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ANTIHYPERTENSIVE DRUGS

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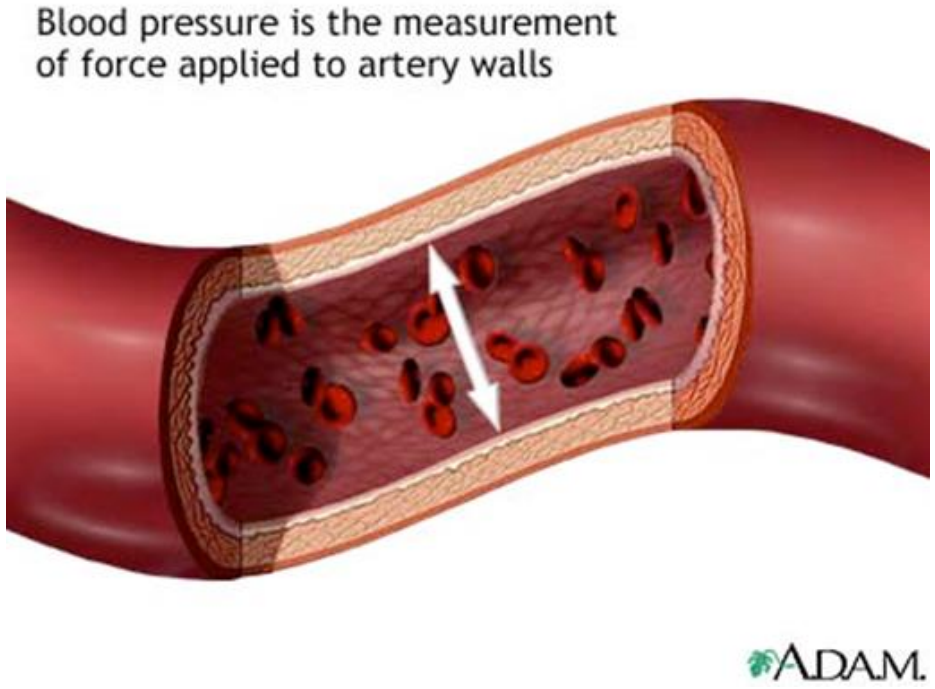
Blood pressure

- Pressure exerted by circulating blood upon the walls of blood vessels
- One of the principal vital signs
- During each heartbeat, BP varies between a maximum (**systolic**) and a minimum (**diastolic**) pressure



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Hypertension

- “the Silent Killer”
- cca 70 million Americans exhibit BP above normal (2.5 million in CZ)
- Estimation: 60-80% of humans will be hypertensive by age 80
- Primary (Essential) vs. Secondary
- Morbidity and mortality due to end organ damage

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Diagnosis

- Based on repeated, reproducible measurements

- Even mild HT increases the risk of **end-organ damage**

= damage of major organs fed by the circulatory system

(heart, kidneys, brain, eyes), due to uncontrolled HT

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Positive risk factors for end-organ damage

- Family history of cardiovascular disease
- Metabolic syndrome (obesity, dyslipidemis, diabetes)
- Manifestations of end-organ damage at diagnosis
- Smoking

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Authoritative guidelines

- JNC (Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure
- American Society of Hypertension
- European Society of Hypertension in conjunction with European Society of Cardiology
- World Health Organization in conjunction with International Society of Hypertension

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Classification of hypertension

Classification	Systolic pressure		Diastolic pressure	
	mmHg	kPa	mmHg	kPa
Normal	90–119	12–15.9	60–79	8.0–10.5
Prehypertension	120–139	16.0–18.5	80–89	10.7–11.9
Stage 1	140–159	18.7–21.2	90–99	12.0–13.2
Stage 2	≥160	≥21.3	≥100	≥13.3
Isolated systolic hypertension	≥140	≥18.7	<90	<12.0

Chobanian AV, Bakris GL, Black HR et al.: Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 2003, 42(6):1206–52

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Hypertension

- Sustained arterial HT **damages** blood vessels in kidney, heart, and brain
- It leads to increased **incidence** of renal failure, coronary disease, cardiac failure, and stroke

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Etiology

- HT is a combination of several abnormalities (i.e. ANS, baroreceptor reflexes, RAA system, kidneys)
- Genetics, psychological stress, environmental and dietary factors contribute to the development of HT
- Heritability is 30%
- Variations of genes for angiotensinogen, ACE, ß-Rp contribute to essential HT

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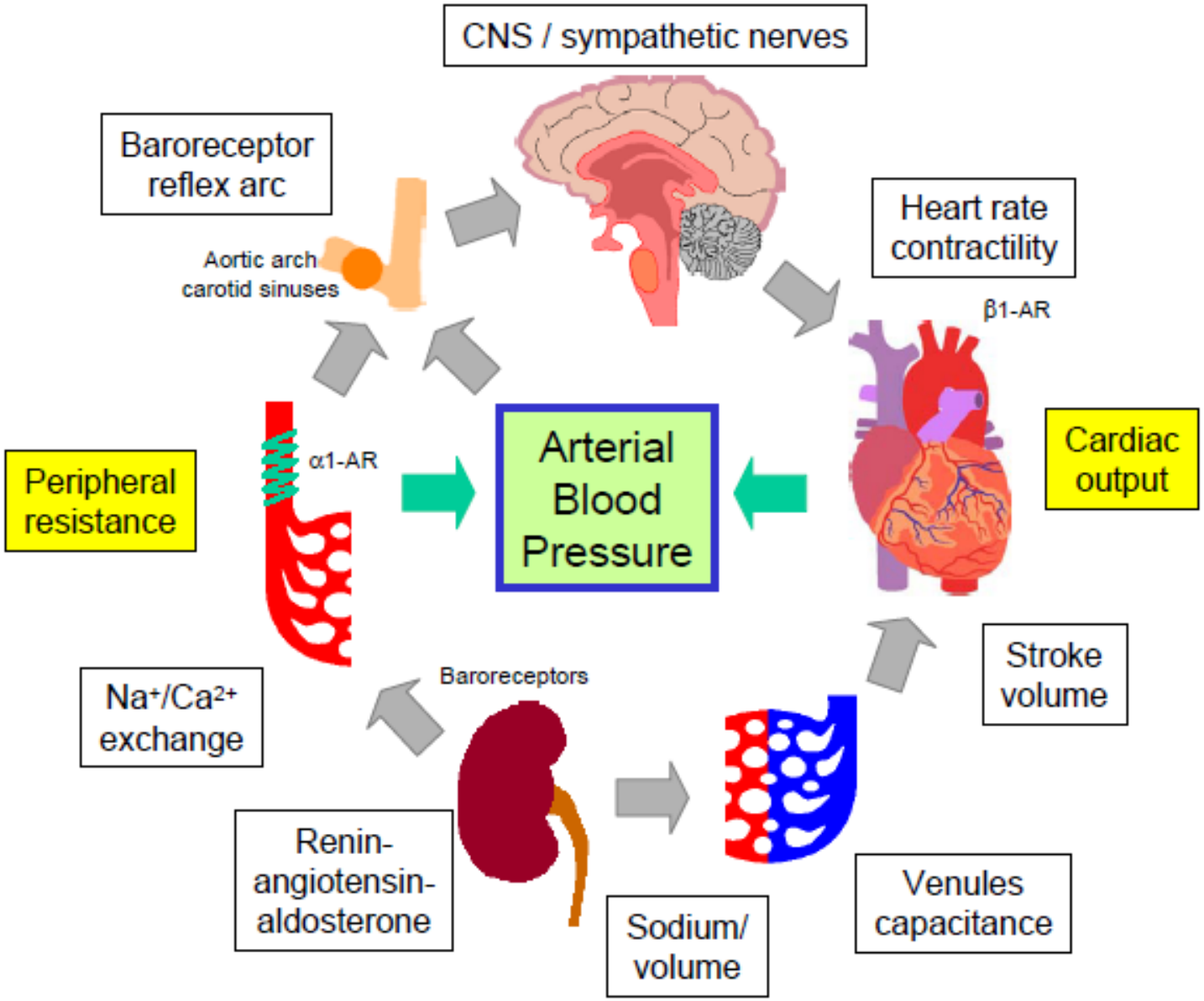
BP = CO × PVR



