PHARMACOLOGICAL ASPECT OF ANTIHYPERTENSIVE DRUGS

Speaker :

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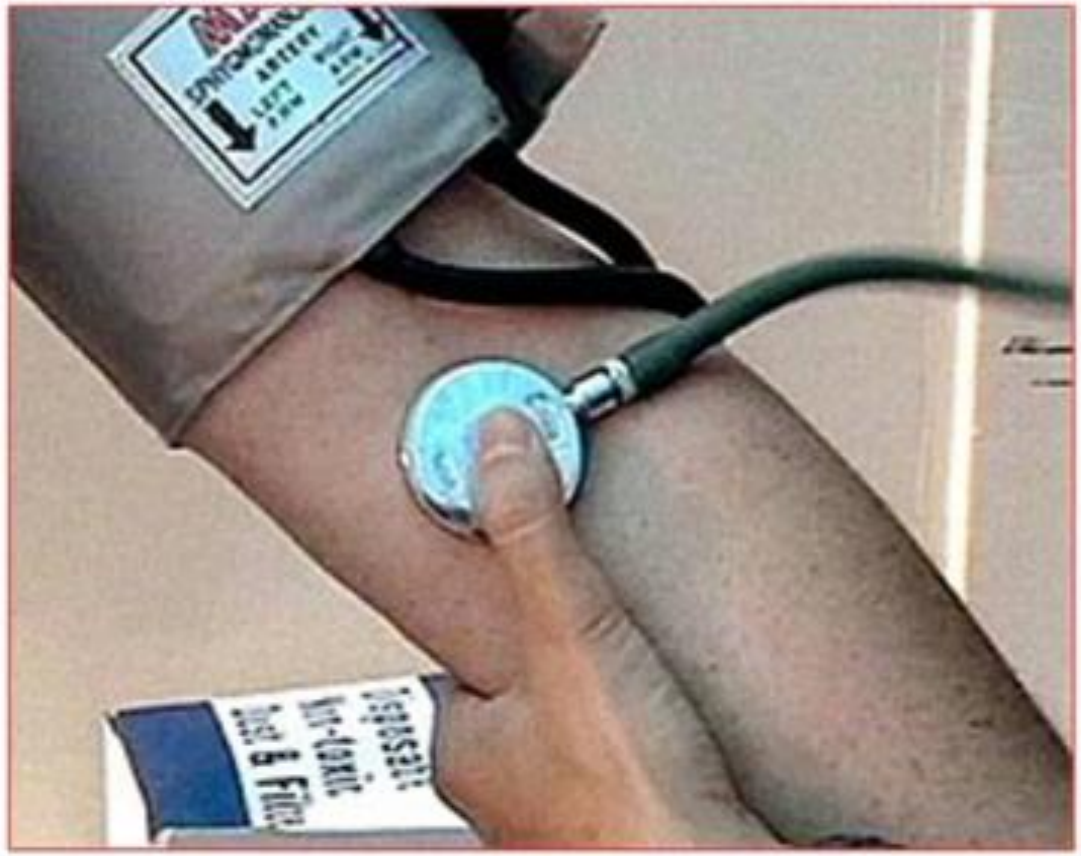
AWMCH



Antihypertensive Drugs

Core content

- Basic physiology of Hypertension
- Pharmacological aspects of anti HTN drugs
  - Pharmacokinetics
  - Mechanism of action
  - Indication
  - Contraindication
  - Adverse effect

Basic facts and regulation of Blood pressure:

Blood Pressure is a lateral pressure exerted by the flowing blood on vessel wall.

BP= CO (Cardiac Output) X TPR (Total Peripheral Resistance)

CO= SV (Stroke Volume) X HR (Heart Rate)

CO= SV (Stroke Volume) X HR (Heart Rate)

Cardiac output= Amount of blood ejected by heart **per minute.**

Heart rate= Beats per minute.

Stroke Volume= Amount of blood ejected by heart **per beat**.

Determinants of Stroke Volume:

- **Force of myocardial contractility:** which depends on strength and integrity of **fiber length**.
- **Electrolytes:** **Sodium and Calcium** increases contractility while **Potassium and Magnesium** decreases it.
- **Venous return:** Depends on **blood volume and vascular tone.**

Heart Rate:

It depends on Autonomic control :

Sympathetic: Increases HR.

Parasympathetic: Decreases Heart Rate.

TPR(Total peripheral resistance):

- **Depends on:**
- **Sympathetic tone-** Increases T.P.R by vasoconstriction
- **Circulatory pressor amines** (Adrenaline, Nor- adrenaline, Dopamine)- Increases TPR by vasoconstriction
- **Nitric Oxide, Bradykinin & PG** - Decreases TPR by vasodilatation.

Regulation of Blood Pressure:

Few organs are involved in regulating blood pressure:

Heart, Blood vessels, Kidney – By Renin angiotensin aldosterone & Kallikrein Kininogen Bradykinin system.

-Renin angiotensin aldosterone mechanism:

Rises Blood pressure in some conditions.

-Kallikrien Kininogen bradykinin system: decreases blood pressure

Baroreflex is responsible for rapid, moment to moment adjustment of Blood Pressure following change of posture, via central sympathetic neurons of medulla.

Blood pressure is maintained by

- Moment-to-moment regulation of cardiac output and peripheral vascular resistance exerted at three anatomic sites arterioles, postcapillary venules (capacitance vessels), and heart.
- Kidney
- Baroreflexes mediated by autonomic nerves (combination with humoral mechanisms, including the renin-angiotensin-aldosterone system)
- Local release of vasoactive substances

Hypertension

Definition of Hypertension (Ref: DAVIDSON 24th edition)

Category	Systolic BP(mmHg)	Diastolic BP(mmHg)
Blood pressure		
Optimal Normal High normal	<120 <150 130-139	<80 85 85-89
Hypertension		
Grade 1 (mild) Grade 2 (moderate) Grade 3 (severe)	140-150 160-179 ≥180	90-99 100-109 >110
Isolated systolic hypertension		
Grade 1 Grade 2	140-159 ≥160	<90 <90

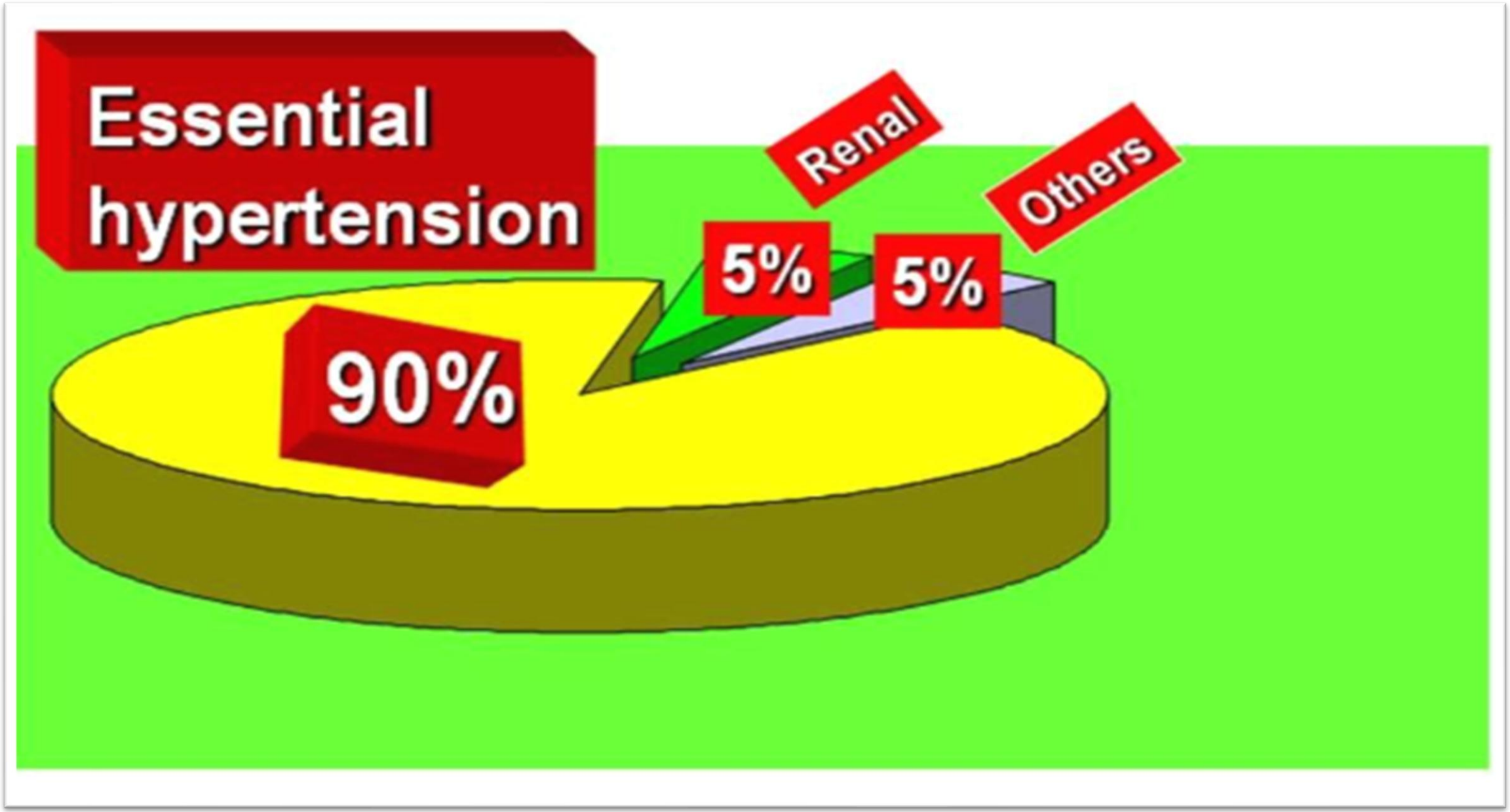
The JNC (Joint National Committee) classification of hypert ension

