**LECTURE 2: ANTIANGINAL DRUGS.**

**ANTIHYPERTENSIVE DRUGS**

**ANTIANGINAL DRUGS**

Ischemic heart disease is one of the most common cardiovascular diseases in developed countries, and angina pectoris is the most common condition involving tissue ischemia in which vasodilator drugs are used.

The most common cause of angina is atheromatous obstruction of the large coronary vessels (coronary artery disease, CAD). Inadequate blood flow in the presence of CAD results in effort angina, also known as classic angina. Diagnosis is usually made on the basis of the history and stress testing. However, transient spasm of localized portions of these vessels, usually associated with underlying atheromas, can also cause significant myocardial ischemia and pain (vasospastic or variant angina). Vasospastic angina is also called Prinzmetal angina. Diagnosis is made on the basis of history.

The primary cause of angina pectoris is an imbalance between the oxygen requirement of the heart and the oxygen supplied to it via the coronary vessels.

**Drug Action in Angina**

The three drug groups traditionally used in angina (organic nitrates, calcium channel blockers, and β blockers) decrease myocardial oxygen requirement by decreasing one or more of the major determinants of oxygen demand (heart size, heart rate, blood pressure, and contractility). In some patients, the nitrates and the calcium channel blockers may cause a redistribution of coronary flow and increase oxygen delivery to ischemic tissue. In variant angina, these two drug groups also increase myocardial oxygen delivery by reversing coronary artery spasm. Newer drugs are discussed later.

**NITRATES & NITRITES**

Chemistry Diets rich in inorganic nitrates are known to have a small blood pressure–lowering action but are of no value in angina. The agents useful in angina are simple organic nitric and nitrous acid esters of polyalcohols. Nitroglycerin may be considered the prototype of the group and has been used in cardiovascular conditions for over 160 years. Although nitroglycerin is used in the manufacture of dynamite, the formulations used in medicine are not explosive.

The conventional sublingual tablet form of nitroglycerin may lose potency when stored as a result of volatilization and adsorption to plastic surfaces. Therefore, it should be kept in tightly closed glass containers. Nitroglycerin is not sensitive to light. All therapeutically active agents in the nitrate group appear to have identical mechanisms of action and similar toxicities, although development of tolerance may vary. Therefore, pharmacokinetic factors govern the choice of agent and mode of therapy when using the nitrates.

**Pharmacokinetics**

The liver contains a high-capacity organic nitrate reductase that removes nitrate groups in a stepwise fashion from the parent molecule and ultimately inactivates the drug. Therefore, oral bioavailability of the traditional organic nitrates (eg, nitroglycerin and isosorbide dinitrate) is low (typically < 10–20%). For this reason, the sublingual route, which avoids the first-pass effect, is preferred for achieving a therapeutic blood level rapidly. Nitroglycerin and isosorbide dinitrate both are absorbed efficiently by the sublingual route and reach therapeutic blood levels within a few minutes. However, the total dose administered by this route must be limited to avoid excessive effect; therefore, the total duration of effect is brief (15–30 minutes). When much longer duration of action is needed, oral preparations can be given that contain an amount of drug sufficient to result in sustained systemic blood levels of the parent drug plus active metabolites. Pentaerythritol tetranitrate (PETN) is another organic nitrate that is promoted for oral use as a “long-acting” nitrate (> 6 hours). Other routes of administration available for nitroglycerin include transdermal and buccal absorption from slow-release preparations (described below). Amyl nitrite and related nitrites are highly volatile liquids. Amyl nitrite is available in fragile glass ampules packaged in a protective cloth covering. The ampule can be crushed with the fingers, resulting in rapid release of vapors inhalable through the cloth covering. The inhalation route provides very rapid absorption and, like the sublingual route, avoids the hepatic first-pass effect. Because of its unpleasant odor and extremely short duration of action, amyl nitrite is now obsolete for angina. Once absorbed, the unchanged organic nitrate compounds have half-lives of only 2–8 minutes. The partially denitrated metabolites have much longer half-lives (up to 3 hours). Of the nitroglycerin metabolites (two dinitroglycerins and two mononitro forms), the 1,2-dinitro derivative has significant vasodilator efficacy and probably provides most of the therapeutic effect of orally administered nitroglycerin. The 5-mononitrate metabolite of isosorbide dinitrate is an active metabolite of the latter drug and is available for oral use as isosorbide mononitrate. It has a bioavailability of 100%. Excretion, primarily in the form of glucuronide derivatives of the denitrated metabolites, is largely by way of the kidney.

**Pharmacodynamics**

**A. Mechanism of Action in Smooth Muscle**

After more than a century of study, the mechanism of action of nitroglycerin is still not fully understood. There is general agreement that the drug must be bioactivated with the release of nitric oxide. Unlike nitroprusside and some other direct nitric oxide donors, nitroglycerin activation requires enzymatic action. Nitroglycerin can be denitrated by glutathione S-transferase in smooth muscle and other cells. A mitochondrial enzyme, aldehyde dehydrogenase isoform 2 (ALDH2) and possibly isoform 3 (ALDH3), appears to be key in the activation and release of nitric oxide from nitroglycerin and pentaerythritol tetranitrate. Different enzymes may be involved in the denitration of isosorbide dinitrate and mononitrate. Free nitrite ion is released, which is then converted to nitric oxide. Nitric oxide (probably complexed with cysteine) combines with the heme group of soluble guanylyl cyclase, activating that enzyme and causing an increase in cGMP. Formation of cGMP represents a first step toward smooth muscle relaxation. The production of prostaglandin E or prostacyclin (PGI2) and membrane hyperpolarization may also be involved. There is no evidence that autonomic receptors are involved in the primary nitrate response. However, autonomic reflex responses, evoked when hypotensive doses are given, are common. As described in the following text, tolerance is an important consideration in the use of nitrates. Although tolerance may be caused in part by a decrease in tissue sulfhydryl groups, eg, on cysteine, tolerance can be only partially prevented or reversed with a sulfhydryl-regenerating agent. Increased generation of oxygen free radicals during nitrate therapy may be another important mechanism of tolerance. Recent evidence suggests that diminished availability of calcitonin gene-related peptide (CGRP, a potent vasodilator) is also associated with nitrate tolerance. Nicorandil and several other antianginal agents not available in the United States appear to combine the activity of nitric oxide release with a direct potassium channel-opening action, thus providing an additional mechanism for causing vasodilation.

