MED441
KING SAUD UNIVERSITY

Revised & Reviewed by: Abdulaziz Bahammam & Faye Wael Sendi

1. Alpha Adrenergic Blockers

Pharmacology
TEAM 441

Objectives:

- Outline the mechanisms of action of adrenergic neuron blockers.
- Classify a-receptor blockers into selective & non-selective.
- Know the pharmacokinetic aspects & pharmacodynamic effects of a adrenergic blockers.
- Identify the specific uses of non selective and selective a-adrenergic blockers.

HELPFUL VIDEOS:

- **Alpha adrenergic blockers**
- **Adrenergic neuron blockers**

Editing file

Color index:
Important
In male's slides only
In female's slides only
Extra information
Doctors notes

Review

*EXTRA :
The following slide is a revision of all adrenergic receptors.
Helpful review before you start the first 2 lectures.

Post-synaptic located in tissue

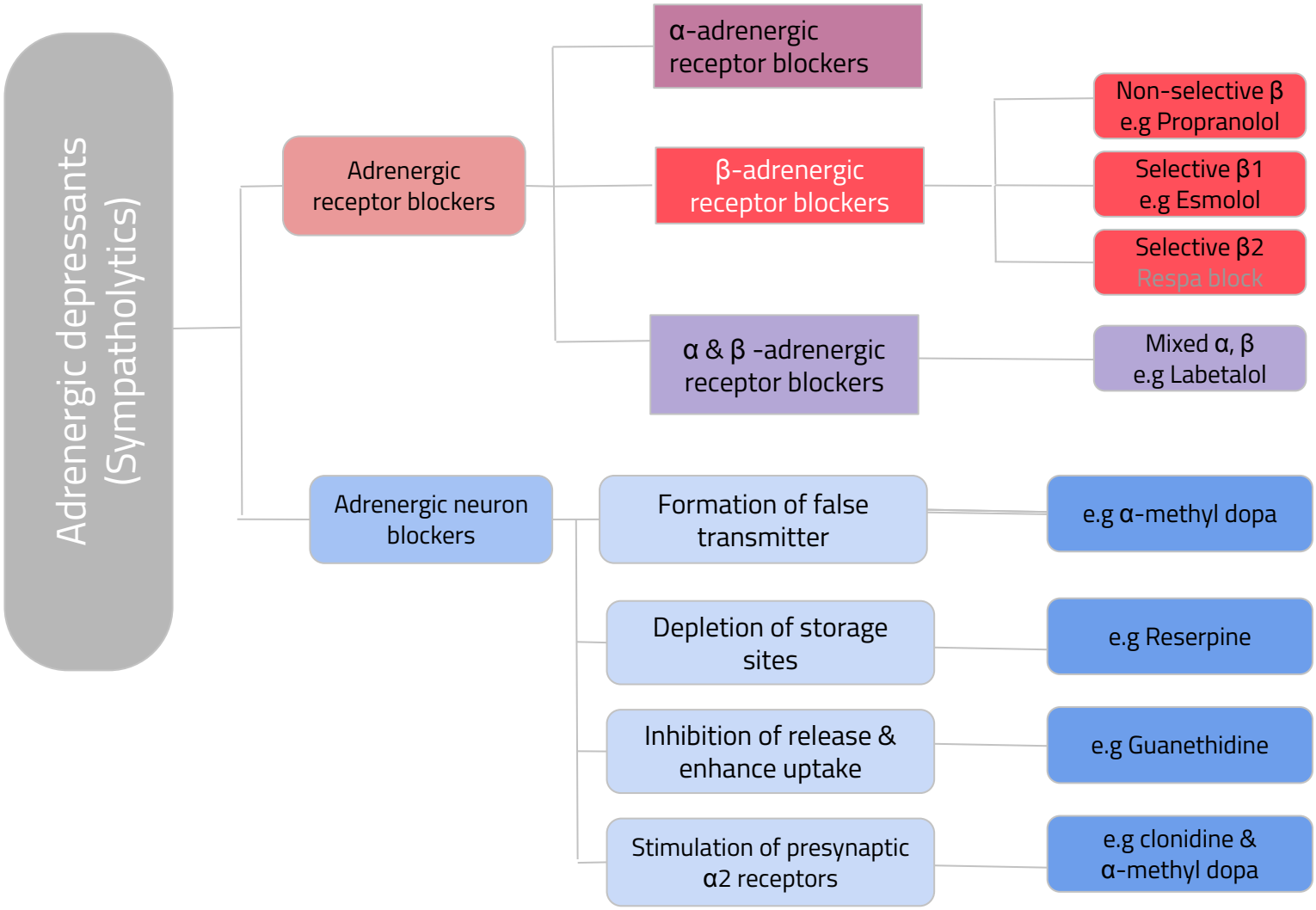
(meaning it is mediated by a neuron which received a signal from a preganglionic neuron by synapsis)

