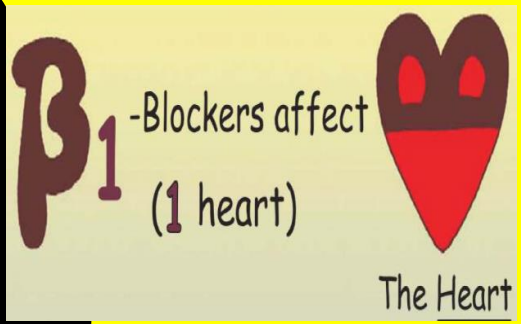
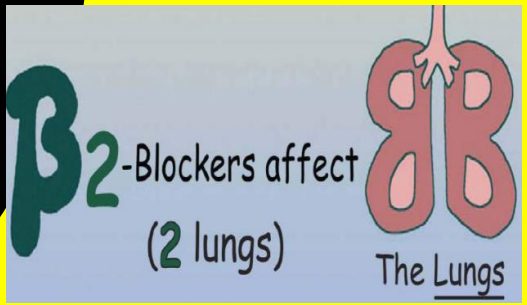
β- ADRENOCEPTORS BLOCKERS

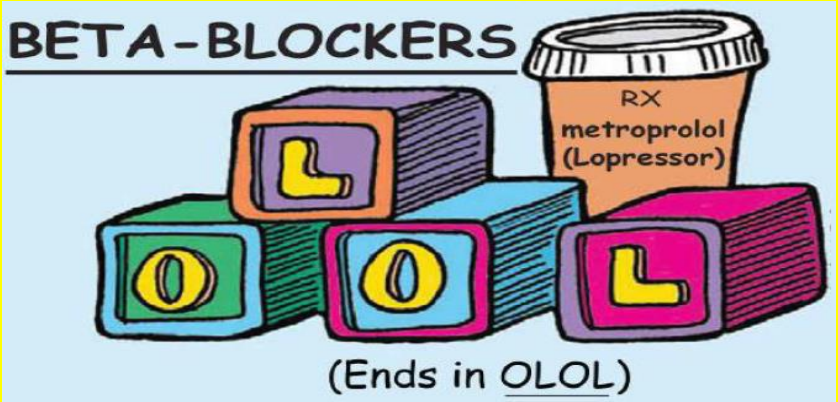




SOTI

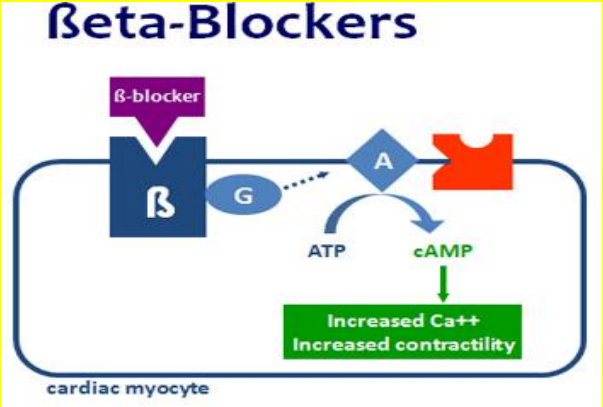
Classify β- blockers

Discuss pharmacokinetic properties, pharmacodynamic actions, clinical uses, ADRs & contraindications of β-blockers

