Adrenergic agonist

EDITING FILE

COLOR INDEX :

- MAIN TEXT
- IMPORTANT
- GIRLS SLIDES
- BOYS SLIDES
- NOTES
- EXTRA

Objectives:

- ADRENERGIC TRANSMISSION.
- ADRENERGIC RECEPTORS AND THEIR ACTIONS.
- CLASSIFICATION OF SYMPATHOMIMETIC AGENTS.
- PHARMACOLOGICAL USES OF SYMPATHOMIMETIC AGENTS.

Sympathomimetic Drugs (Adrenergic Agonists)

ARE DRUGS WHICH MIMIC THE EFFECTS OF ENDOGENOUS AGONISTS OF THE SYMPATHETIC NERVOUS SYSTEM.

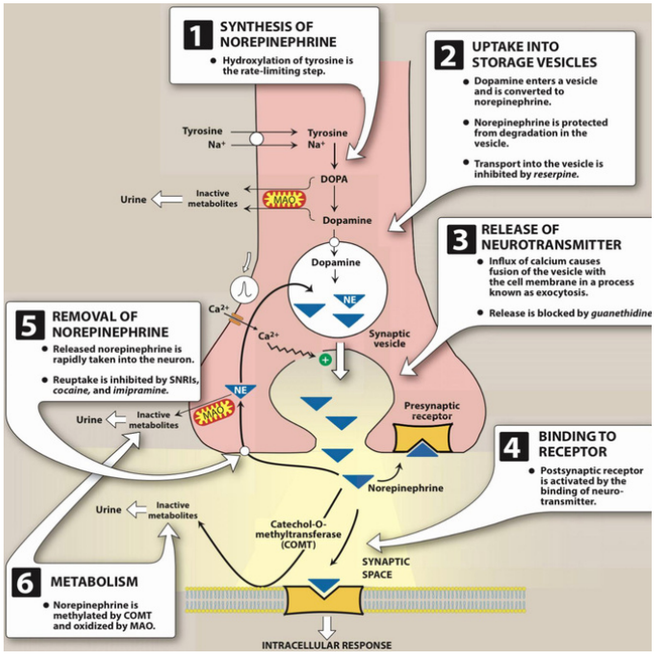
أدوية تحاكي أثر المواد الطبيعية الداخلية للجسم بتأثيرها على الجهاز العصبي السمبثاوي

(NEXT SLIDES ARE IMPORTANT TO UNDERSTAND THE LECTURE)

Adrenergic Transmission

1. Synthesis of norepinephrine
2. Storage of norepinephrine
3. RELEASE OF NOREPINEPHRINE
4. Binding to post synaptic receptors
5. Ending of action- terminate effect by

1-NEURONAL REUPTAKE INTO NEURON
2-MONOAMINE OXIDASE (MAO) IN NEURONAL MITOCHONDRIA
3-CATECHOL -O-METHYL TRANSFERASE (COMT) IN SYNAPTIC SPACE



Dr's note: after NE release -> three possibilities:
1. bind to post-synaptic
2. bind to pre-synaptic
3. reuptake
4. degradation by MAO or COMT

Mono-amine oxidase (MAO):
It's enzyme responsible for the metabolism of catecholamines as adrenaline and serotonin by using the Oxygen to remove an amine group (plus the adjacent hydrogen atom) from a molecule.

Catechol -O-methyl transferase (COMT):
Enzymes that degrade catecholamines (such as epinephrine, and norepinephrine), catecholestrogens, and various drugs and substances having a catechol structure.
وظيفته انه ينقل للأكسجين مجموعة ميثايل CH3
Epinephrine = adrenaline , Norepinephrine = noradrenaline

