PHARMACOLOGY
TEAM 439

MED439
KING SAUD UNIVERSITY

β- Adrenergic blockers

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.

Important

In male and female slides

Only in male slides

Only in female slides

Extra information

helpful video

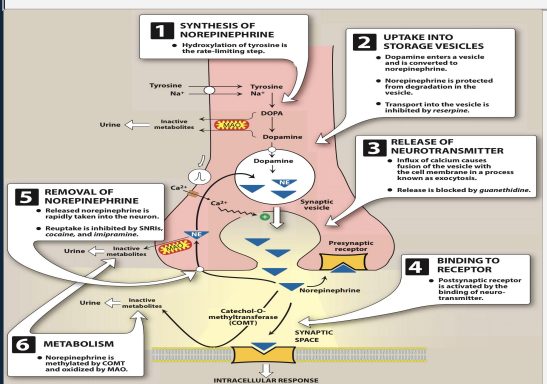
Editing file

REVIEW

For your understanding before studying the lecture

α1	β2	β1	β3
Post-synaptic located in tissue (meaning it is mediated by a neuron which received a signal from a preganglionic neuron by synapsis)			
excitatory in function (cause contraction) except in GIT	Inhibitory in function (cause relaxation)	Excitatory in function , present mainly in heart , juxtaglomerular cells of the kidney	In adipose tissue
Present mainly in smooth muscles			
Contraction of pregnant uterus	Relaxation of the uterus (Delay premature labor) also called tocolytic effect		
Vasoconstriction of skin & peripheral blood vessels →↑ peripheral resistance (resistance to blood flow due to constriction of blood vessels)→ hypertension. Agonists used as nasal decongestants.	Relaxation of skeletal & coronary blood vessels (vasodilatation)	↑ heart rate: chronotropic effect (Tachycardia) ↑ force of contraction : + inotropic effect Increase cardiac output ↑ conduction velocity: + dromotropic effect (via A.V. node)(dromotropic effect means an effect in the speed of conduction of electrical impulses) ↑ blood pressure ↑ renin release (this is an enzyme produced by the kidney in response to stretch receptors found on blood vessels, its function is to increase blood pressure)	↑ lipolysis ↑ free fatty acids
Relaxation of GIT muscles & urinary bladder's muscles. Contraction of GIT sphincter (constipation) & urinary bladder's sphincter urinary retention			
Contraction of radial muscle of eye causes active mydriasis, (dilation of pupil, cholinergic agents have no effect on this muscle)	.Relaxation of bronchial smooth muscles (bronchodilation) .Tremor of skeletal muscles		
↑ blood glucose level (hyperglycemia), by:			
.↑ glycogenolysis	↑ glucagon release from pancreas .↑ liver & muscle glycogenolysis		

α2	β2
Pre-synaptic	
Inhibition of norepinephrine release (negative feedback mechanism) 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 **release** of norepinephrine (Positive feedback mechanism)



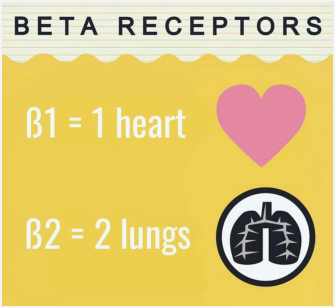
Overview of what goes on inside nerve terminals:

Tyrosine turns into Dopa ⟶ Dopa turns into Dopamine ⟶ Dopamine is stored in vesicles ⟶ inside vesicles dopamine turns into norepinephrine ⟶ release of norepinephrine to the synaptic space is stimulated by an action potential

- Team 439 RESPA block

2-Beta adrenergic blockers & sympatholytic

Overview



Adrenergic depressants (Sympatholytics)

- **Adrenergic receptor blockers**
  - α-adrenergic receptor blockers
  - β-adrenergic receptor blockers
    - Non-selective β e.g **Propranolol**
    - Selective β1 e.g **Esmolol**
    - Selective β2 Respa block
  - α & β -adrenergic receptor blockers
    - Mixed α, β e.g **Labetalol**
- **Adrenergic neuron blockers**
  - Formation of false transmitter
    - e.g **α-methyl dopa**
  - Depletion of storage sites
    - e.g **Reserpine**
  - Inhibition of release & enhance uptake
    - e.g **Guanethidine**
  - Stimulation of presynaptic α2 receptors
    - e.g **clonidine** & **α-methyl dopa**

To help you memorize, drugs that start with the letter:
A→ N = selective except Carvedilol & Labetalol.
O→ Z = non selective
(Only for the drugs mentioned in this lecture)

β- Adrenoceptors Blockers
Pharmacodynamic Classification

*β- blockers can also be classified by generations.