**B. Organ System Effects**

Nitroglycerin relaxes all types of smooth muscle regardless of the cause of the preexisting muscle tone. It has practically no direct effect on cardiac or skeletal muscle.

***1. Vascular smooth muscle***—All segments of the vascular system from large arteries through large veins relax in response to nitroglycerin. Most evidence suggests a gradient of response, with veins responding at the lowest concentrations and arteries at slightly higher ones. The epicardial coronary arteries are sensitive, but concentric atheromas can prevent significant dilation. On the other hand, eccentric lesions permit an increase in flow when nitrates relax the smooth muscle on the side away from the lesion. Arterioles and precapillary sphincters are dilated least, partly because of reflex responses and partly because different vessels vary in their ability to release nitric oxide from the drug. A primary direct result of an effective dose of nitroglycerin is marked relaxation of veins with increased venous capacitance and decreased ventricular preload. Pulmonary vascular pressures and heart size are significantly reduced. In the absence of heart failure, cardiac output is reduced. Because venous capacitance is increased, orthostatic hypotension may be marked and syncope can result. Dilation of large epicardial coronary arteries may improve oxygen delivery in the presence of eccentric atheromas or collateral vessels. Temporal artery pulsations and a throbbing headache associated with meningeal artery pulsations are common effects of nitroglycerin and amyl nitrite. In heart failure, preload is often abnormally high; the nitrates and other vasodilators, by reducing preload, may have a beneficial effect on cardiac output in this condition. The indirect effects of nitroglycerin consist of those compensatory responses evoked by baroreceptors and hormonal mechanisms responding to decreased arterial pressure; this often results in tachycardia and increased cardiac contractility. Retention of salt and water may also be significant, especially with intermediate- and long-acting nitrates. These compensatory responses contribute to the development of tolerance. In normal subjects without coronary disease, nitroglycerin can induce a significant, if transient, increase in total coronary blood flow. In contrast, there is no evidence that total coronary flow is increased in patients with angina due to atherosclerotic obstructive coronary artery disease. However, some studies suggest that redistribution of coronary flow from normal to ischemic regions may play a role in nitroglycerin’s therapeutic effect. Nitroglycerin also exerts a weak negative inotropic effect on the heart via nitric oxide.

***2. Other smooth muscle organs***—Relaxation of smooth muscle of the bronchi, gastrointestinal tract (including biliary system), and genitourinary tract has been demonstrated experimentally. Because of their brief duration, these actions of the nitrates are rarely of any clinical value. During recent decades, the use of amyl nitrite and isobutyl nitrite (not nitrates) by inhalation as recreational (sex-enhancing) drugs has become popular with some segments of the population. Nitrites readily release nitric oxide in erectile tissue as well as vascular smooth muscle and activate guanylyl cyclase. The resulting increase in cGMP causes dephosphorylation of myosin light chains and relaxation, which enhances erection. This pharmacologic approach to erectile dysfunction is discussed in the Box: Drugs Used in the Treatment of Erectile Dysfunction.

***3. Action on platelets***—Nitric oxide released from nitroglycerin stimulates guanylyl cyclase in platelets as in smooth muscle.

The increase in cGMP that results is responsible for a decrease in platelet aggregation. Unfortunately, recent prospective trials have established no survival benefit when nitroglycerin is used in acute myocardial infarction. In contrast, intravenous nitroglycerin may be of value in unstable angina, in part through its action on platelets.

***4. Other effects***—Nitrite ion (not nitrate) reacts with hemoglobin (which contains ferrous iron) to produce methemoglobin (which contains ferric iron). Because methemoglobin has a very low affinity for oxygen, large doses of nitrites can result in pseudocyanosis, tissue hypoxia, and death. Fortunately, the plasma level of nitrite resulting from even large doses of organic and inorganic nitrates is too low to cause significant methemoglobinemia in adults. In nursing infants, the intestinal flora is capable of converting significant amounts of inorganic nitrate, eg, from well water, to nitrite ion. In addition, sodium nitrite is used as a curing agent for meats, eg, corned beef. Thus, inadvertent exposure to large amounts of nitrite ion can occur and may produce serious toxicity. One therapeutic application of this otherwise toxic effect of nitrite has been discovered. Cyanide poisoning results from complexing of cytochrome iron by the CN− ion. Methemoglobin iron has a very high affinity for CN−; thus, administration of sodium nitrite (NaNO2) soon after cyanide exposure regenerates active cytochrome. The cyanomethemoglobin produced can be further detoxified by the intravenous administration of sodium thiosulfate (Na2S2O3); this results in formation of thiocyanate ion (SCN−), a less toxic ion that is readily excreted. Methemoglobinemia, if excessive, can be treated by giving methylene blue intravenously.

