Antihypertensive Agents

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• **Diuretics**	1. Bumetanide (Bumid) 2. Furosemide (Lasix) 3. Hydrochlorothiazide (Aldactazide) 4. Indapamide (Fludex) 5. Spironolactone (Aldactone) 6. Triamterene (Triamteril)
• **β-blockers**	1. Acebutolol (Prent) 2. Atenolol (Tensinor) 3. Carvedilol (Dilatrend) 4. Labetalol (*Trandate*) 5. Metoprolol (Beloc) 6. Nadolol (*Corgard*) 7. Propranolol (Dideral)
• **α-blockers**	1. Doxazosin (Cardura) 2. Prazosin (Minipress) 3. Terazosin (Hytrin) 4. Trimazosin (*Cardovar BD*)
• **Centrally acting sympatho-plegics**	1. Clonidine (*Catapres*) 2. α-Methydopa (Alfamet) 3. Moxonidine (Physiotens) 4. Rilmenidine (Hyperium)

• **Adrenergic nerve blockers**	1. Reserpine (Regroton)
• **Angiotensin receptor blockers**	1. Candesartan (Atacand) 2. Eprosartan (Teveten) 3. Irbesartan (Karvea) 4. Losartan (Cozaar) 5. Telmisartan (Micardis) 6. Valsartan (Diovan)
• **ACE inhibitors**	1. Benazepril (Cibacen) 2. Captopril (Kapril) 3. Cilazapril (Inhibace) 4. Enalapril (Renitec) 5. Fosinopril (Monopril) 6. Lisinopril (Rilace) 7. Moexipril (Univasc) 8. Perindopril (Coversyl) 9. Quinapril (Acuitel) 10. Ramipril (Delix) 11. Trandolapril (Gopten) 12. Zofenopril (Zoprotec)

• **Ca^{2+} channel blockers**	1. Amlodipine (Norvasc) 2. Diltiazem (Diltizem) 3. Felodipine (Plendil) 4. Isradipine (Dynacirc) 5. Lacipidine (Lacipil) 6. Lercadipine (Lercadip) 7. Nifedipine (Adalat Crono) 8. Nilvadipine (Nilvadis) 9. Nisoldipine (Syscor) 10. Nitrendipine (Baypress) 11. Verapamil (Isoptin)
• **Other vasodilators**	1. Diazoxide (*Hyperstat*) 2. Fenoldopam (*Corlopam*) 3. Hydralazine (*Apresoline*) 4. Minoxidile (*Loniten*) 5. Sodium nitroprusside (Nipruss)

- **Combined preparations**

1. Atenolol+ chlorthalidone (Tenoretic)
2. Benazepril + hydrochlorothiazide (Cibadrex)
3. Candesartan + hydrochlorothiazide (Atacand Plus)
4. Cilazapril + hydrochlorothiazide (Inhibace Plus)
5. Enalapril + hydrochlorothiazide (Konveril Plus)
6. Fosinopril + hydrochlorothiazide (Monopril Plus)
7. Irbesartan + hydrochlorothiazide (Karvezide)
8. Lisinopril + hydrochlorothiazide (Rilace Plus)
9. Losartan + hydrochlorothiazide (Hyzaar)
10. Perindopril + indapamid (Coversyl Plus)
11. Quinapril + hydrochlorothiazide (Accuzide)
12. Ramipril + hydrochlorothiazide (Delix Plus)
13. Reserpine + chlorthalidone (Regreton)
14. Trandolapril + verapamil (Tarka)
15. Valsartan + hydrochlorothiazide (Co-Diovan)

Hypertension

- Hypertension is a common and usually progressive disease, which if not effectively treated, results in a greatly increased probability of coronary arterial disease, thrombosis, strokes and renal failure.
- **It is the most common cardiovascular disease!!!**
- Keeping the blood pressure below 140/90 mm Hg (systolic/diastolic) reduces morbidity and mortality of these patients significantly. Personally hypertension is the **story of 80.000** tablets.

Diagnosis

- The diagnosis of hypertension is based on repeated reproducible measurements of elevated blood pressure.
- A specific cause of hypertension can be established in only 10-15% of patients: renal artery constriction, coarctation of the aorta, pheochromocytoma, Cushing's disease and primary aldosteronism.
- Patients in whom no specific cause of hypertension can be found are said to have **essential hypertension.**
- Elevated blood pressure is usually caused by a combination of several abnormalities (multifactorial): genetic inheritance, psychologic stress environmental and dietary factors (increased salt, perhaps decreased potassium or calcium intake).

