β- Adrenoceptors blockers

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Classification of β- Adrenoceptors Blockers

Selective β1 antagonists

Atenolol, Bisoprolol

Esmolol, Metoprolol

Non selective β- Antagonists

Blocks β1& β2 receptors

Propranolol

Sotalol, Timolol (PST)

Mixed α, β receptors blockers

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

β ADRENOCEPTOR BLOCKERS

Pharmacodynamic Classification

1

According to selectivity

Non-Selective

Block β_1 & β_2

Propranolol, Sotalol, Timolol (Eye)

Selective

Block β_1

Atenolol, Bisoprolol, Metoprolol, Esmolol

2

Labetalol, Carvedilol (mixed α, β blockers)

According to presence of agonistic/antagonistic action;
Intrinsic Sympathomimetic Activity **(ISA)**

Without ISA

Atenolol, Bisoprolol, Metoprolol
Propranolol, Sotalol, Timolol, carvedilol

With ISA (may activate beta receptors)

labetalol

3

According to presence of membrane stabilizing effects i.e. Block Na Channels
Quinidine-like action
Antiarrythmic action

Propranolol, labetalol

β ADRENOCEPTOR BLOCKERS

Pharmacokinetic Classification

According to their lipid solubility

Lipophylic — **Hydrophilic**

	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

CNS depressant effects i.e. Sedative effect → ↓ Anxiety

Pharmacokinetis of β–blockers:

- **Most of them are lipid soluble**
- **Lipid soluble β–blockers**
  - **well absorbed orally.**
  - **are rapidly distributed, cross readily BBB**
  - **Have CNS depressant actions**
  - **Metoprolol, propranolol, timolol, labetalol, carvedilol**
- **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.**

β–Adrenergic receptors :

β_1 (Heart):

- **Increase heart Rate → Positive chronotropic effect.**
- **Increase in contractility → Positive inotropic action.**
- **Increase in conduction velocity → Positive dromotropic.**

$\beta_{2:}$ relaxation of smooth muscles

β_2 : Hyperglycemia

β_2 : ↑ Release of glucagon from pancreas

β_2 α1: Glycogenolysis & gluconeogenesis in liver

β3 : ↑ Lipolysis by adipose tissue

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 actions of β–Adrenergic blockers:

Blood vessels β_2

↑ peripheral resistance (PR) by blocking vasodilatory effect β_2

↓blood flow to organs → cold extremities

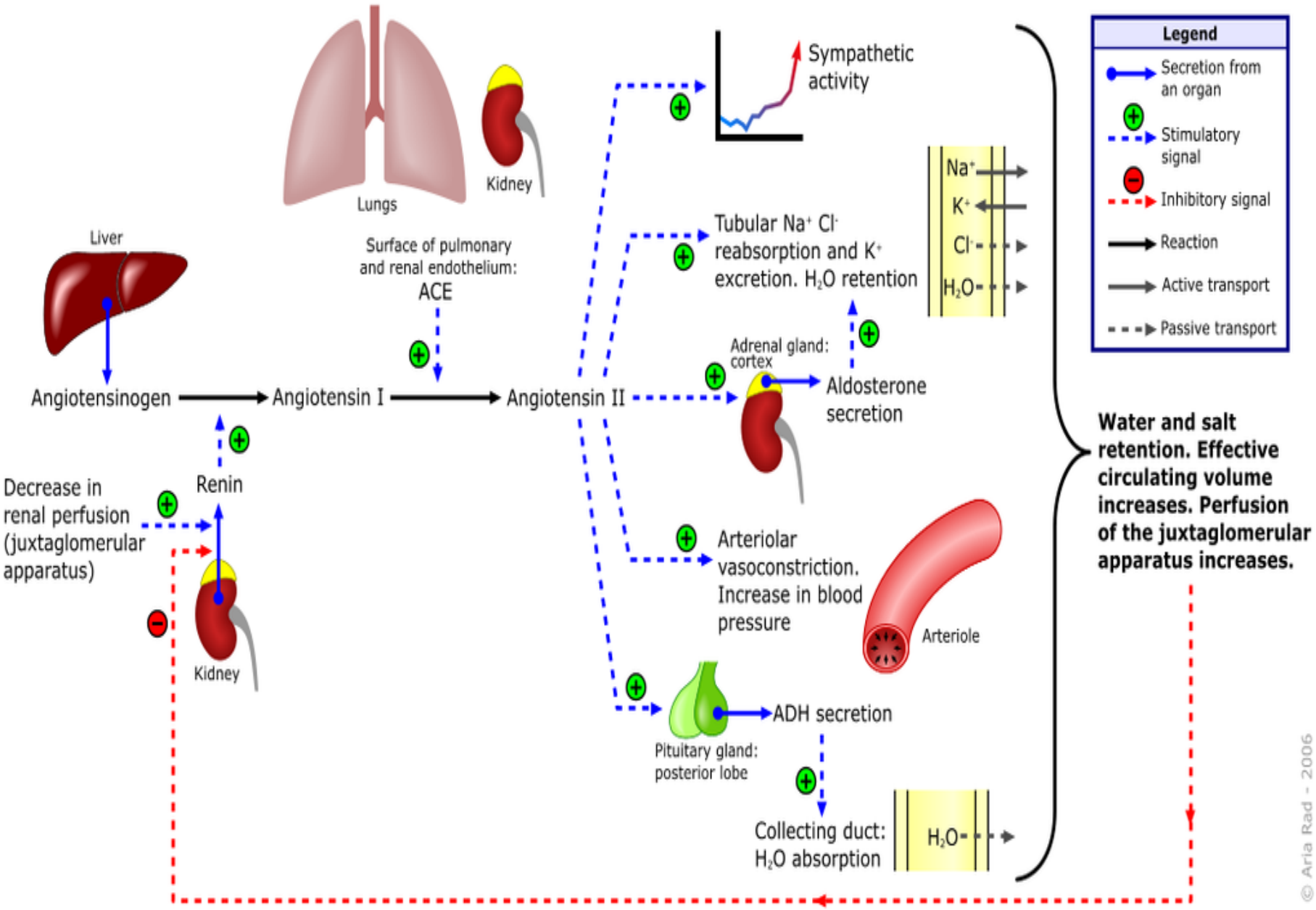
contraindicated in peripheral diseases like Reynaud's disease