This antidote for cyanide poisoning (inhaled amyl nitrite plus intravenous sodium nitrite, followed by intravenous sodium thiocyanate and, if needed, methylene blue) is now being replaced by hydroxocobalamin, a form of vitamin B12, which also has a very high affinity for cyanide and combines with it to generate another form of vitamin B12.

**Toxicity & Tolerance**

**A. Acute Adverse Effects**

The major acute toxicities of organic nitrates are direct extensions of therapeutic vasodilation: orthostatic hypotension, tachycardia, and throbbing headache. Glaucoma, once thought to be a contraindication, does not worsen, and nitrates can be used safely in the presence of increased intraocular pressure. Nitrates are contraindicated, however, if intracranial pressure is elevated. Rarely, transdermal nitroglycerin patches have ignited when external defibrillator electroshock was applied to the chest of patients in ventricular fibrillation. Such patches should be removed before use of external defibrillation to prevent superficial burns.

**B. Tolerance**

With continuous exposure to nitrates, isolated smooth muscle may develop complete tolerance (tachyphylaxis), and the intact human becomes progressively more tolerant when long-acting preparations (oral, transdermal) or continuous intravenous infusions are used for more than a few hours without interruption. The mechanisms by which tolerance develops are not completely understood. As previously noted, diminished release of nitric oxide resulting from reduced bioactivation may be partly responsible for tolerance to nitroglycerin. Supplementation of cysteine may partially reverse tolerance, suggesting that reduced availability of sulfhydryl donors may play a role. Systemic compensation also plays a role in tolerance in the intact human. Initially, significant sympathetic discharge occurs, and after 1 or more days of therapy with long-acting nitrates, retention of salt and water may partiallyreverse the favorable hemodynamic changes initially caused by nitroglycerin. Tolerance does not occur equally with all nitric oxide donors. Nitroprusside, for example, retains activity over long periods. Other organic nitrates appear to be less susceptible than nitroglycerin to the development of tolerance. In cell-free systems, soluble guanylate cyclase is inhibited, possibly by nitrosylation of the enzyme, only after prolonged exposure to exceedingly high nitroglycerin concentrations. In contrast, treatment with antioxidants that protect ALDH2 and similar enzymes appears to prevent or reduce tolerance. This suggests that tolerance is a function of diminished bioactivation of organic nitrates and, to a lesser degree, a loss of soluble guanylate cyclase responsiveness to nitric oxide. Continuous exposure to high levels of nitrates can occur in the chemical industry, especially where explosives are manufactured. When contamination of the workplace with volatile organic nitrate compounds is severe, workers find that upon starting their work week (Monday), they suffer headache and transient dizziness (“Monday disease”). After a day or so, these symptoms disappear owing to the development of tolerance. Over the weekend, when exposure to the chemicals is reduced, tolerance disappears, so symptoms recur each Monday. Other hazards of industrial exposure, including dependence, have been reported. There is no evidence that physical dependence develops as a result of the therapeutic use of short-acting nitrates for angina, even in large doses.

**CALCIUM CHANNEL-BLOCKING DRUGS**

It has been known since the late 1800s that transmembrane calcium influx is necessary for the contraction of smooth and cardiac muscle. The discovery of a calcium channel in cardiac muscle was followed by the finding of several different types of calcium channels in different tissues. The discovery of these channels made possible the measurement of the calcium current, ICa, and subsequently, the development of clinically useful blocking drugs. Although the blockers currently available for clinical use in cardiovascular conditions are exclusively L-type calcium channel blockers, selective blockers of other types of calcium channels are under intensive investigation. Certain antiseizure drugs are thought to act, at least in part, through calcium channel (especially T-type) blockade in neurons.

**Pharmacodynamics**

**A. Mechanism of Action**

The voltage-gated L type is the dominant type of calcium channel in cardiac and smooth muscle and is known to contain several drug receptors. It consists of α1 (the larger, pore-forming subunit), α2, β, γ, and δ subunits. Four variant α1 subunits have been recognized. Nifedipine and other dihydropyridines have been demonstrated to bind to one site on the α1 subunit, whereas verapamil and diltiazem appear to bind to closely related but not identical receptors in another region of the same subunit. Binding of a drug to the verapamil or diltiazem receptors allosterically affects dihydropyridine binding. These receptor regions are stereoselective, since marked differences in both stereoisomer-binding affinity and pharmacologic potency are observed for enantiomers of verapamil, diltiazem, and optically active nifedipine congeners. Blockade of calcium channels by these drugs resembles that of sodium channel blockade by local anesthetics. The drugs act from the inner side of the membrane and bind more effectively to open channels and inactivated channels. Binding of the drug reduces the frequency of opening in response to depolarization. The result is a marked decrease in transmembrane calcium current, which in smooth muscle results in longlasting relaxation and in cardiac muscle results in reduction in contractility throughout the heart and decreases in sinus node pacemaker rate and atrioventricular node conduction velocity.\* Although some neuronal cells harbor L-type calcium channels, their sensitivity to these drugs is lower because the channels in these cells spend less time in the open and inactivated states. Smooth muscle responses to calcium influx through ligandgated calcium channels are also reduced by these drugs but not as markedly. The block can be partially reversed by elevating the concentration of calcium, although the levels of calcium required are not easily attainable in patients. Block can also be partially reversed by the use of drugs that increase the transmembrane flux of calcium, such as sympathomimetics. Other types of calcium channels are less sensitive to blockade by these calcium channel blockers. Therefore, tissues in which these other channel types play a major role—neurons and most secretory glands—are much less affected by these drugs than are cardiac and smooth muscle. Mibefradil is a selective T-type calcium channel blocker that was introduced for antiarrhythmic use but has been withdrawn. Ion channels other than calcium channels are much less sensitive to these drugs. Potassium channels in vascular smooth muscle are inhibited by verapamil, thus limiting the vasodilation produced by this drug. Sodium channels as well as calcium channels are blocked by bepridil, an obsolete antiarrhythmic drug.