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Regulation of blood pressure

- Baroreflexes are mediated by autonomic nerves and act in coordination with humoral mechanisms (i.e. RAA system)

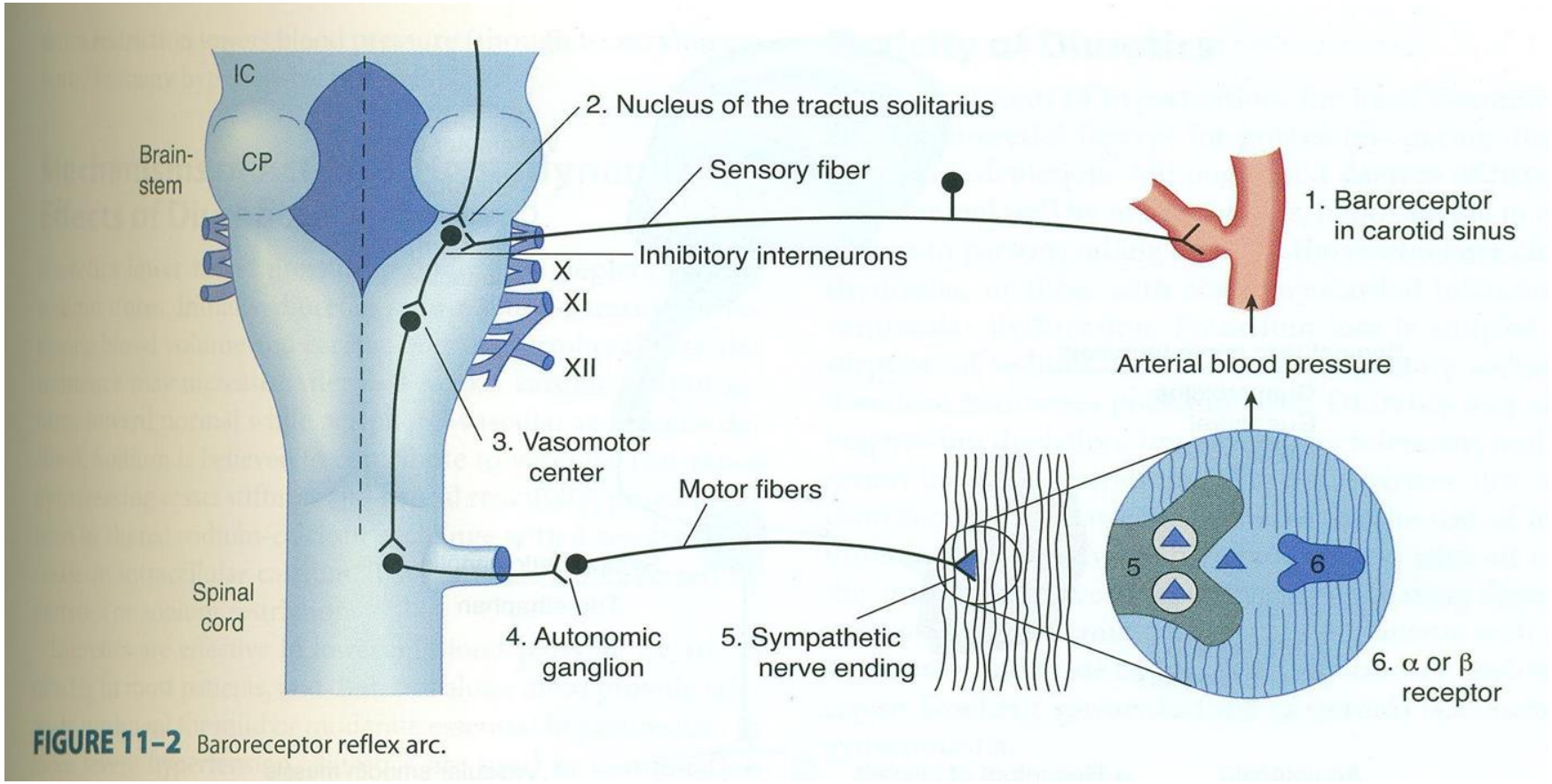

FIGURE 11–2 Baroreceptor reflex arc.

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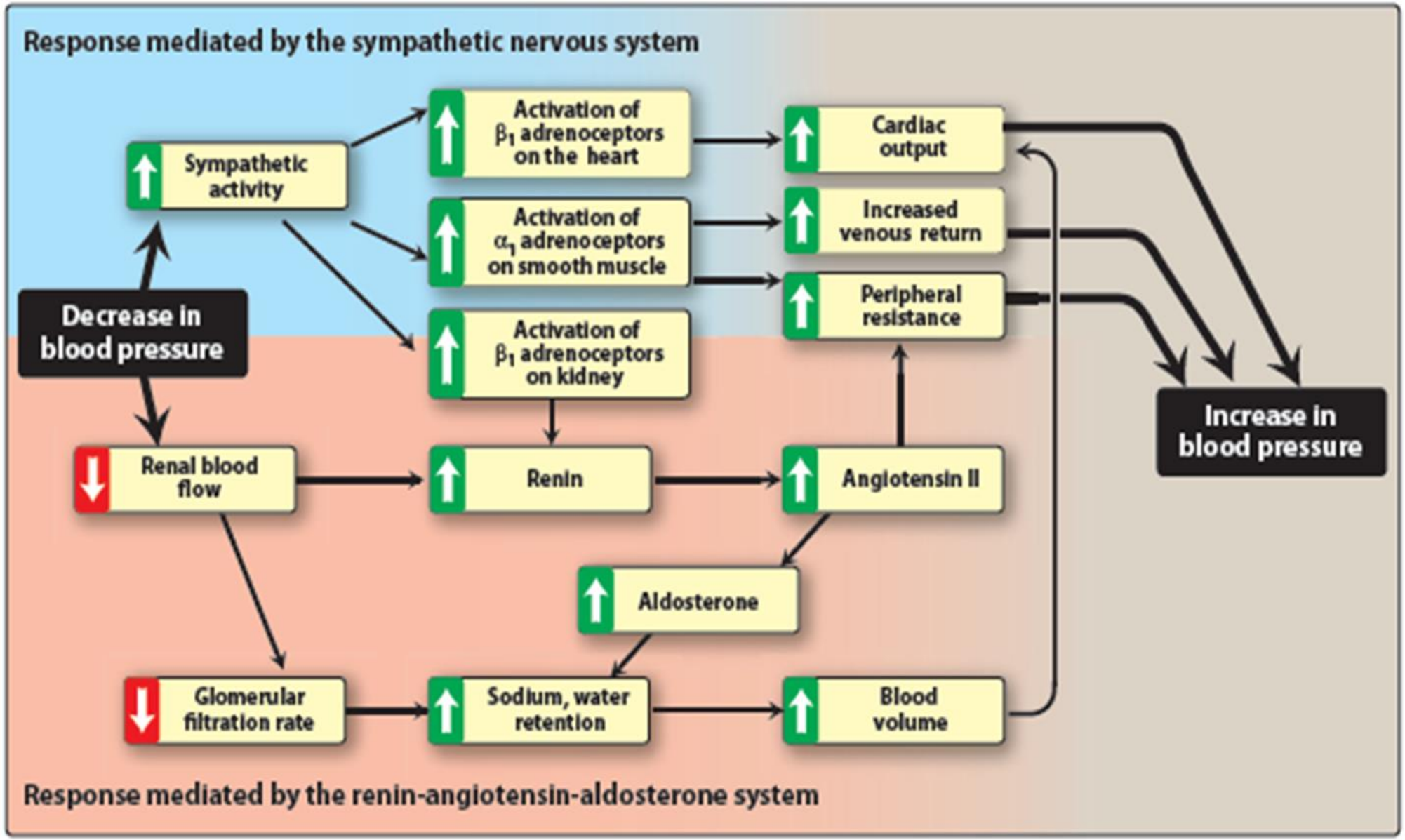

Figure 19.4
Response of the autonomic nervous system and the renin-angiotensin-aldosterone system to a decrease in blood pressure.

