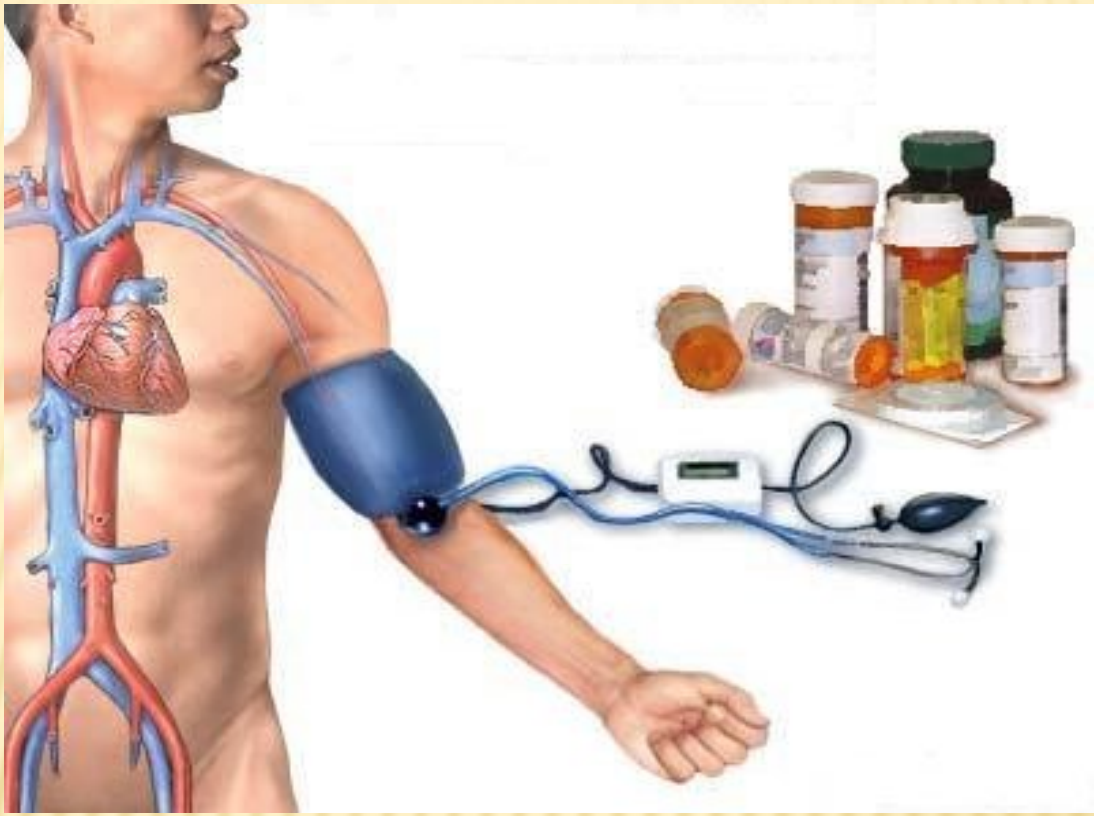


DRUGS USED TO TREAT HYPERTENSION

BY

ALI ALALAWI

3. Vasodilators

Drugs which dilate blood vessels (decrease peripheral vascular resistance) by acting on smooth muscle cells through non-autonomic mechanisms:

* *Release of nitric oxide*

(NO stimulates guanyl cyclase and increase cGMP in smooth muscles → reduction of cytoplasmic Ca^{2+} by causing Ca^{2+} sequestration in the endoplasmic reticulum → relaxation of both arterioles and venous capacitance vessels, lowering peripheral vascular resistance and reducing cardiac pre- as well as after-load)

* *Opening of potassium channels*

(Leads to hyperpolarization and relaxation of vascular smooth muscle)

* *Blockade of calcium channels*

(Reduce intracellular calcium concentration → relax aretriolar smooth muscle, reduce peripheral vascular resistance)

- compensatory responses are preserved (may include salt retention and tachycardia) → suitable combination with diuretics or β-blockers

A) DIRECT ACTING

minoxidil, diazoxide, sodium nitroprusside, hydralazine

Minoxidil

- therapy of severe hypertension resistant to other drugs
- prodrug → its metabolite (minoxidil sulfate) is a potassium channel opener (→ relaxation of vascular smooth muscle)
- more effect on arterioles than on veins
- orally active
- Adverse: Na^+ and water retention → coadministration with beta-vlocker and diuretic is mandatory for this drug, oedemas, hypertrichosis, breast tenderness