**BETA-BLOCKING DRUGS**

Although they are not vasodilators (with the exception of carvedilol and nebivolol), β-blocking drugs (see Chapter 10) are extremely useful in the management of effort angina and are considered first-line drugs in chronic effort angina. The beneficial effects of β-blocking agents are related to their hemodynamic effects— decreased heart rate, blood pressure, and contractility—which decrease myocardial oxygen requirements at rest and during exercise. Lower heart rate is also associated with an increase in diastolic perfusion time that may increase coronary perfusion. However, reduction of heart rate and blood pressure, and consequently decreased myocardial oxygen consumption, appear to be the most important mechanisms for relief of angina and improved exercise tolerance. Beta blockers may also be valuable in treating silent or ambulatory ischemia. Because this condition causes no pain, it is usually detected by the appearance of typical electrocardiographic signs of ischemia. The total amount of “ischemic time” per day is reduced by long-term therapy with a β blocker. Beta-blocking agents decrease mortality of patients with heart failure or recent myocardial infarction and improve survival and prevent stroke in patients with hypertension. Randomized trials in patients with stable angina have shown better outcome and symptomatic improvement with β blockers compared with calcium channel blockers. Undesirable effects of β-blocking agents in angina include an increase in end-diastolic volume and an increase in ejection time, both of which tend to increase myocardial oxygen requirement. These deleterious effects of β-blocking agents can be balanced by the concomitant use of nitrates as described below. Contraindications to the use of β blockers are asthma and other bronchospastic conditions, severe bradycardia, atrioventricular blockade, bradycardia-tachycardia syndrome, and severe unstable left ventricular failure. Potential complications include fatigue, impaired exercise tolerance, insomnia, unpleasant dreams, worsening of claudication, and erectile dysfunction.

**NEWER ANTIANGINAL DRUGS**

Because of the high prevalence of angina, new drugs are actively sought for its treatment. Ranolazine appears to act by reducing a late sodium current (INa) that facilitates calcium entry via the sodium-calcium exchanger. The reduction in intracellular calcium concentration that results from ranolazine reduces diastolic tension, cardiac contractility, and work. Ranolazine is approved for use in angina in the USA. Several studies demonstrate its effectiveness in stable angina, but it does not reduce the incidence of death in acute coronary syndromes. Ranolazine prolongs the QT interval in patients with coronary artery disease (but shortens it in patients with long QT syndrome, LQT3). It has not been associated with torsades de pointes arrhythmia and may inhibit the metabolism of digoxin and simvastatin. Certain metabolic modulators (eg, trimetazidine) are known as pFOX inhibitors because they partially inhibit the fatty acid oxidation pathway in myocardium. Because metabolism shifts to oxidation of fatty acids in ischemic myocardium, the oxygen requirement per unit of ATP produced increases. Partial inhibition of the enzyme required for fatty acid oxidation (long-chain 3-ketoacyl thiolase, LC-3KAT) appears to improve the metabolic status of ischemic tissue. (Ranolazine was initially assigned to this group of agents, but it lacks this action at clinically relevant concentrations.) Trimetazidine does inhibit LC-3KAT at achievable concentrations and has demonstrated efficacy in stable angina.

So-called bradycardic drugs, relatively selective If sodium channel blockers (eg, ivabradine), reduce cardiac rate by inhibiting the hyperpolarization-activated sodium channel in the sinoatrial node. No other significant hemodynamic effects have been reported. Ivabradine appears to reduce anginal attacks with an efficacy similar to that of calcium channel blockers and β blockers. The lack of effect on gastrointestinal and bronchial smooth muscle is an advantage of ivabradine, and it is approved for use in angina and heart failure.

**ANTIHYPERTENSIVE AGENTS**

The diagnosis of hypertension is based on repeated, reproducible measurements of elevated blood pressure. The diagnosis serves primarily as a prediction of consequences for the patient; it seldom includes a statement about the cause of hypertension.

**BASIC PHARMACOLOGY OF ANTIHYPERTENSIVE AGENTS**

A useful classification of these agents categorizes them according to the principal regulatory site or mechanism on which they act. Because of their common mechanisms of action, drugs within each category tend to produce a similar spectrum of toxicities. The categories include the following:

1. **Diuretics**, which lower blood pressure by depleting the body of sodium and reducing blood volume and perhaps by other mechanisms.

2. **Sympathoplegic agents**, which lower blood pressure by reducing peripheral vascular resistance, inhibiting cardiac function, and increasing venous pooling in capacitance vessels. (The latter two effects reduce cardiac output.) These agents are further subdivided according to their putative sites of action in the sympathetic reflex arc.

3. **Direct vasodilators**, which reduce pressure by relaxing vascular smooth muscle, thus dilating resistance vessels and—to varying degrees—increasing capacitance as well.

4. **Agents that block production or action of angiotensin** and thereby reduce peripheral vascular resistance and (potentially) blood volume.

**DRUGS THAT ALTER SODIUM & WATER BALANCE**

Dietary sodium restriction has been known for many years to decrease blood pressure in hypertensive patients. With the advent of diuretics, sodium restriction was thought to be less important. However, there is now general agreement that dietary control of blood pressure is a relatively nontoxic therapeutic measure and may even be preventive. Even modest dietary sodium restriction lowers blood pressure (though to varying extents) in many hypertensive persons.

