circulating glucose and amino acids. This lasts for up to 15 minutes, and, is followed by the postprandial secretion of *insulin*. However, having virtually no functional Î² cells, the Type 1 diabetic can neither maintain a basal secretion level of *insulin* nor respond to variations in circulating fuels (Figure 24.3). The development and progression of neuropathy, nephropathy, and retinopathy are directly related to the extent of glycemic control (measured as blood levels of glucose and/or hemoglobin A_{1c} [HbA_{1c}]).[3]

2. **Treatment:** A Type 1 diabetic must rely on exogenous (injected) *insulin* to control hyperglycemia, avoid ketoacidosis, and maintain acceptable levels of glycosylated hemoglobin (HbA_{1c}). [Note: The rate of formation of HbA_{1c} is proportional to the average blood glucose concentration over the previous 3 months; thus, HbA_{1c} provides a measure of how well treatment has normalized blood glucose in diabetics.] The goal in administering *insulin* to Type 1 diabetics is to maintain blood glucose concentrations as close to normal as possible and to avoid wide swings in glucose levels that may contribute to long-term complications. The use of home blood glucose monitors facilitates frequent self-monitoring and treatment with *insulin* injections. Continuous subcutaneous *insulin* infusionâ€"also called the *insulin* pumpâ€"is another method of *insulin* delivery. This method of administration may be more convenient for some patients, eliminating the multiple daily injections of *insulin*. The pump is programmed to deliver a basal rate

of *insulin* secretion, and it also allows the patient to control delivery of a bolus of *insulin* to compensate for high blood glucose or in anticipation of postprandial needs. Other methods of *insulin* delivery, such as transdermal, buccal, and intranasal, are currently under investigation. Amylin is a hormone that is cosecreted with *insulin* from pancreatic Î² cells following food intake. *Pramlintide* [PRAM-len-tide], a synthetic analog of amylin, may be used as an adjunct to *insulin* therapy.

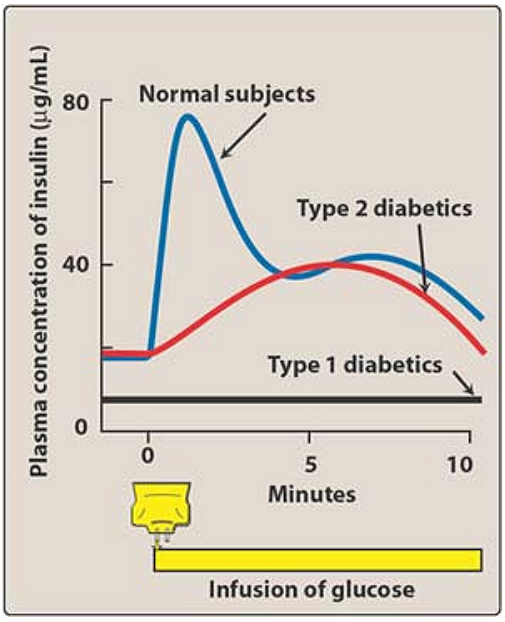


Figure 24.3 Release of insulin that occurs in response to an IV glucose load in normal subjects and diabetic patients.

B. Type 2 diabetes

Most diabetics are Type 2. The disease is influenced by genetic factors, aging, obesity, and peripheral *insulin* resistance rather than by autoimmune processes or viruses. The metabolic alterations observed are milder than those described for Type 1 (for example, Type 2 patients typically are not ketotic), but the long-term clinical consequences can be just as devastating (for example, vascular complications and subsequent infection can lead to amputation of the lower limbs).

1. **Cause:** In Type 2 diabetes, the pancreas retains some Î²-cell function, but variable *insulin* secretion is insufficient to maintain glucose homeostasis (see Figure 24.3). The Î²-cell mass may become gradually reduced in Type 2 diabetes. In contrast to patients with Type 1, those with Type 2 diabetes are often obese. [Note: Not all obese individuals become diabetic.] Type 2 diabetes is frequently accompanied by the lack of sensitivity of target organs to either endogenous or exogenous *insulin* (Figure 24.4). This resistance to *insulin* is considered to be a major cause of this type of diabetes .

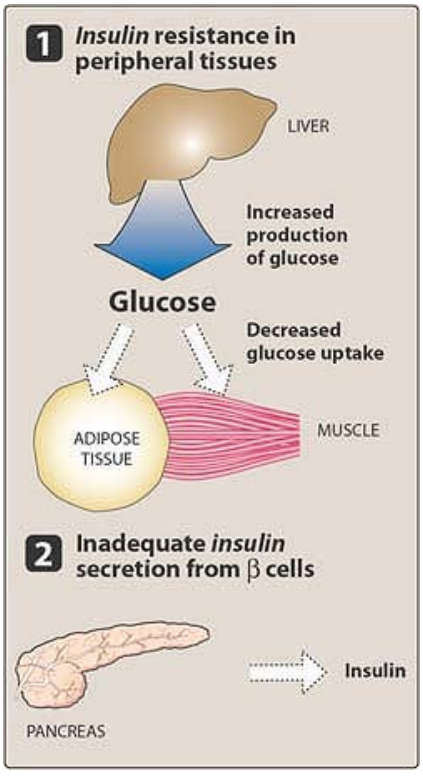


Figure 24.4 Major factors contributing to hyperglycemia observed in Type 2 diabetes.

2. **Treatment:** The goal in treating Type 2 diabetes is to maintain blood glucose concentrations within normal limits and to prevent the development of long-term complications of the disease. Weight reduction, exercise, and dietary modification decrease *insulin* resistance and correct the hyperglycemia of Type 2 diabetes in some patients. However, most patients are dependent on pharmacologic intervention with oral hypoglycemic agents. As the disease progresses, Î²-cell function declines, and *insulin* therapy is often required to achieve satisfactory serum glucose levels (Figure 24.5).

III. Insulin and Its Analogs

Insulin [IN-su-lin] is a polypeptide hormone consisting of two peptide chains that are connected by disulfide bonds. It is synthesized as a precursor (pro-insulin) that undergoes proteolytic cleavage to form *insulin* and C peptide, both of which are secreted by the Î² cells of the pancreas.[4] [Note: Type 2 patients secrete high levels of proinsulin. Because radioimmunoassays do not distinguish between proinsulin and *insulin*, Type 2 patients may have lower levels of the active hormone than the assay indicates. Thus, measurement of circulating C peptide provides a better index of *insulin* levels.]

A. Insulin secretion

Insulin secretion is regulated not only by blood glucose levels but also by certain amino acids, other hormones (see gastrointestinal hormones

below), and autonomic mediators. Secretion is most commonly triggered by high blood glucose, which is taken up by the glucose transporter into the Î² cells of the pancreas. There, it is phosphorylated by glucokinase, which acts as a glucose sensor. The products of glucose metabolism enter the mitochondrial respiratory chain and generate adenosine triphosphate (ATP). The rise in ATP levels causes a block of K^+ channels, leading to membrane depolarization and an influx of Ca^{2+}, which results in pulsatile *insulin* exocytosis. The sulfonylureas and meglitinides owe their hypoglycemic effect to the inhibition of the K^+ channels. [Note: Glucose given by injection has a weaker effect on *insulin* secretion than does glucose taken orally, because when given orally, glucose stimulates production of digestive hormones by the gut, which in turn stimulate *insulin* secretion by the pancreas.]

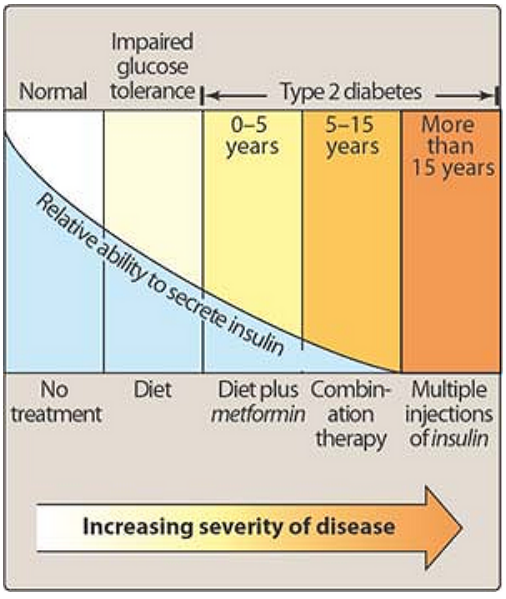


Figure 24.5 Duration of Type 2 diabetes mellitus, suffciency of endogenous insulin, and recommended sequence of therapy.

B. Sources of insulin

Human *insulin* is produced by recombinant DNA technology using special strains of Escherichia coli or yeast that have been genetically altered to contain the gene for human *insulin*. Modifications of the amino acid sequence of human *insulin* have produced *insulins* with different pharmacokinetic properties. For example, three such *insulins*â€"*lispro, aspart*, and *glulisine*â€"have a faster onset and shorter duration of action than regular *insulin*, because they do not aggregate or form complexes. On the other hand, *glargine* and *detemir* are long-acting *insulins* and show prolonged, flat levels of the hormone following injection.

C. Insulin administration

Because *insulin* is a polypeptide, it is degraded in the gastrointestinal tract if taken orally. It therefore is generally administered by subcutaneous injection. [Note: In a hyperglycemic emergency, regular *insulin* is injected intravenously.] Continuous subcutaneous *insulin* infusion has become popular, because it does not require multiple daily injections. *Insulin* preparations vary primarily in their times of onset of activity and in their durations of activity. This is due to differences in the amino acid sequences of the polypeptides. Dose, site of injection, blood supply, temperature, and physical activity can affect the duration of action of the various preparations. *Insulin* is inactivated by *insulin*-degrading enzyme (also called *insulin* protease), which is found mainly in the liver and kidney.

D. Adverse reactions to insulin

The symptoms of hypoglycemia are the most serious and common adverse reactions to an overdose of *insulin* (Figure 24.6). Long-term diabetics often do not produce adequate amounts of the counter-regulatory hormones (glucagon, epinephrine, cortisol, and growth hormone), which normally provide an effective defense against hypoglycemia. Other adverse reactions include weight gain, lipodystrophy (less common with human *insulin*), allergic reactions, and local injection site reactions. Diabetics with renal insufficiency may require adjustment of the *insulin* dose.

IV. Insulin Preparations and Treatment

It is important that any change in *insulin* treatment be made cautiously by the clinician, with strict attention paid to the dose. Figure 24.7 summarizes onset of action, timing of peak level, and duration of action for the various types of *insulins* that are currently in use.

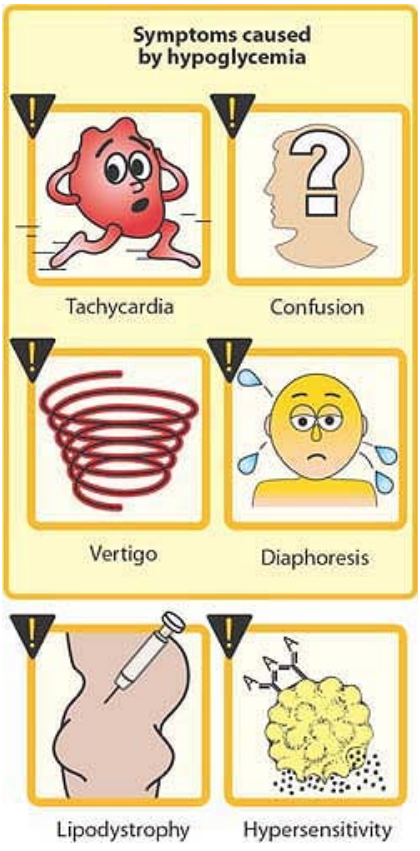


Figure 24.6 Adverse effects observed with *insulin.* [Note: Lipodystrophy is a local atrophy or hypertrophy of subcutaneous fatty tissue at the site of injections.]

A. Rapid-acting and short-acting insulin preparations

Four *insulin* preparations fall into this category: regular *insulin, insulin lispro, insulin aspart,* and *insulin glulisine*. Regular *insulin* is a short-acting, soluble, crystalline *zinc insulin*. Regular *insulin* is usually given subcutaneously (or intravenously in emergencies), and it rapidly lowers blood glucose (Figure 24.8). Regular *insulin, insulin lispro*, and *insulin aspart* are pregnancy category B. *Insulin glulisine* has not been studied in pregnancy. Because of their rapid onset and short duration of action, the *lispro* [LIS-proe], *aspart* [AS-part], and *glulisine* [gloo-LYSE-een] forms of *insulin* are classified as rapid-acting *insulins*. These agents offer more flexible treatment regimens and may lower the risk of hypoglycemia. *Insulin lispro* differs from regular *insulin* in that lysine and proline at positions 28 and 29 in the B chain are reversed. This results in more rapid absorption after subcutaneous injection than is seen with regular *insulin*; as a consequence, *insulin lispro* acts more rapidly. Peak levels of *insulin lispro* are seen at 30 to 90 minutes after injection, as compared with 50 to 120 minutes for regular *insulin*. *Insulin lispro* also has a shorter duration of activity. *Insulin aspart* and *insulin glulisine* have pharmacokinetic and pharmacodynamic properties similar to those of *insulin lispro*. They are administered to mimic the prandial (mealtime) release of *insulin*, and they are usually not used alone but, rather, along with a longer-acting *insulin* to assure proper glucose control. Like regular *insulin*, they are administered subcutaneously. *Insulin lispro* is usually administered 15 minutes prior to a meal or immediately following a meal, whereas *glulisine* can be taken either 15 minutes before a meal or within 20 minutes after starting a meal. *Insulin aspart* must be administered just prior to the meal. All of the rapid-acting formulations are suitable for intravenous administration, although regular *insulin* is most commonly used when the intravenous route is needed. *Insulin lispro, insulin aspart*, and *insulin glulisine* may also be used in external *insulin* pumps.

