Antihypertensive Drugs

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Reference

Basic & Clinical Pharmacology

BG Katzung, SB Masters, AJ Trevor

McGraw Hill LANGE

13th edition, Chapters 11 & 12

Hypertension

- **Sustained arterial hypertension damages blood vessels in kidney, heart, and brain and leads to an increased incidence of renal failure, coronary disease, heart failure, stroke, and dementia.**

Hypertension

- **Lowering of blood pressure leads to prevention of damage to blood vessels and substantially reduces morbidity and mortality rates.**

Hypertension

- **Diagnosis of hypertension depends on measurement of blood pressure and not on symptoms reported by the patient.**
- **Hypertension is usually asymptomatic until overt end-organ damage has already occurred.**

Hypertension

Blood Pressure Categories:

	SBP	DBP
Normal	< 120	< 80
Prehypertension	120-135	80-89
Hypertension		
Stage 1	140-159	90-99
Stage 2	≥ 160	≥ 100

The actual reading by itself may be less important than in the presence of vascular damage or target organ damage.

Etiology of Hypertension

1. **Essential (Primary) hypertension: no specific cause of hypertension could be identified. It constitutes 85-90% of cases.**

- **Elevation of blood pressure is usually multi-factorial.**

Etiology of Hypertension

- **Genetic factors, psychological stress, and environmental and dietary factors (increased salt and decreased potassium or calcium intake) contribute to the development of hypertension.**

Etiology of Hypertension

2. **Secondary hypertension: Constitutes only 10-15% of cases and include renal artery stenosis, coarctation of the aorta, pheochromocytoma, Cushing's disease, and primary aldosteronism.**

- **These are amenable to definitive surgical treatment.**

Hypertension

Physiologic regulation:

1. **Moment-to-moment:**
   - **a. Arterioles**
   - **b. Postcapillary venules**
   - **c. Heart**
2. **Long-term:**
   - **d. Kidney**

Hypertension

- **Baroreflexes + Renin-angiotensin-aldosterone system coordinate function at the 4 control sites.**
- **Local release of hormones from the vascular endothelium may contribute to regulation of vascular resistance:**

Hypertension

1. **Nitric oxide: dilates**
2. **Endothelin-1: constricts**

- **In hypertensive patients, the same mechanisms operate but the control system (baroreceptors and the renal blood volume-pressure control systems) appears to be reset at a higher level of blood pressure.**

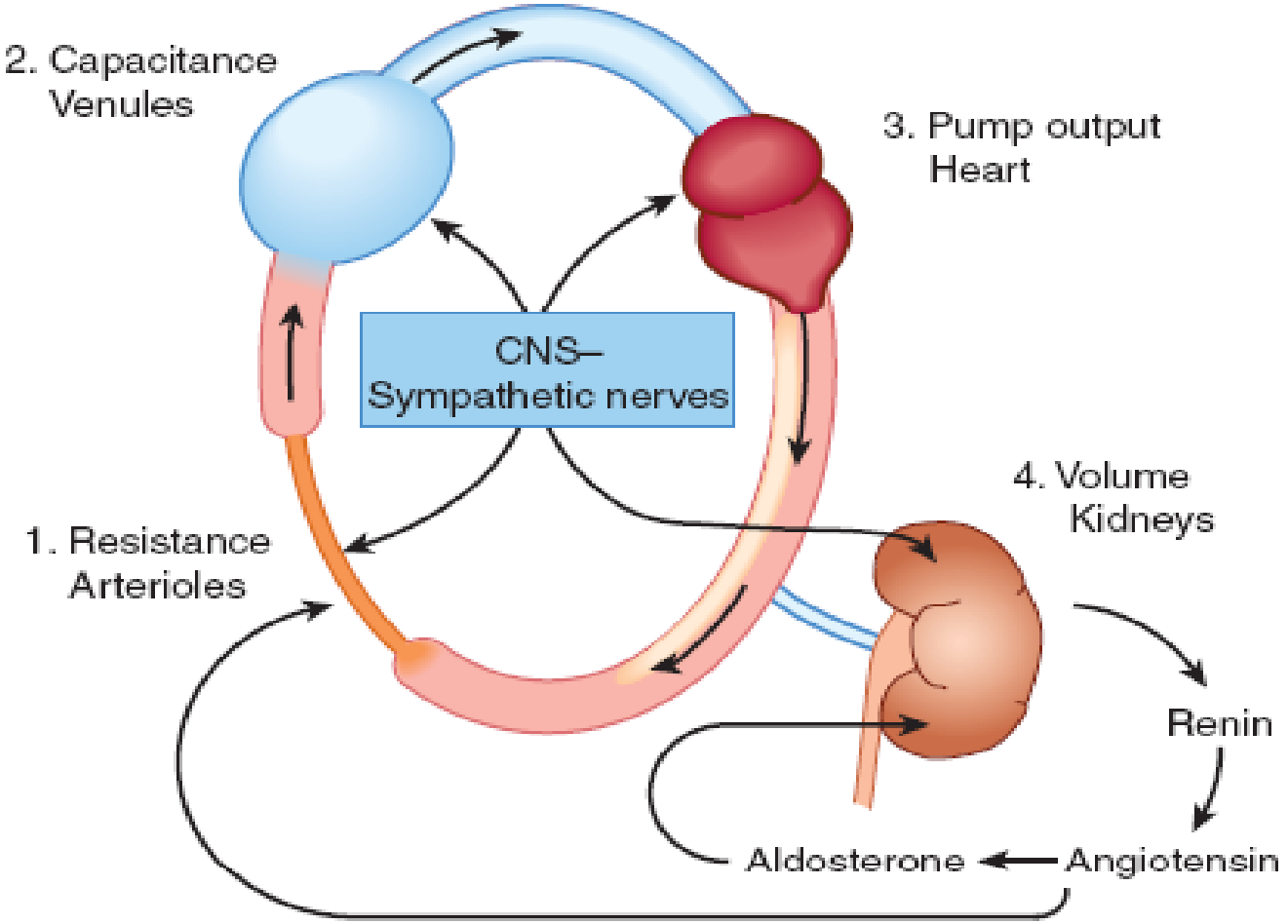


FIGURE 11–1 Anatomic sites of blood pressure control.