**Mechanisms of Action & Hemodynamic Effects of Diuretics**

Diuretics lower blood pressure primarily by depleting body sodium stores. Initially, diuretics reduce blood pressure by reducing blood volume and cardiac output; peripheral vascular resistance may increase. After 6–8 weeks, cardiac output returns toward normal while peripheral vascular resistance declines. Sodium is believed to contribute to vascular resistance by increasing vessel stiffness and neural reactivity, possibly related to altered sodium-calcium exchange with a resultant increase in intracellular calcium. These effects are reversed by diuretics or dietary sodium restriction. Diuretics are effective in lowering blood pressure by 10–15 mm Hg in most patients, and diuretics alone often provide adequate treatment for mild or moderate essential hypertension. In more severe hypertension, diuretics are used in combination with sympathoplegic and vasodilator drugs to control the tendency toward sodium retention caused by these agents. Vascular responsiveness—ie, the ability to either constrict or dilate—is diminished by sympathoplegic and vasodilator drugs, so that the vasculature behaves like an inflexible tube. As a consequence, blood pressure becomes exquisitely sensitive to blood volume. Thus, in severe hypertension, when multiple drugs are used, blood pressure may be well controlled when blood volume is 95% of normal but much too high when blood volume is 105% of normal.

**DRUGS THAT ALTER SYMPATHETIC NERVOUS SYSTEM FUNCTION**

In many patients, hypertension is initiated and sustained at least in part by sympathetic neural activation. In patients with moderate to severe hypertension, most effective drug regimens include an agent that inhibits function of the sympathetic nervous system. Drugs in this group are classified according to the site at which they impair the sympathetic reflex arc. This neuroanatomic classification explains prominent differences in cardiovascular effects of drugs and allows the clinician to predict interactions of these drugs with one another and with other drugs. The subclasses of sympathoplegic drugs exhibit different patterns of potential toxicity. Drugs that lower blood pressure by actions on the central nervous system tend to cause sedation and mental depression and may produce disturbances of sleep, including nightmares. Drugs that act by inhibiting transmission through autonomic ganglia (ganglion blockers) produce toxicity from inhibition of parasympathetic regulation, in addition to profound sympathetic blockade and are no longer used. Drugs that act chiefly by reducing release of norepinephrine from sympathetic nerve endings cause effects that are similar to those of surgical sympathectomy, including inhibition of ejaculation, and hypotension that is increased by upright posture and after exercise. Drugs that block postsynaptic adrenoceptors produce a more selective spectrum of effects depending on the class of receptor to which they bind. Finally, one should note that all of the agents that lower blood pressure by altering sympathetic function can elicit compensatory effects through mechanisms that are not dependent on adrenergic nerves. Thus, the antihypertensive effect of any of these agents used alone may be limited by retention of sodium by the kidney and expansion of blood volume. For this reason, sympathoplegic antihypertensive drugs are most effective when used concomitantly with a diuretic.

**CENTRALLY ACTING SYMPATHOPLEGIC DRUGS**

Centrally acting sympathoplegic drugs were once widely used in the treatment of hypertension. With the exception of clonidine, these drugs are rarely used today. Mechanisms & Sites of Action These agents reduce sympathetic outflow from vasomotor centers in the brain stem but allow these centers to retain or even increase their sensitivity to baroreceptor control. Accordingly, the antihypertensive and toxic actions of these drugs are generally less dependent on posture than are the effects of drugs that act directly on peripheral sympathetic neurons. Methyldopa (l-α-methyl-3,4-dihydroxyphenylalanine) is an analog of l-dopa and is converted to α-methyldopamine and α-methylnorepinephrine; this pathway directly parallels the synthesis of norepinephrine from dopa illustrated in Figure 6–5. Alphamethylnorepinephrine is stored in adrenergic nerve vesicles, where it stoichiometrically replaces norepinephrine, and is released by nerve stimulation to interact with postsynaptic adrenoceptors. However, this replacement of norepinephrine by a false transmitter in peripheral neurons is not responsible for methyldopa’s antihypertensive effect, because the α-methylnorepinephrine released is an effective agonist at the α adrenoceptors that mediate peripheral sympathetic constriction of arterioles and venules. In fact, methyldopa’s antihypertensive action appears to be due to stimulation of central α adrenoceptors by α-methylnorepinephrine or α-methyldopamine. The antihypertensive action of clonidine, a 2-imidazoline derivative, was discovered in the course of testing the drug for use as a nasal decongestant. After intravenous injection, clonidine produces a brief rise in blood pressure followed by more prolonged hypotension. The pressor response is due to direct stimulation of α adrenoceptors in arterioles. The drug is classified as a partial agonist at α receptors because it also inhibits pressor effects of other α agonists. Considerable evidence indicates that the hypotensive effect of clonidine is exerted at α adrenoceptors in the medulla of the brain. In animals, the hypotensive effect of clonidine is prevented by central administration of α antagonists. Clonidine reduces sympathetic and increases parasympathetic tone, resulting in blood pressure lowering and bradycardia. The reduction in pressure is accompanied by a decrease in circulating catecholamine levels. These observations suggest that clonidine sensitizes brain stem vasomotor centers to inhibition by baroreflexes. Thus, studies of clonidine and methyldopa suggest that normal regulation of blood pressure involves central adrenergic neurons that modulate baroreceptor reflexes. Clonidine and α-methylnorepinephrine bind more tightly to α2 than to α1 adrenoceptors. α2 receptors are located on presynaptic adrenergic neurons as well as some postsynaptic sites. It is possible that clonidine and α-methylnorepinephrine act in the brain to reduce norepinephrine release onto relevant receptor sites. Alternatively, these drugs may act on postsynaptic α2 adrenoceptors to inhibit activity of appropriate neurons. Finally, clonidine also binds to a nonadrenoceptor site, the imidazoline receptor, which may also mediate antihypertensive effects. Methyldopa and clonidine produce slightly different hemodynamic effects: clonidine lowers heart rate and cardiac output more than does methyldopa. This difference suggests that these two drugs do not have identical sites of action. They may act primarily on different populations of neurons in the vasomotor centers of the brain stem. Guanabenz and guanfacine are centrally active antihypertensive drugs that share the central α-adrenoceptor-stimulating effects of clonidine. They do not appear to offer any advantages over clonidine and are rarely used.

