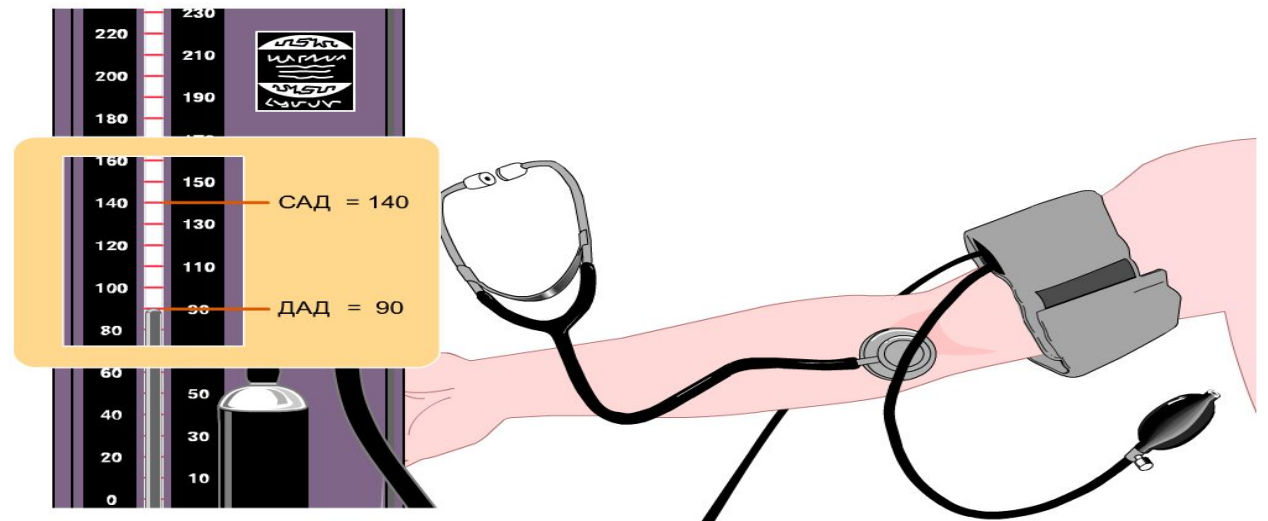
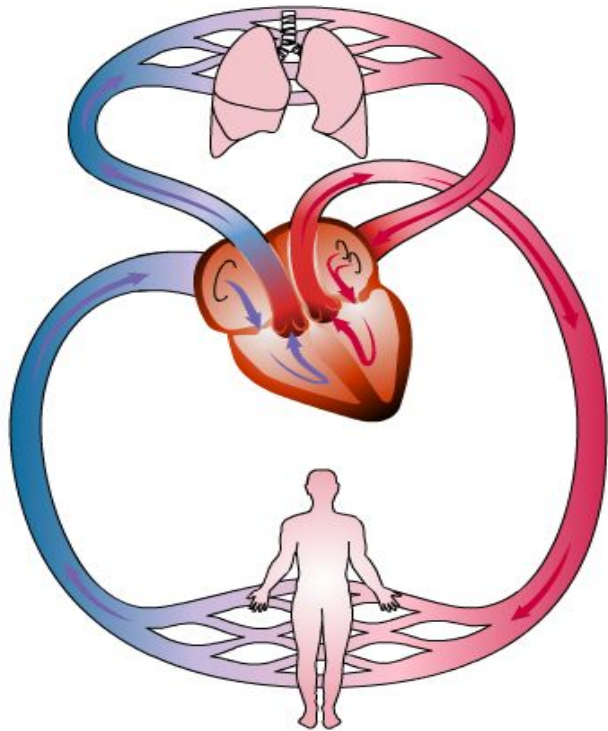


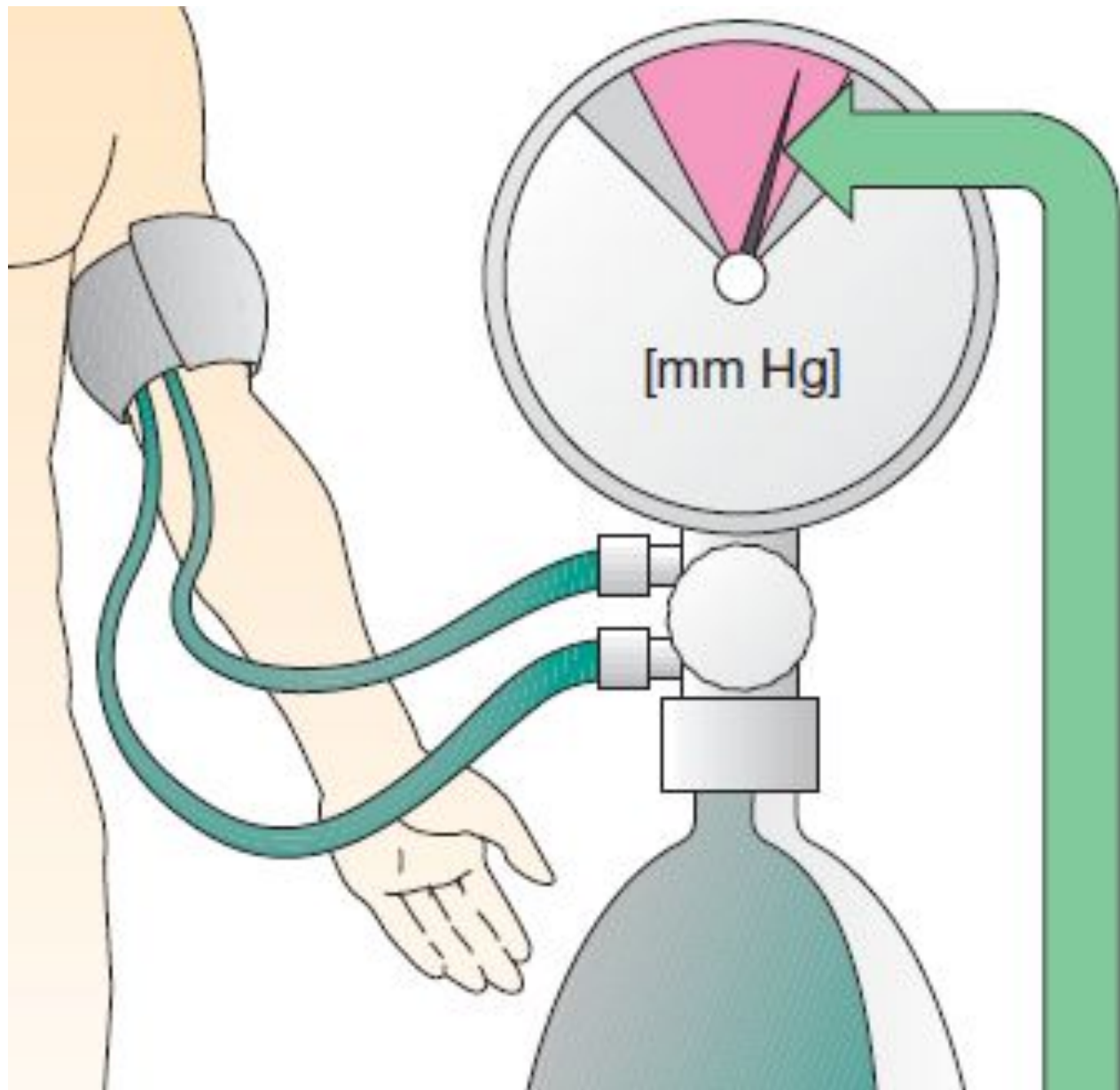
ANTIHYPERTENSIVE DRUGS

HYPOTENSIVE DRUGS



- **Antihypertensive drugs** decrease systemic arterial blood pressure. They are mostly used for the treatment of arterial hypertension.
- The level of arterial blood pressure depends on many factors such as cardiac workload, peripheral vessel tone, volume and electrolytic content of the circulating blood.
- The vascular tone is regulated by the sympathetic nervous system and a great number of vasoactive substances produced by the organism.

- Among vasoconstrictors there are such substances as epinephrine, angiotensin II, vasopressin (ADH), norepinephrine, prostaglandin $F_{2\alpha}$, thromboxane, endothelin.
- There are vasodilators such as acetylcholine, bradykinin, histamine, natriuretic peptide, nitric oxide (NO) or endothelial relaxing factor, prostacyclin, purines (adenosin, ATP).
- An increase in muscle tone is a result of an increase in intracellular calcium ion content also.



