BHARATHIDASAN UNIVERSITY

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Programme: M.Sc., Biomedical Science

Course Title : Pharmacology and Toxicology

Course Code : BM35C7

Unit-IV

Pharmacology of Cardiovascular System - Part 1

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CARDIAC GLYCOSIDES

Cardiac glycoside :

- These are glycosidic drugs having cardiac inotropic property.
- Cardiac glycosides are found in several plants and in toad skin (**Bufotoxin**). Digitalis lanata is the source of **Digoxin**, the only glycoside that is currently in use. Others like **Digitoxin** (from Digitalis purpurea) and **Ouabain** (from Strophan thus gratus), etc. are no longer clinically used or marketed.

PHARMACOLOGICAL ACTIONS:

- All digitalis glycosides have qualitatively similar action. Digoxin is described as prototype.

1.HEART:

- Digitalis has direct effects on myocardial contractility and electrophysiological properties.

Force of contraction :

- Digitalis causes a dose dependent increase in force of contraction of heart—a positive inotropic action.
- This is especially seen in the failing heart which is exquisitely sensitive. There is increased velocity of tension development and higher peak tension can be generated. Systole is shortened, diastole is prolonged.
- When a normal heart is subjected to increased impedance to outflow, it generates increased tension so that stroke volume is maintained upto considerably higher values of impedance , while the failing heart is not able to do so and the stroke volume progressively decreases.

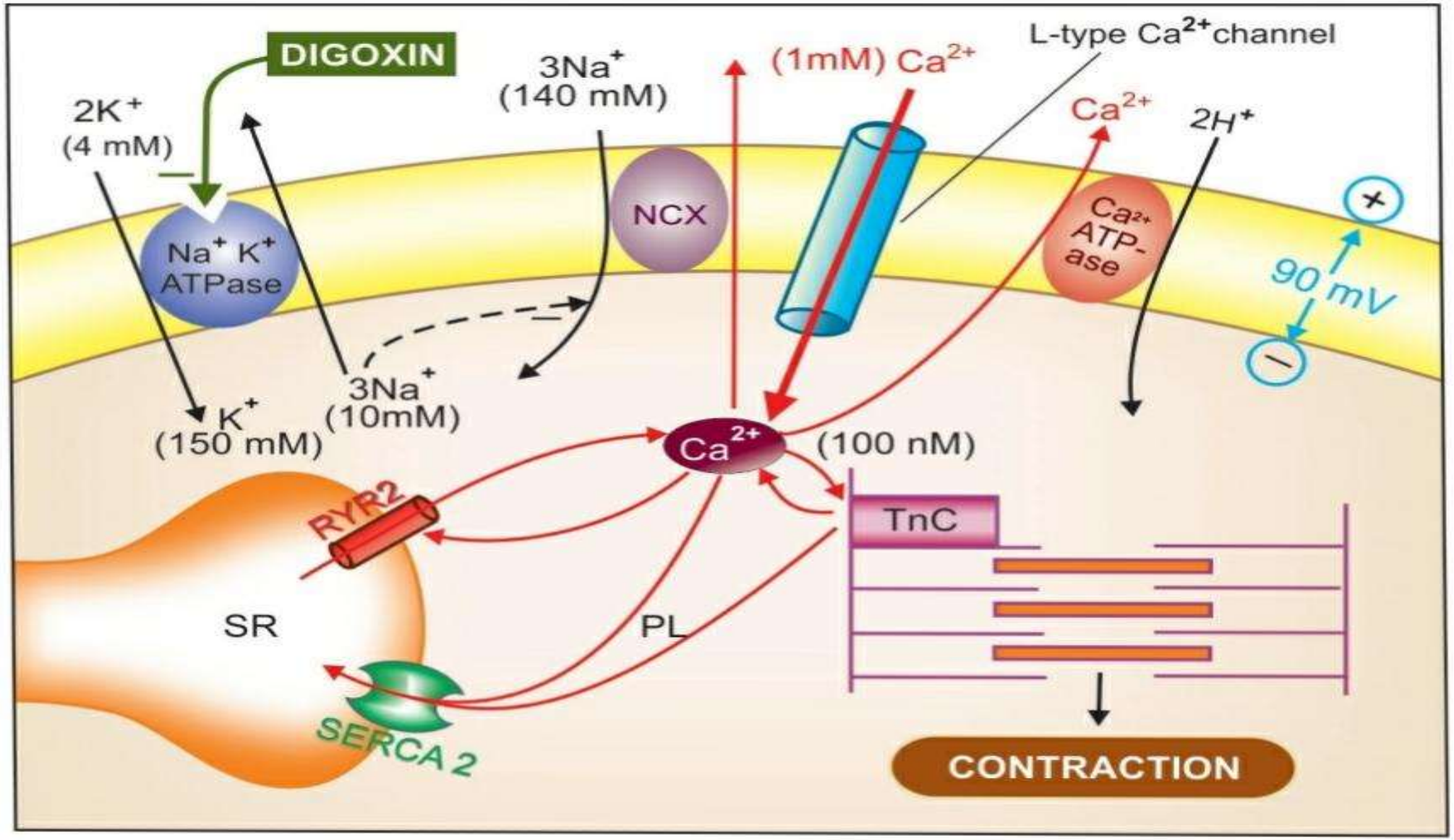
- There is more complete emptying of failing and dilated ventricles—cardiac output is increased and end-diastolic volume is reduced.
- Therapeutic doses of digoxin do not increase resting tension (tone) in myocardial fibres.

RATE:

- Heart rate is decreased by digitalis. Bradycardia is more marked in CHF patients because improved circulation (due to positive inotropic action) restores the diminished vagal tone and abolishes sympathetic overactivity. In addition, digitalis slows the heart by vagal and extravagal actions.

MECHANISM OF ACTION

- Digitalis increases force of cardiac contraction by a direct action independent of innervation
- It selectively binds to extracellular face of the membrane associated Na+K+ ATPase of myocardial fibres and inhibitis this enzyme.
- Inhibition of this cation pump results in progressive accumulation of Na+ intracellularly. This indirectly results in intracellular Ca2+ accumulation.


DIGOXIN
2K+
(4 mM)
3Na+
(140 mM)
(1mM) Ca2+
L-type Ca2+channel
Ca2+
2H+
Na+ K+
ATPase
NCX
Ca2+
ATP-
ase
90 mV
3Na+
(10mM)
K+
(150 mM)
Ca2+
(100 nM)
RYR2
TnC
SR
PL
SERCA 2
CONTRACTION

2. BLOOD VESSEL :

- Digitalis has mild direct vasoconstrictor action—peripheral resistance is increased in normal individuals.
- In CHF patients this is more than compensated by the indirect effect of improvement in circulation.
- Digitalis has no prominent effect on BP: systolic BP may increase and diastolic may fall in CHF patients—pulse pressure increases.

3. KIDNEY:

- Diuresis occurs promptly in CHF patients, secondary to improvement in circulation and renal perfusion. The retained salt and water is gradually excreted.