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Regulation of blood pressure

BP= cardiac output × peripheral vascular resistance

- In both normal and hypertensive individuals, blood pressure is maintained by moment-to-moment regulation of cardiac output and peripheral vascular resistance.

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Anatomic sites of blood pressure control

- **Arterioles** (resistance)
- **Venules** (capacitance)
- **Heart** (pump output)
- **Kidneys** (volume).

- Baroreflexes that are controlled by autonomic nerve system and humoral mechanisms including renin-angiotensin-aldosteron system coordinate these anatomic sites.
- The difference between normal and hypertensive patients is that baroreceptors are set to higher levels.

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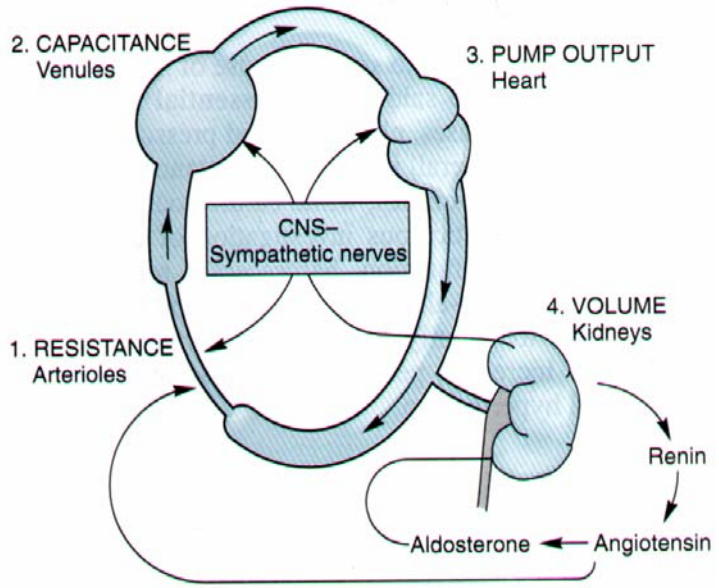

Figure 11–1. Anatomic sites of blood pressure control.

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Basic pharmacology of antihypertensives

- **Diuretics**, which lower blood pressure by depleting the body of sodium and reducing blood volume and by vasodilation.
- **Sympathoplegic agents**, which lower blood pressure by reducing peripheral vascular resistance, inhibiting cardiac function and increasing venous pooling in capacitance vessels.
- **Direct vasodilators,** which reduce blood pressure by relating vascular smooth muscle.
- **Agents that block production or action of angiotensin** and thereby reduce peripheral vascular resistance and blood volume.

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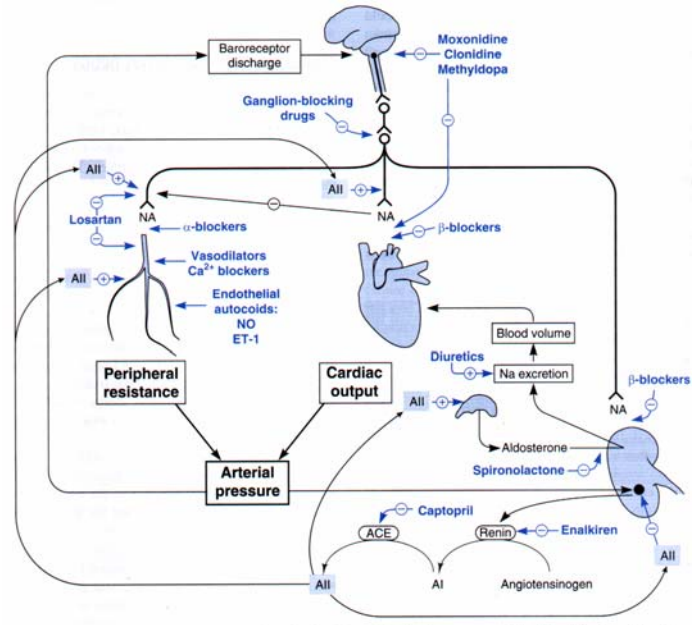

Fig. 15.9 Diagram showing the main mechanisms involved in arterial blood pressure regulation (black lines), and the sites of action of antihypertensive drugs (blue lines). NA = noradrenaline, AI = angiotensin I, AII = angiotensin II, ACE = angiotensin-converting enzyme.