α_1	β_2	β_1	β_3
Excitatory in function (causes contraction) Except in GIT	***Inhibitory*** in function (β_2 = 2 Lungs)	***Excitatory*** In function , present mainly in **Heart**, juxtaglomerular cells in **kidney** (β_1 = 1 Heart)	In adipose tissue
Present mainly in smooth muscles		↑ heart rate: ***chronotropic*** effect (Tachycardia)	↑ lipolysis ↑ Free fatty acids
Contraction of pregnant uterus	**Relaxation** of pregnant uterus (Delay premature labour) called "tocolytic effect"	↑ force of contraction : + ***inotropic*** effect	
Vasoconstriction of skin & peripheral blood vessels leads to: ↑ peripheral resistance ***(resistance to blood flow due to constriction of blood vessels)*** leads to: *hypertension* ***Used as nasal decongestants***	Relaxation of skeletal & coronary blood vessels **(vasodilatation)**	Increase cardiac output How so? ↑ conduction velocity: dromotropic effect (via A.V. Node) (*Dromotropic effect* means an effect in the speed of conduction of electrical impulses)	
Relaxation of GIT muscles & urinary bladder's muscles. **Contraction** of GIT sphincter (constipation) & urinary bladder's sphincter → urinary retention		↑ blood pressure	
Contraction of radial muscle of eye causes active mydriasis (dilation of pupil, cholinergic agents, have no effects on this muscle	Relaxation of bronchial smooth muscles **(bronchodilation)** tremor of skeletal muscles	↑ renin release *Where is this enzyme released?* ***Kidney*** *In response to?* ***stretch receptors on blood vessels*** *what's its function?* ***increase blood pressure***	
↑ blood glucose level (hyperglycemia), by			
↑ glycogenolysis	1- pancreas releases ↑ glucagon 2- ↑ glycogenolysis in liver & muscles		

Pre-synaptic

α_2	β_2
Inhibition of norepinephrine release (Negative feedback) How? this mainly happen by an autoreceptor 'presynaptic receptor' which is present on the neuron releasing the neurotransmitter itself, the neurotransmitter bind to the receptor of the same neuron it was released by and inhibiting further release of the neurotransmitter, producing a negative feedback mechanism	Increase of norepinephrine release (positive feedback)

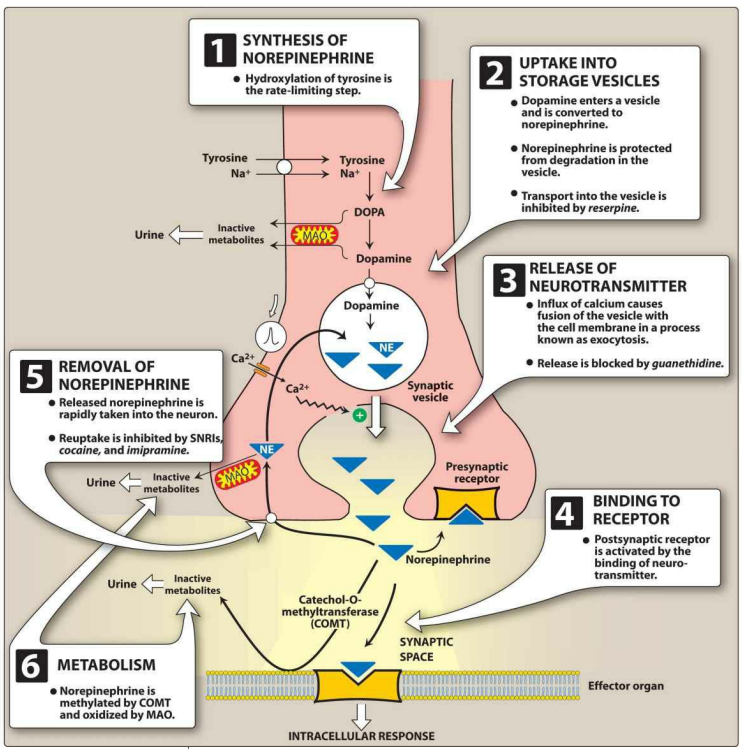
Lecture Overview:



Adrenergic Transmission of NE

1) **Synthesis** of NE
   - Tyrosine -(hydroxylation)→ DOPA
   - DOPA -(decarboxylation)→ Dopamine
   - Dopamine -(inside vesicles only)→ NE
2) **Storage** of NE in vesicles
3) **Release** of NE into synaptic space by exocytosis (fusion of vesicles with PM)
4) **Binding** to receptors
   a) Pre-synaptic
   b) Post-synaptic
5) **End of action** by either:
   a) Reuptake into neuron
   b) Enzymatic degradation
      - MAO (in mitochondria)
      - COMT (in synapse)

- **Neuron blockers** interfere with any of **steps 1**, **2**, **3**, **4a** or **5**.
- While **receptor blockers** interfere with **step 4b** only.