**Methyldopa**

Methyldopa was widely used in the past but is now used primarily for hypertension during pregnancy. It lowers blood pressure chiefly by reducing peripheral vascular resistance, with a variable reduction in heart rate and cardiac output. Most cardiovascular reflexes remain intact after administration of methyldopa, and blood pressure reduction is not markedly dependent on posture. Postural (orthostatic) hypotension sometimes occurs, particularly in volume-depleted patients. One potential advantage of methyldopa is that it causes reduction in renal vascular resistance.

**Clonidine**

Blood pressure lowering by clonidine results from reduction of cardiac output due to decreased heart rate and relaxation of capacitance vessels, as well as a reduction in peripheral vascular resistance. Reduction in arterial blood pressure by clonidine is accompanied by decreased renal vascular resistance and maintenance of renal blood flow. As with methyldopa, clonidine reduces blood pressure in the supine position and only rarely causes postural hypotension. Pressor effects of clonidine are not observed after ingestion of therapeutic doses of clonidine, but severe hypertension can complicate a massive overdose.

**GANGLION-BLOCKING AGENTS**

Historically, drugs that block activation of postganglionic autonomic neurons by acetylcholine were among the first agents used in the treatment of hypertension. Most such drugs are no longer available clinically because of intolerable toxicities related to their primary action (see below). Ganglion blockers competitively block nicotinic cholinoceptors on postganglionic neurons in both sympathetic and parasympathetic ganglia. In addition, these drugs may directly block the nicotinic acetylcholine channel, in the same fashion as neuromuscular nicotinic blockers. The adverse effects of ganglion blockers are direct extensions of their pharmacologic effects. These effects include both sympathoplegia (excessive orthostatic hypotension and sexual dysfunction) and parasympathoplegia (constipation, urinary retention, precipitation of glaucoma, blurred vision, dry mouth, etc). These severe toxicities are the major reason for the abandonment of ganglion blockers for the therapy of hypertension.

**ADRENERGIC NEURON-BLOCKING AGENTS**

These drugs lower blood pressure by preventing normal physiologic release of norepinephrine from postganglionic sympathetic neurons.

**Guanethidine**

In high enough doses, guanethidine can produce profound sympathoplegia. Guanethidine can thus produce all of the toxicities expected from “pharmacologic sympathectomy,” including marked postural hypotension, diarrhea, and impaired ejaculation. Because of these adverse effects, guanethidine is now rarely used. Guanethidine is too polar to enter the central nervous system. As a result, this drug has none of the central effects seen with many of the other antihypertensive agents described in this chapter. Bethanidine and debrisoquin, antihypertensive agents not available for clinical use in the USA, are similar.

**Mechanism and Sites of Action**

Guanethidine inhibits the release of norepinephrine from sympathetic nerve endings. This effect is probably responsible for most of the sympathoplegia that occurs in patients. Guanethidine is transported across the sympathetic nerve membrane by the same mechanism that transports norepinephrine itself (NET, uptake 1), and uptake is essential for the drug’s action. Once guanethidine has entered the nerve, it is concentrated in transmitter vesicles, where it replaces norepinephrine and causes a gradual depletion of norepinephrine stores in the nerve ending. Because neuronal uptake is necessary for the hypotensive activity of guanethidine, drugs that block the catecholamine uptake process or displace amines from the nerve terminal (cocaine, amphetamine, tricyclic antidepressants, phenothiazines, and phenoxybenzamine) block its effects.

**Reserpine**

Reserpine, an alkaloid extracted from the roots of an Indian plant, Rauwolfia serpentina, was one of the first effective drugs used on a large scale in the treatment of hypertension. At present, it is rarely used owing to its adverse effects.

**Mechanism and Sites of Action**

Reserpine blocks the ability of aminergic transmitter vesicles to take up and store biogenic amines, probably by interfering with the vesicular membrane-associated transporter. This effect occurs throughout the body, resulting in depletion of norepinephrine, dopamine, and serotonin in both central and peripheral neurons. Chromaffin granules of the adrenal medulla are also depleted of catecholamines, although to a lesser extent than are the vesicles of neurons. Reserpine’s effects on adrenergic vesicles appear irreversible; trace amounts of the drug remain bound to vesicular membranes for many days. Depletion of peripheral amines probably accounts for much of the beneficial antihypertensive effect of reserpine, but a central component cannot be ruled out. Reserpine readily enters the brain, and depletion of cerebral amine stores causes sedation, mental depression, and parkinsonism symptoms. At lower doses used for treatment of mild hypertension, reserpine lowers blood pressure by a combination of decreased cardiac output and decreased peripheral vascular resistance.

**BETA-ADRENOCEPTOR-BLOCKING AGENTS**

Of the large number of β blockers tested, most have been shown to be effective in lowering blood pressure. The pharmacologic properties of several of these agents differ in ways that may confer therapeutic benefits in certain clinical situations.

