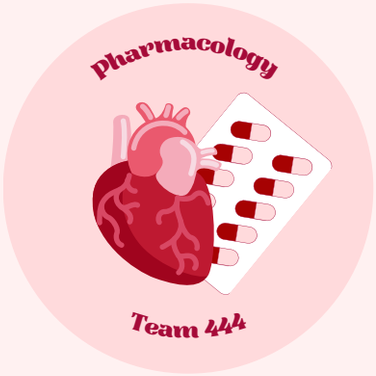
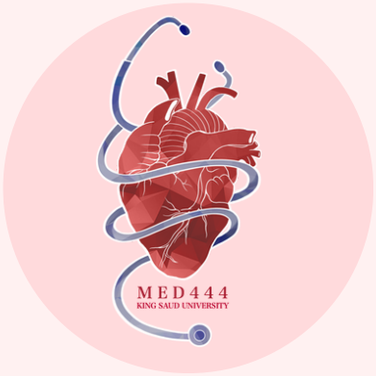
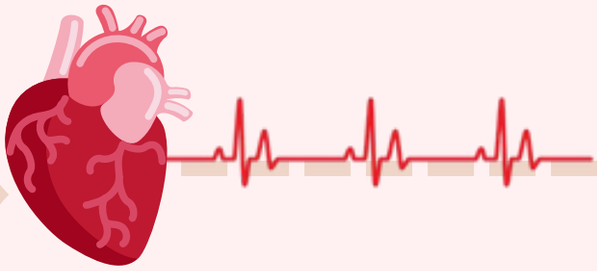




L1.
Alpha adrenergic blockers & sympatholytics

EDITING FILE

COLOR INDEX :
- MAIN TEXT
- IMPORTANT
- GIRL'S SLIDES
- BOY'S SLIDES
- NOTES
- EXTRA



وعندك ألفا ضغطك منهو يرفع؟
ومرض إسمه ريانُد ما يريدك

✍️ علي العبدالعظيم

Objectives:

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

- Intro 0:01 to8:32
- Alpha blockers 8:33
- phenoxybenzamine 11:10
- selective alpha 1 min 20:00
- Tamsulosin min 32:00
- Yohimbine min 42:00

Overview

Adrenergic depressant (Sympatholytics)

Adrenergic neuron blockers: are drugs that prevent the release of noradrenaline from adrenergic nerve ending, thus prevent its interaction with the adrenergic receptors.

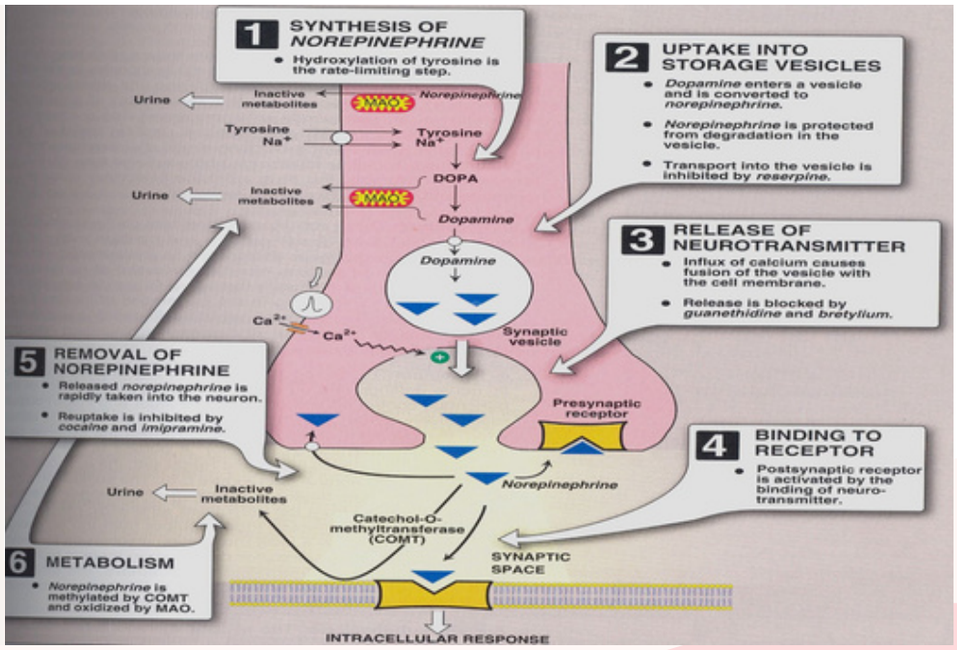
- Depletion of storage site **e.g Reserpine**
- Formation of false transmitters **e.g α-methyl dopa**
- Stimulation of presynaptic α2 receptors **e.g. Clonidine and a-Methyl dopa**
- Inhibition of neurotransmitter release & enhance uptake **e.g. Guanethidine**