Adrenergic Depressants:

Adrenergic receptor blockers

a-receptor antagonists

1.Non-selective (α1, α2)
e.g.phentolamine, phenoxybenzamine

2.Selective α1
e.g Prazosin, Terazosin,doxazosin

3.Selective α2
e.g Yohimbine

b-receptor antagonists
Will be discussed in 2nd lecture.

Nonselective
a & b receptor blockers

Adrenergic neuron blockers

1. Formation of false transmitters.
e.g **α-Methyl Dopa**

2. Depletion of storage sites.
e.g Reserpine

3. Inhibition of release and enhance uptake.
e.g **Guanethidine**

4. Stimulation of presynaptic a2 receptors
e.g Clonidine & α-Methyl Dopa

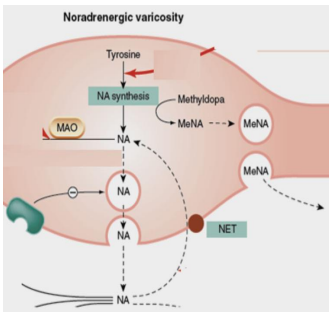
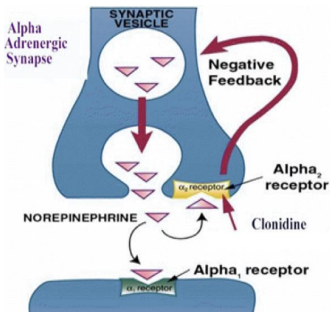
Mneumonic: GMC car
Guanethidine
Methyl-dopa
Clonidine
Apraclonidine
Reserpine
thanks to Abdullah Alomran!

1. Adrenergic Neuron Blocker Drugs

Mechanism	Which step does it interfere with?	Drug
1. Formation of false transmitters	**Step 1** (synthesis)	**α-Methyl dopa**
2. Depletion of storage sites = interferes with NE storage	**Step 2** (storage)	**Reserpine**
3. Stimulation of presynaptic α_2 receptors	**Step 4a** (binding to presynaptic receptors)	**1. Clonidine** **2. α-Methyldopa**
4. Inhibition of release & enhance reuptake	**Step 3** (release) & **Step 5a** (reuptake)	**Guanethidine**

1. Adrenergic Neuron Blocker Drugs continued:

This slide includes 2 examples of adrenergic neuron blockers in detail:
1. a-Methyl Dopa
2. Clonidine & its derivative Apraclonidine

Drug	α-Methyl Dopa مثل الدبة لأنها حامل	Clonidine	Apraclonidine
M.O.A.	**2 Mechanisms:** 1) Centrally acting α_2 adrenergic agonist that inhibits NE release. 2)Forms false transmitter (α-methyl NE) that is released instead of NE. 	Central α_2 receptor agonist to inhibit NE release → suppresses sympathetic outflow activity from the brain → ↓ BP. 	"clonidine derivative" Acts by ↓ aqueous humor formation. ▪ Aqueous humor maintains intraocular pressure.
Use	Drug of choice in treatment of **hypertension** in pregnancy (gestational hypertension & pre-eclampsia). ▪ Very safe in pregnancy as it has no teratogenic effect "تشوه أجنة". ▪ **Pre-eclampsia** (تسمم الحمل): a condition in which problems in the kidney (proteinuria) are associated with hypertension. ▪ **Gestational hypertension:** pregnancy-induced hypertension without proteinuria or end-organ dysfunction.	Little use as an **antihypertensive** drug. ▪ ***Why?*** sudden discontinuation can cause rebound = hypertension due to a rebound in sympathetic outflow. ▪ Thought to be due to down-regulation of α_2 receptors (عددها يقل) after prolonged administration.	Open angle glaucoma as eye drops (topical)

Types of glaucoma:
1) Open-angle: ↑ production of aqueous humor → drugs that ↓ its production
2) Close-angle: ↓ removal of aqueous humor → surgery

2.Adrenergic Receptors Blockers

1a.Selective α_1 antagonists: e.g. Prazosin, Doxazosin, Terazosin

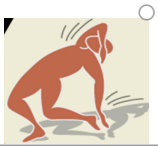
1b. Selective α_{1a} antagonist: e.g. Tamsulosin

2.Selective α_2 antagonists: (presynaptic receptor) e.g.Yohimbine

3.Non-selective α antagonists:
a. Irreversible:Phenoxybenzamine b.Reversible Phentolamine

