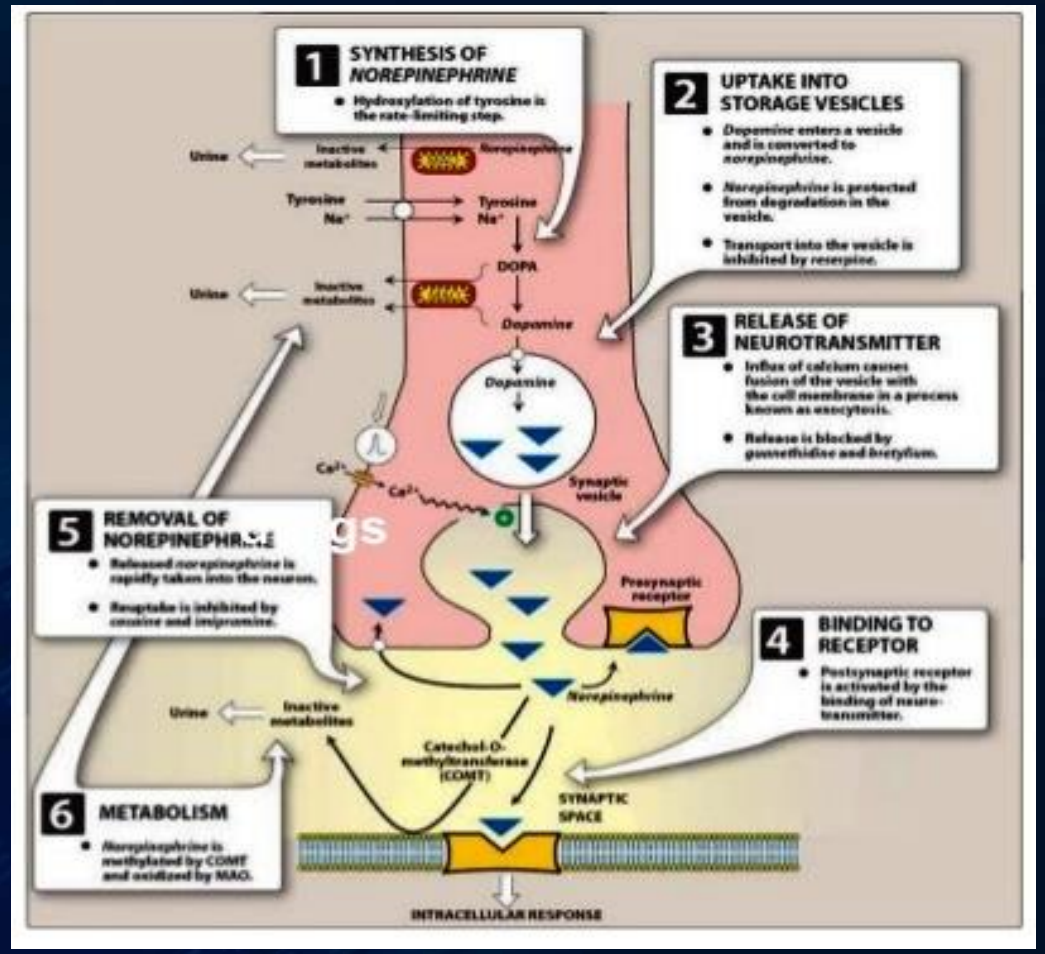
ADERENERGIC ANTAGONIST

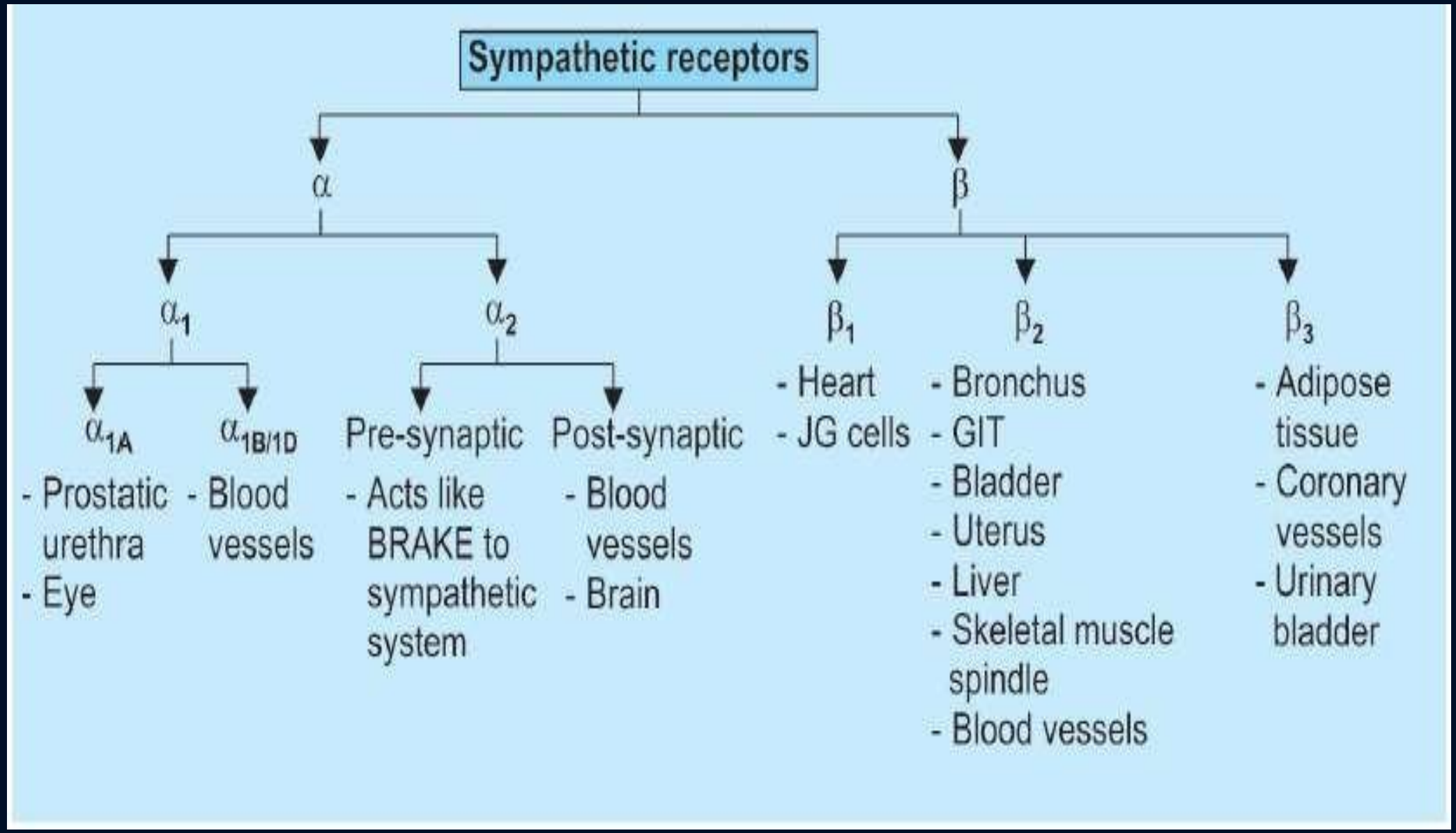


CLASSIFICATION

- ALPHA -ADRENOCEPTOR ANTAGONIST
  - NON-SELECTIVE
    - REVERSIBLE
      - PHENTOLAMINE
      - TOLAZOLINE
    - IRREVERSIBLE
      - PHENOXYBENZAMINE
  - SELECTIVE
    - ALPHA 1 BLOCKERS
      - PRAZOSIN
      - TERAZOSIN
      - DOXAZOCIN
      - ALFUZOSIN
      - BUNAZOSIN
      - TAMSULOSIN
      - SILODOSIN
    - ALPHA 2 BLOCKERS
      - YOHIMBINE
      - IDAZOXAN
  - MISCELLANEOUS
    - ERGOT ALKALOIDS

ALPHA AND BETA RECEPTORS

- Adrenergic receptors are membrane bound G-protein coupled receptors which function primarily by increasing or decreasing the intracellular production of second messengers cAMP or IP3/DAG. In some cases the activated G-protein itself operates K+ or Ca2+ channels, or increases prostaglandin production.
- Ahlquist (1948), on the basis of two distinct rank order of potencies of adrenergic agonists classified adrenergic receptors into two types α and β. This classification was confirmed later by the discovery of selective α and β adrenergic antagonists.