Postural Baroreflex

- **Baroreflexes are responsible for rapid, moment-to-moment adjustments in blood pressure, such as in transition from a reclining to an upright posture.**

Postural Baroreflex

- Carotid baroreceptors are stimulated by the stretch of the vessel walls brought about by arterial blood pressure, resulting in inhibition of central sympathetic discharge (from the vasomotor center in the medulla).
- Conversely, reduction in stretch results in a reduction in baroreceptor activity.

Postural Baroreflex

- **In the case of a transition to upright posture, baroreceptors sense the reduction in arterial pressure that results from pooling of blood in the veins below the level of the heart as reduced wall stretch, and sympathetic discharge is disinhibited.**

Postural Baroreflex

- **This reflex increase in sympathetic outflow increases peripheral vascular resistance (constriction of arterioles) and cardiac output (direct stimulation of the heart) and constriction of capacitance vessels, which increases venous return to the heart, thereby restoring normal blood pressure.**

Postural Baroreflex

- **The same baroreflex acts in response to any event that lowers arterial pressure, including a primary reduction in peripheral vascular resistance (vasodilating agent) or a reduction in intravascular volume (due to hemorrhage or to loss of salt and water via the kidney).**

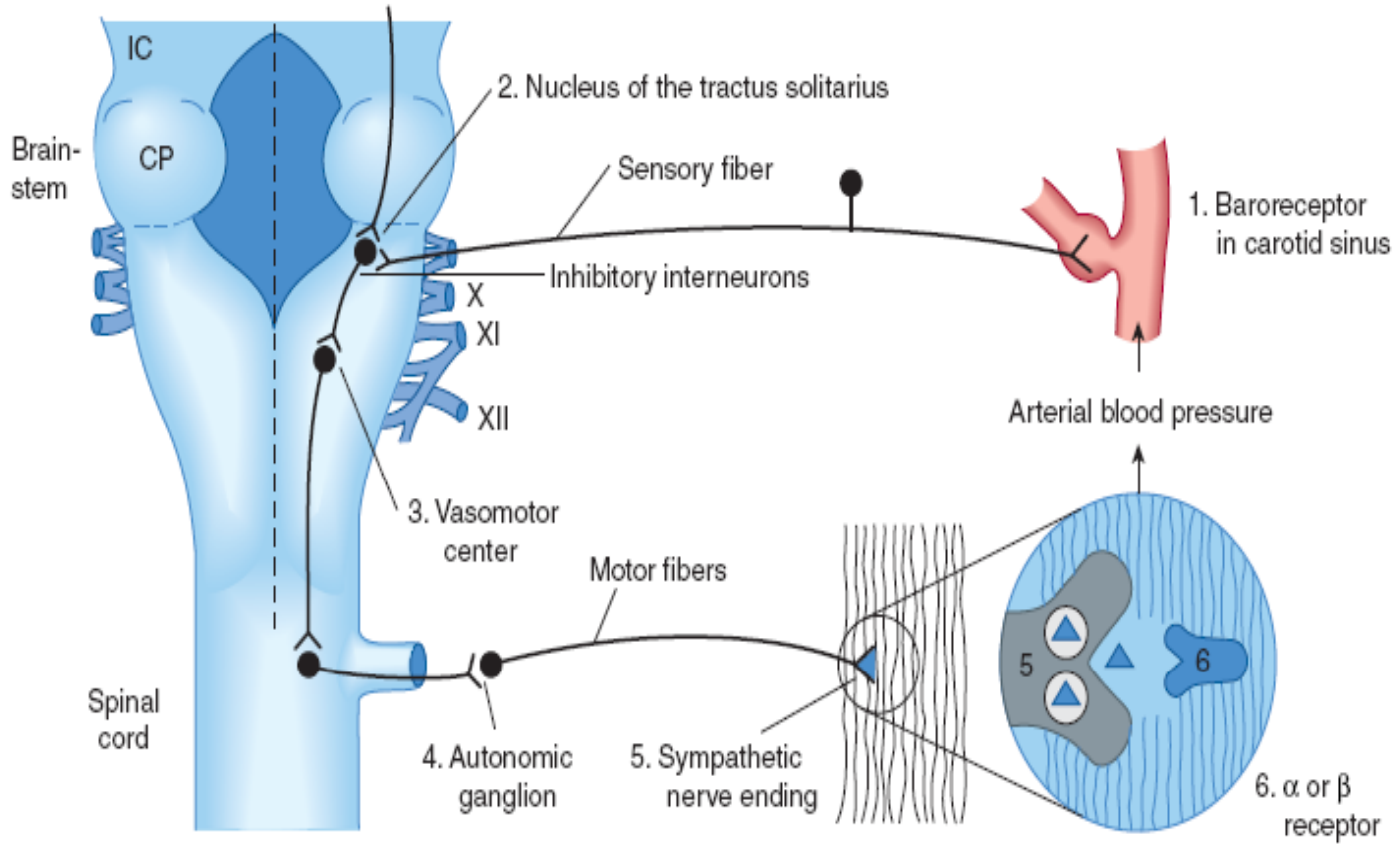


FIGURE 11–2 Baroreceptor reflex arc.

Baroreceptor reflex arc. IC, inferior colliculus; CP, cerebellar peduncle.

Renal Response to Decreased Blood Pressure

- By controlling blood volume, the kidney is primarily responsible for longterm blood pressure control.
- A reduction in renal perfusion pressure causes intrarenal redistribution of blood flow and increased reabsorption of salt and water.

Renal Response to Decreased Blood Pressure

- In addition, decreased pressure in renal arterioles as well as sympathetic neural activity (via β adrenoceptors) stimulates production of renin, which increases production of angiotensin II.