B. Intermediate-acting insulin

Neutral protamine Hagedorn (*NPH*) *insulin* is a suspension of crystalline *zinc insulin* combined at neutral pH with a positively charged polypeptide, protamine. [Note: Another name for this preparation is *insulin isophane*.] Its duration of action is intermediate. This is due to delayed absorption of the *insulin* because of its conjugation with protamine, forming a less-soluble complex. *NPH insulin* should only be given subcutaneously (never intravenously) and is useful in treating all forms of

diabetes except diabetic ketoacidosis or emergency hyperglycemia. It is used for basal control and is usually given along with rapid- or short-

acting *insulin* for mealtime control. [Note: A similar compound called *neutral protamine lispro* (*NPL*) *insulin*, has been prepared that is used only in combination with *insulin lispro* (see below).] Figure 24.8 shows three of many regimens that use combinations of *insulins*.

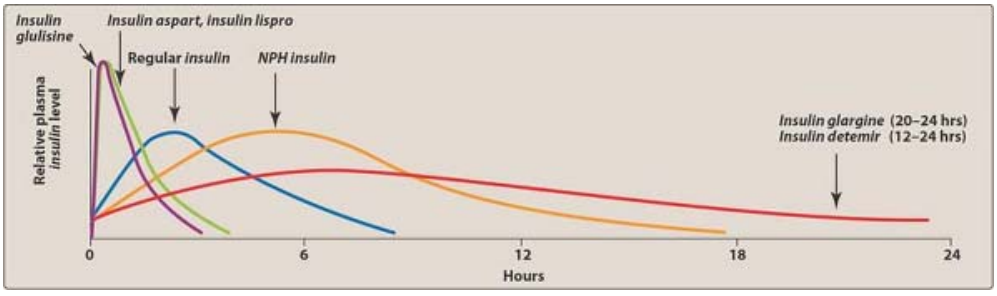


Figure 24.7 Onset and duration of action of human *insulin* and *insulin* analogs. NPH = Neutral Protamine Hagedorn.

C. Long-acting insulin preparations

1. **Insulin glargine:** The isoelectric point of *insulin glargine* (GLAR-geen) is lower than that of human *insulin*, leading to precipitation at the injection site, thereby extending its action. It is slower in onset than *NPH insulin* and has a flat, prolonged hypoglycemic effectâ€"that is, it has no peak (see Figure 24.7). Like the other *insulins*, it must be given subcutaneously.
2. **Insulin detemir:** *Insulin detemir* (deh-TEE-meer) has a fatty-acid side chain. The addition of the fatty-acid side chain enhances association to albumin. Slow dissociation from albumin results in long-acting properties similar to those of *insulin glargine*.

D. Insulin combinations

Various premixed combinations of human *insulins*, such as 70-percent *NPH insulin* plus 30-percent regular *insulin*, 50 percent of each of these, or 75 percent *NPL insulin* plus 25 percent *insulin lispro*, are also available.

E. Standard treatment versus intensive treatment

Standard treatment of patients with diabetes mellitus involves injection of *insulin* twice daily. In contrast, intensive treatment seeks to normalize blood glucose through more frequent injections of *insulin* (three or more times daily in response to monitoring blood glucose levels). Mean blood glucose levels of 170 mg/dL or less can be achieved with intensive treatment, with an HbA_{1c} content of approximately seven percent or less of total hemoglobin. [Note: Normal mean blood glucose is approximately 135 mg/dL or less, with an HbA_{1c} content of six percent or less.] Thus, the frequency of hypoglycemic episodes, coma, and seizures due to excessive *insulin* is particularly high with intensive treatment regimens (Figure 24.9A). Nonetheless, patients on intensive therapy show a significant reduction in the long-term complications of diabetesâ€"retinopathy, nephropathy, and neuropathyâ€" compared to patients receiving standard care (Figure 24.9B). However, the commonly used treatment algorithm of normalizing blood glucose in diabetics has recently been challenged. The ACCORD trial found that among adults with Type 2 diabetes who are at especially high risk of cardiovascular disease, a medical treatment strategy to intensively lower their blood glucose levels below the current guidelines increased the risk of death compared to standard blood glucose-lowering treatment. The intensive therapy arm of the trial, including those patients treated with intensive insulin therapy, was halted.

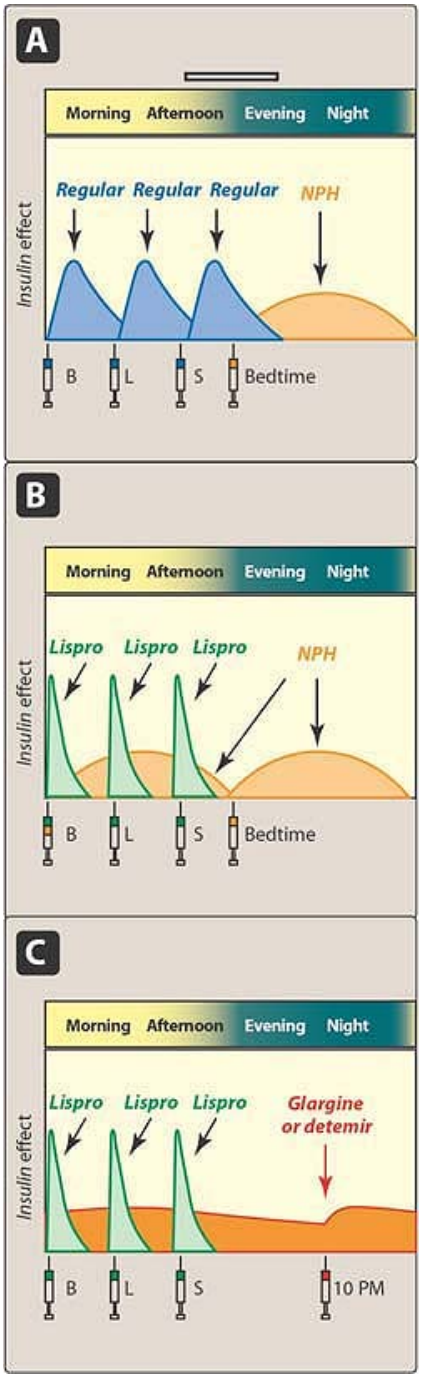


Figure 24.8 Examples of three regimens that provide both prandial and basal *insulin* replacement. B = breakfast; L = lunch; S = supper.

V. Synthetic Amylin Analog

Pramlintide [PRAM-lin-tide] is a synthetic amylin analog that is indicated as an adjunct to mealtime *insulin* therapy in patients with Type 1 or Type 2 diabetes. By acting as an amylinomimetic, *pramlintide* delays gastric emptying, decreases postprandial glucagon secretion, and improves satiety.

Pramlintide is administered by subcutaneous injection and should be injected immediately prior to meals. When *pramlintide* is initiated, the dose of rapid- or short-acting *insulin* should be decreased by 50% prior to meals to avoid a risk of severe hypoglycemia. *Pramlintide* may not be mixed in the same syringe with any *insulin* preparation. Adverse effects are mainly gastrointestinal and consist of nausea, anorexia, and vomiting. *Pramlintide* should not be given to patients with diabetic gastroparesis (delayed stomach emptying)or a history of hypoglycemic

unawareness.

VI. Oral Agents: Insulin Secretagogues

These agents are useful in the treatment of patients who have Type 2 diabetes but who cannot be managed by diet alone. The patient most likely to respond well to oral hypoglycemic agents is one who develops diabetes after age 40 and has had diabetes less than 5 years. Patients with long-standing disease may require a combination of hypoglycemic drugs with or without *insulin* to control their hyperglycemia. *Insulin* is added because of the progressive decline in Î² cells that occurs due to the disease or aging. Oral hypoglycemic agents should not be given to patients with Type 1 diabetes. Figure 24.10 summarizes the duration of action of some of the oral hypoglycemic drugs, and Figure 24.11 illustrates some of the common adverse effects of these agents.

A. Sulfonylureas

These agents are classified as *insulin* secretagogues, because they promote *insulin* release from the Î² cells of the pancreas. The primary drugs used today are *tolbutamide* [tole-BYOO-ta-mide] and the second-generation derivatives, *glyburide* [GLYE-byoor-ide], *glipizide* [GLIP-i-ih-zide], and *glimepiride* [GLYE-me-pih-ride].

1. **Mechanisms of action of the sulfonylureas:** These include 1) stimulation of *insulin* release from the Î² cells of the pancreas by blocking the ATP-sensitive K^+ channels, resulting in depolarization and Ca^{2+} influx; 2) reduction in hepatic glucose production; and 3) increase in peripheral *insulin* sensitivity.
2. **Pharmacokinetics and fate:** Given orally, these drugs bind to serum proteins, are metabolized by the liver, and are excreted by the liver or kidney. *Tolbutamide* has the shortest duration of action (6â€“12 hours), whereas the second-generation agents last about 24 hours.
3. **Adverse effects:** Shortcomings of the sulfonylureas are their propensity to cause weight gain, hyperinsulinemia, and hypoglycemia. These drugs should be used with caution in patients with hepatic or renal insufficiency, because delayed excretion of the drugâ€”resulting in its accumulationâ€”may cause hypoglycemia. Renal impairment is a particular problem in the case of those agents that are metabolized to active compounds, such as *glyburide. Glyburide* has minimal transfer across the placenta and may be a reasonably safe alternative to *insulin* therapy for diabetes in pregnancy. Figure 24.12 summarizes some of the interactions of the sulfonylureas with other drugs.

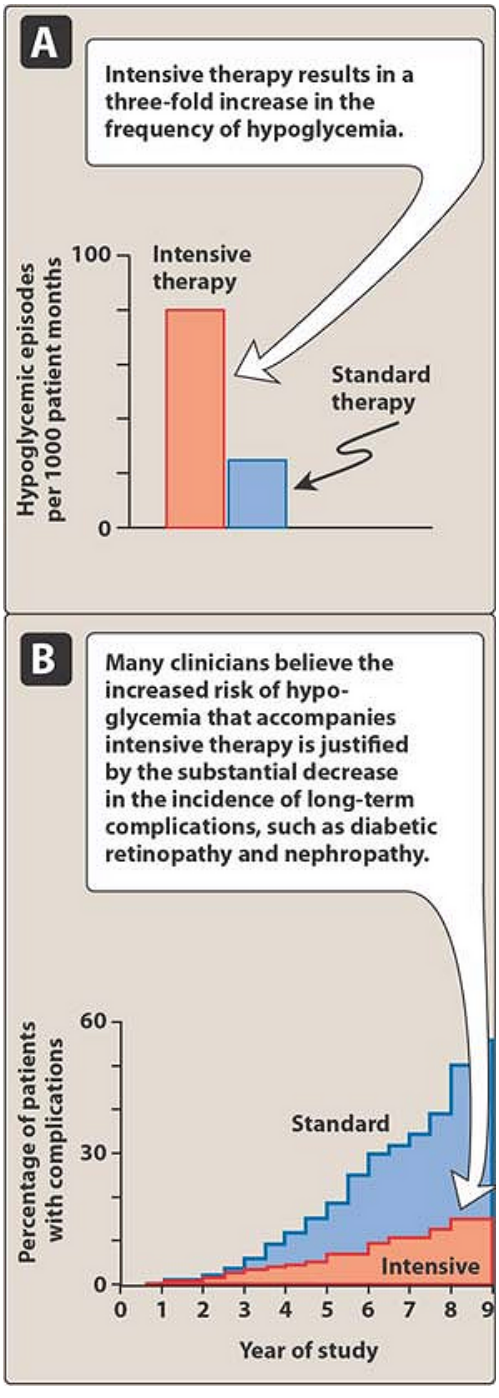


Figure 24.9 A. Effect of tight glucose control on hypoglycemic episodes in a population of patients with Type 1 diabetes receiving intensive or standard therapy.

B. Effect of standard and intensive care on the long-term complications of diabetes.

B. Meglitinide analogs

This class of agents includes *repaglinide* [re-PAG-lin-ide] and *nateglinide* [nuh-TAY-gli-nide]. Although they are not sulfonylureas, they have common actions.

1. **Mechanism of action:** Like the sulfonylureas, their action is dependent on functioning pancreatic Î² cells. They bind to a distinct site on

the sulfonylurea receptor of ATP-sensitive potassium channels, thereby initiating a series of reactions culminating in the release of *insulin*. However, in contrast to the sulfonylureas, the meglitinides have a rapid onset and a short duration of action. They are particularly effective in the early release of *insulin* that occurs after a meal and, thus, are categorized as postprandial glucose regulators. Combined therapy of these agents with *metformin* or the glitazones has been shown to be better than monotherapy with either agent in improving glycemic control. Meglitinides should not be used in combination with sulfonylureas due to overlapping mechanisms of action.