Sympathetic receptors
α
β
α1
α2
β1
β2
β3
α1A
α1B/1D
Pre-synaptic
Post-synaptic
- Prostatic urethra
- Eye
- Blood vessels
- Acts like BRAKE to sympathetic system
- Blood vessels
- Brain
- Heart
- JG cells
- Bronchus
- GIT
- Bladder
- Uterus
- Liver
- Skeletal muscle spindle
- Blood vessels
- Adipose tissue
- Coronary vessels
- Urinary bladder

DIFFERENCES BETWEEN ALPHA AND BETA ADRENERGIC RECEPTORS

TABLE 9.1 **Differences between α and β adrenergic receptors**

	α	β
1. Rank order of potency of agonists	*Adr ≥ NA > Iso	Iso > Adr > NA
2. Antagonist	Phenoxybenzamine	Propranolol
3. Coupling protein	Gq/Gi/Go	Gs
4. Effector pathway	IP_3/DAG↑, cAMP ↓, K^+ channel ↑	cAMP↑, Ca^{2+} channel ↑

* Though inherently NA is equipotent to Adr on α receptors, in test systems with intact neuronal reuptake, it appears less potent due to faster reuptake.

TABLE 9.2 Differences between β_1, β_2 and β_3 receptors

	β_1	β_2	β_3
1. Location	Heart, JG cells in kidney	Bronchi, blood vessels, uterus, liver, g.i.t., urinary tract, eye	Adipose tissue
2. Selective agonist	Dobutamine	Salbutamol, terbutalin	BRL 37344
3. Selective antagonist	Metoprolol, Atenolol	ICI 118551 α-methyl propranolol	CGP 20712A (also β_1) ICI 118551 (also β_2)
4 Relative potency of NA and Adr	NA $\leq$ Adr	NA << Adr	NA > Adr

TABLE 9.3 Differences between α_1 and α_2 receptors

	α_1	α_2
Location	Postjunctional on effector organs	Prejunctional on nerve ending (α_{2A}), also postjunctional in brain, pancreatic β cells and extrajunctional in certain blood vessels, platelets
Function subserved	GU Smooth muscle–contraction Vasoconstriction Gland—secretion Gut—relaxation Liver—glycogenolysis Heart—arrhythmia	Inhibition of transmitter release Vasoconstriction Decreased central sympathetic flow Decreased insulin release Platelet aggregation
Selective agonist	Phenylephrine, Methoxamine	Clonidine
Selective antagonist	Prazosin	Yohimbine, Rauwolscine
Coupling protein	Gq	Gi/Go
Effector pathway	IP_3/DAG ↑ Phospholipase A_2 ↑—PG release	cAMP ↓ K^+ channel ↑ Ca^{2+} channel ↓ or ↑ IP_3/DAG ↑

GU: Genitourinary

- The actions of a particular sympathomimetic amine depend on its relative activity at different types of adrenergic receptors.

Adr : α_1 + α_2 + β_1 + β_2 and weak β_3 action
NA : α_1 + α_2 + β_1 + β_3 but no β_2 action
Iso : β_1 + β_2 + β_3 but no α action

Sympatholytic Drugs

- These drugs may act by competitive antagonists at α and/or β-adrenergic receptors

- ALPHA BLOCKERS
- BETA BLOCKERS
- ALPHA + BETA BLOCKERS.

α ADRENERGIC BLOCKING DRUGS

- These drugs inhibit adrenergic responses mediated through the α adrenergic receptors without affecting those mediated through β receptors.

CLASSIFICATION

I. *Nonequilibrium type*
   (i) β-*Haloalkylamines*—Phenoxybenzamine.

II. *Equilibrium type (competitive)*

A. Nonselective
   (i) *Ergot alkaloids*—Ergotamine, Ergotoxine
   (ii) *Hydrogenated ergot alkaloids*—Dihydroergotamine (DHE), Dihydroergotoxine
   (iii) *Imidazoline*—Phentolamine
   (iv) *Miscellaneous*–Chlorpromazine