3. Vasodilators

Diazoxide

- given by rapid iv. injection (less than 30 seconds)* in hypertensive emergencies
- potassium channel opener
- *glucose intolerance* → due to reduced insulin secretion (used in patients with inoperable insulinoma)
- adverse: Na+ and water retention, hyperglycaemia, hirsutism

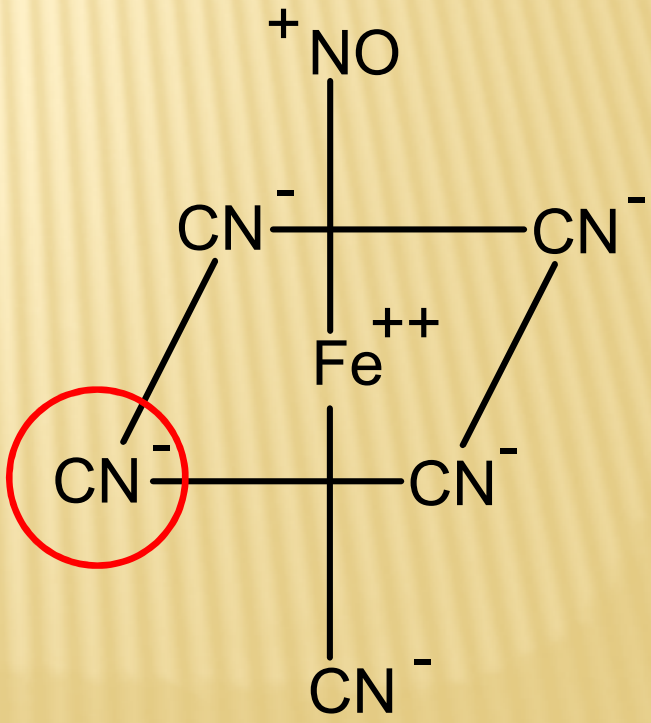
Hydralazine

- rapidly and fairly absorbed after oral administration
- ↓ arteriolar resistance
- useful for hypertensive crisis during pregnancy
- Adverse Effects: Na+ and water retention, systemic lupus erythematosus – suspected if there is unexplained weight loss, arthritis

*BNF 51th edition, 2006

Sodium nitroprusside

- short-acting agent (few minutes) → administrated by infusion in hypertensive emergencies (hypertensive encephalopathy, shock, cardiac dysfunction) for max 24 hours (risk of cumulation of cyanide → toxicity)
- Releases NO
- the stock solution should be diluted and covered with foil to prevent photodeactivation
- adverse effects: too rapid reduction of BP, nausea, palpitation, dizziness



cyanide metabolite accumulation – tachycardia, hyperventilation, arrhythmias, acidosis

B) INDIRECT ACTING - CALCIUM CHANNEL-BLOCKING AGENTS

1. dihydropyridine (nifedipine, nicardipine, amlodipine)
2. diltiazem, verapamil

- they block voltage-dependent „L-type“ calcium channels → relaxation of smooth muscle → vasodilation → reduce peripheral vascular resistance → reduction of BP
- negatively inotropic drugs

- they differ in selectivity for calcium channels in vascular smooth muscles and cardiac tissues

- orally active → suitable for long-term use

	NIFEDIPINE*	DILTIAZEM	VERAPAMIL
coronary arteries dill	+ +	+ +	+ +
peripheral arteries dill	+ + + +	+ +	+ + +
negative inotropic	+	+ +	+ + +
slowing AV cond	↔	+ + +	+ + + +
heart rate	↑ ↔	↓ ↔	↓ ↔
↓ blood presure	+ + + +	+ +	+ + +
depression of SA	↔	+ +	+ +
increase in cardiac output	+ +	↔	↔

* and others dihydropyridines

↓ = decrease

↑ = increase

↔ = without change

3. Vasodilators

DIHYDROPYRIDINES (nifedipine, nicardipine)

- evoke vasodilatation resulting in sympathetic reflex activation,

- relatively selective for vascular smooth muscle (arterial)

amlodipine, lacidipine, isradipine, felodipine – 2nd generation
- longer duration of action – once daily
- do not reduce myocardial contractility – do not produce clinical deterioration in heart failure

nimodipine – preferentially acts on cerebral arteries – prevention of vascular spasm following aneurysmal subarachnoid haemorrhage

Indication: *all grades of essential hypertension*

- alone (nifedipine, amlodipine) in patients with mild hypertension for patients in whom thiazide diuretics and β-blockers are contraindicated

