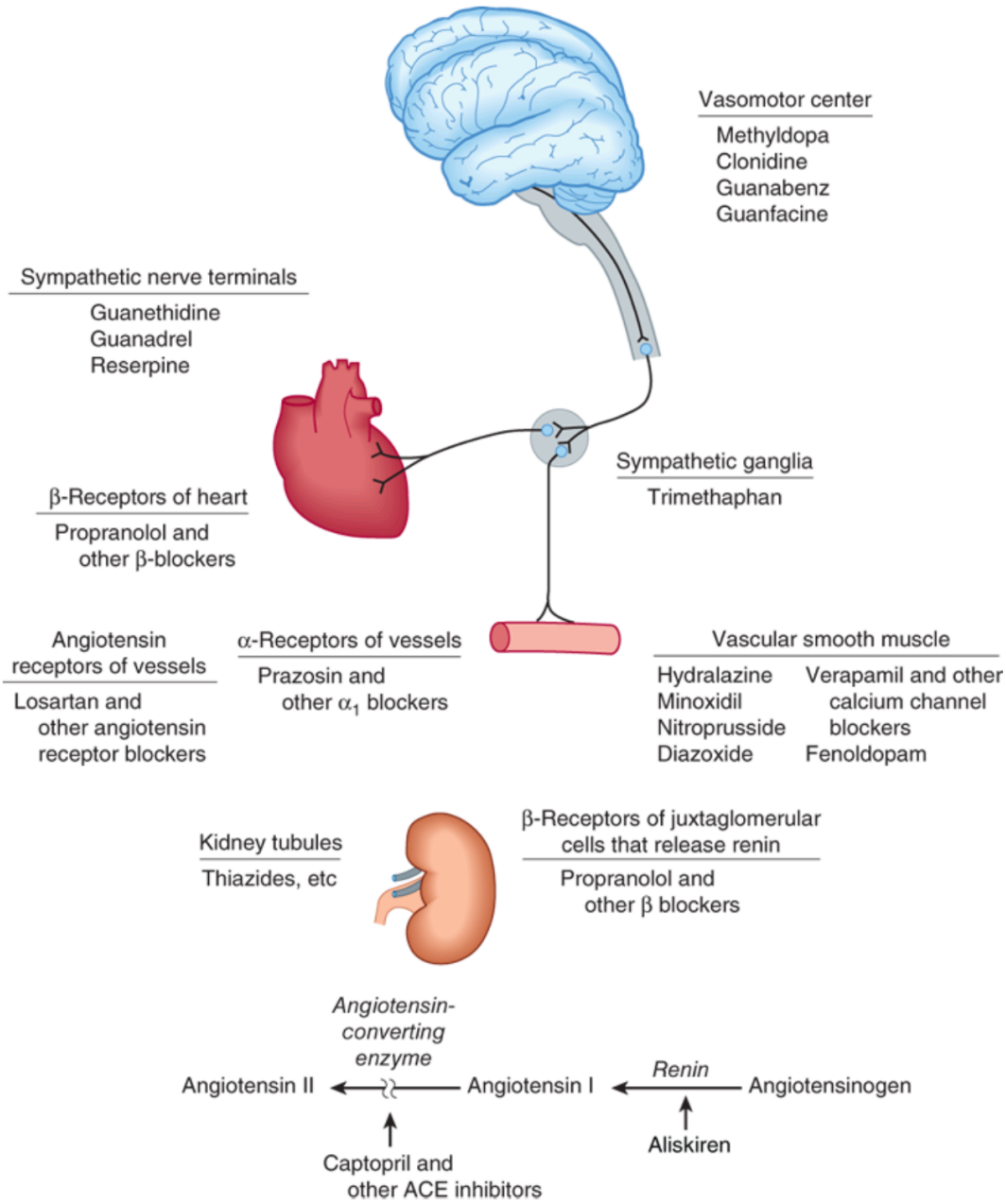
Pharmacology
Antihypertensives

What are the sites of action of the major classes of antihypertensive agents?



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 (see below).

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.

When is more than one antihypertensive agents used?

Monotherapy of hypertension (treatment with a single drug) is desirable because compliance is likely to be better and the cost is lower, and because in some cases adverse effects are fewer. However, most patients with hypertension require two or more drugs acting by different mechanisms (polypharmacy). According to some estimates, up to 40% of patients may respond inadequately even to two agents and are considered to have "resistant hypertension." Some of these patients have treatable secondary hypertension that has been missed, but most do not, and three or more drugs are required.