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

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 2^{ndry} to ↓BP → ↓renal perfusion**
- **All β–Adrenergic blockers mask hypoglycemic manifestations in diabetic patients → COMA**

Clinical Uses of β–receptor blockers

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

Clinical Uses of β–receptor blockers

In Hypertension:

Propranolol, atenolol, bisoprolol

Labetalol: α, β blockers

in hypertensive pregnant & 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 of β–receptor blockers

Congestive heart failure:

e.g. carvedilol:

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

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

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.**

Adverse Effects of β- Adrenoceptors blockers

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**
- **Erectile dysfunction & impotence**
- **Coronary spasm ➔ in variant angina patients**
- **All β–Adrenergic blockers mask hypoglycemic manifestations i.e. tachycardia, sweating,… ➔ COMA**

Intermittent claudication Peripheral artery disease most commonly affects the legs, but other arteries may also be involved. The classic symptom is leg pain when walking which resolves with rest.

Risk factors: Diabetes, hypercholesterolemia, high blood pressure.

Adverse Effects of β- Adrenoceptors blockers

- **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 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 hypoglycaemia / GIVEN CAUSIOUSLY**
- **Hypotension**
- **Alone in pheochromocytoma (must be given with an α-blockers).**

PROPRANOLOL

Is the chosen as prototype

Non-Selective Competitive Blocker of β_1 & β_2
Membrane stabilizing action/ quinidine-like /local anesthetic effect
sedative actions /No ISA

Kinetics

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

Dynamics

β-blocking Effect:

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.

PROPRANOLOL

Actions

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

BP; by block β_1 & β_2

Has antihypertensive action by→

- Inhibiting heart properties → ↓ cardiac output
- B blockade : ↓ renin & RAAS system
- Presynaptic inhibition of NE release from adrenergic nerves
- Inhibiting sympathetic outflow in CNS

PROPRANOLOL

Actions

Mainly by β_2 blockade

Blood Vessels: Vasoconstriction → ↓blood flow specially to muscles, other organs except brain cold extremities

Bronchi: Bronchospasm specially in susceptible patients

Intestine: ↑ Intestinal motility

Metabolism:
In liver: ↓ Glycogenolysis → Hypoglycaemia
In pancreas: ↓ Glucagon secretion
In adipocytes: ↓ Lipolysis
In skeletal muscles: ↓glycolysis

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

PROPRANOLOL

INDICATIONS

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

LABETALOL

Blocks α_1 & β

Rapid acting, non-selective

has ISA and local anesthetic effect.

Do not alter serum lipids or blood glucose

Used in ➔ given p.o and i.v

Severe hypertension in pheochromocytoma

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

Used in pregnancy-induced hypertension

Adverse effects:

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.

Adverse effects: Edema

Selective β1- receptor blockers

- **Selectivity present in low doses but is lost at high doses**
- **no change in lipid or glucose**
- **no bronchoconstriction**
- **are preferable in patients**
  - **With asthma, COPD**
  - **Raynaud's phenomenon & peripheral vascular diseas (PVD).**
  - **Diabetics/ Dyslipidemias.**
  - **Variant Angina (coronary spasm).**

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

β-receptor blockers

Propranolol	Non selective B_1, β_2 blocker	Migraine prophylaxis Hyperthyroidism (thyrotoxicosis) Relieve anxiety (social performance)
Timolol	B_1, β_2 blocker	Glaucoma
Atenolol Bisoprolol Metoprolol	B_1 blocker	Myocardial infarction Hypertension
Esmolol	B_1 blocker Ultra short acting	Cardiac arrhythmia
Carvedilol	Non selective α, B blocker	Congestive heart failure
Labetalol	α, B blocker	Hypertension in pregnancy Hypertensive emergency