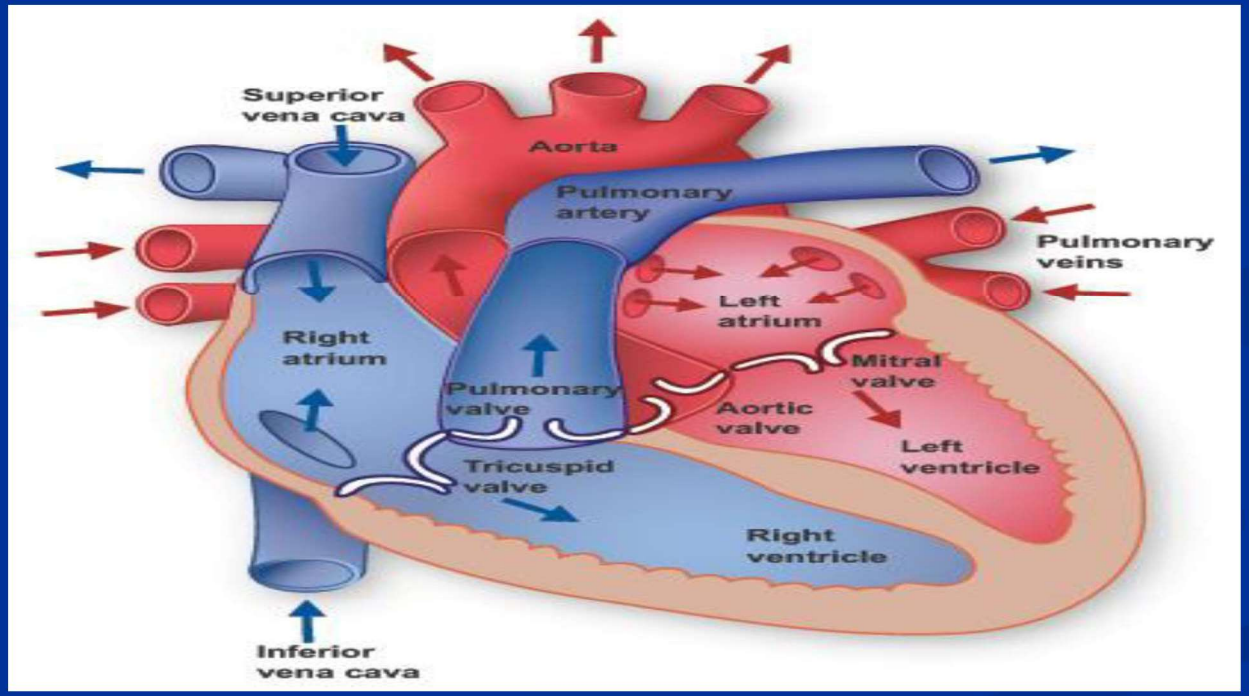
The Islamic University
College of Pharmacy
Pharmacology & Toxicology Dep.

Pharmacology –II

Cardiovascular System (CVS)-Acting Drugs



Level: 4th
Semester: 1st

Lecture- 10

Dr: Mohamed R. Elnagar

Antihypertensive drugs …… cont.

2) Drugs acting on the renin- angiotensin - aldosterone system (RAAS)

i- Angiotensin-converting enzyme inhibitors (ACEI)

ii- Angiotensin receptors blockers.

iii- Direct renin inhibitors

i- Angiotensin-converting enzyme inhibitors (ACEI)

Captopril, Lisinopril, Enalapril, Ramipril

Particularly effective when hypertension results from excess renin production (reno-vascular hypertension, white & young).

Pharmacokinetics:

Polar, excreted in urine.

Do not cross BBB.

Have a long half-life & given once daily.

Rapidly absorbed from GIT after oral administration.

Food reduces their bioavailability.

It takes 2-4 weeks to see the full antihypertensive effect of ACEIs.

Enalapril & ramipril are prodrugs.

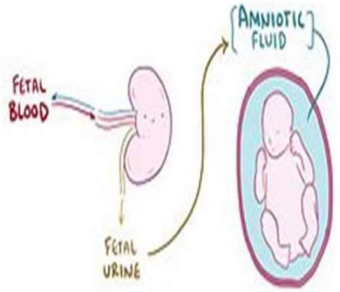
Enalaprilat is the active **metabolite of enalapril** given by i.v. route in **hypertensive emergency.**

Clinical Uses:

1) Treatment of essential **hypertension**
2) Hypertension in patients with **chronic renal disease**, **ischemic heart disease**, **diabetes**
3) Treatment of **heart failure**.

Adverse Drug Reactions:

1) **Dry cough** (about 5% of patients)
2) **Acute renal failure**, especially in patients with **renal artery stenosis**.
3) Severe **hypotension** in hypovolemic patients.
4) Cause **renal agenesis/failure** in the **fetus**, resulting in **oligohydraminosis** (low amniotic fluid during pregnancy). Renal agenesis is a condition in which a newborn is missing one or both kidneys



5) **Angioneurotic edema (angioedema)**, swelling in the nose, throat, tongue, larynx.
6) **First dose effect.** →**hypotension** at first dose of ACEi.

7) **Skin rash, fever**
8) **Dysgeusia** (distortion of the sense of taste).
9) **Proteinuria and neutropenia**.
10) **Metallic taste** (metallic or loss of taste).

ADRs Specific to Captopril

Dry cough:

Bradykinin is also thought to be the **cause of** the **dry cough** in some patients on widely prescribed angiotensin-converting enzyme (ACE) inhibitor drugs. It is thought that **bradykinin** is converted to inactive metabolites by ACE.

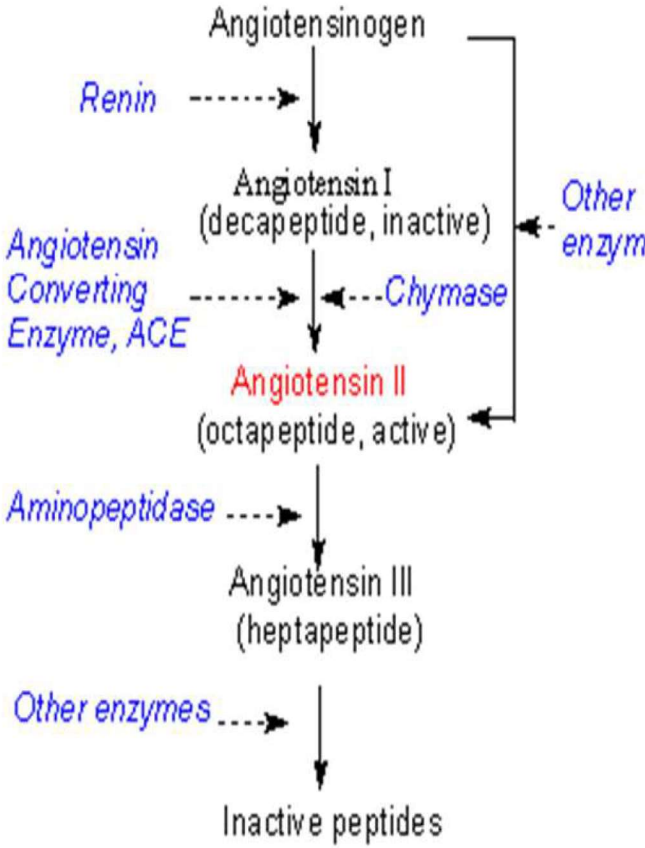
Contraindications:

- During the second and third trimesters of **pregnancy** due to the **risk of fetal hypotension**, **anuria**, **renal failure** & **malformations**.(lung, kidney)
- **Renal** artery ***stenosis***.
- **Potassium-sparing diuretics.**
- **NSAIDs**.

ii- Angiotensin-receptors blockers (ARBs)

Examples: **Losartan, Valsartan.**

- Cause **selective block of AT1 receptors**.
- **No effect on bradykinin, no cough, no angioedema.**
- Produce more complete inhibition of angiotensin.



Pharmacokinetics:

Losartan

Has a potent active metabolite, Orally effective.

Long half-life, taken once daily, Does not cross BBB.

Valsartan

No active metabolites

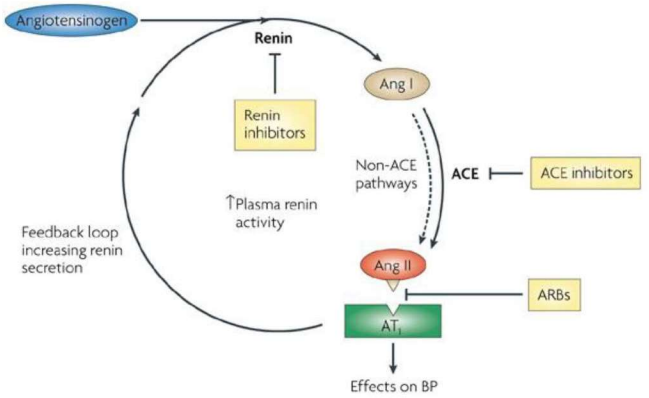
Same contraindications as ACEI.

Same ADRs, except for dry cough & angioneurotic edema

"No bradykinin accumulation"

iii- Direct renin inhibitors

Examples: **Aliskiren .**



- Directly inhibits renin and, thus, acts earlier in the renin–angiotensin–aldosterone system than ACE inhibitors or ARBs
- **Aliskiren should not be combined with an ACE inhibitor or ARB in the treatment of hypertension.**
- **Aliskiren can cause diarrhea, especially at higher doses. It also causes cough and angioedema *but less often than ACE inhibitors*.**
- As with ACE inhibitors and ARBs, aliskiren is **contraindicated during pregnancy**.

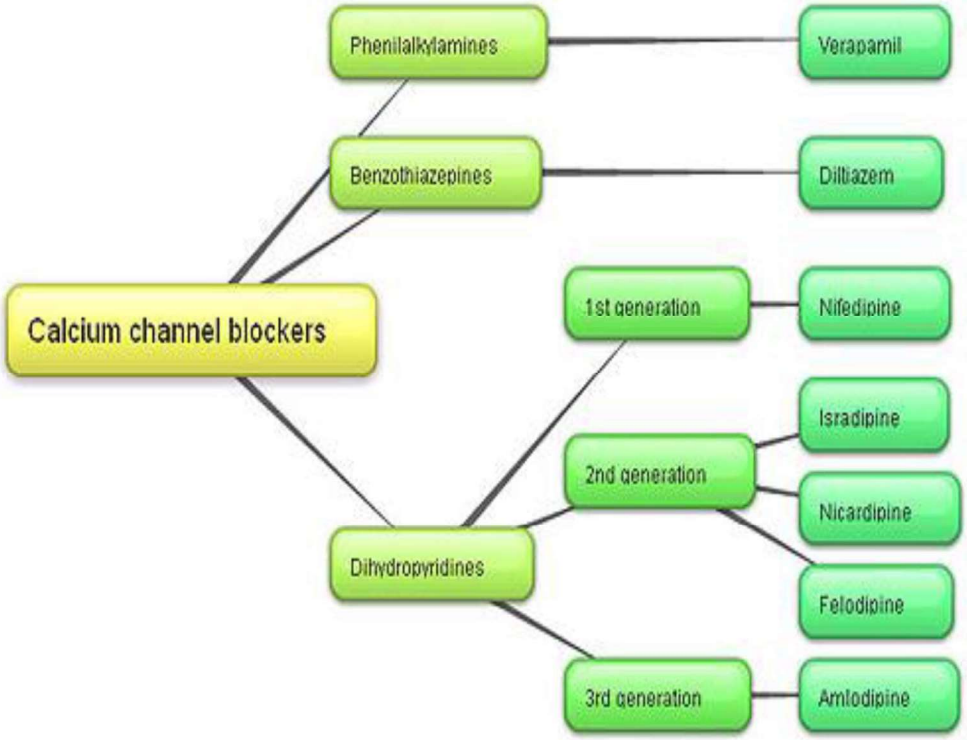
3) Calcium channel blockers

Verapamil act more on the **myocardium**.