2. **Pharmacokinetics and fate:** These drugs are well absorbed orally after being taken 1 to 30 minutes before meals. Both meglitinides are metabolized to inactive products by CYP3A4 (see p. 14) in the liver and are excreted through the bile.

3. **Adverse effects:** Although these drugs can cause hypoglycemia, the incidence of this adverse effect appears to be lower than that with the sulfonylureas. [Note: Drugs that inhibit CYP3A4, like *ketoconazole, itraconazole, fluconazole, erythromycin*, and *clarithromycin*, may enhance the glucose-lowering effect of *repaglinide*, whereas drugs that increase levels of this enzyme, such as barbiturates, *carbamazepine*, and *rifampin*, may have the opposite effect.] *Repaglinide* has been reported to cause severe hypoglycemia in patients who are also taking the lipid-lowering drug *gemfibrozil.* Weight gain is less of a problem with the meglitinides than with the sulfonylureas. These agents must be used with caution in patients with hepatic impairment.

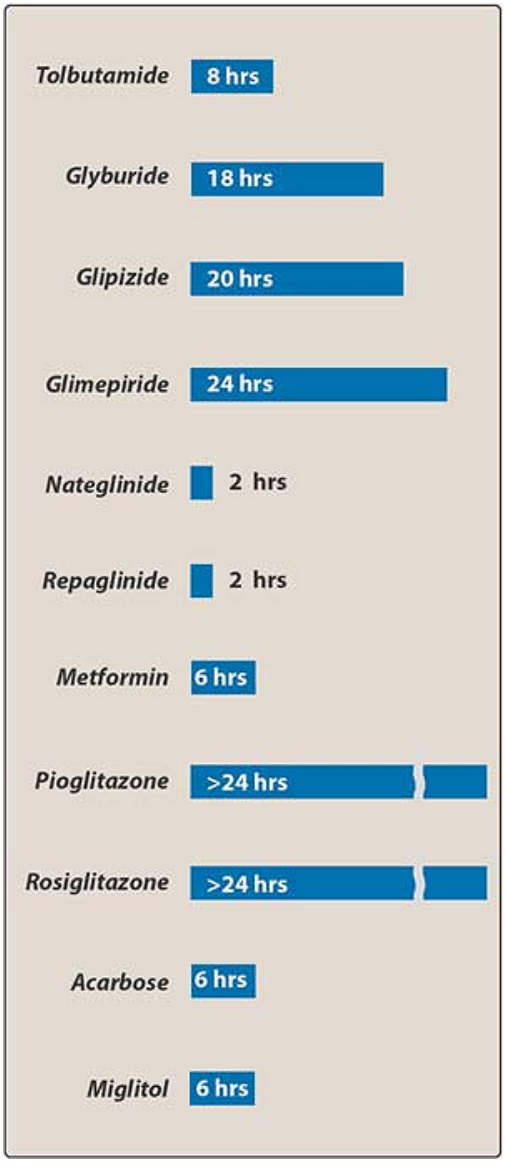


Figure 24.10 Duration of action of some oral hypoglycemic agents.

VII. Oral Agents: Insulin Sensitizers

Two classes of oral agentsâ€”the biguanides and thiazolidinedionesâ€”improve *insulin* action. These agents lower blood sugar by improving

target-cell response to *insulin* without increasing pancreatic *insulin* secretion.

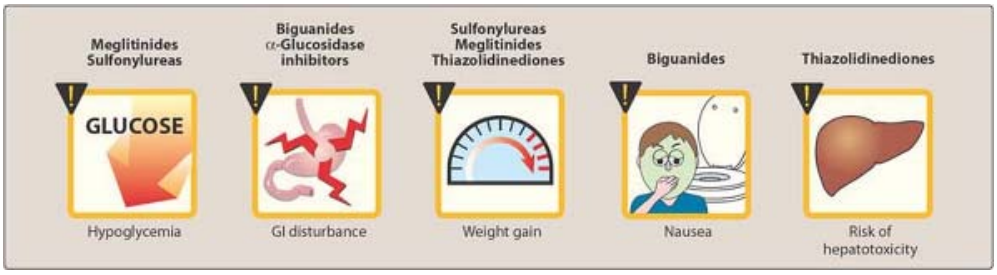


Figure 24.11 Some adverse effects observed with oral hypoglycemic agents.

A. Biguanides

Metformin [met-FOR-min], the only currently available biguanide, is classed as an *insulin* sensitizer; that is, it increases glucose uptake and utilization by target tissues, thereby decreasing *insulin* resistance. Like the sulfonylureas, *metformin* requires *insulin* for its action, but it differs from the sulfonylureas in that it does not promote *insulin* secretion. Hyperinsulinemia is not a problem. Thus, the risk of hypoglycemia is far less than that with sulfonylurea agents, and it may only occur if caloric intake is not adequate or exercise is not compensated for calorically.

1. **Mechanism of action:** The main mechanism of action of *metformin* is reduction of hepatic glucose output, largely by inhibiting hepatic gluconeogenesis. [Note: Excess glucose produced by the liver is the major source of high blood glucose in Type 2 diabetic, accounting for the high blood glucose on waking in the morning.] *Metformin* also slows intestinal absorption of sugars and improves peripheral glucose uptake and utilization. A very important property of this drug is its ability to modestly reduce hyperlipidemia (low-density lipoprotein [LDL] and very-low-density lipoprotein [VLDL] cholesterol concentrations fall, and high-density lipoprotein [HDL] cholesterol rises). These effects may not be apparent until 4 to 6 weeks of use. The patient often loses weight because of loss of appetite. The ADA treatment algorithm recommends *metformin* as the drug of choice for newly diagnosed Type 2 diabetics. *Metformin* may be used alone or in combination with one of the other agents, as well as with *insulin*. Hypoglycemia has occurred when *metformin* was taken in combination. [Note: If used with *insulin*, the dose of *insulin* may require adjustment, because *metformin* decreases the production of glucose by the liver.]
2. **Pharmacokinetics and fate:** *Metformin* is well absorbed orally, is not bound to serum proteins, and is not metabolized. Excretion is via the urine.
3. **Adverse effects:** These are largely gastrointestinal. *Metformin* is contraindicated in diabetics with renal and/or hepatic disease, acute myocardial infarction, severe infection, or diabetic ketoacidosis. It should be used with caution in patients greater than 80 years of age or in those with a history of congestive heart failure or alcohol abuse. [Note: Diabetics being treated with heart-failure medications should not be given *metformin* because of an increased risk of lactic acidosis.] *Metformin* should be temporarily discontinued in patients undergoing diagnosis requiring intravenous radiographic contrast agents. Rarely, potentially fatal lactic acidosis has occurred. Long-term use may interfere with vitamin B_{12} absorption.

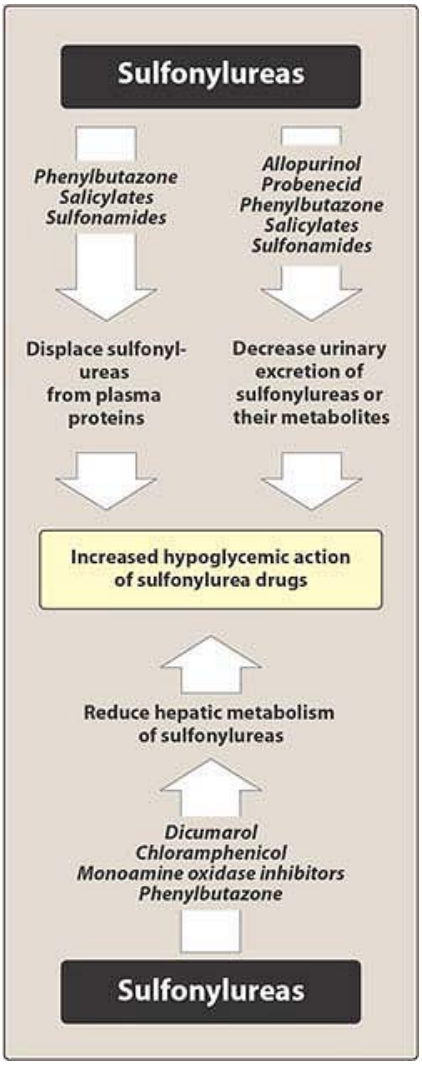


Figure 24.12 Drugs interacting with sulfonylurea drugs.

4. **Other uses:** In addition to the treatment of Type 2 diabetes, *metformin* is effective in the treatment of polycystic ovary disease. Its ability to lower *insulin* resistance in these women can result in ovulation and, possibly, pregnancy.

B. Thiazolidinediones or glitazones

Another group of agents that are *insulin* sensitizers are the thiazolidinediones (TZDs) or, more familiarly the glitazones. Although *insulin* is required for their action, these drugs do not promote its release from the pancreatic Î² cells; thus, hyperinsulinemia does not result.

Troglitazone [TROE-glit-a-zone] was the first of these to be approved for the treatment of Type 2 diabetic, but was withdrawn after a number of deaths due to hepatotoxicity were reported. Presently, two members of this class are available, *pioglitazone* [pye-oh-GLI-ta-zone] and *rosiglitazone* [roe-si-GLIH-ta-zone].

1. **Mechanism of action:** Although the exact mechanism by which the TZDs lower *insulin* resistance remains to be elucidated, they are known to target the peroxisome proliferatorâ€"activated receptor-Î³ (PPARÎ³)â€"a nuclear hormone receptor. Ligands for PPARÎ³ regulate adipocyte production and secretion of fatty acids as well as glucose metabolism, resulting in increased *insulin* sensitivity in adipose tissue, liver, and skeletal muscle. Hyperglycemia, hyperinsulinemia, hypertriacylglycerolemia, and elevated HbA_{1c} levels are improved. Interestingly, LDL levels are not affected by *pioglitazone* monotherapy or when the drug is used in combination with other agents, whereas LDL levels have increased with *rosiglitazone*. HDL levels increase with both drugs. The TZDs lead to a favorable redistribution of fat from visceral to subcutaneous tissues. [Note: Whether the adipogenic effects can be separated from those of increased *insulin* sensitivity is the subject of much research, particularly because of the role of obesity in this disease.] *Pioglitazone* and *rosiglitazone* can be used as monotherapy or in combination with other hypoglycemics or with *insulin*. The dose of *insulin* required for adequate glucose control in

these circumstances may have to be lowered. The glitazones are recommended as a second-line alternative for patients who fail or have contraindications to metformin therapy.

2. **Pharmacokinetics and fate:** Both *pioglitazone* and *rosiglitazone* are absorbed very well after oral administration and are extensively bound to serum albumin. Both undergo extensive metabolism by different cytochrome P450 isozymes (see p. 14). Some metabolites of *pioglitazone* have activity. Renal elimination of *pioglitazone* is negligible, with the majority of the active drug and metabolites excreted in the bile and eliminated in the feces. The metabolites of *rosiglitazone* are primarily excreted in the urine. No dosage adjustment is required in renal impairment. It is recommended that these agents not be used in nursing mothers.

3. **Adverse effects:** Because there have been deaths from hepatotoxicity in patients taking *troglitazone*, it is recommended that liver enzyme levels of patients on these medications be measured initially and periodically thereafter. Very few cases of liver toxicity have been reported with *rosiglitazone* or *pioglitazone*. Weight increase can occur, possibly through the ability of TZDs to increase subcutaneous fat or due to fluid retention. [Note: The latter can lead to or worsen heart failure.] Glitazones have been associated with osteopenia and increased fracture risk. A recent retrospective meta-analysis found that *rosiglitazone* was associated with an increased risk of myocardial infarction and death from cardiovascular causes; however, future prospective studies are needed to better ascertain the cardiovascular risks associated with rosiglitazone. Other adverse effects include headache and anemia. Women taking oral contraceptives and TZDs may become pregnant, because the latter have been shown to reduce plasma concentrations of the estrogen-containing contraceptives.

4. **Other uses:** As with *metformin*, the relief of *insulin* resistance with the TZDs can cause ovulation to resume in premenopausal women with polycystic ovary syndrome.

VIII. Oral Agents: Î±-Glucosidase Inhibitors

Acarbose [AY-car-bose] and *miglitol* [MIG-li-tol] are orally active drugs used for the treatment of patients with Type 2 diabetes.

A. Mechanism of action

These drugs are taken at the beginning of meals. They act by delaying the digestion of carbohydrates, thereby resulting in lower postprandial glucose levels. Both drugs exert their effects by reversibly inhibiting membrane-bound Î±-glucosidase in the intestinal brush border. This enzyme is responsible for the hydrolysis of oligosaccharides to glucose and other sugars. [Note: *Acarbose* also inhibits pancreatic Î±-amylase, thus interfering with the breakdown of starch to oligosaccharides.] Consequently, the postprandial rise of blood glucose is blunted. Unlike the other oral hypoglycemic agents, these drugs do not stimulate *insulin* release, nor do they increase *insulin* action in target tissues. Thus, as monotherapy, they do not cause hypoglycemia. However, when used in combination with the sulfonylureas or with *insulin*, hypoglycemia may develop. [Note: It is important that the hypoglycemic patient be treated with glucose rather than sucrose, because sucrase is also inhibited by these drugs.]

B. Pharmacokinetics

Acarbose is poorly absorbed. It is metabolized primarily by intestinal bacteria, and some of the metabolites are absorbed and excreted into the urine. On the other hand, *miglitol* is very well absorbed but has no systemic effects. It is excreted unchanged by the kidney.