- combinations

angina (with beta-blockers)

3. Vasodilators

verapamil, diltiazem

- effects on the voltage-dependent channels in cardiac conducting tissue
- vasodilatation
- it also blocks Ca^{2+} entry in gastrointestinal smooth muscle and consequently causes constipation

Adverse effects of calcium channel-blocking agents

Drug	Effect on heart rate	Adverse effects
Nifedipine	↑	Headache, flushing, ankle swelling
Amlodipine	↑	Ankle swelling
Nimodipine	±	Flushing, headache
Diltiazem	±	Generally mild
Verapamil	↓	Constipation, marked negative inotropic action

Calcium channel blockers do not affect concentrations of plasma cholesterol or triglycerides, or extracellular calcium homeostasis.

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS (ACEI)

Captopril, enalapril, quinapril, lisinopril, perindopril, ramipril

Indications

- hypertension where thiazide diuretics and beta-blockers are contraindicated
- useful in hypertensive patients with heart failure (beneficial effect)
- can limit the size of myocardial infarction
- diabetic nephropathy

MECAHNIS OF ACTION:

Angiotensinogen

Renin

Angiotension Conversion Enzyme

Angiotensin (in active)

Angiotesin II (active)

AT recptor

Aldesteron

Output of sympathetic nevous system

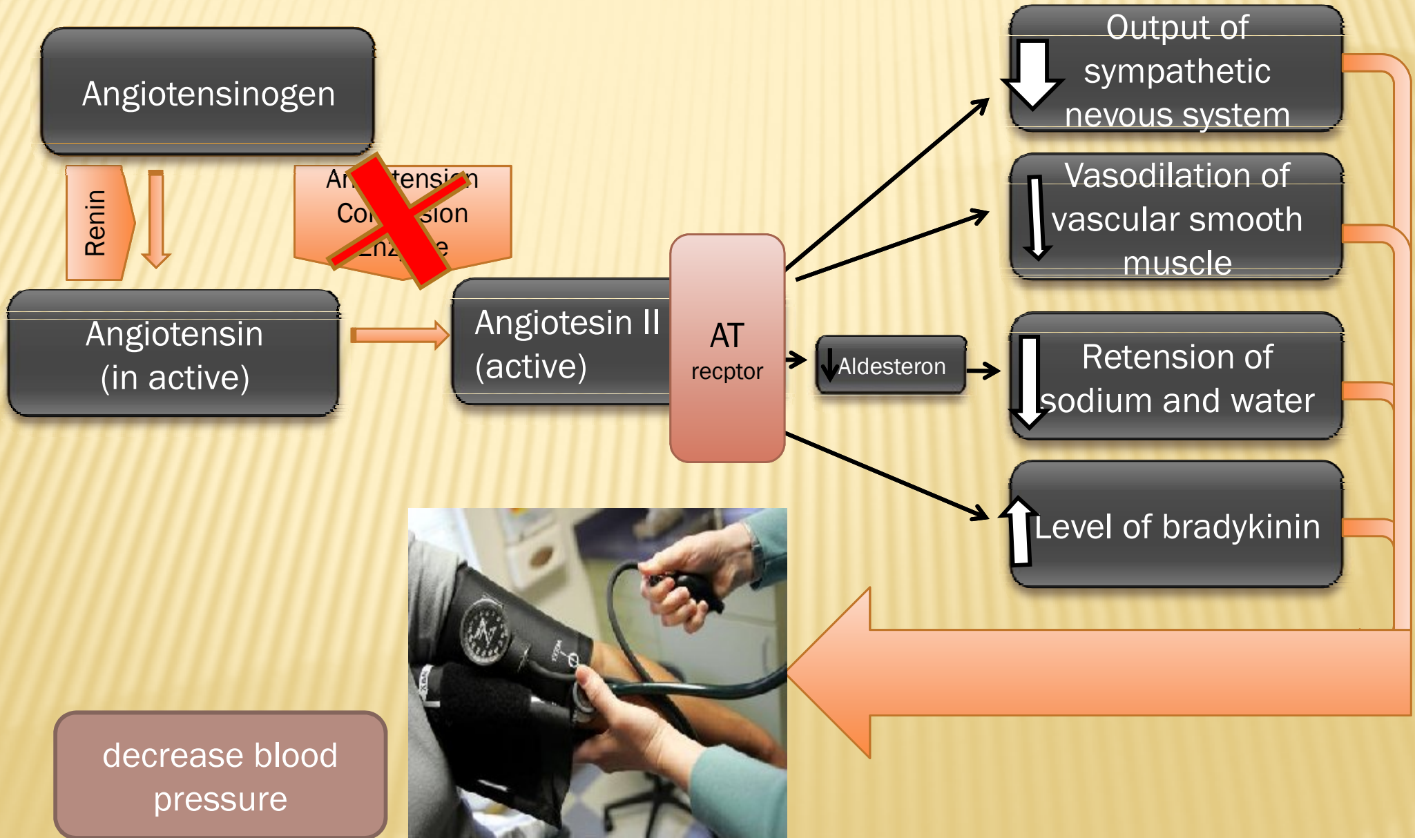
Vasoconstriction of vascular smooth muscle