Nifedipine
Dihydropyridine group act mainly on **smooth muscle**

Diltiazem has **intermediate** effect

Very
Nice
Drugs



***Diltiazem** affect* **both cardiac and vascular smooth muscle cells**, but it has a less pronounced negative inotropic effect on the heart compared to that of *verapamil*. *Diltiazem* has a favorable side effect profile.

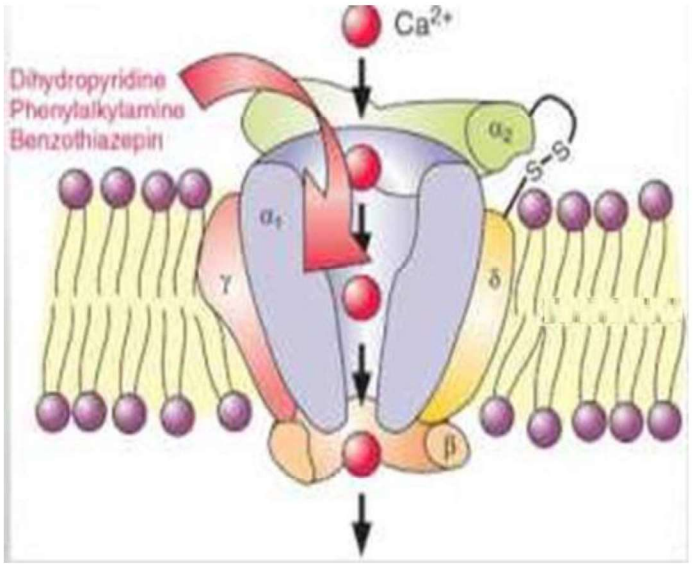
3) Calcium channel blockers

Mechanism of Action:

Block the influx of calcium through calcium channels resulting in:

1- Peripheral vasodilatation

2- Decrease cardiac contractility



Pharmacokinetics

Given **orally or IV**

Well absorbed

Onset 1-3 min after IV, 0.5-2hr after oral

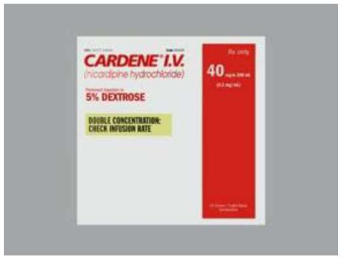
Verapamil & diltiazem have active metabolites,

Nifedipine has not

Verapamil and nifedipine are highly bound to plasma proteins (more than 90%) while diltiazem is less Bound (70-80%).

Sustained-release preparations can permit **once-daily** dosing.

Clinical Uses:



Treatment of **chronic hypertension**

Nicardipine can be given by I.V. route in hypertensive **emergency**.

Sustained- release formulations are preferred for the treatment of hypertension due to the short **half- life of CCBs**.

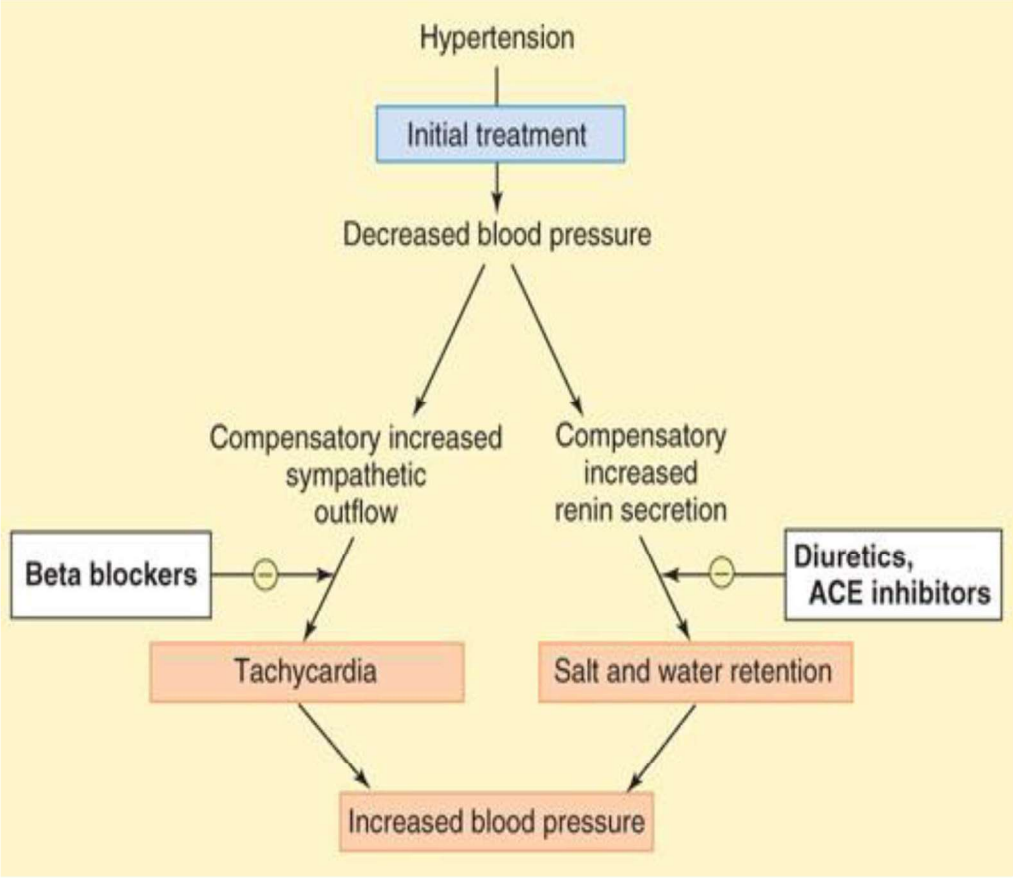
ADRs:

- Headache, Flushing, Hypotension
- **Nifedipine**: **Tachycardia**
- **Verapamil & Diltiazem**: **bradycardia** & Peripheral edema (**ankle edema**)
- **Verapamil**: Constipation.

4) Vasodilators

Classified into:
arterial,
venous or
mixed vasodilators

Once **vasodilators** are administered, **fall in BP** produced, **will activate the sympathetic system & the RAAS.**



Vasodilators also increase plasma renin concentration, resulting in sodium and water retention. These undesirable side effects can be blocked by concomitant use of a diuretic (to decrease sodium retention) and a β-blocker (to balance the reflex tachycardia).

	Hydralazine	Minoxidil	Diazoxide	Sodium nitropruside
Site of action	**Arteriodilator**			**Arterio & venodilator**
Mechanism of action	Release of nitric oxide (NO)	Opening of potassium channels in smooth muscle membranes by minoxidil sulfate (active metabolite)	Opening of potassium channels	Release of nitric oxide (NO)
Route of admin.	Oral	Oral	Rapid intravenous	Intravenous **infusion**

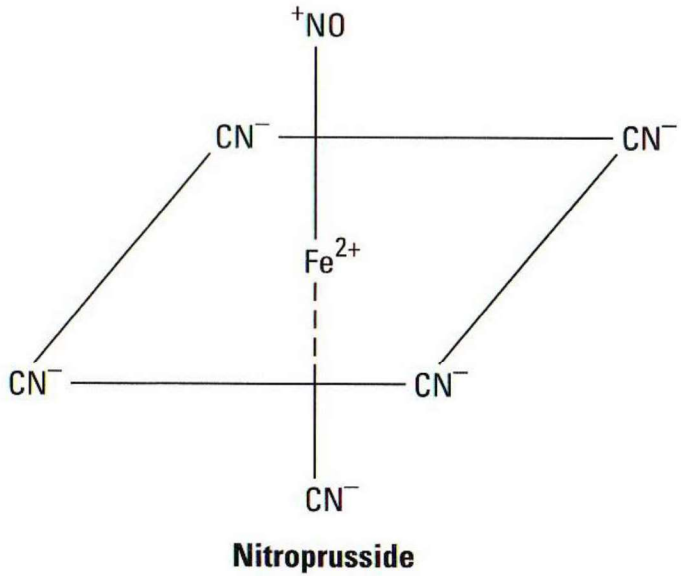
Continue Vasodilators	Hydralazine	Minoxidil	Diazoxide	Sodium nitropruside
Therapeutic uses	1.Moderate - severe hypertension.	1.Moderate –severe hypertension	1.Hypertensive **emergency** malignant hypertension	1.Hpertensive **emergency** malignant hypertension
	In combination with diuretic & β-blockers			
	2.Hypertensive **pregnant** woman (pregnancy-induced hypertension)	2. Baldness (frontal hair loss) 	**2. Treatment** of **hypoglycemia** due to insulinoma Diazoxide is used to treat low blood sugar (hypoglycemia) caused by certain cancers	2.Severe heart failure

Continue Vasodilators	Hydralazine	Minoxidil	Diazoxide	Sodium nitropruside
Adverse effects	Hypotension, reflex tachycardia, palpitation, angina, salt and water retention (edema)			Severe hypotension
Specific adverse effects	**lupus erythematosus** like syndrome	**Hypertrichosis**  Contraindicated in females	Inhibit insulin release from β cells of the pancreas causing **hyperglycemia** Contraindicated in **diabetics**	1. **Methemoglobin** during infusion 2. **Cyanide** toxicity 3. Thiocyanate toxicity

Hypertrichosis : **a condition characterized by excessive hair growth localized anywhere on a person's body.**