4. CNS :

- Digitalis has little apparent CNS effect in therapeutic dose. Higher doses cause CTZ activation → nausea and vomiting

PHARMACOKINETICS :

		DIGOXIN
1.	Oral absorption	60–80%
2.	Plasma protein binding	25%
3.	Time course of action*	
	–Onset	15–30 min
	–Peak	2–5 hr
	–Duration	2–6 days
4.	Plasma t½	40 hr
5.	Therapeutic concn.	0.5–1.4 ng/ml
6.	Toxic concn.	> 2 ng/ml
7.	Daily maintenance dose	0.125–0.5 mg
8.	Daily elimination**	35%
9.	Route of elimination (predominant)	Renal excretion
10.	Route of administration	Oral, i.v.

ADVERSE EFFECTS :

- Toxicity of digitalis is high, margin of safety is low .

EXTRACARDIAC :

Anorexia, nausea, vomiting and abdominal pain are usually reported first: are due to gastric irritation, mesenteric vasoconstriction and CTZ stimulation.

Skin rashes and gynaecomastia are rare.

CARDIAC :

Almost every type of arrhythmia can be produced by digitalis:

pulsus bigeminus

nodal and ventricular extrasystoles

ventricular tachycardia

terminally ventricular fibrillation.

INTERACTIONS :

- Diuretics: cause hypokalemia which increases the risk of digitalis arrhythmias; potassium supplements should be given prophylactically.
- Quinidine: reduces binding of digoxin to tissue proteins as well as its renal and biliary clearance by inhibiting efflux transporter P-glycoprotein → plasma concentration of digoxin is doubled → toxicity can occur.
- Digoxin absorption may be reduced by metoclopramide, sucralfate, antacids, neomycin, sulfasalazine. Absorption of digoxin is increased by atropinic drugs, including tricyclic antidepressants

USES :

- The two main indications of digitalis are :
    1. Congestive Heart Failure
    2. Cardiac Arrhythmias
        i. Atrial Fibrillation
        ii. Atrial Flutter

DRUGS FOR HEART FAILURE

HEART FAILURE:

- Heart failure means that the heart is unable to pump blood around the body properly .It usually happens because the heart has become too weak or stiff.
- It's sometimes called congestive heart failure, although this name is not widely used now.
- Heart failure does not mean your heart has stopped working.it means it need some support to help it work better.
- It can occur at any age , but is most common in older people.
- Heart failure is a long term condition that tends to get gradually worse overtime.
- It cannot usually be cured, but the symptoms can often be controlled for many years.

SYMPTOMS OF HEART FAILURE:

- The main symptoms of heart failure are:
- Breathlessness after the activity or at rest.
- feeling tired most of the time and finding exercise exhausting
- feeling lightheaded or fainting
- swollen ankles and legs
- Some people also experience other symptoms, such as a persistent cough, a fast heart rate and dizziness.

Symptoms can develop quickly (acute heart failure) or gradually over weeks or months (chronic heart failure).

TREATMENT FOR HEART FAILURE

- lifestyle changes – including eating a healthy diet, exercising regularly and stopping smoking
- medicine – a range of medicines can help; many people need to take 2 or 3 different types
- devices implanted in your chest – these can help control your heart rhythm
- surgery – such as a bypass operation or a heart transplant.

MEDICINES FOR HEART FAILURE

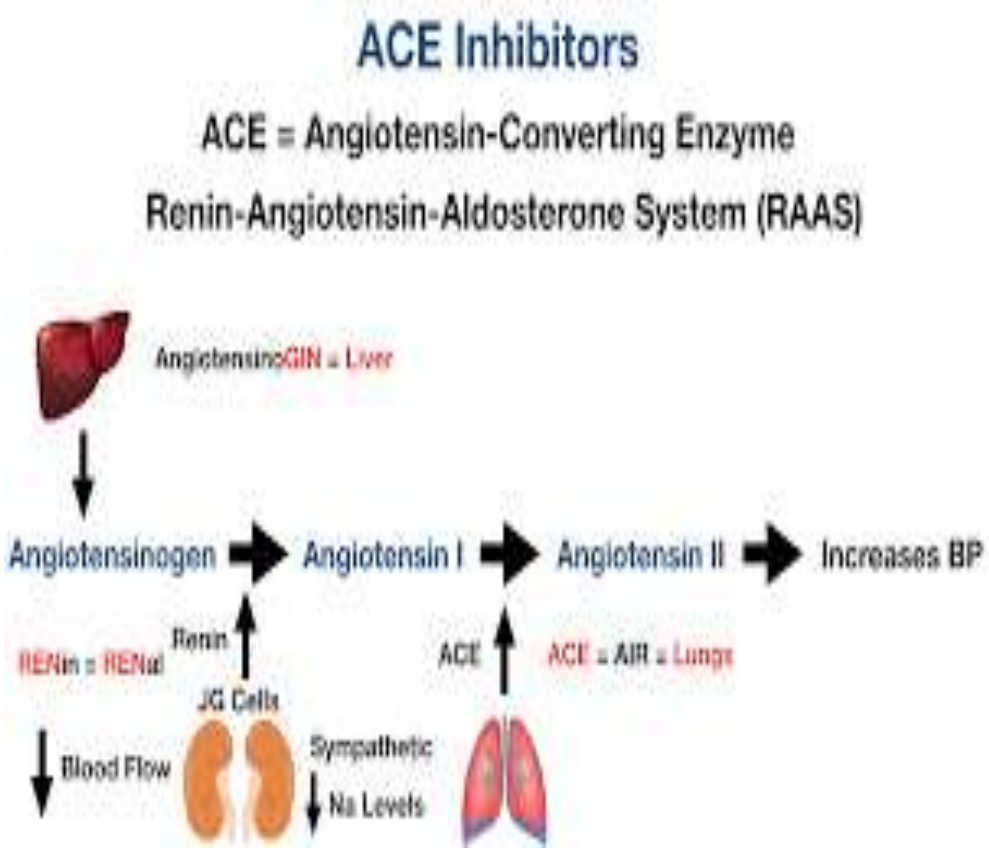
- Most people with heart failure are treated with medication. Often you'll need to take 2 or 3 different medicines.