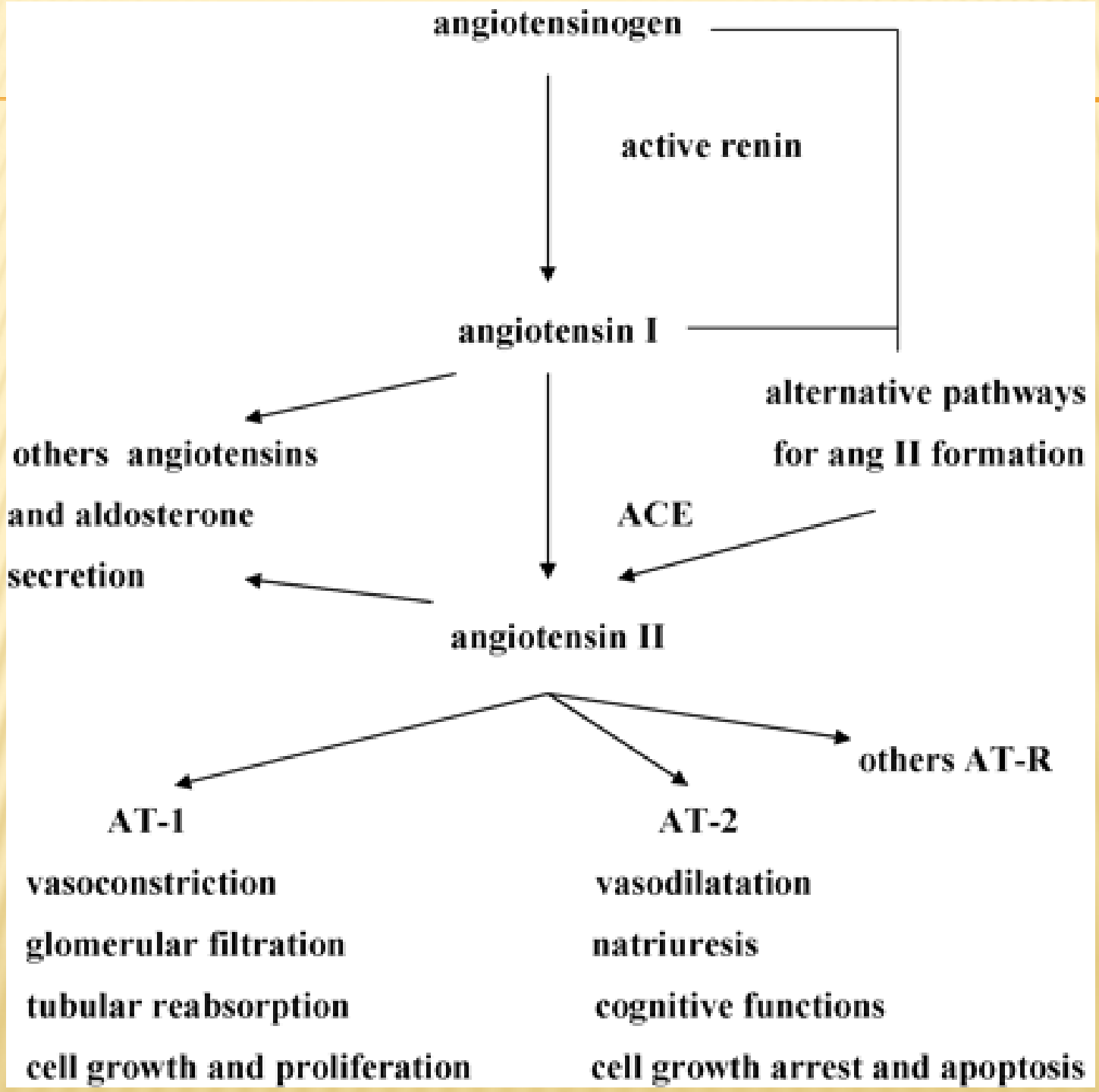
Retension of sodium and water

Level of bradykinin

Increase blood pressure

MECAHNIS OF ACTION:




angiotensinogen
active renin
angiotensin I
alternative pathways
for ang II formation
others angiotensins
and aldosterone
secretion
ACE
angiotensin II
others AT-R
AT-1
AT-2
vasoconstriction
glomerular filtration
tubular reabsorption
cell growth and proliferation
vasodilatation
natriuresis
cognitive functions
cell growth arrest and apoptosis

4. Angiotensin-converting enzyme inhibitors (ACEI), blockers of AT1 rc.

Mechanism of action

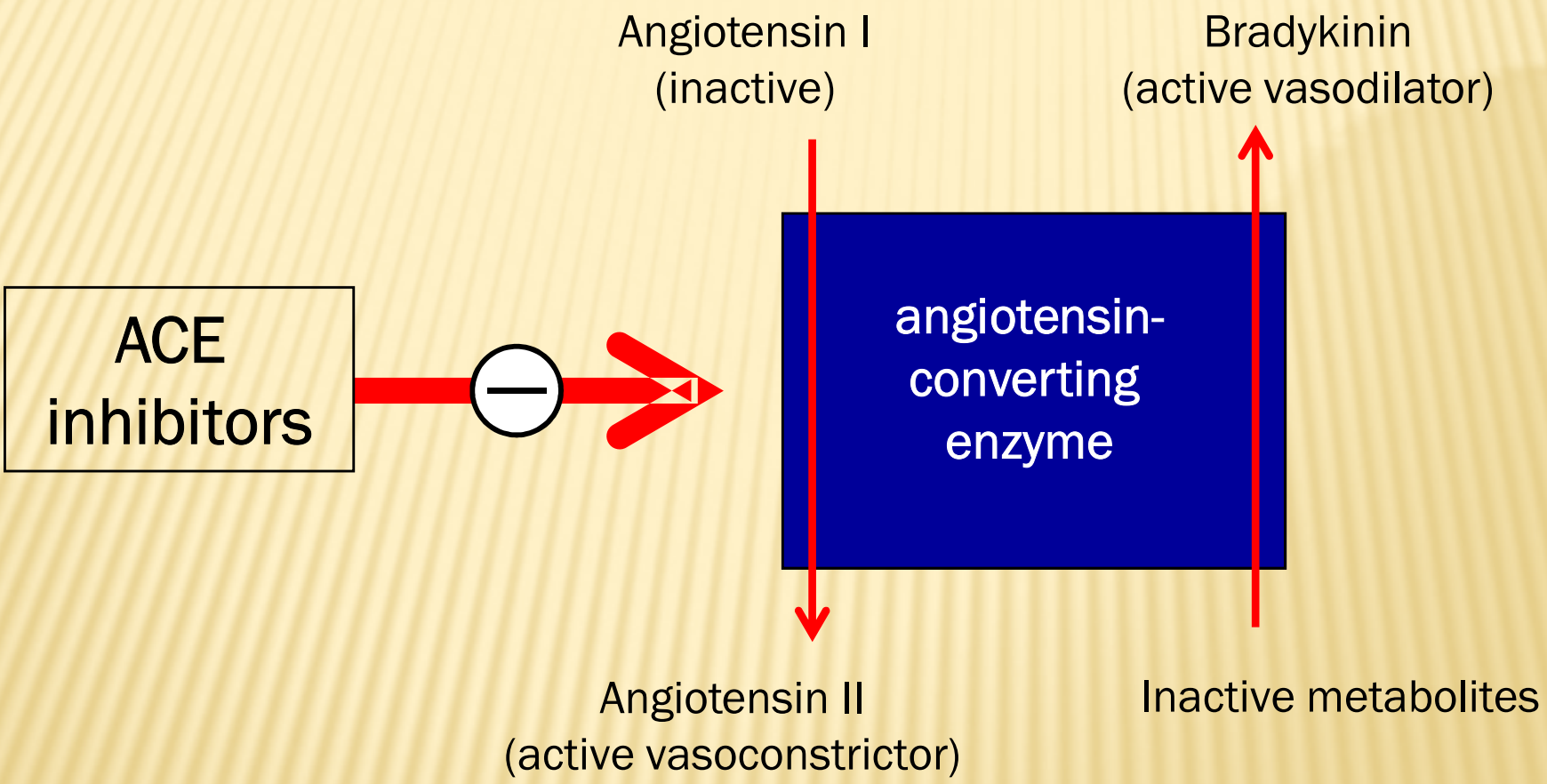
- ACEI regulates balance between bradykinin (vasodilatation, natriuresis) and angiotensin II (vasoconstriction, Na^+-retention)