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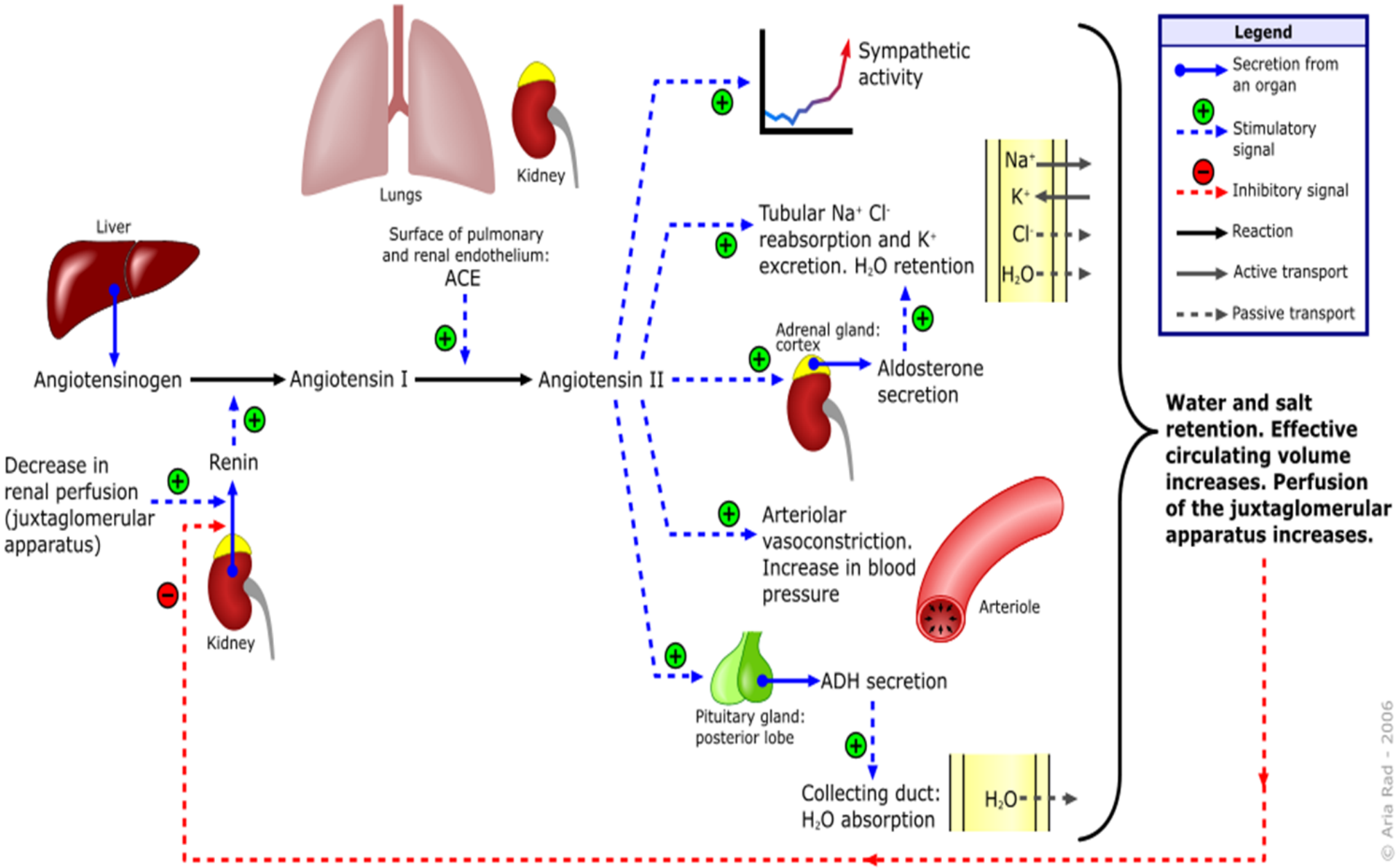
Renin-angiotensin-aldosterone system



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Regulation of blood pressure

- BP control is similar in hypertensive and healthy individuals

- Difference: Baroreceptors and renal volume-pressure control system appears to be „set“ at a higher level of blood pressure in hypertensive patients

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Types and etiology of hypertension

- White coat HT
- Secondary HT: due to specific organ pathology
  - renal artery stenosis
  - pheochromocytoma
  - aortic coarctation
  - adrenal tumor
- Essential HT
  - cause NOT known

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Treatment of hypertension

- Primary HT is treated with drugs that:

1) reduce blood volume (which reduces central venous pressure and cardiac output)
2) reduce systemic vascular resistance
3) reduce cardiac output by depressing heart rate and stroke volume

- Secondary HT is best treated by controlling or removing the underlying disease or pathology (although AHD may still be required)

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Strategies to lower blood pressure

- Diuretics: deplete Na^+ and reduce blood volume (+ other mechanisms)
- Sympathoplegic drugs: reduce PVR, inhibit cardiac function
- Vasodilators: relax vascular smooth muscle
- Drugs that block angiotensin function and/or production: reduce PVR and blood volume

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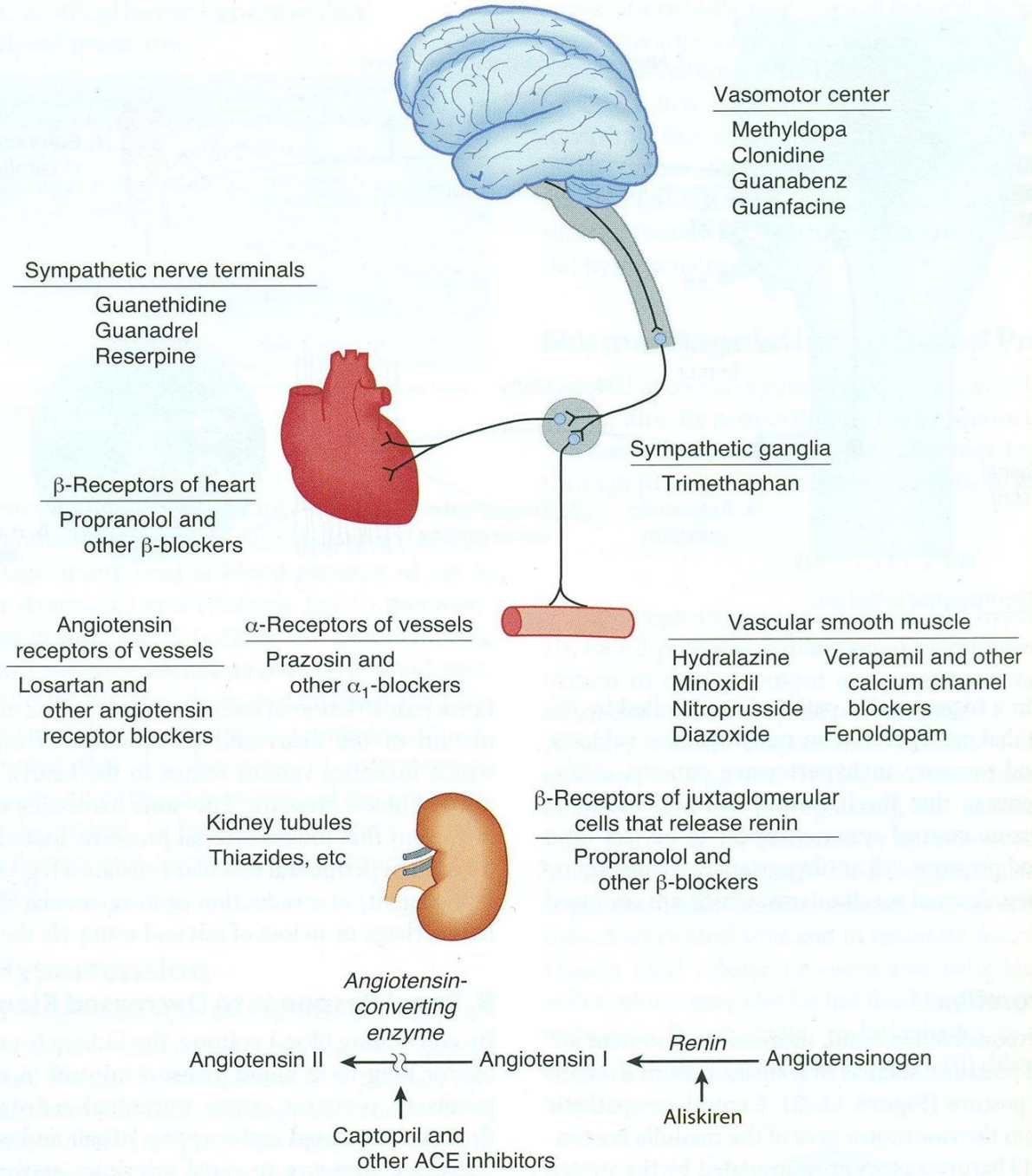

FIGURE 11–3 Sites of action of the major classes of antihypertensive drugs.