Some of the main medicines for heart failure include:

- ACE inhibitors
- angiotensin-2 receptor blockers (ARBs or AIIRAs)
- beta blockers
- mineralocorticoid receptor antagonists
- diuretics
- ivabradine
- sacubitril valsartan
- hydralazine with nitrate
- digoxin
- SGLT2 inhibitors

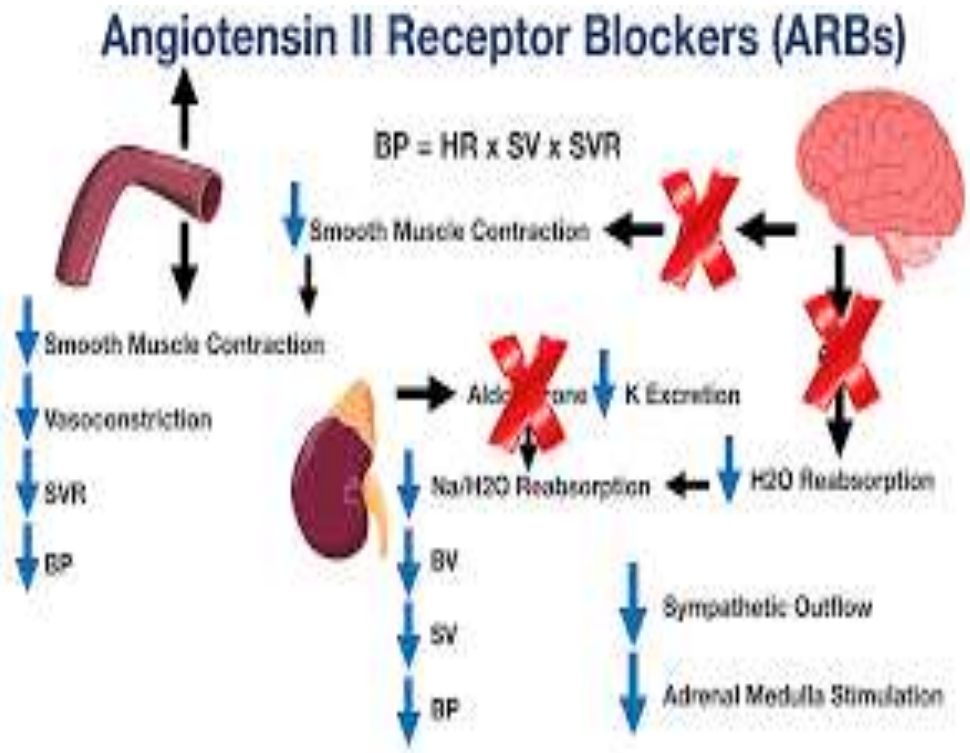
ACE INHIBITORS

- Angiotensin-converting enzyme (ACE) inhibitors work by relaxing and opening up your blood vessels, which makes it easier for your heart to pump blood around the body.
- Examples - ramipril, captopril, enalapril, lisinopril and perindopril.
- Side effects - dry, irritating cough.
- If you have a troublesome cough, an ACE inhibitor may be switched to an ARB.
- ACE inhibitors can also cause your blood pressure to fall too low, and they may cause kidney problems. Your GP will monitor this.



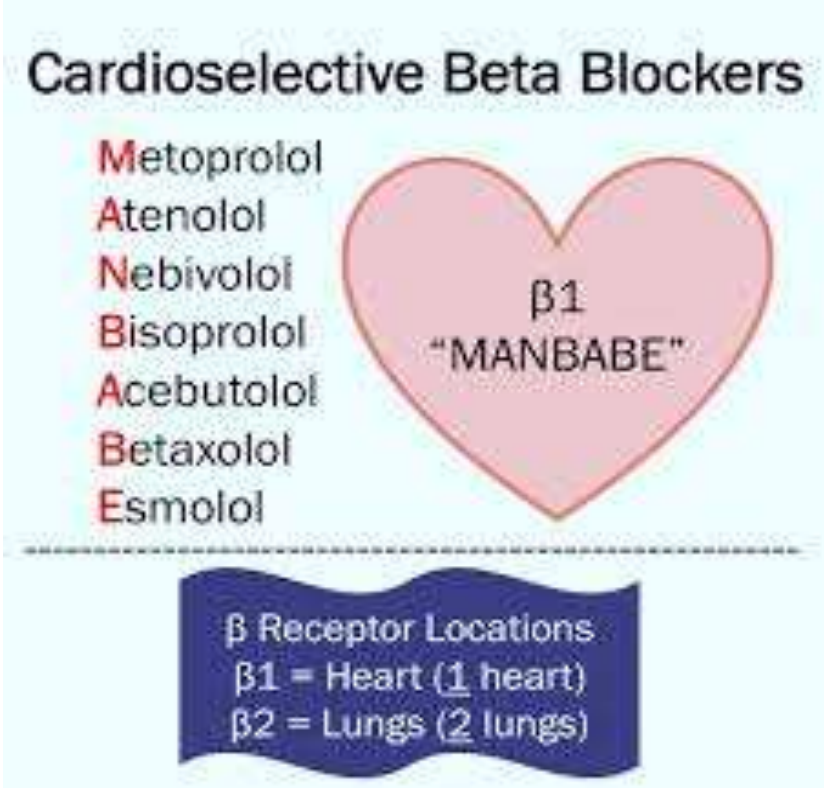
ANGIOTENSIN-2 RECEPTOR BLOCKERS (ARBS)

- Angiotensin-2 receptor blockers (ARBs) work in a similar way to ACE inhibitors by relaxing blood vessels and reducing blood pressure.
- They tend to be used as an alternative to ACE inhibitors because they don't usually cause a cough, although they may not be quite as effective as ACE inhibitors.
- Examples - candesartan, losartan, telmisartan and valsartan.
- Side effects - low blood pressure and high levels of potassium in your blood.
- Your doctor will carry out regular blood tests to monitor your potassium level.



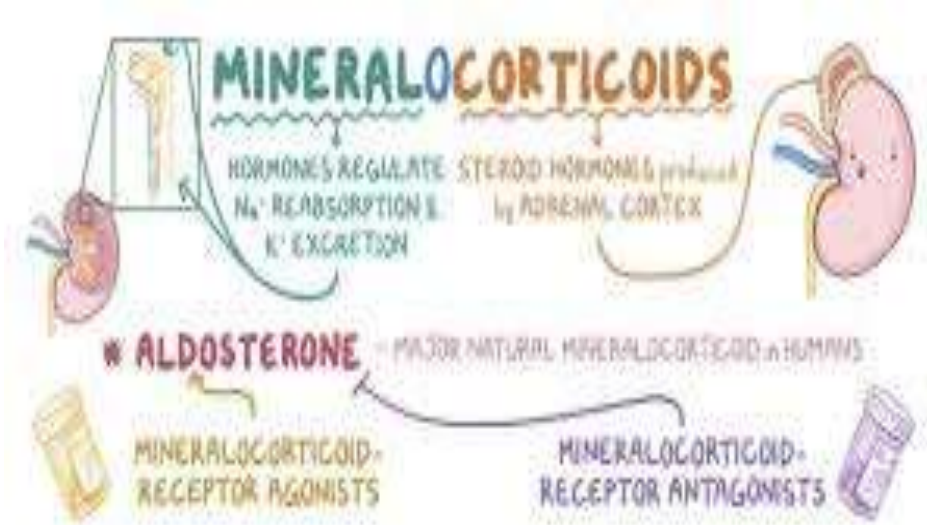
BETA BLOCKERS

- Beta blockers work by slowing your heart down and protecting your heart from the effects of adrenaline and noradrenaline, "fight or flight" chemicals produced by the body.
- Examples - bisoprolol, carvedilol and nebivolol.
- side effects - dizziness, tiredness and blurred vision.
- But most people taking them have either no or very mild side effects that become less troublesome with time.