C. Adverse effects

The major side effects are flatulence, diarrhea, and abdominal cramping. Patients with inflammatory bowel disease, colonic ulceration, or intestinal obstruction should not use these drugs.

IX. Oral Agents: Dipeptidyl Peptidase-IV Inhibitors

Sitagliptin [si-ta-GLIP-tin] is an orally active dipeptidyl peptidase-IV (DPP-IV) inhibitor used for the treatment of patients with Type 2 diabetes. Other agents in this category are currently in development.

A. Mechanism of action

Sitagliptin inhibits the enzyme DPP-IV, which is responsible for the inactivation of incretin hormones, such as glucagon-like peptide-1 (GLP-1). Prolonging the activity of incretin hormones results in increased *insulin* release in response to meals and a reduction in inappropriate secretion of glucagon. *Sitagliptin* may be used as monotherapy or in combination with a sulfonylurea, *metformin* or a *glitazone*.

B. Pharmacokinetics and fate

Sitagliptin is well absorbed after oral administration. Food does not affect the extent of absorption. The majority of *sitagliptin* is excreted unchanged in the urine. Dosage adjustments are recommended for

patients with renal dysfunction.

C. Adverse effects

In general, *sitagliptin* is well tolerated, with the most common adverse effects being nasopharyngitis and headache. Rates of hypoglycemia are comparable to those with placebo when *sitagliptin* is used as monotherapy or in combination with *metformin* or *pioglitazone.*

X. Incretin Mimetics

Oral glucose results in a higher secretion of *insulin* than occurs when an equal load of glucose is given intravenously. This effect is referred to as the â€œincretin effectâ€ and is apparently reduced in Type 2 diabetes. It demonstrates the important role of the gastrointestinal hormonesâ€”notably GLP-1 and gastric inhibitory polypeptideâ€”in the digestion and absorption of nutrients, including glucose. *Exenatide* [EX-e-nah-tide] is an incretin mimetic with a polypeptide sequence about 50-percent homologous to GLP-1. *Exenatide* not only improves glucose-dependent *insulin* secretion but also slows gastric emptying time, decreases food intake, decreases postprandial glucagon secretion, and promotes Î²-cell proliferation. Consequently, weight gain and postprandial hyperglycemia are reduced, and HbA_{1c} levels decline. Being a polypeptide, *exenatide* must be administered subcutaneously. A drawback to its use is its short duration of action, requiring frequent injections. A once-weekly preparation is under investigation. *Exenatide* may be used as an adjunct to therapy in patients with Type 2 diabetes who have failed to achieve adequate glycemic control on a sulfonylurea, *metformin, glitazone*, or combination thereof. Similar to *pramlintide*, the main adverse effects consist of nausea, vomiting, and diarrhea.

A summary of the oral antidiabetic agents is presented in Figure 24.13.

DRUG CLASS	MECHANISM OF ACTION	EFFECT ON PLASMA INSULIN	RISK OF HYPO-GLYCEMIA	COMMENTS
First-generation sulfonylureas *Tolbutamide*	Stimulates insulin secretion	↑	Yes	Well-established history of effectiveness. Weight gain can occur.
Second-generation sulfonylureas *Glipizide* *Glyburide* *Glimepiride*	Stimulates insulin secretion	↑	Yes	Well-established history of effectiveness. Weight gain can occur.
Meglitinides *Nateglinide* *Repaglinide*	Stimulates insulin secretion	↑	Yes (rarely)	Short action with less hypoglycemia either at night or with missed meal. Post-prandial effect.
Biguanides *Metformin*	Decreases endogenous hepatic production of glucose	↓	No	Preferred agent for Type 2 diabetes. Well-established history of effectiveness. Weight loss may occur. Convenient daily dosing. Many contraindications. Monitor renal function.
Thiazolidinediones (glitazones) *Pioglitazone* *Rosiglitazone*	Binds to peroxisome proliferator–activated receptor-γ in muscle, fat and liver to decrease insulin resistance.	↓↓	No	Effective in highly insulin-resistant patients. Once-daily dosing for *pioglitazone* Monitor liver function.
α-Glucosidase inhibitors *Acarbose* *Miglitol*	Decreases glucose absorption	⟺	No	Taken with meals. Adverse gastro-intestinal effects.
DPP-IV inhibitors *Sitagliptin*	Increases glucose-dependent insulin release, decreases secretion of glucagon	↑	No	Once-daily dosing. May be taken with or without food. Well tolerated.

Figure 24.13 Summary of oral agents used to treat diabetes. ⟺ = little or no change.

Study Questions

Choose the ONE best answer.

24.1 A 50-year-old woman has just been diagnosed as a Type 2 diabetic and given a prescription for metformin. Which of the following

statements is characteristic of this medication?

A. Hypoglycemia is a common adverse effect.

B. Metformin undergoes metabolism to an active compound.

C. Many drug-drug interactions have been identified.

D. It decreases hepatic glucose production.

E. The patient often gains weight.

View Answer

24.2 Which of the following statements is true for therapy with insulin glargine?

A. It is primarily used to control prandial hyperglycemia.

B. It should not be combined with any other insulin.

C. It is now used preferentially in Type 1 diabetics who are pregnant.

D. Pharmacokinetically, there is no peak activity, and the activity lasts about 24 hours.

E. It is effective by inhalation.

View Answer

24.3 The ability to reduce insulin resistance is associated with which one of the following classes of hypoglycemic agents?

A. Meglitinides.

B. Sulfonylureas.

C. Î±-Glucosidase inhibitors.

D. Thiazolidinediones.

E. Gastrointestinal hormones.

View Answer

24.4 A 64-year-old woman with a history of Type 2 diabetes is diagnosed with heart failure. Which of the following drugs would be a poor choice in controlling her diabetes?

A. Sitagliptin.

B. Exenatide.

C. Glyburide.

D. Glipizide.

E. Pioglitazone.

View Answer

Editors: **Finkel, Richard; Clark, Michelle A.; Cubeddu, Luigi X.**
Title: *Lippincott's Illustrated Reviews: Pharmacology, 4th Edition*

Chapter 25

Estrogens and Androgens

I. Overview

Sex hormones produced by the gonads are necessary for conception, embryonic maturation, and development of primary and secondary sexual characteristics at puberty. Their activity in target cells is modulated by receptors. The gonadal hormones are used therapeutically in replacement therapy, for contraception, and in management of menopausal symptoms. Several antagonists are effective in cancer chemotherapy. All gonadal hormones are synthesized from the precursor, cholesterol, in a series of steps that includes shortening of the hydrocarbon side chain and hydroxylation of the steroid nucleus. Aromatization is the last step in estrogen synthesis.[1] Figure 25.1 lists the steroid hormones referred to in this chapter.

II. Estrogens

Estradiol [ess-tra-DYE-ole], also known as *17 Î²-estradiol*, is the most potent estrogen produced and secreted by the ovary. It is the principle estrogen in the premenopausal woman. *Estrone* [ESS-trone] is a metabolite of estradiol that has approximately one-third the estrogenic potency of *estradiol. Estrone* is the primary circulating estrogen after menopause, and it is generated mainly from conversion of androstenedione in peripheral tissues. *Estriol* [ess-TRI-ole], another metabolite of *estradiol*, is significantly less potent than *estradiol.* It is present in significant amounts during pregnancy, because it is the principal estrogen produced by the placenta. A preparation of conjugated estrogens containing sulfate esters of *estrone* and *equilin*â€”obtained from pregnant mare's urineâ€”is a widely used oral preparation for hormone replacement therapy. Plant-derived conjugated estrogen products are also available. Synthetic estrogens, such as *ethinyl estradiol* [ETH-ih-nil-ess-tra-DYE-ole], undergo less first-pass metabolism than naturally occurring steroids and, thus, are effective when administered orally at lower doses. Nonsteroidal compounds that bind to estrogen receptors and exert either estrogenic or antiestrogenic effects on target tissues are called selective estrogen-receptor modulators. These include *tamoxifen* and *raloxifene*, among others.

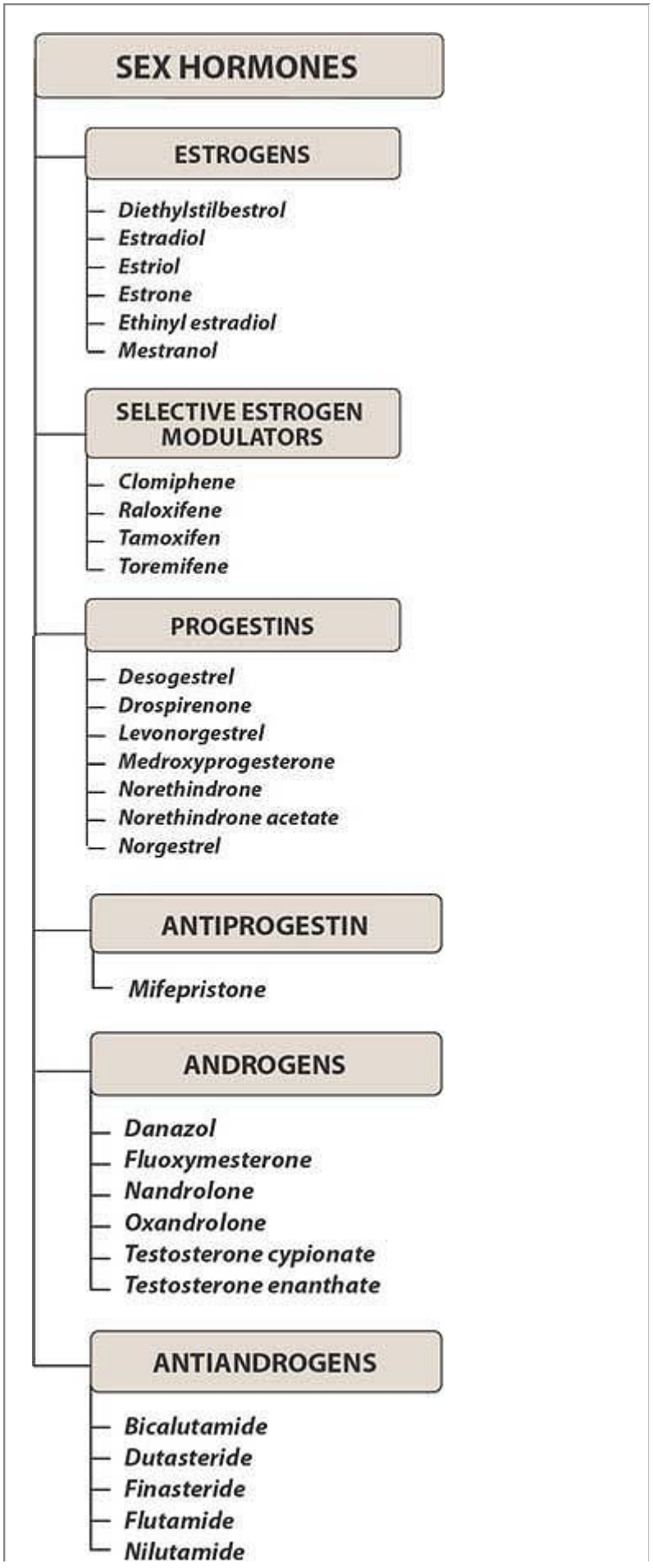

SEX HORMONES
ESTROGENS
Diethylstilbestrol
Estradiol
Estriol
Estrone
Ethinyl estradiol
Mestranol
SELECTIVE ESTROGEN MODULATORS
Clomiphene
Raloxifene
Tamoxifen
Toremifene
PROGESTINS
Desogestrel
Drospirenone
Levonorgestrel
Medroxyprogesterone
Norethindrone
Norethindrone acetate
Norgestrel
ANTIPROGESTIN
Mifepristone
ANDROGENS
Danazol
Fluoxymesterone
Nandrolone
Oxandrolone
Testosterone cypionate
Testosterone enanthate
ANTIANDROGENS
Bicalutamide
Dutasteride
Finasteride
Flutamide
Nilutamide

Figure 25.1 Summary of sex hormones. Summary of sex hormones.

A. Mechanism of action

After dissociation from their binding sites on sex hormoneâ€“binding globulin or albumin in the plasma, steroid hormones diffuse across the cell membrane and bind with high affinity to specific nuclear-receptor proteins. [Note: These receptors belong to a large, nuclear hormoneâ€“receptor family that includes those for thyroid hormones and vitamin D.] Two estrogen-receptor subtypes, Î± and Î², mediate the effects of the hormone. The Î± receptor may be considered as the classic estrogen receptor; the Î² receptor is highly homologous to the Î± receptor. However, the N-terminal portion of the Î± receptor contains a region that promotes transcription activation, whereas the Î² receptor contains a repressor domain. As a result, the transcriptional properties of the Î± and Î² estrogen receptors are different. Affinity for the receptor type varies with the particular estrogen. These receptor isoforms vary in structure, chromosomal location, and tissue distribution. The activated steroid-receptor complex interacts with nuclear chromatin to initiate hormone-specific RNA synthesis. The attachment of two estrogen-linked receptors (estrogen receptor dimer) to the genome is required for a response. This results in the synthesis of specific proteins that mediate a number of physiologic functions. [Note: The steroid hormones may elicit the synthesis of different RNA species in diverse target tissues and, therefore, are both receptor and tissue specific.] Other pathways that require these hormones have been identified that lead to more rapid results. For example, activation of an estrogen receptor in the membranes of hypothalamic cells has been shown to couple to a G protein, thereby initiating a second-messenger cascade.[2] In addition, estrogen-mediated dilation of coronary arteries occurs by the increased formation and release of nitric oxide and prostacyclin in endothelial cells.

