Antihypertensives

This study material is recommended specifically for practical courses from Pharmacology II for students of general medicine and stomatology. These brief notes could be used to prepare for the lesson and as a base for own notes during courses. Addititonal explanations and information are given in single lessons.

Arterial hypertension

- repetititve increase of blood pressure (BP) over 140/90 mm Hg detected at least at 2 out of 3 measurings, carried out at least at two visits

- prevalence among adults 20-30 %

- Risk factors:

Hypertension classification in adults (WHO and International society ofhypertension)			
	SBP mm Hg		**DBP mm Hg**
Optimal	< 120	and	< 80
Normal	< 140	and	< 85
Prehypertension (JNC 7 classification)	130 - 139	or	85 - 89
Grade 1	140 - 159	or	90 - 99
Grade 2	160 - 179	or	100 - 109
Grade 3	> 180	and	> 110
Isolated systolic hypertension	ł 160	and	< 90

Arterial hypertension classification with regard to etiology

- **Primary (essential)** – approximately 95 % of all hypertensions; multifactorial aetiology without known organic cause

- **Secondary** – illnes with detectable organic cause which lead to BP increase
  -
  -
  -
  -
  -

Therapy of arterial hypertension

- Aim: to reach values of BP below 140/90 mm Hg

  in patients with high CVS risk or with DM up to 130/85 mm Hg

Non-pharmacological treatment:

Lifestyle change- restriction of Na^+ intake, smoking, alcohol, NSAIDs, glucocorticoids

-

-

-

Pharmacotherapy of hypertension

1. **ACE-inhibitors (ACE-I)**
2. **Angiotensin II receptor antagonists**
3. **Renin inhibitors**
4. **Ca^{2+} channel blockers**
5. **Diuretics**
6. **Betablockers**

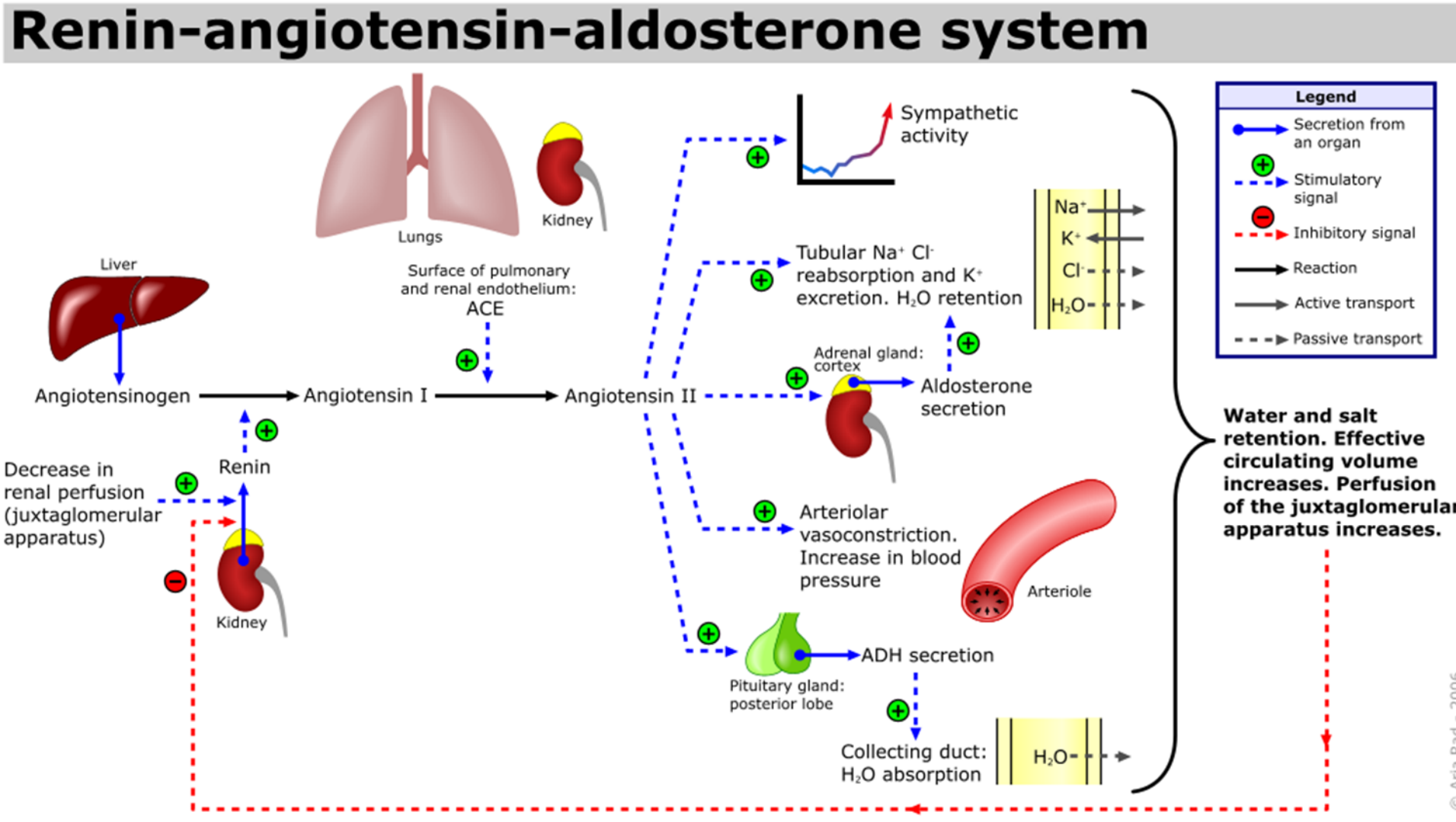
7. **Central antihypertensives**

---

8. **Alpha adrenolytics**
9. **Direct vasodilators**
10. **Ganglioplegics**
11. **Blockers of adrenergic neurons**