Hypertension

Systolic: blood pressure > 160 mmHg

Diastolic: blood pressure > 96 mmHg

Secondary diseases:

Heart failure

Coronary atherosclerosis

angina pectoris, myocardial
infarction, arrhythmia

Atherosclerosis of cerebral vessels

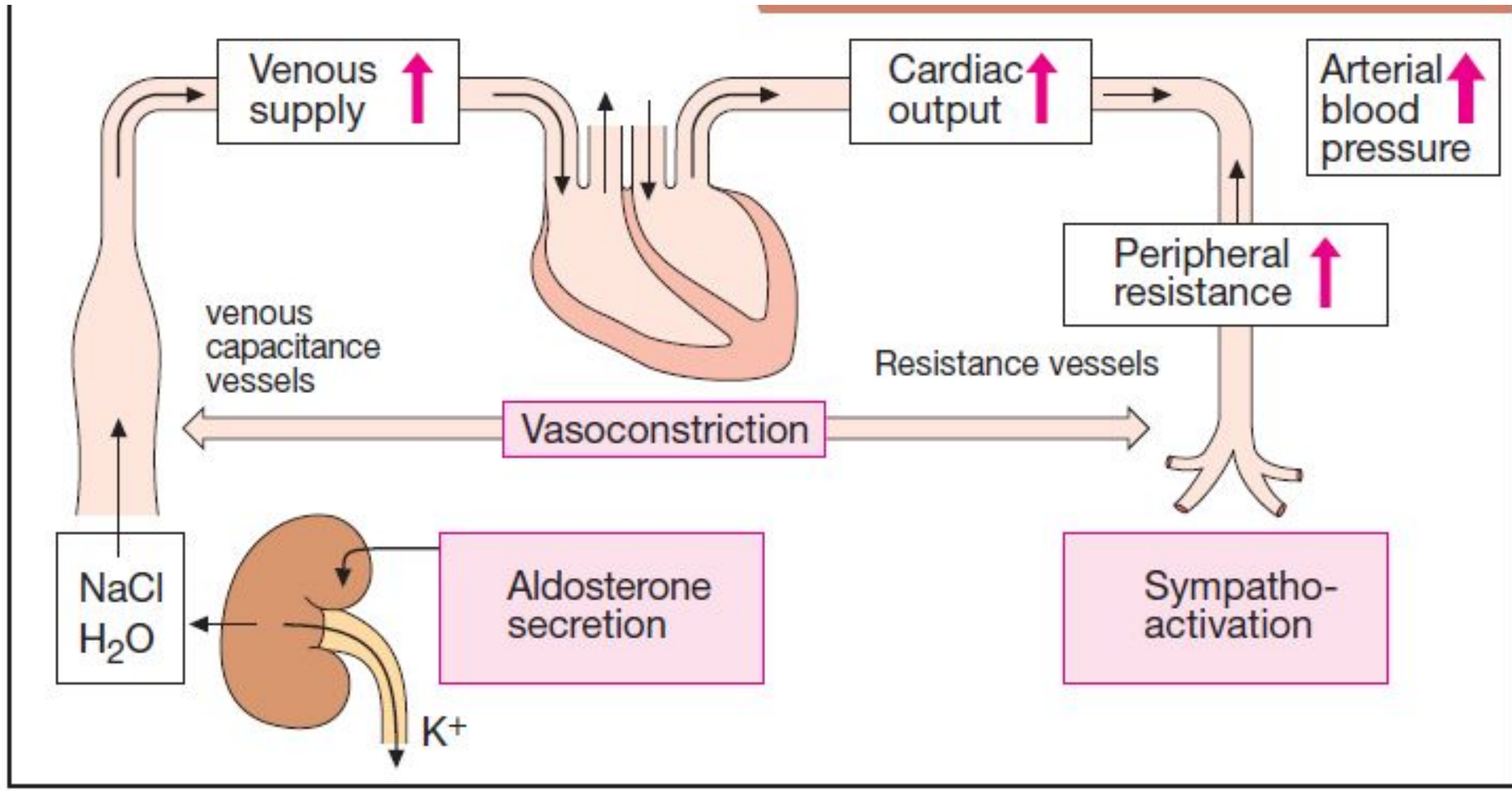
cerebral infarction > stroke

Cerebral hemorrhage

Atherosclerosis of renal vessels

renal failure

Decreased life expectancy



- The effect of antihypertensive drugs may be directed at different parts of the physiological system regulating arterial blood pressure.
- Neurotropic agents can suppress both vasomotor centers and peripheral parts of the adrenergic (sympathetic) system: ganglia, postganglionic fibres terminals, adrenoreceptors.
- Peripheral vascular resistance can be decreased by the influencing on the vascular smooth muscles (drugs affecting ion channels, drugs releasing NO, myotropic spasmolytics).
- One of the possible ways to decrease arterial blood pressure is to decrease circulating blood volume and to change its electrolyte content.

1. Drugs reducing the stimulating effect of adrenergic innervation on the cardiovascular system (neurotropic effect)
 - Drugs decreasing the tone of the vasomotor centers:
clonidin, methyldopa, moxonidine.
 - Drugs blocking autonomic ganglia
 - Sympatholytics
 - Drugs blocking adrenoreceptors

2. Drugs affecting systemic humoral regulation of arterial blood pressure (affecting renin-angiotensin system)

❖ Renin blockers: **aliskiren**

❖ Angiotensin II synthesis inhibitors (inhibitors of angiotensin-converting enzyme): **enalapril, captopril, lisinopril, phosinopril, trandolapril.**

❖ Angiotensin receptors blockers (AT1): **losartan, valsartan, irbesartan, telmisartan.**

3. Drugs of myoptropic action (myotropic drugs)

A. Drugs affecting ion channels:

- ❑ Calcium channels blockers: **phenigidine, amlodipine, diltiazem**
- ❑ Potassium channels activators: **minoxidil, diazoxide**