1a. Selective α_1-receptor Antagonists

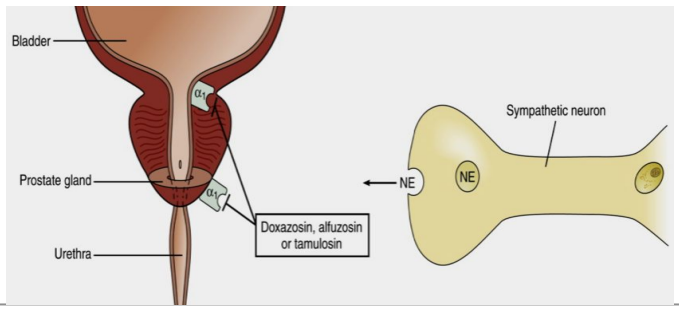
Drug	Prazosin	Doxazosin	Terazosin
M.O.A	Selective α_1-adrenoceptor antagonists		
P.K.	Short half life	Long half life	

Pharmacological Effects	• Vasodilatation
	  ○ Due to relaxation of arterial & venous smooth muscles
	• Fall in arterial pressure
	• Less reflex tachycardia than with non-selective **α** blockers
	  ○ *Why?* Because they block α_1 only. They do not block α_2, so they decrease NE release.(negative feedback)
	• First dose may produce an orthostatic hypotensive response that can result in **syncope** & **fainting** (important side effect لأول جرعة).
	  ○ Hypertensive patients treated with these drugs may develop an exaggerated hypotensive response upon taking the first dose. This may be minimized by adjusting the first dose to ⅓ or ¼. 		

Uses	1. **Urinary obstruction** of benign prostatic hypertrophy **(BPH)**.
	2. Treatment of **essential hypertension** with prostate enlargement.
	  • Essential hypertension: of unknown origin (not secondary).
	  • α-blockers are usually only 2nd-line drugs for the treatment of hypertension, since they do not improve prognosis!
	3. **Raynaud's disease** (vasospasm): causes some areas of the body such as fingers and toes to feel numb & cold in response to cold temperatures or stress.
	  • α_1 blockers will improve blood flow to fingers & toes.		

	1b. Selective α_{1A} Antagonists	2. Selective α_2 antagonists
Drug	**Tamsulosin** تميس ولوزين	**Yohimbine** (Yohim)(bine)(α_2) يو هم بين اثنين

M.O.A.	• **Uroselective**
	  ○ Target α_{1A} receptor present in prostate & neck of bladder & less selective for α_{1B} receptors found in BV.
	• Causes **relaxation** of smooth muscles of bladder neck & prostate → **improves urine flow**.
	• Has **minimal** effect on blood pressure.
	  ○ *Why?* more selective to bladder > BV.
		Increases nitric oxide "NO" released in the corpus cavernosum (male anatomy) thus producing **vasodilator action** and contributing to the erectile process.

Uses	• Treatment of benign prostatic hypertrophy (BPH). • Help with the passage of kidney stones. 	Used as aphrodisiac in the treatment of **erectile dysfunction**. ▪ "Aphrodisiac" = stimulates sexual desire. ▪ Yohimbine is not used clinically nowadays as it has been replaced with phosphodiesterase inhibitors.
ADRs	• Postural (orthostatic) hypotension • Headache • Tachycardia • Nasal stuffiness or congestion • Vertigo & drowsiness caused by the hypotension • Male sexual dysfunction (Inhibits ejaculation) caused by hypotension As with non-selective, but to a lesser degree	

3. Non-selective α-receptor blockers

Drug	Phentolamine	Phenoxybenzamine
M.O.A.	Non-selective antagonists of both α_1 and α_2 receptors	
	Competitive reversible block of both α_1 & α_2 receptors.- Shift to the right.	**Irreversible** blocking of α_1 & α_2 receptors (Forms stable covalent bonds) - No parallel shift.
P.K.	Short acting (4 h)	Long acting (24 h)
Pharmacological Actions	**1- Increase cardiac output (α_2 block).** **2- Decrease peripheral vascular resistance** due to block of a_1. **3- Postural (orthostatic) hypotension.** **"Due to baroreceptor reflex, pull of gravity & reduced BP contribute to low venous return which causes hypotension when standing"** **4- Reflex tachycardia** • **Due to fall in BP, mediated by baroreceptor reflex & due to block α_2 in heart.** • **Baroreceptors are sensors in the aortic arch that sense BP changes & relay this info to the brain. When they sense sudden drop in BP, reflex tachycardia is stimulated.**	
Indication	In **pheochromocytoma**: should be given before surgical removal to protect against hypertensive crisis. • **Pheochromocytoma** is a tumor of the adrenal medulla that causes ↑ release of NE → episodic hypertension, diaphoresis (sweating), headache & palpitations. The tumor may be surgically removed, but it is essential to manage BP before surgery is begun: ○ **Non-selective α-blockers** are the **best** as they produce stronger hypotension. ○ **β-blockers** may be used for additional control (but never alone).	
ADRs	• Postural (orthostatic) hypotension • Headache • Vertigo & drowsiness caused by the hypotension • Male sexual dysfunction (Inhibits ejaculation) caused by hypotension • Tachycardia • Nasal stuffiness or congestion P-palpitations H-headache E-episodic sweating (diaphoresis)	
Contradiction	Patients with decreased coronary perfusion • *Why?* because both drugs can precipitate arrhythmias & angina.	