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First line antihypertensive agents: ABCD

- Angiotensin antagonists
- Beta blockers
- Calcium channel blockers
- Diuretics

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Diuretics I

- Dietary sodium restriction has been known for many years to decrease blood pressure in hypertensive patients.
- Dietary control of blood pressure is a relatively nontoxic therapeutic measure and may even be preventive.
- Diuretics lower blood pressure primarily by depleting body sodium stores. Initially they 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 peripheric vascular resistance declines.

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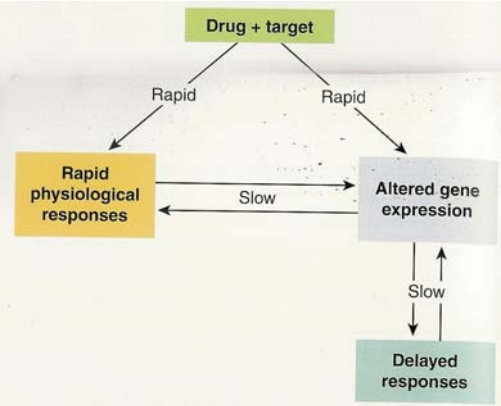

Fig. 2.13 Early and late responses to drugs. Many drugs act directly on their targets (left-hand arrow) to produce an immediate physiological response. If this is maintained, it is likely to cause changes in gene expression that give rise to delayed effects. Some drugs (right-hand arrow) have their primary action on gene expression, producing delayed physiological responses. Drugs can also work by both pathways. Note the bidirectional interaction between gene expression and response.

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Diuretics II

- Sodium is believed to contribute to vascular resistance due to increases sodium-calcium exchange with a resultant increase in intracellular calcium.
- Some diuretics like **indapamide** have direct vasodilator properties.
- **Amiloride** inhibits effects of contractile impulses on vascular smooth muscle with a mechanism independent from its natriuretic effect, which is preventing transmembrane and intracellular calcium movements.

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Diuretics III

- Diuretics are effective in lowering blood pressure by 10-15 mm Hg in most patients and often provide adequate treatment for mild or moderate essential hypertension when used alone. 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.
- For most patients **thiazide** diuretics are appropriate when renal and cardiac function is normal.

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Diuretics IV

- More powerful diuretics (**loop agents**) are necessary in severe hypertension, renal insufficiency (GFR< 30-40 ml/min), and in cardiac failure or cirrhosis where sodium retention is marked.
- **Potassium-sparing** diuretics are useful both to avoid excessive potassium depletion, particularly in patients taking digitalis and to enhance the natriuretic effects of other diuretics.

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Adverse effects

- The most common is potassium depletion, which is especially important in persons taking digitalis, those who have chronic arrhythmias or those with acute myocardial infarction. Restriction of sodium intake may minimize potassium loss.
- Diuretics may also cause magnesium depletion, impair glucose tolerance and increase serum lipid concentrations.
- They may increase uric acid concentration and precipitate gout.

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Table 15–3. Thiazides and related diuretics: Dosages.

	Daily Oral Dose	Frequency of Dosage
Bendroflumethazide	2.5–10 mg	As single dose
Benzthiazide	25–100 mg	In two divided doses
Chlorothiazide	0.5–1 g	In two divided doses
Chlorthalidone[1]	50–100 mg	As single dose
Hydrochlorothiazide	25–100 mg	As single dose
Hydroflumethiazide	25–100 mg	In two divided doses
Indapamide[1]	2.5–10 mg	As single dose
Methyclothiazide	2.5–10 mg	As single dose
Metolazone[1]	2.5–10 mg	As single dose
Polythiazide	1–4 mg	As single dose
Quinethazone[1]	50–100 mg	As single dose
Trichlormethiazide	2–8 mg	As single dose

[1]Not a thiazide but a sulfonamide qualitatively similar to the thiazides.