According to the JNC 8 guidelines, hypertension is classified as:

Classification Stages	Systolic BP	Diastolic BP
Normal	< 120 mm Hg	< 80 mm Hg
Elevated	120-129 mm Hg	< 80 mm Hg
Stage 1 Hypertension	130-139 mm Hg	80-89 mm Hg
Stage 2 Hypertension	≥ 140 mm Hg	≥ 90 mm Hg

Causes of Hypertension

- **Primary/ Essential/ Idiopathic (Cause not known)**
- **Secondary causes**


Essential hypertension
90%
Renal
5%
Others
5%

Secondary causes

- **Renal diseases** (Glomerulonephritis, Polycystic Kidney disease, Renal vascular disease)
- **Pregnancy**
- **Endocrine**: Cushing syndrome, Acromegaly, Thyrotoxicosis, Primary or secondary aldosteronism
- **Drugs** (Contraceptives, Corticosteroids, NSAIDS, Sympathomimetic drugs)
- **Coarctation of Aorta**

Anti-hypertensive drugs lower elevated blood pressure towards normal level

Classical anti-hypertensives.

Importance of Antihypertensive Therapy

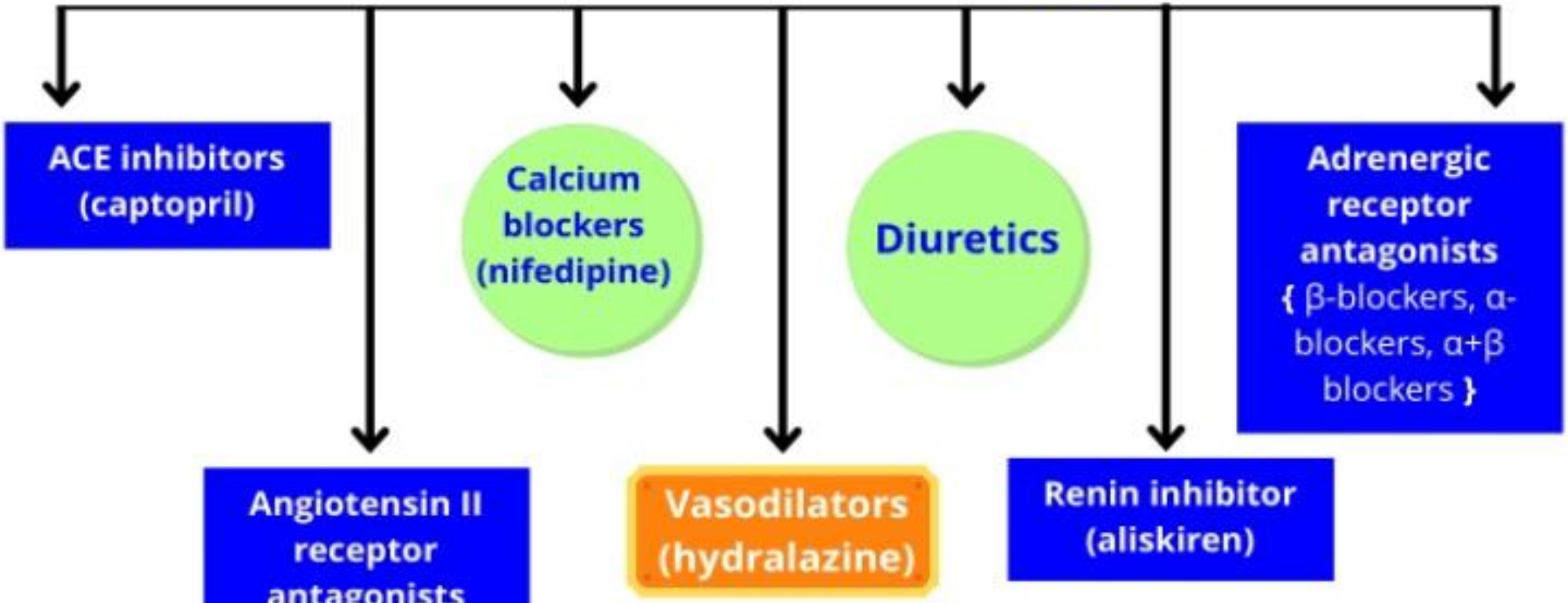
Effective management of hypertension is crucial to prevent serious health complications such as:

- **Myocardial Infarction**
- **Stroke**
- **Heart failure and**
- **Kidney failure**

Overview of Antihypertensive Drugs

- Antihypertensive medications are **classified into several categories based on their mechanisms of action.**
- Each class works differently to lower blood pressure

Classification Of Antihypertension



Classification of antihypertensive drugs

According to M/A:

A. Sympatholytic

a. **Central Sympatholytic**: Alpha methyl-dopa, Clonidine

b. **Peripheral Sympatholytic:**

i) Alpha Blockers: Prazosin, Terazosin etc.

ii) Beta Blockers:

a)Non-selective beta blockers: Propranolol

b) Cardio selective beta blockers: Atenolol, Metoprolol, Bisoprolol

iii) Both Alpha beta blocker: Labetalol, Carvedilol

iv) Adrenergic Neuron Blocker: Reserpine, Guanethidine

v) Ganglion Blocker: Mecamylamine

B.Angiotensin Converting Enzyme inhibitor (ACEI): Captopril, Ramipril, Lisinopril, Enalapril.

C.Angiotensin Receptor Blocker (ARB): Losartan, Valsartan, Olmesartan.

D.Direct Renin Inhibitor : Aliskiren

E.Calcium Channel Blocker (CCB): Amlodipine, Nifedipine (Vasoselective), Verapamil, Diltiazem.

F. Diuretics: Thiazide, Frusemide, Amiloride

G.Vasodilators: Hydralazine, Minoxidil, Diazoxide, Nitroprusside

Clinically used antihypertensive drugs can be categorized alphabetically-

A. ACEI and ARB

B. Beta Blocker

C. CCB

D. Diuretics

A and B are suitable for youngers and white race while C and D are suitable for elderly and black race.

ACEI

ANGIOTENSIN CONVERTING ENZYME INHIBITORS

Angiotensin Converting Enzyme inhibitor (ACEI):

- Captopril
- Ramipril
- Lisinopril
- Enalapril
- Fosinopril
- Cilazapril
- Perindopril
- Quinapril etc.