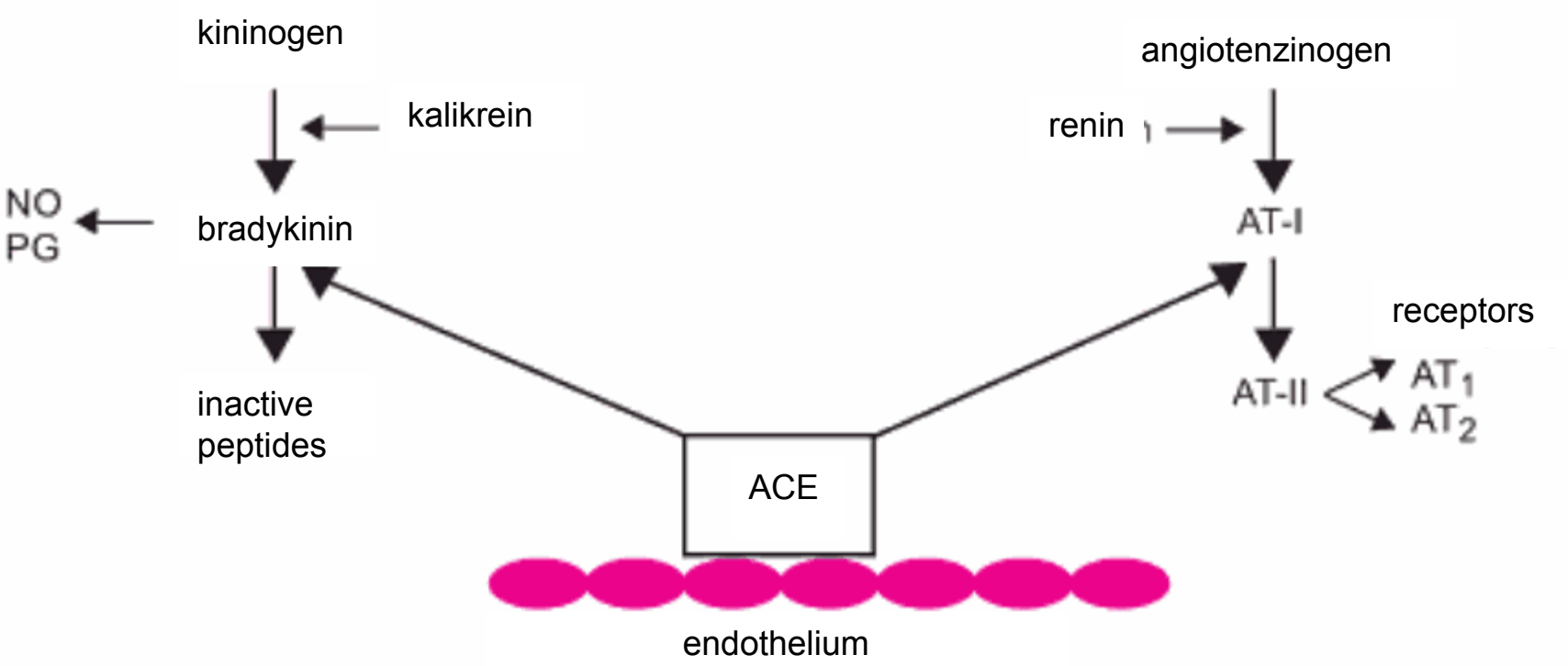
1. ACEi

Angiotensin **C**onverting **E**nzyme **i**nhibitors



1. ACEi

Angiotensin **C**onverting **E**nzyme **i**nhibitors



1. ACEi

Drugs of 1st choice in the therapy of hypertension

Mode of action:

1) ACE reversible inhibition

2) block of bradykinin degradation

Decrease of BP is related to the actual activity of RAAS before treatment (amounts of Na, volume of plasma, administration of diuretics)

1. ACEi

Effects:

BP decrease -

-

↓ aldosterone

Indications:

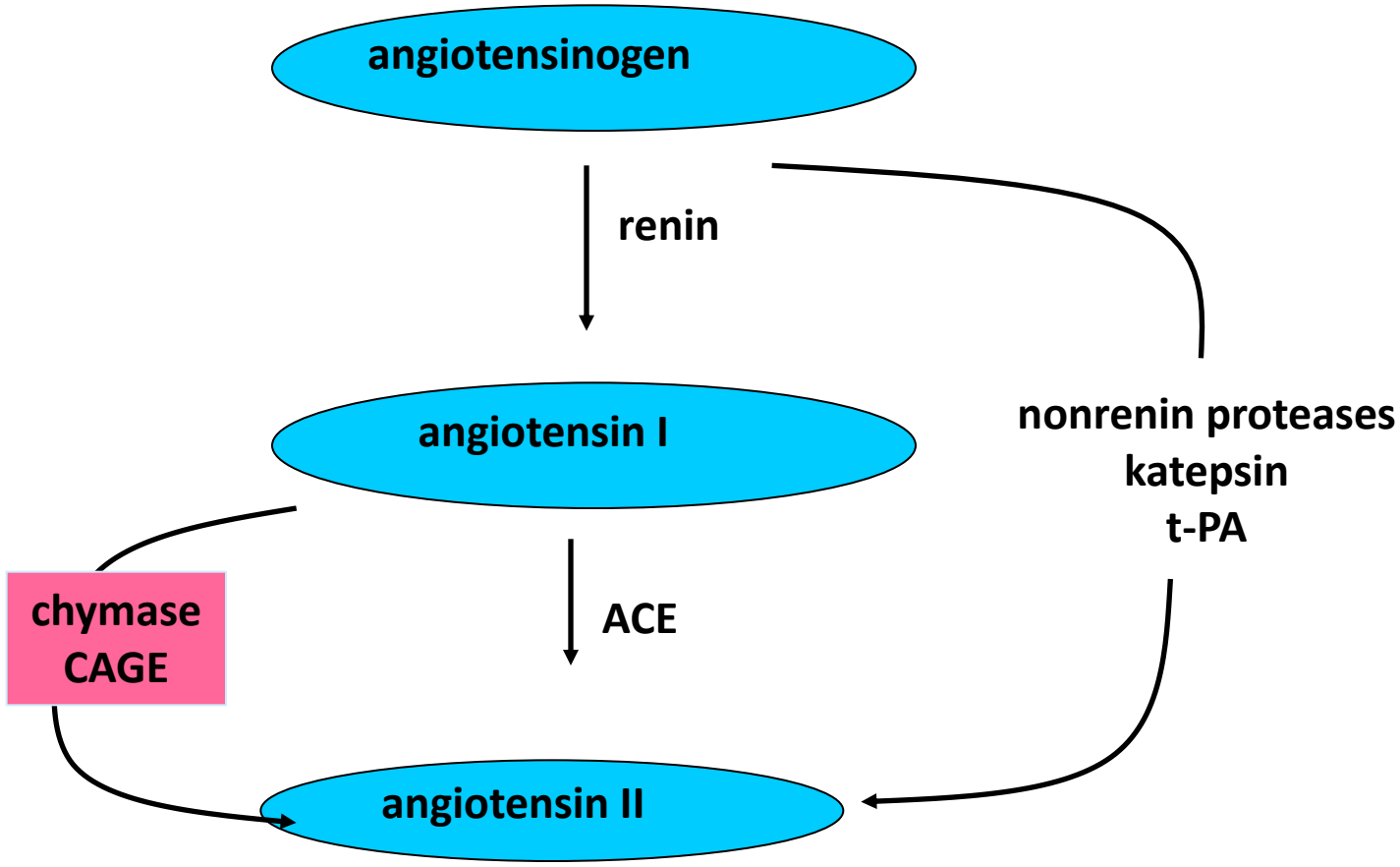
hypertension

…

…

…

1. ACEi do not inhibit the alteranative pathways of AT-II synthesis



CAGE (chymostatin sensitive AT-II generating enzyme in vessels
t-PA – tissue plasmin activator
katepsin – serum protease