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Sympathoplegic agents

Centrally acting sympathoplegic agents
- Methyldopa
- Clonidine

Ganglion blockers
- Trimethaphan

Adrenergic neuron blockers
- Guanethidine
- Reserpine
- Pargyline

Adrenergic receptor blockers
- α-blockers
- β-blockers

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β-blockers

- **Propranalol:** It blocks both β_1 and β_2 receptors. It primarily decreases blood pressure as a result of a decrease in cardiac output.
- Beta blockade in brain, kidney and peripheral adrenergic neurons has been proposed as contributing to the antihypertensive effect.
- Propranolol inhibits the stimulation of renin production by catecholamines (β_1 mediated).

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Propranolol (continued)

- It has significant first-pass hepatic inactivation.
- The principal toxicity occur in patients with reduced myocardial reserve, asthma, peripheral vascular insufficiency and diabetes when discontinued after prolonged use, some patients experience a withdrawal syndrome, manifested by nervousness, tachycardia, increased intensity of angina or increased blood pressure.
- It may increase plasma triglycerides and reduce HDL.

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Other β-blocker agents I

- **Metoprolol:** It is approximately equipotent to propranolol in inhibiting stimulation of β_1 receptors, but 50 to 100 fold less potent than propranolol in blocking β_2 receptors. This relative cardioselectivity may be advantageous in patients who also suffer from asthma, diabetes or peripheral vascular disease.
- **Nadolol** and **carteolol** are also non-selective. They are not metabolized and are excreted in the urine.

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Other β-blocker agents II

- **Atenolol** is β_1 selective and not metabolized.
- **Betaxolol** and **bisoprolol** are β_1 selective, they are metabolized in the liver but their half-life is long.
- **Pindolol, acetobutolol, penbutolol:** They are partial agonists (i.e. ISA). Probably they have agonist activity on β_2 receptors rather than antagonism.

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Other β-blocker agents III

- **Labetalol** and **carvedilol:**
- Labetalol has 4 stereoisomers.
- Two of these isomers are inactive, one β blocker and one α blocker.
- Carvedilol has 2 stereoisomers.
- S isomer→ α and β blocker
- R isomer→ α blocker.
- The combined α and β receptor blockade with labetalol makes it useful in pheochromocytoma and hypertensive emergencies.
- Preliminary studies suggest that carvedilol may be useful in some cases of congestive heart failure.

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Table 10–2. Properties of several beta-receptor-blocking drugs.

	Selectivity	Partial Agonist Activity	Local Anesthetic Action	Lipid Solubility	Elimination Half-Life (Hours)	Approximate Bioavailability
Acebutolol	β_1	Yes	Yes	Low	3–4	50
Atenolol	β_1	No	No	Low	6–9	40
Betaxolol	β_1	No	Slight	Low	14–22	90
Bisoprolol	β_1	No	No	Low	9–12	80
Carteolol	None	Yes	No	Low	6	85
Carvedilol[1]	None	No	No	No data	7–10	25–35
Celiprolol	β_1	Yes[2]	No	No data	4–5	70
Esmolol	β_1	No	No	Low	10	~0
Labetalol[1]	None	Yes[1]	Yes	Moderate	5	30
Metoprolol	β_1	No	Yes	Moderate	3–4	50
Nadolol	None	No	No	Low	14–24	33
Penbutolol	None	Yes	No	High	5	>90
Pindolol	None	Yes	Yes	Moderate	3–4	90
Propranolol	None	No	Yes	High	3.5–6	30[3]
Sotalol	None	No	No	Low	12	90
Timolol	None	No	No	Moderate	4–5	50

[1]Carvedilol and labetalol also cause α_1 adrenoceptor blockade.
[2]Partial agonist effects at β_2 receptors.
[3]Bioavailability is dose-dependent.

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Table 10–1. Relative selectivity of antagonists for adrenoceptors.

	Receptor Affinity
Alpha antagonists	
Prazosin, terazosin, doxazosin	$\alpha_1 >>>> \alpha_2$
Phenoxybenzamine	$\alpha_1 > \alpha_2$
Phentolamine	$\alpha_1 = \alpha_2$
Rauwolscine, yohimbine, tolazoline	$\alpha_2 >> \alpha_1$
Mixed antagonists	
Labetalol, carvedilol	$\beta_1 = \beta_2 \geq \alpha_1 > \alpha_2$
Beta antagonists	
Metoprololol, acebutolol, alprenolol, atenolol, betaxolol, celiprolol, esmolol	$\beta_1 >>> \beta_2$
Propranolol, carteolol, nadolol, penbutolol, pindolol, timolol	$\beta_1 = \beta_2$
Butoxamine	$\beta_2 >>> \beta_1$

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α_1 blockers I

- **Prazosin, terazosin, doxazosin:** They are α_1 selective blockers. α_2 receptors are intact thus feedback mechanisms for noradrenalin remains intact and less reflex tachycardia is observed than non-selective α-blockers.
- They produce their antihypertensive effects by blocking α_1 receptors in arterioles and venules. The drugs are more effective when used in combination with other agents, such as a beta-blocker and a diuretic than when use alone.