Mechanism of action of ACEI

Inhibits conversion of angiotensin I to angiotensin II.

Angiotensin II has got three important effects:

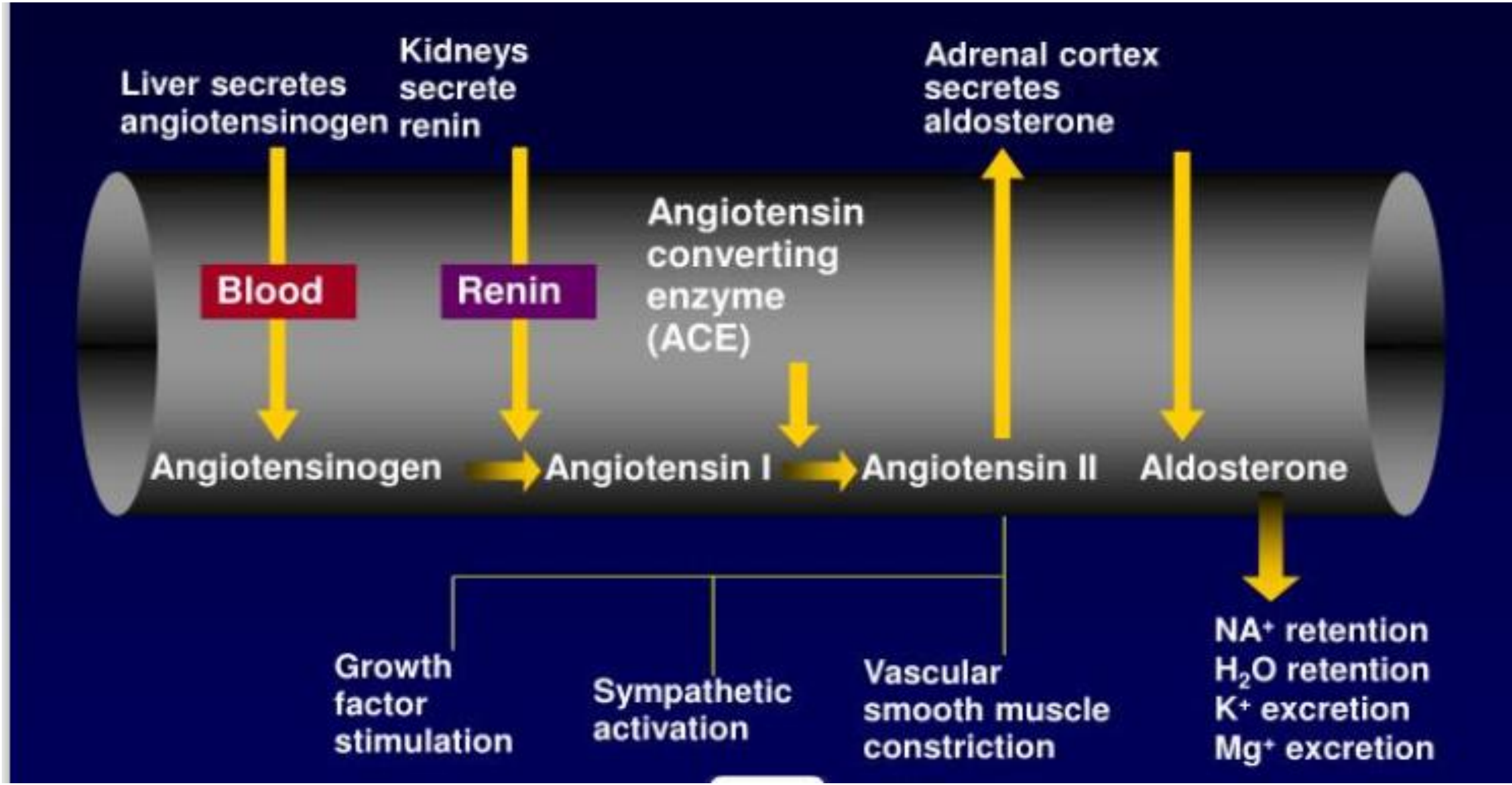
i) It is a powerful vasoconstrictor- thereby increasing peripheral resistance.

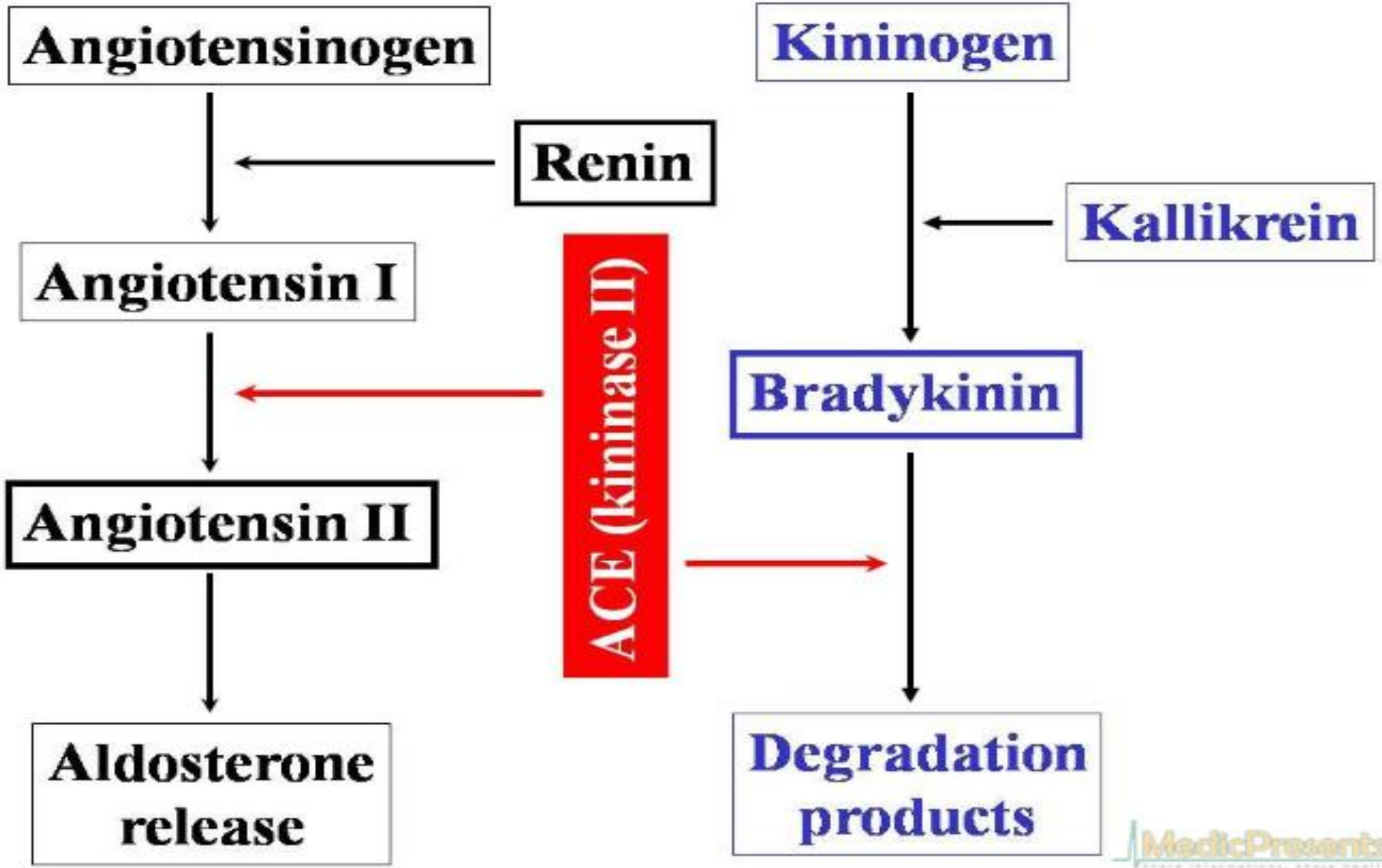
ii) It causes release of aldosterone from zona glomerulosa: which increases tubular reabsorption of sodium thereby increases blood volume.