B. Therapeutic uses of estrogens

The most frequent uses of estrogens are for contraception and postmenopausal hormone therapy, also called estrogen-progestogen therapy (EPT). Due to recent concerns over the risks of EPT, the National American Menopause Society recommends that EPT be prescribed at the lowest effective dose for the shortest possible time to relieve vasomotor symptoms and vaginal atrophy. Women that have only urogenital symptoms should be treated with vaginal rather than systemic estrogen. Estrogens were previously widely used for prevention and treatment of osteoporosis, but current guidelines recommend use of other therapies over estrogen. Estrogens are also used extensively for replacement therapy in premenopausal patients who are deficient in this hormone. Such a deficiency can be due to lack of development of the ovaries, premature menopause, or surgical menopause.

1. **Postmenopausal hormone therapy:** The primary indication for estrogen therapy is menopausal symptoms such as vasomotor instability (for example, â€œhot flashesâ€ or â€œhot flushesâ€) and vaginal atrophy. (Figure 25.2). For women who have not undergone a hysterectomy, a progestin is always included with the estrogen therapy, because the combination reduces the risk of endometrial carcinoma associated with unopposed estrogen. For women whose uterus

has been surgically removed, unopposed estrogen therapy is recommended, because progestins may unfavorably alter the beneficial effects of estrogen on lipid parameters. [Note: The amount of estrogen used in replacement therapy is substantially less than the doses used in oral contraception. Thus, the adverse effects of estrogen r eplacement therapy tend to be less severe than the adverse effects seen in women who are taking estrogen for contraceptive purposes.] Delivery of *estradiol* by transdermal patch is also effective in treating postmenopausal symptoms. Osteoporosis is effectively treated with estrogen; however, other drugs, such as *alendronate,* should be considered first-line therapy over estrogen. (See p. 343 for a summary of some of the agents that are useful in the treatment of osteoporosis.)

2. **Primary hypogonadism:** Estrogen therapy mimicking the natural cyclic pattern, and usually in combination with progestins, is instituted to stimulate development of secondary sex characteristics in young women (11â€“13 years of age) with hypogonadism. Continued treatment is required after growth is completed.

C. Pharmacokinetics

1. **Naturally occurring estrogens:** These agents and their esterified or conjugated derivatives are readily absorbed through the gastrointestinal tract, skin, and mucous membranes. Taken orally, *estradiol* is rapidly metabolized (and partially inactivated) by the microsomal enzymes of the liver. Micronized *estradiol* is available and has better bioavailability. Although there is some first-pass metabolism, it is not sufficient to lessen the effectiveness when taken orally.

2. **Synthetic estrogen analogs:** These compounds, such as *ethinyl estradiol* and *mestranol* [MES-trah-nole]), are well absorbed after oral administration or through the skin or mucous membranes. *Mestranol* is quickly demethylated to *ethinyl estradiol*, which is metabolized more slowly than the naturally occurring estrogens by the liver and peripheral tissues. Being fat soluble, they are stored in adipose tissue, from which they are slowly released. Therefore, the synthetic estrogen analogs have a prolonged action and a higher potency compared to those of natural estrogens.

3. **Metabolism:** Estrogens are transported in the blood while bound to serum albumin or sex hormoneâ€“binding globulin. As mentioned above, bioavailability of *estrogen* taken orally is low due to first-pass metabolism in the liver. To reduce first-pass metabolism, the drugs may be administered by transdermal patch, topical gel or emulsion, intravaginally, or by injection. They are hydroxylated in the liver to derivatives that are subsequently glucuronidated or sulfated. The parent drugs and their metabolites undergo excretion into the bile and are then reabsorbed through the enterohepatic circulation. Inactive products are excreted in the urine. [Note: In individuals with liver damage, serum estrogen levels may increase due to reduced metabolism, causing feminization in males or signs of estrogen excess in females.]

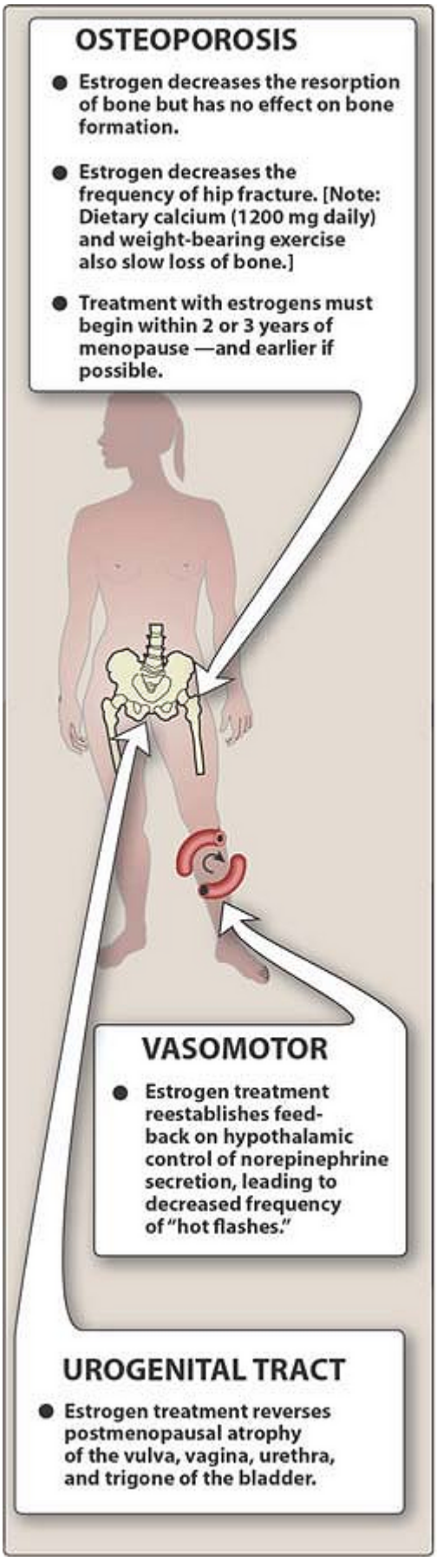

OSTEOPOROSIS
Estrogen decreases the resorption of bone but has no effect on bone formation.
Estrogen decreases the frequency of hip fracture. [Note: Dietary calcium (1200 mg daily) and weight-bearing exercise also slow loss of bone.]
Treatment with estrogens must begin within 2 or 3 years of menopause —and earlier if possible.
VASOMOTOR
Estrogen treatment reestablishes feed-back on hypothalamic control of norepinephrine secretion, leading to decreased frequency of "hot flashes."
UROGENITAL TRACT
Estrogen treatment reverses postmenopausal atrophy of the vulva, vagina, urethra, and trigone of the bladder.

Figure 25.2 Benefits associated with postmenopausal estrogen replacement.

D. Adverse effects

Nausea and breast tenderness are among the most common adverse effects of *estrogen* therapy. Postmenopausal uterine bleeding can occur.

In addition, the risk of thromboembolic events, myocardial infarction, and breast and endometrial cancer is increased with use of estrogen therapy. [Note: The increased risk of endometrial cancer can be offset by including a progestin along with the estrogen therapy.] Other effects of *estrogen* therapy are shown in Figure 25.3. The synthetic nonsteroidal estrogen *diethylstilbestrol* has been implicated as the possible cause of a rare, clear-cell cervical or vaginal adenocarcinoma observed among the daughters of women who took the drug during pregnancy.

Info Link

[3]See p. 360 in *Lippincott's Illustrated Reviews: Biochemistry* (4th ed.) for a discussion of LDLs, HDLs, and health.

III. Selective Estrogen-Receptor Modulators

Selective estrogen-receptor modulators (SERMs) are a new class of estrogen-related compounds. In the past, a number of these agents had been categorized as antiestrogens, and consequently, there is some confusion. The term SERM is now reserved for compounds that interact at estrogen receptors but have different effects on different tissues; that is, they display selective agonism or antagonism according to the tissue type. For example, *tamoxifen* is an estrogen antagonist in breast cancer tissue but can cause endometrial hyperplasia by acting as a partial agonist in the uterus. Other SERMs are *toremifene* and *raloxifene*. *Clomiphene* is also sometimes designated as a SERM.

A. Tamoxifen

Considered to be the first SERM, *tamoxifen* [tah-MOKS-ih-fen] competes with estrogen for binding to the estrogen receptor in breast tissue and is currently used in the palliative treatment of metastatic breast cancer in postmenopausal women. It may also be used as adjuvant therapy following mastectomy or radiation and to reduce the risk of breast cancer in high-risk patients. [Note: Normal breast growth is stimulated by estrogens. It is therefore not surprising that some breast tumors regress following treatment with *tamoxifen*.] The most frequent adverse effects of *tamoxifen* treatment are hot flashes and nausea. Menstrual irregularities and vaginal bleeding can also occur. Due to its estrogenic activity in the endometrium, hyperplasia and malignancies have been reported in women who have been maintained on *tamoxifen*. This has led to recommendations for limiting the length of time on the drug for some indications.

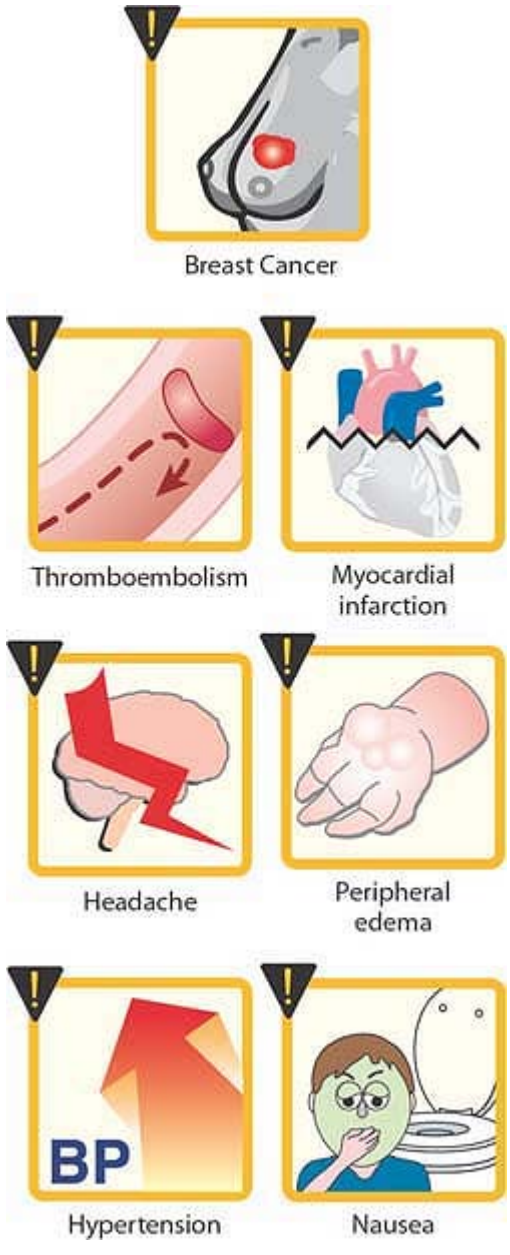


Figure 25.3 Some adverse effects associated with estrogen therapy.

B. Raloxifene

Raloxifene [rah-LOX-ih-feen] is a second-generation SERM that is related to *tamoxifen*. Its clinical use is based on its ability to decrease bone resorption and overall bone turnover. Bone density is increased, and vertebral fractures are decreased (Figure 25.4). Unlike *estrogen* and *tamoxifen*, it apparently has little to no effect on the endometrium and, therefore, may not predispose to uterine cancer. *Raloxifene* lowers total cholesterol and low-density lipoprotein (LDL) in the serum, but it has no effect on high-density lipoprotein (HDL) or triacylglycerol levels. To date, clinical trials have not shown any significant reduction in coronary events with *raloxifene*. The drug is currently approved only for the prevention and treatment of osteoporosis in postmenopausal women. *Raloxifene* has been shown to reduce the incidence of invasive breast cancer in postmenopausal women. [Note: At present, an U.S. Food and Drug Administration advisory panel has recommended that *raloxifene* be approved for the prevention

of breast cancer in high-risk postmenopausal women.]

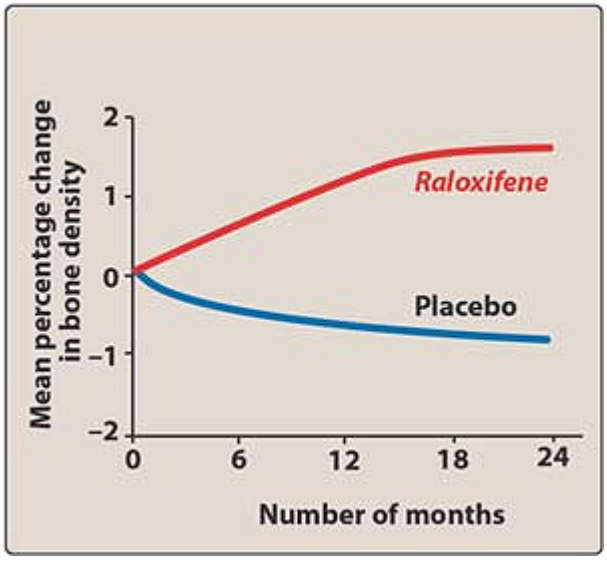


Figure 25.4 Hip bone density increases with *raloxifene* in postmenopausal women.