B. Nitric oxide donors (NO): **nitroprussid sodium**

C. Other drugs: **apressin, dibazolium, magnesium sulphate**

4. Drugs affecting water and electrolyte balance (diuretics): **hydrochlothiazide, furosemide, spironolactone**

Initial monotherapy with one of the five drug groups

Drug selection according to conditions and needs of the individual patient

Diuretics

β -blockers

ACE inhibitors
AT₁-antagonists

Ca-antagonists

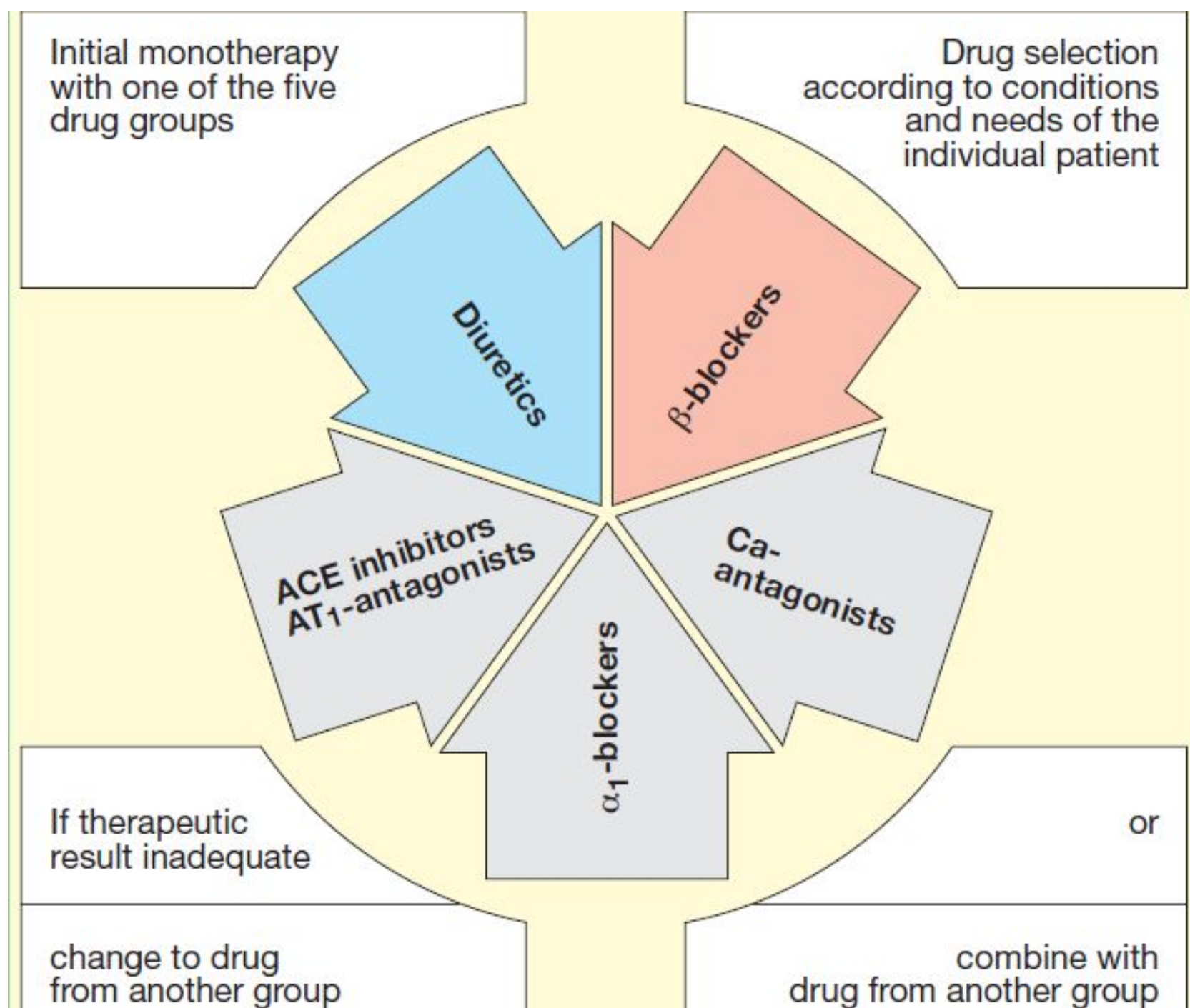
α_1 -blockers

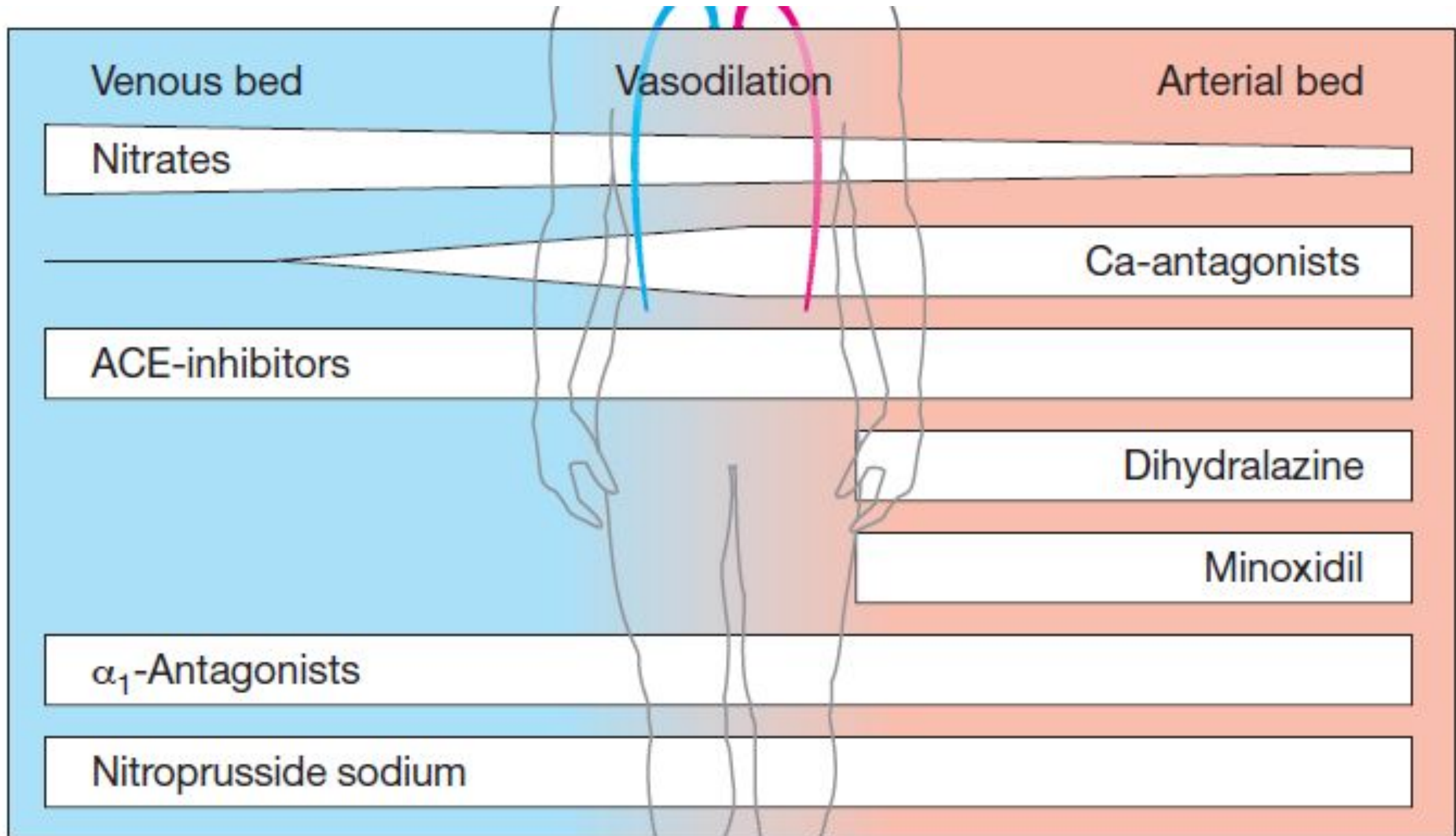
If therapeutic result inadequate

or

change to drug from another group

combine with drug from another group





Venous bed

Vasodilation

Arterial bed

Nitrates

Ca-antagonists

ACE-inhibitors

Dihydralazine

Minoxidil

α_1 -Antagonists

Nitroprusside sodium

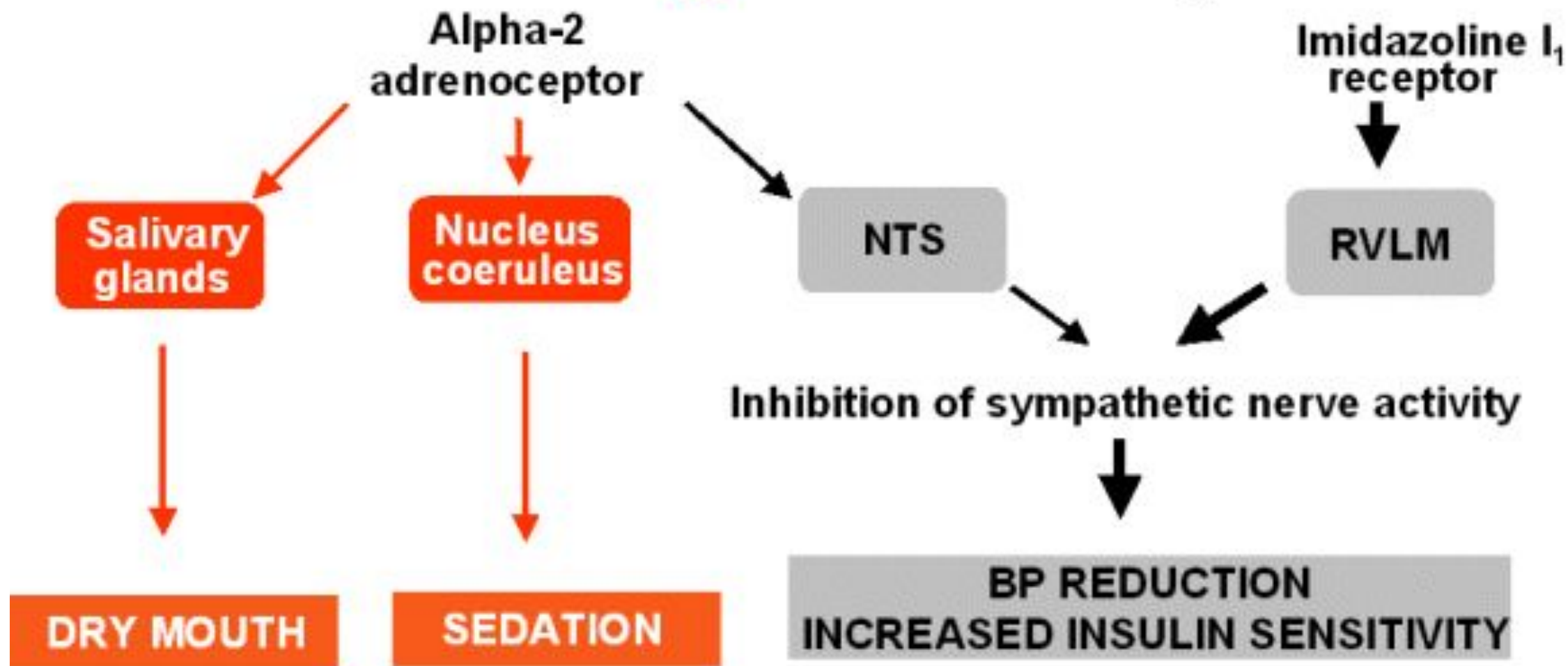
- ❑ **Clonidin** stimulates α_2 -adrenoreceptors and imidazoline I_1 -receptors of the solitary tract nucleus neurons in the medulla oblongata. This leads to the suppression of the vasomotor center neurons of the medulla oblongata and a reduction in the sympathetic tone. At the same time the vagal tone increases.
- ❑ Marked and stable hypotension is associated with a decrease in cardiac work and general peripheral vascular resistance. The release of renin also decreases.
- ❑ Stimulating peripheral presynaptic α_2 - adrenoreceptors clonidin decreases the release of norepinephrine from varicosities.

