ANTIHYPERTENSIVE AGENTS

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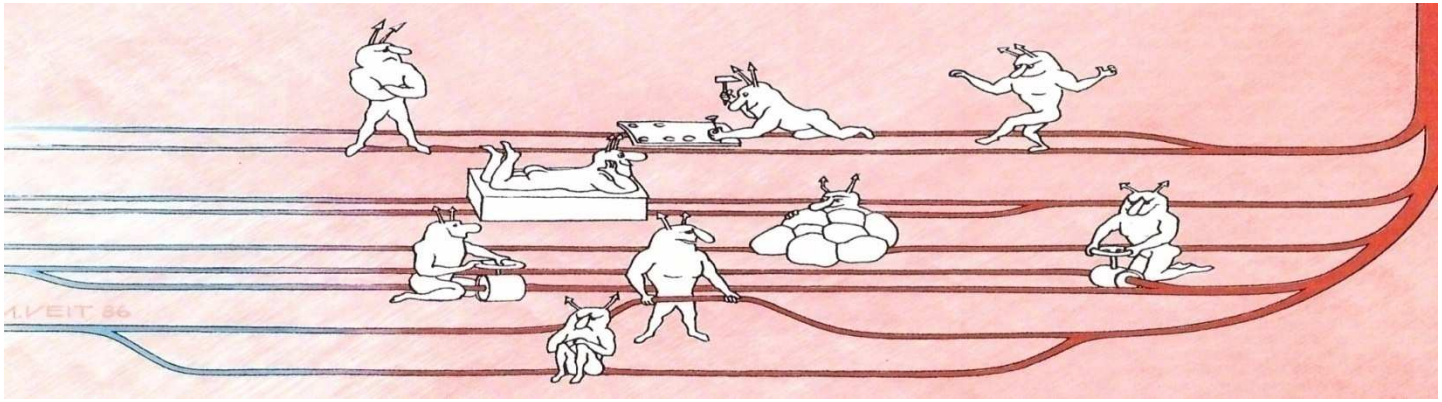
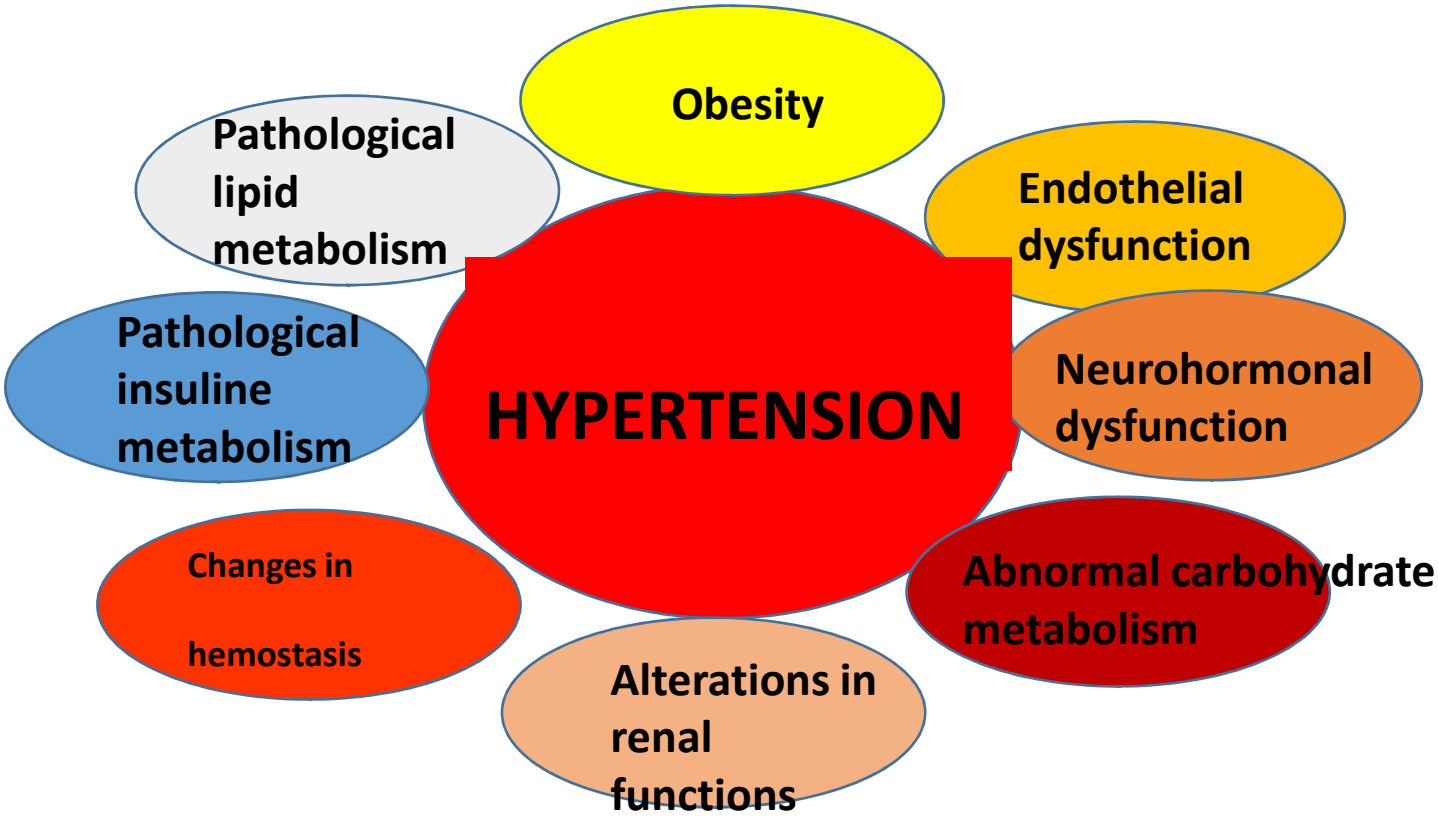


HYPERTENSION

- What is hypertension? Generally, when the blood pressure is over 140/90 Hgmm
- Incidence of hypertension: cca. 30% of adult population
- According to predictions, the number of hypertensives will increase by 60% until 2025. (cca. 1,6 billion people!)
- The most prominent consequences of hypertension: damage of the vessels
  - **Heart: myocardial infarction**
  - **Brain: stroke**
  - **Kidney: renal insufficiency**
  - **Eye: retinopathy**

Multimetabolic X-syndrome



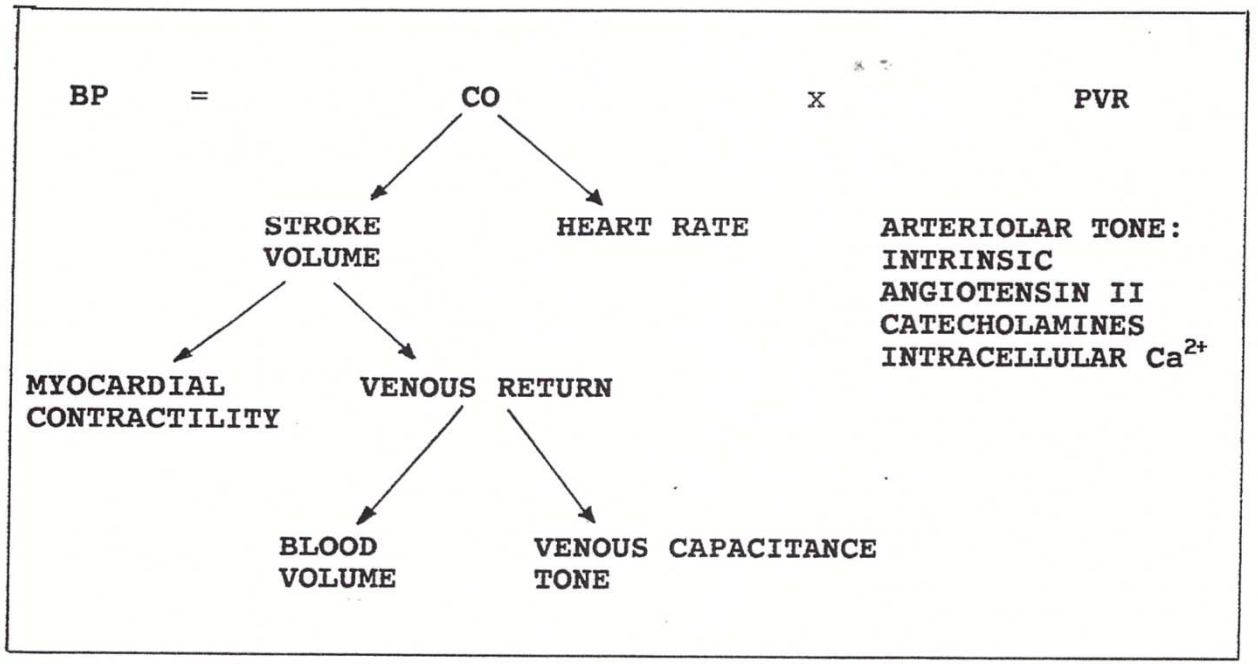
Cardiovascular risk factors

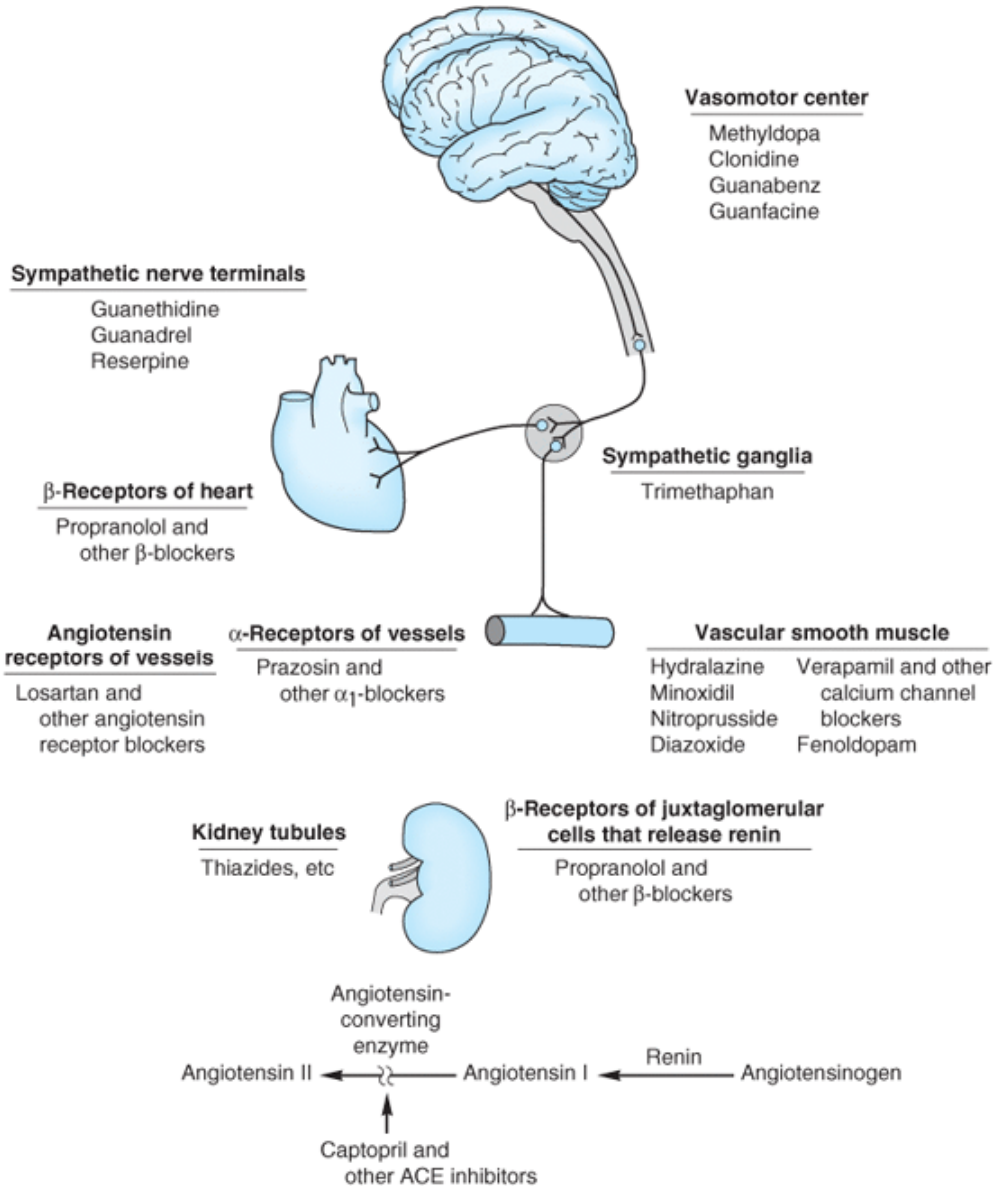
RISK FACTOR	HEART	BRAIN	EXTREMITIES
Hyperlipoproteinemia	+++	-	+
Smoking	++	+	+++
Hypertension	+	+++	+

Antihypertensive treatment

- Main goal: reduction of elevated blood pressure
- 2 Hgmm decrease in BP :
- Reduces the cardiovascular mortality by 7%
- Reduces the incidency of stroke by 10%