**Propranolol**

Propranolol was the first β blocker shown to be effective in hypertension and ischemic heart disease. Propranolol has now been largely replaced by cardioselective β blockers such as metoprolol and atenolol. All β-adrenoceptor-blocking agents are useful for lowering blood pressure in mild to moderate hypertension. In severe hypertension, β blockers are especially useful in preventing the reflex tachycardia that often results from treatment with direct vasodilators. Beta blockers have been shown to reduce mortality after a myocardial infarction and some also reduce mortality in patients with heart failure; they are particularly advantageous for treating hypertension in patients with these conditions.

**Mechanism and Sites of Action**

Propranolol’s efficacy in treating hypertension as well as most of its toxic effects result from nonselective β blockade. Propranolol decreases blood pressure primarily as a result of a decrease in cardiac output. Other β blockers may decrease cardiac output or decrease peripheral vascular resistance to various degrees, depending on cardioselectivity and partial agonist activities. Propranolol inhibits the stimulation of renin production by catecholamines (mediated by β1 receptors). It is likely that propranolol’s effect is due in part to depression of the renin-angiotensinaldosterone system. Although most effective in patients with high plasma renin activity, propranolol also reduces blood pressure in hypertensive patients with normal or even low renin activity. Beta blockers might also act on peripheral presynaptic β adrenoceptors to reduce sympathetic vasoconstrictor nerve activity. In mild to moderate hypertension, propranolol produces a significant reduction in blood pressure without prominent postural hypotension.

**PRAZOSIN & OTHER ALPHA1 BLOCKERS**

**Mechanism & Sites of Action**

Prazosin, terazosin, and doxazosin produce most of their antihypertensive effects by selectively blocking α1 receptors in arterioles and venules. These agents produce less reflex tachycardia when lowering blood pressure than do nonselective α antagonists such as phentolamine. Alpha1-receptor selectivity allows norepinephrine to exert unopposed negative feedback (mediated by presynaptic α2 receptors) on its own release; in contrast, phentolamine blocks both presynaptic and postsynaptic α receptors, with the result that reflex activation of sympathetic neurons by phentolamine’s effects produces greater release of transmitter onto β receptors and correspondingly greater cardioacceleration. Alpha blockers reduce arterial pressure by dilating both resistance and capacitance vessels. As expected, blood pressure is reduced more in the upright than in the supine position. Retention of salt and water occurs when these drugs are administered without a diuretic. The drugs are more effective when used in combination with other agents, such as a β blocker and a diuretic, than when used alone. Owing to their beneficial effects in men with prostatic hyperplasia and bladder obstruction symptoms, these drugs are used primarily in men with concurrent hypertension and benign prostatic hyperplasia.

**VASODILATORS**

**Mechanism & Sites of Action**

This class of drugs includes the oral vasodilators, hydralazine and minoxidil, which are used for long-term outpatient therapy of hypertension; the parenteral vasodilators, nitroprusside and fenoldopam, which are used to treat hypertensive emergencies; the calcium channel blockers, which are used in both circumstances; and the nitrates, which are used mainly in ischemic heart disease but sometimes also in hypertensive emergencies. All the vasodilators that are useful in hypertension relax smooth muscle of arterioles, thereby decreasing systemic vascular resistance. Sodium nitroprusside and the nitrates also relax veins. Decreased arterial resistance and decreased mean arterial blood pressure elicit compensatory responses, mediated by baroreceptors and the sympathetic nervous system as well as renin, angiotensin, and aldosterone. Because sympathetic reflexes are intact, vasodilator therapy does not cause orthostatic hypotension or sexual dysfunction. Vasodilators work best in combination with other antihypertensive drugs that oppose the compensatory cardiovascular responses.

**Minoxidil**

Minoxidil is a very efficacious orally active vasodilator. The effect results from the opening of potassium channels in smooth muscle membranes by minoxidil sulfate, the active metabolite. Increased potassium permeability stabilizes the membrane at its resting potential and makes contraction less likely. Like hydralazine, minoxidil dilates arterioles but not veins. Because of its greater potential antihypertensive effect, minoxidil should replace hydralazine when maximal doses of the latter are not effective or in patients with renal failure and severe hypertension, who do not respond well to hydralazine.

**Sodium nitroprusside**

Sodium nitroprusside is a powerful parenterally administered vasodilator that is used in treating hypertensive emergencies as well as severe heart failure. Nitroprusside dilates both arterial and venous vessels, resulting in reduced peripheral vascular resistance and venous return. The action occurs as a result of activation of guanylyl cyclase, either via release of nitric oxide or by direct stimulation of the enzyme. The result is increased intracellular cGMP, which relaxes vascular smooth muscle. In the absence of heart failure, blood pressure decreases, owing to decreased vascular resistance, whereas cardiac output does not change or decreases slightly. In patients with heart failure and low cardiac output, output often increases owing to afterload reduction.