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α_1 blockers I

- Treatment should be initiated with a low dose to prevent postural hypotension and syncope administered at bedtime. Unlike diuretics and beta-blockers, the α_1-blockers do not adversely and may even beneficially affect plasma lipid profiles.
- Other selective α_1-blockers for antihypertensive use are: **alfuzosin, tamsulosin, indoramin**, and **urapidil** (it is also a weak α_2-agonist, 5-HT_{1A}-agonist and weak β_1 antagonist).

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Non-selective α-blockers

- **Phentolamine** and **phenoxybenzamine** are non-selective α-blockers.
- They are useful in diagnosis and treatment of pheochromocytoma and in other clinical situations associated with exaggerated release of catecholamines (eg. in clonidine withdrawal syndrome combined with propranolol).

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Centrally acting sympathoplegic drugs I

- **Methyldopa:** It is an analog of L-dopa and is converted to α-methyldopamine and α-methylnorepinephrine, which are false transmitters. Methyldopa's antihypertensive action appears to be due to stimulation of central α_2 receptors.
- It may result in postural hypotension one of its advantage is that it decreases renal vascular resistance.

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Centrally acting sympathoplegic drugs II

- **Clonidine** is an α_2 and imidazoline receptor agonist. Its antihypertensive action is due to decrease in heart rate, and decrease in cardiac output because of relaxation of capacitance vessels. Renal vascular resistance also decreases.
- After clonidine application circulating catecholamine levels decrease (chemical sympatectomy).
- **Guanabenz** and **guanfacine** are centrally active antihypertensive agents that share the central alpha-adrenoceptor- stimulating effects of clonidine.

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Ganglion-blocking agents

- They act by inhibiting the stimulating action of acetylcholine on postganglionic autonomic neurons.
- **Trimethaphan:** It is used intravenously in hypertensive crisis, acute aorta dissection and controlled hypotension in neurosurgery. It has rapid and short action.

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Adrenergic neuron blockers I

- These drugs decrease blood pressure by inhibiting the release of noradrenaline from sympathetic neurons.
- **Guanethidine, bethanidine, debrisoquin:** They are transported across membrane by uptake-1. They are concentrated in transmitter vesicles and cause gradual depletion of norepinephrine. Uptake-1 inhibitors such as cocaine, amphetamine, tricyclic antidepressants decrease their effects. They increase sensitivity to the hypertensive effects of exogenously administered sympathomimetic amines.

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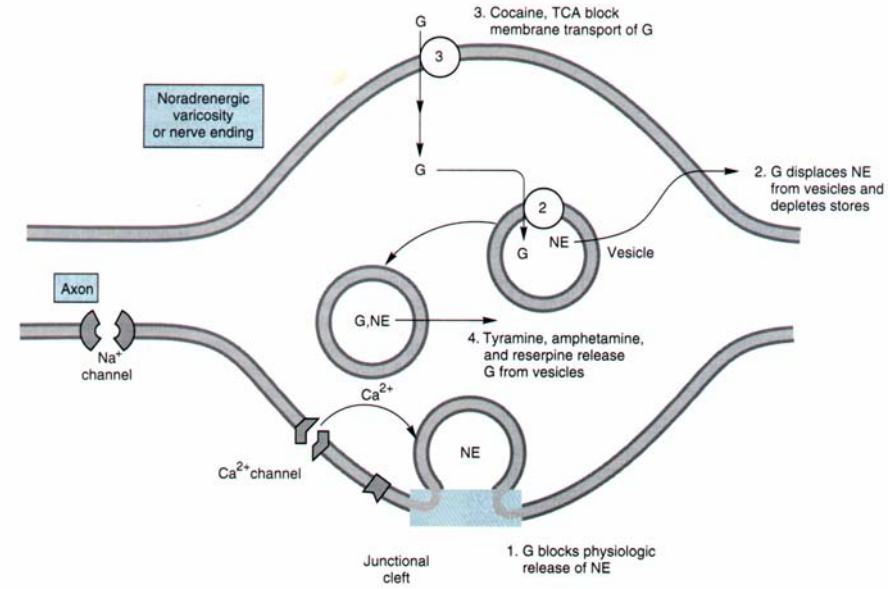