According to selectivity

First generation Non selective β- Antagonists Blocks β1& β2 receptors Mnemonic "STOP"	Second generation Selective β1 antagonists	Mixed α, β receptors blockers
Sotalol	Acebutolol	Carvedilol (α1 adrenergic receptor blockade) (Ca2+ entry blockade) (Antioxidant action)
Timolol (eye)	Atenolol	
	Bisoprolol	
Oxprenolol	Betaxolol	
Propranolol	Celiprolol (increased production of NO) also the drug "Nebivolol" has the same effect. (β2 agonist properties)- Celiprolol only.	Labetalol (α1 adrenergic receptor blockade)
	Esmolol	
Pindolol	Metoprolol	

* The third generation of β- blockers with additional effects . The drugs of this generation include: Labetalol , carvedilol , Tilislol. The drug "Tilisolol" can open the K+ channels (Other effects were mentioned within the table) .

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

Without ISA (pure antagonist)	With ISA (may activate beta receptors) Work as agonist at low doses. APOC ISA= أبوك عيسى
Atenolol	Acebutolol
Bisoprolol	
Metoprolol	Pindolol
Propranolol	
Sotalol	Oxprenolol
Timolol	
Carvedilol	Celiprolol

According to presence of membrane stabilizing effects

Drugs برب البيت انه ثابت	Effects
Propranolol (non selective)	- Block Na Channels (So no action potential→↓excitability of cell→ ↓ contraction of muscles) - Quinidine-like action - Antiarrhythmic action
labetalol	

Pharmacokinetic Classification

According to lipid solubility		
	Lipophilic	Hydrophilic
Oral absorption	Complete	Irregular
Liver metabolism (Most of them excreted in urine)	Yes	No
$t_{1/2}$ Most of them have half-life from 3-10 hrs	Short Rapidly distributed	Long except Esmolol (10 min. given intravenously) (iv) (rapid action 10min) ايش اسمو ؟ اسمو لول
CNS side effects	High cross readily BBB Have CNS depressant actions i.e. Sedative effect which decrease Anxiety	Low
Drugs	Metoprolol - Propranolol – Timolol - Labetalol - Carvedilol	Atenolol – Bisoprolol - Esmolol - Sotalol

Pharmacological actions

CVS

Negative inotropic (Force of contraction) , chronotropic (HR) , dromotropic (Conduction velocity) → ↓ CO (cardiac output)

Antianginal effects (ischemic heart disease):

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

*When the heart beats faster it needs more O2 to pump efficiently. Angina patients have coronary vasospasm (↓ blood flow to heart→ less O2) so increased contraction of the heart will tire the heart because its O2 supply is already low so the heart can't work properly. Which means it's working harder than normal to supply O2 demands to myocytes in order to pump.

Antiarrhythmic effects:

↓excitability, ↓ automaticity & ↓ conductivity (due to its sympathetic blocking).

Automaticity: the process of generating impulses from the pacemaker
Conductivity: the speed at which an electrochemical signal propagates.

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
(Reynaud's disease is treated by a1 antagonist blocker)

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). (↑ Aldosterone → ↑ water retention ↑hypertension) ↓renin →↓B.P
- Presynaptic inhibition of NE release from adrenergic nerves→ ↓ sympathetic

Eye

↓Aqueous humor production from ciliary body ↓Reduce intraocular pressure (IOP)

- e.g. timolol as eye drops (Time for eye drop)
  (The only drug from sympatholytic drugs used for glaucoma)

Respiratory tract β_2

- Bronchoconstriction
- Contraindicated in asthmatic patients.
  (unless if selective β1 blockers were given not β2)

Metabolic effects & intestine

- Hypoglycemia - ↓ Glycogenolysis in liver - ↓ Glucagon secretion in pancreas
- ↓ Lipolysis in adipocytes
- manifestations in diabetic patients →COMA (Because All b–Adrenergic blockers mask hypoglycemia manifestations)
- Na^+ retention 2ndry to ↓BP →↓renal perfusion. β blocker ↓ cardiac output so renal perfusion ↓ which will lead to ↓BP. When renal blood flow ↓ it will cause for Renin to be ↑ as a reflex. This will ↑ aldosterone and cause water retention.(so if β1 didn't block completely, it will cause Na retention)
- ↑ Intestinal motility

Clinical uses

Cardiovascular disorders :

Cardiac Arrhythmias

- In supraventricular (above ventricles) & ventricular(in ventricles) arrhythmias .
- Bisoprolol and carvedilol are preferred

Hypertension

- Propranolol, atenolol, bisoprolol
- Labetalol: α, β blockers in hypertensive pregnant (doesn't harm the baby although it crosses BBB) & hypertensive crisis(because it's given parenterally).