- AT1 receptors - widely distributed in the body (lung - huge surface area of endothelial cells, heart, kidney, striated muscle and brain) and present on the luminal surface of vascular endothelial cells

Angiotensin II

- vasoconstriction
- noradrenaline release from sympathetic nerve terminals
- aldosterone secretion from the zona glomerulosa of the adrenal cortex
- ADH
- is a growth factor for vascular smooth muscle and some other cells = remodelling

4. Angiotensin-converting enzyme inhibitors (ACEI), blockers of AT1 rc.



Mechanism of action:

Converting enzyme inhibitors lower blood pressure by reducing angiotensin II, and also by increasing vasodilator peptides such as bradykinin.

- Dilatation of arteriol → reduction of peripheral vascular resistance, blood pressure and afterload
- Increase of Na^+ and decrease of K^+ excretion in kidney
- Decrease noradrenaline release → reduction of sympathetic activity (use is not associated with reflex tachycardia despite causing arterioral and venous dilatation)
- Inhibition of aldosterone secretion from the zona glomerulosa contributes to the antihypertensive effects of ACEI
- Influence on the arteriolar and left ventricular remodelling that are believed to be important in the pathogenesis of human essential hypertension and post-infarction state

Pharmacokinetics:

- active when administered orally
- most of ACEIs are highly polar, eliminated in the urine, without CNS penetration

fosinopril - metabolized by the liver
captopril, lisinopril - active per se
enalapril, quinapril - prodrugs → require metabolic conversion to active metabolites

enalapril, quinapril and lisinopril - given once daily
captopril - administered twice daily

However, ACE inhibitors are effective in many patients with low renin as well as those with high renin hypertension and there is only a poor correlation between inhibition of plasma-converting enzyme and chronic antihypertensive effect, possibly because of the importance of converting enzyme in various key tissues rather than in the plasma.

ACE inhibitors

	Drug	Duration of effect (hours)
Short-acting:	*captopril*	***6-8***
Medially-acting:	*enalapril*	***12***
	quinapril	
Long-acting:	*perindopril*	***24***
	lisinopril	
	spirapril	
	ramipril	

Adverse effects and contraindications of ACEI:

-are generally well tolerated. Adverse effects include:

First dose hypotension - particularly in those receiving diuretic therapy; the first dose should preferably be given at bedtime.

Dry cough

- the most frequent (5-30%) symptom; could be reduced by treatment with sulindac (inhibits prostaglandin biosynthesis)

Urticaria and angioneurotic edema

- ↑ kinin concentrations → urticarial reactions and angioneurotic edema)

Functional renal failure

- occurs predictably in patients with hemodynamically bilateral renal artery stenosis, and in patients with renal artery stenosis in the vessel supplying a single functional kidney (though they protect the diabetic kidney) - !!! renovascular disease !!!

Fetal injury

- results in oligohydramnios, craniofacial malformations
- contraindication in pregnancy

4. Angiotensin-converting enzyme inhibitors (ACEI), blockers of AT1 rc.

Hyperkalemia – monitor !!

- ACEIs cause a modest increase in plasma potassium as a result of reduced aldosterone secretion. This may usefully counter the small reduction in potassium ion concentration caused by thiazide diuretics.

Potassium accumulation may be marked, especially if the patient is consuming high-potassium diet and/or *potasssium-sparing diuretics*. Under these circumstances, potassium concentrations may reach toxic levels (hazardous in patients with renal impairment).

THERAPEUTIC COMBINATION:

- Useful interaction ACEIs with diuretics: Converting enzyme inhibitors interrupt by *diuretics* increased plasma renin activity (and the consequent activation of angiotensin II and aldosterone) and *enhance the antihypertensive efficacy of diuretics, as well as reducing thiazide-induced hypokalemia*.