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Classes of Antihypertensive Drugs

– Diuretics
- thiazide diuretics
- loop diuretics
- K^+ sparing diuretics

– Vasodilators
- direct acting arterial dilators
- Ca^{2+} channel blockers
- α_1-blockers
- angiotensin converting enzyme inhibitors (ACE-I)
- angiotensin receptor blockers (ARBs)
- renin inhibitors

– Cardioinhibitory Drugs
- β-blockers
- Ca^{2+} channel blockers

– Centrally-acting adrenergic drugs
- α_2-agonists
- I_2-agonists

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Diuretics

- First-line drugs for HT. Relatively safe and effective. Suitable for older adults
- Lower BP by depleting body Na^+ stores
- Effects take 2 stages:

1) reduction of total blood volume and therefore cardiac output; initially causes increase of PVR
2) when CO returns to normal level (6-8 weeks), PVR declines

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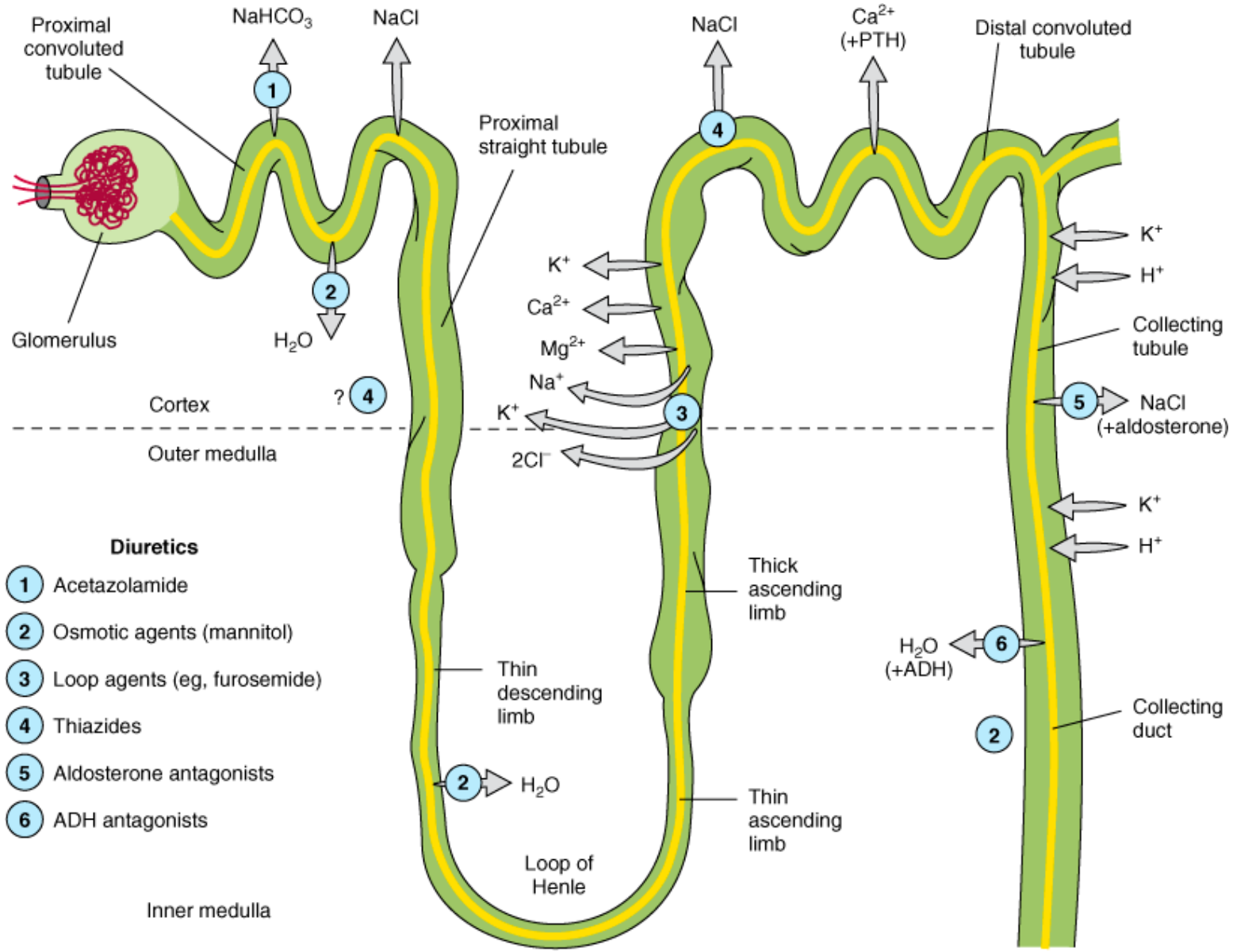
Diuretics Sites of Action



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition*: http://www.accessmedicine.com

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Thiazides

- **MoA**:
  - act in the distal tubule to decrease Na^+ reabsorption (inhibit Na^+/Cl^- symport)
- As a result of decreased Na^+ and Cl^- reabsorption, hyperosmolar diuresis follows
- Delivery of more Na^+ to the distal tubule results in K^+ loss by an exchange mechanism

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Thiazides

- Hydrochlorothiazide
- Chlorthalidone
- Chlorothiazide
- Indapamide
- Metipamide

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Loop diuretics

- **MoA**:
  - act primarily at the ascending limb of the loop of Henle
- Effectiveness is related to their site of action because reabsorption of about 30 - 40% of filtered Na^+ and Cl^- load occurs at the ascending loop

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Loop diuretics

- Furosemide
- Torasemide
- Ethacrynic acid

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Potassium sparing diuretics

- Enhance the natriuretic effects of other diuretics
- Counteract the K^+-depleting effect of these diuretics

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Potassium sparing diuretics

- Amiloride
- Spironolactone
- Triamterene

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Diuretics

- **SE**:
  - Depletion of K^+ (except K^+sparing diuretics), leading to hypokalemia
  - Increase uric acid conc. and precipitate (gout)
  - Increase serum lipid conc.
  - Impair glucose utilization

- NOT suitable for treatment of HT in patients with hyperlipidemia or DM

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β-blockers

- **MoA**:
  - Reduce cardiac output
  - Inhibit renin release and AT-II and aldosterone production, and lower peripheral resistance
  - Decrease adrenergic outflow from CNS
- Decrease BP by decreasing myocardial contractility (neg. inotropism) and decreasing HR (neg. chronotropism)