Angina pectoris
الذبحة الصدرية

- ↓ 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.

Myocardial infarction

- ↓ Infarct size ↓ Morbidity & mortality → ↓ myocardial O2 demand

B blockers help your heart beat more slowly & with less force, & they help in opening up veins & arteries which ↑blood flow→ ↓ischemia→ ↓necrotic (infarcted tissue)

- Antiarrhythmic action
- ↓ Incidence of sudden death

Myocardial infarction is due to inadequate blood supply to the heart tissue→ ischemic tissue→ necrosis

Congestive heart failure
Heart failure with edema

- e.g. carvedilol:
- antioxidant and non selective α,β blocker
- ↓ myocardial remodeling & ↓risk of sudden death.

Other disorders :

Glaucoma

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

Anxiety(Social and performance type)

- e.g. Propranolol
- Controls symptoms due to sympathetic system stimulation as tachycardia, tremors, sweating.

تخيلوا شخص عنده رهاب اجتماعي او رهاب مسرح وكل ما سنحت له الفرصة يقول برب (PROPranolol عشان يتهرب منهم.)

Hyperthyroidism
(thyrotoxicosis)

- Protect the heart against sympathetic over stimulation caused by overproduction of thyroid hormone
- Controls symptoms; Tachycardia - Tremors - Sweating

Migraine

- Prophylactic

↓ episodes of chronic migraine
↓catecholamine-induced vasodilatation in the brain vasculature , e.g. propranolol

A migraine is due to vasodilation.

شخص عنده مرض الشقيقة ومن ألمها يمشي ويقول بربك هذا ألم يستحمل!

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 adrenoceptors blockers

Mnemonic: C THE BALD FISH

***Note:** Written next to each ADR is the type of (blocked) receptor causing each ADR, if no receptor is written both β receptors are responsible

C	• Cold extremities (β2) → due to vasoconstriction. Vasoconstriction will ↓ blood flow to extremities so it will lead to cold extremities • Coronary spasm (β2)→ in variant angina (type of angina) patients
T	• ↑ triglycerides→ Hypertriglyceridemia (β2)
H	• Hypotension (β1) • Heart failure (β1) • Hypoglycemia (β2) • Hallucinations if the drug was lipophilic
E	• Erectile dysfunction & impotence (β2) due to ↓ blood flow (vasoconstriction)
B	• Bradycardia or heart block (β1) • Bronchoconstriction (β2)→ contraindicated in asthma,emphysema
A	• Arrhythmia
L	• lack of energy
D	• Depression if the drug was lipophilic • Disturbance of GIT
F	• Fatigue
I	• Intermittent claudication (limping) (β2)→ due to vasoconstriction
S	• Sodium Retention • Sweating
H	

*The uses become side effects when we don't want the actions produced by β blockers to occur.

-β2 adverse effects are only with non selective β blockers
-All β–Adrenergic blockers mask hypoglycemic manifestations i.e. tachycardia, sweating→ COMA
Normally, when hypoglycemia occurs, reflex tachycardia occurs which will indicate to the diabetic patient that he has hypoglycemia, but if β blocker is given tachycardia won't occur and the patient might be hypoglycemic without realizing it which might lead to a coma.

EXTRA
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. It is caused by the narrowing of the artery supplying blood to the leg.
Risk factors of Intermittent claudication:Diabetes, hypercholesterolemia, hypertension

Precautions

Sudden stoppage will give rise to a withdrawal syndrome: Rebound angina, arrhythmia, myocardial infarction & Hypertension

Why? Due to Up-regulation of β-receptors.
لأنه محروم سنين من ال catecholamines فبمجرد ما يصير له unblock الخلايا تصير حساسة لأي كمية من ال NE وتطلع ال receptors ويتأثر الجسم من اي كمية.

How to prevent withdrawal manifestations? drug withdrawn gradually.