1. ACEi

Drugs		Dosing
captopril	3x	12,5 - 50 mg
enalapril	2x	5 - 20 mg
perindopril	1x	4 - 8 mg
quinapril	1 -2x	5 - 20 mg
lisinopril	1x	20 - 80 mg
spirapril	1x	6 mg
trandolapril	1x	2 - 4 mg
ramipril	1x	2,5 - 10 mg

1. ACEi

Kinetics: transporters for small peptides
liver microsomal biotransformation (enalapril = prodrug)
variable halftime

Adverse effects: hypotension
dry iritating cough

Contraindications: pregnancy, breastfeeding
renal arteries stenosis
primary hyperaldosteronism

1. **ACEi**

First choice drug in:

after MI, thrombotic stroke
cardiac remodeling, left ventricle hypertrophy,
cardiac failure,
DM, hyperlipoproteinemia
(do not deteriorate metabolic parameters)

2. Angiotensin II receptor antagonists „Sartans“

Mode of action:

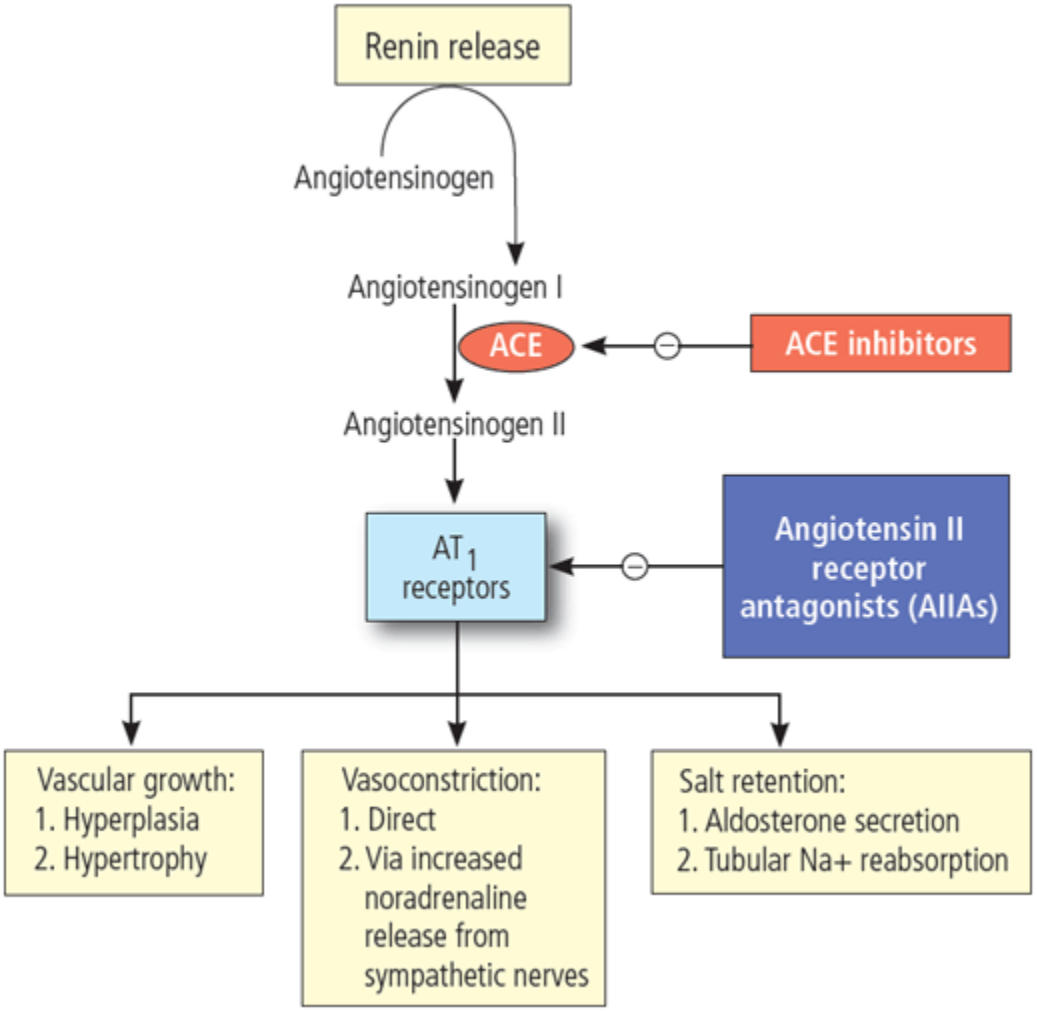
competitive antagonists on angiotensin AT_1 receptors

Do not inhibit bradikinin metabolism – do not cause the dry cough ☺

Effects:

-
-
-
-
-
-

2. Angiotensin II receptor antagonists „Sartans“



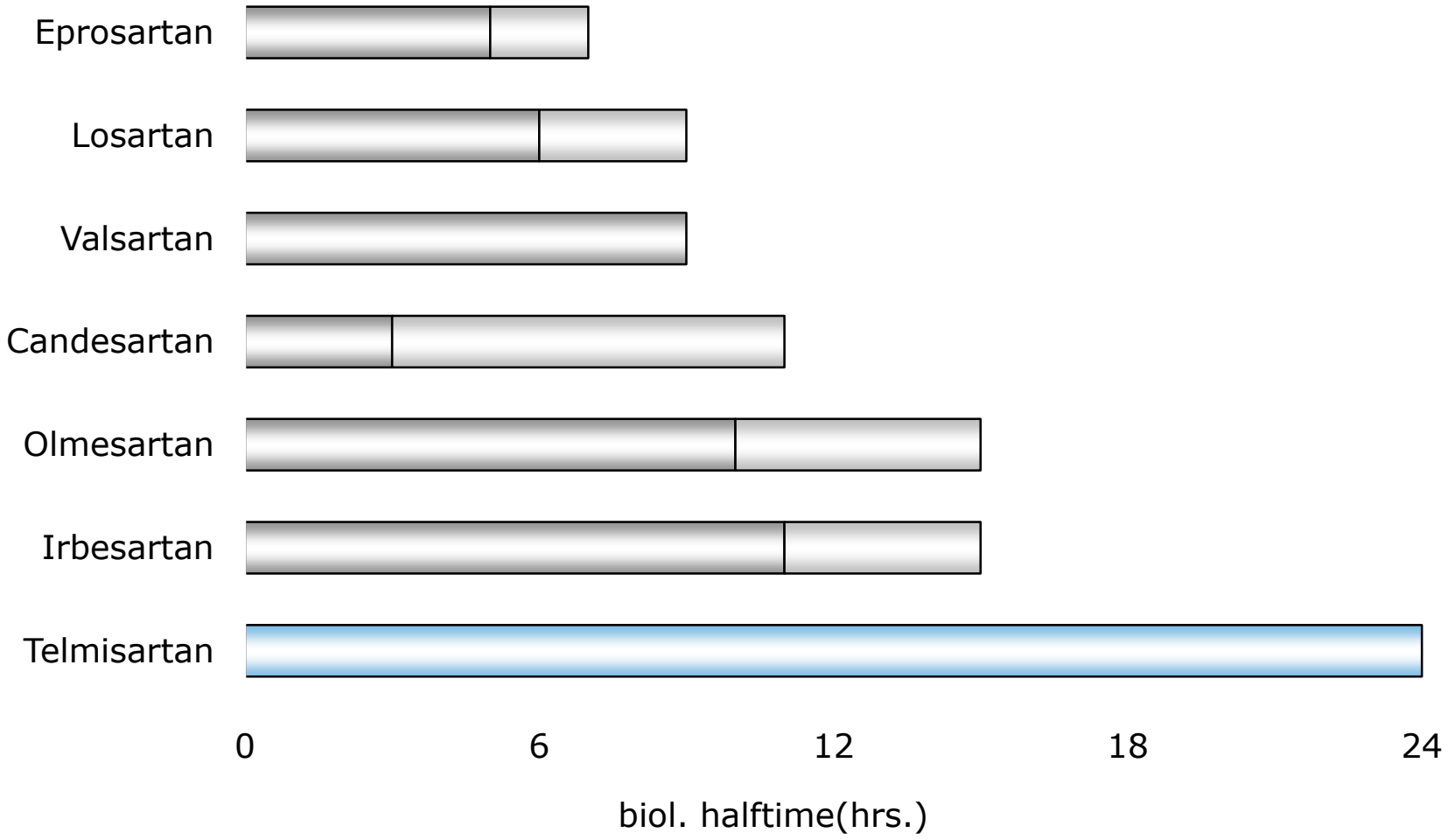
2. Angiotensin II receptor antagonists „Sartans“