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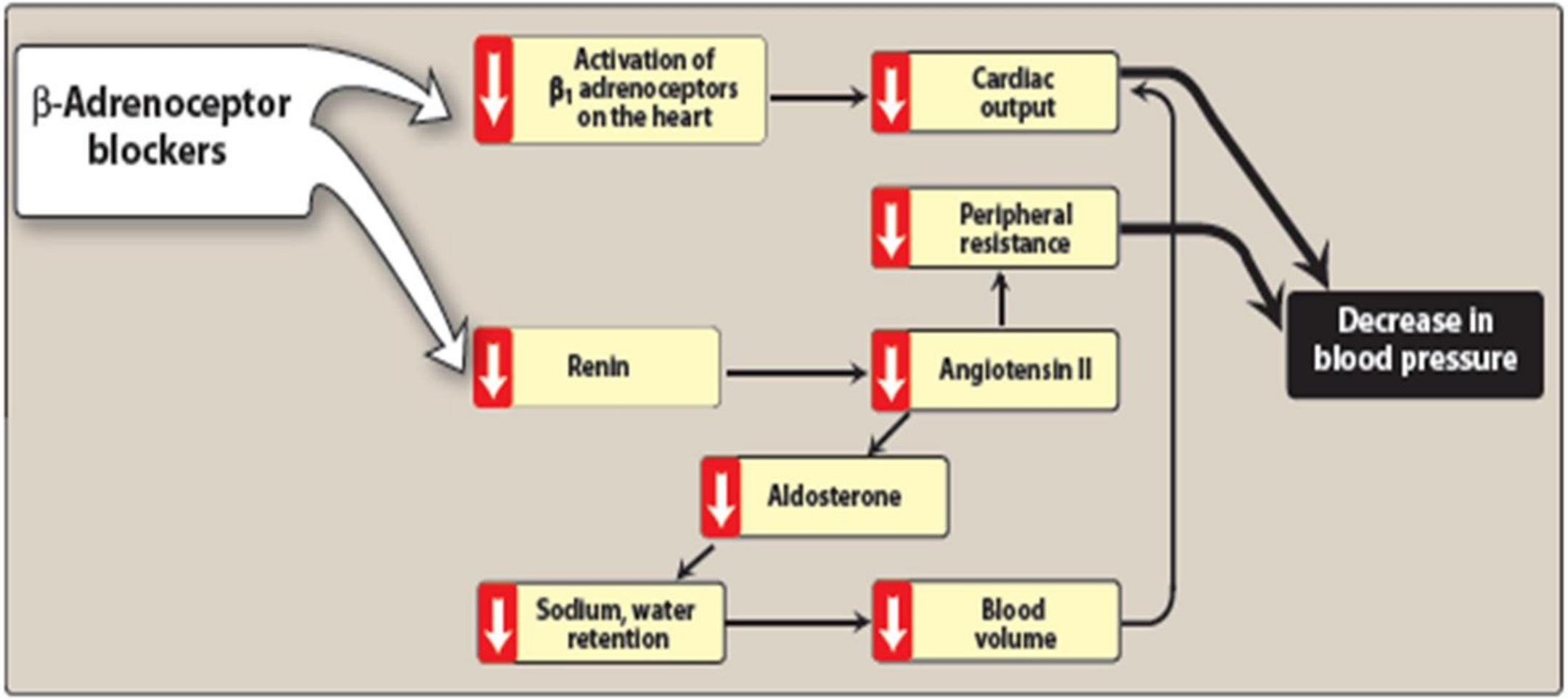

Lippincott's Pharmacology

Figure 19.9
Actions of β–adrenoceptor blocking agents.

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Classes of β-blockers

– Non-selective β_1/β_2:

- propranolol, nadolol
- with ISA: pindolol (ISA), penbutolol (ISA), labetalol (ISA), carteolol (ISA)
- carvedilol (+ α_1-blocker)

– Cardioselective (β_1-selective):

- atenolol, betaxolol, bisoprolol, metoprolol, acebutolol (ISA)

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	Clinical Uses					
Class/Drug	**HTN**	**Angina**	**Arrhy**	**MI**	**CHF**	**Comments**
Non-selective β_1/β_2						
carteolol	X					ISA; long acting; also used for glaucoma
carvedilol	X				X	α-blocking activity
labetalol	X	X				ISA; α-blocking activity
nadolol	X	X	X	X		long acting
penbutolol	X	X				ISA
pindolol	X	X				ISA; MSA
propranolol	X	X	X	X		MSA; prototypical beta-blocker
sotalol			X			several other significant mechanisms
timolol	X	X	X	X		primarily used for glaucoma
β_1-selective						
acebutolol	X	X	X			ISA
atenolol	X	X	X	X		
betaxolol	X	X	X			MSA
bisoprolol	X	X	X			
esmolol	X		X			ultra short acting; intra or postoperative HTN
metoprolol	X	X	X	X	X	MSA
nebivolol	X					relatively selective in most patients; vasodilating (NO release)

Abbreviations: HTN, hypertension; Arrhy, arrhythmias; MI, myocardial infarction; CHF, congestive heart failure; ISA,

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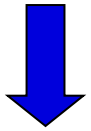
Side effects of β-blockers

- Bradycardia, bronchospasm, masking of hypoglycemia, sedation
- GLU intolerance may develop or be worsened
- Increased blood TG levels and decreased levels of HDL-chol
- Rebound HT following sudden discontinuation of β-blockade



NOT suitable for patients with: DM, AB, COPD, hyperlipidemia, bradycardia

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Ca^{2+} channel blockers

- **MoA:**
  - block voltage-gated L-type Ca2+ channels in cardiac muscle & blood vessels
- Dihydropyridines: nifedipine, amlodipine, felodipine, isradipine, nicardipine, lacidipine, nitrendipine, nimodipine (CNS)
- **I:** mild to moderate HT, angina pectoris, limb ischemia
- **SE:** flushing, headache, excessive hypotension, edema, reflex tachycardia

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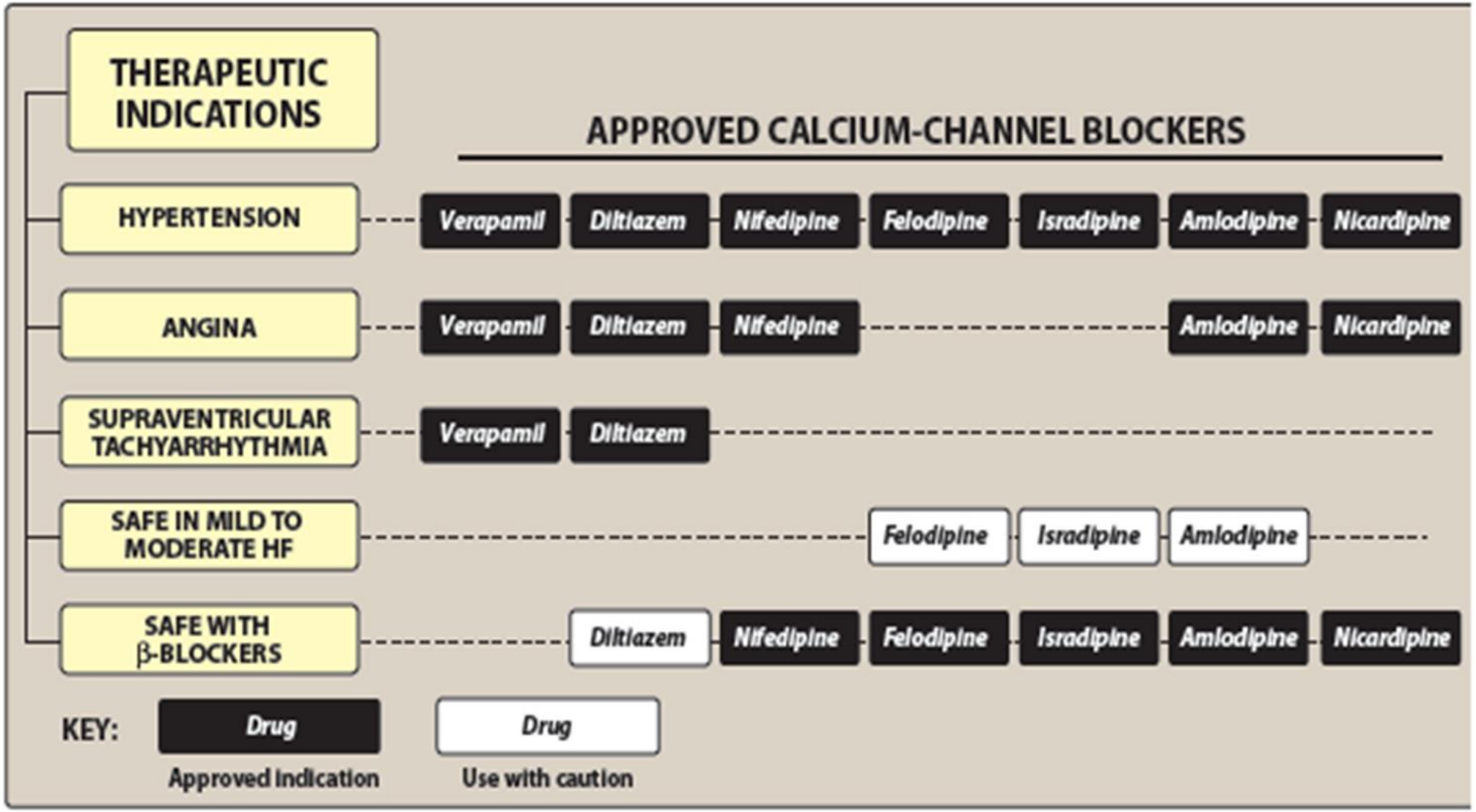