Figure 11–4. Guanethidine actions and drug interactions involving the adrenergic neuron. (G, guanethidine; NE, norepinephrine; TCA, tricyclic antidepressants.)

Adrenergic neuron blockers II

- **Reserpine:** It blocks the ability of aminergic transmitter vesicles to take up and store biogenic amines. It was widely used previously. It may result in depression.
- It has no indication in modern antihypertensive therapy but found in the prescriptions of **old doctors.**
- **Pargyline:** It is a MAO inhibitor and is believed to increase the concentration of an ineffective false transmitter. It has no modern use.

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Direct vasodilators

- Calcium channel blockers
- Hydralazine
- Minoxidil
- Sodium nitroprusside
- Diazoxide

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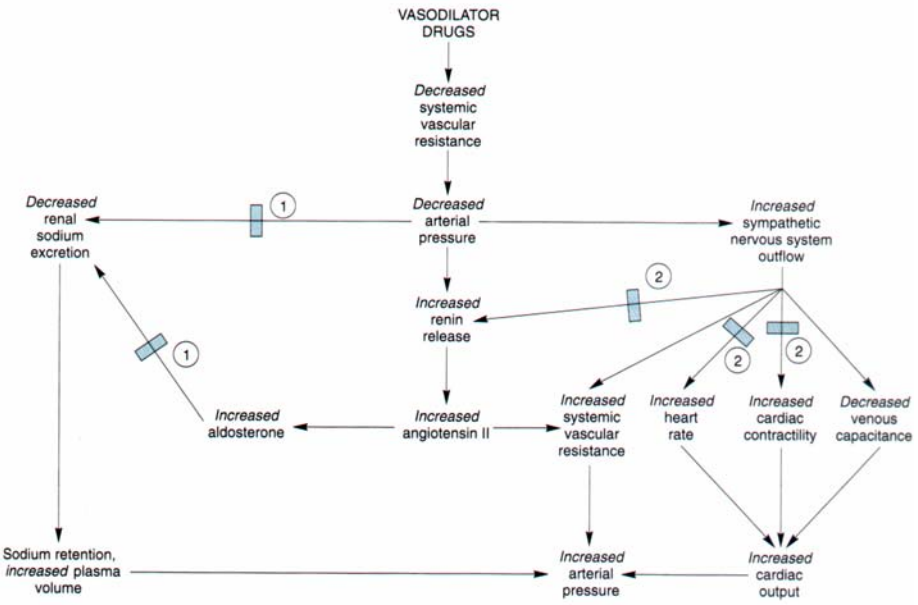

Figure 11–5. Compensatory responses to vasodilators; basis for combination therapy with beta-blockers and diuretics. ① Effect blocked by diuretics. ② Effect blocked by beta-blockers.

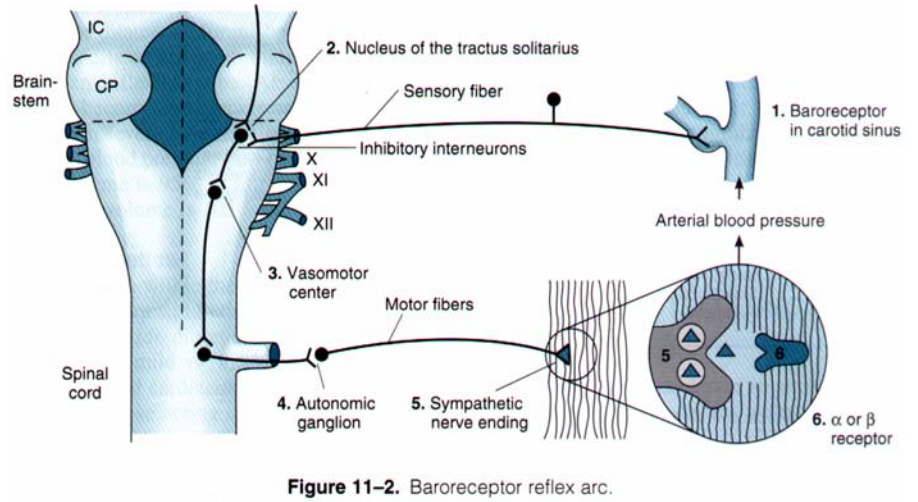

Figure 11–2. Baroreceptor reflex arc.