MINERALOCORTICOID RECEPTOR ANTAGONISTS (MRAS)

- MRAs make you pass more urine, and help lower blood pressure and reduce fluid around the heart, but they don't reduce potassium levels.
- Examples - spironolactone and eplerenone.
- Spironolactone may cause enlarged breasts in men (gynaecomastia) and breast tenderness and increased hair growth in women.
- Eplerenone can cause sleeping difficulties, dizziness and headaches.
- The most serious side effect of these medicines is that they can cause the level of potassium in your blood to become dangerously high.
- Your doctor will carry out regular blood tests to check for this.



DIURETICS

- Diuretics (water pills) make you pass more urine and help relieve ankle swelling and breathlessness caused by heart failure.
- There are many different types of diuretic, but the most widely used for heart failure are furosemide (also called frusemide) and bumetanide.
- Side effects - dehydration and reduced levels of sodium and potassium in the blood.

IVABRADINE

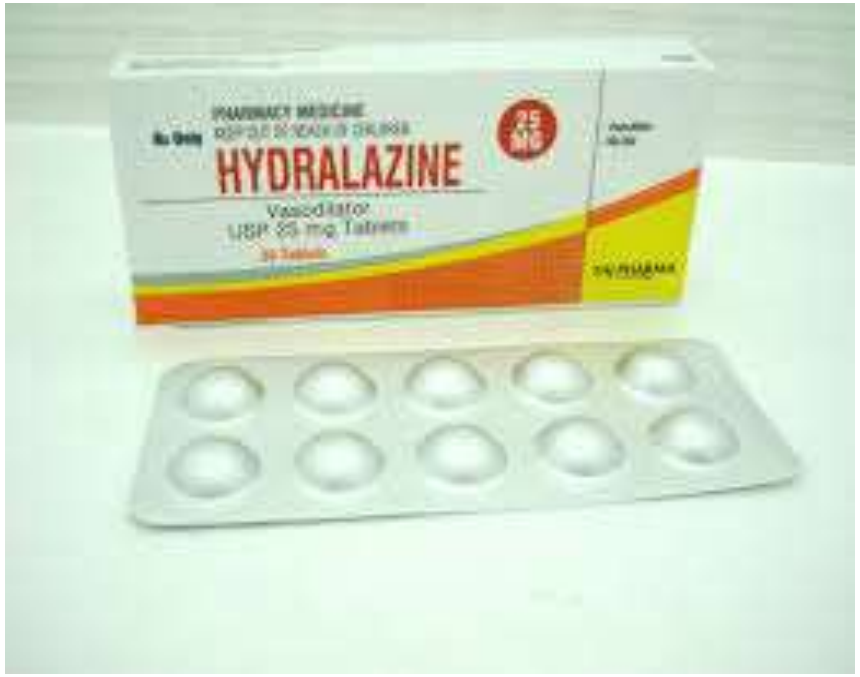
- Ivabradine is a medicine that can help slow your heart down.
- It's a useful alternative to beta blockers if you can't take them or they cause troublesome side effects.
- It can also be used alongside beta blockers if they don't slow the heart enough.
- side effects - headaches, dizziness and blurred vision.

SACUBITRIL VALSARTAN

- Sacubitril valsartan is a single tablet that combines an ARB and a medication called a neprilysin inhibitor.
- It's suitable for people with more severe heart failure, whose heart is only able to pump a reduced amount of oxygenated blood around the body despite taking other medication.
- Side effects - low blood pressure, high potassium levels and kidney problems.

HYDRALAZINE WITH NITRATE

- Hydralazine in combination with nitrate can help relax and open up the blood vessels.
- These medicines are sometimes prescribed by heart specialists (cardiologists) for people who are unable to take an ACE inhibitor or ARB.
- Side effects - headaches, a fast heartbeat and a pounding, fluttering or irregular heartbeat (palpitations).



DIGOXIN

- Digoxin can improve your symptoms by strengthening your heart muscle contractions and slowing down your heart rate.
- It's normally only recommended for people who have symptoms despite treatment with ACE inhibitors, ARBs, beta blockers and diuretics.
- Side effects - dizziness, blurred vision, feeling and being sick, diarrhoea and an irregular heartbeat.

SGLT2 INHIBITORS

- SGLT2 inhibitors are tablets that can help lower your blood sugar levels.
- Empagliflozin and dapagliflozin are types of SGLT2 inhibitor. They can be used to treat some types of heart failure, as an add-on to other medicines.
- Side effects - thrush, peeing more than usual, a mild skin rash and back pain.

ANTI-HYPERTENSIVE DRUGS

CLASSIFICATION

1. *Diuretics*
   Thiazides: Hydrochlorothiazide, Chlorthalidone, Indapamide
   High ceiling: Furosemide, etc.
   K^+ Sparing: Spironolactone, Amiloride
2. *ACE inhibitors*
   Captopril, Enalapril, Lisinopril, Perindopril, Ramipril, Fosinopril, etc.
3. *Angiotensin (AT_1 receptor) blockers*
   Losartan, Candesartan, Irbesartan, Valsartan, Telmisartan
4. *Calcium channel blockers*
   Verapamil, Diltiazem, Nifedipine, Felodipine, Amlodipine, Nitrendipine, Lacidipine, etc.
5. *β Adrenergic blockers*
   Propranolol, Metoprolol, Atenolol, etc.
6. *β + α Adrenergic blockers*
   Labetalol, Carvedilol
7. *α Adrenergic blockers*
   Prazosin, Terazosin, Doxazosin
   Phentolamine, Phenoxybenzamine
8. *Central sympatholytics*
   Clonidine, Methyldopa
9. *Vasodilators*
   Arteriolar: Hydralazine, Minoxidil, Diazoxide
   Arteriolar + venous: Sodium nitroprusside