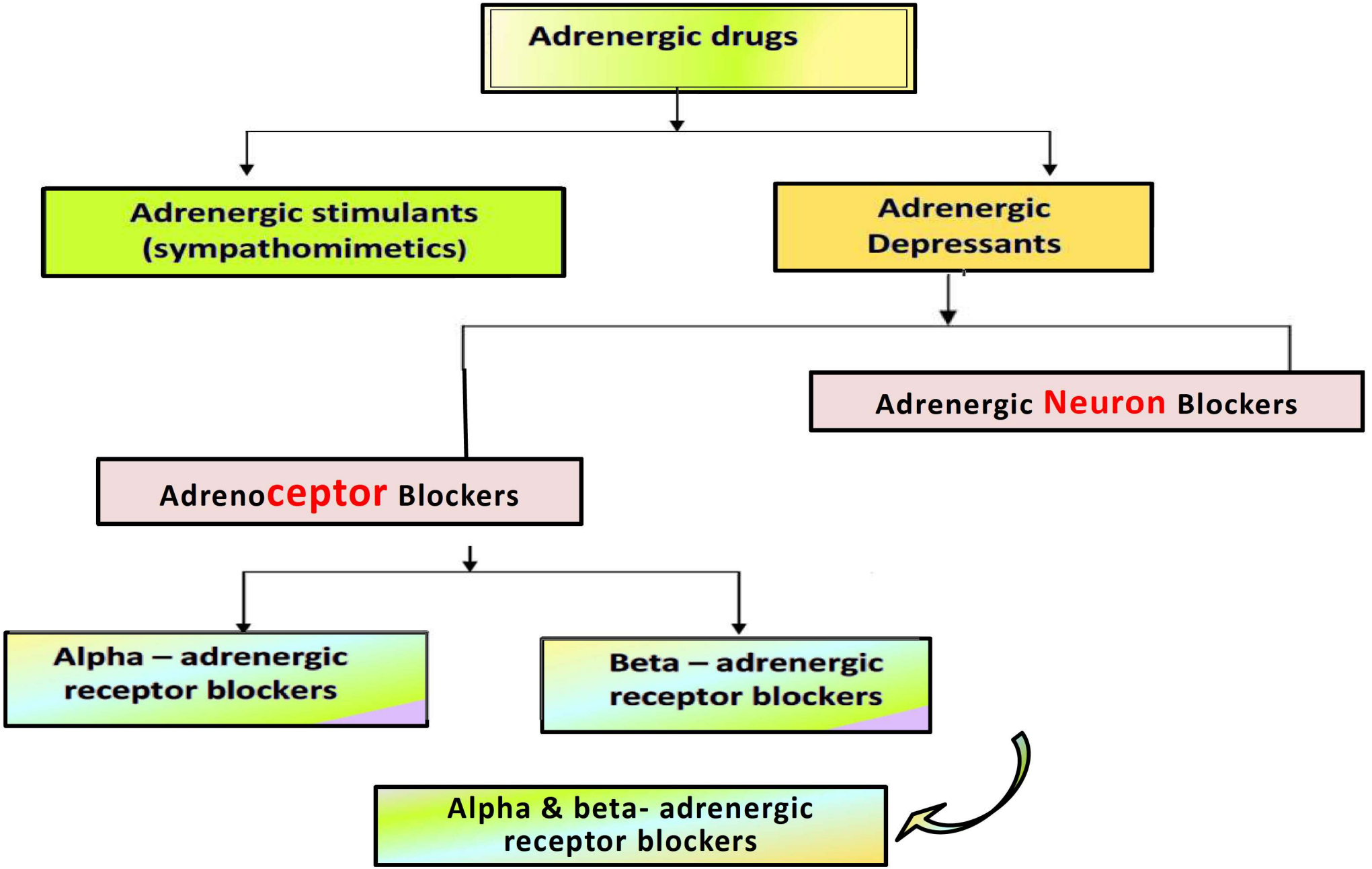
Sodium nitroprusside (ADRs):

Headache, palpitations which disappear when infusion is stopped.



Nitroprusside

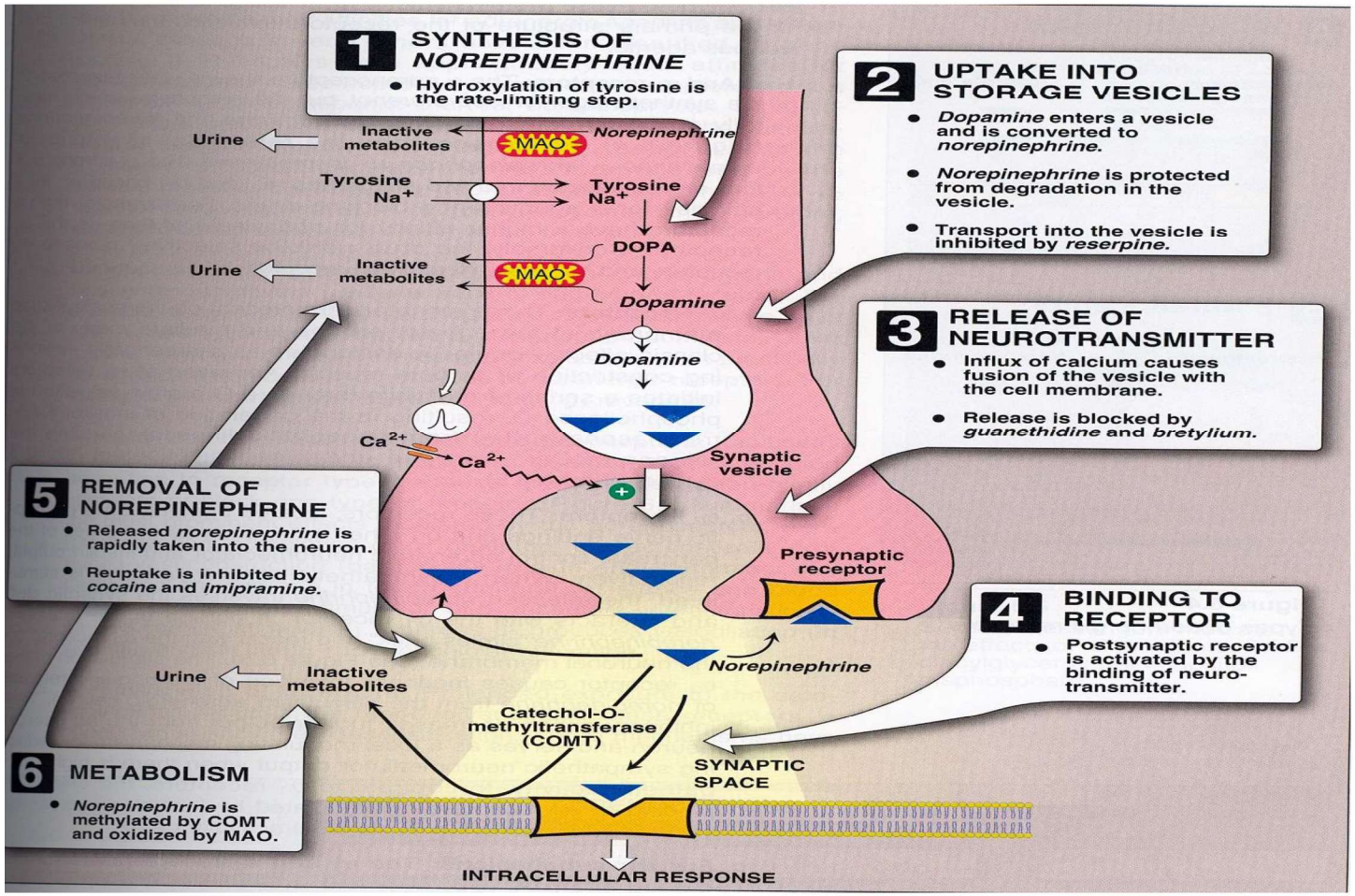
Cyanide accumulation cause cyanide poisoning (metabolic acidosis, arrhythmias, severe hypotension and death).


Adrenergic drugs
Adrenergic stimulants (sympathomimetics)
Adrenergic Depressants
Adrenergic Neuron Blockers
Adrenoceptor Blockers
Alpha – adrenergic receptor blockers
Beta – adrenergic receptor blockers
Alpha & beta- adrenergic receptor blockers

5) Sympatholytic Drugs

- ***Adrenergic neuron blockers***
- ***Adrenergic receptor blockers***

Classification of sympatholytics



Classification of sympatholytics

➢ *Adrenergic neuron blockers*

- **Formation of False Transmitters**

  e.g. α -Methyl dopa

- **Depletion of storage sites**

  e.g. Reserpine

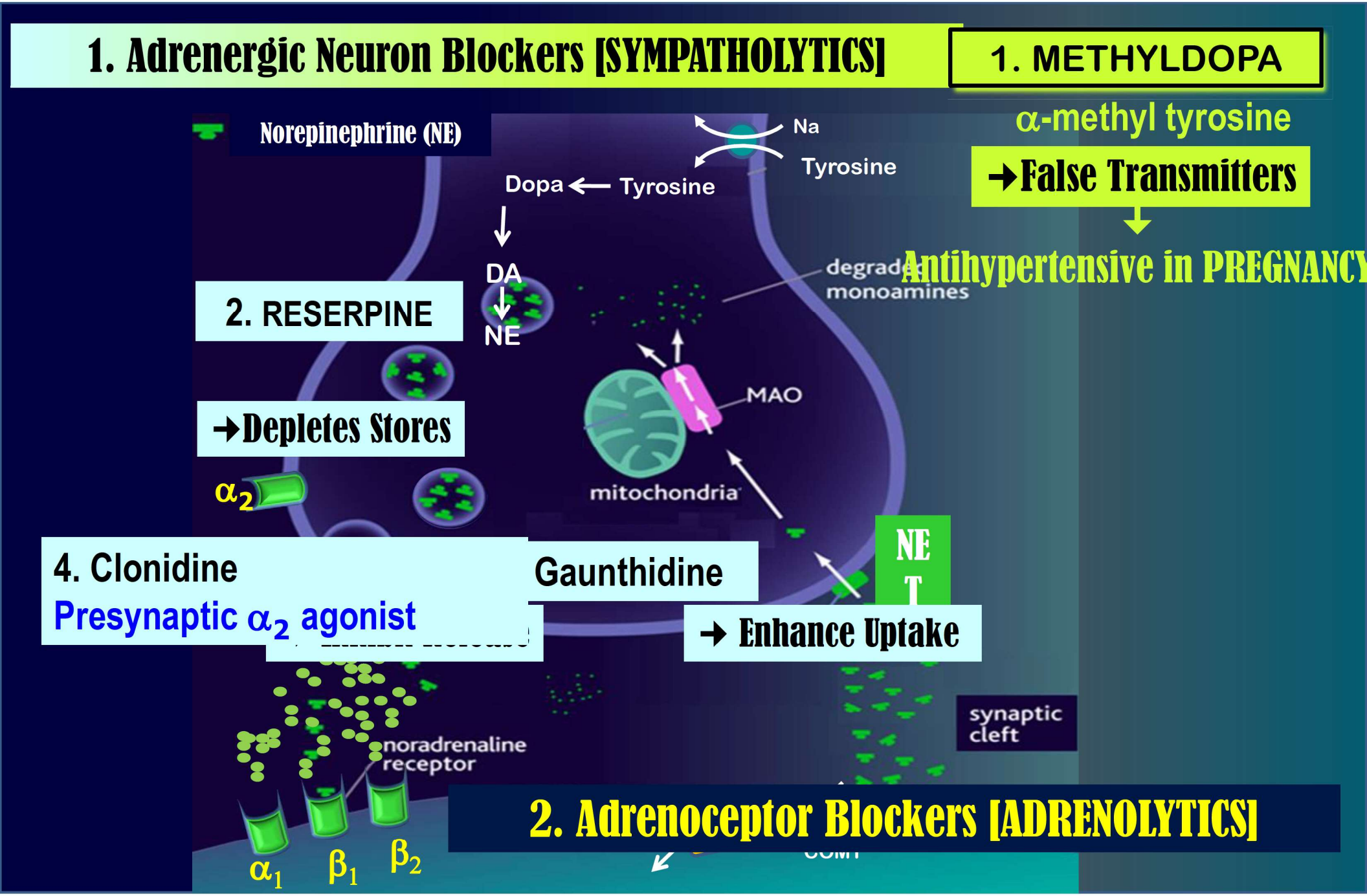
- **Inhibition of release & enhance uptake**