iii) Also releases Adrenaline from adrenal medulla: which stimulates alpha and beta receptors causing rise of blood pressure

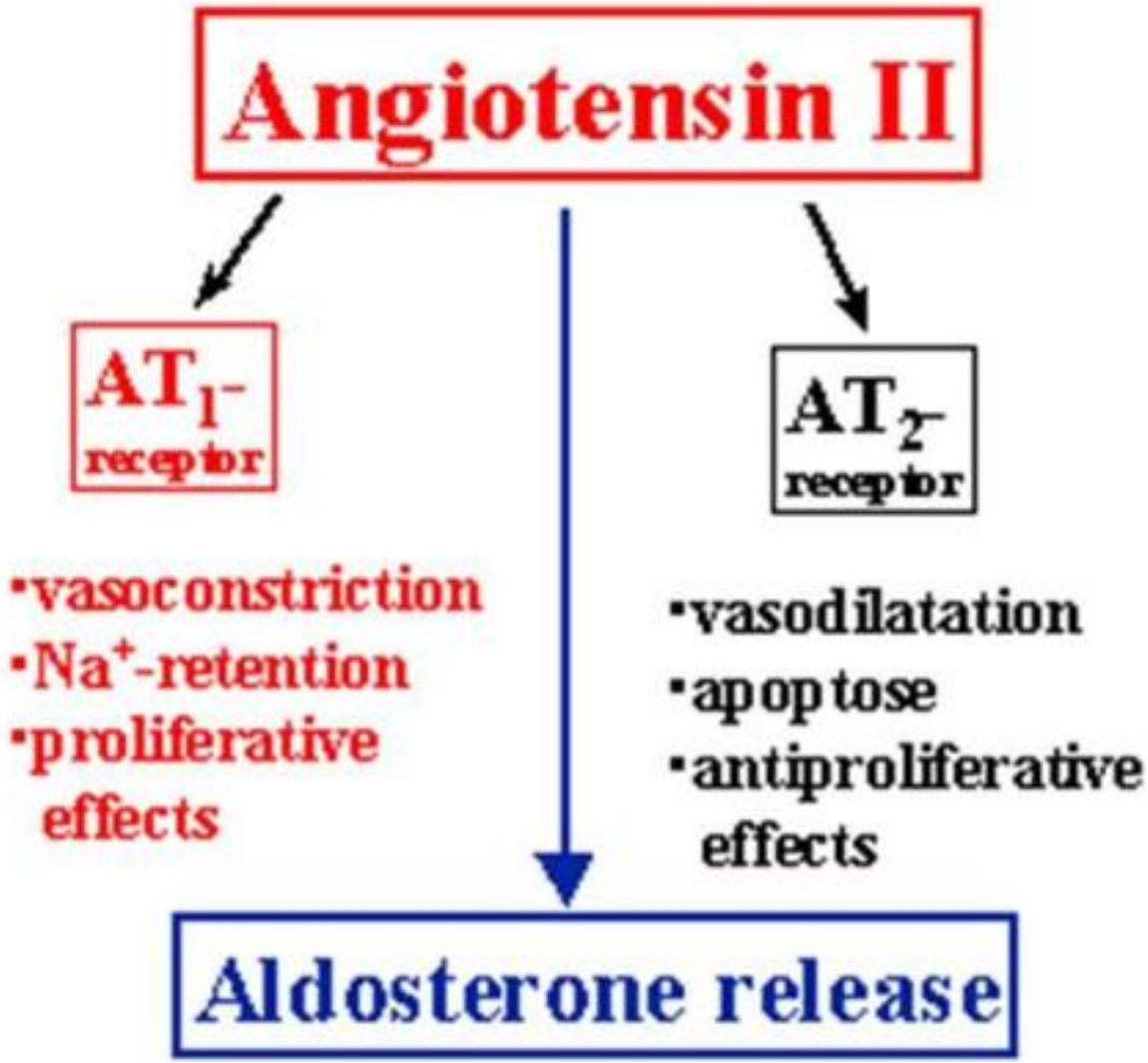
All these effects are blocked by ACEI, also

Bradykinin level is increased which plays contributory role to lowering of blood pressure.

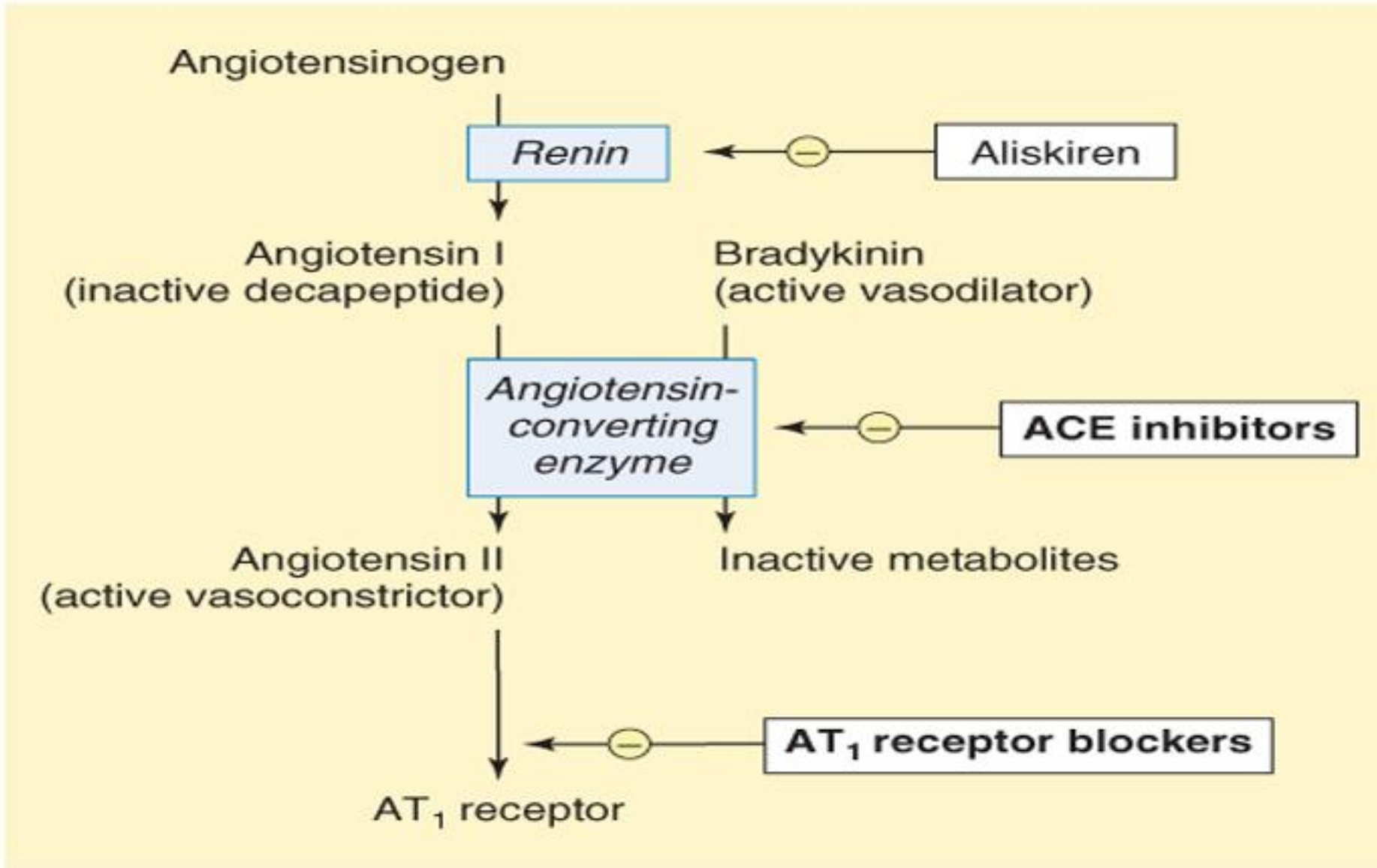

Liver secretes angiotensinogen
Kidneys secrete renin
Adrenal cortex secretes aldosterone
Blood
Renin
Angiotensin converting enzyme (ACE)
Angiotensinogen
Angiotensin I
Angiotensin II
Aldosterone
Growth factor stimulation
Sympathetic activation
Vascular smooth muscle constriction
NA+ retention
H2O retention
K+ excretion
Mg+ excretion