Blood pressure




Vasomotor center
Methyldopa
Clonidine
Guanabenz
Guanfacine
Sympathetic nerve terminals
Guanethidine
Guanadrel
Reserpine
Sympathetic ganglia
Trimethaphan
β-Receptors of heart
Propranolol and other β-blockers
Angiotensin receptors of vessels
Losartan and other angiotensin receptor blockers
α-Receptors of vessels
Prazosin and other α1-blockers
Vascular smooth muscle
Hydralazine
Minoxidil
Nitroprusside
Diazoxide
Verapamil and other calcium channel blockers
Fenoldopam
Kidney tubules
Thiazides, etc
β-Receptors of juxtaglomerular cells that release renin
Propranolol and other β-blockers
Angiotensin-converting enzyme
Renin
Angiotensin II
Angiotensin I
Angiotensinogen
Captopril and other ACE inhibitors

CLASSIFICATION OF ANTIHYPERTENSIVE DRUGS:

1. **DIURETICS**

   1.1. Thiazides
   1.2. Loop diuretics
   1.3. Potassium sparing diuretics

2. **SYMPATHOLYTIC DRUGS**

   2.1. Centrally acting sympathoplegic drugs
   2.2. Ganglion blocking agents
   2.3. Adrenergic neuron blocking drugs
   2.4. Beta-adrenergic antagonist
   2.5. Alpha-adrenergic antagonists
   2.6. Mixed antagonist

3. **VASODILATORS**

4. **INHIBITORS OF ANGIOTENSIN**

First-line antihypertensive drugs

- 1. Diuretics
- 2. Beta adrenergic receptor blockers
- 3. Calcium channel blockers
- 4. ACE inhibitors
- 5. Angiotensin receptor blockers

Second line antihypertensive drugs

- 1. Centrally acting sympatholytic drugs
- 2. Adrenergic neuron blockers
- 3. Alpha1 adrenergic receptor blockers
- 4. Directly acting vasodilators

First-line antihypertensive drugs 1. DIURETICS

- One of the most frequently used drugs for treatment of hypertension.
- Prototypic drugs:
- Hydrochlorothiazide (thiazide)
- Furosemide (loop diuretic)
- Indapamid (non-thiazide)

First-line antihypertensive drugs 1. DIURETICS

- THIAZIDEs (e.g. hydrochlorothiazide)
- Hemodynamic actions

PHASES	Blood pressure	Heart rate	Cardiac output	Peripheral resistance
Acute phase (appr. First 1 month)	↓	↑	↓	↑
Chronic phase	↓	↔	↔	↓

First-line antihypertensive drugs
1. DIURETICS

- **MECHANISM OF ACTION OF THIAZIDE-TYPE DIURETICS**

1. Increase of diuresis. Decrease of circulating blood volume. Reduction of preload. Reduction of cardiac output.
2. Decrease of sensitivity of vessels against vasoconstrictors.
3. Increased kallikrein production (kininogen-kallikrein-bradykinin pathway)
4. Increment of complience of vessels (reduction of vascular edema)

First-line antihypertensive drugs
1. DIURETICS

- Diuretics are necessary during antihypertensive treatment.
- Why?: because of long-term vasodilator treatment water and sodium retention → resistance against antihypertensive treatment.
- Solution: diuretics
- Adverse reactions:
- 1. Potassium depletion
- 2. Increase of blood glucose (propensity to diabetes)
- 3. Hyperlipidemia (temporary)
- 4. Increase of uric acid level (risk factor)

First-line antihypertensive drugs
1. DIURETICS

- Favourite diuretic with few side effects. Non-thiazid
- diuretic: **indapamid**

Pharmacological and clinical advantages of Indapamid:

1. Lower incidence of hypokalemia
2. Vasodilator:

2.1. Increment of PG synthesis

2.2. Intracellular Ca2+ antagonist (calmodulin complex)

3. Lower incidence of insulin resistance
4. Does not alter glucose and lipid metabolism
5. Only sligh increment in uric acid level

First-line antihypertensive drugs
2. Beta receptor blockers

- **BETA-ADRENERGIC RECEPTOR BLOCKERS**
- **1st generation (non-selective)**

Drug	Membr.stab. effect	ISA	Lipide sol.
Pindolol	+	+ + +	+
Timolol	-	+ -	+
Sotalol	-	-	+
Propranolol	+ +	-	+ +
Oxprenolol	+	+	+ +

First-line antihypertensive drugs
2. BETA RECEPTOR BLOCKERS

- 2nd generation (beta1 selective drugs)

Drug	Membr.stab. effect	ISA	Lipid solubility
Metoprolol	+ -	-	+ +
Atenolol	-	-	-
Esmolol	-	-	+ -
Bisoprolol	-	-	+ -

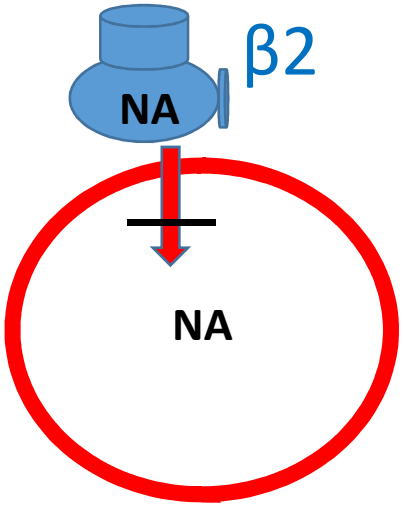
First-line antihypertensive drugs
2. Beta receptor blockers

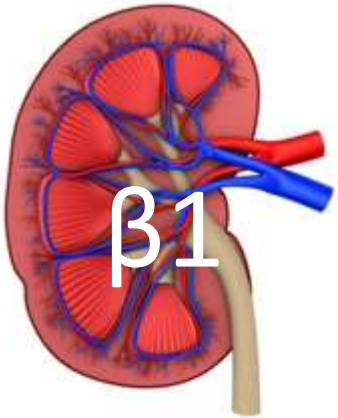
- 3rd generation (vasodilatory beta blockers)

Drug	Lipid solubility	Mechanism of vasodilation
Labetalol	+ + +	Alpha-receptor blockade
Carvedilol	+	Alpha-receptor blockade
Nebivolol	+ -	NO production

First-line antihypertensive drugs
2. Beta receptor blockers

- Mechanism of antihypertensive actions of beta receptor blockers:
-
-





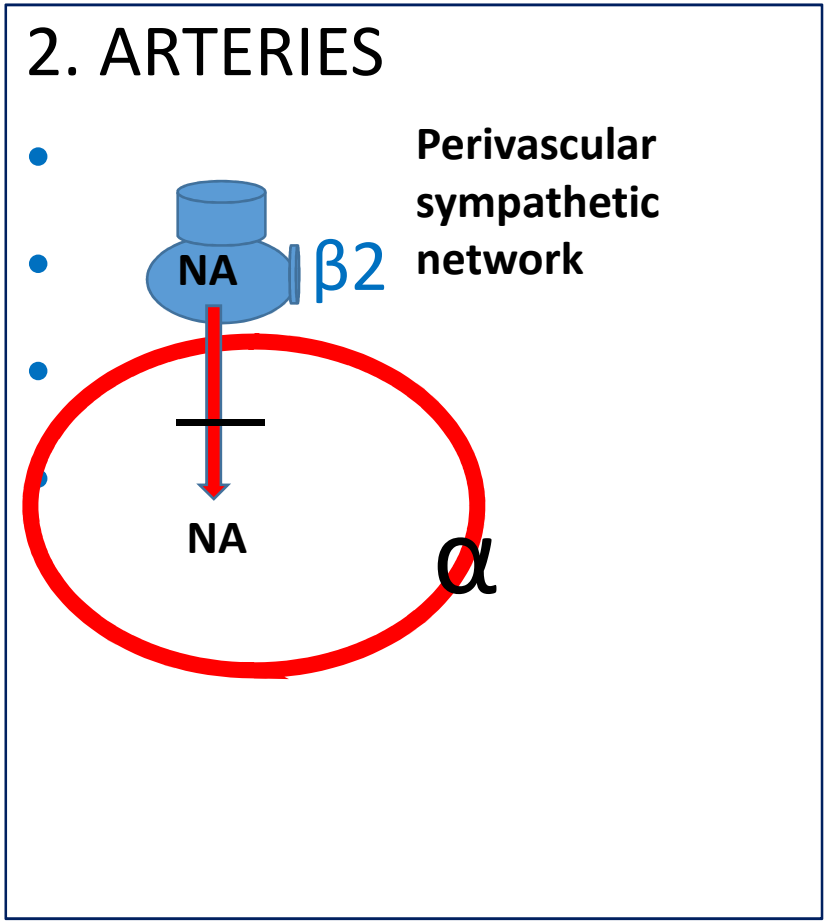
1. HEART
2. ARTERIES
3. KIDNEY

First-line antihypertensive drugs
2. Beta receptor blockers

- 1. HEART

- Beta1 and beta2 adrenergic receptors:
- Pacemaker activity
- Myocardial contractility
- Reduced cardiac output after blockade of beta receptors → decrease of blood pressure

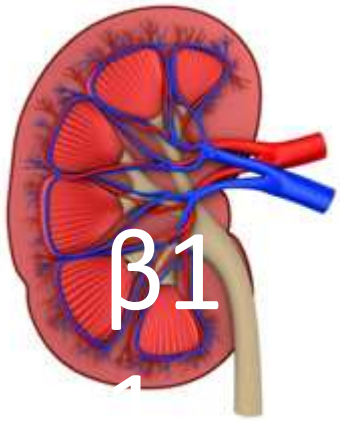
First-line antihypertensive drugs
2. Beta receptor blockers



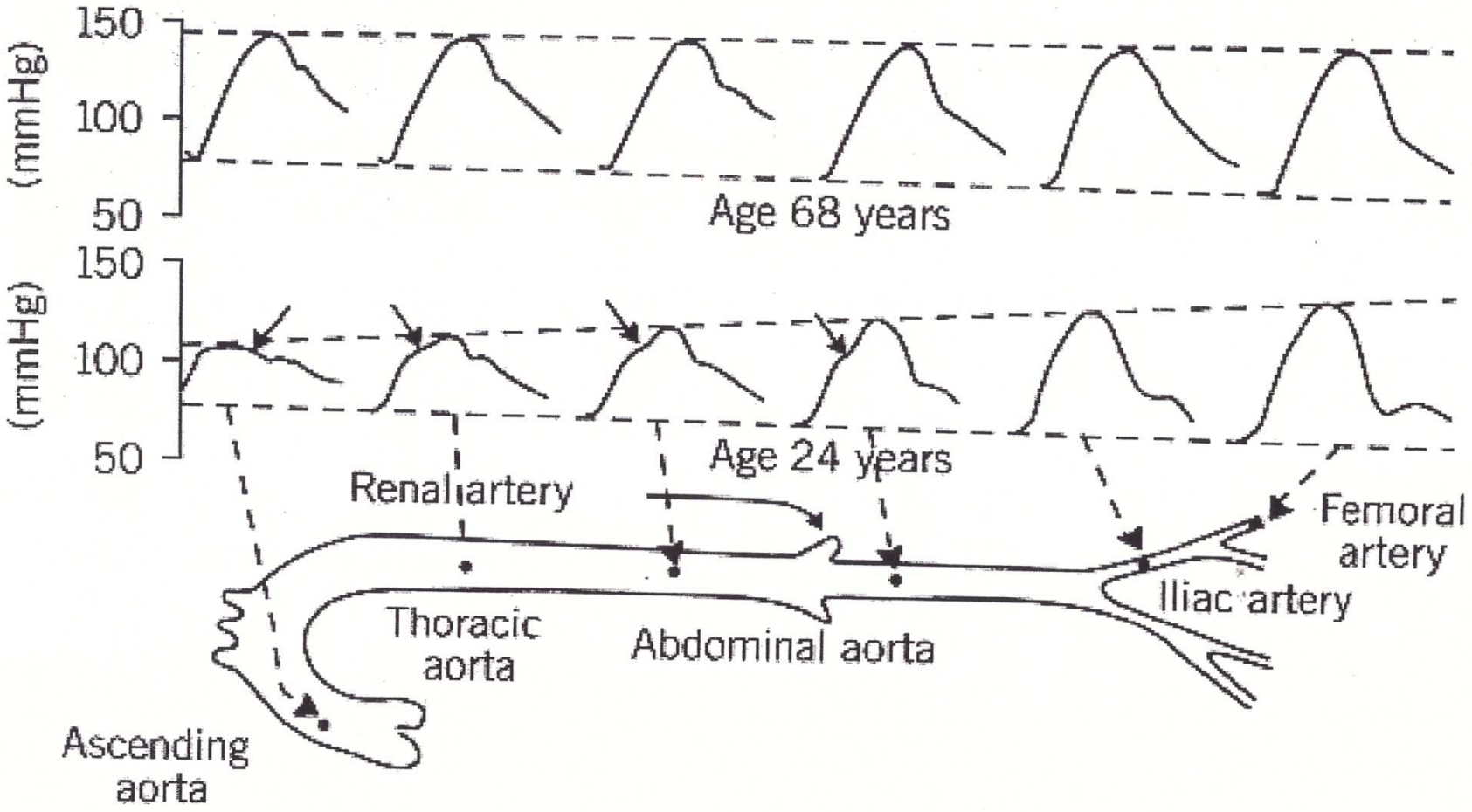
- Acute effects of beta blockers: vasoconstriction
- After long-term blockade of beta2 receptors – inhibition of noradrenaline release - vasodilation