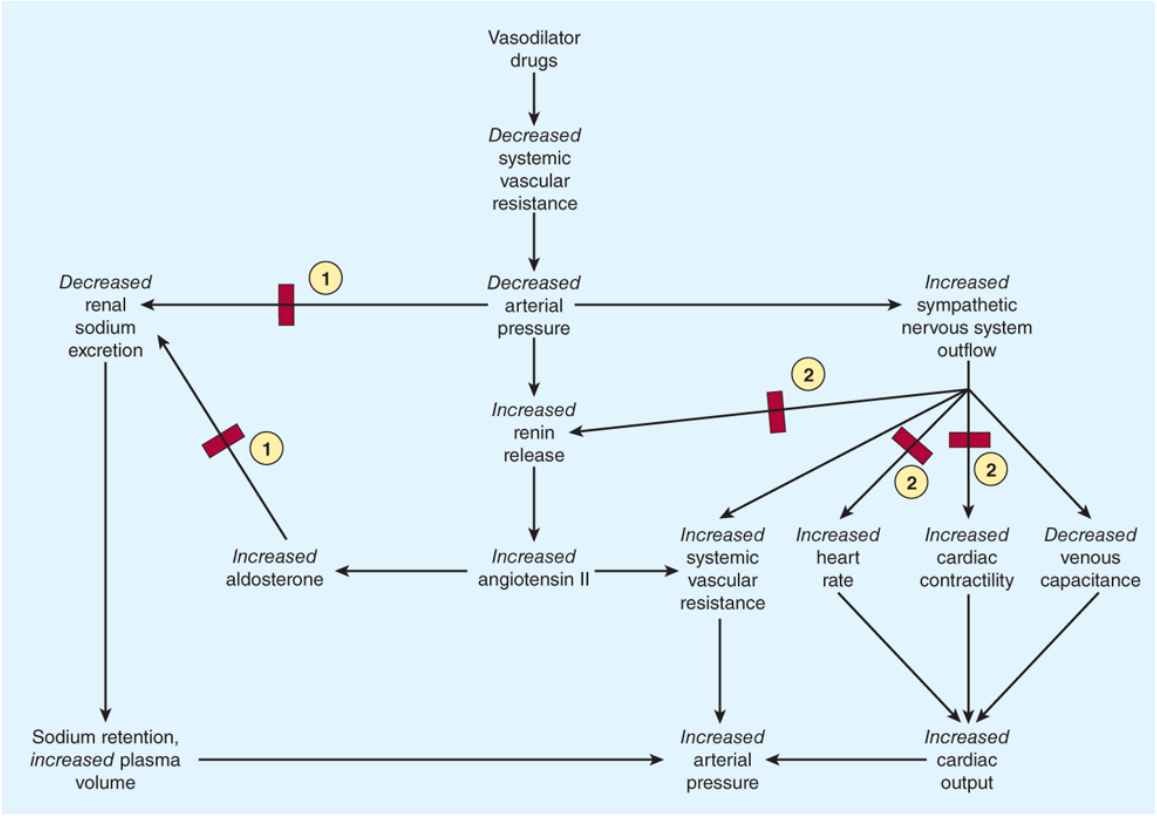
One rationale for polypharmacy in hypertension is that most drugs evoke compensatory regulatory mechanisms for maintaining blood pressure (see Figures 6–7 and 11–1), which may markedly limit their effect. For example, vasodilators such as hydralazine cause a significant decrease in peripheral vascular resistance, but evoke a strong compensatory tachycardia and salt and water retention (Figure 11–4) that are capable of almost completely reversing their effect. The addition of a β blocker prevents the tachycardia; addition of a diuretic (eg, hydrochlorothiazide) prevents the salt and water retention. In effect, all three drugs increase the sensitivity of the cardiovascular system to each other's actions.

A second reason is that some drugs have only modest maximum efficacy but reduction of long-term morbidity mandates their use. Many studies of angiotensin-converting enzyme (ACE) inhibitors report a maximal lowering of blood pressure of less than 10 mm Hg. In patients with more severe hypertension (pressure > 160/100 mm Hg), this is inadequate to prevent all the sequelae of hypertension, but ACE inhibitors have important long-term benefits in preventing or reducing renal disease in diabetic persons and in reduction of heart failure. Finally, the toxicity of some effective drugs prevents their use at maximally effective doses.

In practice, when hypertension does not respond adequately to a regimen of one drug, a second drug from a different class with a different mechanism of action and different pattern of toxicity is added. If the response is still inadequate and

compliance is known to be good, a third drug should be added. If three drugs (usually including a diuretic) are inadequate, other causes of resistant hypertension such as excessive dietary sodium intake, use of nonsteroidal anti-inflammatory or stimulant drugs, or the presence of secondary hypertension should be considered. In some instances, an additional drug may be necessary, and mineralocorticoid antagonists, such as spironolactone, have been found to be particularly useful. Occasionally patients are resistant to four or more drugs, and nonpharmacologic approaches have been considered. Two promising treatments that are still under investigation, particularly for patients with advanced kidney disease, are renal denervation and carotid barostimulation.

What are the compensatory responses to vasodilators?



Compensatory responses to vasodilators; basis for combination therapy with β blockers and diuretics. ① Effect blocked by diuretics. ② Effect blocked by β blockers