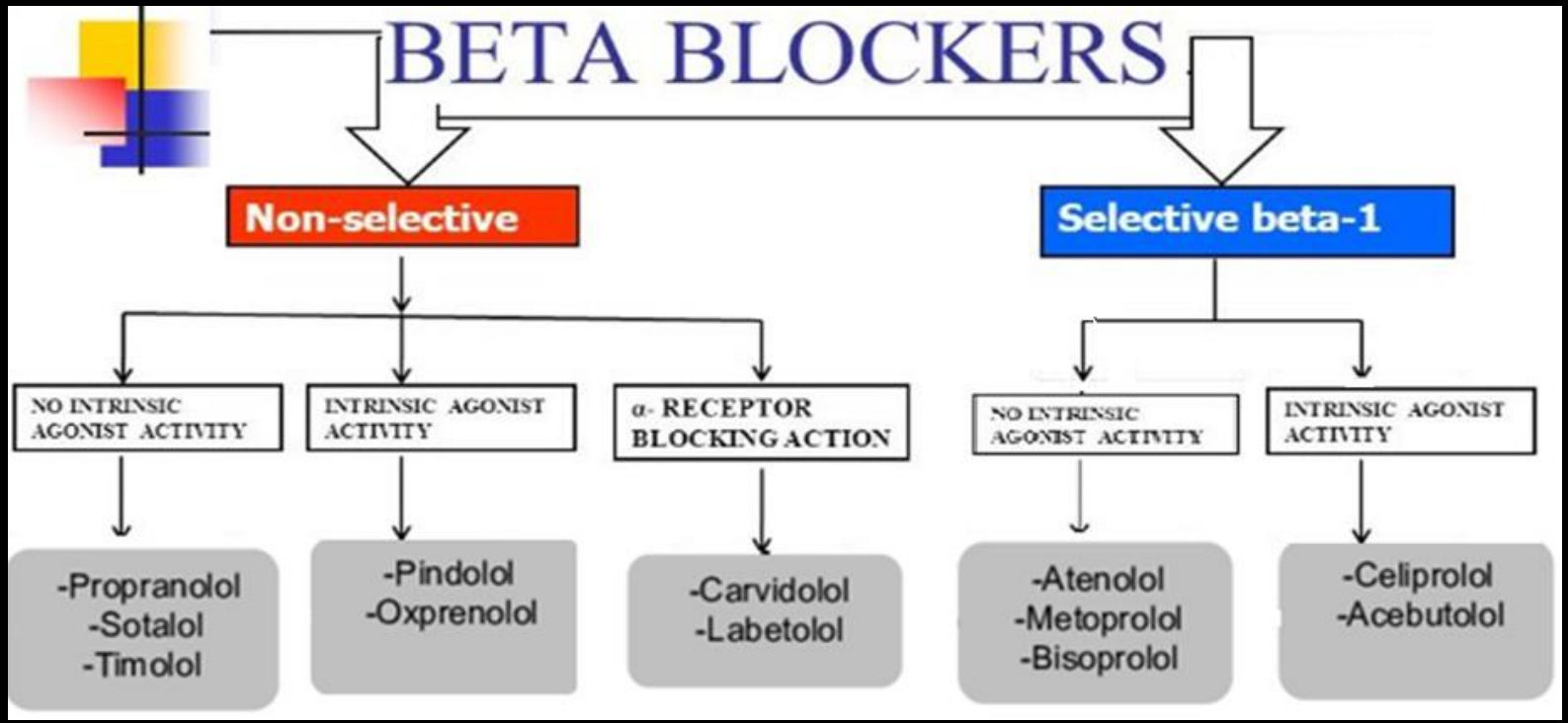


Study in detail the pharmacokinetic properties & pharmacodynamic effects of selected β- blockers

SOLI



Classification of β- Adrenoceptors Blockers



ACCORDING TO WATER & LIPID SOLUBILITY

	Lipophilic	Hydrophilic
Oral absorption	Complete	Irregular
Liver metabolism	Yes	No
$t_{1/2}$	Short	Long
CNS side effects	High	low
	Metoprolol Propranolol, Timolol Labetalol , Carvedilol	Atenolol, Bisprolol, Esmolol Sotalol

1-First generation:- Non-selective ß- blockers

2-Second generation:- ß1- selective blockers

3-Third generation:- ß- blockers with additional effects

α1 adrenergic receptor blockade (labetalol, carvedilol)

Increased production of NO (celiprolol, nebivolol)

Ca2+ entry blockade (carvedilol)

β2 agonist properties (celiprolol)

Antioxidant action (carvedilol)

Opening of K+ channels (tilisolol)

PHARMACOKINETICS

Most of them are lipid soluble

Lipid soluble β–blockers are well absorbed orally

are rapidly distributed, cross readily BBB

Have CNS depressant actions

Most of them have half-life from 3-10 hrs except Esmolol (10 min. given intravenously).

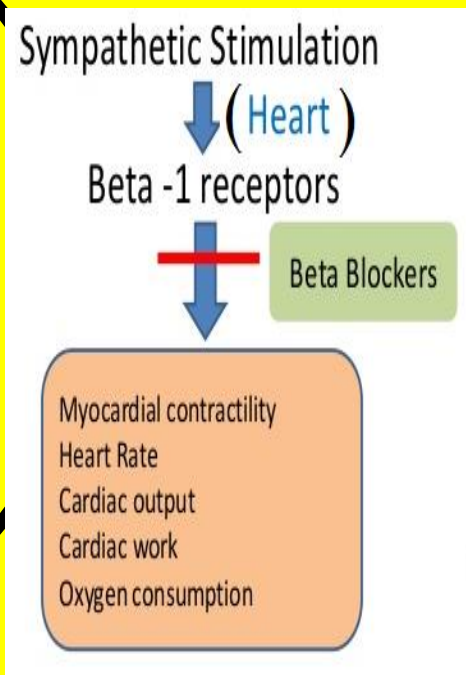
Most of them metabolized in liver & excreted in urine