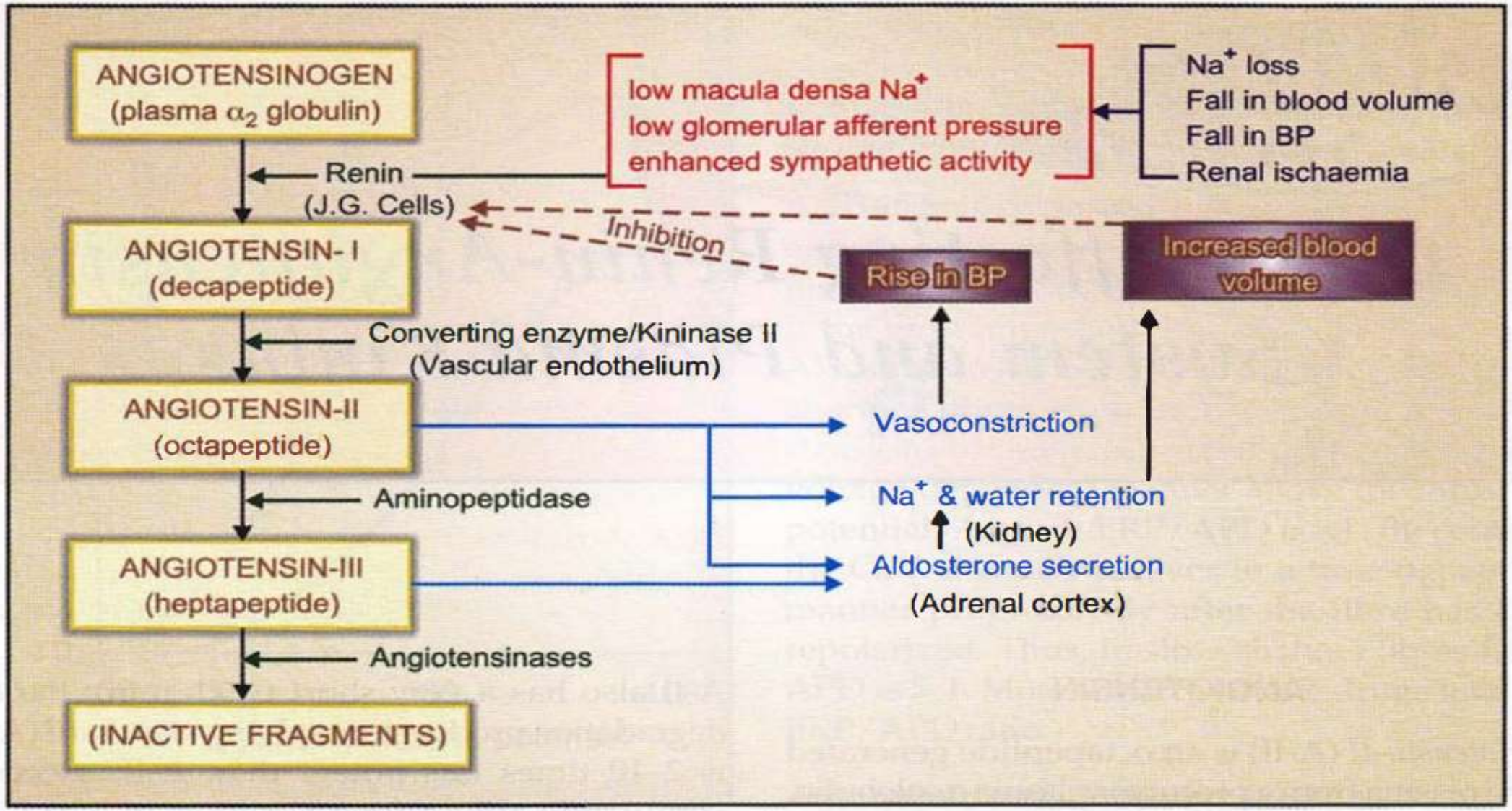
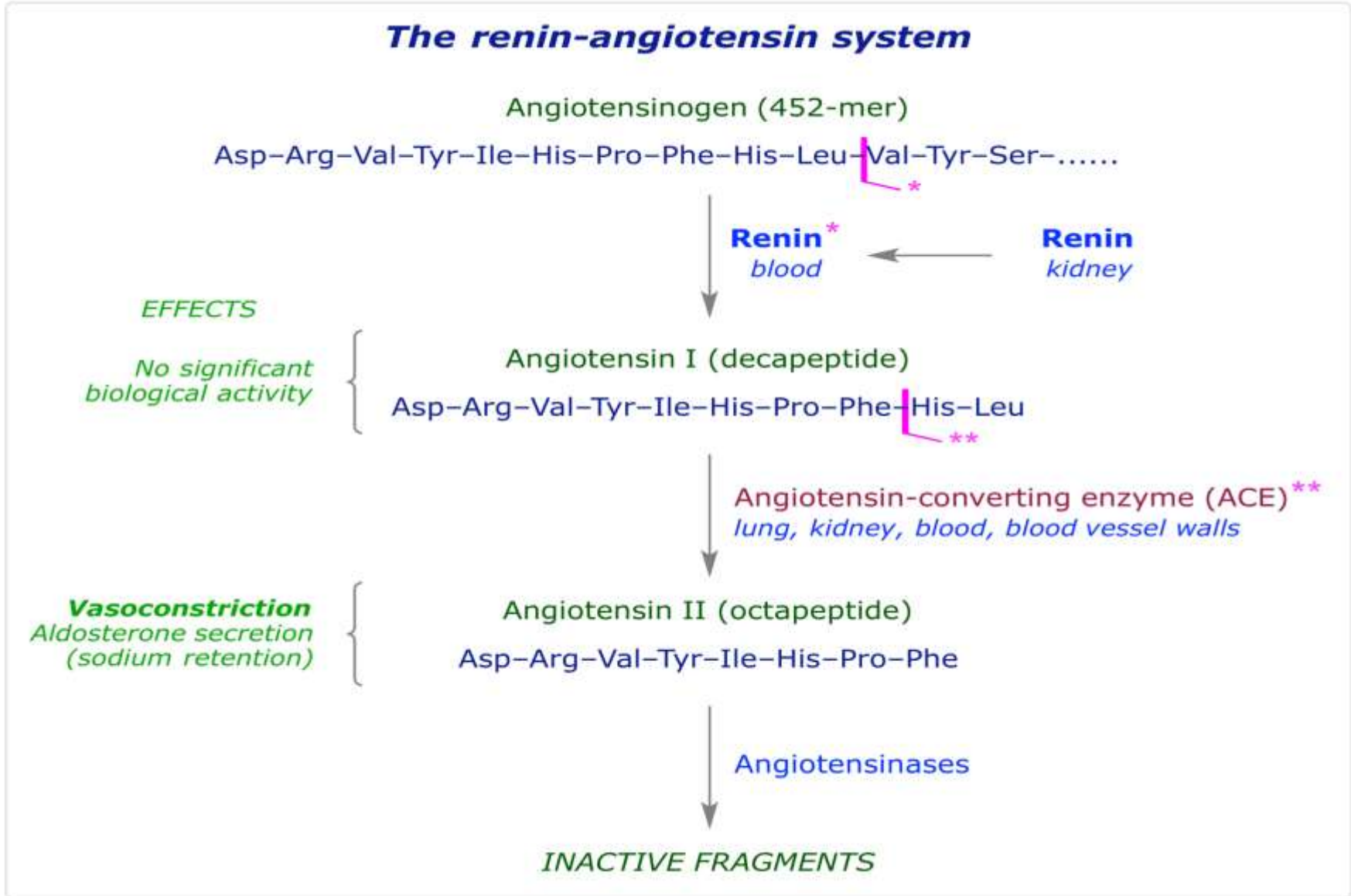


Fig. 36.1: Physiological regulation of electrolyte balance, plasma volume and blood pressure by the renin-angiotensin system