First-line antihypertensive drugs
2. Beta receptor blockers

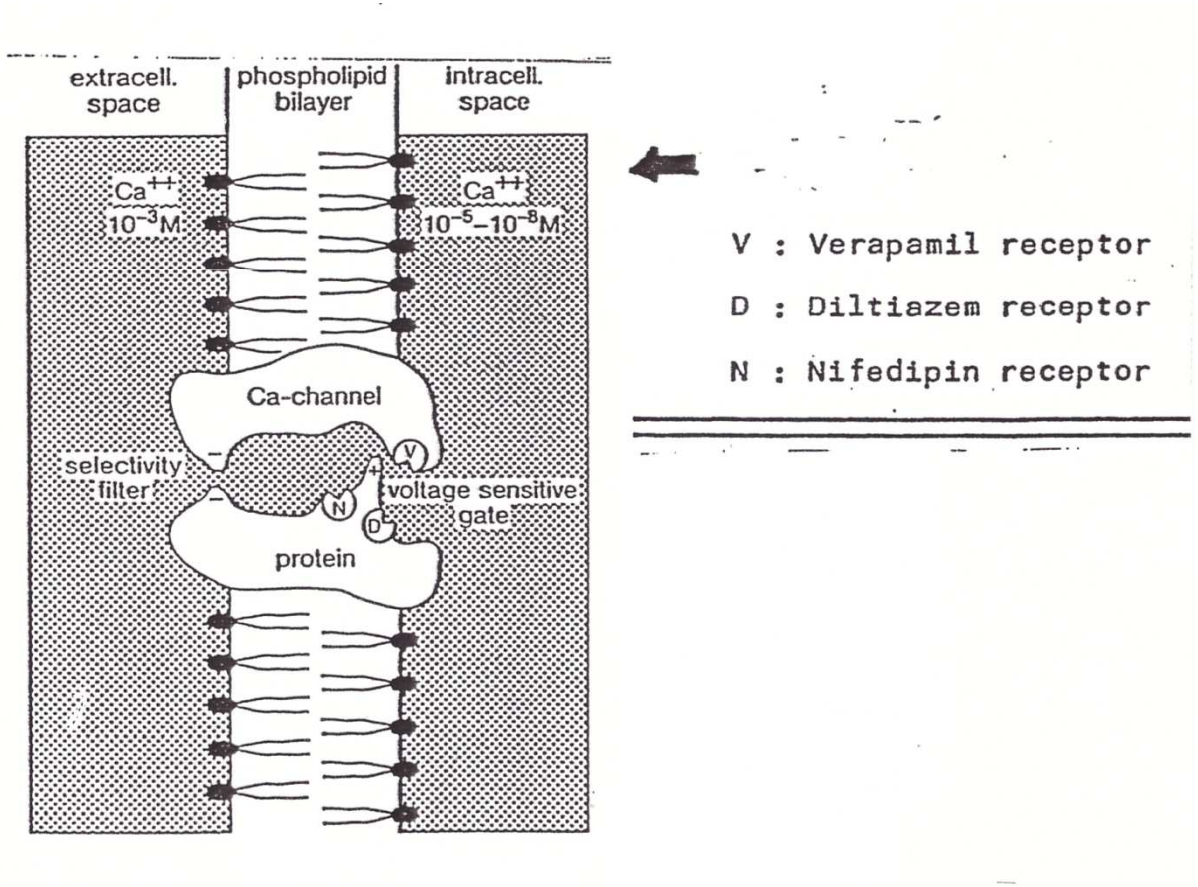
3. KIDNEY



- Juxtaglomerular apparatus. Beta 1 receptors – renin production (ANG I – renin – ANG II)
- After beta receptor blockade, renin-induced ANG II
- production decreases


150
100
50
(mmHg)
Age 68 years
150
100
50
(mmHg)
Age 24 years
Renal artery
Femoral artery
Iliac artery
Thoracic aorta
Abdominal aorta
Ascending aorta

First-line antihypertensive drugs
3. Calcium channel blockers



First-line antihypertensive drugs
3. Calcium channel blockers

FIRST GENERATION DRUGS
VERAPAMIL (fenilalkilamin)
NIFEDIPIN (dihydropiridin)
DILTIAZEM (benzothiazepin)

First-line antihypertensive drugs
3. Calcium channel blockers

SECOND GENERATION DRUGS
FELODIPIN
ISRADIPIN
NIMODIPIN
NITRENDIPIN
NISOLDIPIN

First-line antihypertensive drugs
3. Calcium channel blockers

THIRD GENERATION DRUGS
AMLODIPIN
LACIDIPIN
LERCANIDIPIN

First-line antihypertensive drugs
3. Calcium channel blockers

- 1st generation agents: short action
- Verapamil and diltiazem: specific drugs for sinuatrial and AV node. Antiarrhythmic agents
- Nifedipin: specific for smooth muscle. Antianginal and antihypertensive drugs.
- 2nd generation drugs: long acting, tissue specificity (e.g. nimodipin: specificity for brain vessels)
- 3nd generation agents: highly lipophylic drugs, long-lasting vasodilation, antiatherosclerotic effect

First-line antihypertensive drugs
3. Calcium channel blockers

- Mechanism of antihypertensive actions:
- Dilation of arteries, veins, precapillary arterioles – decreased preload and afterload, increased microcirculation
- Side effects:
- Ankle edema (N)
- Tachycardia, palpitation (N)
- Constipation (V és D)
- Bradycardia (V és D)
- AV block (V és D)
- 60% increase in AMI (short acting nifedipine)

First-line antihypertensive drugs
4. ACE inhibitors

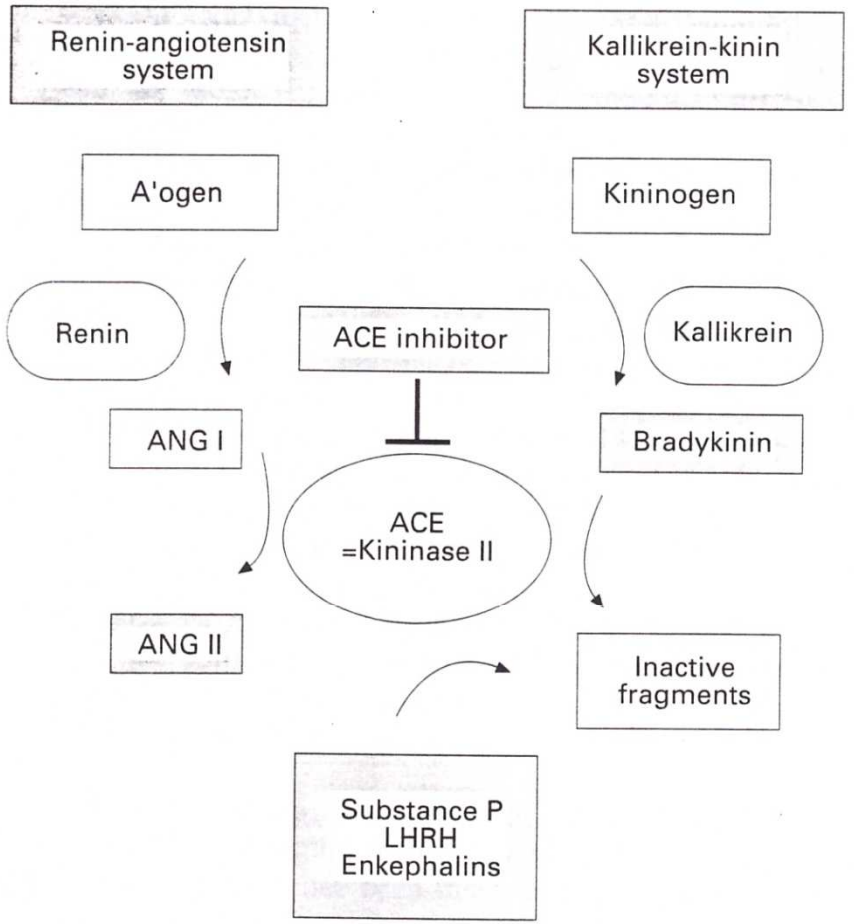
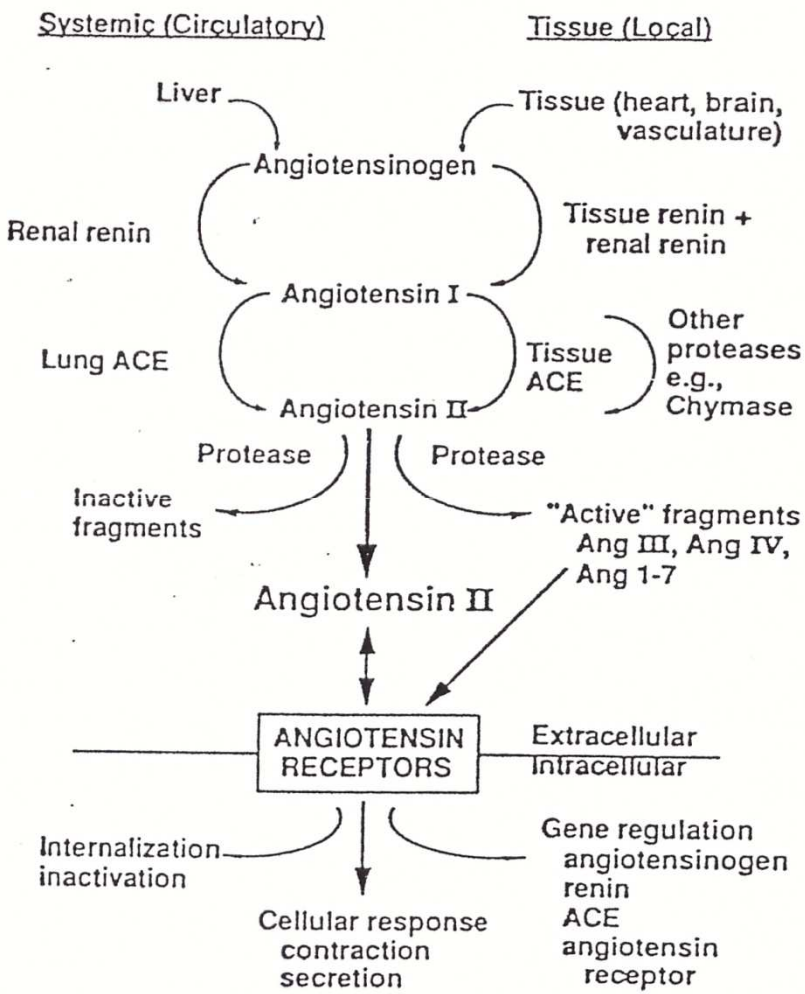


Figure 1 *Schematic representation of the role of angiotensin converting enzyme (ACE) in the renin-angiotensin and kallikrein-kinin system and peptide metabolism. A'ogen = angiotensinogen; ANG I = angiotensin I, ANG II = angiotensin II; LHRH = luteinising hormone releasing hormone.*



The angiotensin system.