Indications:

hypertension
cardiac insufficiency
AMI

Protective effect on kidneys in microalbuminuria

2. Angiotensin II receptor antagonists „Sartans“



2. Angiotensin II receptor antagonists „Sartans“

Pharmacokinetics: dobrá dostupnost bez ohledu na jídlo
aktivní metabolity (většinou stačí 1x denně)

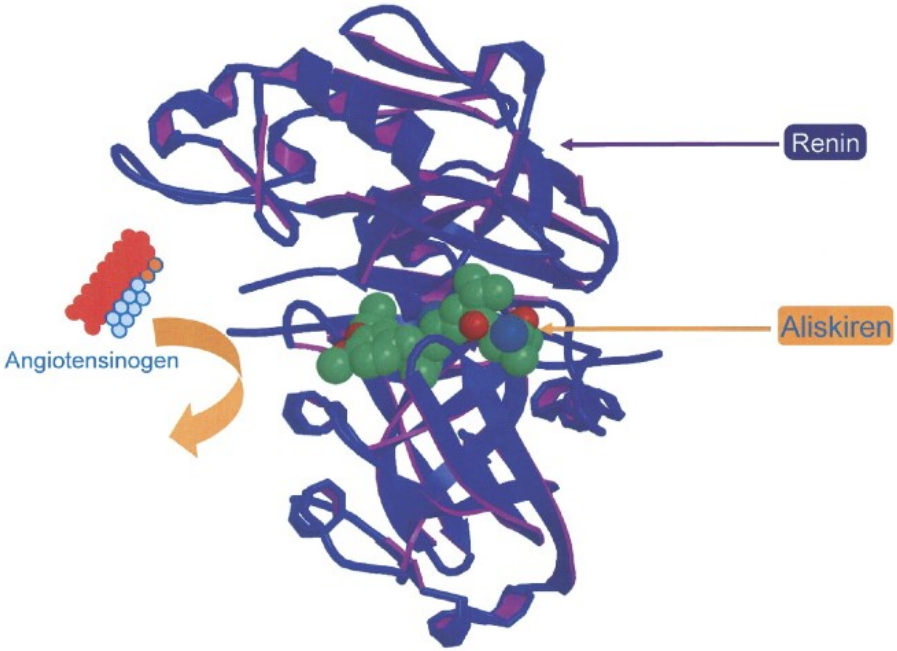
Adverse effects: hypotension

Contraindications: pregnancy, breastfeeding
renal arteries stenosis
primary hyperaldosteronism
women without contraceptives(?)