- Clonidin is used for the treatment of hypertensive disease and hypertensive crises. It is administered orally and parenterally. Hypotensive effect develops in 5 min after sublingual administration, in 2 h – after oral. The duration of the effect is usually 6-12 h.
- Clonidin can increase blood pressure after fast intravenous administration. It has sedative and analgesic effects also.
- Clonidine enhances the effects of hypnotic drugs, general anesthetics, ethanol. It increases appetite, decreases secretory activity of the salivary glands (mouth dryness), stomach glands. It can cause constipation, retention of water and ions in the organism.
- Its' using should be abolished off gradually to avoid “rebound” syndrome (hypertensive crisis, sleeplessness).

- ❑ **Moxonidine** is a predominant agonist of imidazoline I₁-receptors.
- ❑ It has marked hypotensive activity. It decreases arterial blood pressure due to a reduction in peripheral resistance, a decrease in renin production and cardiac work. Moxonidine does not have the sedative effect.
- ❑ Moxonidine is used for the treatment of hypertensive disease. It is usually taken once a day.
- ❑ The main adverse effect is dryness of the mouth.

Relative Selectivity I1/Alpha-2

Moxonidine	33
Clonidine	4
Guanabenz	1



- ❑ **Methyldopa** is metabolized into α -methylnorepinephrin, which stimulates α_2 adrenoreceptors in the CNS and suppresses the activity of neurons regulating the level of arterial blood pressure. It decreases peripheral vascular resistance. The drug has sedative effect.
- ❑ The drug is administered orally or intravenously. The effect develops slowly.
- ❑ Adverse effects: depression, parkinsonism, dyspeptic disturbances, dryness in the mouth, sodium and water retention, skin rash, impotence, agranulocytosis, thrombocytopenia, hemolytic anemia.

B-adrenoblockers

They decrease cardiac output, because they block receptors of the heart.

They decrease peripheral vascular resistance because they suppress presynaptic β_2 AR and eliminate norepinephrine release. They also reduce renin production.

Their hypotensive effect is associated with the depression of the CNS.

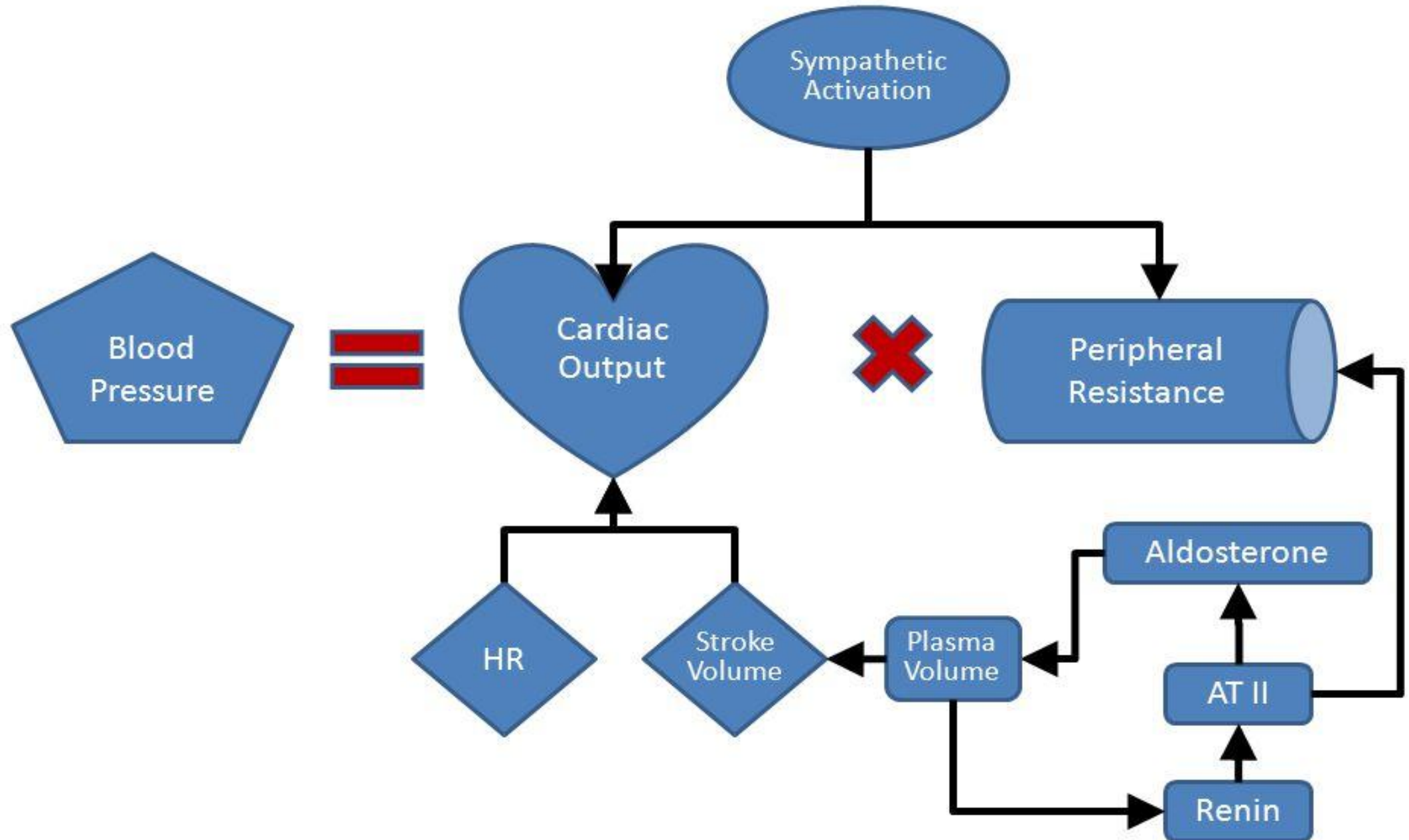
They are used for the treatment of hypertension.

$\beta_{1,2}$ – blocker: propranolol

β_1 – blockers: metoprolol, talinolol, atenolol, acebutolol.

α, β – blocker: carvedilol, labetalol.

Beta Blockers – Mechanism of Action



A-adrenoblockers

They cause the dilation of peripheral vessels, so they decrease the peripheral resistance.