Adrenergic receptor blockers: are drugs that prevent the interaction of NA, A and other sympathomimetics with the receptors

- α-adrenergic receptor blockers
  - Non-selective antagonists **e.g. phenoxybenzamine & phentolamine.**
  - α1-selective antagonists **e.g. prazosin, doxazosin.**
  - α1A-selective antagonists **e.g. Tamsulosin**
  - α2-selective antagonists **e.g. yohimbine**
- β-adrenergic receptor blockers
  Will be discussed in the Beta lecture in details

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
4) Binding to receptors;
   a) Pre-synaptic
   b) Post-synaptic
5) removal of NE by either:
   a) Reuptake into neuron
   b) Enzymatic degradation
      - MAO (in mitochondria)
      - COMT (in synapse)



Post-Synaptic receptors (Located in tissues).

Extra Slide(revision of all Adrenergic receptors).

α1	β2	β1	β3
Excitatory in function Causes smooth muscle contraction Except in GIT (Inhibition).	Inhibitory in function Causes smooth muscle relaxation.	Excitatory in function.	In Adipose tissues.
Present mainly in smooth muscles.		Present in -heart(SA,AV,conduction pathways, & myocardial fibrils), -Juxtaglomerular cells of the kidneys.	↑ lipolysis ↑ Free fatty acids
Contraction of uterus (Helps in delivery/Abortion).	Relaxation of uterus (Delay premature labor).	- ↑ Heart rate: Chronotropic effect (Tachycardia) - ↑ Force of contraction: (Inotropic effect) Contraction of ventricles & ↑ Cardiac output - ↑ Conduction velocity: (Dromotropic effect) Pulse is conducted faster causing Tachycarda - ↑ Blood pressure ↑Automaticity & conduction velocity ↑ Renin release: Enzyme released by the juxtaglomerular cells of the kidneys in response to low blood pressure, causing the transformation of angiotensinogen to angiotensin I which in turn stimulates release of aldosterone (Which Causes vasoconstriction & increases BP). This is useful during hemorrhaging to conserve blood	
Vasoconstriction of skin & peripheral blood vessels →increased peripheral resistance resistance to blood flow due to constriction of blood vessels) →hypertension.	Relaxation of skeletal & coronary blood vessels (vasodilatation).		
-Relaxation of GIT muscles (constipation) & Urinary bladder muscles. -Contraction of GIT sphincter & Urinary bladder 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.		
BOTH Increase blood glucose level (hyperglycemia) either by:			
↑ Glycogenolysis → Hyperglycemia.	↑ Glucagon release from pancreas. ↑ Liver & muscles glycogenolysis. ↑ Gluconeogenesis.		

Pre-synaptic receptors (Regulation of Noradrenaline release).

α2	β2
Inhibition of Norepinephrine release (Negative feedback mechanism) This feedback decrease NE when it's elevated.	Stimulation of Norepinephrine release (Positive feedback mechanism) This feedback increase NE release when its levels are low.

Adrenergic neuron blockers:
are drugs that prevent the release of noradrenaline from adrenergic nerve ending, thus prevent its interaction with the adrenergic receptors.

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- Stimulation of presynaptic α2 receptors **e.g. Clonidine and a-Methyl dopa**
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Adrenergic Neuron Blocker Drugs

Drug	reserpine	α-Methyl dopa الحامل مثل الدبه	Clonidine & α-Methyl dopa	Guanethidine
MOA	Interferes with NA storage = Depletion of storage sites	1) Forms false transmitter that is released instead of NE 2) Acts as central α 2 receptor **agonist** to inhibit NE release	Stimulation of presynaptic α2 receptors	Interference with the release of noradrenaline and increases the neuronal uptake of noradrenaline (Inhibition of Transmitter Release)
Use	-	Drug of choice in treatment of hypertension in pregnancy (gestational hypertension & pre-eclampsia).	-	-

Adrenergic Neuron Blocker Drugs

Drug	Clonidine	Apraclonidine (New drug) "clonidine derivative"
MOA	Acts as central α2 receptor **agonist** to inhibit NE release ▪ suppresses sympathetic outflow activity from the brain.	Acts by ↓ decreasing aqueous humor formation. ↓ Sympathetic nervous system → ↓ Aqueous humor •Aqueous humor maintains intraocular pressure.
Use	Little used as antihypertensive agent due to rebound hypertension upon abrupt withdrawal.	used in Open angle glaucoma as eye drops (topical).