Renal Response to Decreased Blood Pressure

Angiotensin II causes:

1. **Direct constriction of resistance vessels.**
2. **Stimulation of aldosterone synthesis in the adrenal cortex, which increases renal sodium absorption and intravascular blood volume.**

Renal Response to Decreased Blood Pressure

- **Vasopressin released from the posterior pituitary gland also plays a role in maintenance of blood pressure through its ability to regulate water reabsorption by the kidney.**

Antihypertensive Agents

Include the following:

1. **Diuretics, which lower blood pressure by depleting the body of sodium and reducing blood volume and perhaps by reducing blood vessels responsiveness to vasoconstrictors.**

Antihypertensive Agents

2. **Sympathoplegic agents, which lower blood pressure by reducing peripheral vascular resistance, inhibiting cardiac function, and increasing venous pooling in capacitance vessels.**

Antihypertensive Agents

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

Antihypertensive Agents

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

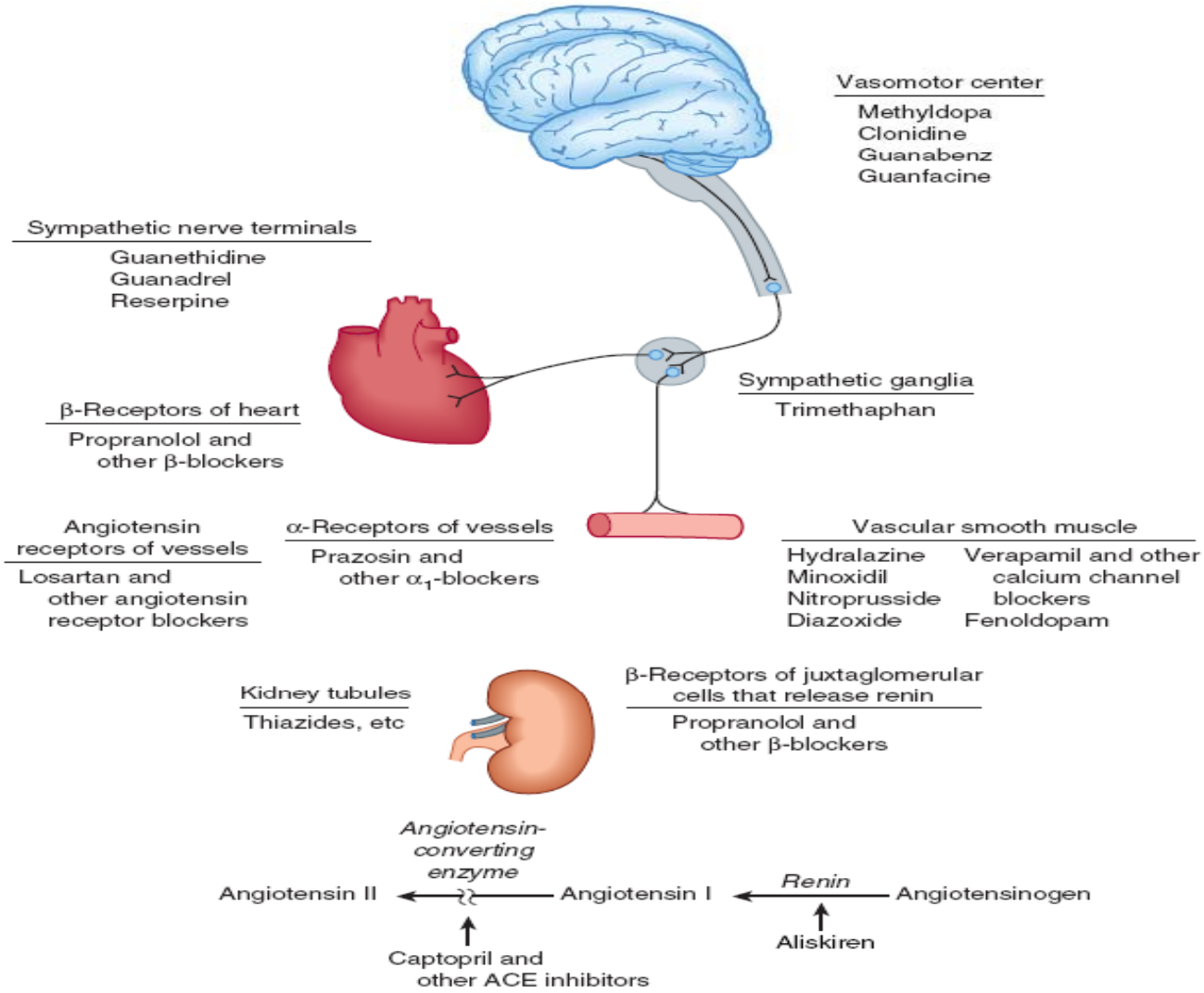


FIGURE 11–3 Sites of action of the major classes of antihypertensive drugs.

Antihypertensive Agents

Define (you should know):

1. **Systemic vascular resistance.**
2. **Cardiac output.**
3. **Preload.**
4. **Afterload.**
5. **Postural (orthostatic) hypotension.**

Drugs That Alter Sodium & Water Balance

- Dietary sodium restriction decreases blood pressure in hypertensive patients.
- Diuretics lower blood pressure by depleting body Na^+, thus reducing blood volume and cardiac output.

Diuretics

- After 6-8 weeks of therapy, cardiac output returns to normal but the systemic vascular resistance drops, due to decreased response to vasoconstrictors due to sodium depletion.
- Sodium contributes to vascular resistance by increasing vessel stiffness and neural reactivity.

Diuretics

- This effect may be related to altered sodium-calcium exchange which increases intracellular calcium.
- These effects are reversed by diuretics or dietary sodium restriction.

Diuretics

- **Indapamide also has direct vasodilator action.**
- **Thiazide diuretics are effective for mild-to-moderate hypertension in patients with normal renal and cardiac function.**
- **Potassium-sparing diuretics are useful to avoid excessive potassium depletion.**

Diuretics

- **Loop diuretics are necessary in severe hypertension with:**

1. **Multiple drugs that retain Na^+ and water.**
2. **When GFR is < 30-40 mL/min.**
3. **Cardiac failure.**
4. **Cirrhosis when sodium retention is marked (??).**

Drugs That Alter Sympathetic Nervous System Function

Include the following:

1. Centrally acting sympathoplegic drugs.
2. Ganglion-blocking agents.
3. Adrenergic neuron-blocking agents.
4. Adrenoceptor antagonists.

Drugs That Alter Sympathetic Nervous System Function

- All of these agents can elicit compensatory effects through adrenergic nerve-independent mechanisms: Retention of sodium by the kidney → expansion of blood volume.
- Thus, they are most effective when used concomitantly with a diuretic.