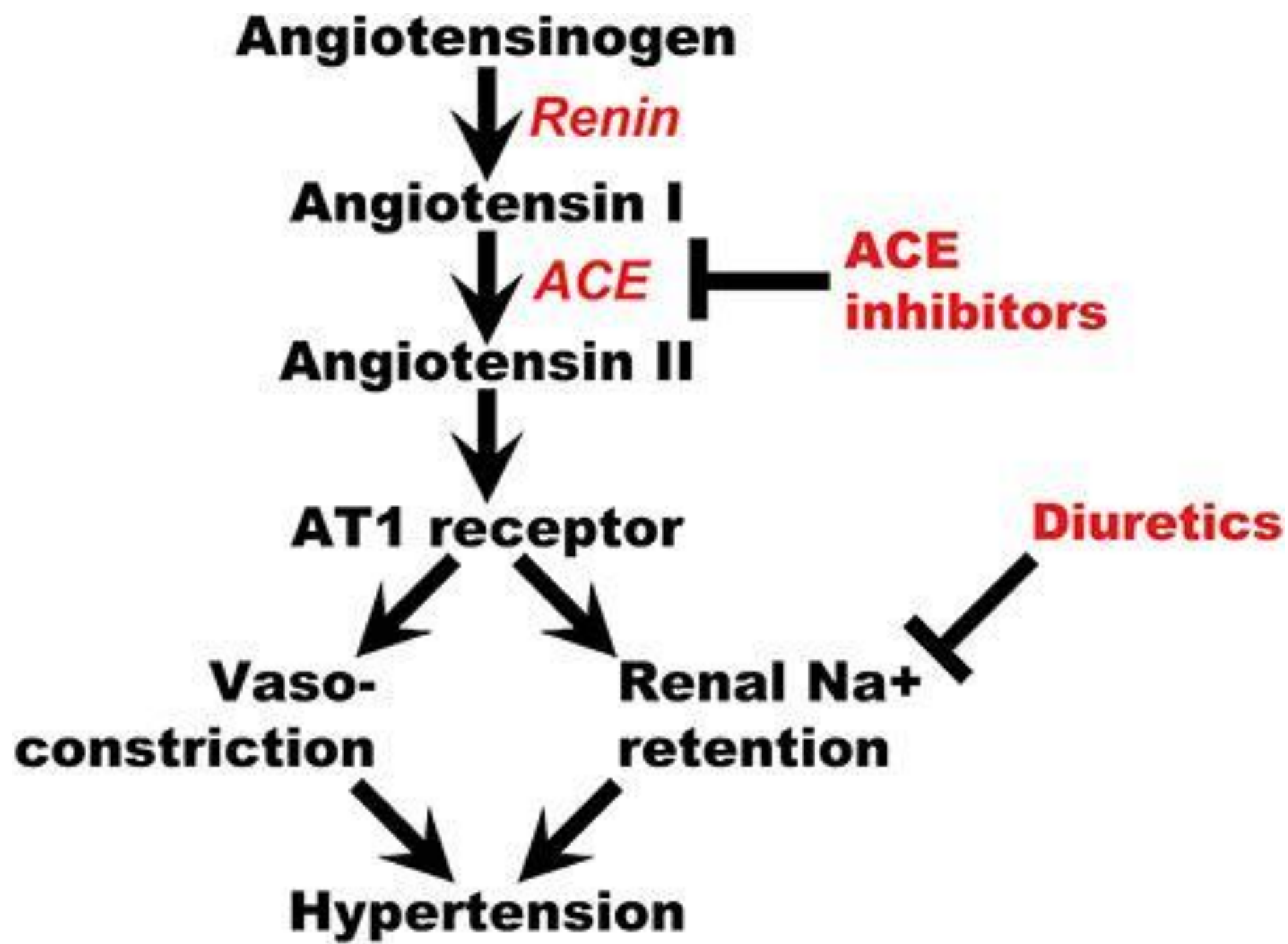
They are used for the treatment of hypertension and heart failure, benign hyperplasia of the prostatic gland.

Adverse effects: headache, palpitation, sleepiness, orthostatic hypotension, dizziness, water retention.

The duration of effect: **prazosin** – 6-8 h; **doxazosin** – 24 h.

Drugs affecting renin-angiotensine system

- ❑ **Renin** occurs in juxtaglomerular cells of the kidneys. It provides the conversion of **angiotensinogen** into **angiotensin I**. Both agents are inactive.
- ❑ **The angiotensin-converting enzyme (ACE)** converts **angiotensin I** into highly active **angiotensin II**.
- ❑ In the organism ACE is produced by the vascular endothelium, lungs, kidneys and other tissues.
- ❑ **Angiotensin II** stimulates its receptors.
- ❑ Angiotensin II produces **angiotensin III**, which is more potent in its vasopressor activity.

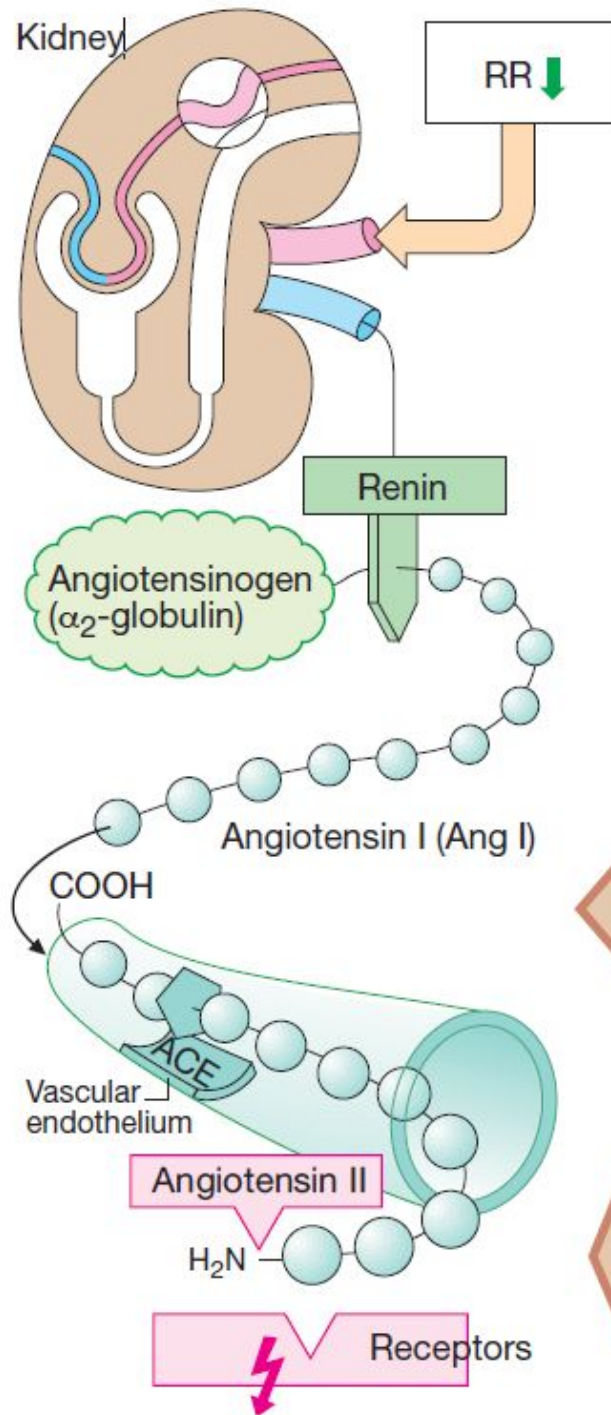


Renin' secretion is elevated in the following cases:

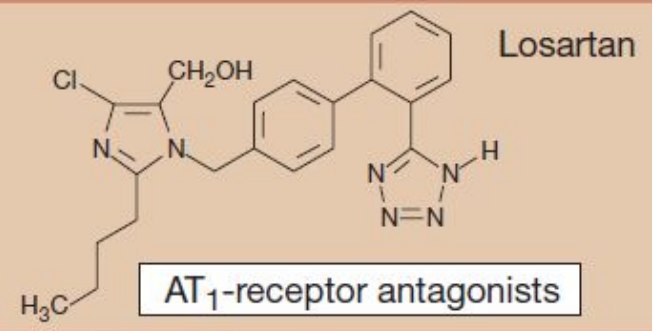
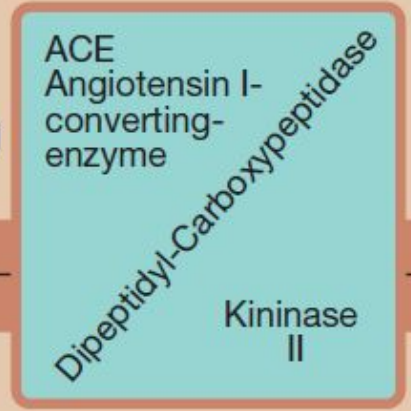
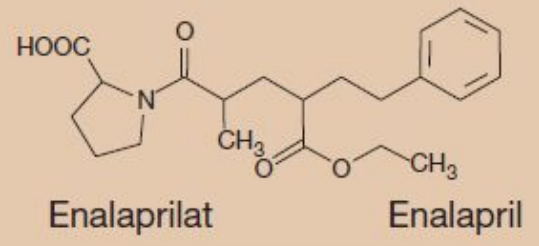
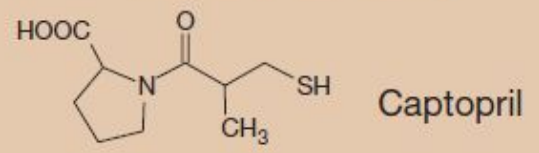
- decreased blood pressure and a reduction of blood volume in afferent arterioles of the renal glomeruli,
- decreased NaCl content in the distal tubule of the kidneys,
- increased adrenergic tone,
- increased prostacyclin and prostaglandin E2 production.