- Adverse interaction ACE inhibitors with potassium-sparing diuretics and potassium supplements, leading to hyperkalemia especially in patients with renal impairment !!! NSAID – ↑ renal damage

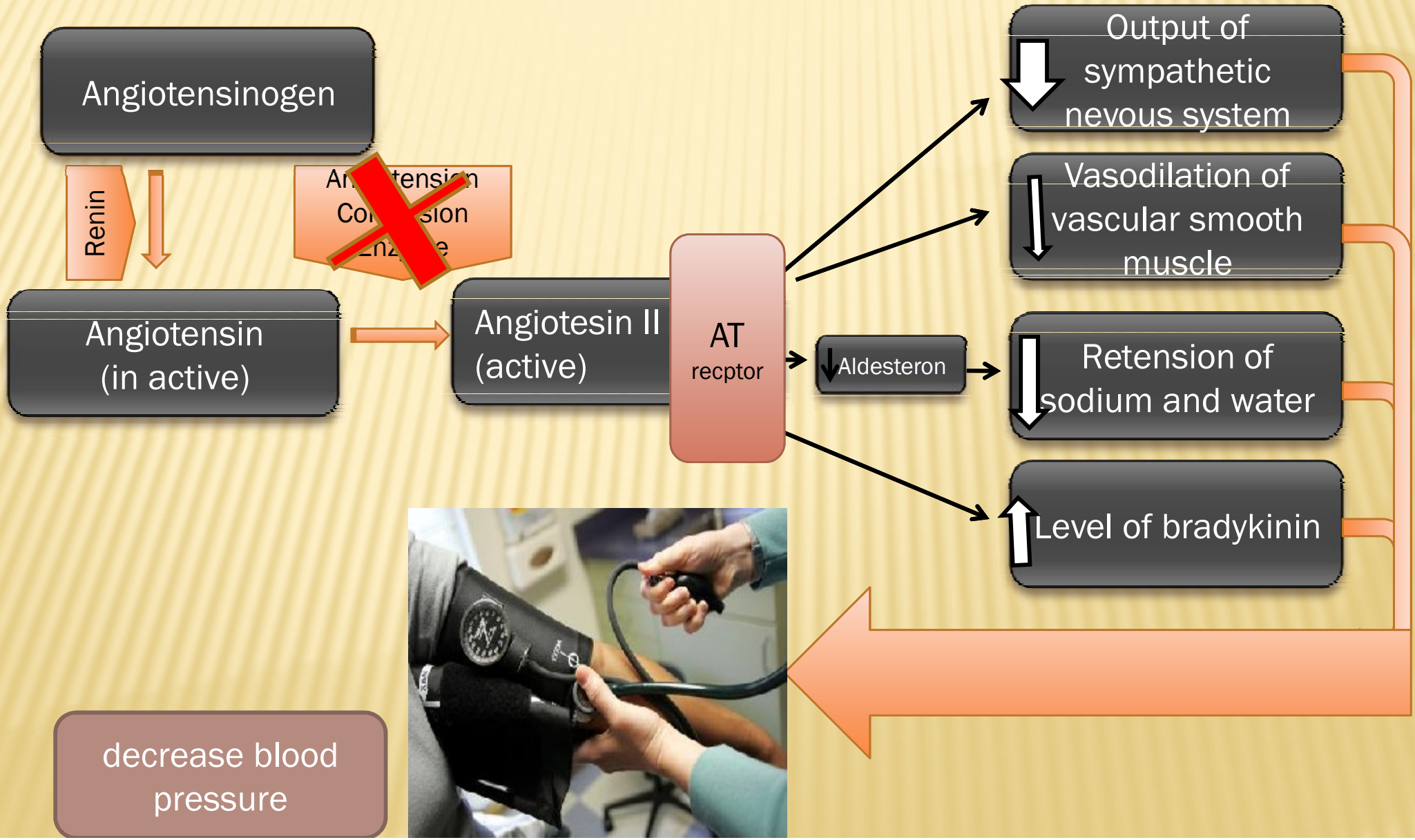
B) BLOCKERS OF AT1 RECEPTOR

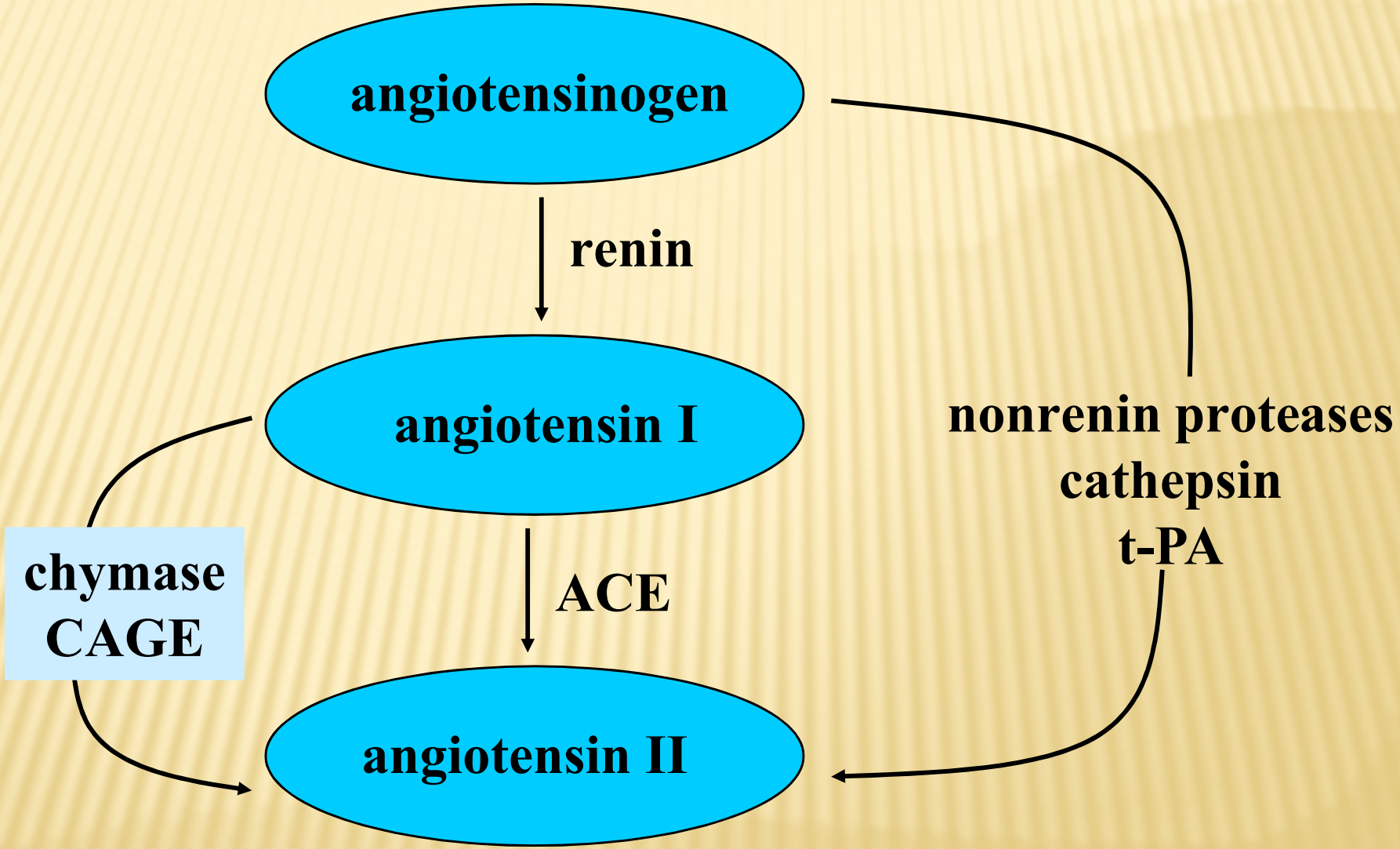
losartan, valosartan, irbesartan

- the receptor blockers - *competitively inhibit angiotensin II* at its AT_1 receptor site

- most of the effects of angiotensin II - including vasoconstriction and aldosterone release - are mediated by the AT_1 receptor
- AT_1-blockers do not block AT_2 receptor, which is exposed to high concentration of angiotensin II during treatment with AT_1-blockers
- they influence RAS more effective because of selective blockade (angiotensin II synthesis in tissue **is not** completely dependent only on renin release, e.g. in heart, but could be promote by serin-protease - stronger influence on the myocard **remodelling**)

MECAHNIS OF ACTION:




angiotensinogen
renin
angiotensin I
ACE
angiotensin II
chymase
CAGE
nonrenin proteases
cathepsin
t-PA

- these drugs lower blood pressure as the ACE inhibitors and have the advantage of much lower incidence of adverse effects resulting from accumulation of bradykinin (cough, angioneurotic oedema)
- they cause fetal renal toxicity (like that of the ACE inhibitors)
- these drugs reduce aldosterone levels and cause potassium accumulation (attainment of toxic levels - hazardous in patients with renal impairment).

Thank you