1. **Pharmacokinetics:** The drug is readily absorbed orally and is rapidly converted to glucuronide conjugates through first-pass metabolism. More than 95 percent of *raloxifene* is bound to plasma proteins. Both the parent drug and the conjugates undergo enterohepatic cycling. The primary route of excretion is through the bile into the feces.

2. **Adverse effects:** Hot flashes and leg cramps are common adverse effects with *raloxifene*. As with the estrogens and *tamoxifen*, the use of *raloxifene* has an increased risk of deep-vein thrombosis, pulmonary embolism, and retinal-vein thrombosis. *Raloxifene* should be avoided in women who are or may become pregnant. In addition, women who have a past or active history of venous thromboembolic events should not take the drug. Coadministration with *cholestyramine* can reduce the absorption of *raloxifene* by 60 percent; therefore, these drugs should not be taken together. In one study, *raloxifene* caused a 10 percent drop in prothrombin time in patients taking *warfarin*. Thus, it is prudent to monitor prothrombin time in these individuals.

C. Toremifene

Toremifene [tor-EH-mih-feen] is a SERM with properties and side effects similar to those of *tamoxifen*. Data on the risk of endometrial hyperplasia and cancer with *toremifene* are lacking. The use of *toremifene* is restricted to postmenopausal women with metastatic breast cancer.

D. Clomiphene

By acting as a partial estrogen agonist and interfering with the negative feedback of estrogens on the hypothalamus, *clomiphene* [KLOE-mi-feen] increases the secretion of gonadotropin-releasing hormone and gonadotropins, leading to a stimulation of ovulation. The drug has been used successfully to treat infertility associated with anovulatory cycles, but it is not effective in women with ovulatory dysfunction due to pituitary or ovarian failure. Adverse effects are dose related and include headache, nausea, vasomotor flushes, visual disturbances, and ovarian enlargement.

IV. Progestins

Progesterone, the natural progestin, is produced in response to luteinizing hormone (LH) by both females (secreted by the corpus luteum, primarily during the second half of the menstrual cycle, and by the placenta) and by males (secreted by the testes). It is also synthesized by the adrenal cortex in both sexes. In females, progesterone promotes the development of a secretory endometrium that can accommodate implantation of a newly forming embryo. The high levels of progesterone that are released during the second half of the menstrual cycle (the luteal phase) inhibit the production of gonadotropin and, therefore, prevent further ovulation. If conception takes place, progesterone continues to be secreted, maintaining the endometrium in a favorable state for the continuation of the pregnancy and reducing uterine contractions. If conception does not take place, the release of progesterone from the corpus luteum ceases abruptly. This decline stimulates the onset of menstruation. (Figure 25.5 summarizes the hormones produced during the menstrual cycle.) Progestins exert their mechanism of action in a manner analogous to that of the other steroid hormones. They cause: 1) an increase in hepatic glycogenâ€"probably through an insulin-mediated mechanism; 2) a decrease in Na^+ reabsorption in the kidney due to competition

with aldosterone at the mineralocorticoid receptor; 3) an increase in body temperature through an unknown mechanism; 4) a decrease in some plasma amino acids; and 5) an increase in excretion of urinary nitrogen.

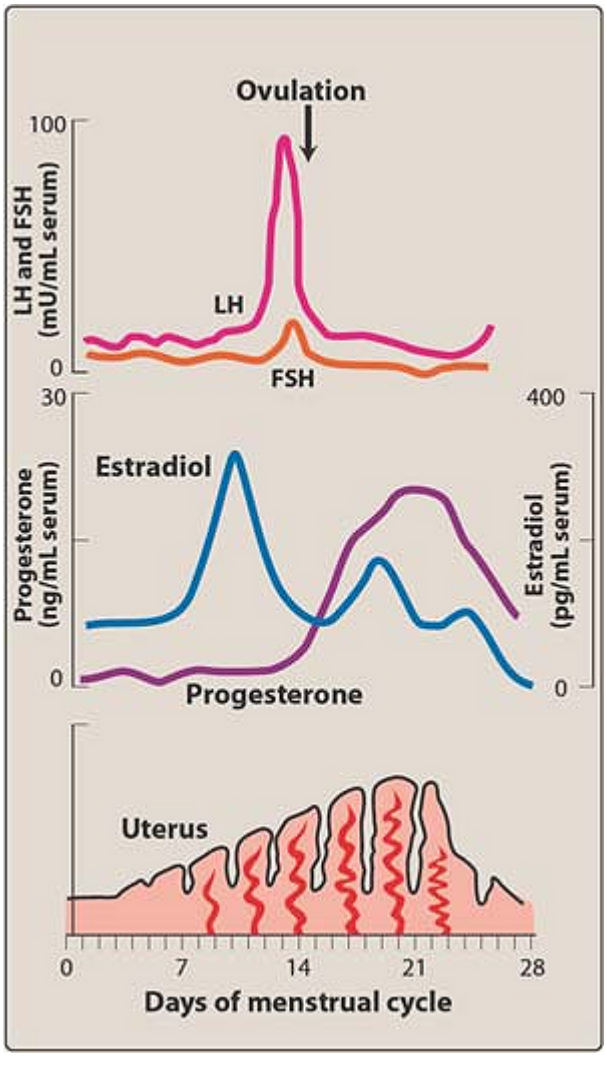


Figure 25.5 The menstrual cycle with plasma levels of pituitary and ovarian hormones and a schematic

representation of changes in the morphology of the uterine lining. FSH = follicle-stimulating hormone; LH = luteinizing hormone.

A. Therapeutic uses of progestins

The major clinical uses of progestins are to rectify a hormonal deficiency and for contraception, in which they are generally used with estrogens, either in combination or in a sequential manner. Progesterone by itself is not used widely as a therapy because of its rapid metabolism, resulting in low bioavailability. Synthetic progestins used in contraception are more stable to first-pass metabolism, allowing lower doses when administered orally. These agents include *norethindrone* [nor-ETH-in-drone], *norethindrone acetate, norgestrel* [nor-JES-trel], *levonorgestrel* [lee-voe-nor-JES-trel], *desogestrel* [des-oh-JES-trel], *norgestimate* [nor-JES-tih-mate], and *drospirenone* [dro-SPY-re-none]. Most synthetic progestins used in oral contraceptives (for example, *norethindrone, norethindrone acetate, norgestrel, levonorgestrel*) are derived from 19-nortestosterone and possess some androgenic activity because of their structural similarity to *testosterone*. *Medroxyprogesterone* [me-DROK-see-proe-JES-ter-one] *acetate* is an injectable contraceptive, and the oral form is a common progestin component of postmenopausal EPT. Other clinical uses of the progestins are in the control of dysfunctional uterine bleeding, treatment of dysmenorrhea, and management of endometriosis.

B. Pharmacokinetics

A micronized preparation of *progesterone* is rapidly absorbed after oral administration. It has a short half-life in the plasma and is almost completely metabolized by the liver. The glucuronidated metabolite (pregnanediol glucuronide) is excreted primarily by the kidney. Synthetic progestins are less rapidly metabolized. *Medroxyprogesterone acetate* is injected intramuscularly or subcutaneously and has a duration of action of 3 months. The other progestins last from 1 to 3 days.

C. Adverse effects

The major adverse effects associated with the use of progestins are headache, depression, weight gain, and changes in libido (Figure 25.6). Some progestins, such as the 19-nortestosterone derivatives, have androgenic activity and can increase the ratio of LDL to HDL cholesterol and cause acne and hirsutism. Less androgenic progestins, such as *norgestimate* and *drospirenone,* may be preferred in women with acne. Injectable *medroxyprogesterone acetate* has been associated with an increased risk of osteoporosis, which has led to recommendations for limiting the duration of use.

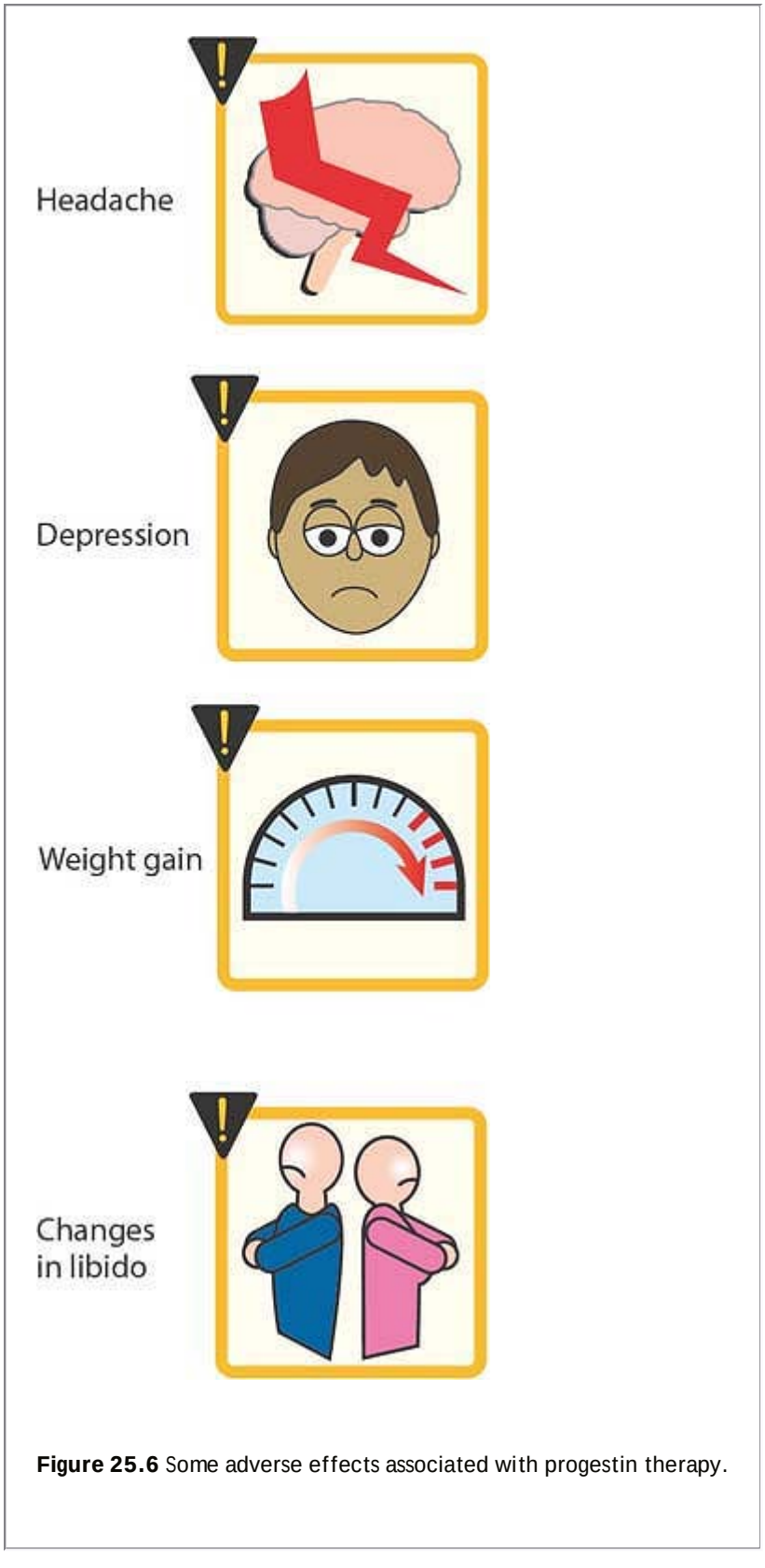


Figure 25.6 Some adverse effects associated with progestin therapy.

D. Antiprogestin

Mifepristone [mih-feh-PRIH-stone] (also designated as RU 486) is a progesterone antagonist with partial agonist activity. [Note: *Mifepristone* also has potent antiglucocorticoid activity.] Administration of this drug to females early in pregnancy results, in most cases (up to 94 percent), in abortion of the fetus due to the interference with

progesterone and the decline in human chorionic gonadotropin. The major adverse effects are significant uterine bleeding and the possibility of an incomplete abortion. However, administration of *misoprostol* orally or intravaginally after a single oral dose of *mifepristone* effectively terminates gestation. *Mifepristone* is being investigated as an oral contraceptive and an emergency contraceptive agent.

V. Contraceptives

Drugs are available that decrease fertility by a number of different mechanisms, such as preventing ovulation, impairing gametogenesis or gamete maturation, or interfering with gestation. Currently, interference with ovulation is the most common pharmacologic intervention for preventing pregnancy (Figure 25.7).

A. Major classes of contraceptives

1. **Combination oral contraceptives:** Products containing a combination of an estrogen and a progestin are the most common type of oral contraceptives. Monophasic combination pills contain a constant dose of estrogen and progestin given over 21 days. Triphasic oral contraceptive products attempt to mimic the natural female cycle and contain a constant dose of estrogen with increasing doses of progestin given over three successive 7-day periods. With either type of combination oral contraceptive, active pills are taken for 21 days followed by 7 days of placebo. Withdrawal bleeding occurs during the hormone-free interval. [Note: Estrogens that are commonly present in the combination pills are *ethinyl estradiol* and *mestranol*. The most common progestins are *norethindrone, norethindrone acetate, norgestrel, levonorgestrel, desogestrel, norgestimate*, and *drospirenone*.] These preparations are highly effective in achieving contraception (Figure 25.8). Use of extended-cycle contraception (84 active pills followed by 7 days of placebo) results in less frequent withdrawal bleeding. A continuous oral contraceptive product (active pills taken 365 days of the year) is also available.