Centrally Acting Sympathoplegic Agents

- **Reduce sympathetic outflow from vasomotor centers in the CNS, but allow these centers to retain or increase their sensitivity to baroreceptor control, and thus, are less likely to produce postural hypotension.**

Methyldopa

Mechanism of Action:

- **It is converted in the CNS →**

  α-methyldopamine →

  α-methylnorepinephrine, which is stored in adrenergic nerve vesicles, replaces norepinephrine, and is released by nerve stimulation.

Methyldopa

- However, α-methylnorepinephrine released is an effective agonist at the α-adrenoceptors and can not explain the antihypertensive effect.
- It stimulates central α_2-adrenoceptors that mediate the negative feedback on catecholamine release.

Methyldopa

- This reduces sympathetic outflow from CNS, decreases catecholamine release, reduces peripheral vascular resistance and cardiac output, and thus blood pressure.
- Used primarily for hypertension of pregnancy.

Methyldopa

Adverse Effects:

1. **Little postural hypotension, but may occur in volume-depleted patients.**
2. **Sedation – most frequent at onset of treatment.**
3. **Impairs mental concentration.**

Methyldopa

4. Nightmares, mental depression, vertigo.
5. Lactation: due to inhibition of dopaminergic transmission which stimulates prolactin.
6. Hepatitis and drug fever.

Methyldopa

7. **Positive Coomb's test in 10-20% of patients taking the drug for > 12 months:**

   a. Makes cross-matching of blood difficult.

   b. Rarely associated with hemolytic anemia.

Clonidine

- **Clonidine is a 2-imidazoline derivative.**
- **It is a direct agonist at central α_2-adrenoceptors, decreases circulating catecholamine levels, and reduces blood pressure.**
- **It may sensitize brainstem vasomotor centers to inhibition by baroreflexes.**

Clonidine

- **After intravenous injection, it 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.**

Clonidine

- **The drug is classified as a partial agonist at α-receptors because it also inhibits pressor effects of other α agonists.**
- **It reduces sympathetic and increases parasympathetic tone, resulting in blood pressure lowering and bradycardia.**

Clonidine

- Clonidine also binds to a 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.

Clonidine

- 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 brainstem.

Clonidine

- **Reduction in arterial blood pressure by clonidine and methyldopa is accompanied by decreased renal vascular resistance and maintenance of renal blood flow.**

Clonidine

Adverse effects:

1. **Dry mouth and sedation** are common. Both effects are centrally mediated and dose-dependent and coincide temporally with the drug's antihypertensive effect.

Clonidine

2. **Clonidine should not be given to patients who are at risk for mental depression and should be withdrawn if depression occurs during therapy.**

Clonidine

3. **Concomitant treatment with tricyclic antidepressants may block the antihypertensive effect of clonidine, due to α-adrenoceptor-blocking actions of the tricyclics.**

Clonidine

4. **Withdrawal of clonidine after prolonged use (and at high dosages), can result in life-threatening hypertensive crisis mediated by increased sympathetic nervous activity.**

Clonidine

- **The withdrawal syndrome is manifested by nervousness, tachycardia, headache, and sweating after omitting one or two doses of the drug.**
- **All patients who take clonidine should be warned of this possibility.**

Clonidine

- When the drug must be stopped, it should be done gradually while other antihypertensive agents are being substituted.
- Treatment of the hypertensive crisis consists of reinstitution of clonidine therapy or administration of both α- and β-adrenoceptor-blocking agents.

Adrenoceptor Antagonists

- **The pharmacology of α- and β-adrenoceptor blockers was presented in the autonomic nervous system pharmacology lectures in second year.**

β-Adrenoceptor Antagonists

- **Propranolol (non-selective, blocks β_1- and β_2-adrenoceptors) was the first β blocker shown to be effective in hypertension and ischemic heart disease.**
- **It has now been replaced by cardioselective β_1-blockers such as bisoprolol, metoprolol and atenolol.**

β-Adrenoceptor Antagonists

- All β-adrenoceptor blockers are useful for lowering blood pressure in mild-to-moderate hypertension.
- In severe hypertension, they are especially useful in preventing the reflex tachycardia that results from treatment with direct vasodilators.

β-Adrenoceptor Antagonists

- They reduce mortality after a myocardial infarction, and some also reduce mortality in patients with heart failure.
- They are indicated for treating hypertension in these conditions.
- Reduce blood pressure without prominent postural hypotension.

β-Adrenoceptor Antagonists

Mode of action:

1. **Reduction of cardiac output (β_1).**
2. **Inhibition of renin secretion (β_1) → depression of renin-angiotensin-aldosterone system.**
3. **Block presynaptic β-adrenoceptors to reduce sympathetic vasoconstrictor nerve activity.**

β-Adrenoceptor Antagonists

Major adverse effects:

1. **Bradycardia (β_1-block)**
2. **Cardiac block (β_1-block)**
3. **Increased peripheral vascular resistance (β_2-block)**
4. **Bronchoconstriction (β_2-block)**
5. **Masking signs and symptoms of hyperglycemia.**

β-Adrenoceptor Antagonists

6. **Withdrawal syndrome (nervousness, tachycardia, increased intensity of angina, increase of blood pressure, and myocardial infarction). β-blockers should not be discontinued abruptly. The withdrawal syndrome may involve upregulation or supersensitivity of β-adrenoceptors.**

α-Adrenoceptor Antagonists

- **Prazosin, terazosin, and doxazosin are selective α_1-receptors blockers in arterioles and venules → dilation.**
- **These agents produce less reflex tachycardia when lowering blood pressure than do nonselective a antagonists such as phentolamine.**

α-Adrenoceptor Antagonists

- **α_1-Receptors selectivity allows norepinephrine to exert unopposed negative feedback (mediated by presynaptic α_2-receptors) on its own release.**

α-Adrenoceptor Antagonists

- In contrast, phentolamine blocks both presynaptic and postsynaptic α-receptors.
- Block of α_2-receptors results in reflex activation of sympathetic neurons and greater release of norepinephrine and greater cardio-acceleration.

α-Adrenoceptor Antagonists

- α-Receptor blockers reduce arterial pressure by dilating both resistance and capacitance vessels.
- Blood pressure is reduced more in the upright than in the supine position (postural hypotension).

α-Adrenoceptor Antagonists

- Retention of salt and water is a recognized adverse effect.
- The drugs are more effective when used in combination with other agents, such as a β blocker and a diuretic, than when used alone.