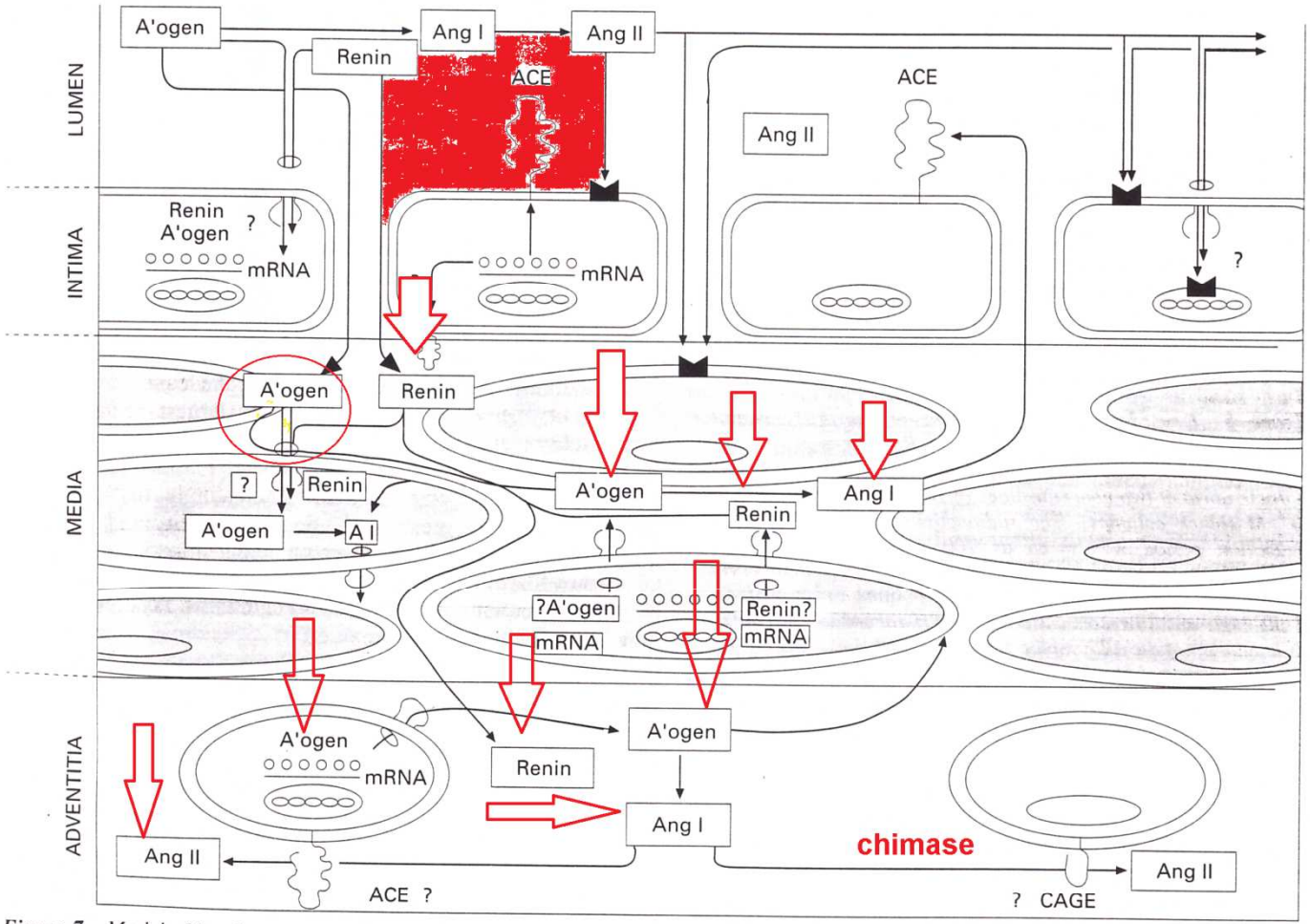
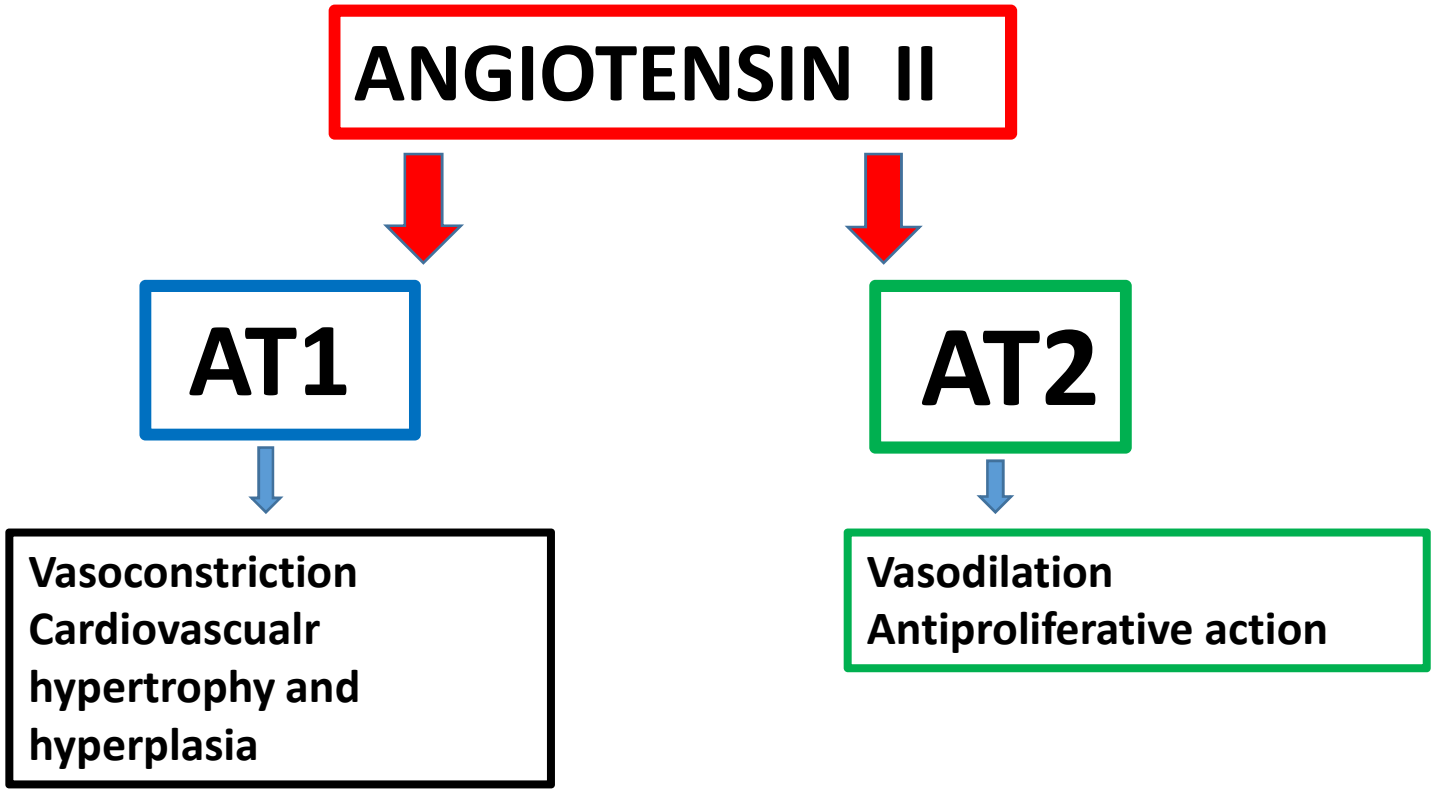
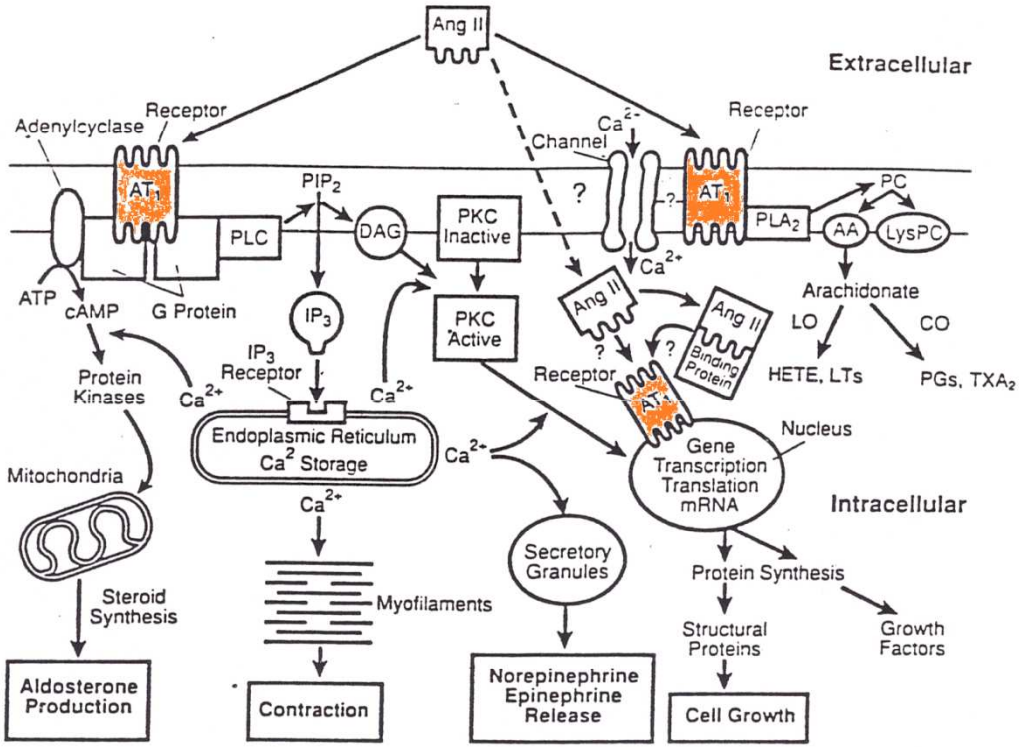


Figure 7 *Model of local angiotensin II (ANG II) generation in the vascular wall. Renin can be taken up from the circulating blood whereas local synthesis of renin in the intimal, medial, or adventitial layer of the vascular wall is still controversial. Angiotensinogen (A'ogen) can be taken up from the circulating blood and be synthesised in the adventitial layer while synthesis in the intimal and medial layer has not yet been unequivocally demonstrated. Angiotensin I (ANG I), the direct precursor for ANG II, can be synthesised locally in the vascular wall and has to be secreted from intracellular tissue compartments to be activated by extracellular angiotension converting enzyme (ACE). ANG II can become part of the circulating renin-angiotensin system (endocrine) or bind to receptors on the same cell (autocrine) or an adjacent cell (paracrine). Note that most of the ANG II molecules are generated by ACE localised at the luminal site of the endothelial cells. However, there might be alternative pathways as shown for the adventitial layer. The adventitial layer consists of a number of different cell types including endothelial cells (vaso vasorum), fibroblasts, neuronal cells, or smooth muscle cells. However, which of these cells express the components of the renin-angiotensin system is currently unknown. CAGE = chymostatin sensitive angiotensin II generating enzyme.*

First-line antihypertensive drugs
4. ACE inhibitors



ANGIOTENSIN II RECEPTORS AND RECEPTOR ANTAGONISTS



Ang II receptor-cellular response coupling. PLC, phospholipase C; DAG, diacylglycerol; IP_3, inositol triphosphate; G protein, guanosine triphosphate-binding protein; PKC, protein kinase C; AA, arachidonic acid; PC, phosphatidylcholine; LysPC, lysophosphatidylcholine; LO, lipoxygenase; CO, cyclooxygenase; HETE, hydroxyeicostatetraenoic acid; TXA_2, thromboxane A_2; PGs, prostaglandins (e.g., prostaglandin E_2); Channel; calcium channel; PIP_2, phosphatidylinositol diphosphate; LTs, leukotrienes.

First-line antihypertensive drugs
4. ACE inhibitors

- MECHANISM OF ANTIHYPERTENSIVE EFFECT OF ACEIs
- 1. Inhibition of direct vasoconstrictor effect of Ang II.
- **VASODILATION**
- 2. Inhibition of Ang II-induced aldosteron secretion
- **REDUCED BLOOD VOLUME (increased Na excretion)**
- 3. Increase of tissue bradykinin
- 3.1. Enhanced PG synthesis **VASODILATION**
- 3.2. Increased NO production **VASODILATION**
- 4. Inhibition of presynaptic Ang II action INHIBITION OF NA RELEASE

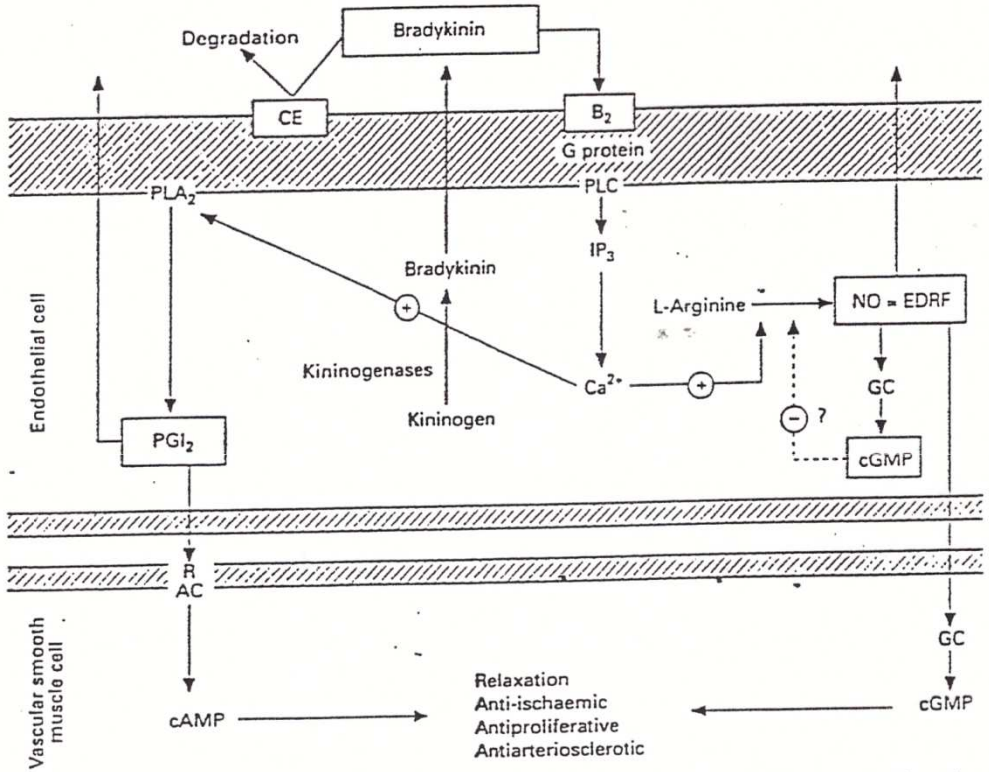


Figure 5 Model of the endothelial cell to explain the mechanism by which converting enzyme inhibitors stimulate the production of ni oxide and prostacyclin. CE = converting enzyme; cGMP = cyclic guanosine monophosphate; B_2 = B_2 kinin receptor; PLC = phospholipase IP_3 = inositoltriphosphate; NO = nitric oxide (EDRF); GC = guanylyl cyclase; PLA_2 = phospholipase A_2; AC = adenylyl cyclo PGI_2 = prostacyclin. (See text for further explanation.)