  e.g. Guanethidine

- **Stimulation of presynaptic α_2 receptors**

  e.g. Clonidine and α-Methyl dopa

1. Adrenergic Neuron Blockers [SYMPATHOLYTICS]



1. METHYLDOPA

α-methyl tyrosine

→ False Transmitters

→ Antihypertensive in PREGNANCY

2. RESERPINE

→ Depletes Stores

4. Clonidine

Presynaptic α_2 agonist

Gaunthidine

NE T

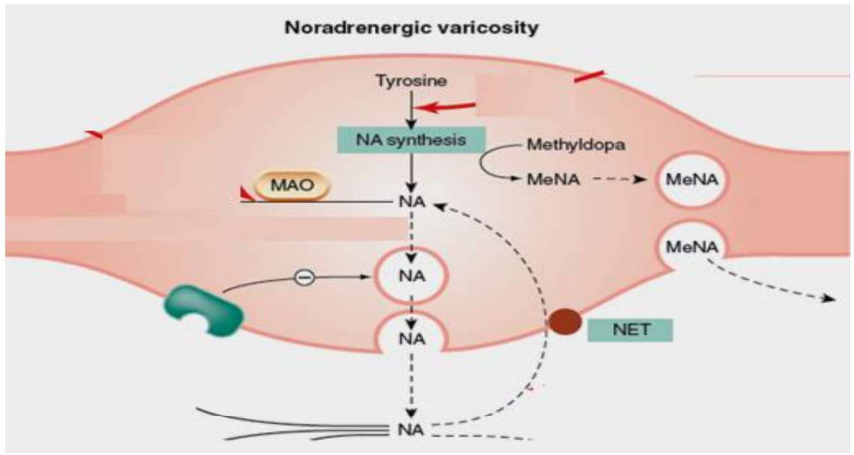
→ Enhance Uptake

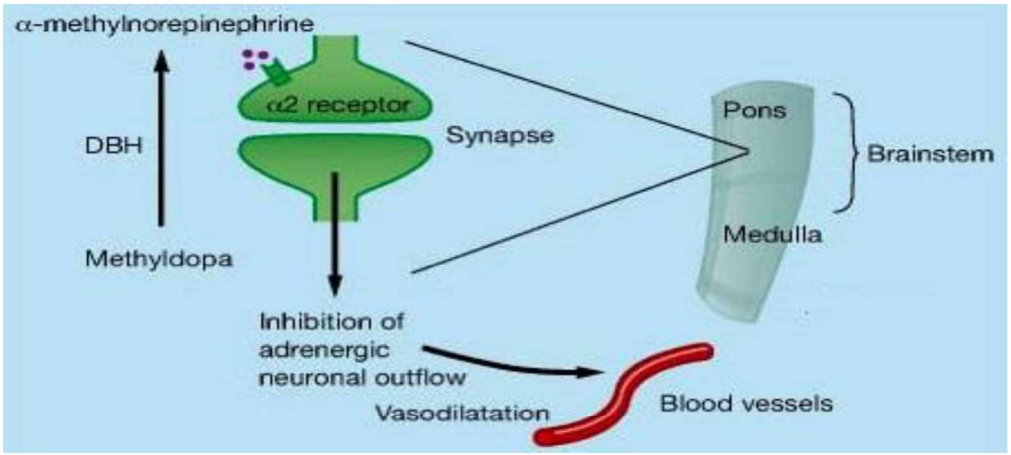
2. Adrenoceptor Blockers [ADRENOLYTICS]

Mechanisms of Adrenergic **Neuron** blockers

α -Methyl dopa

- **Forms false transmitter that is released instead of NE**
- **Acts as central α_2 receptor agonist to inhibit NE release**
- **Drug of choice in Treatment of hypertension in pregnancy (gestational hypertension & pre-eclampsia).**



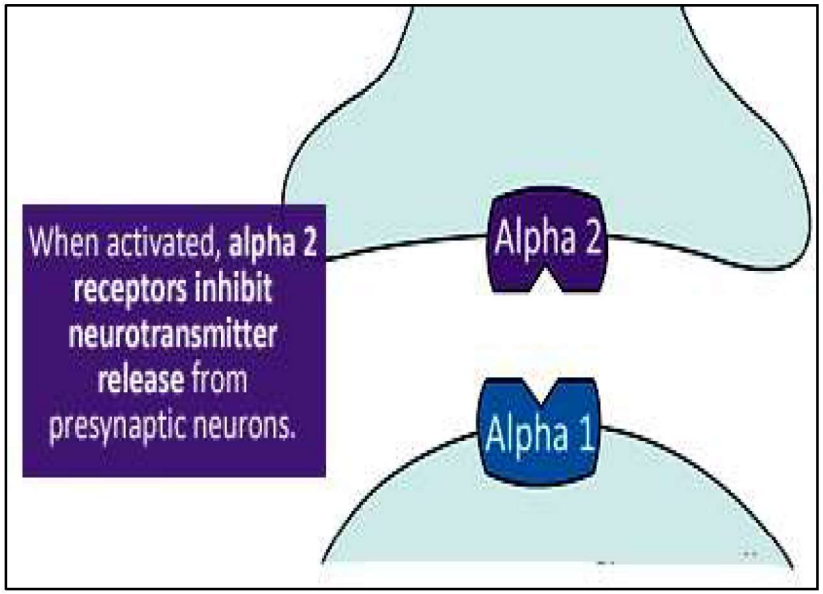


Clonidine

- Acts as central α_2 receptor agonist to inhibit NE release
- suppresses sympathetic outflow activity from the brain.
- Little used as antihypertensive agent due to rebound hypertension upon abrupt withdrawal.

Apraclonidine

- is used in open angle glaucoma as eye drops.
- acts by decreasing aqueous humor formation.



Adrenergic **receptor** blockers

Include

- **α-receptor antagonists**
- **β-receptor antagonists**

Classification of α-receptor Antagonists

- **Non-selective antagonists e.g. phenoxybenzamine & phentolamine.**
- **α_1-selective antagonists e.g. prazosin, doxazosin.**
- **α_{1A}-selective antagonists e.g. Tamsulosin**
- **α_2-selective antagonists e.g. yohimbine**

CLASSIFICATION

α-Adrenoceptor Antagonists

Non-selective
block α_1 & α_2

Reversible
- Phentolamine

Irreversible
- Phenoxybenzamine

Selective

α_1-blockers
- Prazosin
- Terazosin
- Doxazosin

α_2-blockers
- Yohimbine

Selective α_{1A}

↓

Tamsulosin

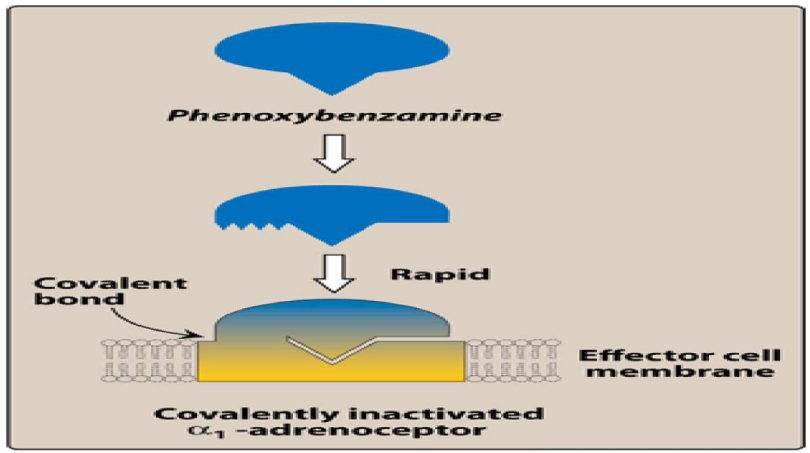
BPH

Non-Selective α- Adrenoceptor Antagonists

Phenoxybenzamine:

Irreversible block of both α_1 and α_2 receptors

Long-acting (24 hrs)



Phentolamine:

reversible blocking of α_1 & α_2 receptors.

Short acting (4 hrs).

Pharmacological actions

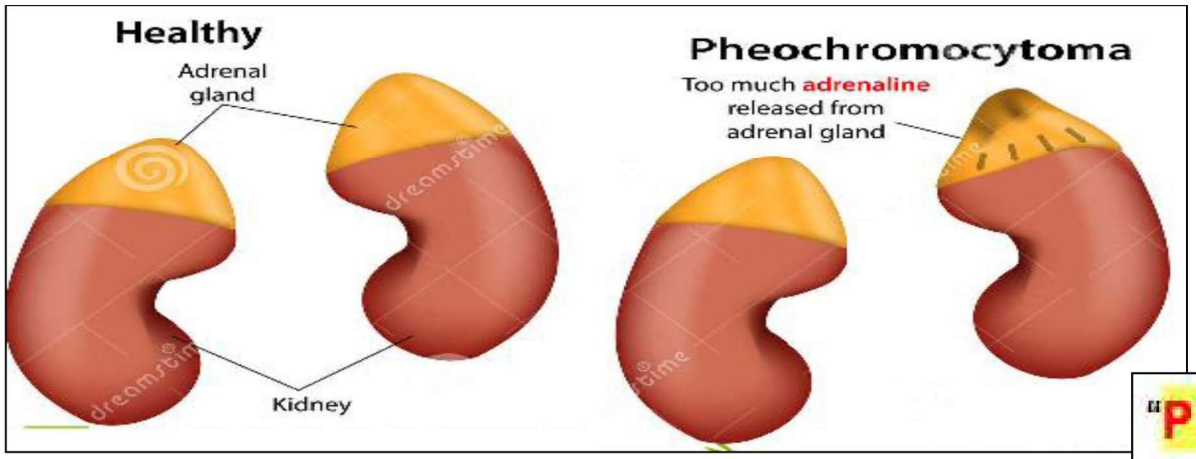
Both drugs cause:

1) **Decrease peripheral vascular resistance**
2) **Postural hypotension.**
3) **Reflex tachycardia.**

Reflex tachycardia due to the fall in B.P,
mediated by baroreceptor reflex and due to block α_2 in heart.

Therapeutic Uses:

Pheochromocytoma: Should be given before surgical removal to protect against hypertensive crisis.



"PHEochromocytoma"

- Palpitations
- Headache
- Episodic sweating (diaphoresis)

Contraindicated:

Both drugs can precipitate arrhythmias and angina and are contra-indicated in patients with decreased coronary perfusion.