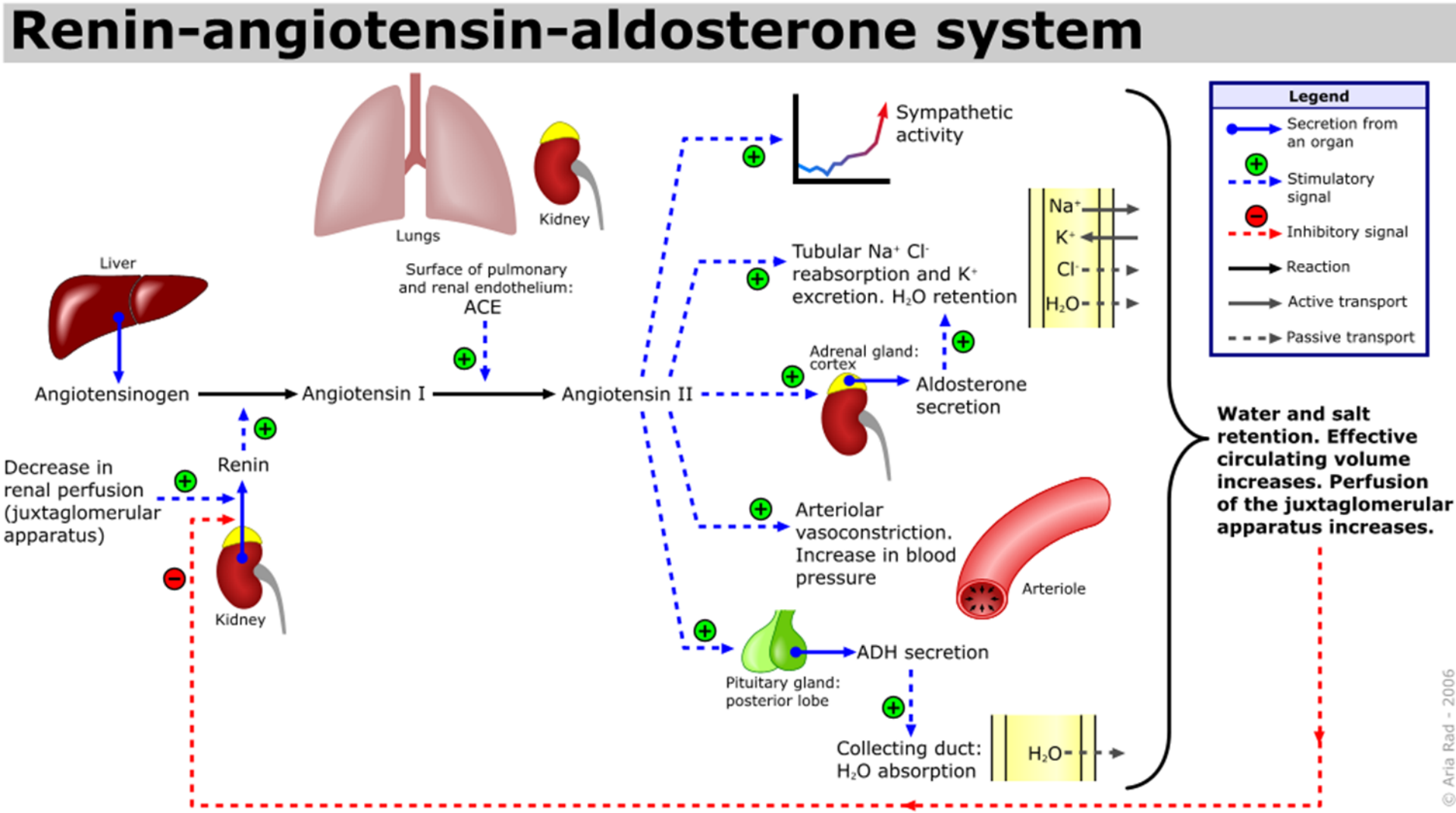
3. Renin antagonists

Mechanism of action:

antibodies
peptide analogues of angiotensinogen N-terminus
also called as renin inhibiting peptide



3. Renin antagonists



3. Renin antagonists

Drugs

Enalkiren
Remikiren
Aliskiren
Zankiren
Ciprokiren
SPP635
SPP1148

Kinetics: absorption NOT influenced by food

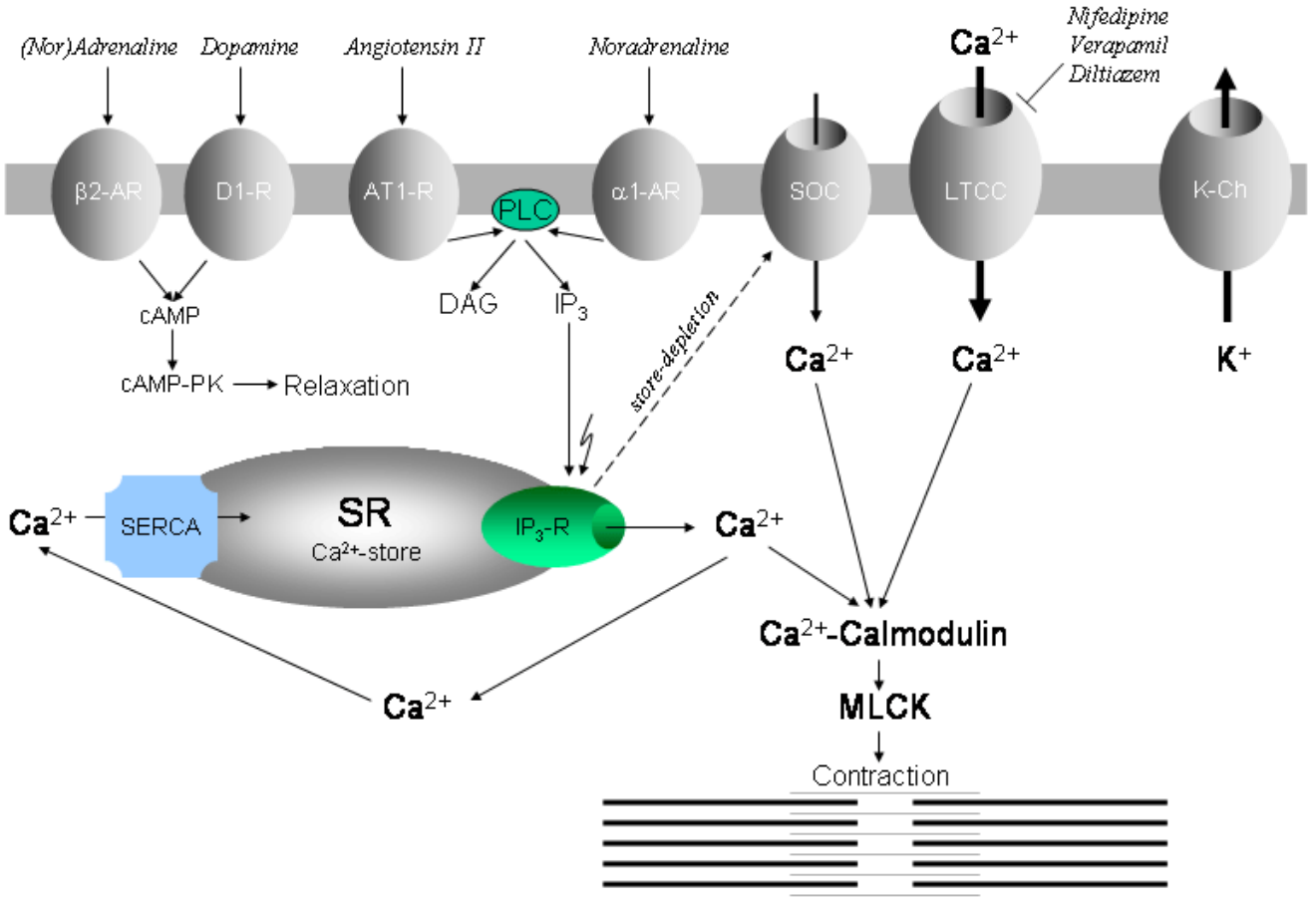
Combined with hydrochlorothiazid or AT II antagonists

Adverse effects: diarrhoea, angioedema

4. Calcium channel blockers

Mode of action:

4. Calcium channel blockers



SOC = store-operated channels
LTCC= L-Type Calcium Channel
K-Ch= K^+ channel

4. Calcium channel blockers

Effects:

decrease BP by systemic vasodilation

regression of left ventricular hypertrophy

do NOT cause orthostatic hypotension

do NOT cause sodium retention (in comparison to other vasodilators) ☺

do NOT influence metabolism

do NOT cause bronchoconstriction

4. Calcium channel blockers

Dihydropyridines -

1.Generation – nifedipine

2.Generation

-felodipine, isradipine, nisoldipine, nitrendipine, nilvadipine, nimodipine

3.Generation

amlodipine, lacidipine, lerkanidipine, manidipine, barnidipine, benidipine

Non-dihydropyridines

diltiazem

verapamil

4. Calcium channel blockers

Indications:

hypertension
angina pectoris

Interactions:
quinidine - hypotension
diltiazem, verapamil – NOT combined with beta blockers
(serious bradycardia)
verapamil x digoxine !!