B. α_1 selective—Prazosin, Terazosin, Doxazosin, Alfuzosin, Tamsulosin

C. α_2 selective—Yohimbine

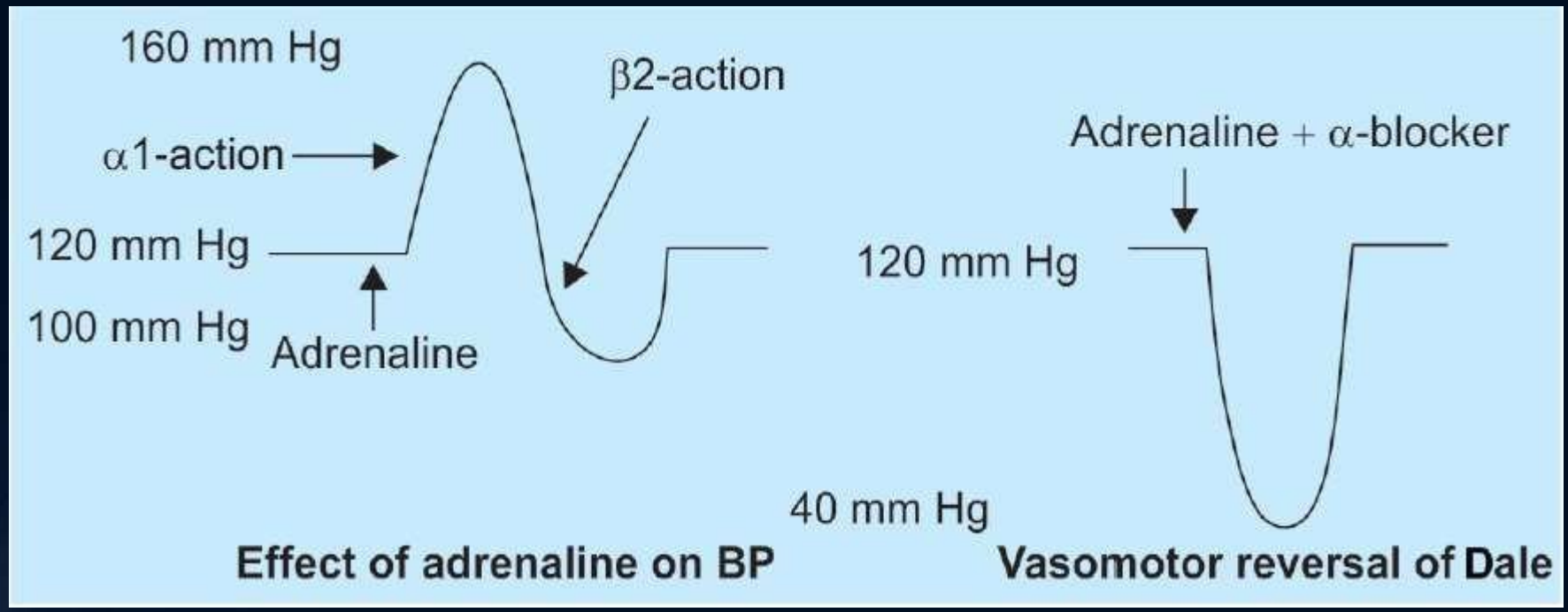
○ ALPHA BLOCKERS

Nonselective α-Blockers

- **Phenoxybenzamine is an *irreversible antagonist whereas phentolamine and tolazoline are reversible*** blockers of α1 and α2 receptors. These agents result in *vasodilatation and postural hypotension (due* to antagonism of vasoconstrictor α1 receptors).

- Use of these drugs before adrenaline results in **vasomotor reversal of Dale.**
- Intravenous injection of adrenaline normally causes increase in blood pressure (α effect) followed by prolonged fall (β2 effect). If it is administered after giving α blockers, only fall in BP is seen *(vasomotor reversal of Dale).*

Vasomotor reversal of dale



- *Phentolamine and tolazoline are preferred agents for the treatment of hypertensive* crisis in *clonidine withdrawal and cheese reaction.*

Equilibrium type (competitive)

Nonselective

- Ergot alkaloids are the adrenergic antagonists with which Dale demonstrated the vasomotor reversal phenomenon.

- The α blockade produced by ergot alkaloids is low grade and clinically not useful. Their principal use is in migraine *Dihydroergotoxine has been used as a cognition* enhancer .

•*Selective α1-Blockers*

•These drugs (*prazosin, terazosin, doxazosin and alfuzosin) cause decrease in blood pressure with* lesser tachycardia than non selective blockers (due to lack of α2 blocking action, sympathetic outflow is not increased).