Adverse Effects of non-Selective α- Adrenoceptor Antagonists :

- **Postural hypotension**
- **Tachycardia**
- **Headache**
- **Nasal stuffiness or congestion**
- **Vertigo & drowsiness**
- **Male sexual dysfunction (inhibits ejaculation).**

Selective α1- Antagonists

Prazosin, Doxazosin, Terazosin

Prazosin (short half-life)

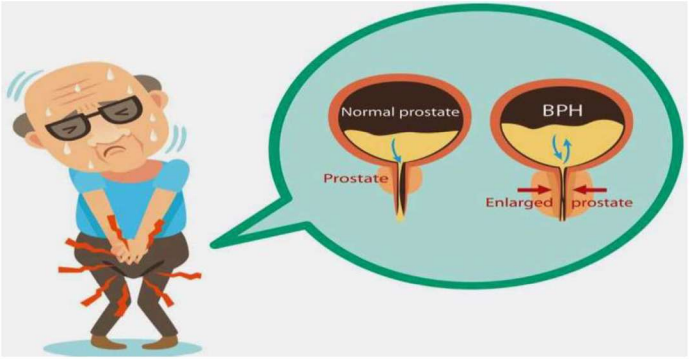
Doxazosin, terazosin (long half life)

Pharmacological effects of α_1–antagonists:

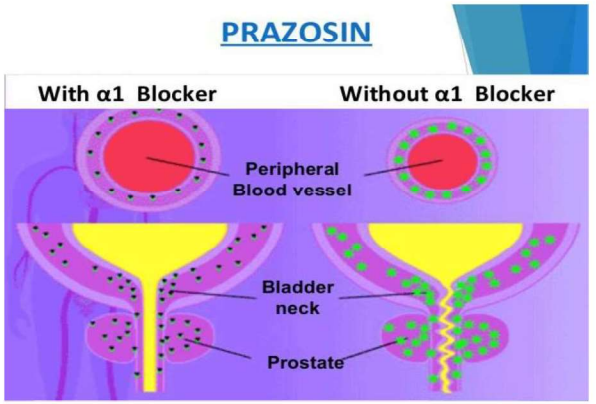
- **Vasodilatation due to relaxation of arterial and venous smooth muscles**
- **Fall in arterial pressure**
- **less reflex tachycardia than with non-selective α blockers**
- **First dose effect.**

First dose of α_1 receptor blocker may produce an orthostatic hypotensive response that can result in syncope (fainting).

Therapeutic Uses:

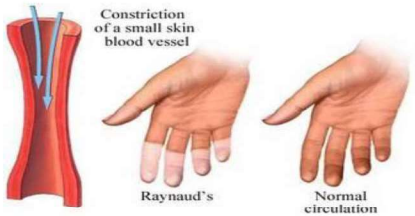


- Treatment of **essential hypertension** with **prostate enlargement**.



- Urinary obstruction of **benign prostatic hypertrophy (BPH)**.

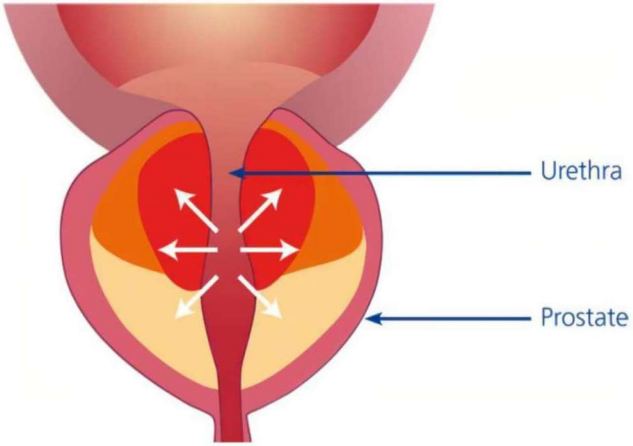
- **Reynaud's disease (vasospasm):** causes fingers and toes to feel **numb and cold** in response to cold temperature



Selective α1A–antagonists

Tamsulosin

- Is a selective α_{1A} antagonist (Uroselective).
- α_{1A} receptors present in prostate
- Causes relaxation of smooth muscles of bladder neck & prostate →improve urine flow.
- Has minimal effect on blood pressure.
- Is used in the treatment of benign prostatic hypertrophy (BPH).



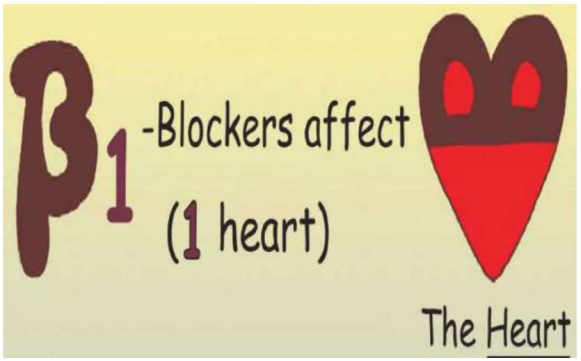
α2-selective antagonists

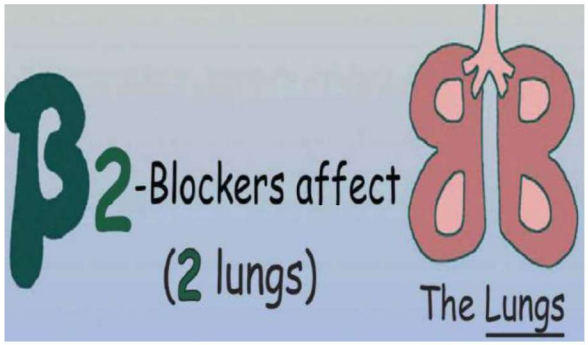
e.g. ***Yohimbine***

selective competitive α2-blocker that works at the level of the CNS to increase sympathetic outflow to the periphery. It is found as a component of the bark of the **yohimbe tree** (*Pausinystalia yohimbe*) and has been used as a **sexual stimulant** and in the **treatment of erectile dysfunction**.

- **Increase nitric oxide released in the corpus cavernosum thus producing vasodilator action and contributing to the erectile process.**
- **Used as aphrodisiac in the treatment of erectile dysfunction.**

β- Adrenoceptors blockers





Classification of β- Adrenoceptors Blockers

Selective β1 antagonists

Acebutolol, Atenolol

Bisoprolol, Betaxolol

Celiprolol

Esmolol, Metoprolol

Non selective β- Antagonists

Blocks β1& β2 receptors

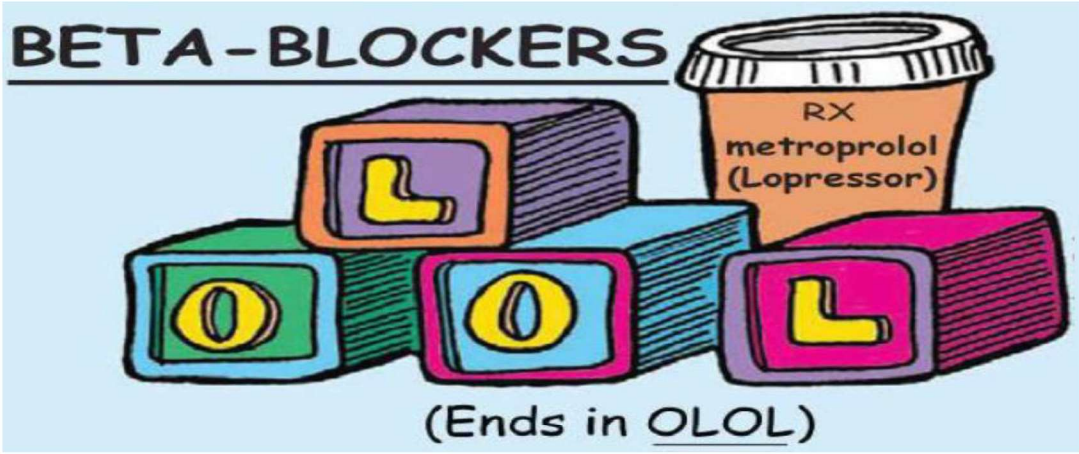
Oxprenolol

Propranolol, Pindolol

Sotalol, Timolol (STOP)

Mixed α, β receptors blockers

- **Carvedilol**
- **Labetalol**

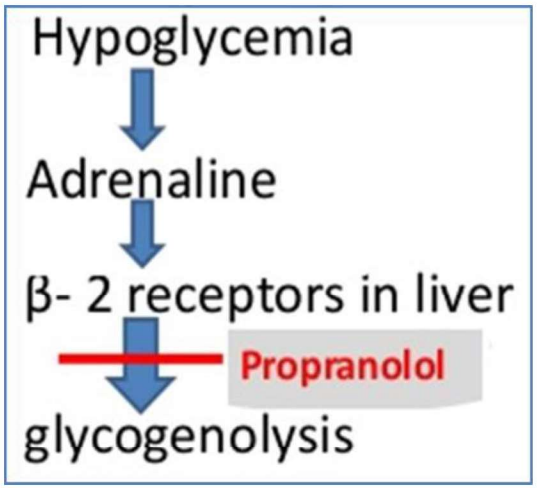


Pharmacological actions of β–Adrenergic blockers:

CVS: Negative inotropic, chronotropic, dromotropic → ↓ CO

Antianginal effects (ischemic heart disease):

- ↓ Heart rate (bradycardia)
- ↓ force of contraction → ↓ cardiac work
- ↓ Oxygen consumption due to bradycardia