Angiotensinogen
Renin
Angiotensin I
ACE (kininase II)
Angiotensin II
Aldosterone release
Kininogen
Kallikrein
Bradykinin
Degradation products

Angiotensin II and ACE inhibitors



- Captopril
- Cilazapril
- Enalapril
- Fosinopril
- Lisinopril
- Perindopril
- Ramipril
- Trandolapril



Mechanism of action

Indications of ACEI and ARB:

1. Hypertension
2. Heart Failure
3. Diabetic Nephropathy
4. Following MI

Contraindications of ACEI:

- Renal Artery Stenosis (Unilateral and Bilateral)
- Aortic stenosis
- Left ventricular outflow obstruction
- Pregnancy
- Angioneurotic odema
- Renal failure

Adverse effects of ACEI:

- Persistent dry cough
- Glossitis
- Aphthous ulcer
- Dysgusia
- Hyperkalemia
- Teratogenicity
- Urticaria and and angioneurotic odema
- Neutropenia

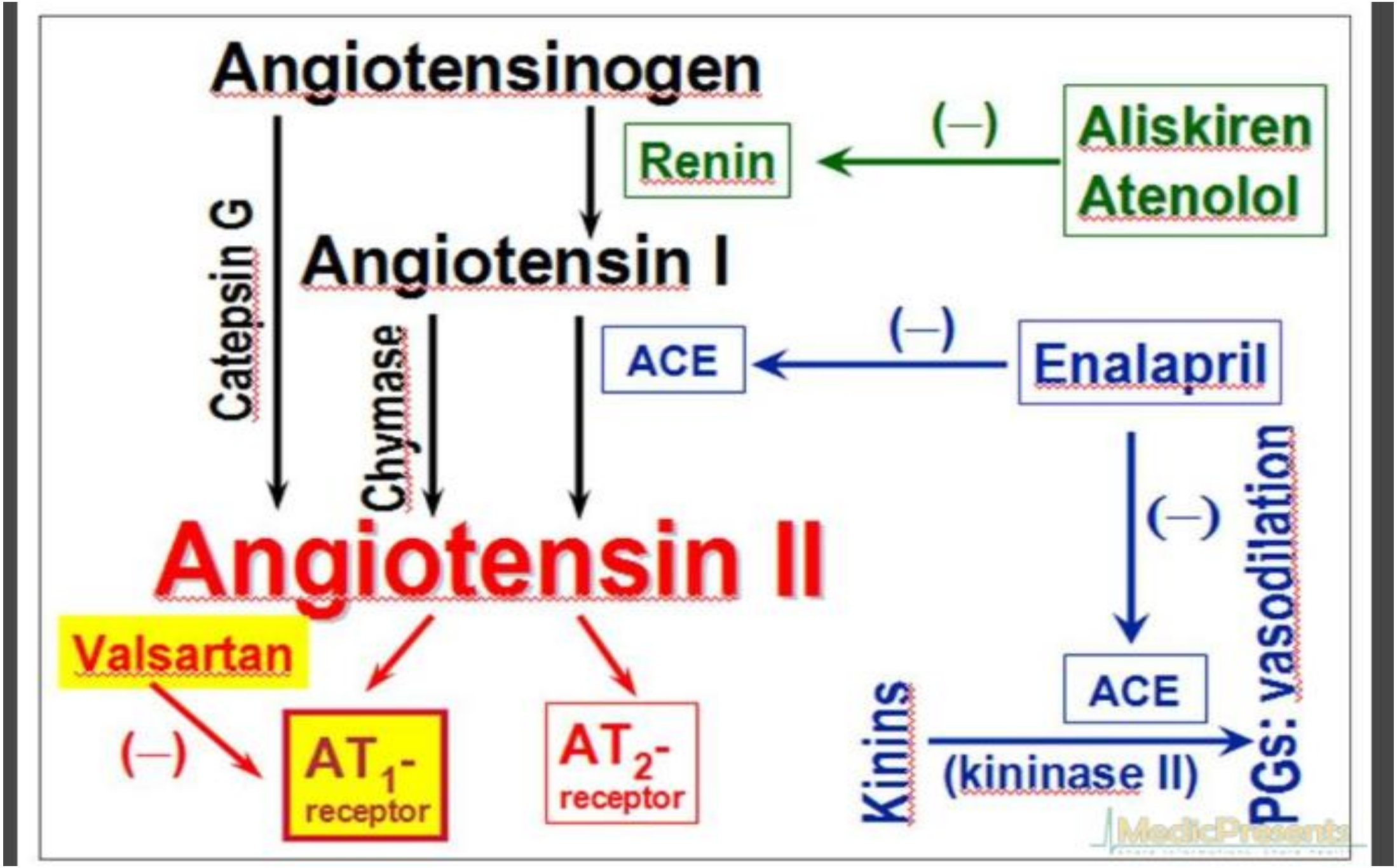
Angiotensin Receptor Blocker (ARB)

- Losartan
- Valsartan
- Olmesartan
- Candesartan etc.

Mechanism of action of ARB:

ARB acts by blocking **receptor AT- I,** keeping kininase II (ACE) enzyme unaffected.

So, in this drug there is **no chance of persistent cough.**


Angiotensinogen
Renin
(–)
Aliskiren
Atenolol
Catepsin G
Angiotensin I
Chymase
ACE
(–)
Enalapril
Angiotensin II
(–)
PGs: vasodilation
Valsartan
(–)
AT1-receptor
AT2-receptor
Kinins
ACE
(kininase II)

Alpha methyldopa

- Alpha methyldopa, commonly known as methyldopa
- Primarily used to treat high blood pressure Especially in pregnant women.
- Methyldopa is a prodrug
- It is converted into its active form, L-α-methyldopa, after administration.

Mechanism of action of Alfa methyl Dopa:

- Alfa Methyl dopa acts as a centrally acting alpha-2 adrenergic agonist.
- Reducing sympathetic outflow and lowering blood pressure through its active metabolite, alpha-methylnorepinephrine.

Formation of False Neurotransmitters:

- The drug is converted into alpha-methylnorepinephrine, which acts as a **"false neurotransmitter."**
- This means that it replaces norepinephrine at nerve endings but produces a weaker response, leading to decreased vascular resistance and lower blood pressure.

Indications of Alfa Methyl Dopa:

- **Hypertension:** Methyldopa is primarily used to manage high blood pressure particularly in pregnant women, as it was considered safe during pregnancy.
- **Hypertensive crisis:** It can also be used in acute situations where rapid blood pressure control is necessary.

- **Adverse effects of Alfa methyl dopa:**
- Fever
- Mental depression or anxiety
- Nightmares or unusually vivid dreams
- Swelling of feet or lower legs
- Headache
- Stuffy nose, and
- Weakness,

- **Serious side effects include:**
- Anemia (low red blood cell count
- Water retention (edema or swelling of the legs) or weight gain, and
- High blood pressure (hypertension) in certain dialysis patients and in patients with cerebrovascular disease.

- **Drug interactions of Alfa methyl dopa** include **monoamine oxidase inhibitors (MAOIs**), a class of medications used to treat depression, because combining these drugs may lead to **dangerous side effects.**

ALPHA BLOCKERS

Alpha blockers, also known as **α-adrenoreceptor antagonists**, are a class of pharmacological agents that act as antagonists on α-adrenergic receptors (α-adrenoceptors)

- **Classification of Alfa blocker:**
- **A. Selective:**
- **Selective α_1-adrenergic receptor antagonists include:**
- Prazosin(inverse agonist)
- Doxazosin
- Alfuzosin
- Tamsulosin
- Terazosin
- Silodosin

- **Selective α_2-adrenergic receptor antagonists include:**
- Atipamezole
- Idazoxan
- Yohimbine
- Finally, the agents carvedilol and labetalol are both α and β-blockers

- **Non-selective α-adrenergic receptor antagonists include:**
- Doxazocine
- Phenoxybenzamine
- Phentolamine
- Tolazoline

- **Alpha blockers can treat a small range of diseases such as(Indications):**
- Sever Hypertension
- Raynaud's disease,
- Benign prostatic hyperplasia (BPH) and
- Erectile dysfunction.