Mnemonics:

- The drug that has a shorter name "Phentolamine" has a shorter duration of action.
  - Thus, it is used for the diagnosis & short-term management of pheochromocytoma.
- Phenoxybenzamine & Phentolamine are indicated in pheochromocytoma

α blockers in hypertension:

- **Non-selective α blockers** are unsatisfactory in treating hypertension because of their tendency to produce tachycardia, postural hypotension & GIT symptoms.
- **Selective α_1 blockers** are, however, useful. They do not directly affect cardiac function appreciably, and postural hypotension is less troublesome. However, they are not 1st line agents.

Extra: *How does the body overcome the irreversible blockade of receptors by Phenoxybenzamine?*
By synthesis of new alpha receptors, which can take up to 3 days or even longer.

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2.Beta adrenergic blockers

Make sure to take a look at the 1st two pages of the previous lecture before you start.

Pharmacology
TEAM 441

Objectives:

- Outline the mechanisms of action of B-blockers.
- Classify B-receptor blockers into selective & non- selective.
- Know the pharmacokinetic aspects & pharmacodynamic effects of B- adrenergic blockers.
- Identify the specific uses of non selective and selective B -adrenergic blockers.

HELPFUL VIDEO:

Beta adrenergic blockers

Color index:
Important
In male's slides only
In female's slides only
Extra information
Doctors notes

β- Adrenoceptors Blockers

Mnemonics (only for drugs mentioned in this lecture):

- All β-blockers end in **"olol"** except **mixed** blockers → end in **"lol"** only.
- All **cardioselective** β-blockers begin with the letters A→ M

"**E**xclusive **B**eta **B**lockers **A**re **A**cting **M**ainly **C**ardioselectively" → thanks to Abdullah Alomran!

- All **non-selective** β-blockers begin with the letters O→ Z (β_2 = second half of the alphabet).

Pharmaco***dynamic Classification***

According to **selectivity**

Non selective β- Antagonists Blocks β1& β2 receptors **"STOP"** "O → Z"	**Selective β_1 antagonists** (Cardiogenic) "A → M" "ABCEM"	**Mixed β-α Receptors Blockers**
Sotalol	Acebutolol	Carvedilol
Timolol (eye)	Atenolol	
	Bisoprolol	
Oxprenolol	Betaxolol	
Propranolol	Celiprolol	Labetalol
	Esmolol	
Pindolol	Metoprolol	

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

Without ISA (Pure Antagonists)	**With ISA**
Atenolol	Acebutolol
Bisoprolol	
Metoprolol	Pindolol
Propranolol	
Sotalol	Oxprenolol
Timolol	
Carvedilol	Celiprolol

With ISA = may partially activate B receptors

- **Mnemonic:** "**CO**ntain **P**artial **A**gonistic **A**ctivity": **C**eliprolol + **O**xprenolol + **P**indolol + **A**cebutolol
- **Extra note:** Beta-blockers **with ISA** may not be as effective as the pure antagonists in the secondary prevention of MI. They cause less bradycardia & less peripheral vasoconstriction. However, this may be useful in patients who develop symptomatic bradycardia or bronchoconstriction in response to beta-blockers, which makes **ISA** favorable in particular cases.
- Never use ISA drugs with angina or arrhythmia (we do not want any simple stimulation).

According to presence of **membrane stabilizing effects**

Drugs برب البيت إنه ثابت	Effects
Propranolol	- Block Na Channels (makes muscle cells unresponsive to pacemaker stimulation → ↓ excitability → no action potential → ↓ contraction of muscles) - Quinidine-like action (Quinidine is a class of antiarrhythmic drugs) - Antiarrhythmic action
Labetalol	

Pharmaco***kinetic Classification***

	According to lipid solubility	
	Lipophilic (most)	**Hydrophilic**
Oral absorption	Complete → given orally	Irregular → given IV
Liver metabolism Most are excreted in urine	Yes (undergo hepatic clearance)	No (undergo renal clearance)
$t_{1/2}$	Short	Long except Esmolol (10 min. given IV) (rapid action, so used in urgent care, perioperatively, & postoperatively) ايش اسمو؟ اسمو لول
CNS side effects CNS depressant effects i.e. Sedative effect ↓Anxiety	High (e.g. nightmares & insomnia)	Low
Drugs	**M**etoprolol, **L**abetalol, **P**ropranolol, **C**arvedilol, **T**imolol MLPCT (ما لبست)	**B**isoprolol, **A**tenolol, **S**otalol, **E**smolol BASE

To sum up . . .