Drug		**Propranolol (prototype)**
MAO		• Non-Selective competitive blocker of β1 & β2 • 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	❖ Antiarrhythmic effects • Membrane Stabilization: Block Na channels→ direct depressant to myocardium→ has local anesthetic effect (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 ❖ CNS Effect: Has sedative action, ↓ tremors & anxiety→ used to protect against social anxiety performance anxiety.
	β1	❖ CVS • Inhibit heart properties→ ↓cardiac output • anti-ischemic action→ ↓ cardiac work +O2 consumption • antiarrhythmic effects→ ↓ excitability, automaticity & conductivity + by membrane stabilizing activity.
	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 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 • Angina • Myocardial infarction • Migraine [Prophylaxis] • Pheochromocytoma; used with α-blockers (never alone) • Chronic glaucoma • Tremors • Anxiety: (specially social & performance type) • Hyperthyroidism

Drug	Labetalol	Carvedilol
MAO	• non-selective α1 & β blocker Labetalol = L(α)(beta)LOL so Mixed , blockers • with ISA رجع ISA لبيته • Has local anesthetic effect • Rapid acting	• Non-selective α1 & β blocker CarveDILOL→ DI mean two so mixed blocker • Favorable Metabolic profile • no ISA • no local anesthetic effect. • Antioxidant action. Patients who have heart failure have ↓ CO. Normally, when there is a decrease in CO, the sympathetic system gets activated which stimulate β1(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 to the heart & ↑ 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 and i.v	
Actions	• Does not alter serum lipids or blood glucose • Produce 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 • sedation • dizziness	• Orthostatic hypotension • Edema

Contraindications of β Adrenoceptors blockers

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

1 Bronchial Asthma (safer with cardio-selective β-blockers).

2 Heart Block (β-blockers can precipitate heart block)

3 Peripheral vascular disease like raynaud's disease. (safer with cardio-selective β1 blocker)

4 Diabetic patients→ Masking of hypoglycemia / GIVEN CAUTIOUSLY
β blockers themselves cause hypoglycemia + masks hypoglycemic manifestation.

5 Hypotension

6 Alone in pheochromocytoma (must be given with an α blockers). Because β blockers alone cancel out the vasodilatory effects of β2→ vasoconstriction→ hypertension which we want to prevent.

Summary of β-blockers

Disorder	Drugs
Hypertension	Atenolol, Bisoprolol, Metoprolol, Propranolol
cardiac arrhythmia	Propranolol, Esmolol (ultra-short acting), Atenolol*PEA
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

MCQ

1-Which drug can be used in pheochromocytoma?			
A- α, β blockers	B-β blocker	C-α blocker	D- A & C

2-Which one of the following is true about Carvedilol?			
A-Has ISA	B- Has anesthetic action	C-Selective α_1	D-Has antioxidant action

3-Which one of the following is a contraindication for β2 blockers?			
A-Asthma	B-Anemia	C-Pregnant women	D-Children under 8

4-a drug that is only given i.v and have short half life of 10 minutes?			
A-Bisoprolol	B-Esmolol	C-Sotalol	D-Atenolol

5-Which one of the following should be given to a patient suffering from Anxiety?			
A-Carvedilol	B-Bisoprolol	C-Propranolol	D-Metoprolol

6-What is the main use of Timolol?			
A-Glaucoma	B-Hyperthyroidism	C-Myocardial infarction	D-Migraine

Answers

1	2	3	4	5	6
D	D	A	B	C	A

SAQ

Q1) List 4 Adverse effects of β blockers.

Q2) Why does the sudden stoppage of β blockers give rise to a withdrawal syndrome?

Q3) List some uses of Propranolol.

Q4) List 4 drugs of Lipophilic drugs.

Q5) Which disorder is treated by α and β-blockers? list the actions of each blocker in treating it.

Q6) List the membrane stabilizing effects

Answers

A1) Hypotension,Heart failure, Hypoglycemia,Hallucinations

A2) Due to Up-regulation of β-receptors

A3) Hypertension, Arrhythmias, Angina, Myocardial infarction

A4) Metoprolol ,Propranolol ,Timolol ,Labetalol ,Carvedilol

A5) Pheochromocytoma , α-blockers lower the elevated blood pressure , β-blockers protect the heart from NE.

A6) Block Na Channels , Quinidine-like action , Antiarrhythmic action

GOOD LUCK!

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