The renin-angiotensin system
Angiotensinogen (452-mer)
Asp–Arg–Val–Tyr–Ile–His–Pro–Phe–His–Leu–Val–Tyr–Ser–.....
*
Renin*
blood
Renin
kidney
EFFECTS
No significant biological activity
Angiotensin I (decapeptide)
Asp–Arg–Val–Tyr–Ile–His–Pro–Phe–His–Leu
**
Angiotensin-converting enzyme (ACE)**
lung, kidney, blood, blood vessel walls
Vasoconstriction
Aldosterone secretion (sodium retention)
Angiotensin II (octapeptide)
Asp–Arg–Val–Tyr–Ile–His–Pro–Phe
Angiotensinases
INACTIVE FRAGMENTS

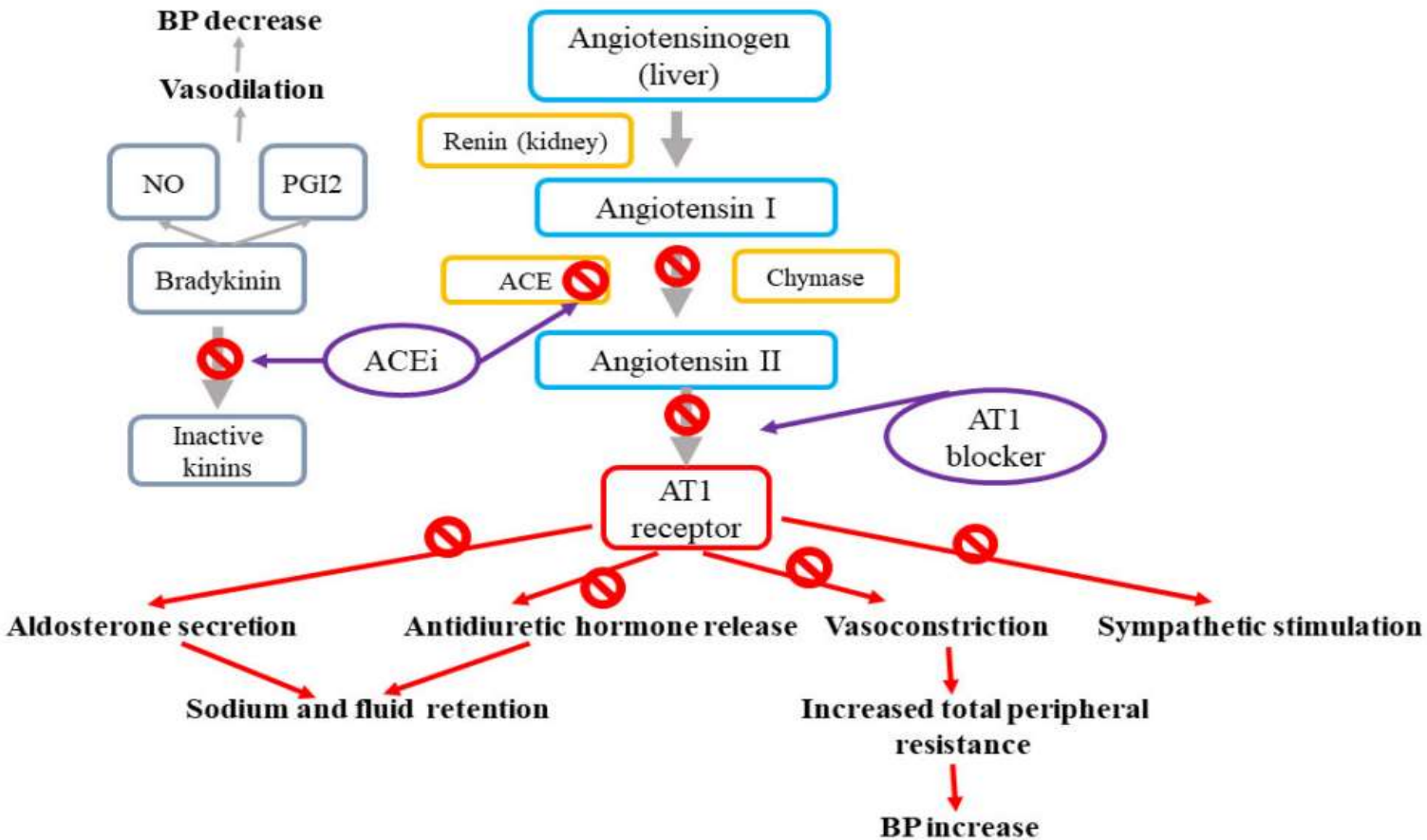


Figure 2. Mechanisms of action of angiotensin-II receptor blockers and angiotensin-converting enzyme inhibitors.

Captopril

- It is a sulfhydryl containing dipeptide surrogate of proline which abolishes the pressor action of A-I but not that of A-II: does not block A-II receptors.
- Captopril can also increase plasma kinin levels and potentiate the hypotensive action of exogenously administered bradykinin.
- Pretreatment with B2 kinin receptor antagonist has shown that kinins do contribute to the acute vasodepressor action of ACE inhibitors.

- Captopril induced hypotension
- Decrease in total peripheral resistance.
- The arterioles dilate and compliance of larger arteries is increased.
- Both systolic and diastolic BP fall.
- It has no effect on cardiac output.

Pharmacokinetics

- About 70% of orally administered captopril is absorbed.
- Presence of food in stomach reduces its bioavailability.
- Penetration in brain is poor.
- It is partly metabolized and partly excreted unchanged in urine.
- The plasma t1/2 is -2 hours, but actions last for 6-12 hours.

Adverse effects

- Hypotension -an initial sharp fall in BP in diuretic treated and CHF patients
- Hyperkalaemia -more likely in patients with impaired renal function
- Cough
- Rashes urticaria
- Angioedema
- Dysgeusia
- Fetopathy- fetal growth retardation, hypoplasia organs & fetal death
- Acute renal failure: is precipitated by ACE inhibitors in patients with bilateral renal artery stenosis

ANGIOTENSIN ANTAGONISTS (Angiotensin receptor blockers or ARBs)

- Nonpeptide orally active AT 1 receptor antagonists
- Losartan, candesartan, valsartan, telmisartan and irbesartan.
- It is a competitive antagonist and inverse agonist of A-II, 10,000 times more selective for AT 1 than AT 2 receptor

ACTION

- It blocks all overt actions of A-II
- viz. vasoconstriction, central and peripheral sympathetic stimulation, release of aldosterone and Adr from adrenals, renal actions promoting salt and water reabsorption
- Central actions like thirst, vasopressin release and growth-promoting actions on heart and blood vessels

Pharmacokinetics

- Oral absorption not affected by food
- Oral bioavailability is only 33% due to first pass metabolism.
- It is partially carboxylated in liver to an active metabolite (E3174) which is a 10-30 times more potent noncompetitive AT 1 receptor antagonist.
- Plasma levels are attained at 1 hr for losartan and at 3-4 hours for E3174.
- Both compounds are 98% plasma protein bound, do not enter brain and are excreted by the kidney.
- The plasma t1/2 of losartan is 2 hr, but that of E3174 is 6-9 hr.
- No dose adjustment is required in renal insufficiency, but dose should be reduced in presence of hepatic dysfunction.