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Calcium channel blockers I

- They are blockers of L-type calcium channels.
- **Verapamil:** It is cardioselective.
- **Dihydropyridines (amlodipine, felodipine, isradipine, nicardipine, nisoldipine):** They are vascular smooth muscle selective.
- **Diltiazem:** Intermediate

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Calcium channel blockers II

- Verapamil may decrease heart rate and cardiac output
- Dihydropyridines are minimally cardiodepressive with reflex sympathetic activations and mild tachycardia, cardiac output is preserved or even slightly increased.
- With the use of short acting nifedipine, there is an increase in MI and mortality.
- In the treatment of hypertension sustained release nifedipine preparations and drugs with long plasma half-life control blood pressure safely.

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Other direct vasodilators I

- **Hydralazine:** It relaxes arterioles but not veins. When used alone tachyphlaxis to hypertensive effects develops rapidly. With combination therapy it may be used particularly in severe hypertension.
- Its bioavailability is low. There is genetic variability for its metabolism. Dosage should be regulated according to individual responses.

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Other direct vasodilators II

- **Minoxidil:** It is a very efficacious orally active vasodilator. Its effect results from the opening of potassium channels in smooth muscle membrane. It dilates arterioles like hydralazine. Clinical responses are better than hydralazine and particularly in renal failure it should be preferred.
- Topical minoxidil (Rogaine) is used as a stimulant to hair growth for correction of baldness.
- If it is not combined with a beta-blocker and a loop diuretic, sympathetic stimulation, angina, sodium and fluid retention may occur.

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Other direct vasodilators III

- **Diazoxide:** It is an effective and relatively long-acting parenterally administered arteriolar dilator. It opens potassium channels like minoxidil. Its antihypertensive effect initiates within 5 min. and lasts for 4-12 hours.
- It inhibits insulin release from pancreas and causes renal salt and water retention.

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Other direct vasodilators IV

- **Sodium nitroprusside:** It is a powerful parenterally administered vasodilator that is used in treating hypertensive emergencies as well as severe cardiac failure.
- It dilates both arterioles and venules. The action occurs as a result of activation of guanylyl cyclase. The result is increased intracellular cGMP, which relates vascular smooth muscle.

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Sodium nitroprusside (continued)

- In the absence of cardiac failure, blood pressure decreases, owing to decreased vascular resistance, while cardiac output changes slightly. In patients with cardiac failure, cardiac output increases owing to afterload reduction.
- It is a complex of iron, cyanide groups. With infusions more than 10 μg/kg/min, cyanide toxicity occurs.→ metabolic acidosis, arrhythmia, hypotension, dead.
- Aqueus solution is sensitive to light.

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Inhibitors of angiotensin

Angiotensin converting enzyme (ACE) inhibitors

- Captopril and other drugs in this class inhibit the converting enzyme that hydrolyzes angiotensin I to angiotensin II.
- The same enzyme inactivates bradykinin a potent vasodilator that works at least in part by stimulating release of nitric oxide and prostacyclin. Angiotensin II is vasoconstrictor and has salt and water retaining activity via aldosteron secretion.