PHARMACODYNAMIC EFFECTS

CVS:- Negative inotropic, chronotropic, dromotropic → ↓ CO

Antianginal effects (ischemic heart disease):
↓ Heart rate (bradycardia)
↓ force of contraction → ↓ cardiac work
↓ Oxygen consumption due to bradycardia

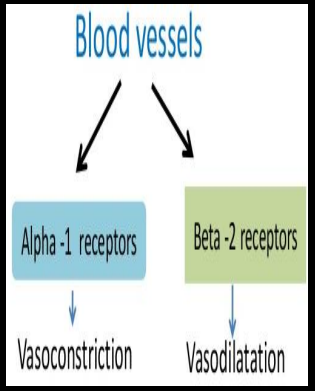
Anti-arrhythmic effects:
↓excitability, ↓ automaticity & ↓ conductivity (due to its sympathetic blocking)



PHARMACODYNAMIC EFFECTS

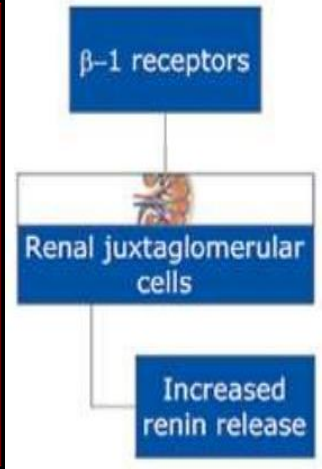
Blood vessels β_2

▲ peripheral resistance (PR) by blocking vasodilator effect ▼blood flow to organs ➔ cold extremities. Contraindicated in peripheral diseases like Reynaud's disease



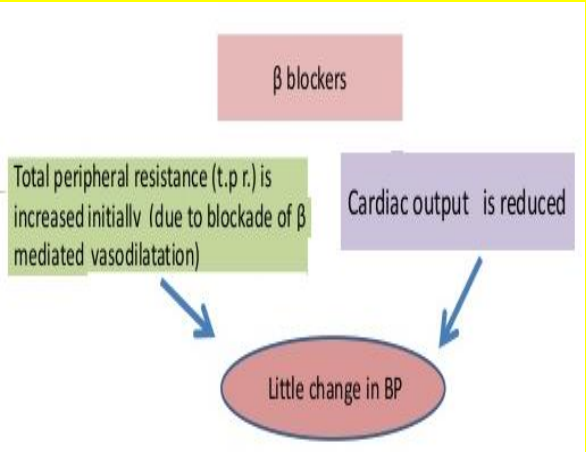
Blood pressure:- Antihypertensive ➔ ▼ BP in hypertensive patients due to effects on:

- 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



PHARMACODYNAMIC EFFECTS

Respiratory tract: β_2
- Bronchoconstriction
- Contraindicated in asthmatic patients



Intestine: ↑ Intestinal motility

Eye:
↓Aqueous humor production from ciliary body
↓Reduce intraocular pressure (IOP)
e.g. timolol as eye drops

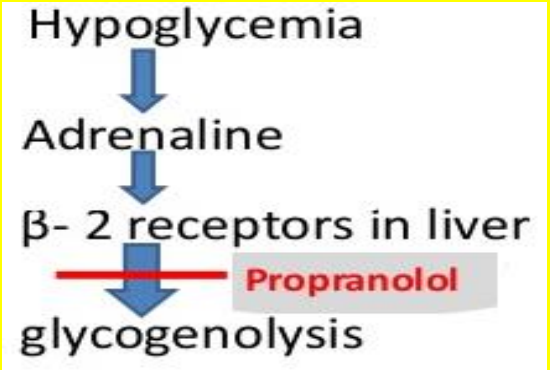
PHARMACODYNAMIC EFFECTS

Metabolic effects:

-Hypoglycemia

-↓ glycogenolysis in liver

-↓ glucagon secretion in pancreas



-↓ lipolysis in adipocytes

-Na^+ retention 2ndry to ↓BP → ↓renal perfusion

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

CLINICAL USES

In Hypertension:

Propranolol, atenolol, bisoprolol

Labetalol: α, β blockers

in hypertensive pregnant women & hypertensive crisis.

In cardiac arrhythmias:

In supraventricular & ventricular arrhythmias.