α-Adrenoceptor Antagonists

- They relax prostatic smooth muscle.
- They are used primarily in men with concurrent hypertension and benign prostatic hyperplasia and bladder neck obstruction.

Vasodilators

- **Produce direct relaxation of vascular smooth muscle → vasodilation → decrease total peripheral vascular resistance (TPVR).**
- **Relax arterial smooth muscle more than venous smooth muscle → minimal postural hypotension.**

Vasodilators

- **Neuroendocrine and autonomic reflexes compromise their antihypertensive effects:**

1. **Reflex sympathetic stimulation → increases heart rate, cardiac output and peripheral vascular resistance and thus, myocardial O_2 demand.**

Vasodilators

2. **Elevation of plasma renin activity → elevation of angiotensin II:**

   a. vasoconstriction: increases peripheral vascular resistance

   b. elevation of aldosterone: Na^+ and H_2O retention which increases blood volume.

Vasodilators

- **Inadequate as monotherapy for hypertension because of tolerance, but more useful when combined with diuretics and/or β-blockers.**

Hydralazine

- **It acts mainly by releasing nitric oxide (NO), EDRF.**
- **Used orally.**
- **It dilates arterioles but not veins.**

Pharmacokinetics:

- **t½ is ~ 1.5 -3 hours, which increases in slow acetylators and renal insufficiency.**

Hydralazine

- **Well absorbed after oral administration, extensive first-pass metabolism by hydroxylation and acetylation.**
- **There is genetic defects in the capacity to acetylate the drug (In Jordan, ~ 65% of the population are slow acetylators).**

Hydralazine

Adverse effects:

1. **Headache, flushing, nasal congestion, palpitations, tachycardia, and thus, myocardial ischemia.**
2. **Peripheral neuropathy and drug fever are other serious but uncommon adverse effects.**

Hydralazine

3. **Lupus-erythematosus like syndrome, especially in slow acetylators (arthralgia, myalgia, skin rashes, and fever, but no renal damage).The syndrome is reversed by discontinuation of the drug.**

Minoxidil

Mechanism of Action:

Metabolized in the liver to minoxidil sulfate, which is a K^+-channel opener in smooth muscle → hyperpolarization and relaxation of smooth muscle

- **Used orally.**
- **It dilates arterioles but not veins.**

Minoxidil

Adverse Effects:

1. **Those of hydralazine in “1”.**
2. **Growth of body hair (hypertrichosis): Troublesome for women.**

- **Can be used for male pattern baldness topically (Rogaine), but the effect is lost after stopping the drug.**

Diazoxide

- Chemically similar to thiazide diuretics but without a diuretic action

Mechanism of Action:

Opens K^+-channels and cause hyperpolarization of vascular smooth muscle.

- Long-acting agent.
- Tolerance develops rapidly.

Diazoxide

Pharmacodynamics:

1. Has some direct antinatriuretic action → severe retention of Na^+ and water.
2. Inhibition of insulin secretion.

Therapeutic uses:

1. Hypertensive emergency.
2. Insulinomas.

Diazoxide

Pharmacokinetics:

- Used by IV injection or infusion
- Extensive binding to plasma proteins and vascular tissue.
- Partially metabolized, and the remainder excreted by the kidney.
- t½ is ~ 24 hours

Diazoxide

Adverse effects:

1. **The most significant is hypotension.**
2. **Same as hydralazine in “1”.**
3. **Hyperglycemia.**
4. **May stop labor if used in pregnancy.**

Sodium Nitroprusside

Mechanism of Action:

- **It dilates both arterial and venous vessels, resulting in reduced peripheral vascular resistance and venous return.**

Sodium Nitroprusside

- 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.

Sodium Nitroprusside

- **Used for hypertensive emergencies, and severe heart failure.**
- **In the absence of heart failure, blood pressure decreases, owing to decreased vascular resistance, whereas cardiac output does not change or decreases slightly.**

Sodium Nitroprusside

- **In patients with heart failure and low cardiac output, output often increases owing to after-load reduction.**

Sodium Nitroprusside

Pharmacokinetics:

- **Nitroprusside is a complex of ferrous iron, cyanide groups, and a nitroso moiety.**
- **It is rapidly metabolized by uptake into red blood cells with release of nitric oxide and cyanide.**

Sodium Nitroprusside

- **Cyanide in turn is metabolized by the mitochondrial enzyme rhodanese, in the presence of a sulfur donor, to the less toxic thiocyanate.**
- **Thiocyanate is distributed in extracellular fluid and slowly eliminated by the kidney.**

Sodium Nitroprusside

- **Has a short duration of action after IV injection (~ 2 min), and should be infused continuously but not more than one hour. The effect dissappears after 1-10 min of discontinuation.**

Sodium Nitroprusside

- **Aqueous solution is sensitive to light and must be made up fresh before each administration and covered with opaque foil.**

Sodium Nitroprusside

Adverse effects:

1. **Nausea, vomiting, headache.**
2. **Postural hypotension.**
3. **Methemoglobinemia.**
4. **Accumulation of cyanide (CN^{-}): Metabolic acidosis, arrhythmias, hypotension and death.**

Sodium Nitroprusside

5. **Prolonged treatment may produce thiocyanate toxicity especially in patients with renal failure: weakness, disorientation, muscle spasms, convulsions, delirium, psychosis, hypothyroidism.**

Sodium Nitroprusside

- Administration of sodium thiosulfate as a sulfur donor facilitates metabolism of cyanide to thiocyanate.
- Hydroxocobalamin combines with cyanide to form the nontoxic cyanocobalamin (a form of vitamin B_{12}).
- Both may be used for prophylaxis or treatment of cyanide poisoning during nitroprusside infusion.

Fenoldopam

- It is an arteriolar dilator.
- Used for hypertensive emergencies and postoperative hypertension.
- Agonist at dopamine D_1-receptors → dilates arterioles and produce natriuresis.

Fenoldopam

- **Metabolized by conjugation, t½ ~10 min, used by infusion.**
- **Adverse effects: reflex tachycardia, headache, flushing, and increased intraocular pressure.**

Calcium Channel Blockers

- **Transmembrane calcium influx is necessary for contraction of smooth and cardiac muscle.**

Classification of CCBs:

1. **Verapamil**
2. **Diltiazem**
3. **Dihydropyridines: Nifedipine, Amlodipine, Nicardipine, ..**

TABLE 12–5 Clinical pharmacology of some calcium channel-blocking drugs.