First-line antihypertensive drugs
4. ACE inhibitors

- PLEIOTROPIC ACTIONS OF ACE INHIBITORS:
- 1. Improvement of cognitive functions (primarily at centrally acting ACE inhibitors: captopril, fosinopril, lisinopril, perindopril, trandorapril. Non-centrally acting ACEIs: slight effects: enalapril, quinapril)
- 2. Mood elevation
- 3. Increase of tissue insulin sensitivity (K concentration increases)

First-line antihypertensive drugs
4. ACE inhibitors

- **ADVERSE EFFECTS OF ACE INHIBITORS**
- **1. Dry cough (3-30 %)**
- **2. Loss of taste**
- **3. Allergic skin reactions, angioneurotic edema**
- **4. Headacke, dizziness, weakness**
- **5. Hyperkalemia**

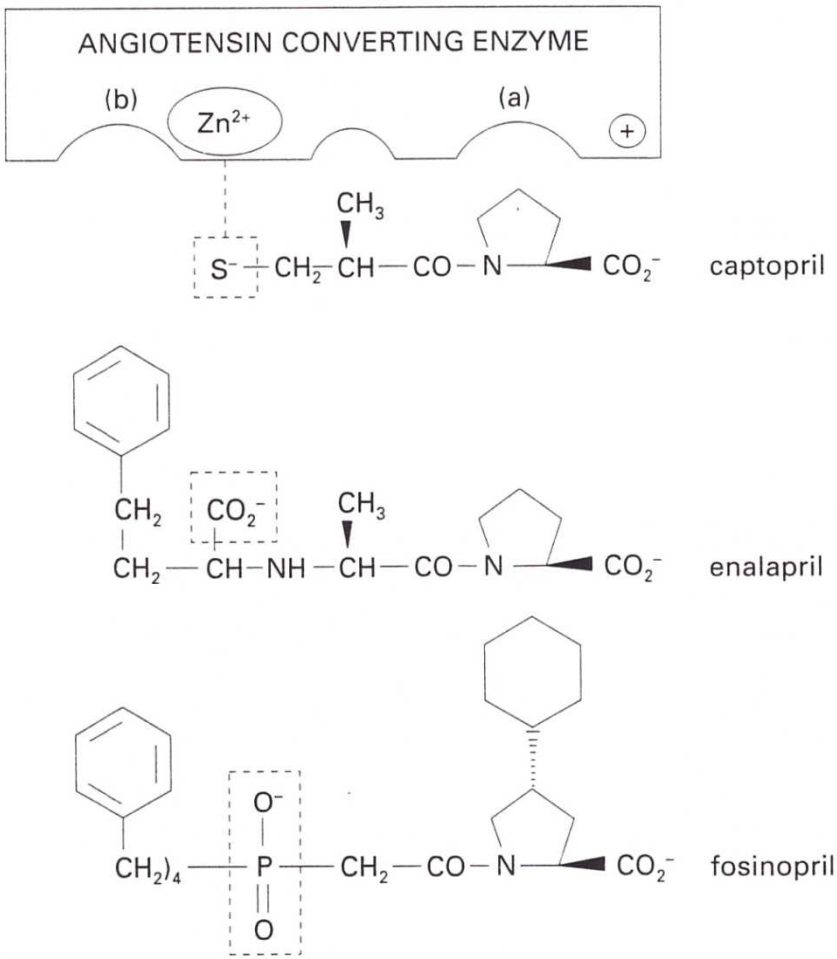


Figure 6 *Hypothetical model of the active site of ACE and the interaction of three classes of ACE inhibitors with the zinc ion, a positively charged group, a hydrophobic pocket (a), and auxiliary binding sites (b) of the enzyme (adapted from Ondetti[33]).*

First-line antihypertensive drugs
4. ACE inhibitors

- Classification of ACE inhibitors:
- 1. Sulphydryl containing drugs: e.g. captopril
- 2. Carboxyl containing drugs: e.g. enalapril
- 3. Phosphorus containing drugs: e.g. fosinopril

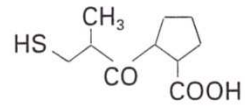
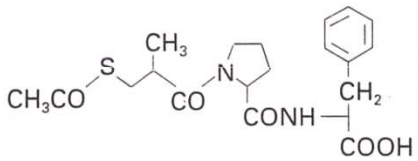
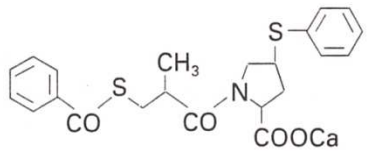
Compound (status)	Structure	Prodrug	MW	Potency *IC_{50} nM active drug	Daily dose (mg) frequency
Captopril (L)		no	217	23–35	12·5–50 1–2x
Alacepril (L)		yes	400	–	25–75 1x
Zofenopril (III)		yes	460	8	2x30 1x60

Figure 3 *Sulphydryl containing ACE inhibitors. MW = molecular weight; *I_{50} = concentration required for 50% inhibition of the enzyme activity (ACE from rabbit lung) (see refs 5, 33); L = launched; III = Phase III clinical trials.*

First-line antihypertensive drugs
4. ACE inhibitors

Drugs	Prodrug	Active compound	Tissue ACE inhibition
Enalapril	+	-	-
Ramipril	+	-	+
Perindopril	+	-	+
Quinapril	+	-	+
Cilazapril	+	-	-
Lisinopril	-	+	-
Trandorapril	+	-	++

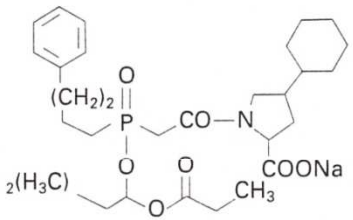
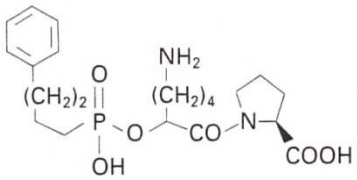
Compound (status)	Structure	Prodrug	MW	Potency *IC_{50} nM active drug	Daily dose (mg) frequency
Fosinopril (L)		yes	585	11	10–40 1x
Ceranapril (II)		no	440	36	

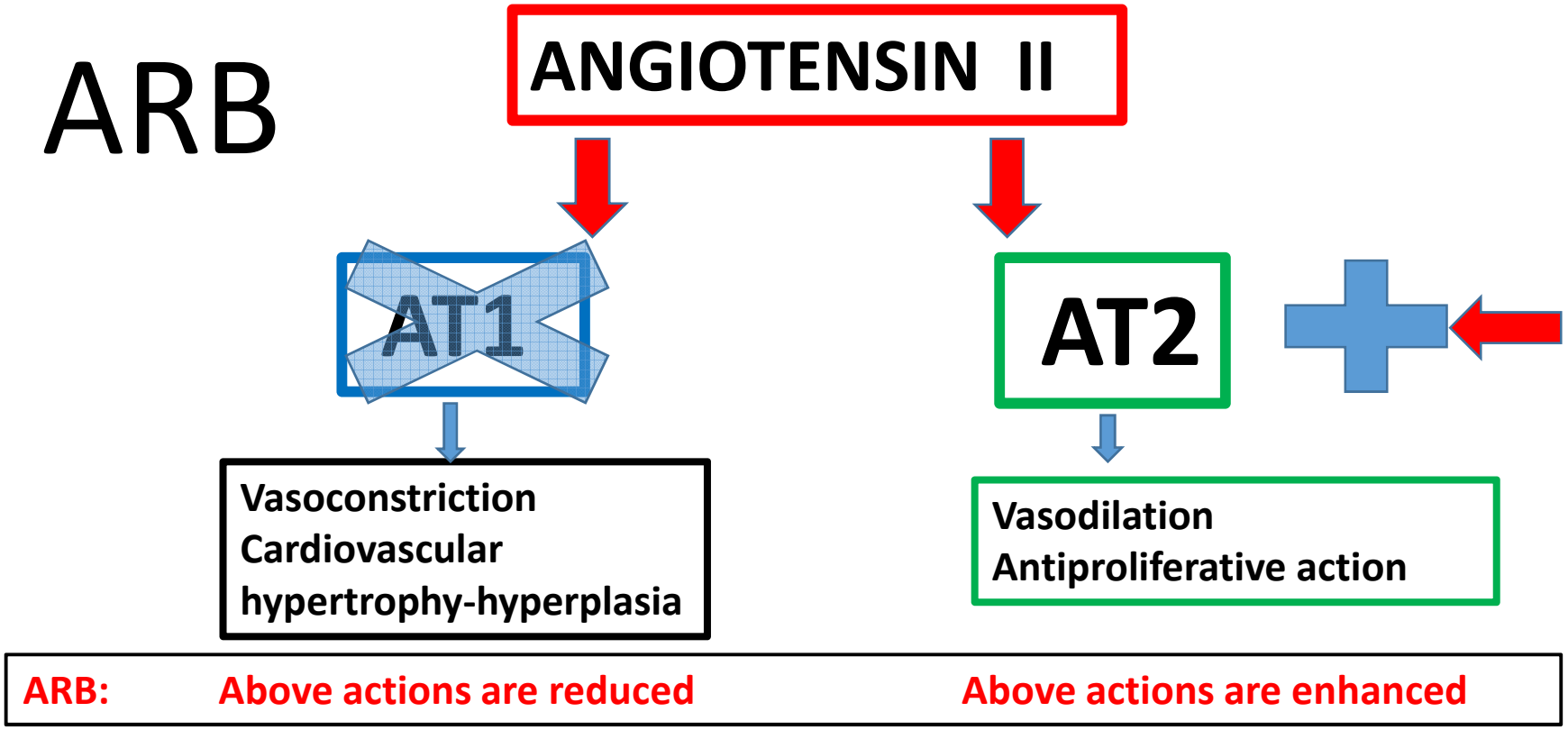
Figure 5 *Phosphorus containing ACE inhibitors. MW = molecular weight; *I_{50} = concentration required for 50% inhibition of the enzyme activity (ACE from rabbit lung) (see ref 33); L = launched, II = Phase II clinical trials.*

First-line antihypertensive drugs
5. ANG II RECEPTOR BLOCKERS

- Inhibitors of AT1 receptors. Similar action to ACEIs. More favorable profile of side effects: (e.g. dry cough is not typical).
- ACE inhibitors: decreased blood Ang II
- AT1 receptor blockers: increased AngII concentration
- Mechanism of action: Reduced activation of AT1 receptors. AT2 receptor activation increases. (see next figure)

First-line antihypertensive drugs
5. ANG II RECEPTOR BLOCKERS

ARB



First-line antihypertensive drugs
5. ANG II RECEPTOR BLOCKERS

- **MOST FREQUENTLY USED ARBs:**
- LOSARTAN
- VALSARTAN
- CANDESARTAN
- IRBESARTAN
- EPROSARTAN
- TELMISARTAN

Second line antihypertensive drugs

- 1. Centrally acting sympatholytic drugs
- 2. Adrenergic neuron blockers
- 3. Alpha1 adrenergic receptor blockers
- 4. Directly acting vasodilators