Renin secretion is decreased by the inhibition of the synthesis of prostaglandins by NSAIDs.

There are some drugs, which produce direct inhibitory effects on renin (aliskiren, enalkiren), decreasing its activity.



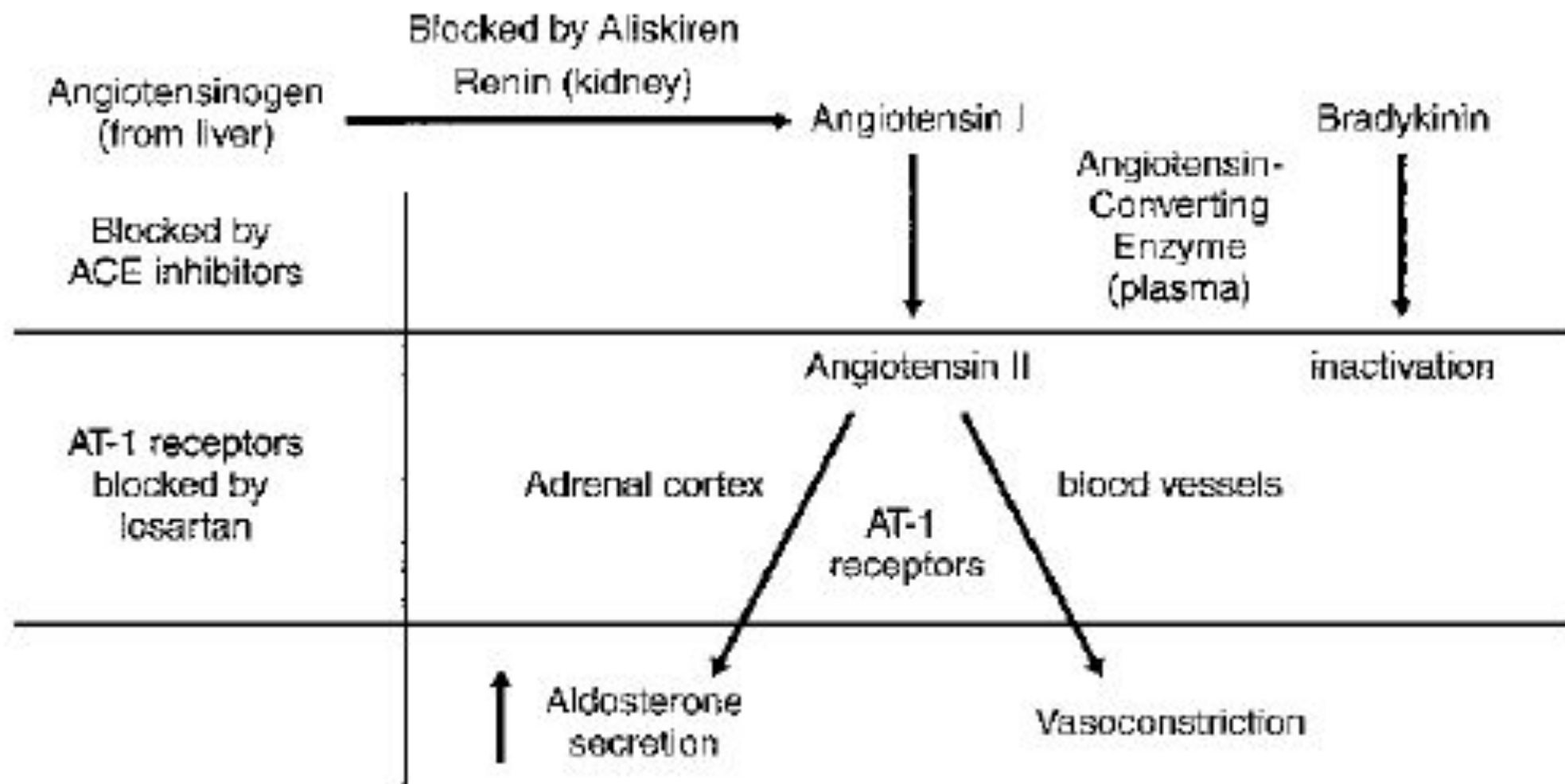
ACE inhibitors



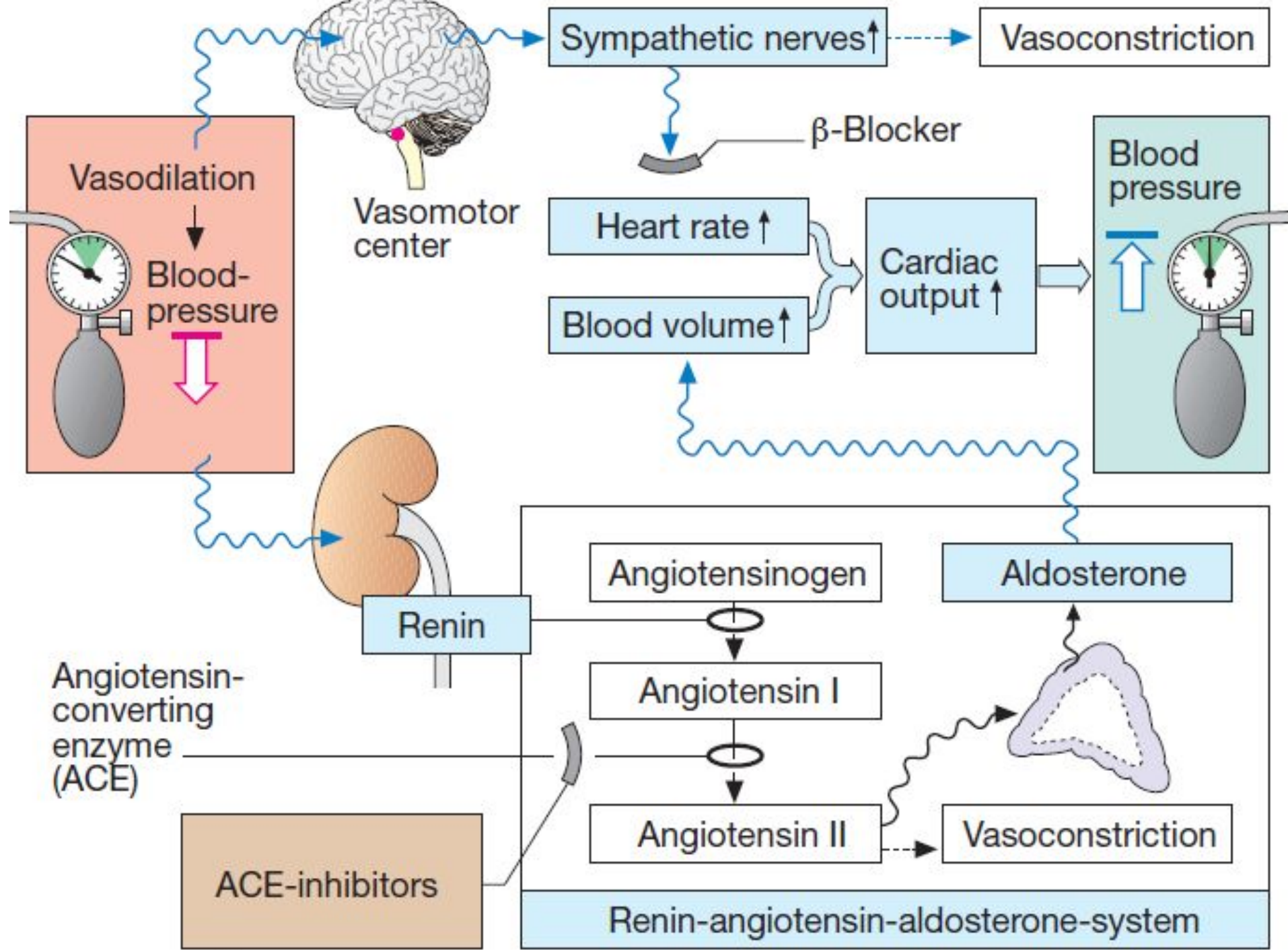
The effects of angiotensin II

Organ	Effects
Heart	Increase contractility, hypertrophy
Vessels	Constriction, hyperplasia and hypertrophy of muscles
Adrenals	The secretion of aldosterone and catecholamines ↑
Kidneys	Reabsorption of sodium and water ↑
Peripheral sympathetic endings	Norepinephrine release ↑