Figure 19.14
Some therapeutic applications of calcium-channel blockers. HF = heart failure.

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Direct vasodilators

- **MoA**:
  - relax smooth muscle of arterioles (and sometimes veins), thereby reduce systemic vascular resistance
- Hydralazine
- Minoxidil
- Sodium nitroprusside
- Diazoxide
- **SE**: tachycardia, palpitation, AP

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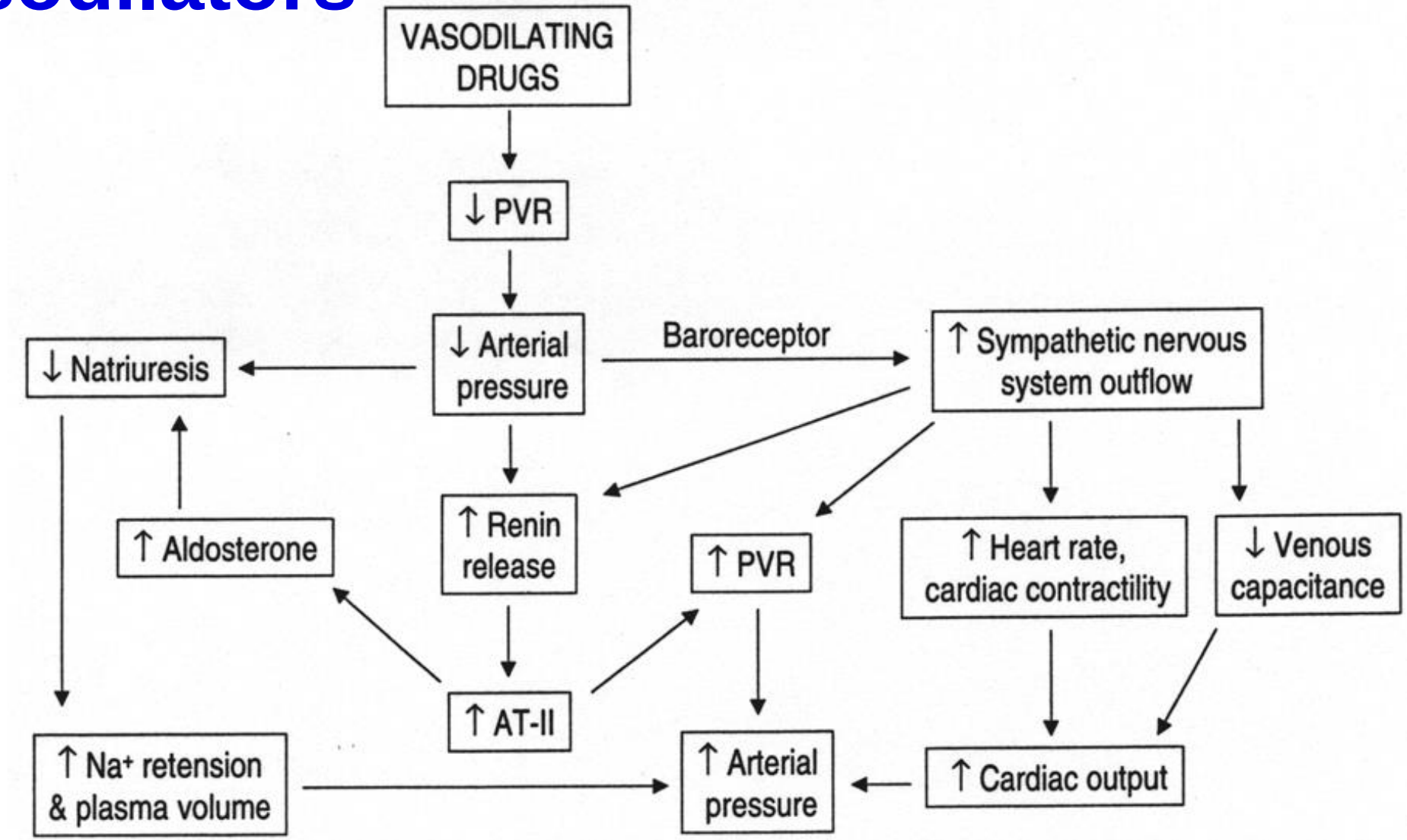
Compensatory responses of direct vasodilators



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α_1-blockers

- prazosin, terazosin, doxazosin, metazosin
- **MoA**:
  - competitive antagonists for α_1-AR → relaxation of both arterial and venous smooth muscles and thereby reduces PVR
- **I**: mild to moderate HT, could be used also in BPH
- **SE**: 1st dose syncope and reflex tachycardia, postural hypotension and often retention of salt and H_2O

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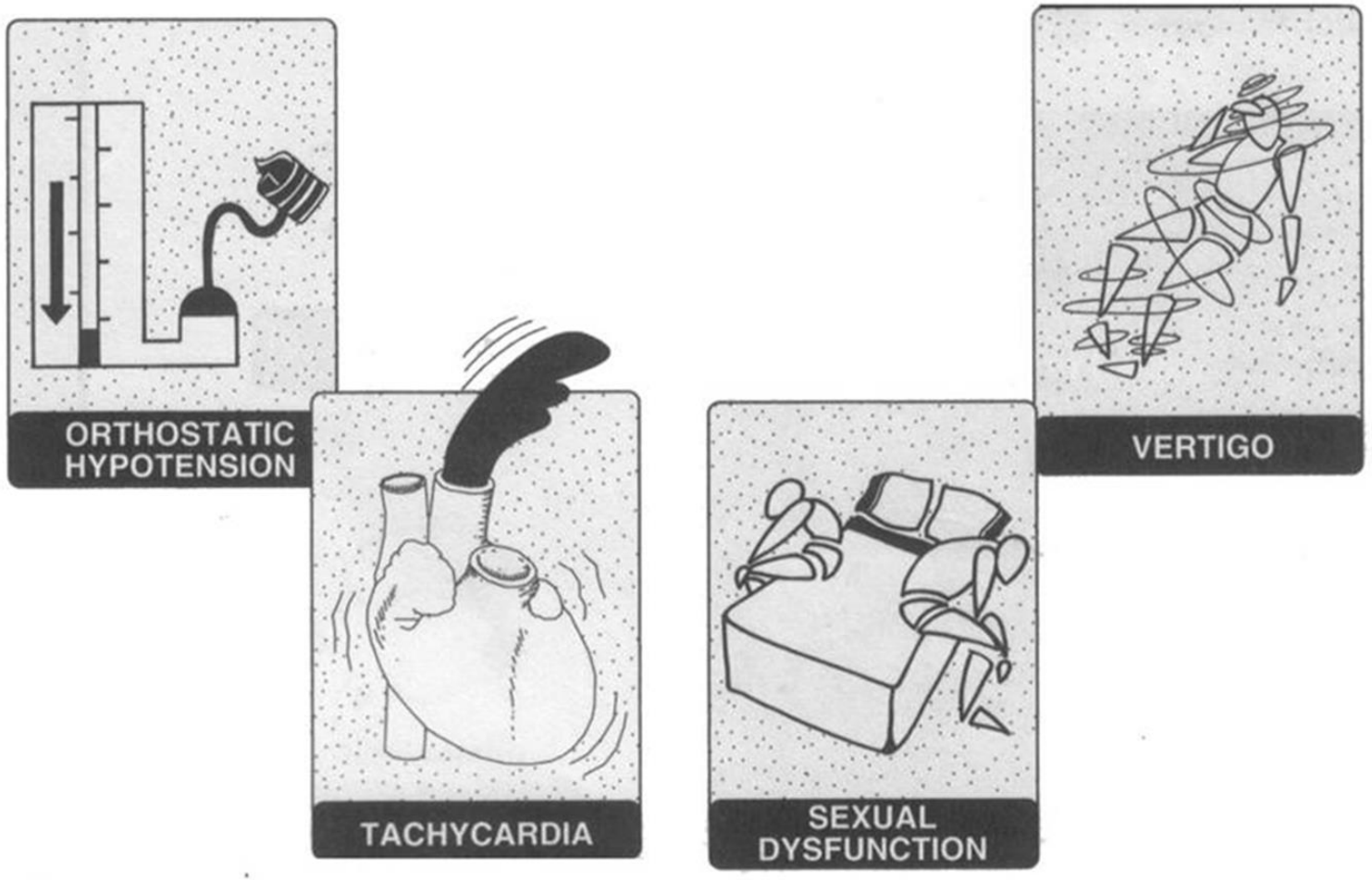
Common adverse effects of α_1- blockers