Drugs: (14)	**Selectivity**	**Sympathomimetic Activity (ISA)**	**Membrane stabilizing effects**	**Lipid solubility**
Sotalol	Non selective β-Antagonists	without ISA	—	Hydrophilic
Timolol		without ISA		Lipophilic
		—		—
Oxprenolol		with ISA		—
Propranolol		without ISA	Present	Lipophilic
Pindolol		with ISA	—	—
Acebutolol	Selective β-1	with ISA		—
Atenolol		without ISA		Hydrophilic
Bisoprolol		without ISA		Hydrophilic
Betaxolol		—		—
Celiprolol		with ISA		—
Esmolol		—		Hydrophilic
Metoprolol		without ISA		Lipophilic
Carvedilol	Mixed nonselective β-α	without ISA		Lipophilic
Labetalol		with ISA	Present	Lipophilic

Pharmacological Actions

CVS

Negative inotropic (force of contraction), chronotropic (HR), dromotropic (conduction velocity) → ↓ COP (cardiac output)

Antianginal effects (ischemic heart disease):	▪ ↓ Heart rate (bradycardia) → ↓ Oxygen consumption due to bradycardia ▪ ↓ Force of contraction → ↓ Cardiac work	Angina patients have coronary vasospasm → ↓ blood flow to heart→ less O_2. Thus, ↑ contraction (e.g. during physical activity) will tire the heart & increase its O_2 demand. B-blockers can reduce myocardial O_2 demand by: 1) Bradycardia 2) Elongating diastole → ↑ coronary flow
Anti-arrhythmic effects:	↓ excitability, ↓ automaticity & ↓ conductivity (due to its sympathetic blocking).	*__Automaticity:__ generation of impulses from the pacemaker *__Conductivity:__ speed at which an e^- impulse propagates.
Blood vessels (β_2):	Block vasodilatory effect of β_2 → ↑ peripheral resistance (PR) → ↓blood flow to organs → cold extremities → contraindicated in peripheral diseases like Raynaud's disease	Raynaud's disease is treated by a_1 blockers
Blood pressure:	Antihypertensive **↓ BP in hypertensive patients due to effects on:** ▪ Inhibiting heart properties → ↓ cardiac output (β1) ▪ β Blockade ↓ renin secretion ↓ Ang II & aldosterone secretion (β1) ▪ Presynaptic inhibition of NE release from adrenergic nerves→ ↓ sympathetic	**Renin** increases BP by 2 main mechanisms: 1) Direct arteriolar vasoconstriction (**Ang II** is the strongest vasoconstrictor mediator in our body) 2) ↑ Aldosterone → ↑ Na & water retention → ↑ blood volume
Eye	↓ Aqueous humor production from ciliary body ↓Reduce intraocular pressure (IOP) ▪ e.g. Timolol as eye drops (mnemonic: time for eye drop) (The only drug from β blockers used for glaucoma)	
Respiratory tract β2	Bronchoconstriction → contraindicated in asthmatic patients. (unless if selective β_1 blockers were given not β_2)	
Metabolic effects & intestine	▪ Hypoglycemia due to ↓ Glycogenolysis in liver & ↓ Glucagon secretion in pancreas ▪ ↓ Lipolysis in adipocytes ▪ All mask hypoglycemic manifestations in diabetic patients → COMA ▪ Na^+ retention 2^{ndry} to ↓BP → ↓ renal perfusion. β blockers ↓ cardiac output, which lowers the BP & ↓ renal perfusion. This will cause renin to be ↑ as a reflex (to restore BP). Renin will ↑ aldosterone, which in turn causes Na & water retention. ▪ ↑ Intestinal motility	

Clinical uses

Cardiovascular disorders :

Cardiac Arrhythmias

- In supraventricular (above ventricles) & ventricular (in ventricles) arrhythmias .
- *Bisoprolol* and *Carvedilol* are preferred
- B-blockers are class II antiarrhythmic agents & are used for tachyarrhythmias only.

Hypertension

- *Propranolol, Atenolol, Bisoprolol*
- Labetalol: α, β blocker in hypertensive pregnant (doesn't harm the baby although it crosses BBB) & hypertensive crisis (because it's given parenterally). [very important]

Angina pectoris

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

Angina: a condition marked by severe pain in the chest, often also spreading to the shoulders, arms, and neck, owing to an inadequate blood supply to the heart.

Congestive heart failure
Heart failure with edema

- *Carvedilol*
- Non selective α,β blocker & antioxidant (an extra effect)
- ↓ myocardial remodeling & ↓risk of sudden death

Myocardial infarction

- ↓ infarct size ↓ morbidity & mortality □ ↓ myocardial O_2 demand.
- Antiarrhythmic action.
- ↓ incidence of sudden death.

Other disorders:

Chronic Glaucoma

- e.g. Timolol as eye drops
- ↓ secretion of aqueous humor by ciliary body.
- ↓ Intraocular pressure (IOP)

Anxiety
(Social & performance type)

- eg. *Propranolol*
- Controls symptoms due to sympathetic system stimulation as tachycardia, tremors, sweating (somatic symptoms)[للقلق علاج نفسي أيضاً؛ هذا للأعراض الجسمانية فقط].