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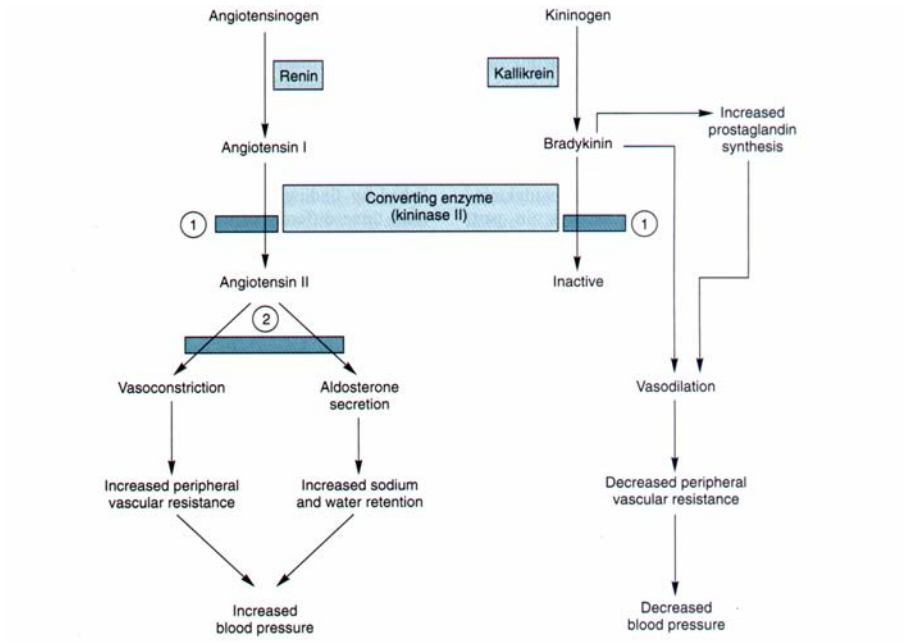

Figure 11–6. Sites of action of ACE inhibitors and receptor blockers. ① Site of ACE blockade. ② Site of receptor blockade.

ACE inhibitors I

- **Captopril** and **lisinopril** are orally active agents.
- Enapril is a prodrog and is converted to active form enaprilat in liver. Enaprilat is only available in IV form for hypertensive emergencies.
- Benazepril, fosinopril, moexepril, quinapril and ramipril are all prodrugs and hydrolyzed in liver to active forms.

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ACE inhibitors II

- ACE inhibitors decrease blood pressure by decreasing peripheral vascular resistance. Cardiac output and heart rate do not change significantly. As they do not cause reflex sympathetic activation, they are safe in patients with ischemic heart disease.
- The absence of reflex tachycardia may be due to downward resetting of the baroreceptors or to enhanced parasympathetic activity.

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ACE inhibitors III

- They are particularly useful in treating patients with diabetic nephropathy, diminishing proteinuria and stabilizing renal function. They are also useful in congestive heart failure and after MI.
- All ACE inhibitors are excreted via kidneys except **fosinopril** and **moexipril.**
- In hypervolemic patients (due to diuretics, salt restriction, GI fluid loss), first doses may result in severe hypotension. Other adverse effects include acute renal failure, hyperkalemia, dry cough, sometimes wheezing and angioedema (dry cough and angioedema due to increased effects of bradykinin).

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ACE inhibitors IV

- ACE inhibitors are contraindicated during the second and third trimesters of pregnancy because of the risk of fetal hypotension, anuria and renal failure, sometimes associated with fetal malformations or death.
- Potassium supplements or potassium sparing diuretics can result in hyperkalemia.
- NSAI drugs may impair hypotensive effects by blocking bradykinin-mediated vasodilation which is at least in part PG mediated.

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Angiotensin receptor blockers I

- **Losartan** and **valsartan** are AT_1 receptor blockers. Adverse effects are the same as ACE inhibitors except cough and angioedema, which are not observed. They may be more effective in decreasing the effects of angiotensin because there are other enzymes that produce angiotensin II. Both drugs can be administered orally. Now many “sartans” are available.
- **Saralasin** is also a similar drug which is IV administered. It is out of marked because its vascular effects elated to dose-response cannot be predicted.

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Hypertensive emergency I

- It is a rare but life threatening situation. In patients with no complication, a diastolic blood pressure more than **150 mm Hg (systolic >210 mm Hg)** is an emergency. In patients with encephalopathy, cerebral hemorrhagia, left ventricular failure, aorta stenosis, diastolic blood pressure the emergency limit is >130 mm Hg.
- Aim is to decrease diastolic pressure to 100-110 mm Hg.

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Hypertensive emergency II

- Sodium nitroprusside and diazoxide are the drugs most commonly used. Other effective IV drugs include nitroglycerin, labetalol, calcium channel blockers, hydralazine, reserpine and methyldopa.
- Nonparenteral therapy with oral nifedipine, captopril, prazosin or clonidin has also been shown to be useful.

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Thank you...

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