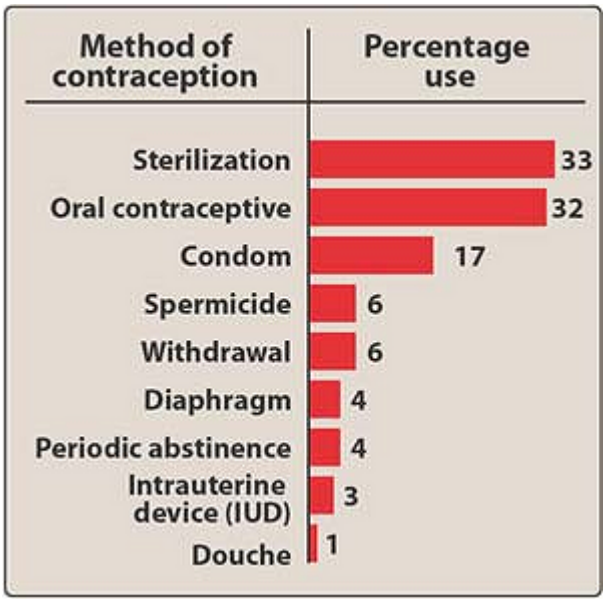


Figure 25.7 Comparison of contraceptive use among United States women ages 15 to 44 years.

2. **Transdermal patch:** An alternative to combination oral contraceptive pills is a transdermal contraceptive patch containing *ethinyl estradiol* and the progestin *norelgestromin*. One contraceptive patch is applied each week for 3 weeks to the abdomen, upper torso, or buttock. Week 4 is patch-free, and withdrawal bleeding occurs.

The transdermal patch has efficacy comparable to that of the oral contraceptives; however, it has been shown to be less effective in women weighing greater than 90 kilograms. Contraindications and adverse effects for the patch are similar to those of oral contraceptives. Recent data have indicated that total estrogen exposure with the transdermal patch is up to 60 percent greater than that seen with a 35 Âµg estrogen oral contraceptive. Increased exposure to estrogen may increase the risk of adverse events such as thromboembolism.

3. **Vaginal ring:** An additional contraceptive option is a vaginal ring containing *ethinyl estradiol* and *etonogestrel*. The ring is inserted into the vagina and is left in place for 3 weeks. Week 4 is ring-free, and withdrawal bleeding occurs. The contraceptive vaginal ring has efficacy, contraindications, and adverse effects similar to those of oral contraceptives. One caveat with the vaginal ring is that it may occasionally slip or be expelled accidentally.

4. **Progestin-only pills:** Products containing a progestin only, usually *norethindrone* or *norgestrel* (called a â€œmini-pillâ€), are taken daily on a continuous schedule. Progestin-only pills deliver a low, continuous dosage of drug. These preparations are less effective than the combination pill (see Figure 25.8), and they may produce irregular menstrual cycles more frequently than the combination product. The progestin-only pill has limited patient acceptance because of

anxiety over the increased possibility of pregnancy and the frequent occurrence of menstrual irregularities. The progestin-only pill may be used for patients who are breast-feeding (unlike estrogen, progestins do not have an effect on milk production), are intolerant to estrogen, or are smokers or have other contraindications to estrogen-containing products.

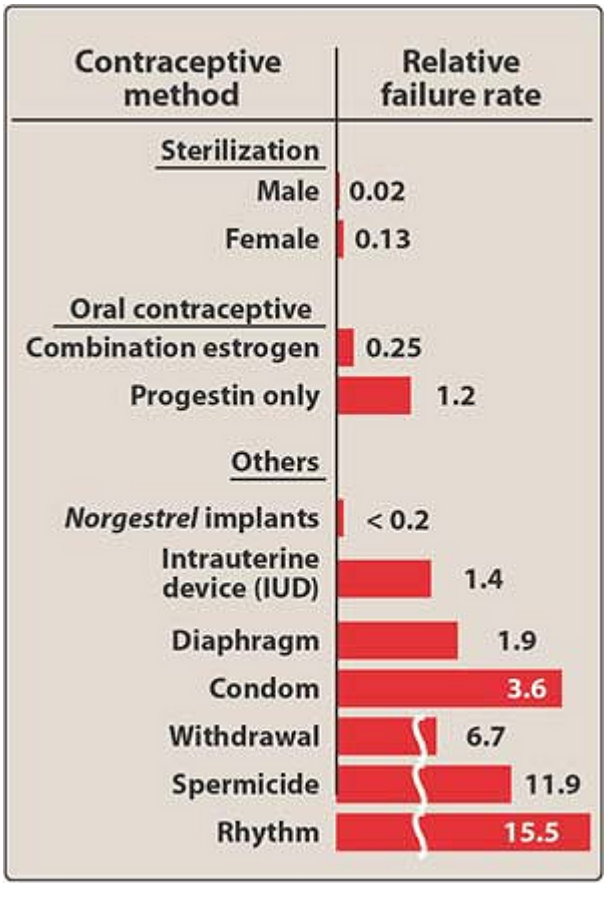


Figure 25.8 Comparison of failure rate for various methods of contraception. Longer bars indicate a higher failure rateâ€“that is, more pregnancies.

5. **Progestin implants:** A subdermal implant containing *etonogestrel* offers long-term contraception. One 4-cm capsule is placed subcutaneously in the upper arm and provides contraception for approximately 3 years. The implant is nearly as reliable as sterilization, and the effect is totally reversible when surgically removed. Once the progestin-containing capsule is implanted, this method of contraception does not rely on patient compliance. This may, in part, explain the low failure rate for this method. Principal side effects of the implants are irregular menstrual bleeding and headaches.

6. **Progestin intrauterine device:** A *levonorgestrel*-releasing intrauterine system offers a highly effective method of long-term contraception. This intrauterine device provides contraception for up to 5 years. It is a suitable method of contraception for women who already have at least one child and do not have a history of pelvic inflammatory disease or ectopic pregnancy.

7. **Postcoital contraception:** The overall risk of pregnancy after an episode of coitus without effective contraception is shown in the Figure 25.9. Postcoital or emergency contraception reduces the probability of pregnancy to between 0.2 and 3 percent. Emergency contraception uses high doses of progestin (for example, 0.75 mg of *levonorgestrel*) or high doses of estrogen (100 Âµg of *ethinyl estradiol*) plus progestin (0.5 mg of *levonorgestrel*) administered within 72 hours of unprotected intercourse (the â€œmorning-afterâ€ pill). A second dose of emergency contraception should be taken 12 hours after the first dose. For maximum effectiveness, emergency contraception should be taken as soon as possible after unprotected intercourse. The progestin-only emergency contraceptive regimens are generally better tolerated than the estrogen-progestin combination regimens. A single dose of *mifepristone* has also been used for emergency contraception.

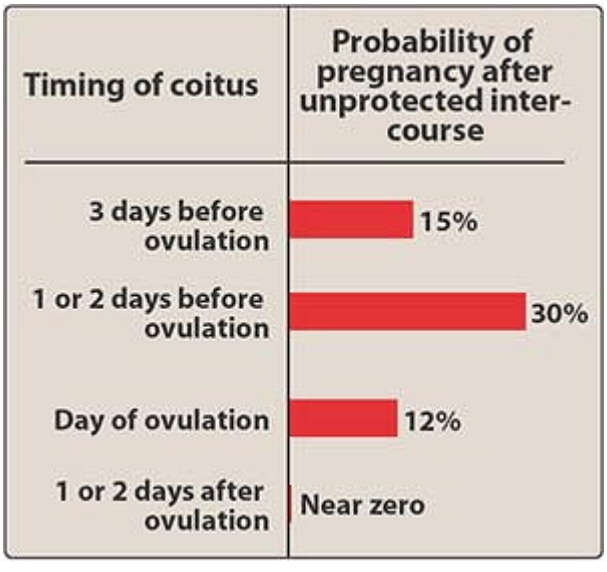


Figure 25.9 Risk of pregnancy after unprotected intercourse in young couples in their mid twenties.

B. Mechanism of action

The mechanism of action for these contraceptives is not completely understood. It is likely that the combination of estrogen and progestin administered over an approximately 3-week period inhibits ovulation. [Note: The estrogen provides a negative feedback on the release of LH and follicle-stimulating hormone (FSH) by the pituitary gland, thus preventing ovulation. The progestin also inhibits LH release and thickens the cervical mucus, thus hampering the transport of sperm. Withdrawal of the progestin stimulates menstrual bleeding during the placebo week].

C. Adverse effects

Most adverse effects are believed to be due to the estrogen component, but cardiovascular effects reflect the action of both estrogen and progestin. The incidence of adverse effects with oral contraceptives is relatively low and is determined by the specific compounds and combinations used.

1. **Major adverse effects:** The major adverse effects are breast fullness, depression, fluid retention, headache, nausea, and vomiting.
2. **Cardiovascular:** Although rare, the most serious adverse effect of oral contraceptives is cardiovascular disease, including thromboembolism, thrombophlebitis, hypertension, increased incidence of myocardial infarction, and cerebral and coronary thrombosis. These adverse effects are most common among women who smoke and who are older than 35 years, although they may affect women of any age.
3. **Carcinogenicity:** Oral contraceptives have been shown to decrease the incidence of endometrial and ovarian cancer. Their ability to induce other neoplasms is controversial. The production of benign tumors of the liver that may rupture and hemorrhage is rare.
4. **Metabolic:** Abnormal glucose tolerance (similar to the changes seen in pregnancy) is sometimes associated with oral contraceptives. Weight gain is common in women who are taking the *nortestosterone* derivatives.
5. **Serum lipids:** The combination pill causes a change in the serum lipoprotein profile: Estrogen causes an increase in HDL and a decrease in LDL (a desirable occurrence), whereas progestins may negate some of the beneficial effects of estrogen. [Note: The potent progestin *norgestrel* causes the greatest increase in the LDL:HDL ratio. Therefore, estrogen-dominant preparations are best for individuals with elevated serum cholesterol.]
6. **Contraindications:** Oral contraceptives are contraindicated in the presence of cerebrovascular and thromboembolic disease, estrogen-dependent neoplasms, liver disease, and pregnancy. Combination oral contraceptives should not be used in patients over the age of 35 who are heavy smokers.

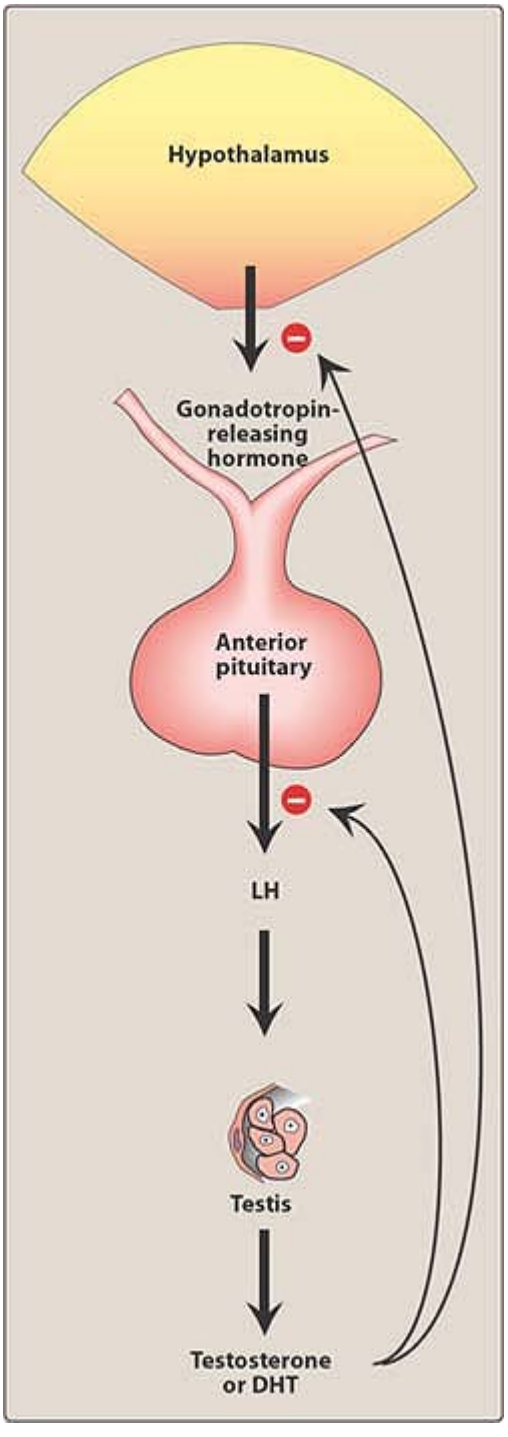


Figure 25.10 Regulation of secretion of testosterone. DHT = 5-Î±-dihydro testosterone; LH = luteinizing hormone.