Drug	Oral Bioavailability (%)	Half-life (hours)	Indication	Dosage
Dihydropyridines				
Amlodipine	65–90	30–50	Angina, hypertension	5–10 mg orally once daily
Felodipine	15–20	11–16	Hypertension, Raynaud's phenomenon	5–10 mg orally once daily
Isradipine	15–25	8	Hypertension	2.5–10 mg orally twice daily
Nicardipine	35	2–4	Angina, hypertension	20–40 mg orally every 8 hours
Nifedipine	45–70	4	Angina, hypertension, Raynaud's phenomenon	3–10 mcg/kg IV; 20–40 mg orally every 8 hours
Nisoldipine	< 10	6–12	Hypertension	20–40 mg orally once daily
Nitrendipine	10–30	5–12	Investigational	20 mg orally once or twice daily
Miscellaneous				
Diltiazem	40–65	3–4	Angina, hypertension, Raynaud's phenomenon	75–150 mcg/kg IV; 30–80 mg orally every 6 hours
Verapamil	20–35	6	Angina, hypertension, arrhythmias, migraine	75–150 mcg/kg IV; 80–160 mg orally every 8 hours

Calcium Channel Blockers

- They are exclusively L-type CCBs.
- These drugs are orally active (some can be injected), characterized by high first-pass effect and high plasma protein binding.
- Their metabolism is inhibited by grapefruit juice.

Calcium Channel Blockers

Mechanism of Action:

- Block L-type Ca^{2+}- channels in cardiac and smooth muscles (L = long, large high threshold Ca^{2+} current).
- Dihydropyridines bind to one type of receptors.
- Verapamil and diltiazem bind to related but <u>not</u> identical receptors.

Calcium Channel Blockers

- **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.**

Calcium Channel Blockers

- **The result is a marked decrease in transmembrane calcium current, which in smooth muscle results in long-lasting relaxation.**
- **In cardiac muscle results in reduction in contractility and decreases in sinus node pacemaker rate and atrio-ventricular node conduction velocity.**

Calcium Channel Blockers

- **Potassium channels in vascular smooth muscle are inhibited by verapamil, thus limiting the vasodilation produced by this drug.**

Calcium Channel Blockers

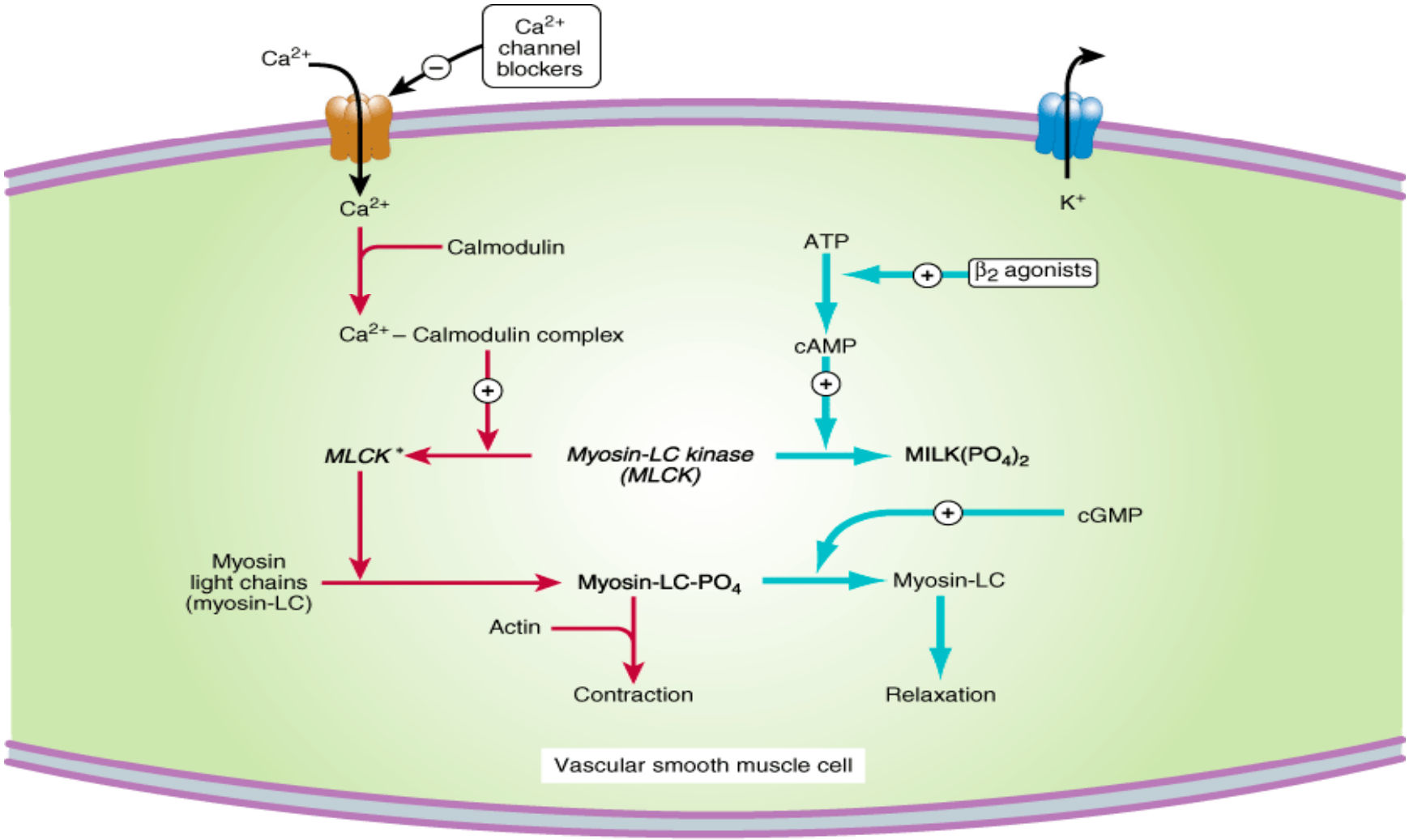
Organ-system effects:

1. **Smooth muscle relaxation:**

- **Arterioles are more sensitive than veins → reduce systemic vascular resistance. Therefore, orthostatic hypotension is not a common adverse effect.**

Calcium Channel Blockers

- **Women may be more sensitive than men to the hypotensive action of diltiazem.**
- **Improve angina of effort by reduction of peripheral vascular resistance, and relieve of coronary artery improves variant angina.**



Calcium Channel Blockers

- **Dihydropyridines are more selective to vascular smooth muscle ↔ negligible effect on cardiac myocytes.**
- **Blockade of vascular smooth muscle potassium channels reduce the effect of verapamil on vasodilation.**

Calcium Channel Blockers

- **Dihydropyridines may differ in potency in different vascular beds. Nimodipine is more selective to cerebral blood vessels → relieves spasm following subarachnoid hemorrhage (withdrawn).**
- **Nicardipine has similar effects.**

Calcium Channel Blockers

2. Cardiac muscle:

- Cardiac muscle is highly dependent on calcium influx during each action potential for normal function.