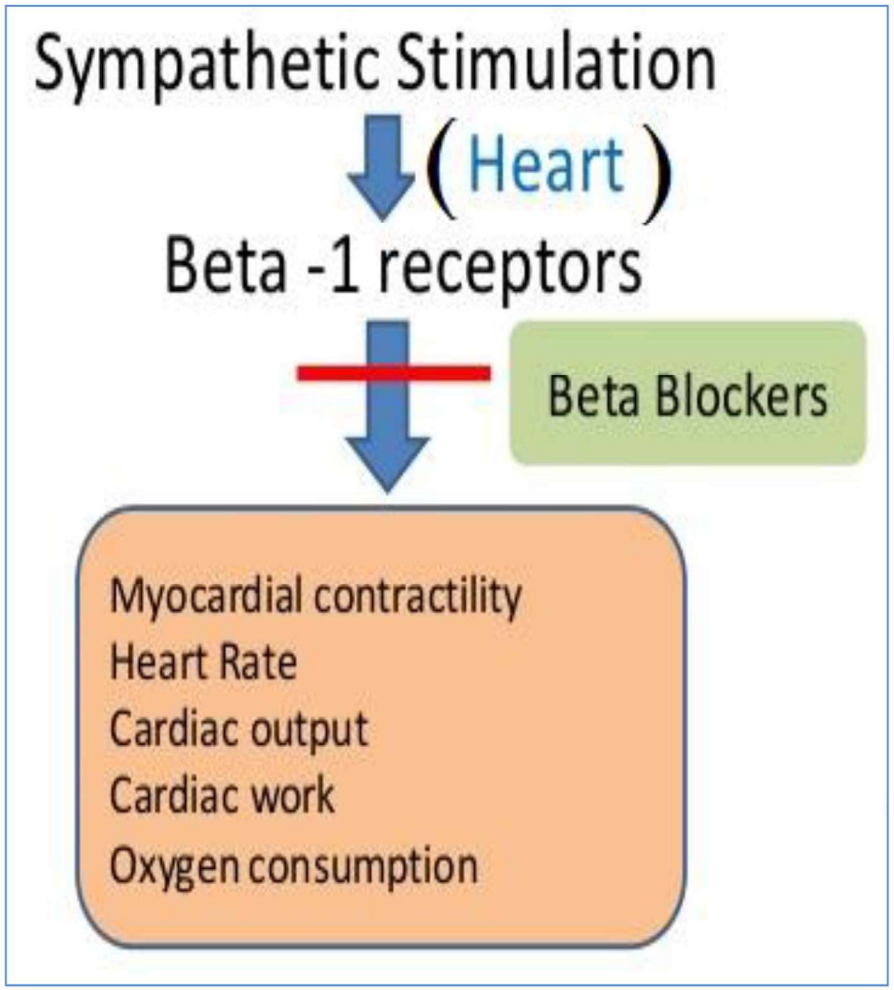


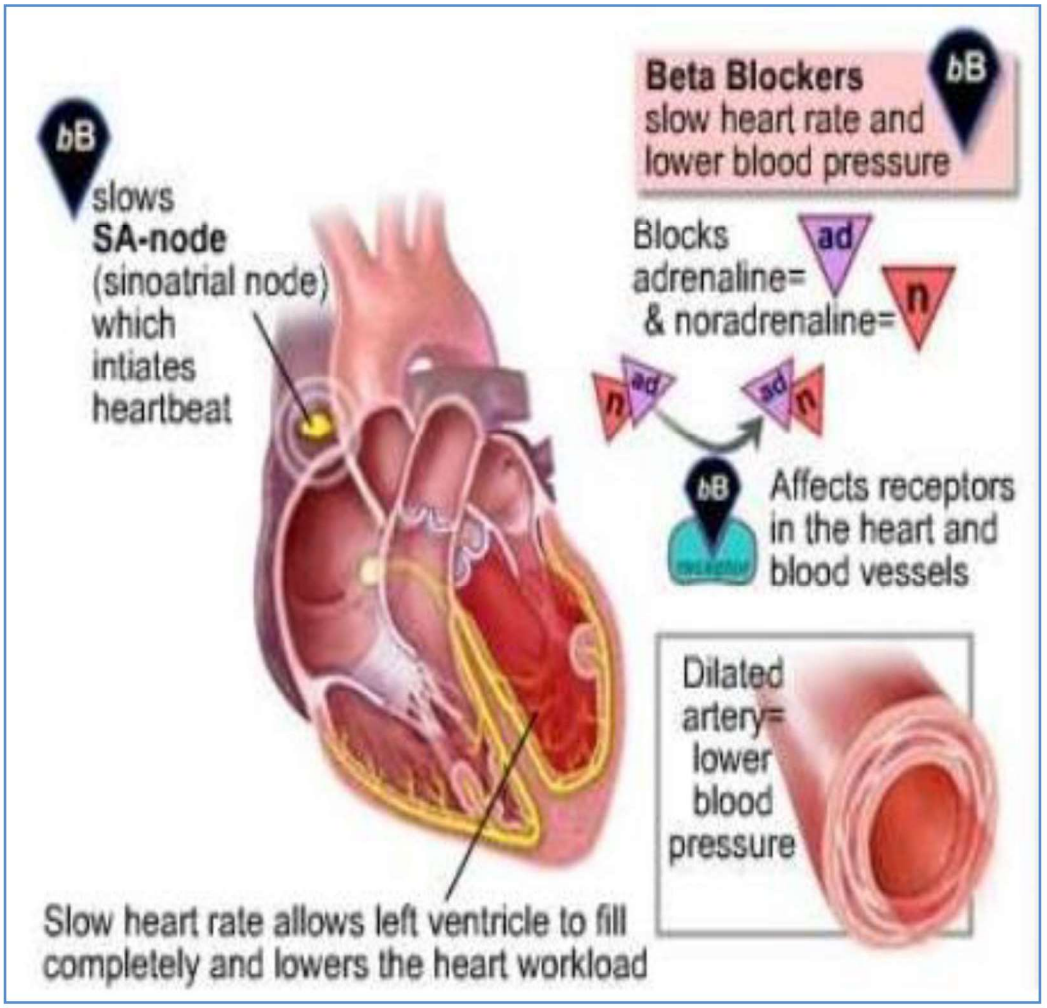
Anti-arrhythmic effects:

↓excitability, ↓ automaticity

& ↓ conductivity (due to its sympathetic blocking).

Pharmacological effects of β–blockers on CVS





Pharmacological actions of β–Adrenergic blockers:

Blood vessels β_2

↑ peripheral resistance (PR) by blocking vasodilatory effect b_2

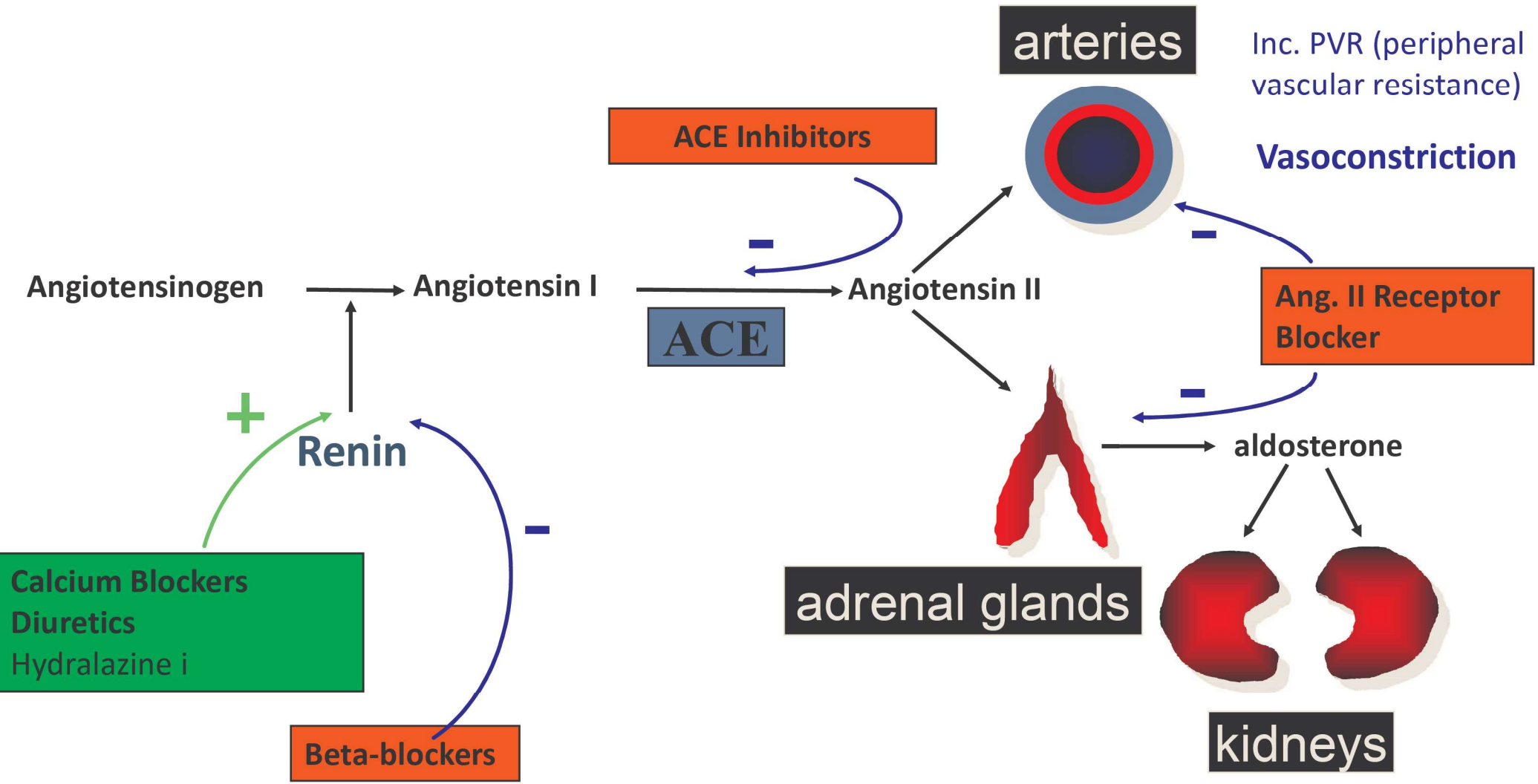
↓blood flow to organs → cold extremities

contraindicated in peripheral diseases like **Reynaud's disease**

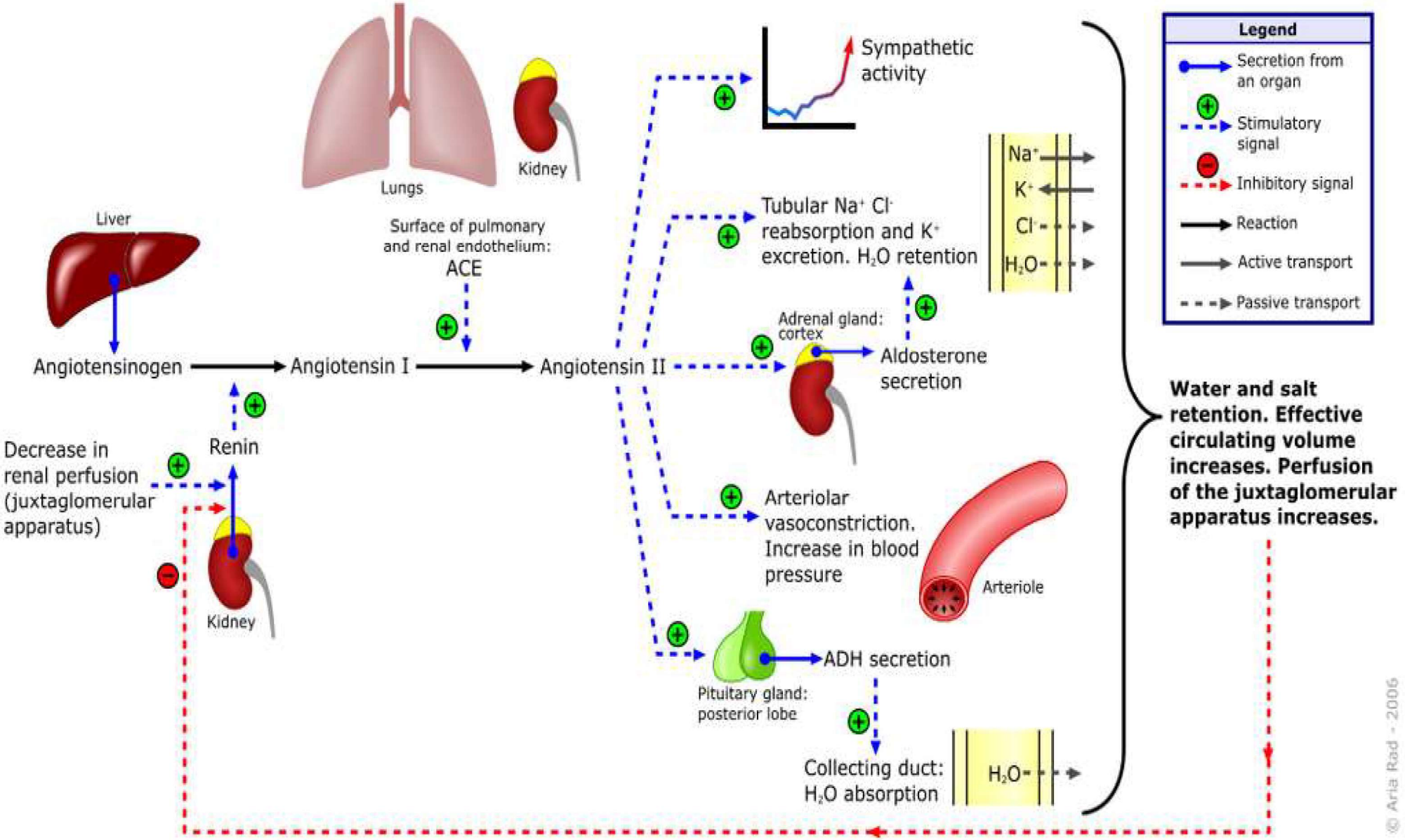
Blood pressure

Antihypertensive → ↓ BP in hypertensive patients due to effects on:

- Inhibiting heart properties → ↓ cardiac output (β_1)
- β Blockade ↓ renin secretion ↓ Ang II & aldosterone secretion (β_1).
- Presynaptic inhibition of NE release from adrenergic nerves


arteries
Inc. PVR (peripheral vascular resistance)
Vasoconstriction
ACE Inhibitors
Angiotensinogen
Angiotensin I
ACE
Angiotensin II
Ang. II Receptor Blocker
Renin
aldosterone
Calcium Blockers
Diuretics
Hydralazine i
Beta-blockers
adrenal glands
kidneys
Aldosterone → (inc. reabsorb. of Na+) → Inc. blood volume

Renin-angiotensin-aldosterone system



Pharmacological actions of β–Adrenergic blockers:

Respiratory tract: β_2

- **Bronchoconstriction**
- **contraindicated in asthmatic patients.**

Eye:

↓ aqueous humor production from ciliary body

↓ Reduce intraocular pressure (IOP)

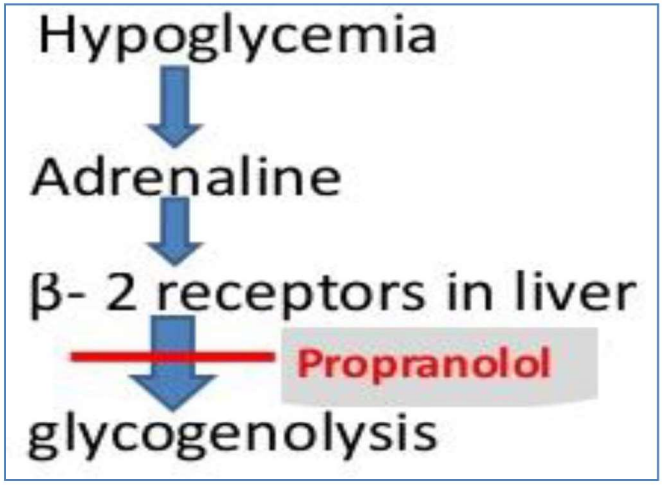
e.g. Timolol as eye drops

Intestine: ↑ Intestinal motility

Pharmacological actions of β–Adrenergic blockers:

Metabolic effects:

- **Hypoglycemia**
  - **↓ glycogenolysis in liver**
  - **↓ glucagon secretion in pancreas**
- **↓ lipolysis in adipocytes**
- **Na^+ retention 2ry to ↓BP → ↓renal perfusion !!!**



All β–Adrenergic blockers mask hypoglycemic manifestations in diabetic patients → COMA

The perception of symptoms of hypoglycemia such as tremor, tachycardia, and nervousness are blunted by β-blockers.

[**Note**: Diaphoresis with hypoglycemia still occurs, as this is mediated through the neurotransmitter acetylcholine.]

Clinical Uses of β–receptor blockers:

- **Cardiovascular disorders**
  - Hypertension
  - Arrhythmia
  - Angina pectoris
  - Myocardial infarction
  - Congestive heart failure
- **Pheochromocytoma**
- **Chronic glaucoma mainly Timolol**
- **Hyperthyroidism (thyrotoxicosis)**
- **Migraine headache prophylaxis**
- **Anxiety (somatic symptoms)**

Clinical Uses of β–receptor blockers

In Hypertension: e.g. Propranolol, atenolol, bisoprolol

* **Labetalol:** α, β blockers in hypertensive pregnant & hypertensive crisis.

In cardiac arrhythmias:

In supraventricular & ventricular arrhythmias.

e.g. Bisoprolol and carvedilol are preferred

Angina pectoris:

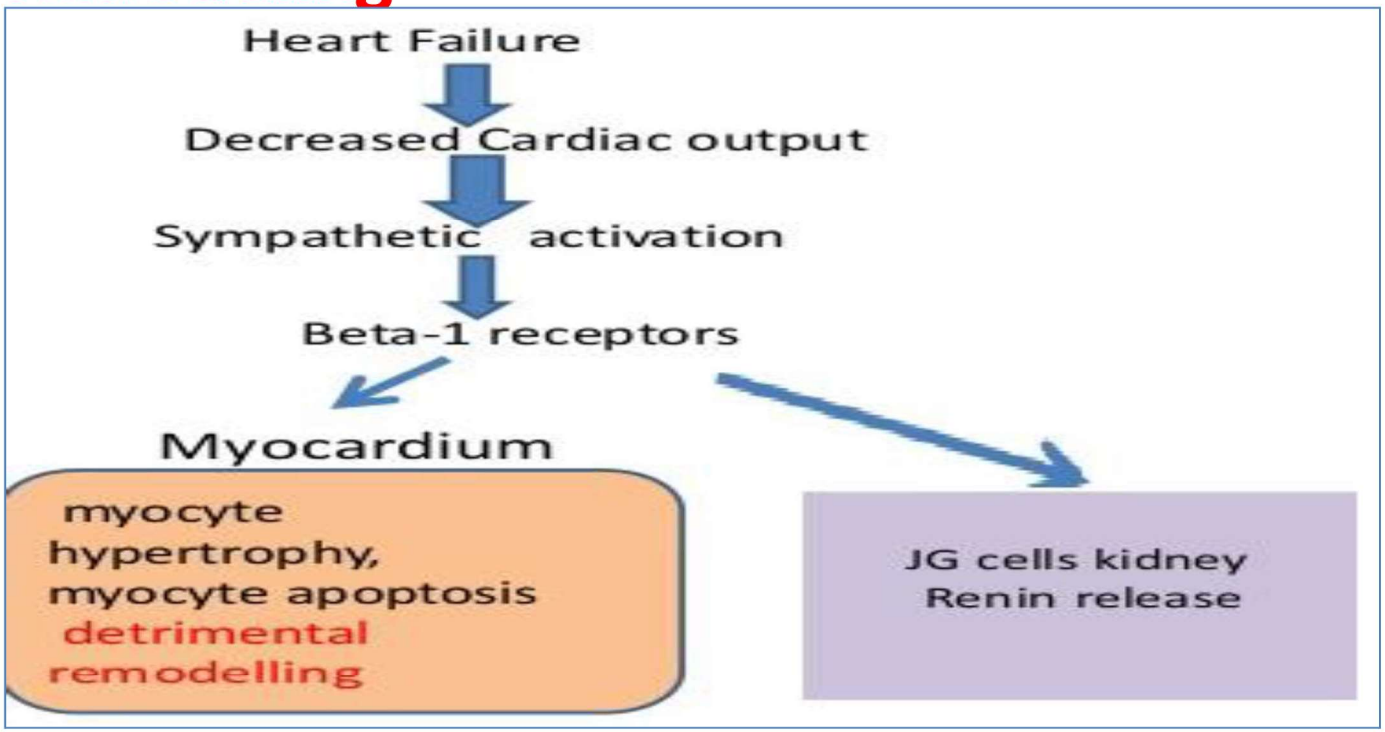
- ↓ heart rate, ↓ cardiac work & oxygen demand.
- ↓ the frequency of angina episodes.

Clinical Uses of β–receptor blockers

Congestive heart failure:

e.g. Carvedilol:

- **antioxidant** and non selective **α,β** blocker
- **↓ myocardial remodeling** & ↓risk of sudden death.



Clinical Uses of β–receptor blockers

Myocardial infarction:

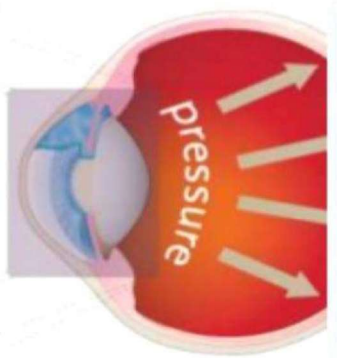
Have cardio-protective effect

- ↓ infarct size
- ↓morbidity & mortality →
- ↓ myocardial O2 demand.
- Anti-arrhythmic action.
- ↓ incidence of sudden death.

In glaucoma

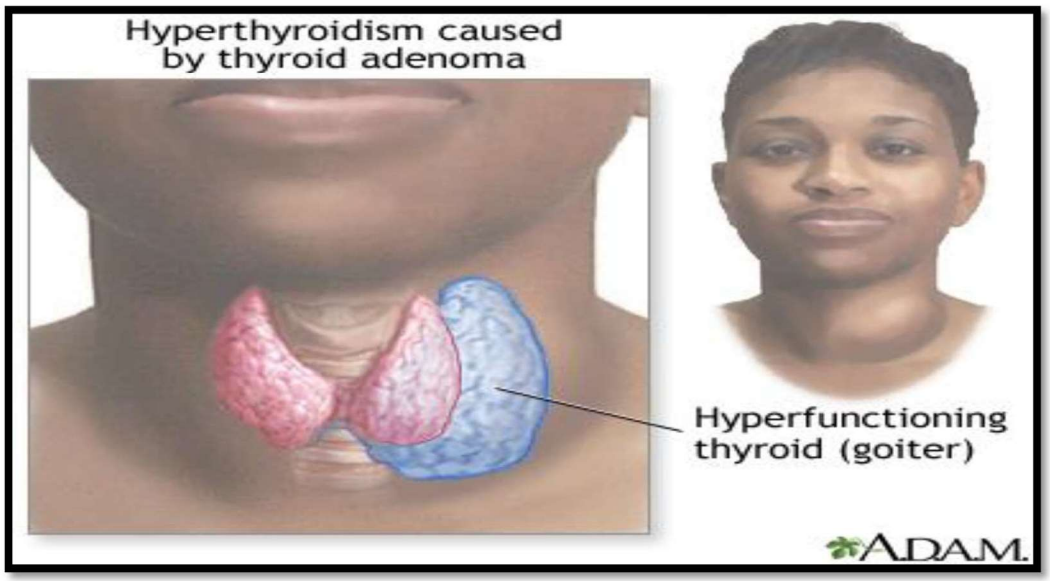
e.g. Timolol as eye drops

- Decreases secretion of aqueous humor by ciliary body.
- Decreases Intraocular pressure (IOP)



In Hyperthyroidism

- Protect the heart against sympathetic over stimulation
- Controls symptoms;
  - Tachycardia
  - Tremors
  - Sweating



In anxiety (Social and performance type)

e.g. Propranolol

Controls symptoms due to sympathetic system stimulation

as tachycardia, tremors, sweating.