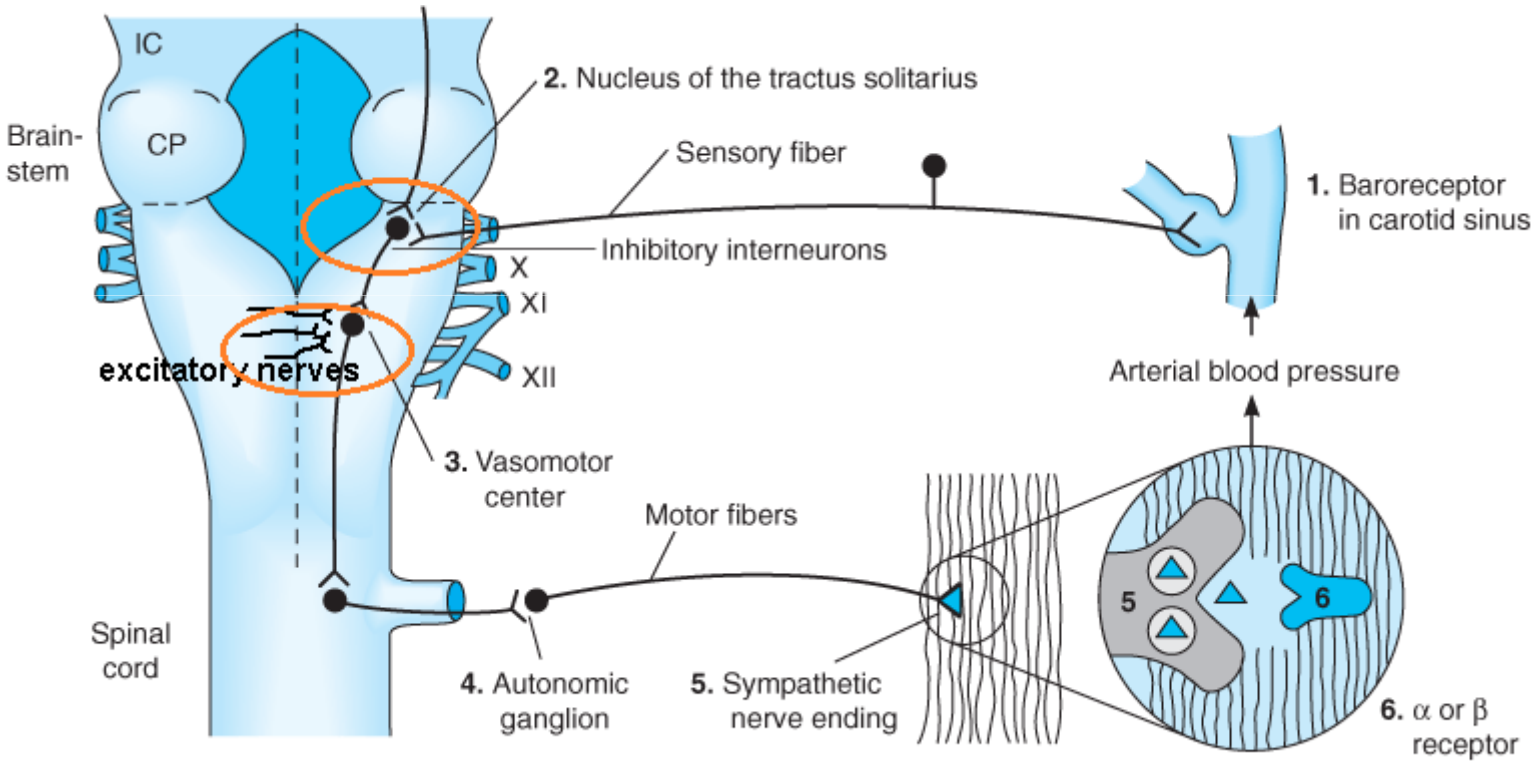
Second line antihypertensive drugs:
1. Centrally acting sympatholytics

CENTRALLY ACTING SYMPATHOLYTIC DRUGS

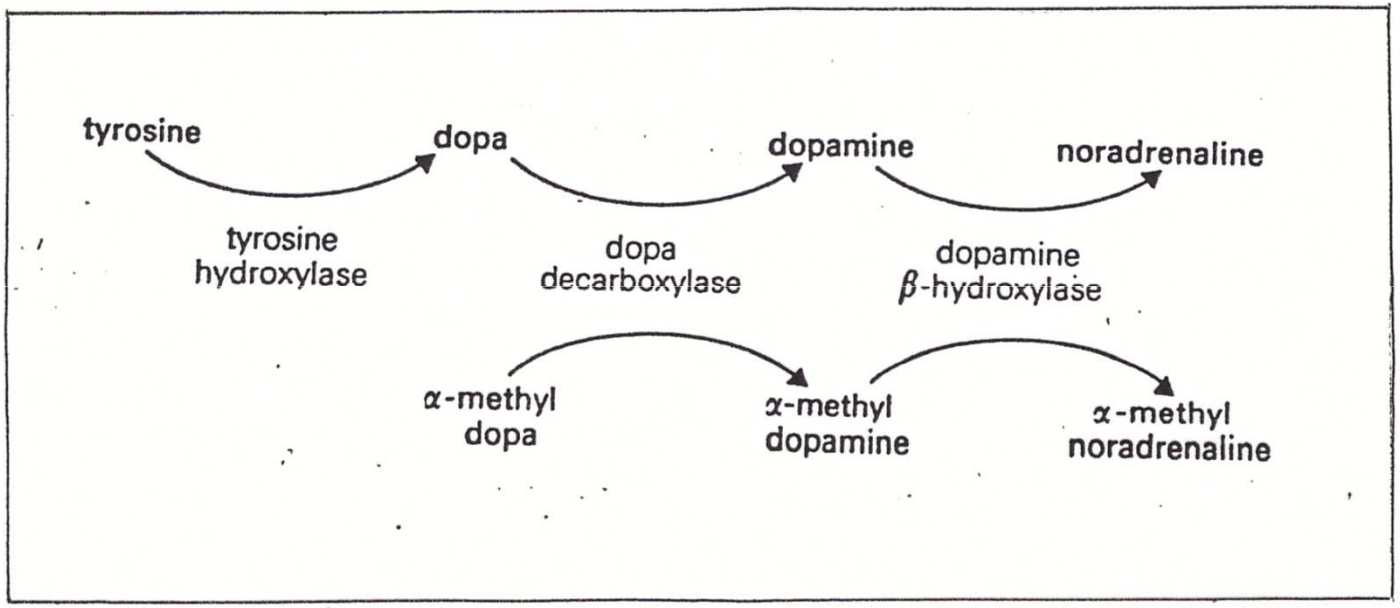
1st GENERATION : ALPHA2 ADRENERGIC ACTIVATORS
CLONIDINE
GUANFACINE
ALPHA-METHYLDOPA

2nd GENERATION: IMIDAZOLINE RECEPTOR AGONISTS
MOXONIDINE (CYNT)
RILMENIDINE (TENAXUM)
(Endogenous ligand: agmatine Antagonist: efaroxan)

Second line antihypertensive drugs:
1. Centrally acting sympatholytics



Second line antihypertensive drugs:
1. Centrally acting sympatholytics



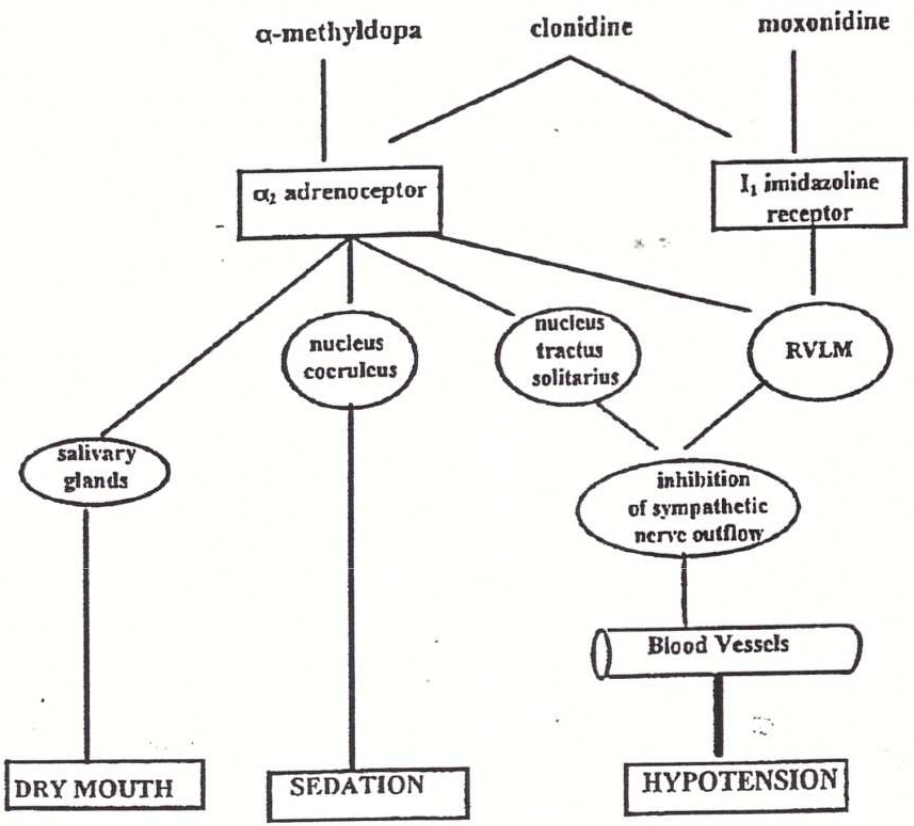


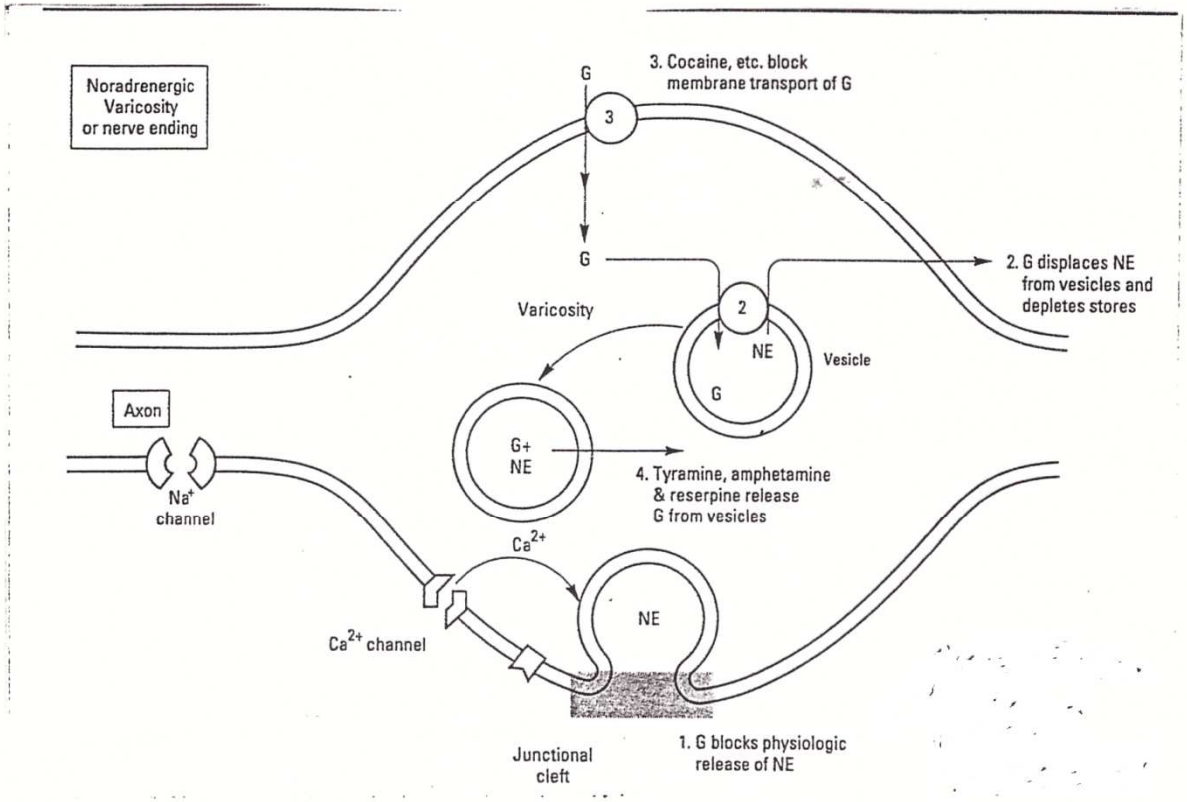
Figure 2 Illustrates that hypotensive effect of moxonidine is mediated via I_1 imidazoline receptors, while sedation and dry mouth (commonly seen with α-methyldopa and clonidine) are mediated via α_2 adrenoreceptors. (Adapted from reference 57).