Hyperthyroidism (Thyrotoxicosis)

- Protect the heart against sympathetic over stimulation cause by overproduction of thyroid hormone (thyrotoxicosis)
- Controls symptoms; Tachycardia - Tremors - Sweating
- Propranolol is the drug of choice.

Migraine

- Prophylactic
- ↓ episodes of chronic migraine
- ↓catecholamine-induced vasodilatation in the brain vasculature , e.g. propranolol. A migraine is due to vasodilation

Pheochromocytoma

- **Used with α-blockers (never alone)**
- α-blockers lower the elevated blood pressure
- β-blockers protect the heart from NE.

" A small vascular tumor of the adrenal medulla, causing irregular secretion of epinephrine and norepinephrine, leading to attacks of raised blood pressure, palpitations, and headache "

ADRS of β-blockers

Thanks to Team 439!

Note: if no receptors are written then both receptors are involved.

Mnemonic: C THE BALD FISH

C	• **C**old extremities **(β_2)** → due to vasoconstriction (↓ blood flow). • **C**oronary spasm **(β_2)**→ in variant angina patients *Variant* angina is a type of angina where common atherosclerotic risk factors do not usually apply.
T	• ↑ **T**riglycerides (TG) → Hypertriglyceridemia **(β_2)**
H	• **H**ypotension **(β_1)** • **H**eart failure **(β_1)** • **H**ypoglycemia **(β_2)** • **H**allucinations if the drug was lipophilic
E	• **E**rectile dysfunction & impotence **(β_2)** due to ↓ blood flow (vasoconstriction).
B	• **B**radycardia or heart block **(β_1)** • **B**ronchoconstriction **(β_2)** → contraindicated in asthma & emphysema (Both are less pronounced with β-blockers with ISA)
A	• **A**rrhythmia
L	• **L**ack of energy
D	• **D**epression if the drug was lipophilic • **D**isturbance of GIT
F	• **F**atigue
I	• **I**ntermittent claudication (limping) **(β_2)**→ due to vasoconstriction
S	• **S**odium Retention
H	

- **β_2** adverse effects are only with **non-selective β** blockers.
  - However, the cardioselectivity of β_1 blockers decreases at high doses.
- All **β-blockers** mask hypoglycemic manifestations i.e. tachycardia, sweating → **COMA**.
  - Thus, regular monitoring of blood glucose (especially in diabetic pts) is recommended.

Precautions

- Sudden stoppage will give rise to a withdrawal syndrome: rebound angina, arrhythmia, myocardial infarction & hypertension.
  - *Why?* due to up-regulation of β-receptors (عددها يزيد).
    - Prolonged β blockade can cause a compensatory rise in β receptors. Abrupt termination then leads to increased sympathetic activity (rebound reaction).
- To prevent withdrawal manifestations the drug is **withdrawn gradually.**
  - **Applies to 2 classes of drugs:** β-blockers + corticosteroids.

Propranolol (prototype)

M.O.A.

- Non-selective competitive blocker of β_1 & β_2
- Membrane stabilizing action / quinidine-like / local anesthetic effect
- Sedative actions (because it's lipophilic) / No ISA

P.K.

Lipophilic:

- Completely absorbed
- 70% destroyed during 1st pass hepatic metabolism
- 90-95% protein bound
- Cross BBB
- Excreted in urine
- Given p.o or parenteral

Actions

General

- **Membrane Stabilization:** Block Na channels⟶ direct depressant to myocardium ⟶ has local anesthetic + antiarrhythmic effects. Blocking the Na channels will ↓ the generation of impulses from the pacemaker, so it ↓ arrhythmia & give a local anesthetic action.
- **β-blocking Effect** (antiarrhythmic effects)
- **CNS Effect**: has sedative action, ↓ tremors & anxiety⟶ used to protect against social performance type anxiety.

β1

CVS

- Inhibit heart properties ⟶ ↓ cardiac output
- Anti-ischemic action ⟶ ↓ cardiac work + O_2 consumption
- Antiarrhythmic effects ⟶ ↓ excitability, automaticity & conductivity + by membrane stabilizing activity
- Propranolol has now been replaced by cardioselective β-blockers

β2

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

Bronchi: Bronchospasm specially in susceptible patients

Intestine: ↑ Intestinal motility

Metabolism:

- Liver: ↓ Glycogenolysis⟶ Hypoglycemia
- Pancreas: ↓ Glucagon secretion
- Adipocytes: ↓ Lipolysis
- Skeletal muscles: ↓glycolysis

Peripheral & central nervous systems: local anesthetic effect ↓ tremors & ↓ anxiety

β1 & β2

Antihypertensive action (blood pressure) by:

- Inhibiting heart properties⟶ ↓ cardiac output
- β blockade: ↓ **renin & RAAS system** (renin angiotensin aldosterone system)
- Presynaptic inhibition of NE release from adrenergic nerves
- Inhibiting sympathetic outflow in CNS

Uses

- Hypertension
- Arrhythmias
- Myocardial infarction
- Angina
- Pheochromocytoma; used with α-blockers (never alone)
- Tremors ⟶ can be managed by non-selective β-blockers only as they're caused by β_2..
- Chronic glaucoma
- Migraine [Prophylaxis; to prevent attacks]
- Anxiety: (specially social & performance type)
- Hyperthyroidism ⟶ tachycardia

	Labetalol	Carvedilol
MOA	• Non-selective α_1 & β blocker Ends in "lol" only → mixed • With ISA • Has local anesthetic effect • Rapid acting	• Non-selective α_1 & β blocker Ends in "lol" only → mixed • No ISA & no local anesthetic effect • Antioxidant action Patients who have heart failure have ↓ COP. Normally, when there is a decrease in COP, the sympathetic system gets activated which stimulate β_1 (tachycardia). But because the patient has HF, the heart is exerting more effort than normal which will cause hypertrophy to the heart which will lead to irreversible remodeling or changes in the myocytes. These changes are harmful & ↑ the risk of sudden death. A drug with antioxidant activity ↓ the chance of these changes to occur which ↓ the risk of sudden death.
P.K.	Given **p.o** & **IV**	-
Actions	• Does NOT alter serum lipids or blood glucose • Peripheral vasodilation→ ↓ BP	-
Uses	• Severe hypertension in pheochromocytoma (instead of giving 2 medications to block α & β, labetalol is given because it's non selective) • Hypertensive crisis (e.g. during abrupt withdrawal of clonidine). • Pregnancy-induced hypertension	Congestive heart failure to reverse its pathophysiological changes
ADRs	• Orthostatic hypotension (α_1) • Sedation & dizziness	• Orthostatic hypotension (α_1) • Edema (α_1)

Contraindications of β-blockers

Mnemonic: ABCD
A= Asthma
B= Block (heart block)
C= Vascular disease
D= Diabetes

1. Hypotension
2. Never Alone in **pheochromocytoma** (must be given with α blockers)
   β blockers alone cancel out the vasodilatory effects of β_2 → unopposed α_1 vasoconstriction → hypertension [except β blockers with α_1 antagonism]
3. Bronchial **A**sthma (safer with cardio-selective β-blockers).
4. Heart **B**lock
   β-blockers can precipitate heart block as they cause bradycardia
5. Peripheral vas**c**ular disease (e.g. Raynaud's) (safer with cardio-selective β1 blocker)
6. **D**iabetic patients → Masking of hypoglycemia → GIVEN CAUTIOUSLY

Summary

Thanks to Team 439!

Disorder	Drugs
Hypertension	Atenolol, Bisoprolol, Metoprolol, Propranolol
Cardiac arrhythmia	Propranolol, Esmolol (ultra-short acting), Atenolol*PEA (drugs without ISA)
Congestive heart failure	Metoprolol, Bisoprolol, Carvedilol*MBC
Myocardial infarction	Metoprolol, Atenolol, Propranolol *MAP
Glaucoma	**Timolol**
Migraine prophylaxis Relief of anxiety (social & performance) Thyrotoxicosis	**Propranolol**

Drug	Selectivity	Uses
Propranolol	Non selective β1, β2	Migraine prophylaxis Hyperthyroidism (thyrotoxicosis) Relieve anxiety (social performance)
Timolol	β1, β2	Glaucoma
Atenolol Bisoprolol Metoprolol	β1	Myocardial infarction Hypertension
Esmolol	β1 (Ultra short acting)	Cardiac arrhythmia
Carvedilol	α, β	Congestive heart failure
Labetalol	α, β	Hypertension in pregnancy Hypertensive emergency

SAQs:

Q1: List three adverse effects of **Phenoxybenzamine**.

Q2: A 34-year-old pregnant female was brought to the ER, after investigations she was diagnosed with Gestational Hypertension. What is the drug of choice of this case?

Q3: A 70-year-old male needs to be treated with an α-blocker for overflow incontinence due to his enlarged prostate. Which drug would you suggest to this patient that will not affect his blood pressure significantly?

Q4: Why does the sudden stoppage of β blockers give rise to a withdrawal syndrome?

Q5: List 4 ADRS of β adrenoceptors blockers.

Answers:
A1: Headache, tachycardia, vertigo & drowsiness
A2: α-Methyl Dopa
A3: Tamsulosin
A4: Due to Up-regulation of β-receptors
A5: Bradycardia, Bronchoconstriction, cold extremities, coronary spasm (check p.14 for the rest of them).

Test yourself
From our amazing Qbank team

Click here!

Good luck!

Pharmacology
TEAM 441

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