- **Adverse effects of alfa blocker:**
- Postural hypotension
- First-dose effect
- Reflex tachycardia/palpitation
- Dizziness
- Weakness

Beta Blockers

- **Classification of Beta blockers:**
- **A. Selective**
- **B. Non selective**
- **A. Selective (Cardioselective):**
- **a. Beta 1 selective:** Atenolol, Metoprolol, Bisoprolol etc.
- **b. Beta 2 selective:** Butoxamine

Cardioselective beta blockers:

They **will block all the parameters like contractility, Stroke volume, Heart rate and Cardiac output** thereby decreases blood pressure.

Also **inhibits renin release**.

Some of the members have **got anxiolytic effects** which contributes to lowering of blood pressure.

Advantages of Cardio selective Beta blockers over non -selective blockers:

1. safer in asthmatics
2. safer in diabetics
3 .Peripheral vascular disease
4. less deleterious effect on lipid profile
5. Less liable to impair exercise capacity

Pharmacokinetics

- Well absorbed after oral administration
- Propranolol- extensive first-pass metabolism- low oral bioavailability
- Chronic use of propranolol - itself decreases hepatic blood flow- bioavailability of propranolol is increased

β–1 receptors

Heart

Increased chronotropy and inotropy

Increased AV-node conduction velocity

Renal juxtaglomerular cells

Increased renin release

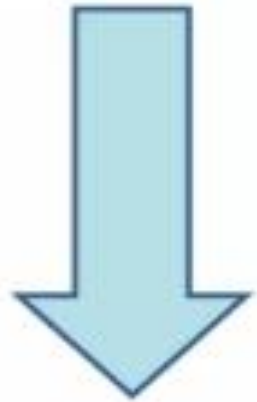
Pharmacological Actions:

1. Heart:

Sympathetic Stimulation

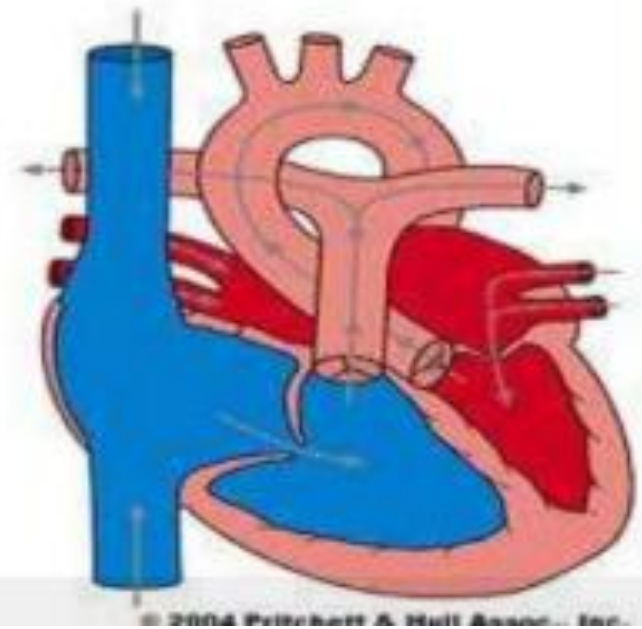
Beta -1 receptors on myocardium

Beta Blockers



Myocardial contractility
Heart Rate
Cardiac output
Cardiac work
Oxygen consumption

- Increase refractory period
- A-V conduction is delayed
- Decreases automaticity



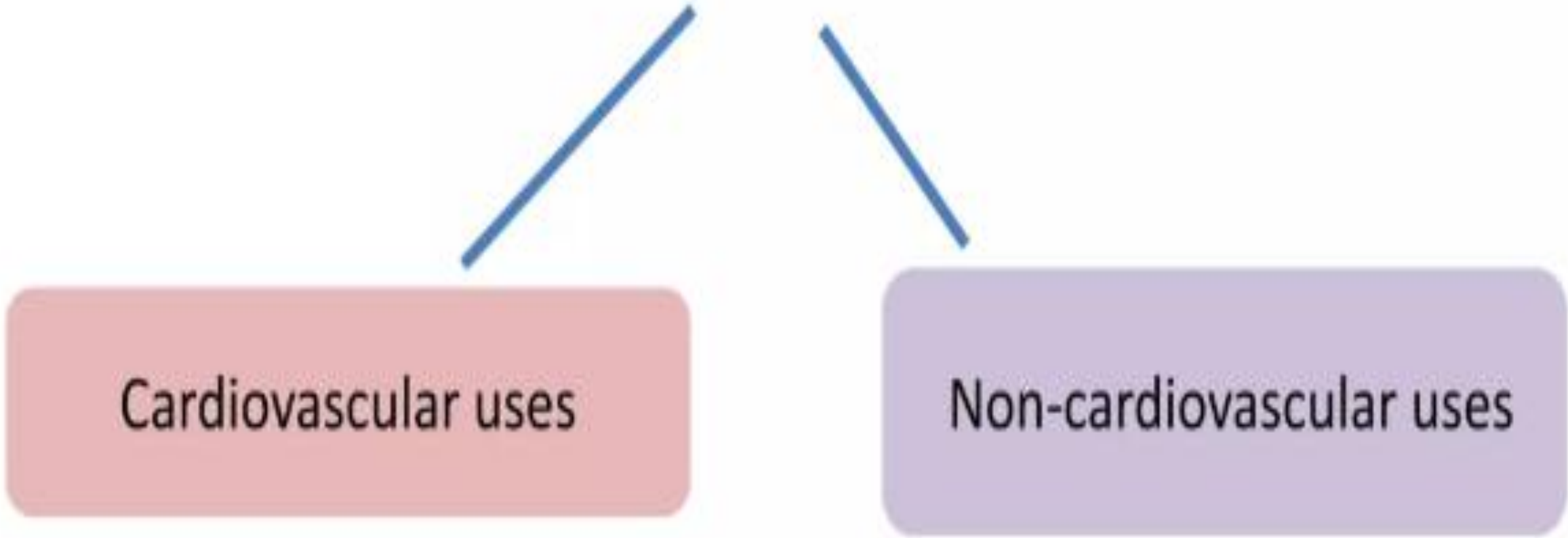
Other mechanisms for Anti- hypertensive action:

(i) Reduced NA release from sympathetic terminals due to blockade of pre- synaptic β receptor mediated facilitation of the release process.

(ii) Decreased renin release from kidney

(iii) Decrease in Central sympathetic outflow

Therapeutic uses



Indications of Beta blocker:

Cardiac use

- **Cardiac:** Angina Pectoris, Heart Failure, Hypertension, MI, Hypertrophic Sub aortic stenosis, Fallouts Tetralogy, Portal Hypertension
- **Non Cardiac use**
- **Endocrine:** Thyrotoxicosis, Pheochromocytoma, Cushings Syndrome, Acromegaly
- **CNS:** Anxiety, Migraine Prophylaxis, Tremor, Alcoholic and Opioid acute withdrawal
- **Ophthalmic:** Glaucoma

Contraindications

1. **Bronchial Asthma**
2. **Uncontrolled heart failure**
3. **Very slow heart rate (bradycardia)**
4. **Low blood pressure (hypotension)**
5. **Certain heart rhythm problems:**

Sick sinus syndrome and high-degree AV block

- Beta -2 receptors → bronchi → bronchodilation
- Beta blockers → broncho constriction
- Asthmatics - severe attack may be precipitated

Contraindicated in Asthma

4.Metabolic Effects:

- Hypoglycemia

Adrenaline

β- 2 receptors in liver

glycogenolysis

Propranolol

- Masks sympathetic manifestations of hypoglycemia
- Plasma triglyceride levels increase
- LDL/HDL ratio is increased

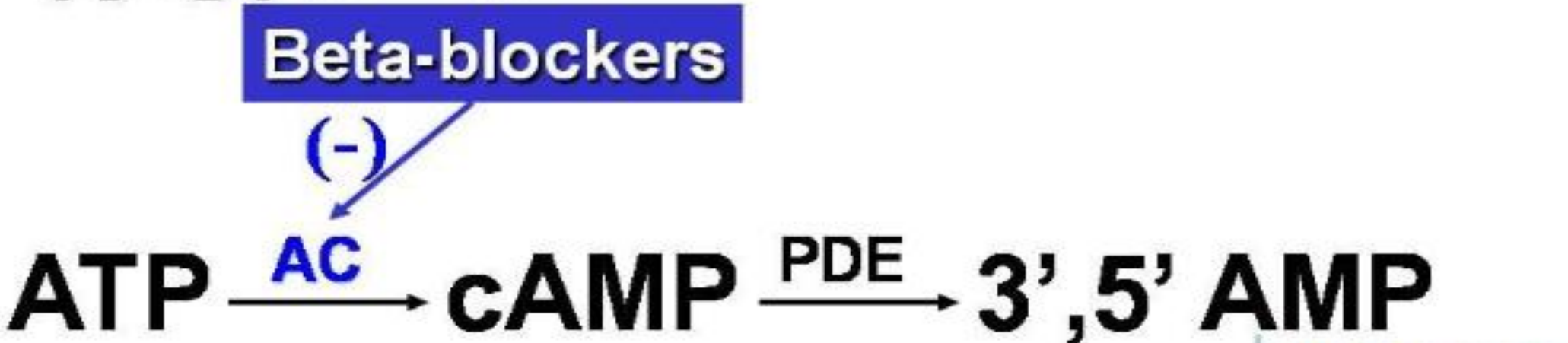
Adverse effects of beta blockers:

- Bradycardia
- Heart block
- Bronchoconstriction
- Hyperlipidemia
- Raynaud's phenomenon

[Raynaud's Disease: Inappropriate vasoconstriction of small arteries and arterioles gives rise to Raynod’s phenomenon.]

Adverse reactions of β-blockers

- **Blockade of β_1-receptors may cause bradycardia, AV block, heart failure.**
- **Blockade of β_2-receptors may cause bronchospasm, intermittent claudication (reducing peripheral blood flow) and hypoglycemia.**



CCB
(Calcium Channel Blocker)

CCB (Calcium Channel Blocker):

Calcium is essential for cardiac contraction, muscular contraction, glandular secretion and release of neurotransmitters.

Calcium channel blockers block all the parameters of heart except refractory period of AV node, also decreases peripheral resistance.

Classification of CCB

i) **Dihydropyridine derivatives**: Vasoselective mostly used as antihypertensives. Eg. Amlodipine, Nifedipine, CiInidipine, Nimodipine, Nicardipine.

ii) Phenylalkylamine: Mostly used as anti arrhythmic. Eg. Verapamil

iii) **Benzothiazepines**: Mixed activity. Eg. Diltiazem

Mechanism of Action

- CCBs has four effects:

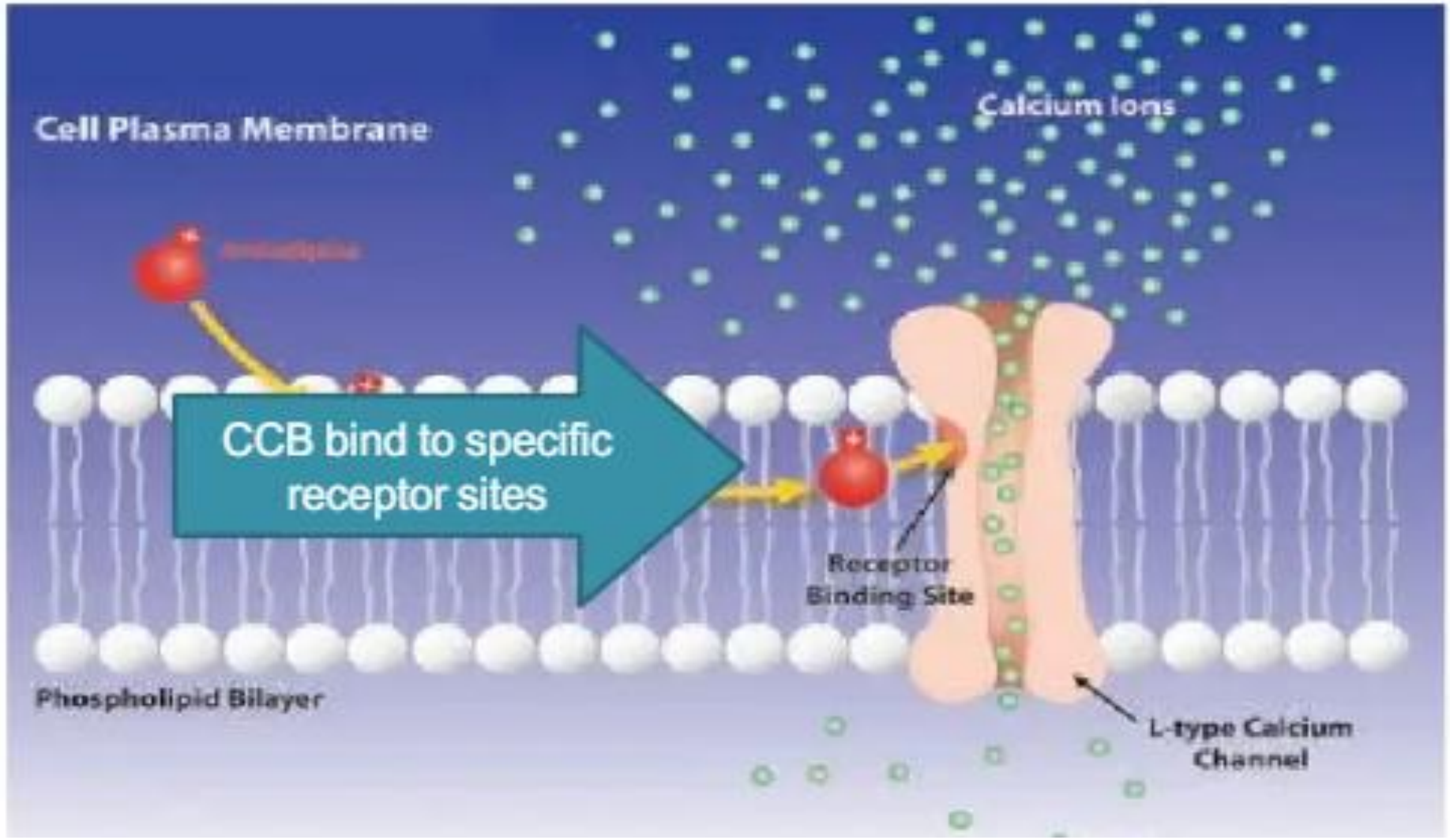
1)They act on vascular smooth muscle, reduce contraction of the arteries and cause vasodilation .

2)They act on cardiac muscles (myocardium), they reduce the force of contraction of the heart (Negative inotropic).

3) They slow down the conduction of electrical activity within the heart, slow down the heartbeat (Negative chronotropic).

4)They block the calcium signal on adrenal cortex cells, they directly reduce aldosterone production, which correlates to lower blood pressure.

CCB - Mechanism of Action



Indications of CCB:

- Hypertension
- Angina
- Tachyarrhythmia
- Raynaud's phenomenon
- Prevention of ischemic neurological damage following subarachnoid hemorrhage
- **Raynaud's Disease:** Inappropriate vasoconstriction of small arteries and arterioles gives rise to Raynod’s phenomenon.