Adverse effects

- Hypotension and hyperkalemia, but first dose hypotension is uncommon.
- Free of cough and dysgeusia
- Angioedema is reported in fewer cases.
- Headache, dizziness, weakness and upper G.I side effects are mild
- Fetopathic -not to be administered during pregnancy.

PLASMA KININS (Bradykinin and Kallidin)

- Plasma kinins are polypeptides split off from a plasma globulin Kininogen by the action of specific enzymes Kallikreins.
- The two important plasma kinins, Kallidin (decapeptide) and Bradykinin (nonapeptide)

CVS

- Kinins are more potent vasodilators
- The **dilatation is mediated through endothelial NO and PGI2 generation, and involves mainly the arterioles.**
- Larger arteries, most veins and vessels with damaged endothelium are constricted through direct action on the smooth muscle.
- Injected i.v. kinins cause flushing, throbbing headache and fall in BP.
- Kinins have no direct action on heart; reflex stimulation occurs due to fall in BP.

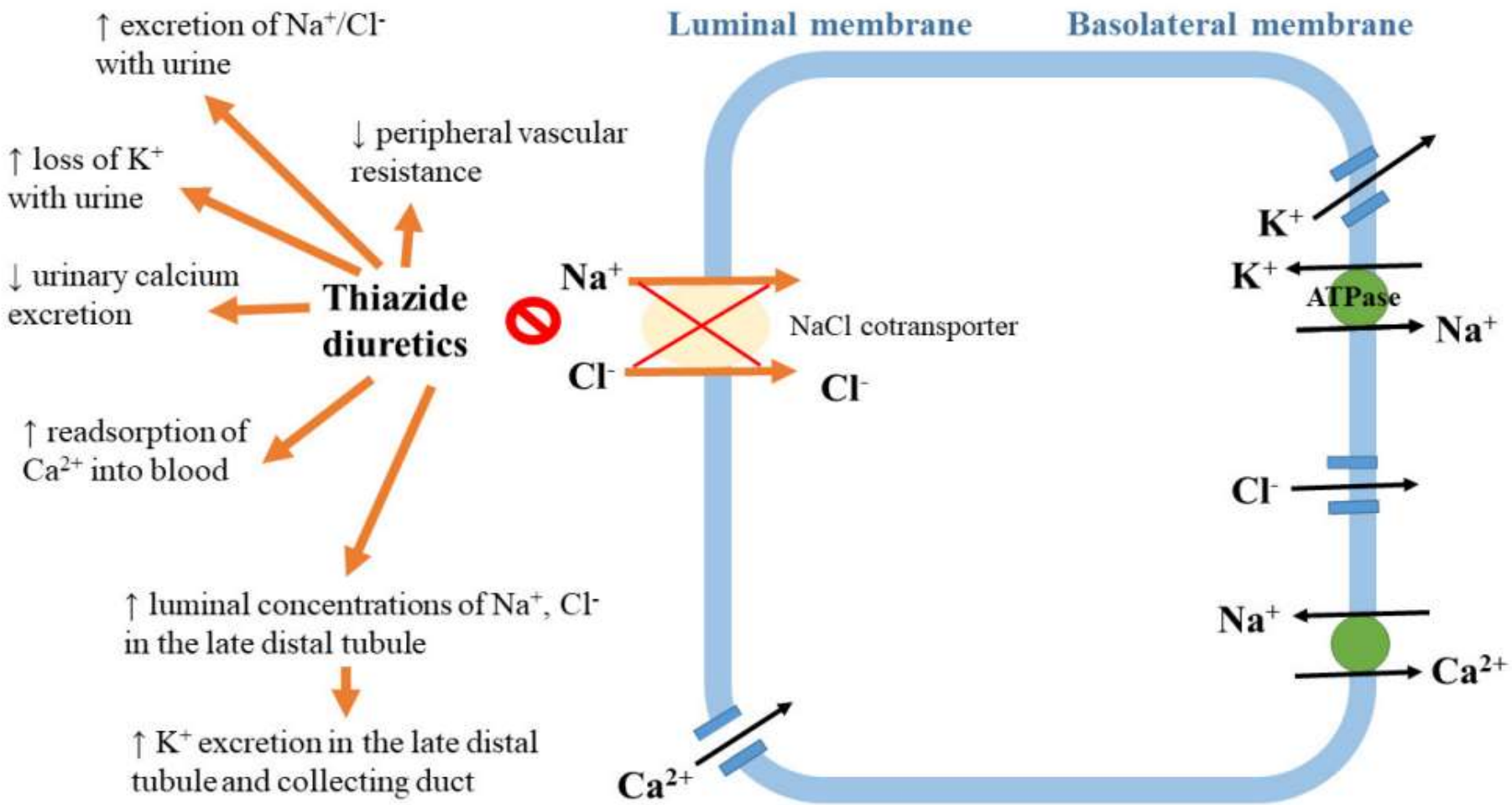


Figure 4. Effects of action of thiazide diuretics.

Thiazide Diuretic Hydrochlorothiazide

- **Inhibits the sodium chloride cotransporter** expressed in the distal convoluted tubule of the nephron
- The initial antihypertensive effects of these drugs involve the enhancement of sodium excretion (natriuresis)
- Diminishing of extracellular volume, which results in a reduction in cardiac output.
- Moreover, these drugs exert long-term effects via a decrease in vascular resistance, possibly resulting from an inhibition of the sympathetic nervous and/or renin– angiotensin systems