VI. Androgens

The androgens are a group of steroids that have anabolic and/or masculinizing effects in both males and females. *Testosteron*e [tess-TOSS-te-rone], the most important androgen in humans, is synthesized by Leydig cells in the

testes and, in smaller amounts, by cells in the ovary of the female and by the adrenal gland in both sexes. Other androgens secreted by the testes are *5Î±-dihydrotestosterone* (*DHT*), *androstenedione*, and *dehydroepiandrosterone* (DHEA) in small amounts. In adult males, *testosterone* secretion by Leydig cells is controlled by gonadotropin-releasing hormone from the hypothalamus, which stimulates the anterior pituitary gland to secrete FSH and LH. [Note: LH stimulates steroidogenesis in the Leydig cells, whereas FSH is necessary for spermatogenesis.] *Testosterone* or its active metabolite, *DHT*, inhibits production of these specific trophic hormones through a negative feedback loop and, thus, regulates *testosterone* production (Figure 25.10). The androgens are required for 1) normal maturation in the male, 2) sperm production, 3) increased synthesis of muscle proteins and hemoglobin, and 4) decreased bone resorption. Synthetic modifications of the androgen structure are designed to modify solubility and susceptibility to enzymatic breakdown (thus prolonging the half-life of the hormone) and to separate anabolic and androgenic effects.

A. Mechanism of action

Like the estrogens and progestins, androgens bind to a specific nuclear receptor in a target cell. Although *testosterone* itself is the active ligand in muscle and liver, in other tissues it must be metabolized to derivatives, such as *DHT*. For example, after diffusing into the cells of the prostate, seminal vesicles, epididymis, and skin, *testosterone* is converted by 5Î±-reductase to *DHT*, which binds to the receptor. In the brain, liver, and adipose tissue, *testosterone* is biotransformed to *estradio*l by cytochrome P450 aromatase. The hormone-receptor complex binds to DNA and stimulates the synthesis of specific RNAs and proteins. [Note: *Testosterone* analogs that cannot be converted to DHT have less effect on the reproductive system than they do on the skeletal musculature.]

B. Therapeutic uses

1. **Androgenic effects:** Androgenic steroids are used for males with inadequate androgen secretion. [Note: Hypogonadism can be caused by testicular dysfunction (primary hypogonadism) or due to failure of the hypothalamus or pituitary (secondary hypogonadism). In each instance, androgen therapy is indicated.]

2. **Anabolic effects:** Anabolic steroids can be used to treat senile osteoporosis and chronic wasting associated with human immunodeficiency virus or cancer. They may also be used as adjunct therapy in severe burns and to speed recovery from surgery or chronic debilitating diseases.

3. **Endometriosis:** *Danazol* [DAH-nah-zole], a mild androgen, is used in the treatment of endometriosis (ectopic growth of the endometrium) and fibrocystic breast disease. It inhibits release of FSH and LH but has no effect on the aromatase. Weight gain, acne, decreased breast size, deepening voice, increased libido, and increased hair growth are among the adverse effects. *Danazol* has been reported occasionally to suppress adrenal function.

4. **Unapproved use:** Anabolic steroids are used to increase lean body mass, muscle strength, and endurance in athletes and body builders (see below). In some popular publications, *DHEA* (a precursor of *testosterone* and estrogen) has been touted as the anti-aging hormone as well as a â€œperformance enhancer.â€ With its ready availability in health food stores, the drug has been abused. There is no definitive evidence that it slows aging, however, or that it improves performance at normal therapeutic doses.

C. Pharmacokinetics

1. **Testosterone:** This agent is ineffective orally because of inactivation by first-pass metabolism. As with the other sex steroids, *testosterone* [tes-TOS-ter-own] is rapidly absorbed and is metabolized to relatively or completely inactive compounds that are excreted primarily in the urine. *Testosterone* and its C_{17}-esters (for example, *testosterone cypionate* or *enanthate*) are administered intramuscularly. [Note: The addition of the esterified lipid makes the hormone more lipid soluble, thereby increasing its duration of action.] Transdermal patches, topical gels, and buccal tablets of *testosterone* are also available. Figure 25.11 shows serum levels of testosterone achieved by injection and by a transdermal patch in hypogonadal men. *Testosterone* and its esters demonstrate a 1:1 relative ratio of androgenic to anabolic activity.

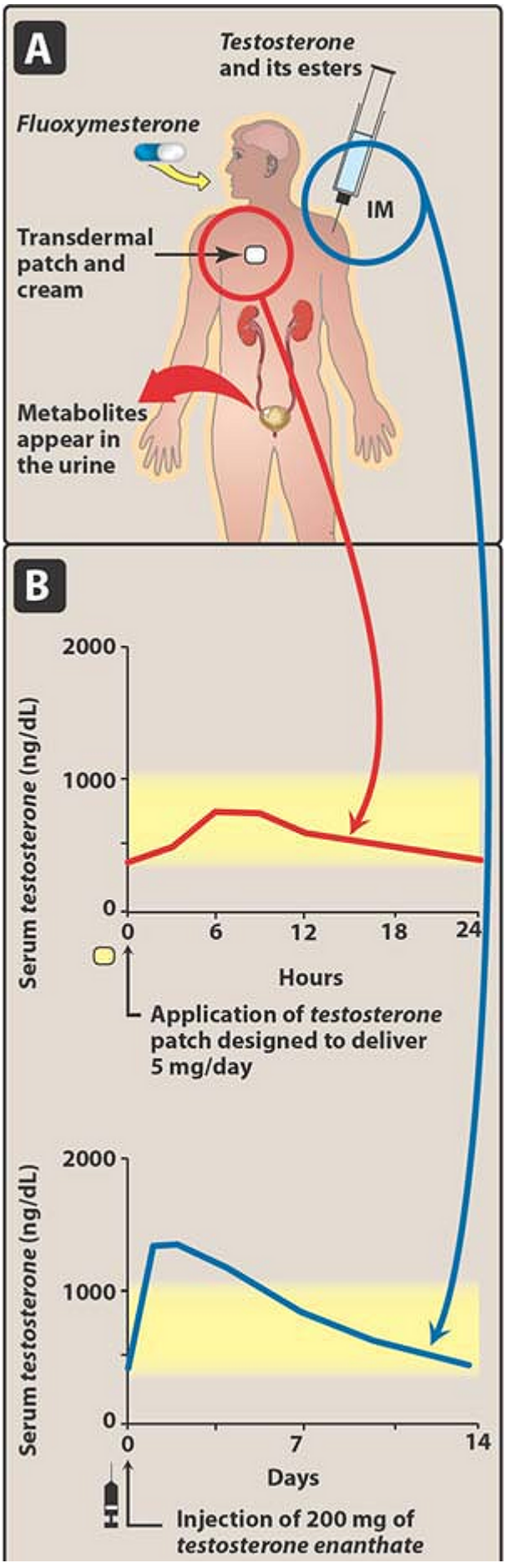

A
Testosterone and its esters
Fluoxymesterone
IM
Transdermal patch and cream
Metabolites appear in the urine
B
Serum testosterone (ng/dL)
2000
1000
0
0
6
12
18
24
Hours
Application of testosterone patch designed to deliver 5 mg/day
Serum testosterone (ng/dL)
2000
1000
0
0
7
14
Days
Injection of 200 mg of testosterone enanthate

Figure 25.11 A. Administration and fate of androgens. B. Serum testosterone concentrations after administration by injection or transdermal patch to hypogonadal men. The yellow band indicates the upper and lower limits of normal range.

2. **Testosterone derivatives:** Alkylation of the 17Î± position of *testosterone* allows oral administration of the hormone. Agents such as *fluoxymesterone* [floo-ox-ee-MESS-teh-rone] have a longer half-life in the body than that of the naturally occurring androgen. *Fluoxymesterone* is effective when given orally, and it has a 1:2 androgenic to anabolic ratio. *Oxandrolone* [ox-AN-droe-lone] is another orally active testosterone derivative with anabolic activity 3 to 13 times that of *testosterone*. Hepatic adverse effects have been associated with the 17Î±-alkylated androgens.

D. Adverse effects

1. **In females:** Androgens can cause masculinization, with acne, growth of facial hair, deepening of the voice, male pattern baldness, and excessive muscle development. Menstrual irregularities may also occur. *Testosterone* should not be used by pregnant women because of possible virilization of the female fetus.
2. **In males:** Excess androgens can cause priapism, impotence, decreased spermatogenesis, and gynecomastia. Cosmetic changes such as those described for females may occur as well. Androgens can also stimulate growth of the prostate.
3. **In children:** Androgens can cause abnormal sexual maturation and growth disturbances resulting from premature closing of the epiphyseal plates.
4. **General effects:** Androgens increase serum LDL and lower serum HDL levels; therefore, they increase the LDL:HDL ratio and potentially increase the risk for premature coronary heart disease. Androgens can also cause fluid retention, leading to edema.
5. **In athletes:** Use of anabolic steroids, (for example, *DHEA* or *nandrolone* [NAN-dro-lone]) by athletes can cause premature closing of the epiphysis of the long bones, which stunts growth and interrupts development. The high doses taken by these young athletes may result in reduction of testicular size, hepatic abnormalities, increased aggression (â€œroid rageâ€), major mood disorders, and the other adverse effects described above.

E. Antiandrogens

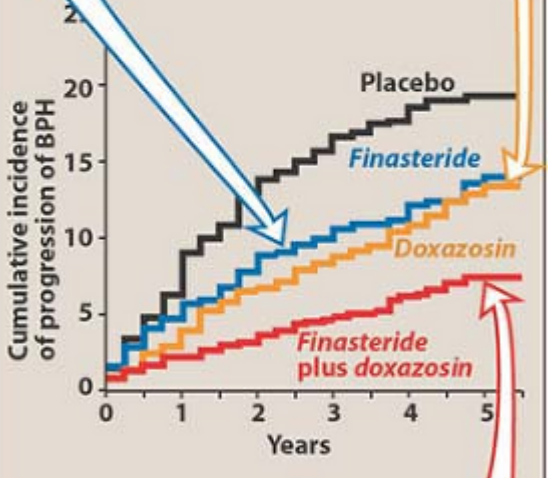
Antiandrogens counter male hormonal action by interfering with the synthesis of androgens or by blocking their receptors. For example, at high doses, the antifungal drug *ketoconazole* inhibits several of the cytochrome P450 enzymes involved in steroid synthesis. *Finasteride* [fin-AS-ter-ide] and *dutasteride* [doo-TAS-ter-ride], agents used for the treatment of benign prostatic hypertrophy, inhibit 5Î±-reductase (Figure 25.12). The resulting decrease in formation of *DHT* in the prostate leads to a reduction in prostate size. Antiandrogens, such as *flutamide* [FLOO-tah-mide], act as competitive inhibitors of androgens at the target cell. *Flutamide* is used in the treatment of prostatic carcinoma in males. Two other potent antiandrogens, *bicalutamide* [bye-ka-LOO-ta-mide] and *nilutamide* [nye-LOO-tah-mide], are effective orally for the treatment of metastatic prostate cancer.

α_1-Adrenergic antagonists

- *Terazosin, doxazosin, tamsulosin,* and *alfuzosin* relieve outlet obstruction of the bladder by reducing the tension of prostatic smooth muscle in the prostate, prostate capsule, and bladder neck.
- The most important side effects are orthostatic hypotension and dizziness.

5 α-Reductase inhibitors

- *Finasteride* and *dutasteride* act by reducing the size of the prostate gland. Treatment for 6 to 12 months is generally needed before prostate size is sufficiently reduced to improve symptoms.
- The major side effects of the 5 α-reductase inhibitors are decreased libido and ejaculatory or erectile dysfunction.



Combination therapy

- Combination therapy with an α_1-adrenergic antagonist plus a 5 α-reductase inhibitor produces the greatest reduction in the symptoms of BPH, such as acute urinary retention, urinary incontinence, renal insufficiency,

Figure 25.12 Therapy for benign prostatic hyperplasia (BPH).

Study Questions

Choose the ONE best answer.

25.1 Young athletes who abuse androgens should be made aware of the side effects of these drugs. Which one of the following is, however, not of concern?

A. Increased muscle mass.

B. Anemia due to bone marrow failure.

C. Overly aggressive behavior.

D. Decreased spermatogenesis.

E. Stunted growth.

View Answer

25.2 A 70-year-old woman is being treated with raloxifene for osteoporosis. There is an increased risk of her developing:

A. Breast cancer.

B. Uterine cancer.

C. Vein thrombosis.

D. Atrophic vaginitis.

E. Hypercholesterolemia.

View Answer

25.3 A 23-year-old woman has failed to become pregnant after 2 years of unprotected intercourse. Which of the following would be effective in treating infertility due anovulatory cycles?

A. A combination of an estrogen and progestin.

B. Estrogen alone.

C. Clomiphene.

D. Raloxifene.

View Answer

25.4 Which of the following is inappropriate for treating osteoporosis?

A. Dehydroepiandrosterone.

B. Estradiol.

C. Tamoxifen.

D. Norethindrone.

E. Mestranol.

View Answer

25.5 Estrogen replacement therapy in menopausal women:

A. Restores bone loss accompanying osteoporosis.

B. May induce â€œhot flashes.â€

C. May cause atrophic vaginitis.

D. Is most effective if instituted at the first signs of menopause.

E. Requires higher doses of estrogen than with oral contraceptive therapy.

View Answer