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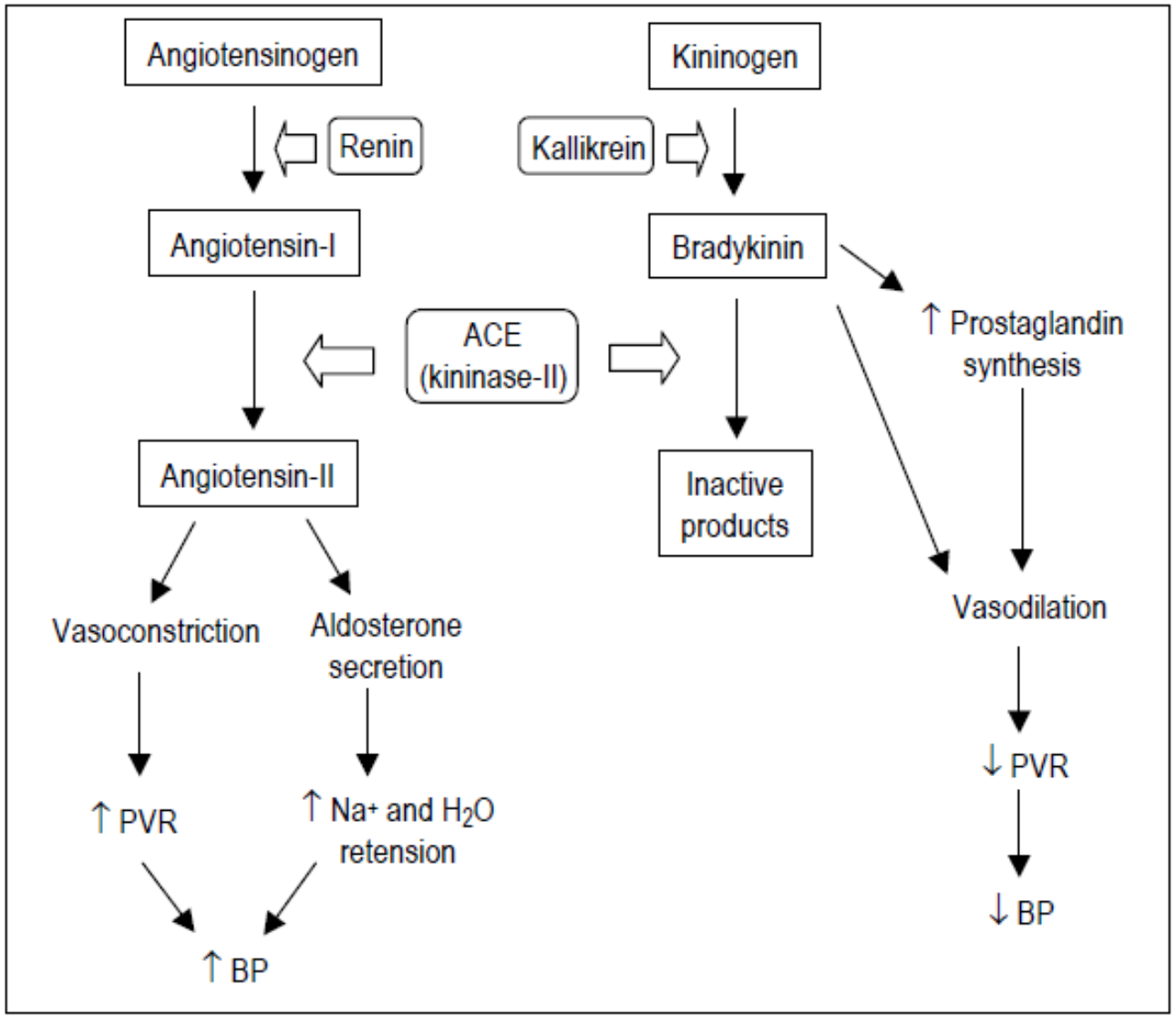
ACE inhibitors and angiotensin II receptor antagonists



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ACE inhibitors and angiotensin II receptor antagonists

- **ACE inhibitors:**

  captopril, enalapril, ramipril, perindopril, lisinopril, benazepril, fosinopril, etc.

- **Angiotensin II antagonists on AT1 receptor:**

  losartan, valsartan, candesartan, irbesartan, telmisartan, eprosartan, zolasartan

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ACE inhibitors and angiotensin II receptor antagonists

– Side effects and toxicity:

- In hypovolemic patients, severe hypotension may occur after initial doses
- Fetotoxic (teratogenic) and should not be used in pregnant women
- Other adverse effects: angioedema (rare), dry cough (ACE-I), rashes, proteinuria, hyperkalemia