Migraine:

Prophylactic

- ↓ reduce episodes of chronic migraine
- ↓ catecholamine-induced vasodilatation in the brain vasculature

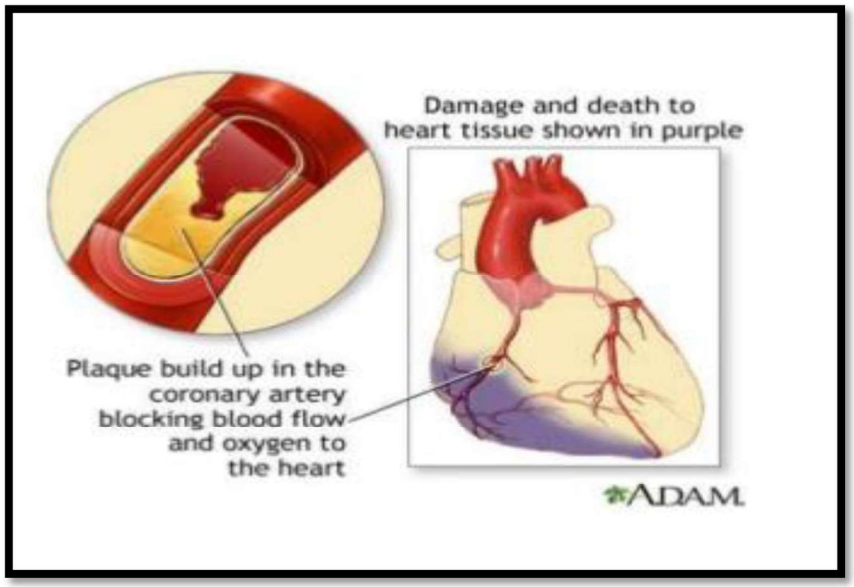
e.g. propranolol

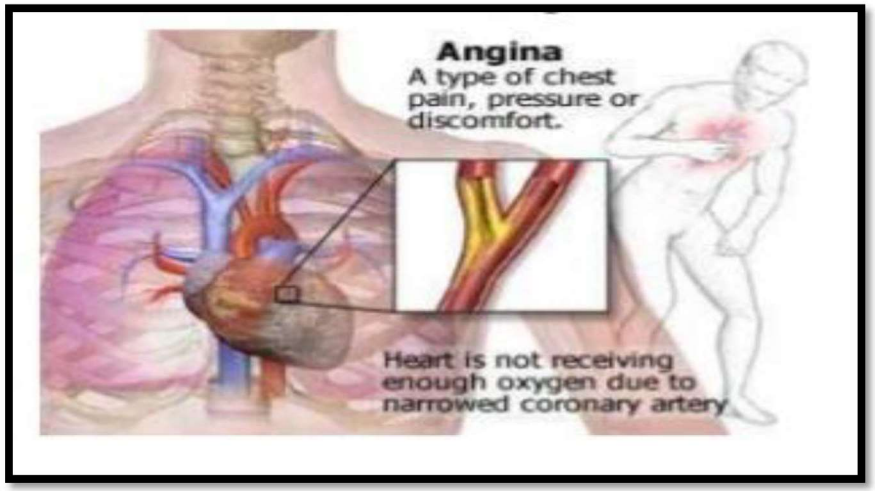
Pheochromocytoma

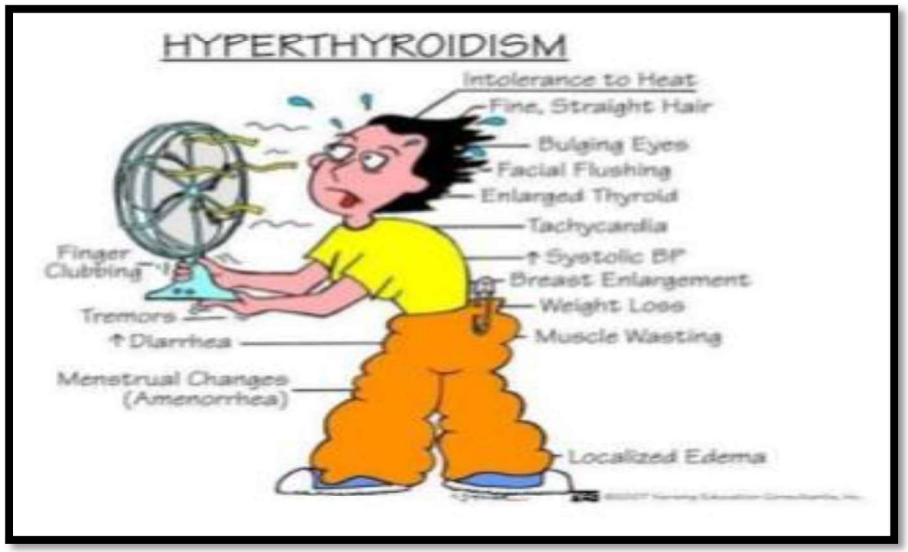
used with α-blockers (never alone)

- **α-blockers lower the elevated blood pressure.**
- **β-blockers protect the heart from NE.**

Uses of B-blockers



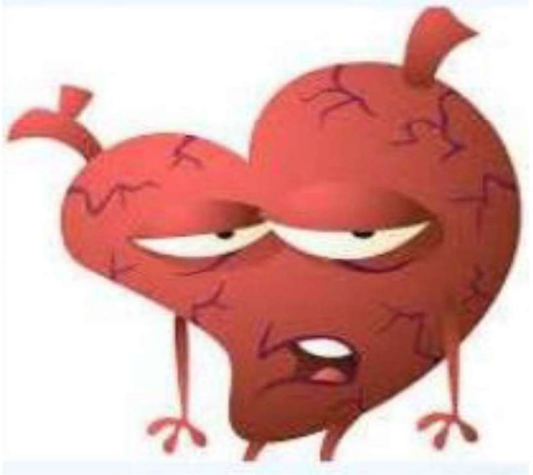




Adverse Effects of β- Adrenoceptors blockers

Due to blockade of β1- receptor:

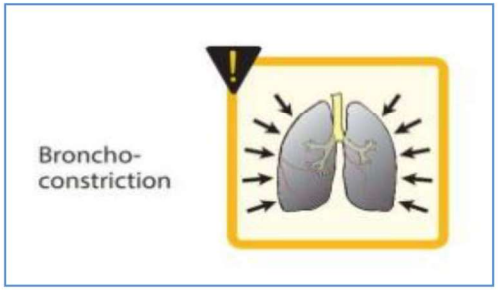
- **Bradycardia, hypotension, heart failure**



Adverse Effects of β- Adrenoceptors blockers

Due to blockade of β2- receptor: only with non-selective β blockers

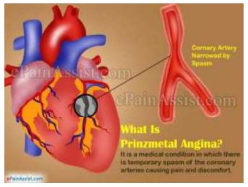
- **Hypoglycemia**
- **↑ TG → hypertriglyceridemia**
- **Bronchoconstriction**
  (# Asthma, emphysema).

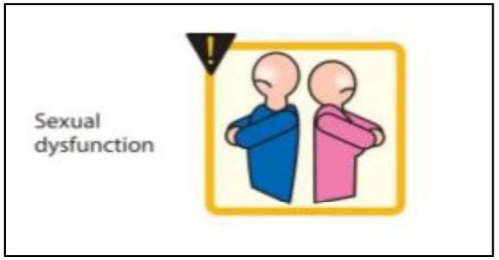


- **Cold extremities & intermittent claudication (due to vasoconstriction).**

claudication = muscle pain on mild exertion (ache, cramp, numbness or sense of fatigue)

- **Erectile dysfunction & impotence**
- **Coronary spasm → in variant angina patients**





Adverse Effects of β- Adrenoceptors blockers

- Depression, and hallucinations.
- Gastrointestinal disturbances.
- Sodium retention
- Fatigue

- All β–Adrenergic blockers mask hypoglycemic manifestations i.e. tachycardia, sweating, ➔ COMA

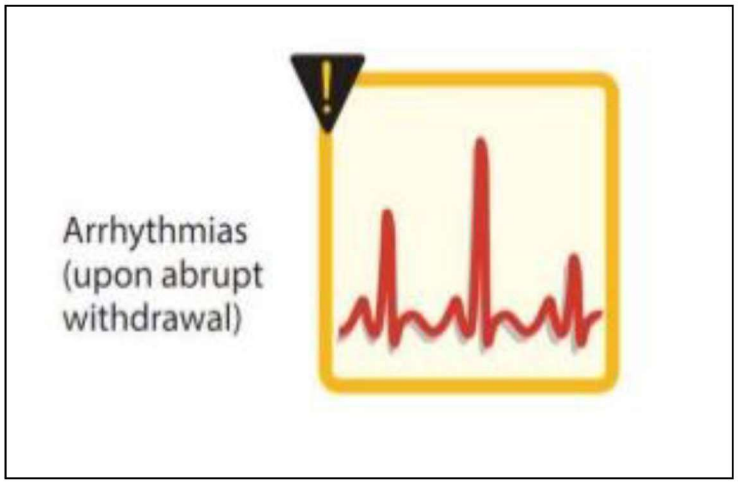
Precautions

Sudden stoppage will give rise to a withdrawal syndrome:

- ✓ **Rebound angina, arrhythmia, myocardial infarction &**
- ✓ **Hypertension**

WHY ? ➔ Up-regulation of β-receptors.

- ✓ **To prevent withdrawal manifestations ➔ drug withdrawn gradually.**



Contraindications of β- Adrenoceptors blockers

- **Heart Block (beta blockers can precipitate heart block).**
- **Bronchial Asthma (safer with cardio-selective β-blockers).**
- **Peripheral vascular disease (safer with cardio-selective β-blockers).**
- **Diabetic patients ➔ Masking of hypoglycemia / GIVEN CAUSIOUSLY**
- **Hypotension**
- **Alone in pheochromocytoma (must be given with an α blockers).**

Summary of B-blockers uses

- **Hypertension** Atenolol, Bisoprolol, Metoprolol, Propranolol
- **cardiac arrhythmia** Esmolol (**ultra-short acting**), Atenolol, Propranolol
- **Congestive heart failure** Carvedilol, Bisoprolol, Metoprolol
- **Myocardial infarction** Atenolol, Metoprolol, Propranolol
- **Glaucoma** Timolol
- **Migraine prophylaxis** Propranolol
- **Relief of anxiety (social & performance)** Propranolol
- **Thyrotoxicosis** Propranolol