•Selective α1 blockers have **favorable effect on lipid profile (increase HDL and** decrease LDL and TG)

• Due to relaxation of smooth muscle in the neck of urinary bladder and prostatic urethra, urinary flow is improved by these drugs. Therefore, selective α1 blockers are *drugs of choice for patients with hypertension and benign hyperplasia of prostate (BHP).*

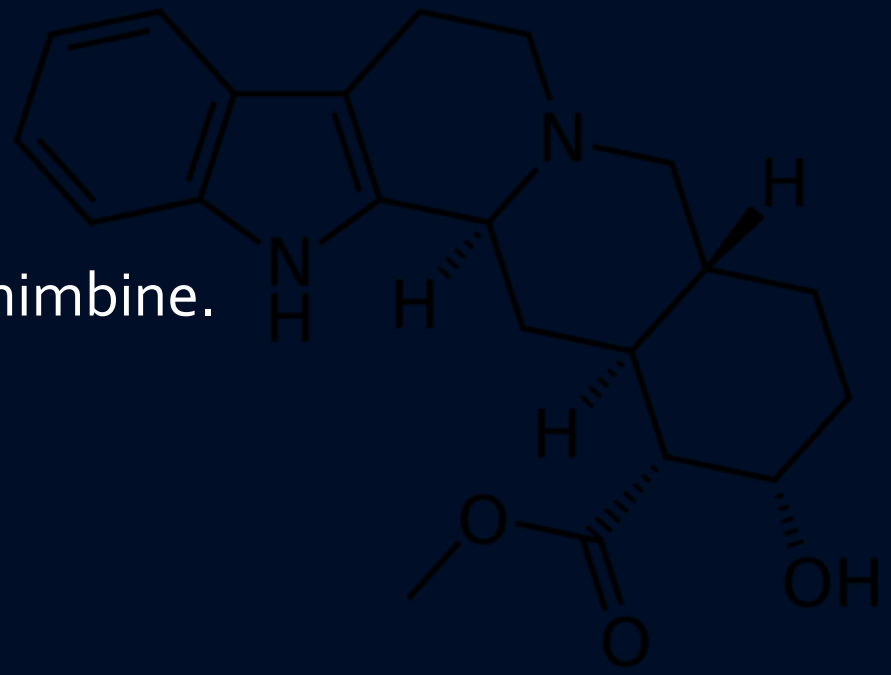
• **Prazosin (and other α1 blockers) are useful for the treatment of scorpion sting.**

•**Major adverse effect of these drugs is *postural hypotension. It is seen with first few*** doses or on dose escalation (*First dose effect). If used continuously, tolerance develops* to this adverse effect. **Inhibition of ejaculation is another side effect of these agents**

Tamsulosin and **Silodosin** ***selectively inhibits subtype of α1 receptors present in the*** *prostate (α1A) without affecting those present in the blood vessels. These are therefore* preferred for the treatment of BHP because of their reduced propensity to cause postural hypotension.

Selective α2-Blockers

Yohimbine An alkaloid from the West African plant
Yohimbehe. It is a relatively selective α2 blocker with
short duration of action.



There are no valid indications for clinical use of yohimbine.

BETA BLOCKERS

- The beta blockers are classified in two system they are :
- NON SELECTIVE AND CARDIOSELECTIVE
- BETA BLOCKERS INTO 3 GENERATIONS

CLASSIFICATION

Nonselective (β_1 and β_2)

a. *Without intrinsic sympathomimetic activity*
   Propranolol, Sotalol, Timolol.
b. *With intrinsic sympathomimetic activity*
   Pindolol
c. *With additional α blocking property*
   Labetalol, Carvedilol

Cardioselective (β_1)

Metoprolol, Atenolol, Acebutolol, Bisoprolol, Esmolol, Betaxolol, Celiprolol, Nebivolol

The pharmacology of propranolol is described as prototype.

Another system classifies β blockers into 3 generations.

First generation (older, nonselective)	**Second generation** (β_1 selective)	**Third generation** (with additional α blocking and/or vasodilator property)
Propranolol	Metoprolol	Labetalol
Timolol	Atenolol	Carvedilol
Sotalol	Acebutolol	Celiprolol
Pindolol	Bisoprolol	Nebivolol
	Esmolol	Betaxolol

Nonselective β-Blockers [First generation β-blockers)

•*propanolol, timool, nadolol, pindolol, alprenolol and Oxprenolol.*

Important effects of these drugs are:

•Myocardial oxygen demand is decreased due to blockade of β1 receptors in the heart (*useful in classical angina) but coronary vasoconstriction can occur due to blockade of* vasodilatory β2 receptors (*contraindicated in variant angina).*