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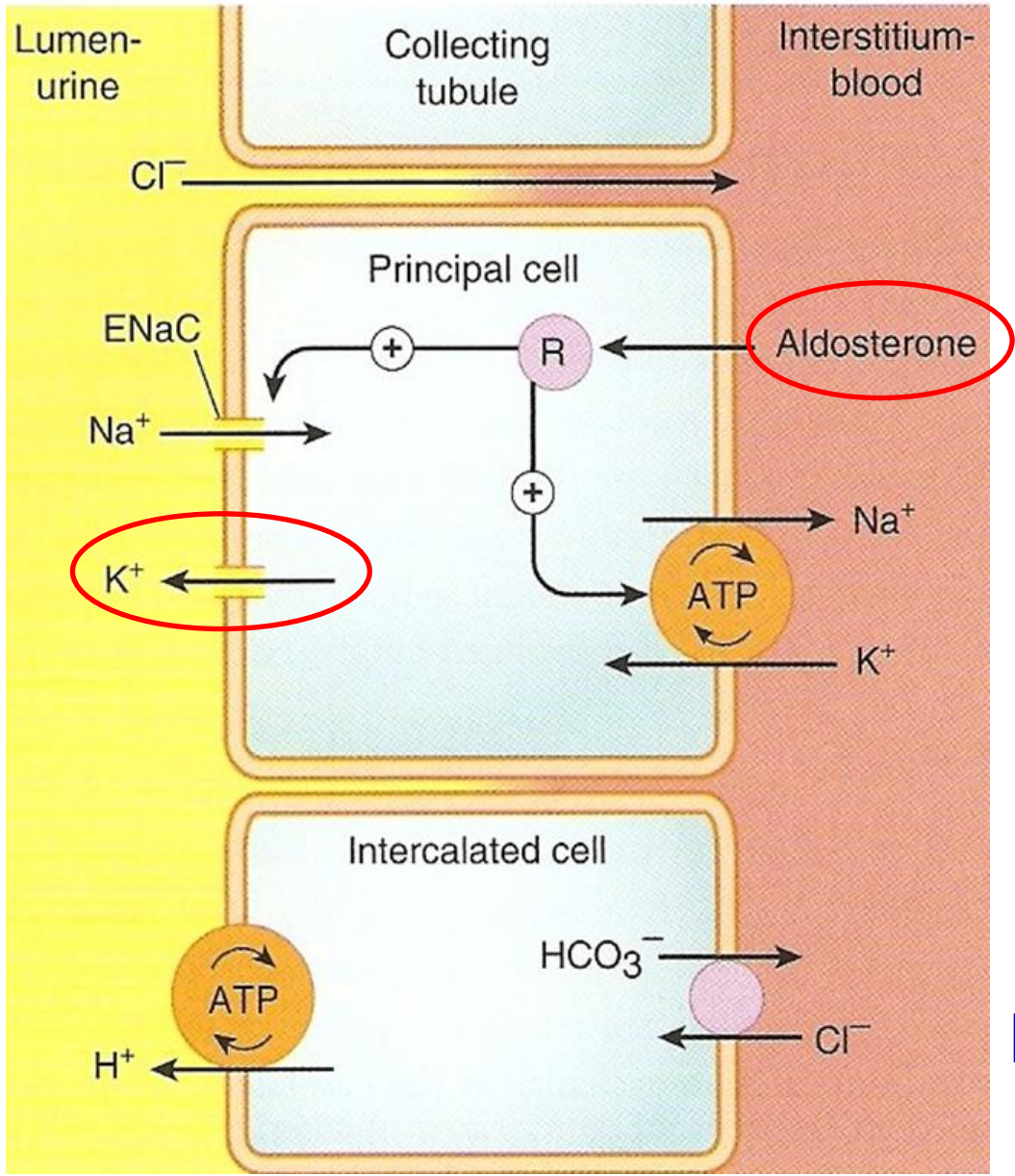
Hyperkalemia

- Decrease in aldosterone results in K^+ retention



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Renin inhibitors

- aliskiren (Rasilez®, Riprazo®, Sprimeo®)
- **MoA**:
  - direct renin inhibitor decreases renin plasma activity by 50-70%

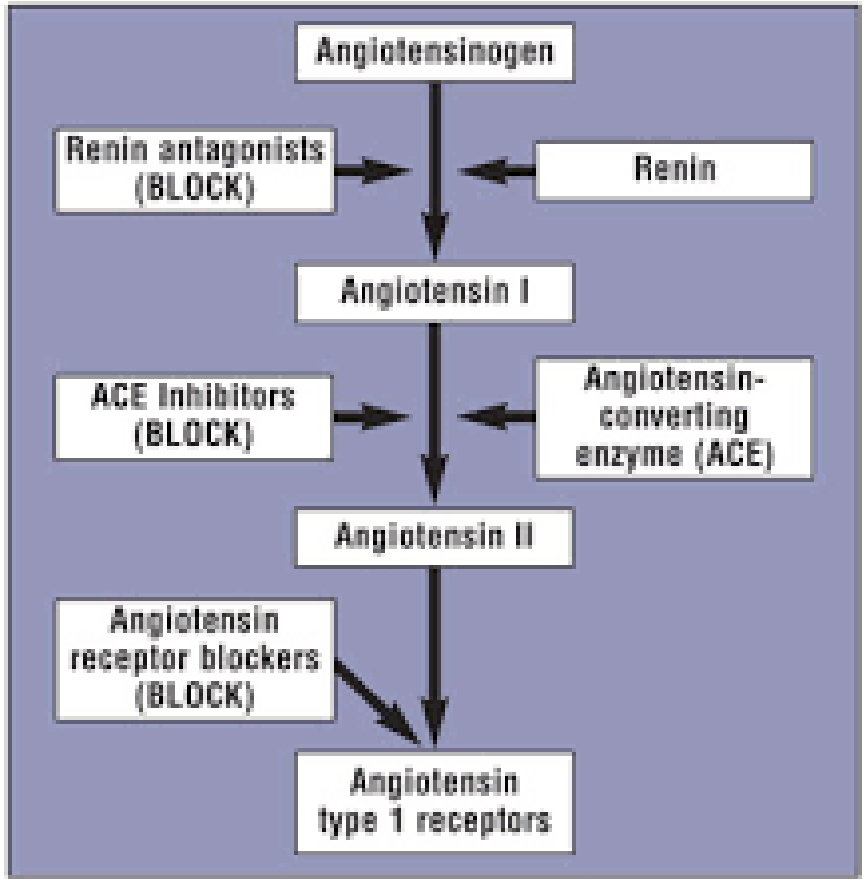

Figure 1. Renin-angiotensin system and medications that affect it.

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Aliskiren in therapy

- Administration: 1 daily dose of 150-300mg
- **I:** monotherapy or combination with RAA inhibitors

  (aditive effect by 20-30%) in HT patients
- **SE:** diarrhea, up to 300mg no serious SE

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Centrally-acting adrenergic drugs

– I_2-agonists
- rilmenidine
- moxonidine

MoA: imidazoline I_1-receptor agonist in the CNS (medulla oblongata), decrease sympathetic activity, improve INS resistance and GLU tolerance

– α_2-agonists
- clonidine
- α-methyldopa

MoA: α_2-agonistic activity contributes to its BP-lowering effect due to negative feedback at the presynaptic neurons

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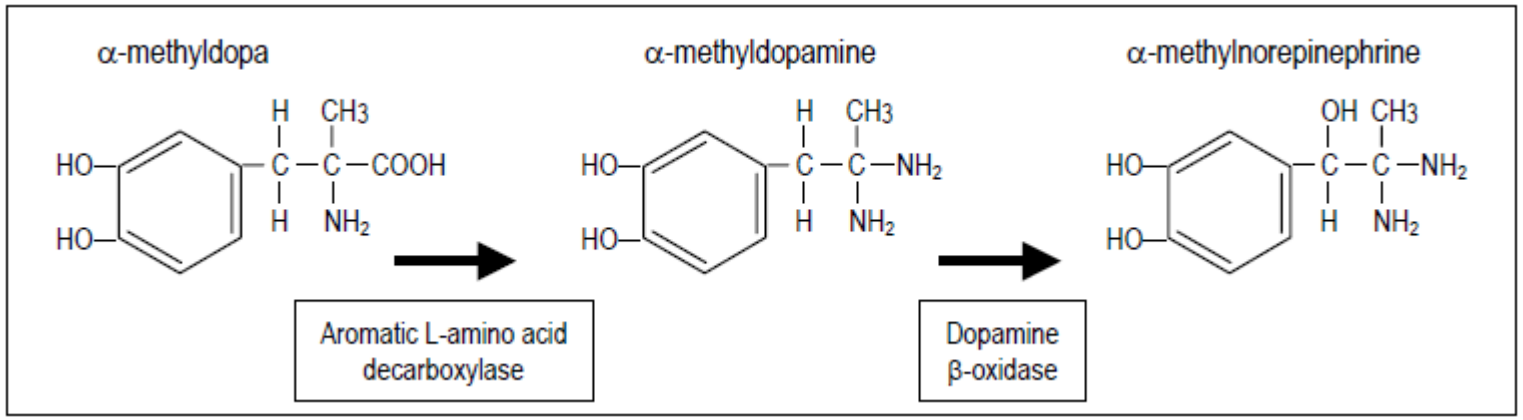
α_2-agonists

α-methyldopa = prodrug



- **SE:** Sedation, rebound phenomena and mental depression (clonidine), lactation and autoimmune reaction (α-MD)
- **I:** α-MD is drug of choice for HT in pregnancy

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Thank you
for your attention

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