ANGIOTENSIN-CONVERTING INHIBITORS (ACEIs) AND ANGIOTENSIN-RECEPTOR BLOCKERS (ARBs)



- ❑ Inhibitors of the angiotensin-converting enzyme reduce formation of angiotensin II. This manifests in less significant activation of the vascular angiotensin receptors and the adrenal cortex. The stimulatory effect on sympathetic innervation is also reduced.
- ❑ Resistant vessels tone is decreased. The release of aldosterone is reduced. This leads to lower sodium retention and a reduction in extracellular fluid volume.
- ❑ Cardiac output and cardiac contraction rate are decreased slowly (if drugs are used continuously).



- ❑ ACE inactivates bradykinin also. The inhibition of ACE slows inactivation of bradykinin and increases its vasodilating effect.
- ❑ Inhibitors of ACE are used for the treatment of arterial hypertension and for relief of hypertensive crisis.
- ❑ They are combined with diuretics, β -adrenoblockers and myotropic vasodilating drugs.
- ❑ Adverse effects: various allergic reactions (skin eruption, fever), taste disorder, angioneurotic edema (face, lips, eyelids), dry cough, leucopenia, hyperpotassiumemia, proteinuria.
- ❑ They are contraindicated in pregnancy due to teratogenic effects.

- **Captopril** is used orally and sublingually. The effect begins quickly (after 3-5 min) and lasts during 6-8 h.
- **Enalapril** is a prodrug. Its active metabolite (enalaprilat) is produced in the liver. It is more active than captopril, but it can not be used in a case of hypertensive crisis. The effect lasts 18-24h. Enalapril does not contain SH-groups and it causes less side effects than captopril.
- **Lisinopril** is such effective as enalapril. It acts 24h

- **Phosinopril** is a prodrug. It is converted into phosinoprilate in the liver. Phosinopril and its metabolites are excreted not only by kidneys, but also in the bile. It is very important in patients with abnormal kidneys function.
- **Trandolapril** is a prodrug. In the liver it is converted into trandolaprilate. It is one of the most effective and long acting drugs of this group. It is highly lipophilic and penetrates in the heart, brain, kidneys. Its' effect on ACE is more powerful than that of E. Trandolapril is taken orally every 24 h.

- The inhibitors of ACE do not completely block biosynthesis of angiotensin I, because its formation is regulated by other enzymes.
- The complete deactivation of the renin-angiotensin system is achieved by the use of angiotensin receptors (AT1) blockers.
- **Losartan** blocks AT1 receptors. Angiotensin II can not stimulate them. It can stimulate AT2 receptors, but their stimulation leads to the opposite effects.
- Losartan eliminates all effects of angiotensin II: vasopressor effect, increase in aldosterone production, stimulation of adrenergic innervation.

- The drug decreases arterial blood pressure by reducing peripheral vascular resistance. It reduces cardiac work.
- Losartan decreases aldosterone concentration in the blood. It has diuretic and uricosuric effect.
- It is administered orally once a day for the treatment of arterial hypertension.
- Adverse effects: headache, dizziness, allergic reaction.
- Contraindications: pregnancy, lactation, cases of hypersensitivity.

This group also includes **valsartan, irbesartan, telmisartan**. For arterial hypertension these drugs are administered orally once a day.

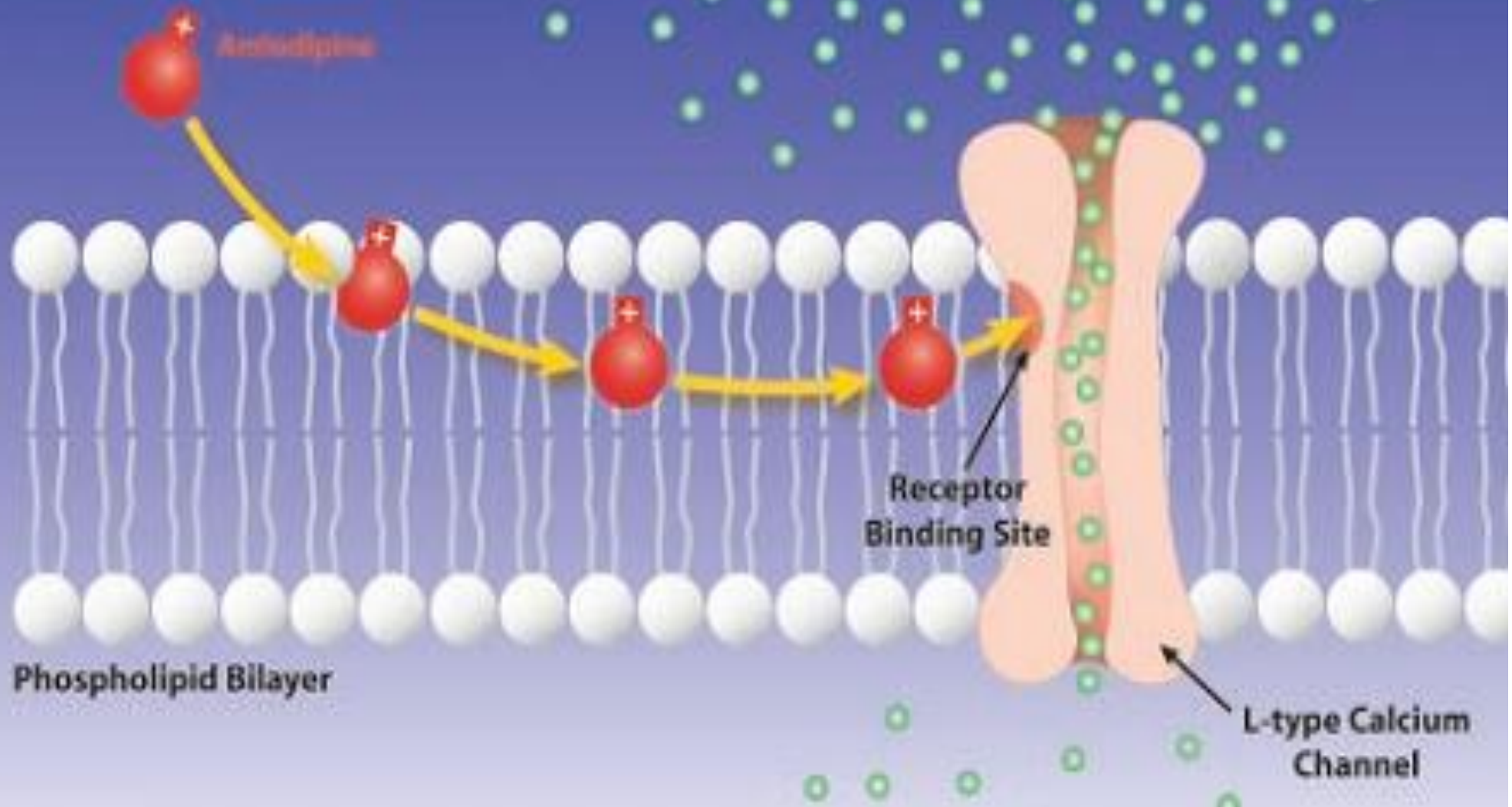
Myotropic drugs

Drugs blocking Ca channels of L-type.