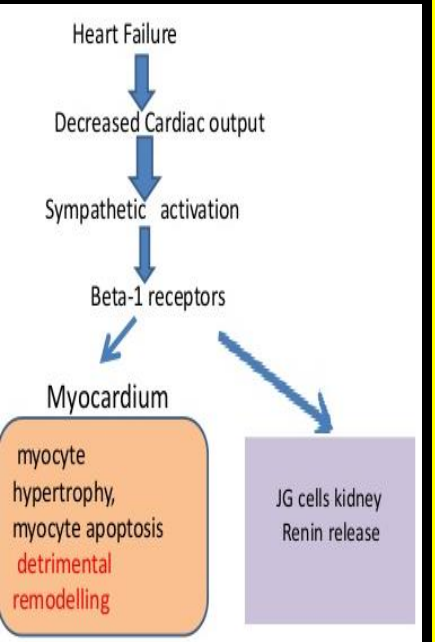
Bisoprolol and carvedilol are preferred

Angina pectoris:

-↓ heart rate, ↓ cardiac work & oxygen demand.

-↓ the frequency of angina episodes.

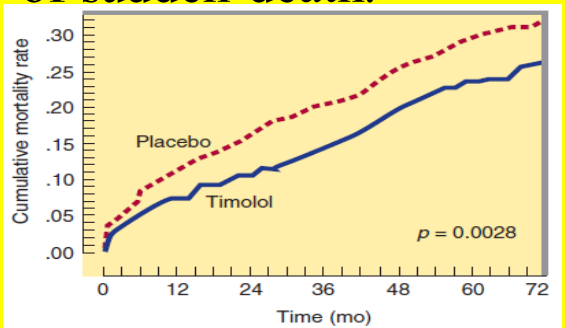
CLINICAL USES



Congestive heart failure:

e.g. carvedilol:

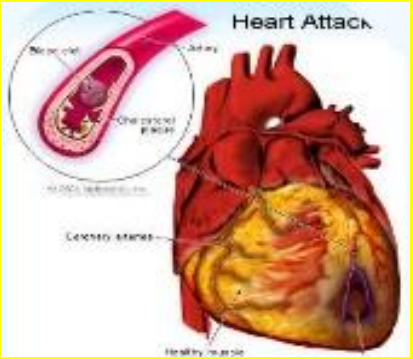
- antioxidant and non selective α & β blocker
- ↓ myocardial remodeling & ↓ risk of sudden death.



Myocardial infarction:

Have cardio-protective effect

- ↓ infarct size
- ↓morbidity & mortality →
- ↓ myocardial O_2 demand.
- ⊙ Anti-arrhythmic action.
- ⊙ ↓ incidence of sudden death



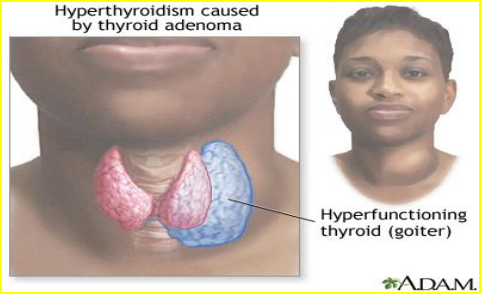
CLINICAL USES

In glaucoma e.g.

Timolol as eye drops

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; tachycardia, tremors, sweating.

CLINICAL USES

Migraine:

Prophylactic

↓reduce episodes of chronic migraine

↓catecholamine-induced vasodilatation in the brain vasculature

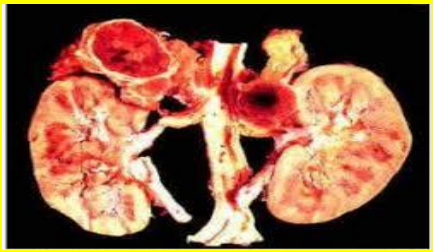
e.g. propranolol

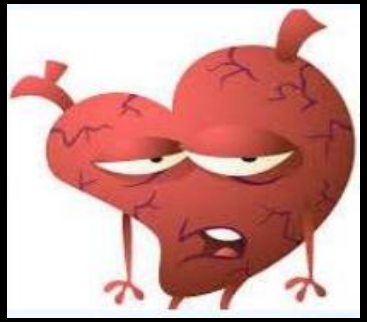
Pheochromocytoma

used with α-blockers (never alone)

⊙α-blockers lower the elevated blood pressure.

⊙β-blockers protect the heart from NA.