4. Calcium channel blockers

Kinetics: variable bioavailability (diltiazem app. 20 %)

variable halftime
(nifedipine vs. amlodipine – 2 vs. 40 hrs)
intensive protein binding
CYP liver metabolism

Adverse effects: hypotension, headache, reflex. tachycardia (DH pyridines), bradycardie (non-DH pyridines), constipation

Contraindications: AV block, cardiac failure (verapamil, diltiazem) tachycardia (DH pyridines)

5. Diuretics

Mode of antihypertensive activity:

-

-

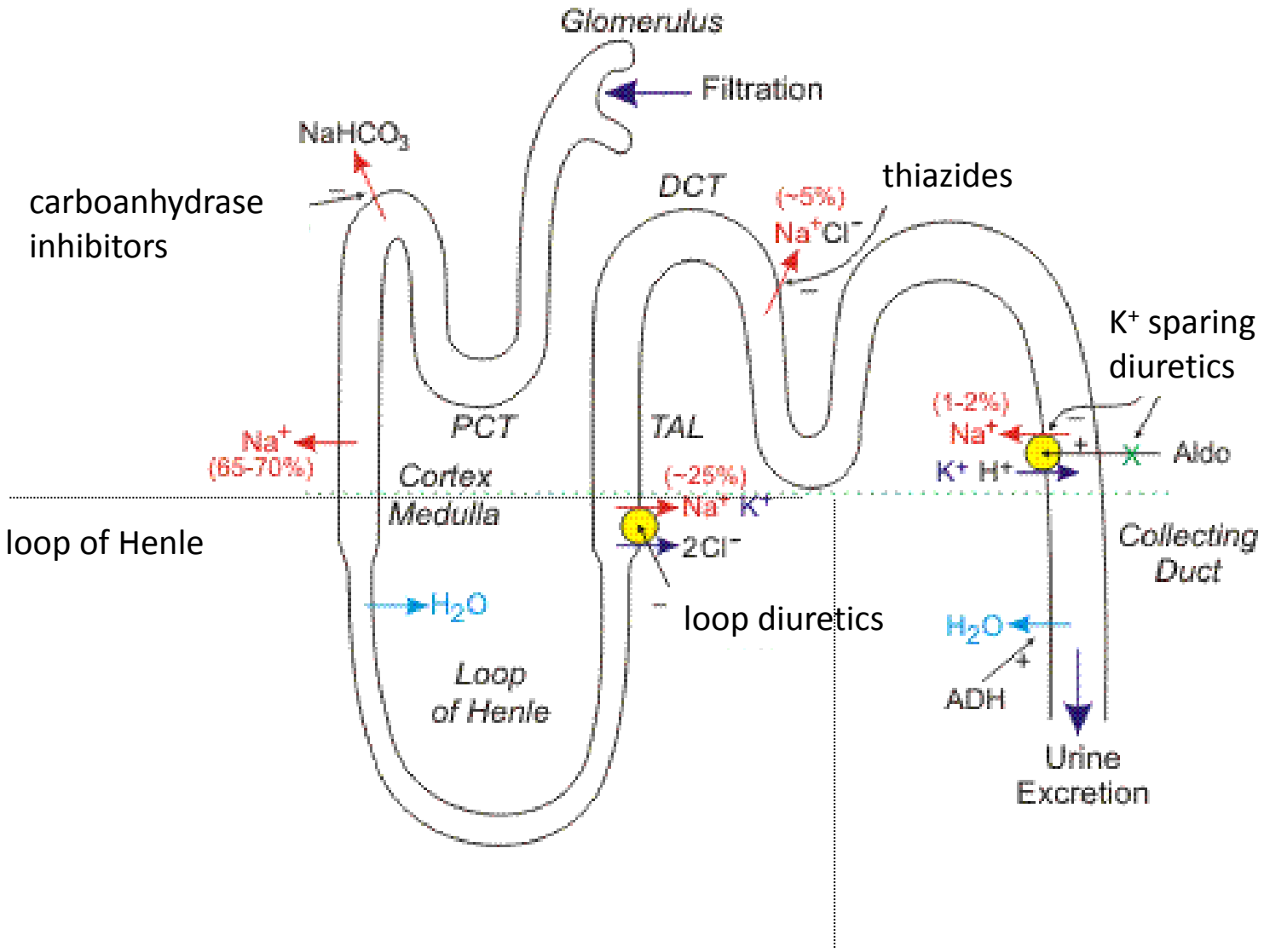
-

act by different mechanisms directly in kidneys in different parts of nephron

Most important nephronal segments:

proximal tubule
ascending limb of loop of Henle
distal tubule
collection duct

5. Diuretics


Glomerulus
Filtration
NaHCO3
carboanhydrase inhibitors
DCT
(~5%)
Na+Cl−
thiazides
K+ sparing diuretics
(1-2%)
Na+
K+ H+
X
Aldo
Na+ (65-70%)
PCT
TAL
(~25%)
Na+ K+
2Cl−
Cortex
Medulla
loop of Henle
Collecting Duct
H2O
loop diuretics
Loop of Henle
H2O
ADH
Urine Excretion

5. Diuretics

Thiazides - inhibit resorption of Na^+ and Cl^- in distal tubule

hydrochlorothiazide
chlorthalidone (thiazide analogue)

indapamide } less saluretic
metipamide

5. Diuretics

Thiazides

Kinetics: well absorbed from GIT,
excreted into urine in proximal tubule

diuresis persist up to 12 hrs,
hypotensive effect onset after 3-4 days and latency of effect after withdrawal.

Indications:

5. Diuretics

Loop

very strong but short duration of diuretic effect
vasodilating effect
depletion of Na, Cl, K, Ca, Mg

Indications:
HT
pulmonary oedema
congestive heart failure
hyperkalcemia

5. Diuretics

Loop- drugs

furosemide
torasemide
etacrynic acid

5. Diuretics

Potassium sparing agents

weaker diuretic effect, lower K^+ depldetion
block Na^+ reabsorption

- triamteren, amiloride

- aldosterone antagonist- spironolactone

Indications: combined HT therapy

5. Diuretics

Proximal tubule- carboanhydrase inhibitors

- not used in therapy of HT
-

Osmotic - „pulls“ osmotic equivalent of water

- not used in therapy of HT

(mannitol)

5. Diuretics

Adverse effects:

-

-

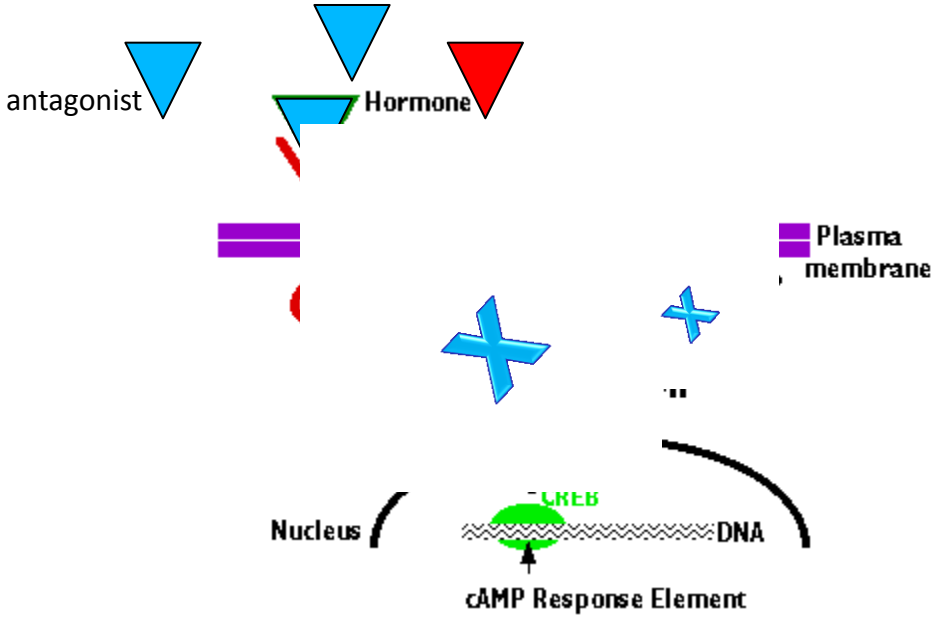
-

Contraindications:

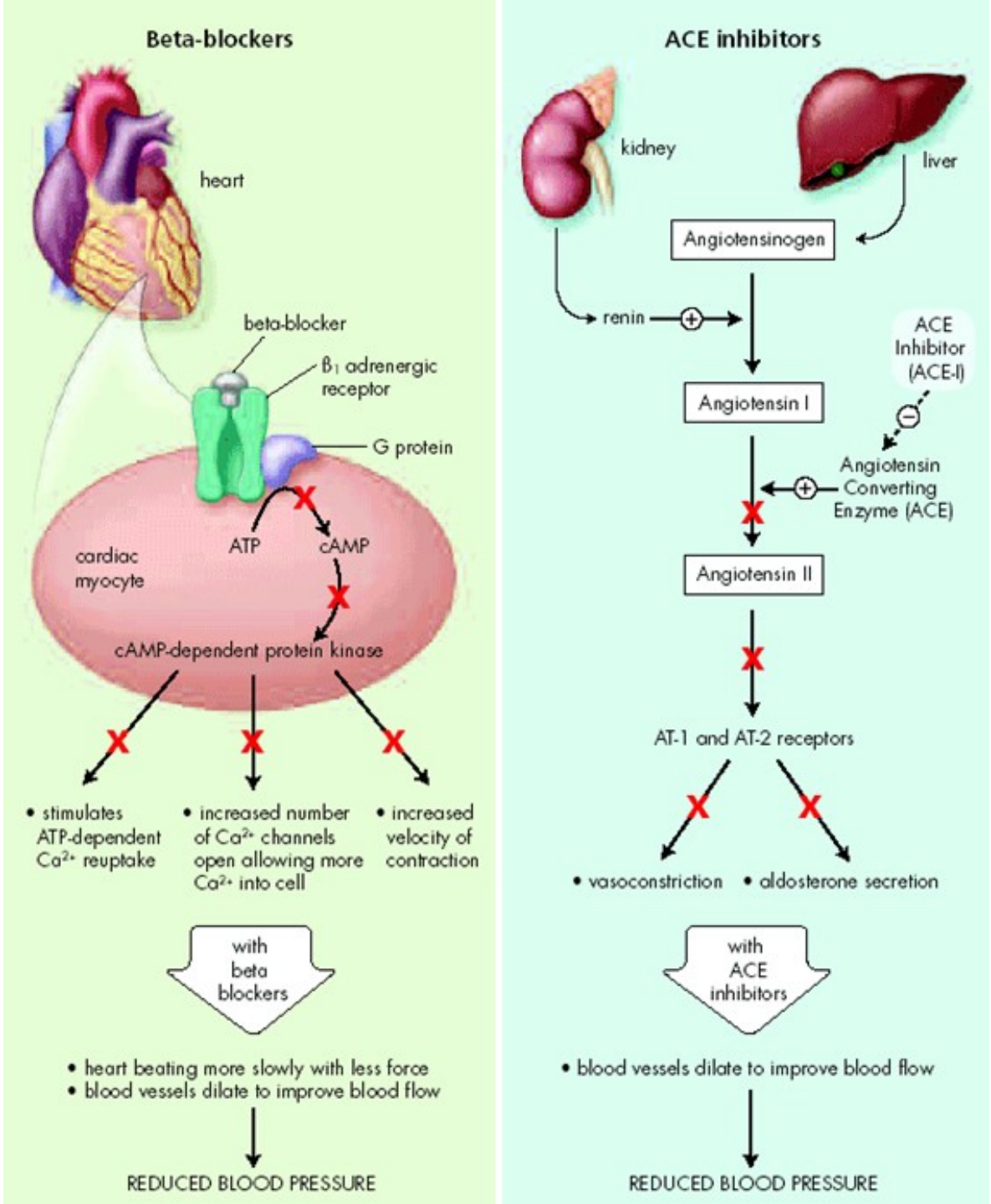
gout (namely thiazides)
renal failure, hyperkalemia (K+ sparing)
Relative: pregnancy, metabolic syndrome

6. Beta sypatholytics.
= „betablockers“

Mode of action:



6.


Beta-blockers
heart
beta-blocker
β1 adrenergic receptor
G protein
ATP
cAMP
cardiac myocyte
cAMP-dependent protein kinase
• stimulates ATP-dependent Ca2+ reuptake
• increased number of Ca2+ channels open allowing more Ca2+ into cell
• increased velocity of contraction
with beta blockers
• heart beating more slowly with less force
• blood vessels dilate to improve blood flow
REDUCED BLOOD PRESSURE
ACE inhibitors
kidney
liver
Angiotensinogen
renin
ACE Inhibitor (ACE-I)
Angiotensin I
Angiotensin Converting Enzyme (ACE)
Angiotensin II
AT-1 and AT-2 receptors
• vasoconstriction
• aldosterone secretion
with ACE inhibitors
• blood vessels dilate to improve blood flow
REDUCED BLOOD PRESSURE

6. Beta sypatholytics.
= „betablockers“

Mode of antihypertensive activity is is still not fully clear – theories:

- decreases overall sympathetic activity
- decreases renin release
- decreases cardiac output and venous return
- change baroreceptor settings
- stimulation of vasodilating prostaglandines production
- ↑ANF
- blockade of presynaptic β receptors ↓ NA release
- ↓presoric response to catecholamines in stress and physical activity

6. Beta sypatholytics.
= „betablockers“

Pharmacological effects:

-

-

-

-

-

6. Beta sypatholytics.
= „betablockers“

Cardioprotective effects:

- antiischemic- ↓ of cardiac work = ↓ oxygen consumption
- antidysrhytmic- ↑fibrilation treshold
- increase of coronary perfusion due to longer diastole and bradycardia

6. Beta sypatholytics.
= „betablockers“

Classification

1

metipranolol, propranolol, timolol, nadolol, sotalolol

2

metoprolol, atenolol, bisoprolol, betaxolol, esmolol

3.

pindolol, bopindolol, oxprenolol, carteolol (glaukom, lok.)