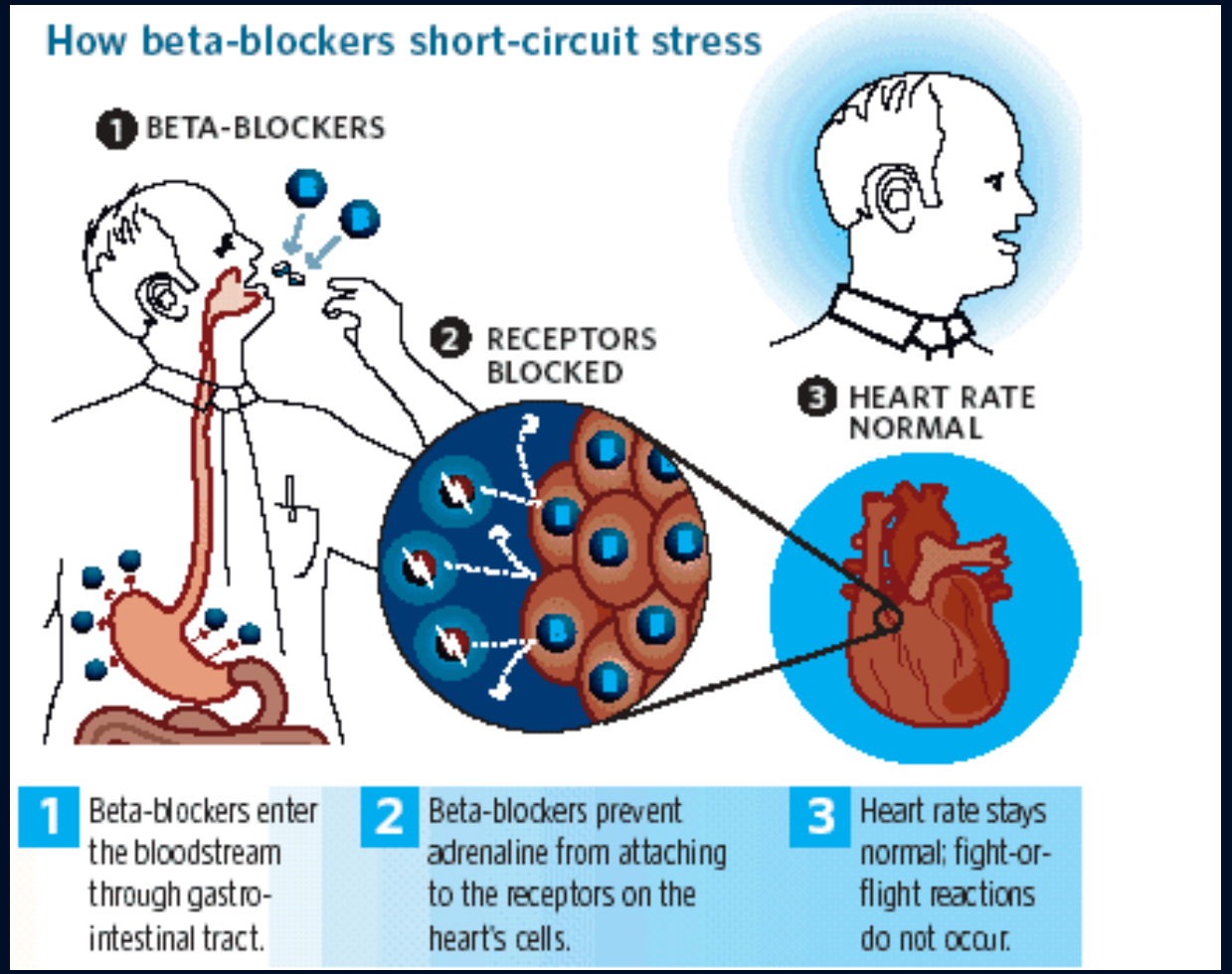
• *Decrease in blood pressure (mainly due to β1 blockade).*

•*Bronchoconstriction may occur due to blockade of β2 receptors (contraindicated in asthmatics).*

• *Dyslipidemia characterized by increase in LDL and decrease in HDL may be seen (β2* blockade).