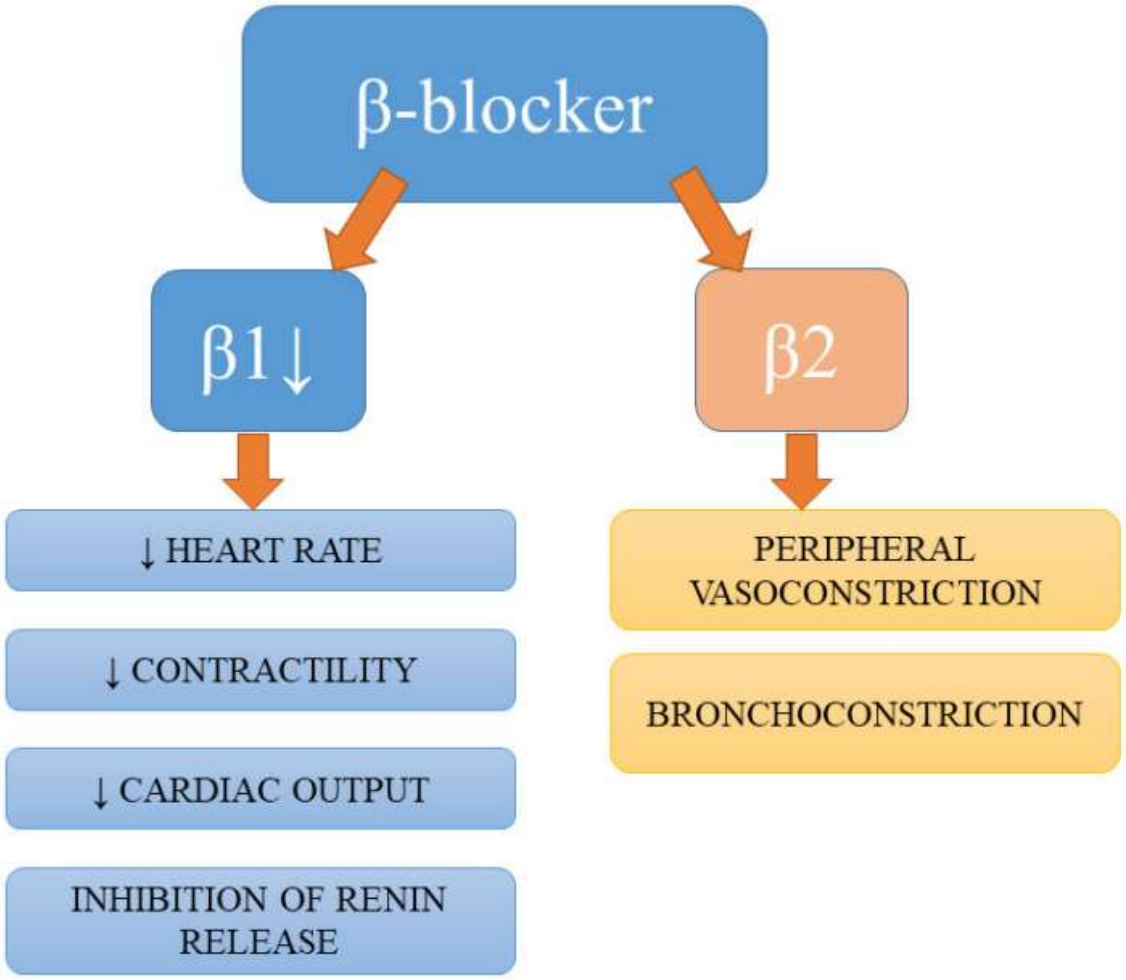


Figure 3. Effects of action of β-blockers.

β-blockers resulting from the blockage of their targets on the juxtaglomerular cells of the kidney, the reduction in renin secretion, and subsequent hampering of circulating angiotensin II production, these drugs also diminish myocardial contractility, heart rate, and cardiac output

Calcium channel blockers (CCBs)

- Bind to and block mainly the L-type calcium channels present on cardiac and vascular smooth muscle cells (SMCs)/
- They prevent calcium ions from entering into vascular smooth muscles, which results in muscle relaxation and vasodilation and leads to a decrease in vascular resistance and, consequently, diminished arterial BP
- Each subclass of calcium channel blocking agent binds at a specific location.

- Dihydropyridines (e.g., amlodipine and nifedipine) exert vascular selectivity
- Verapamil has cardiac selectivity
- Diltiazem can act in both the heart and blood vessels

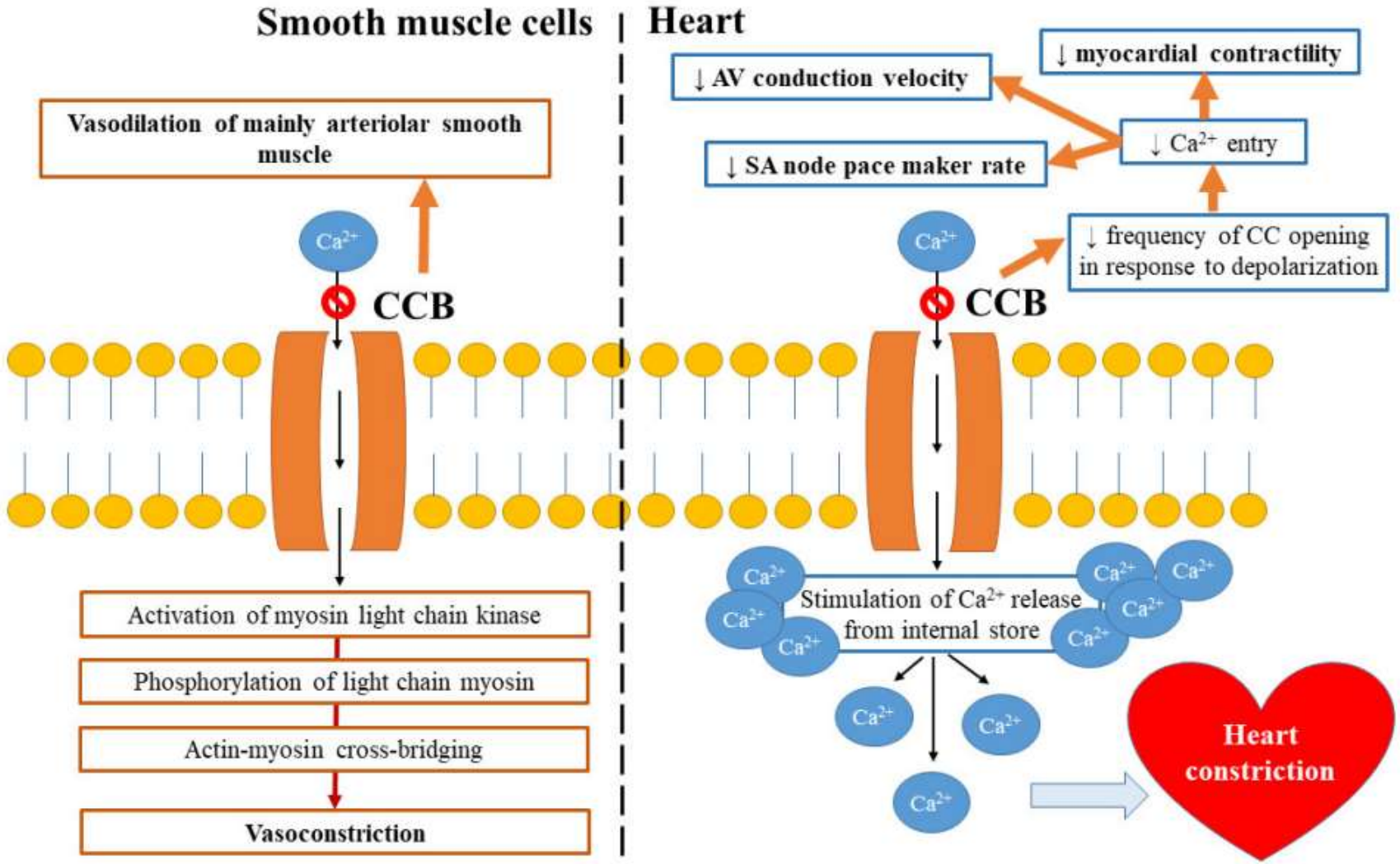


Figure 1. Mechanism of calcium channel blockers' (CCBs) action.

Acknowledgement

- The Presentation is being used for educational and non commercial Purposes
- Thanks are due to all the original contributors and entities whose pictures were used in the creation of this presentation.