**CALCIUM CHANNEL BLOCKERS**

In addition to their antianginal and antiarrhythmic effects, calcium channel blockers also reduce peripheral resistance and blood pressure. The mechanism of action in hypertension (and, in part, in angina) is inhibition of calcium influx into arterial smooth muscle cells. Verapamil, diltiazem, and the dihydropyridine family (amlodipine, felodipine, isradipine, nicardipine, nifedipine, nisoldipine, and nitrendipine) are all equally effective in lowering blood pressure. Clevidipine is a newer member of this group that is formulated for intravenous use only. Hemodynamic differences among calcium channel blockers may influence the choice of a particular agent. Nifedipine and the other dihydropyridine agents are more selective as vasodilators and have less cardiac depressant effect than verapamil and diltiazem. Reflex sympathetic activation with slight tachycardia maintains or increases cardiac output in most patients given dihydropyridines. Verapamil has the greatest depressant effect on the heart and may decrease heart rate and cardiac output. Diltiazem has intermediate actions. Doses of calcium channel blockers used in treating hypertension are similar to those used in treating angina. Some epidemiologic studies reported an increased risk of myocardial infarction or mortality in patients receiving short-acting nifedipine for hypertension. It is therefore recommended that short-acting oral dihydropyridines not be used for hypertension. Sustained-release calcium blockers or calcium blockers with long half-lives provide smoother blood pressure control and are more appropriate for treatment of chronic hypertension. Intravenous nicardipine and clevidipine are available for the treatment of hypertension when oral therapy is not feasible; parenteral verapamil and diltiazem can also be used for the same indication. Nicardipine is typically infused at rates of 2–15 mg/h. Clevidipine is infused starting at 1–2 mg/h and progressing to 4–6 mg/h. It has a rapid onset of action and has been used in acute hypertension occurring during surgery. Oral short-acting nifedipine has been used in emergency management of severe hypertension.

**INHIBITORS OF ANGIOTENSIN**

Renin, angiotensin, and aldosterone play important roles in some people with essential hypertension. Approximately 20% of patients with essential hypertension have inappropriately low and 20% have inappropriately high plasma renin activity. Blood pressure of patients with high-renin hypertension responds well to drugs that interfere with the system, supporting a role for excess renin and angiotensin in this population.

**Mechanism & Sites of Action**

Renin release from the kidney cortex is stimulated by reduced renal arterial pressure, sympathetic neural stimulation, and reduced sodium delivery or increased sodium concentration at the distal renal tubule. Renin acts upon angiotensinogen to yield the inactive precursor decapeptide angiotensin I. Angiotensin I is then converted, primarily by endothelial ACE, to the arterial vasoconstrictor octapeptide angiotensin II, which is in turn converted in the adrenal gland to angiotensin III Angiotensin II has vasoconstrictor and sodium-retaining activity. Angiotensin II and III both stimulate aldosterone release. Angiotensin may contribute to maintaining high vascular resistance in hypertensive states associated with high plasma renin activity, such as renal arterial stenosis, some types of intrinsic renal disease, and malignant hypertension, as well as in essential hypertension after treatment with sodium restriction, diuretics, or vasodilators. However, even in low-renin hypertensive states, these drugs can lower blood pressure (see below). A parallel system for angiotensin generation exists in several other tissues (eg, heart) and may be responsible for trophic changes such as cardiac hypertrophy. The converting enzyme involved in tissue angiotensin II synthesis is also inhibited by ACE inhibitors. Three classes of drugs act specifically on the renin-angiotensin system: ACE inhibitors; the competitive inhibitors of angiotensin at its receptors, including losartan and other nonpeptide antagonists; and aliskiren, an orally active renin antagonist. A fourth group of drugs, the aldosterone receptor inhibitors (eg, spironolactone, eplerenone), is discussed with the diuretics. In addition, β blockers, as noted earlier, can reduce renin secretion.

**ANGIOTENSIN-CONVERTING ENZYME (ACE) INHIBITORS**

Captopril and other drugs in this class inhibit the converting enzyme peptidyl dipeptidase that hydrolyzes angiotensin I to angiotensin II and (under the name plasma kininase) inactivates bradykinin, a potent vasodilator that works at least in part by stimulating release of nitric oxide and prostacyclin. The hypotensive activity of captopril results both from an inhibitory action on the renin-angiotensin system and a stimulating action on the kallikrein-kinin system. The latter mechanism has been demonstrated by showing that a bradykinin receptor antagonist, icatibant, blunts the blood pressurelowering effect of captopril. Enalapril is an oral prodrug that is converted by hydrolysis to a converting enzyme inhibitor, enalaprilat, with effects similar to those of captopril. Enalaprilat itself is available only for intravenous use, primarily for hypertensive emergencies. Lisinopril is a lysine derivative of enalaprilat. Benazepril, fosinopril, moexipril, perindopril, quinapril, ramipril, and trandolapril are other longacting members of the class. All are prodrugs, like enalapril, and are converted to the active agents by hydrolysis, primarily in the liver. Angiotensin II inhibitors lower blood pressure principally by decreasing peripheral vascular resistance. Cardiac output and heart rate are not significantly changed. Unlike direct vasodilators, these agents do not result in reflex sympathetic activation and can be used safely in persons with ischemic heart disease. The absence of reflex tachycardia may be due to downward resetting of the baroreceptors or to enhanced parasympathetic activity.

**ANGIOTENSIN RECEPTOR-BLOCKING AGENTS**

Losartan and valsartan were the first marketed blockers of the angiotensin II type 1 (AT1) receptor. Azilsartan, candesartan, eprosartan, irbesartan, olmesartan, and telmisartan are also available. They have no effect on bradykinin metabolism and are therefore more selective blockers of angiotensin effects than ACE inhibitors. They also have the potential for more complete inhibition of angiotensin action compared with ACE inhibitors because there are enzymes other than ACE that are capable of generating angiotensin II. Angiotensin receptor blockers provide benefits similar to those of ACE inhibitors in patients with heart failure and chronic kidney disease. The adverse effects are similar to those described for ACE inhibitors, including the hazard of use during pregnancy. Cough and angioedema can occur but are uncommon. Angiotensin receptor-blocking drugs are most commonly used in patients who have had adverse reactions to ACE inhibitors. Combinations of ACE inhibitors and angiotensin receptor blockers or aliskiren, which had once been considered useful for more complete inhibition of the renin-angiotensin system, are not recommended due to toxicity demonstrated in recent clinical trials.