A. Reduction in cardiac contractility reduces cardiac output and myocardial O_2 requirements in patients with angina.

Calcium Channel Blockers

B. Reduction of sinus rate.

C. Reduction of conduction through the AV-node. (slow-response, or calcium-dependent, action potentials)

- Dihydropyridines are not effective on cardiac muscle.

Calcium Channel Blockers

- **Relaxation of bronchial, GI and uterine smooth muscle may also occur.**

3. **Skeletal muscles are <u>not</u> affected because they use intracellular Ca^2 pool and do not need much transmembrane Ca^2 influx.**

Calcium Channel Blockers

4. **Others:**

- **Verapamil blocks p-glycoproteins, efflux-transporter, and thus, may reduce resistance of cancer cell to chemotherapeutic agents.**

Calcium Channel Blockers

Adverse Effects:

1. Cardiac depression: bradycardia, cardiac arrest, AV-block, and congestive heart failure (verapamil, diltiazem).
2. Flushing, dizziness, nausea, constipation and peripheral edema.

Calcium Channel Blockers

3. **Dihydropyridines:**

   a. Reflex sympathetic stimulation → reflex tachycardia.

   b. Renin secretion: retention of Na^+ and water & vasoconstriction.

Calcium Channel Blockers

Notes and precautions:

1. **Verapamil and diltiazem should NOT be co-administered with β-blockers. Why? Dihydropyridines can! Why?**
2. **Dihydropyridines can be combined with verapamil and diltiazem.**
3. **Immediate release short-acting dihydropyridines can precipitate angina pectoris in patients with coronary artery disease – contraindicated. Why?**
4. **All can increase digoxin serum levels.**

Calcium Channel Blockers

Therapeutic Uses:

1. Hypertension
2. Angina pectoris and myocardial infarction
3. Supraventricular tachyarrhythmia's (Supraventricular tachycardia, atrial fibrillation and atrial flutter). NOT the dihydropyridines. Why?

Inhibitors of the Renin-Angiotensin-Aldosterone System

Renin release from the renal cortex is stimulated by:

1. **Reduced renal arterial pressure.**
2. **Sympathetic nerve stimulation (β_1).**
3. **Reduced sodium delivery to or increased sodium concentration at the distal renal tubule.**

Inhibitors of the Renin-Angiotensin-Aldosterone System

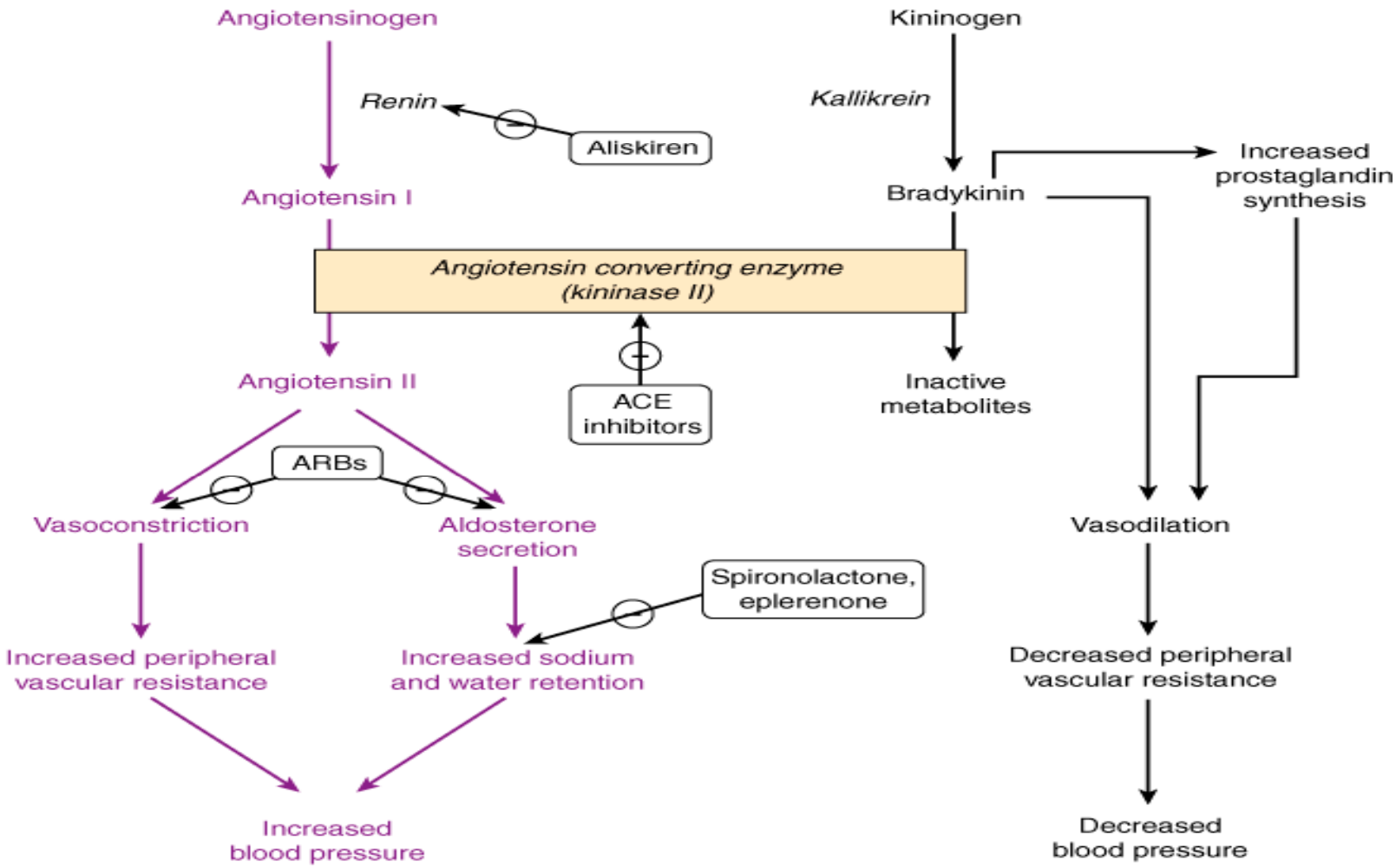
- Angiotensin I is converted, primarily by endothelial ACE, to the arterial vasoconstrictor angiotensin II, which is in turn converted in the adrenal gland to angiotensin III.