- They diminish penetration of Ca into the smooth muscle cells. They decrease vascular tone and blood pressure.
- Drugs: nifedipine, felodipine, amlodipine, lacidipine.
- They are used orally for the treatment of arterial hypertension.
- Adverse effects: dizziness, headache, palpitation, nausea, ankle edema, skin rash.

Cell Plasma Membrane

Calcium Ions



Phospholipid Bilayer

Receptor Binding Site

L-type Calcium Channel

Potassium channels activation: minoxidil, diazoxide. They cause:

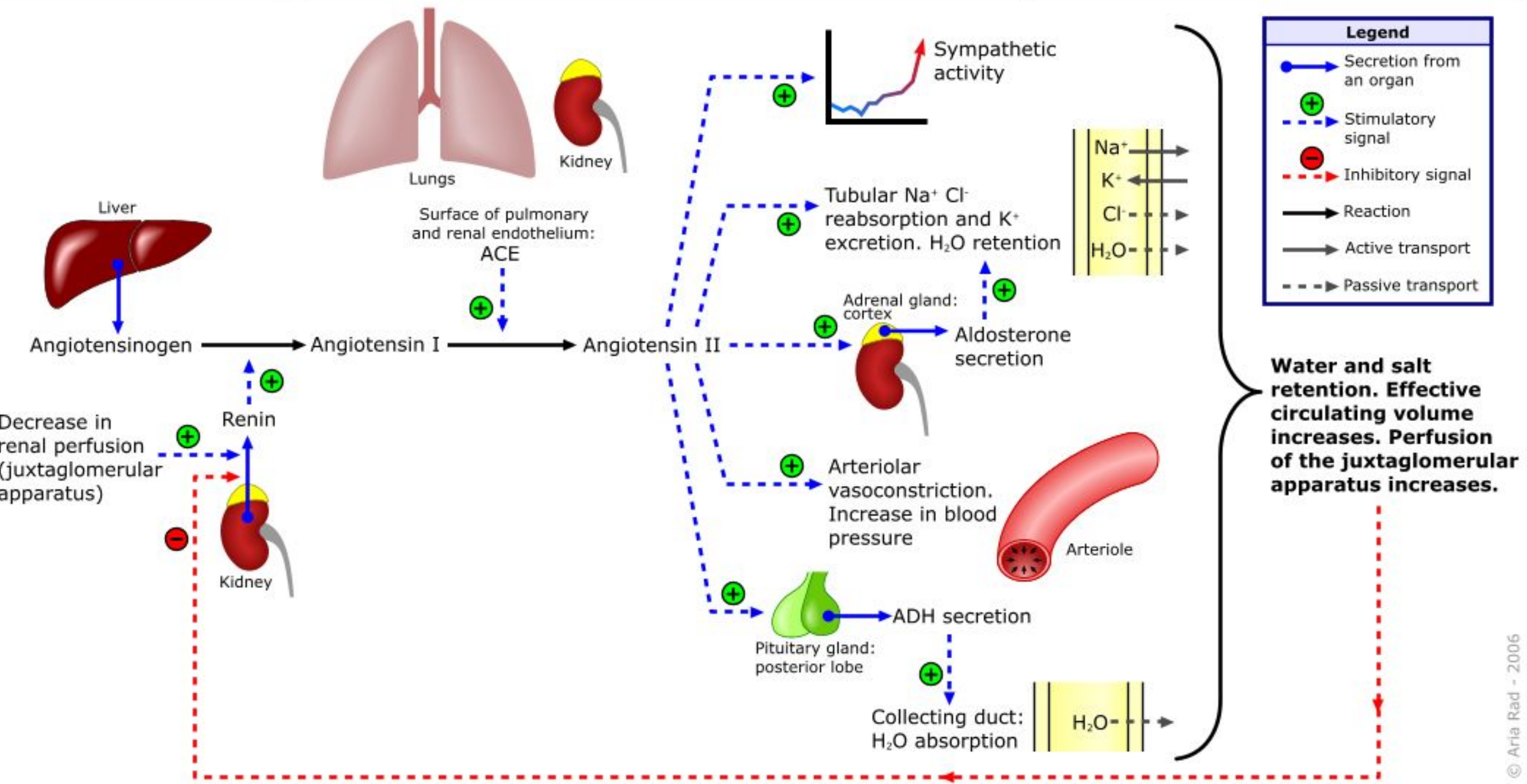
- ❖ **K⁺**-channels opening; **K⁺** release from the cell
- ❖ Hyperpolarization
- ❖ Voltage-dependent **Ca²⁺**-channels do not open
- ❖ Reduced influx of **Ca²⁺** into the cells
- ❖ Vascular smooth muscle tone is decreased
- ❖ Vessels (arterioles) dilate, blood pressure is decreased.
- **Minoxidil** is used orally. The effect lasts for up 24 h.
Adverse effect: hirsutism, edema.
- **Diazoxide** is administered intravenously. The duration of effect is 12-18h. Adverse effects: edema, hyperglycemia, hyperuricemia.

Nitric oxide donors – sodium nitroprusside affects resistive (arterioles, small arteries) and capacitant vessels (venulas, small veins). It decreases the venous return to the heart, so does not increase cardiac output. There is reflex increase in heart rate.

- ❖ Nitric oxide stimulates cytosolic guanylyl cyclase, increases cGMP content, reduces the concentration of free calcium ions. Vascular tone of the vascular smooth muscles is decreased.
- ❖ The drug is administered intravenously drip for the treatment of hypertensive crisis, heart failure, to induce controlled hypotension.
- ❖ Adverse effects: tachycardia, headache, dispeptic disturbances, muscle fasciculations.

- ❑ **Dibazolium** produces a spasmolytic effect on all smooth muscle organs. It dilates blood vessels, reduces cardiac output, decreases arterial blood pressure.
- ❑ It has moderate hypotensive activity and a short-term effect.
- ❑ It is used together with other antihypertensive drugs for the treatment of hypertension.
- ❑ It is administered intravenously in cases of hypertensive crisis.

- **Magnesium sulphate** is administered intramuscularly or intravenously for the treatment of hypertensive crisis, an attacks of cramps and in eclampsia. Its effect is associated with direct myotropic activity.
- It suppresses transmission in the autonomic ganglia, reducing acetylcholine release from the preganglionic fibres.
- This drug produces an inhibitory effect on vasomotor centres.
- The drug has sedative and anticonvulsant effect. In high doses it produces a general anesthetic effect.
- It can suppress neuromuscular transmission, can cause respiratory depression.



- ✓ **Diuretics (hydrochlorothiazide, furosemide, spironolactone)**
- ✓ They reduce extracellular fluid volume, reduce cardiac output, decrease peripheral vascular resistance. Arterial blood pressure decreased.
- ✓ They reduce the content of sodium ions in the cells of the vascular wall. They improve the elasticity of blood vessels.
- ✓ They increase the sensitivity of vascular wall to the action of vasodilator substances. The effect of pressor drugs is decreased.

Literature

- 1. Tripathi K.D. Essentials of Medical Pharmacology. Eighth Edition. -2019.- Jaypee Brothers Medical Publishers. The Health Sciences Publisher. -New Delhi. London. Panama
- 2. D.A.Kharkevich. Pharmacology. Textbook for medical students. Translation of 12th edition of Russian textbook “Pharmacology” (2017). – М., ГЭОТАР-Медиа, 2017.
- 3. Review of pharmacology. Gobind Rai Garg, Sparsh Gupta. 13th edition.- 2019.- Jaypee Brothers Medical Publishers. The Health Sciences Publisher. -New Delhi. London. Panama
- 4. Whalen Karen. Lippincott Illustrated Reviews: Pharmacology. Sixth Edition.- 2015.-Wolters Kluwer.- Philadelphia
- 5. Color Atlas of Pharmacology. 2nd edition, revised and expanded.Heinz Lüllmann.- 2000 Thieme
- 6. Pharmacology Examination & Board Review. Tenth Edition. Trevor Anthony J., Katzung Bertram G., Kruidering-Hall Marieke, Susan B. Masters. - a LANGE medical book.- 2013.-New York
- 7. Medical Pharmacology at a Glance. Eighth Edition. Neal Michael J. – 2016.- John Wiley & Sons, Ltd.
- 8. USMLE Step 1. Lecture Notes. Pharmacology. Lionel P.Raymon and others.- 2009.-Kaplan Medical.Inc.