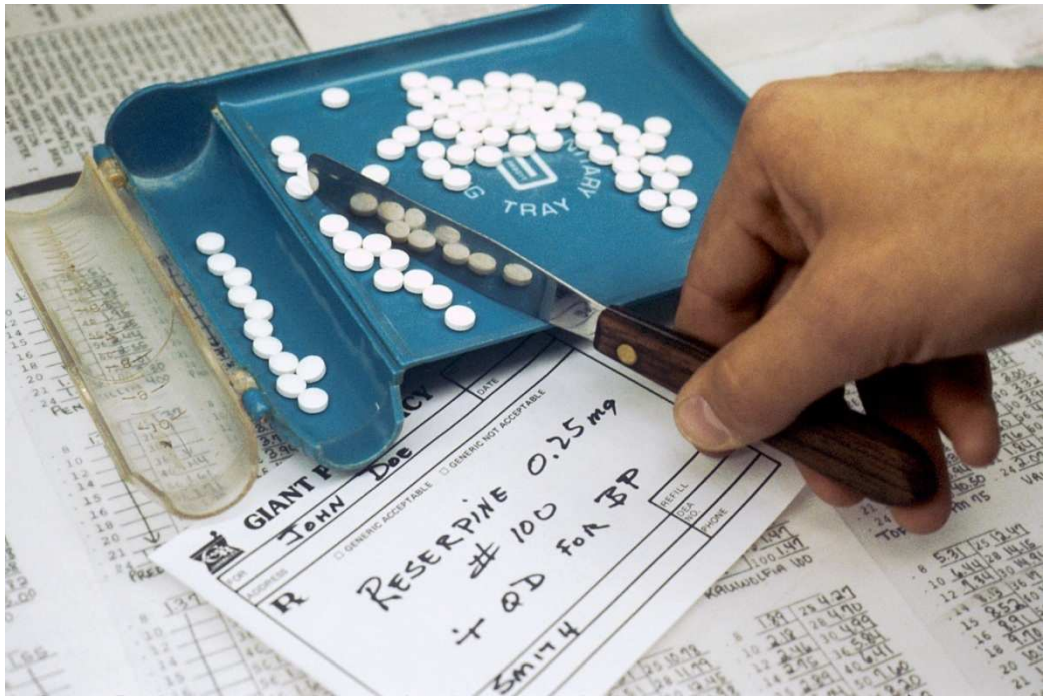
Second line antihypertensive drugs:
2. Adrenergic neuron blockers

GANGLION BLOCKING AGENTS: TRIMETHAPHAN

ADRENERGIC NEURON BLOCKING DRUGS

GUANETHIDINE




TRAY
GIANT
John Doe
RESERPINE 0.25 mg
#100
1 QD for BP
SMITH


AllPosters


FOTO PROVENIENTE DAL BLOG LA FARMACIA D'EPOCA
50 compresse
Serpasil
Nome depositato
Alcaloide puro cristallizzato di Rauwolfia
ad azione ipotensiva e sedativa
0,1
mgr
CIBA Industria Chimica S.p.A. - Milano
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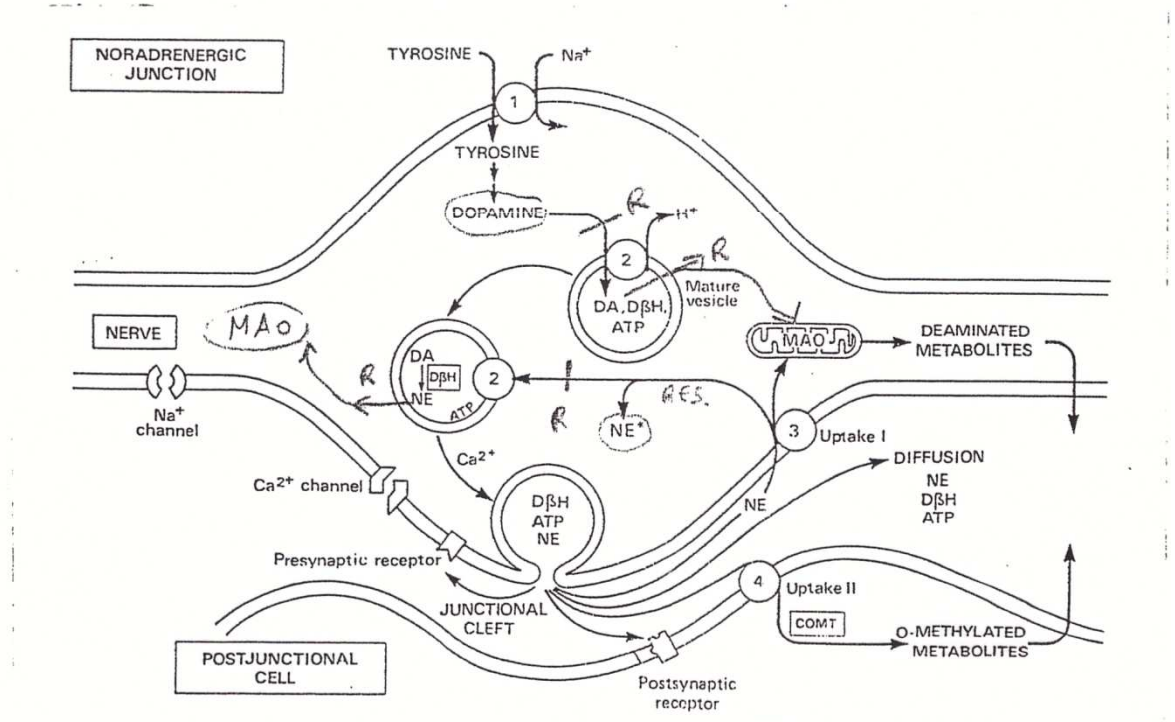
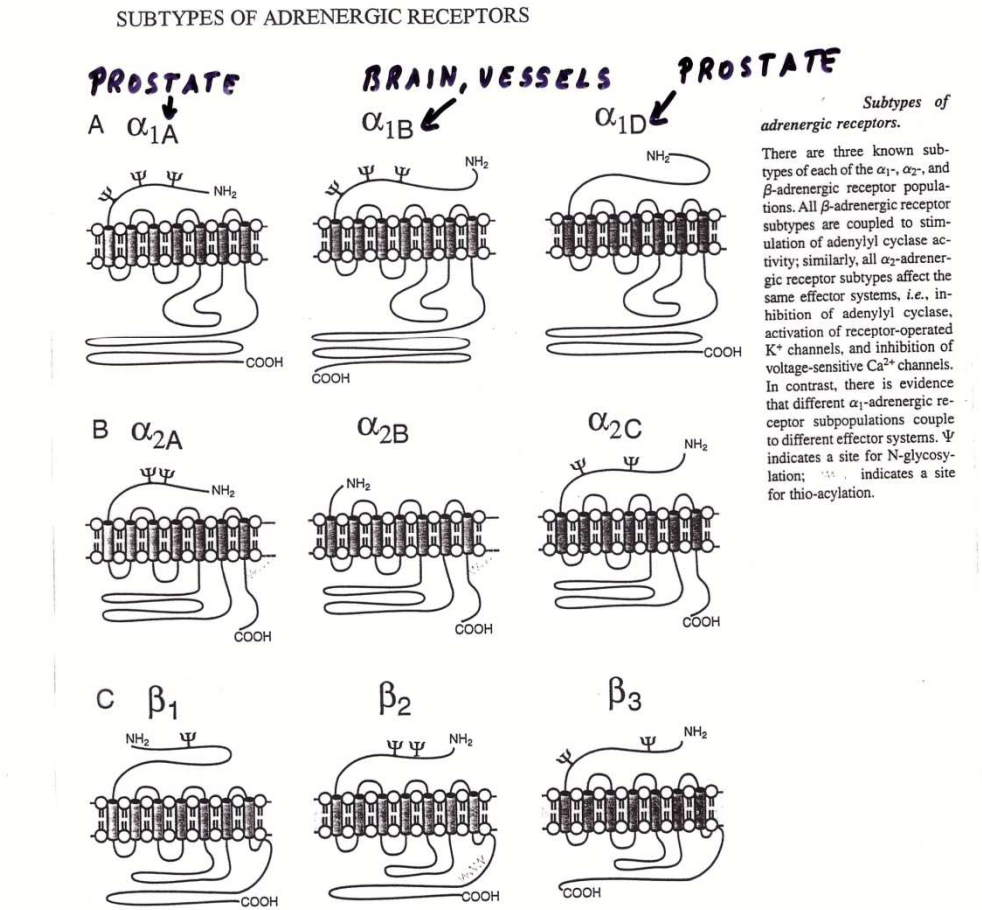
Second line antihypertensive drugs: 2. Adrenergic neuron blockers

RESERPINE



Second line antihypertensive drugs:
3. Alpha1 adrenergic receptor blockers

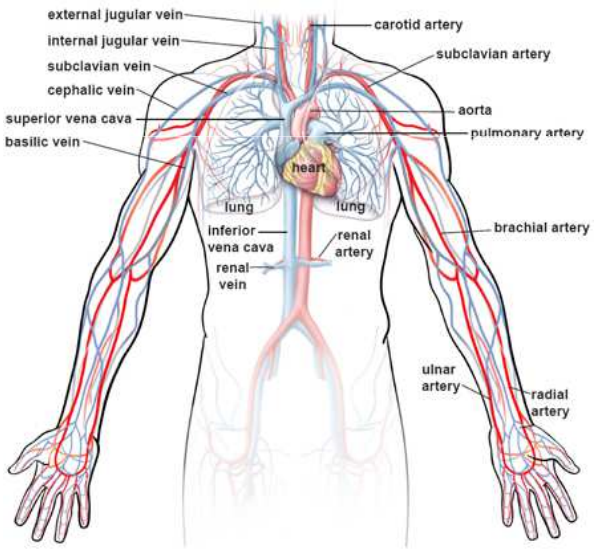


Subtypes of adrenergic receptors.

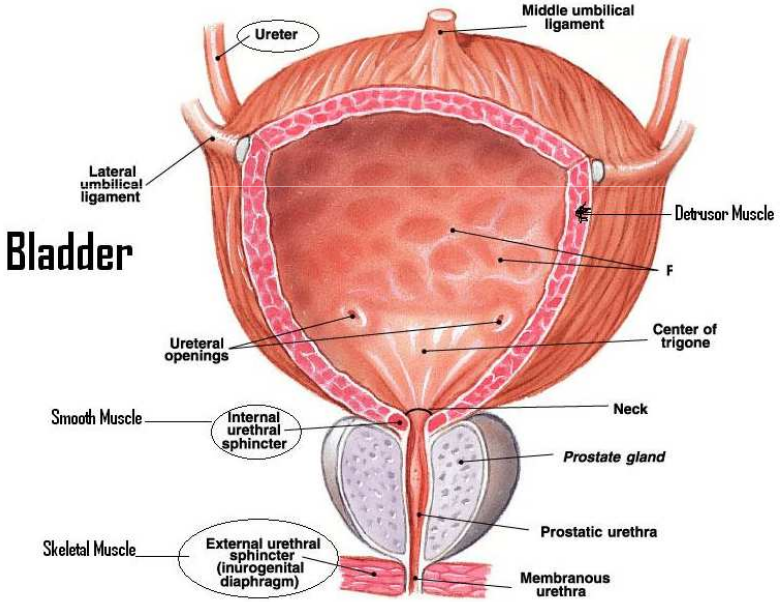
There are three known subtypes of each of the α_1-, α_2-, and β-adrenergic receptor populations. All β-adrenergic receptor subtypes are coupled to stimulation of adenylyl cyclase activity; similarly, all α_2-adrenergic receptor subtypes affect the same effector systems, *i.e.*, inhibition of adenylyl cyclase, activation of receptor-operated K^+ channels, and inhibition of voltage-sensitive Ca^{2+} channels. In contrast, there is evidence that different α_1-adrenergic receptor subpopulations couple to different effector systems. Ψ indicates a site for N-glycosylation; ⋯ indicates a site for thio-acylation.

Second line antihypertensive drugs: 3. Alpha1 adrenergic receptor blockers

alfa1B



alfa1A alfa1D



Second line antihypertensive drugs:
3. Alpha1 adrenergic receptor blockers

ALPHA-ADRENERGIC RECEPTOR ANTAGONISTS

Non-specific

Phentolamine

Alpha1-specific

Phenoxybenzamine (irreversible)
Prazosin (HT)

Doxazosin (HT + PH)
Terazosin (HT + PH)

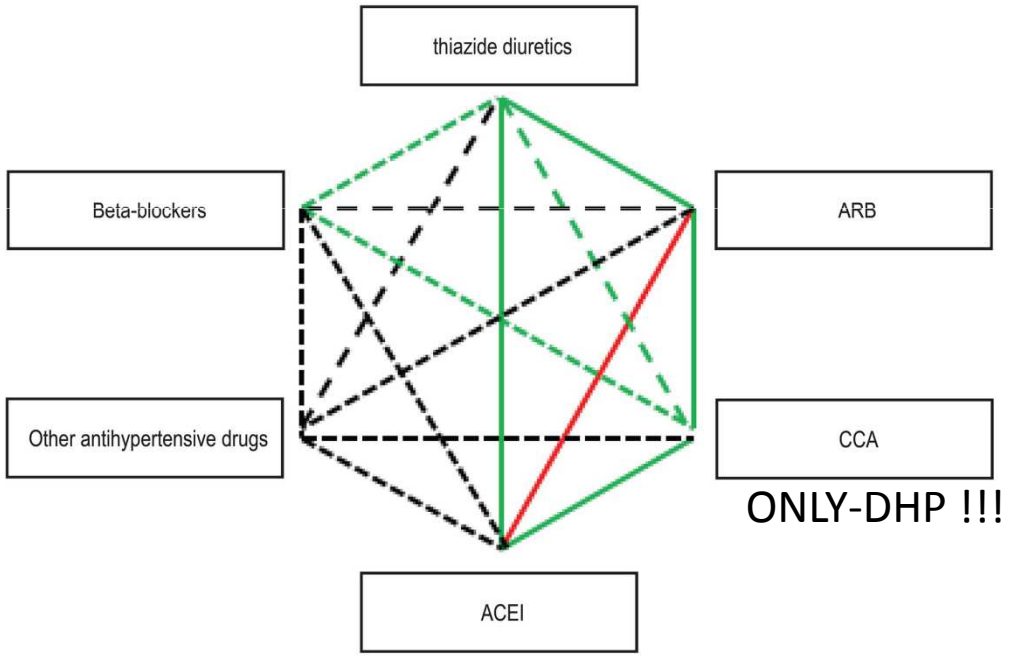
Alfuzosin (PH)
Tamsulosin (PH) $alfa_{1A}$