Inhibitors of the Renin-Angiotensin-Aldosterone System

- Angiotensin II has vasoconstrictor and sodium-retaining activity.
- Angiotensin II and III both stimulate aldosterone release.
- Salt restriction, diuretics & vasodilators stimulate angiotensin production.

Inhibitors of the Renin-Angiotensin-Aldosterone System

- A system for angiotensin exists in several other tissues (heart), and may be responsible for trophic changes such as cardiac hypertrophy.
- The ACE involved in tissue angiotensin II synthesis is also inhibited by ACE inhibitors.



Inhibitors of the Renin-Angiotensin-Aldosterone System

Classification:

1. β-Adrenoceptor blockers.
2. Renin antagonist: aliskiren
3. Angiotensin converting enzyme inhibitors.
4. Angiotensin receptor blockers.
5. Aldosterone antagonists – spironolactone

Angiotensin Converting Enzyme Inhibitors (ACEIs)

Captopril – short acting.

Enalapril – prodrug (enalaprilat, IV).

Lisinopril – derivative of enalaprilat.

Ramipril, benazepril, fosinopril, moexipril, perindopril, quinapril, and trandolapril – prodrugs – long acting.

TABLE 10-5 Pharmacokinetic Properties of Selected Angiotensin Inhibitors

DRUG	ORAL BIOAVAILABILITY	ABSORPTION REDUCED BY FOOD	ACTIVE METABOLITE	DURATION OF ACTION (HOURS)
Angiotensin-Converting Enzyme Inhibitors				
Benazepril	37%	No	Benazeprilat	24
Captopril	75%	30%-40%	None	6-12
Enalapril	60%	No	Enalaprilat*	24
Fosinopril	36%	No	Fosinoprilat	24
Lisinopril	25%	No	None	24
Quinapril	60%	25%-30%	Quinaprilat	24
Ramipril	55%	No	Ramiprilat	24
Angiotensin Receptor Antagonists				
Candesartan	15%	No	None	24
Losartan	33%	10%	Carboxylic acid metabolite	24
Valsartan	25%	40%	None	24
Direct Renin Inhibitor				
Aliskiren	2.5%	Yes (high fat)	None	24

*Enalaprilat is available as a separate drug for intravenous administration.

ACEIs

Mechanism of Action:

- Inhibit peptidyl dipeptidase that hydrolyzes angiotensin I to angiotensin II, and inactivates bradykinin (plasma kininase), a potent vasodilator.
- Bradykinin also stimulates release of nitric oxide and prostacyclin.

ACEIs

- Angiotensin II is a vasoconstrictor. and bradykinin is a vasodilator.
- ACEIs prevent formation of a vaso-constrictor and prevent degradation of a vasodilator.
- They decrease peripheral vascular resistance without significantly changing cardiac out put and heart rate.

ACEIs

- They reduce sodium and water retention (due to reduced aldosterone).
- They do NOT cause reflex sympathetic stimulation, may be because:

1. Of downward resetting of the baroreceptors.

ACEIs

2. **Of enhanced parasympathetic activity.**
3. **They may block angiotensin presynaptic effects on catecholamine release**

- **They are effective in hypertensive patients irrespective of plasma renin activity.**

ACEIs

Clinical Pharmacology:

1. Hypertension
2. Diabetic nephropathy (even without hypertension): They reduce proteinuria and stabilize renal function by reducing efferent arteriolar resistance in glomeruli and decreasing intraglomerular capillary pressure.

ACEIs

3. **Heart failure: They reduce both preload and afterload.**
4. **Myocardial infarction: They reduce cardiac remodeling.**
5. **Reduce the incidence of diabetes in patients with high cardiovascular risk.**

ACEIs

Adverse Effects:

1. **Severe hypotension after initial doses, especially in hypovolemia as a result of diuretics, salt restriction, or gastrointestinal fluid loss.**

ACEIs

2. **Acute renal failure, particularly in patients with bilateral renal artery stenosis or renal artery stenosis of a solitary kidney.**

   In renal artery stenosis, renal perfusion is maintained by vasoconstriction of the efferent arteriole.

ACEIs

3. Hyperkalemia (Why?)
4. Dry cough, wheezing, angioedema (due to bradykinin or substance P).
5. Captopril may cause proteinuria and neutropenia at high doses, especially in patients with renal insufficiency.

ACEIs

6. **Others: Altered sense of taste, allergic skin rash, drug fever (10% of patients).**

- **Contraindicated during pregnancy: Fetal hypotension, anuria, renal failure, malformations and death.**

ACEIs

Drug Interactions:

1. K^+ supplements and K^+-sparing diuretics → Hyperkalemia.
2. Nonsteroidal antiinflammatory drugs may impair the antihypertensive effect of ACEIs by blocking bradykinin-mediated vasodilation (PG portion).

Angiotensin-Receptor Blockers (ARBs)

Losartan, Valsartan, Candesartan, eprosartan, irbesartan, telmisartan, and olmesartan.

- **Block angiotensin II type 1 receptors (AT_1-R).**
- **No effect on bradykinin.**

ARBs

- More complete inhibition of angiotensin II actions (Why?). Other enzymes generate angiotensin II.
- Uses similar to ACEIs.
- Adverse effects are similar to ACEIs except, wheezing, angioedema and cough which may occur much less commonly.