4.

acebutolol, celiprolol

Other - β_1, α_1, α_2, vasodilation (β_2 ISA) = celiprolol

β_1, β_2, α_1-labetalol, carvedilol

6. Beta sypatholytics.

= „betablockers“

How to select the right one:

older	β_1 or with ISA
younger	NS
IHD,Ami	not with high ISA
IHD, AP	suitable more than othet antiHT
DM II.	low doses of β_1 with ISA
pregnancy	β_1, alpha+beta
bradycardia below 50	with ISA
heart failure	carve,bisopr,metopr
lower limb ischemia	β_1 with ISA,vasodil.
hyperliproteinemia	with ISA
perioperational HT	esmolol

6. Beta sypatholytics.
= „betablockers“

Indications:

Contraindications:

7. Centrally acting antihypertensives

Imidazoline receptor agonists

imidazoline receptor differs from α rc.
I_1,I_2- in medulla, I_1 in CNS and kidney

↓ heart and vessel (sympathetic) stimulation
↓ renine secretion
↓ kidney sympathetic stimulation
↓ vasopressin secretion

moxonidine
rilmenidine

7. Centrally acting antihypertensives

Central α_2 agonists

α –methyldopa – false precursor of NA/ α_2 stimulation
NO influence on glomerular filtration

clonidine - α_2 stimulation
- rebound phenomenon

Central + peripheral α_2 agonist

urapidil

8. Alpha adrenolytics

selective reversible α_1-lytics
NO activity on $\alpha_2$rc. - do not increase NA activity

Adverse effects:

prazosin
doxazosin
terazosin

9. Direct vasodilators

Mode of action: interfere with Ca^{2+}
direct vasodilation(arterioles = ↓risk of orthost. hypoten.)
↓ chronic efficacy (endocrine, vegetative regulation)
↑ renine = ↑ peripheral vascular resistence
unsuitable for monotherapy, combinations with BB

hydralazine
minoxidil
diazoxide
sodium nitroprusside

10. Ganglioplegics

Mode of action: both sympathetic and parasympathetic blockade

→ frequent adverse affects (postural hypotension, blurred vision, xerostomia, constipation, urine retention, impotence)

trimetaphan

Exclusively for hypertension crisis or during surgeries

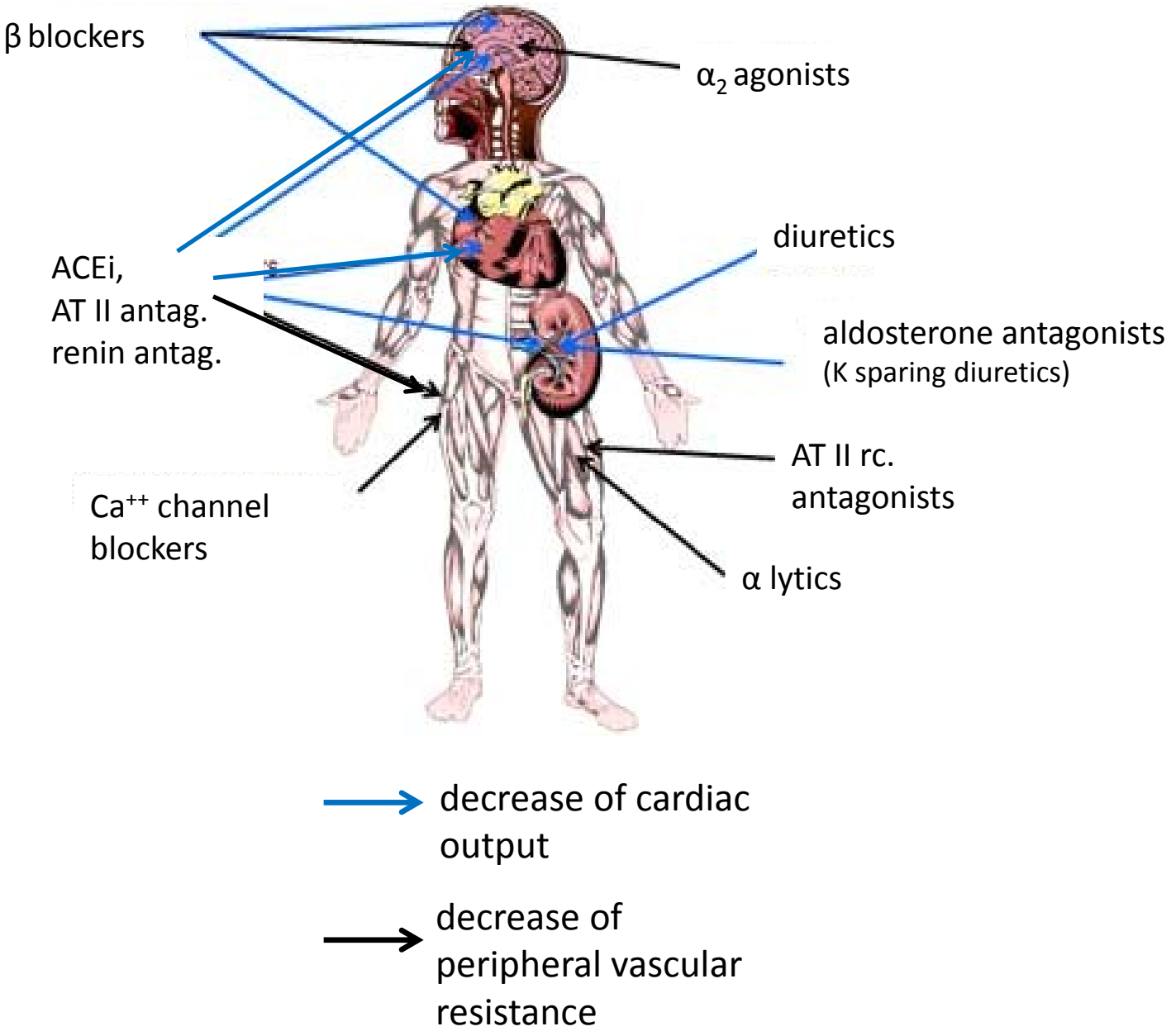
11. Drugs blocking adrenergic neurons

Mode of action: decrease of NA release

guanethidin – NA release → pressoric response →
→ decrease („consumption“) NA → pressoric response disappear
Adverse effects: orthostat. hypoten., decreased renasl and splanchnic perfusion

reserpine - ↓ NA in adrenergic neurons (including storage)

Adverse effects: depressions, nightmares, parkins. sy. postural hypotenze, congestion,
Indications: HT crisis


β blockers
α_2 agonists
diuretics
ACEi,
AT II antag.
renin antag.
aldosterone antagonists
(K sparing diuretics)
AT II rc.
antagonists
Ca^{++} channel
blockers
α lytics
decrease of cardiac output
decrease of peripheral vascular resistance

Antihypertensives combinations (suitable and most frequent)