•Decreased chances of *reversal of hypoglycemia in patients on insulin and other hypoglycemic agents (β2 blockade).*

- Decreased production of aqueous humor (*useful in glaucoma) by β2 blocking action.*
- *Impaired exercise capacity due to blockade of β2 receptors in blood vessels of skeletal* muscle.
- *Abolishes sympathetic tremors (β2 blockade).*



Limitations of Non-selective β-Blockers

- Contraindicated in bronchial asthma due to their *bronchoconstrictor action.*

- Hypoglycemia is commonly observed in diabetic patients receiving insulin and oral hypoglycemic drugs. Symptoms of hypoglycemia (like tachycardia, sweating and tremors) are due to sympathetic stimulation that act as warning signs for the patient. *Beta blockers mask these symptoms (**except sweating because it is mediated by sympathetic** cholinergic system) and patient can go directly into coma. Further, these agents delay the recovery from hypoglycemia due to inhibition of β2 mediated hyperglycemia.* These drugs are therefore *contraindicated in diabetic patients.*
- On long term use non selective β blockers can *adversely affect serum lipid profile and can cause glucose intolerance.*
- By causing vasoconstriction (β2 is vasodilatory), these drugs can *worsen peripheral vascular disease (contraindicated in Raynaud's disease).*
- These drugs can *impair exercise capacity due to blockade of skeletal vascular β2* receptors.

Contra-indications of non-selective β-blockers

A – Asthma

B – Block (AV)

C – CHF

D – Diabetes

Cardioselective (Selective β1) β-Blockers [Also known as second generation β-blockers)

The drugs can be remembered as:

* **N**ew	– **N**ebivolol (**Most cardioselective)**
* **B**eta	– **B**etaxolol
* **B**lockers	– **B**isoprolol
* **A**cting	– **A**cebutolol
* **E**xclusively	– **E**smolol
* **A**t	– **A**tenolol
* **M**yo	– **M**etoprolol
* **C**ardium	– **C**eliprolol

Advantages of cardioselective β-blockers

- Safe in asthma
- Safe in diabetes
- Safe in PVD
- Less likely to impair exercise capacity
- Less risk of hyperglycemia
- Less risk of dyslipidemia

Beta-Blockers with Intrinsic Sympathomimetic Activity (ISA)

The drugs can be remembered as:

* **CO**ntain	– **C**eliprolol, **O**xprenolol
* **P**artial	– **P**indolol, Penbutolol
* **A**gonistic	– **A**lprenolol
* **A**ctivity	–**A**cebutolol

•These drugs are partial agonists at β1 receptors (apart from having β blocking property). *These* are preferred in the *patients prone to develop severe bradycardia with β blocker therapy. However,* these drugs are less useful in angina (because of stimulation of heart by β1 receptors.

Beta-Blockers with Membrane Stabilizing Activity

The drugs are remembered as:

*Possess	– Propanolol (*maximum*)
*Membrane stabilizing or	– Metoprolol
*Local	– Labetalol
*Anaesthetic	– Acebutolol
*Property	– Pindolol

•These drugs possess Na+ channel blocking (local anaesthetic) activity. It can contribute to *antiarrhythmic action. These drugs should be avoided in glaucoma due to the risk of corneal* anaesthesia.

Lipid Insoluble β-Blockers

- These agents are mainly *excreted by kidney and are therefore contraindicated in renal failure.*
- Most of these have *long duration of action*

*Not	– Nadolol (*longest acting β blocker*)
*Soluble	– Sotalol
*A	– Atenolol
	– Acebutolol
*B	– Betaxolol
	– Bisoprolol
* C	– Celiprolol

Beta blockers contra-indicated in renal failure

A – Atenolol
N – Nadolol
S – Sotalol

USES OF β-BLOCKERS

Cardiac (due to β_1 blockade)	Extra cardiac (due to β_2 blockade)
Hypertension	Pheochromocytoma (after α blockade)
Classical angina	Hyperthyroidism
Myocardial infarction	Performance anxiety
Supraventricular arrhythmias	Tremors
Chronic CHF	Akathisia
Hypertrophic obstructive cardiomyopathy (DOC)	Prophylaxis of migraine
Emergency management of symptoms of TOF	Glaucoma (*timolol and betaxolol*)
Mitral valve prolapse	Alcohol and opioid withdrawal
	Prophylaxis of bleeding in portal hypertension

COMBINED ALPHA AND BETA BLOCKERS

- *Labetalol and carvedilol are the important drugs in this group. These are useful for the control of* hypertensive episodes in *pheochromocytoma.*

- ***Carvedilol is the most commonly used beta blocker***
  in chronic CHF due to its ***antioxidant and antimitogenic properties***

THANKYOU