Adrenergic Receptors Blockers

CLASSIFICATION OF A-RECEPTOR ANTAGONISTS

Non-selective antagonists
(act in both α1& α2):

-Irreversible: Phenoxybenzamine
-Reversible: Phentolamine

Selective α1 antagonists:

-Prazosin
-Doxazosin
-Terazosin
-Tamsulosin (α1A)

Selective α2 antagonists:

-Yohimbine

Non-selective α-receptor blockers

Drug	Phenoxybenzamine	Phentolamine (safer)
MOA	- Irreversible blocker of both α1 and α2 receptors. - Greater affinity for α1. - Forms covalent bond with the receptor.	- Reversible blocker. - Competitive **antagonist** of both α1 & α2 receptors.
PK	Long acting (24 h)	Short acting (4 h)
Pharmacological Action	1. Vasodilation → Decrease peripheral vascular resistance due to α1 blockade. 2. Postural (Orthostatic) hypotension 3. Reflex tachycardia due to: the fall in B.P mediated by baroreceptor reflex and due to α2 blockade.	
Therapeutic Uses	1.Pheochromocytoma removal: Should be given before surgical removal to protect against hypertensive crisis. "pheochromocytoma is a tumor of the adrenal medulla that causes an excessive release of Adrenaline + NA (synthesized in the medulla), resulting in an overstimulation of α1 receptors, resulting in hypertension" -both can be used but phenoxybenzamine is preferred" • **PHE**ochromocytoma symptoms: • **P**alpitations • **H**eadache • **E**pisodic sweating (diaphoresis) 2.Hypertension 3.Peripheral vascular diseases as Reynaud's disease (vasospasm): • causes fingers and toes to feel numb and cold in response to cold temperature.	
ADR	Orthostatic hypotension (first dose effect) • Reflex tachycardia • Headache, vertigo & drowsiness • Nasal stuffiness or congestion • Male sexual dysfunction (inhibits ejaculation).	
Contraindications	Both drugs can precipitate arrhythmias and angina and are contra-indicated in patients with decreased coronary perfusion	

Adrenergic Receptors Blockers

Selective α1 -receptor Antagonists

Drugs	Prazosin	Doxazosin	Terazosin
MOA	Selective α1 -adrenoceptor antagonists.		
Administration	• Given Orally. • Should be given at night to minimize orthostatic hypotension.		
PK	Short half life	Long half life	
Pharmacological Effects	• Relaxation of arterial and venous smooth muscles → Vasodilatation →reduce peripheral vascular resistance. • Postural hypotension. • Reflex tachycardia (less than non-selective α blockers) due to α1 blockade only. • Relaxation of smooth muscle in the prostate and bladder →increase the urine outflow through the urethra. • It can cause first-dose hypotension, syncope, dizziness, and headache due to: 1-vasodilation 2-vascular smooth muscle relaxation. • Medications should be given at night to minimize orthostatic hypotension.		
Therapeutic Uses	1. **Benign prostatic hypertrophy (BPH)** Benign prostatic hypertrophy (BPH): Men experience urinary obstruction and are unable to urinate, thus leading to urinary retention. α1 specific blockers have been used to relax the smooth muscle in the bladder and enlarged prostate. 2. Treatment of hypertension. 3. Reynaud's disease.		
ADRS	Similar to non-selective alpha blockers • orthostatic hypotension (first dose effect) • Headache • Vertigo & drowsiness • Male sexual dysfunction (Inhibits ejaculation) • Nasal stuffiness or congestion • reflex Tachycardia		

Adrenergic Receptors Blockers

	Selective α1A Antagonists	Selective α2 antagonists
Drugs	**Tamsulosin** تميس ولوزين	**Yohimbine** يوهم بين اثنين (Yohim)(bine)(α2)
MOA	● Is a selective α1A (Uroselective). ● α1A receptor present in prostate & neck of bladder. ● Causes relaxation of smooth muscles of bladder neck & prostate → improves urine flow. ● Has minimal effect on blood pressure.	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).	Used as aphrodisiac in the treatment of erectile dysfunction. "Aphrodisiac" = stimulates sexual desire.
ADRS	As before with non selective but to a lesser degree. ● orthostatic hypotension (first dose effect) ● Headache ● Vertigo & drowsiness ● Male sexual dysfunction (Inhibits ejaculation) ● Nasal stuffiness or congestion ● reflex Tachycardia	-