Second line antihypertensive drugs: 4. Directly acting vasodilators

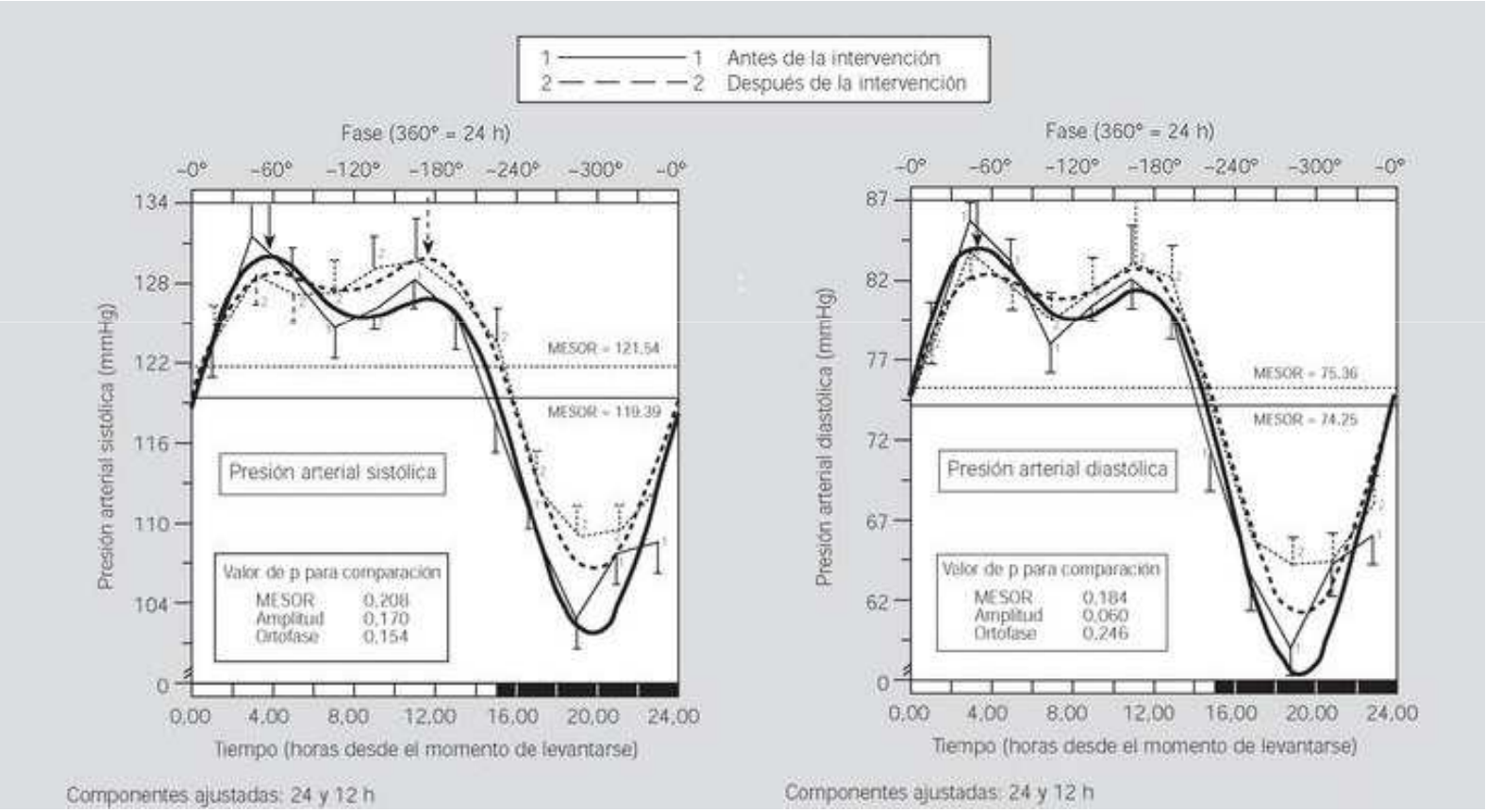
- 1. Hydralazine
- 2. Minoxidil
- 3. Ca2+ channel blockers
- 4. Nitroprusside sodium
- 5. Diazoxide

Combination of antihypertensives.

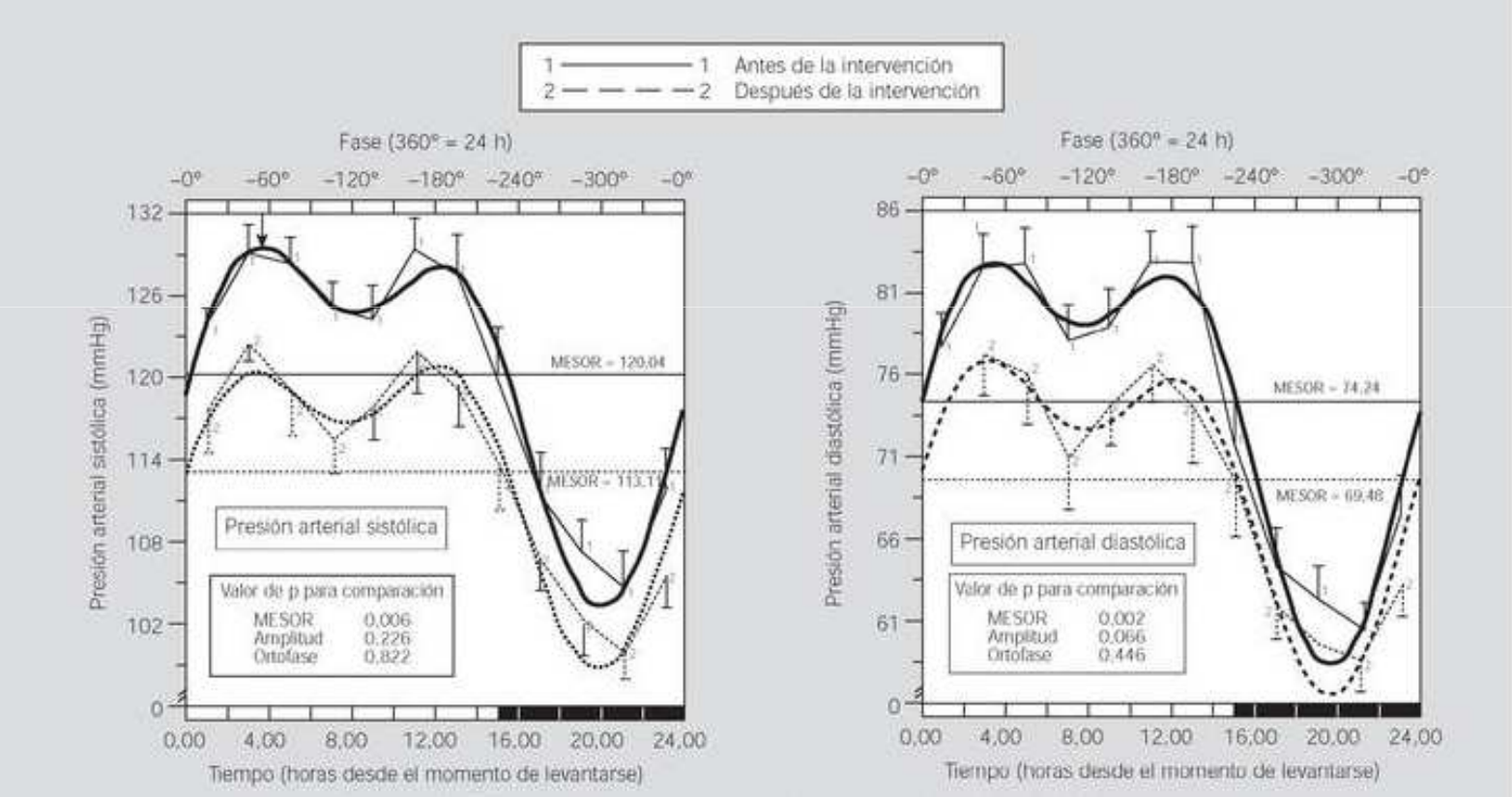
green line: recommended,
dotted green line: acceptable,
dotted black line: less usual,
red: unusual



Chronopharmacology: aspirin (antihypertensive action: morning administration)



Chronopharmacology: aspirin (antihypertensive action: late afternoon administration)



Chronopharmacological considerations of antihypertensive drugs

Drug	Cmax (ng/ml)		P
	Morning	Evening	
Propranolol 80 mg	38,6	26,2	> 0,05
Nifedipine 10 mg	82,0	45,7	> 0,05

Lemmer B.: Pharmacol Res 33:107115, 1996

Endothelial dysfunction: improvement

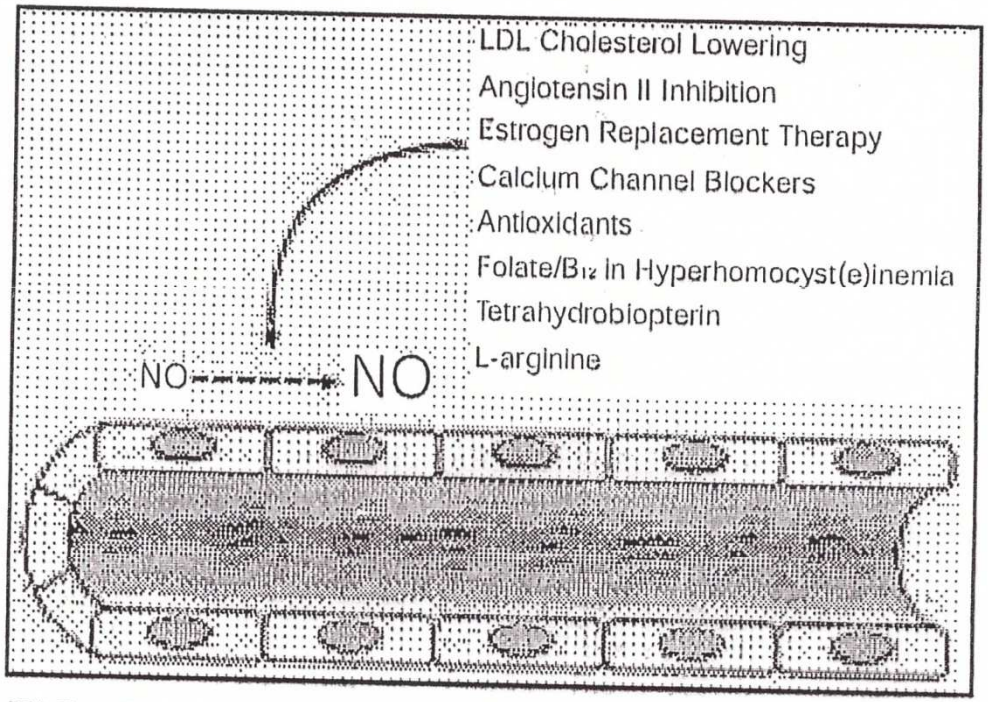
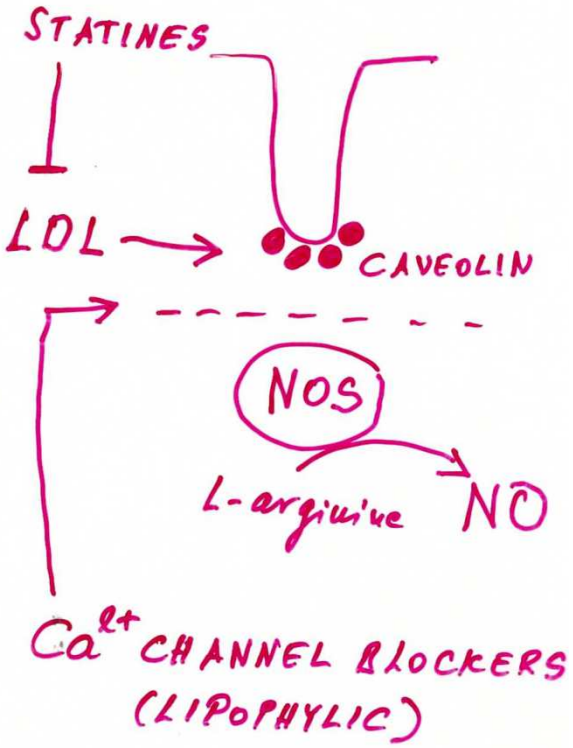


FIG. 3. *Available treatments of endothelial vasodilator dysfunction.*



- PROBLEM OF VARIOUS DIPPERS

RECOMMENDED ANTIHYPERTENSIVE TREATMENT IN VARIOUS CONDITIONS

CONDITION	Diuretic	Beta blocker	Alpha blocker	Ca2+ant.	ACE inhibitor	ANG.rec blocker
ELDERLY AGE	++	+-	+	+	+	+
BLACK PEOPLE	++	+-	+	+	+-	+-
ANGINA	+-	++	+	++	+	+
HEART FAILURE	++	-	+	+-	+	+
DIABETES	-	-	++	+	+	+
HYPERLIPIDEMIA	-	-	++	+	+	+
PROST. HYPERPL.			++			