ADRS

Due to blockade of β1- receptor:

- Bradycardia, hypotension, heart failure

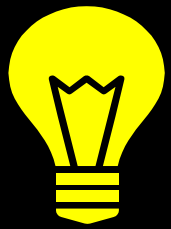
Due to blockade of β2- receptor:
(only with non-selective β blockers)

- Hypoglycemia
- Bronchoconstriction (# Asthma, emphysema).
- Cold extremities & intermittent claudication
  ➔by vasoconstriction

ADRS

- Erectile dysfunction & impotence, Nebivolol → NO
- ↑ TG → hypertriglyceridemia
- Coronary spasm → in variant angina patients
- Fatigue

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



ADRS

- Depression, and hallucinations
- Gastrointestinal disturbances
- Sodium retention

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

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

PROPRANOLOL

Non-Selective Competitive Blocker of β_1 & β_2

Membrane stabilizing action/ quinidine-like /local anesthetic effect sedative actions /No ISA

PHARMACOKINETICS

Lipophilic, completely absorbed, 70% destroyed during 1st pass hepatic metabolism, 90-95% protein bound, cross BBB and excreted in urine.

Can be given p.o. or parenteral

PHARMACODYNAMIC EFFECTS

Membrane Stabilization: Block Na channels → direct depressant to myocardium→ has local anesthetic effect (anti-arrhythmic effects).

CNS Effect: Has sedative action, ↓ tremors & anxiety → used to protect against social anxiety & performance anxiety.

Heart; by block β_1

Inhibit heart properties → ↓ cardiac output

Has anti -ischemic action → ↓ cardiac work + ↓ O_2 consumption

Has anti-arrhythmic effects → ↓excitability, automaticity & conductivity + by membrane stabilizing activity

PHARMACODYNAMIC EFFECTS

BP; by block β_1

Has antihypertensive action by➔

- **Inhibiting heart properties ➔ ↓ cardiac output**
- **β blockade : ↓ renin & RASS system**
- **Presynaptic inhibition of NE release from adrenergic nerves**
- **Inhibiting sympathetic outflow in CNS**

Blood Vessels [BV]; by blocking β_2 ➔Vasoconstriction ➔ ↓blood flow specially to muscles, other organs except brain ➔ cold extremities

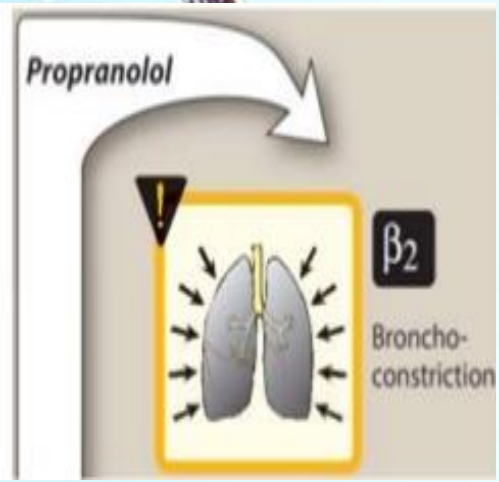
PHARMACODYNAMIC EFFECTS

Bronchi: by block β_2. Bronchospasm specially in susceptible patients

Intestine: by block β_2 ↑ Intestinal motility

Metabolism: by blocking mainly β_2
In liver; ↓ Glycogenolysis → Hypoglycemia
In pancreas; ↓ Glucagon secretion
In adipocytes; ↓ Lipolysis
In skeletal muscles; ↓glycolysis

On peripheral & central nervous systems:- Has local anesthetic effect. ↓ tremors & ↓ anxiety



INDICATIONS

- Hypertension)
- Angina
- Arrhythmias
- Tremors
- Myocardial infarction
- Hyperthyroidism
- Chronic glaucoma
- Migraine [*Prophylaxis*]
- Pheochromocytoma; used with α-blockers (never alone)
- Anxiety; *(specially social & performance type)*

LABETALOL

Blocks α_1 & β

Rapid acting, non-selective with ISA & local anesthetic effect

Does not alter serum lipids or blood glucose

Used in:- (given p.o and i.v)

Hypertensive crisis (e.g. during abrupt withdrawal of clonidine)

Used in pregnancy-induced hypertension

ADRs:- Orthostatic hypotension, sedation & dizziness

CARVEDILOL

Blocks α_1 & β

Non-selective with no ISA & no local anesthetic effect

Has ANTIOXIDANT action

Favorable metabolic profile

Used effectively in ➔ CONGESTIVE HEART FAILURE ➔ reverses its pathophysiological changes.

ADR;- Edema

etoprolol

isoprolol

arvedilol