“ study smarter , not harder “

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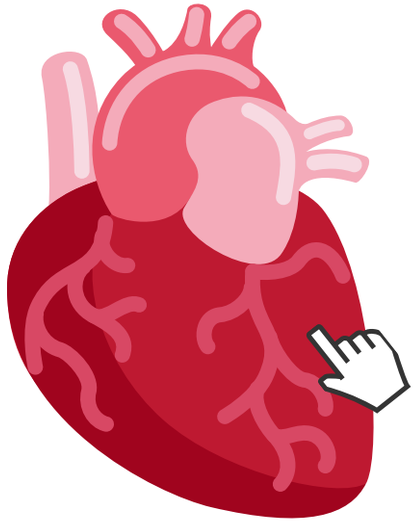
summary



MCQs

1 Which of the following drugs Interference with the transport of noradrenaline into the storage vesicles?

A Clonidine
B Chlorothiazide
C Reserpine
D α-Methyl dopa

2 What is the drug of choice for the treatment of hypertension in pregnancy, including gestational hypertension and pre-eclampsia?

Important

A Reserpine
B phentolamine
C α-Methyl dopa
D Tamsulosin

3 The mechanism of action of α-Methyl dopa involves:

A Blocking calcium channels
B Inhibiting angiotensin-converting enzyme
C Acting as a direct vasodilator
D Acting as a central α2 receptor agonist

4 Which of the following drugs causes rebound hypertension as an adverse effect upon abrupt withdrawal?

A Clonidine
B Chlorothiazide
C Digoxin
D Captopril

Answer
1) C 2)C 3)D 4)A

MCQs

5 People living in extreme cold (-50C) usually take reversible non-selective a-receptor blockers before they sleep to protect them from what? and what drug is used?

A Reynaud's Phentolamine
B BPH Phentolamine
C Reynaud's Phenoxybenzamine
D BPH Phenoxybenzamine

6 A patient was about to have surgery to remove his pheochromocytoma, Doctors were worried he might have a hypertensive crisis so they gave him:

A Infliximab
B Yohimbine
C Phenoxybenzamine
D Minoxidil 5% S.C

7 Patient told his family doctor that he had difficulty urinating, Upon further inspection it was revealed that he had Benign Prostate Hypertrophy. Which of the following is the most appropriate drug for treatment?

A Yohimbine
B Terazosin
C Alprostadil
D Phentolamine

8 The family doctor mentioned above didn't focus in pharmacology lectures when he was a student, the patient had Hypotension which was contraindicated, which of these drugs should you use now? (Uroselective)

A Prazosin
B Terazosin
C Tamsulosin
D Doxazosin

Answer
5) A 6)C 7)B 8)C

SAQs

1 **How does clonidine and α-methyl dopa exert their action as adrenergic neuron blockers?**

Answer: by stimulating presynaptic α2 receptors.

2 **What is the mechanism of action of α-Methyl dopa (ALDOMET) as an adrenergic blocker?**

—Formation of False Transmitters
— Stimulation of presynaptic α2 receptors

3 **Why you should use Phenoxybenzamine for management of Pheochromocytoma?**

Long acting
Irreversible Blocker
Better for management

4 SAQ example question

Class	drug	Selectivity	Action agonist /antagonist	Site of receptor	MOA
adrenoceptor					

answers in the next slide

Important

Class	drug	Selectivity	Action agonist /antagonist	Site of receptor	MOA
Sympatholytics Pre-synaptic	a-Methyl dopa	a2	agonist	CNS Pre-Synaptic	inhibit norepinephrine release
	Colnidine				
Adrenoceptors Post-synaptic	phenoxybenzamine	non selective	antagonist	Pre & Post Synapse	Vasodilation, Decrease peripheral vascular resistance
	phentolamine				
	Prazosin	a1		Vascular smooth muscle	
	Doxazosin				
	Terazosin				
	Tamsulosin (Uroselective)	a1A		Bladder neck & Prostate	Relaxation of smooth muscles of bladder neck and prostate to improve urine flow
Sympatholytics Pre-synaptic	Yohimbine	a2		CNS Pre-synaptic	Increase NO release in Corpus Cavernosum

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