Contraindications of CCB:

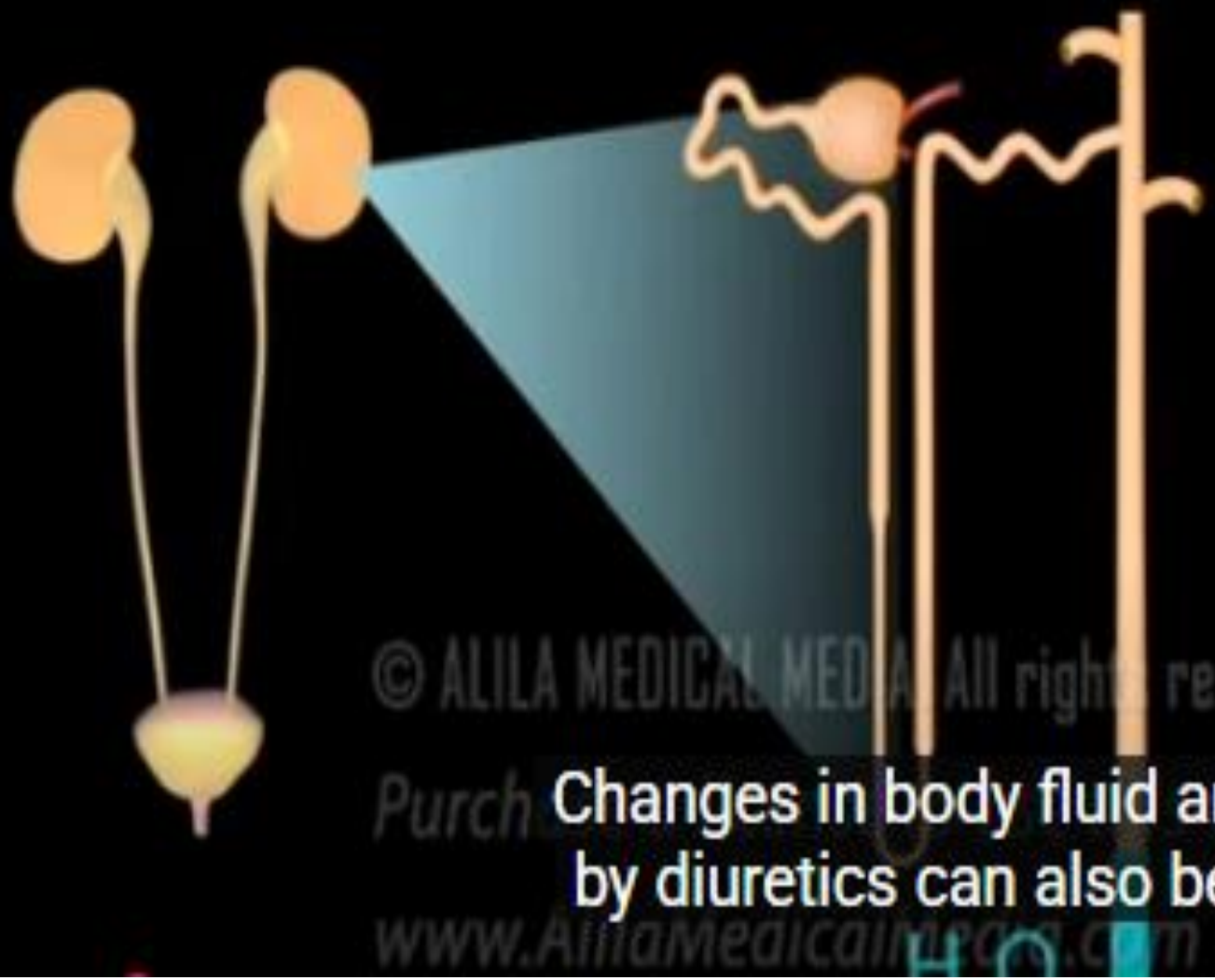
1. Heart failure
2. Bradycardia
3. A-V block
4. Sick-sinus syndrome(SSS)
5. WPW syndrome (Wolf parkinson white syndrome)

Adverse drug reactions

- Ankle oedema (due to raised intra arterial pressure)
- Reflex tachycardia
- Flushing of face
- Throbbing headache
- Constipation
- Nausea
- Vomiting
- Lethargy
- Heart block

DIURETICS

Diuretics



For treatment of:

- Primary/essential hypertension
- Edema (pulmonary & systemic)

Changes in body fluid and electrolytes induced by diuretics can also be therapeutic for some

DIURETICS

Are drugs or agents which increase the renal excretion of sodium & water by inhibiting the renal tubular re-absorption of sodium & water.

Classification of Diuretics:

A. According to the site of action

1. Drugs acting on PCT

Acetazolamide, Mannitol.

2. Drugs acting on thick ALLH (Loop diuretics)

Frusemide, Bumetanide, Ethacrynic acid

3. Drugs acting on proximal part of DCT

Thiazide group: Chlorothiazide, Hydrochlorothiazide

4. Drugs acting on distal part of DCT & CT

Spironolactone, Amiloride

B. According to potency

i. **High efficacious:** Frusemide, Bumetanide
ii. **Moderate efficacy:** Thiazide diuretics
iii. **Low efficacy:** Spironolactone, Mannitol

Thiazides are less powerful than loop diuretics but are preferred in treating uncomplicated hypertension.

Indications:

1. Mild to moderate hypertension
2. Idiopathic Hypercalciuria, to prevent recurrent stone formation
3. Nephrogenic diabetes insipidus.

- **Mechanism of action of Thiazide Diuretics:**
- Thiazide diuretics inhibits the **Na^+-Cl^- co-transport** system in proximal part of DCT, inhibiting its action and causing natriuresis with loss of Na+ and Cl- ions in the urine. So, Nacl re-absorption is not occurred – **Diuresis.**
- Hyponatremia causes ↓reabsorption of Na^+ & water- ↓blood volume- ↓**BP**
- Have a direct vasodilator action - ↓TPR--↓BP – Vasodilatation contributes to the later phase in BP reduction.

- **Hypokalemia causes relaxation of arteriolar smooth muscle-** vasodilatation -↓ TPR- ↓ **BP.**
- 1.Diuresis- ↓ Blood volume- ↓ CO- ↓**BP.**
- 2. Direct vasodilatation
- 3.Decreases sensitivity to circulatory monoamines.

- **Pharmacological actions of Thiazide Diuretics:**
- 1. Diuresis
- 2. ↓BP
- 3. Metabolic effects:
    - Hyponatremia
    - Hypokalemia
    - Hyperglycemia
    - Hyperuricemia- Gout
    - Hyperlipidemia

Indications:

- Mild to moderate hypertension
- Heart failure
- Hypercalcaemia
- Idiopathic hypercalciuria
- SIADH(Syndrome of Inappropriate ADH)
- Nephrogenic Diabetes Insipidus
- Frusemide is used for severe hypertension

Adverse effects of Thiazide Diuretics:

- Hypokalemia
- Hyponatremia
- Hyperglycemia
- Hyperuricemia
- Hyperlipidemia
- Muscle cramp
- Lethargy
- Thrombocytopenia
- Agranulocytosis

Frusemide

- Acts by blocking Na K 2Cl transport system
- Thereby increase excretion of Na+ ,water ,K+
- Used in severe hypertension

Adverse effect including Hyponatremia

Hypokalemia

Hyperglycemia

Hyperlipidemia

Ototoxicity etc

Drug therapy for pregnant hypertensive mother:

- Labetalol
- Alpha methyldopa
- Calcium Channel blocker
- Hydralazine
- Magnesium Sulphate

Newer antihypertensives

HOW DO NEPRILYSIN INHIBITORS WORK?

- **Neprilysin inhibitors** are a new class of drugs used to treat **high blood pressure and heart failure.**
- They work by blocking the action of **Neprilysin** thus **preventing the breakdown of natriuretic peptides.**

- **Neprilysin enzyme** is also called **neutral endopeptidase** that plays a role in the **degradation of natriuretic peptides and other vasoactive peptides including bradykinin.**
- **Natriuretic peptides** remove sodium from the blood and excrete it in the urine.
- In the absence of natriuretic peptides, sodium levels increase in the blood, leading to increased blood pressure.

THANK YOU ☺


Any
Question?
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