THANKS TEAM 437

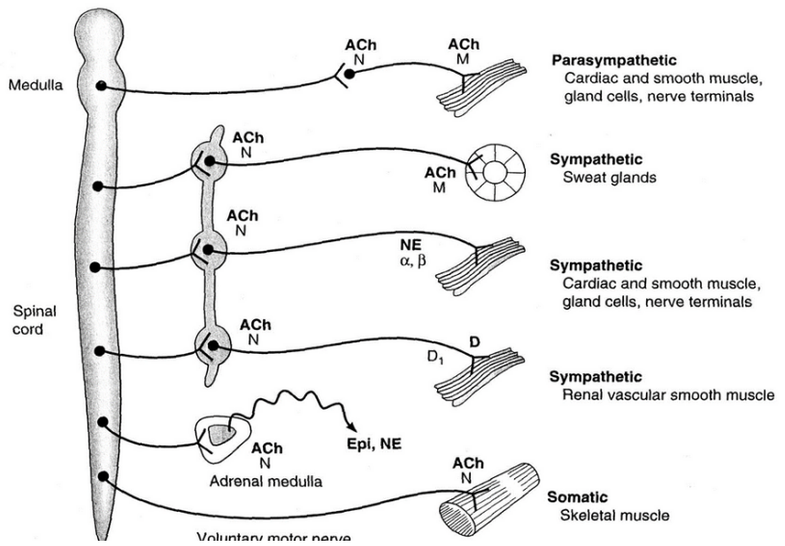
Adrenergic Receptors

ADRENERGIC RECEPTORS

- ALPHA - ADRENOCEPTORS
  - A1
  - A2
- BETA - ADRENOCEPTORS
  - B1
  - B2
  - B3
- DOPAMINERGIC RECEPTORS
  - E.G.D1

Dr's note: Norepinephrine and epinephrine another name-> adrenaline and Noradrenaline, synthesis from adrenal medulla, NE are main neurotransmitter in sympathetic.

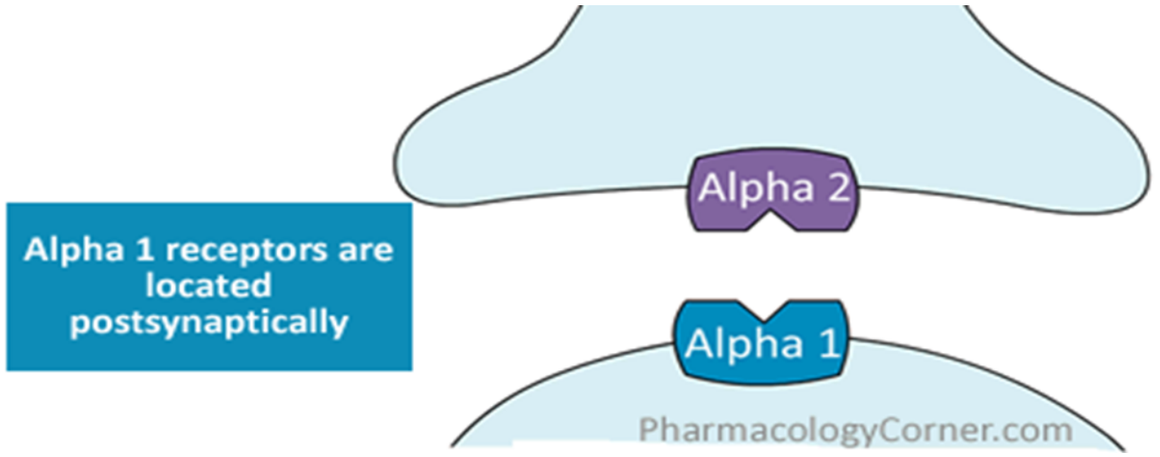
Adrenergic receptors are found in organs innervated by post-ganglionic fibers from sympathetic nervous system, except sweat gland



Location of Receptors

LOCATION OF RECEPTORS

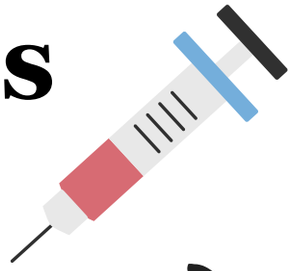
- PRE-SYNAPTIC
  - α2
    Stimulation of it lead to: Inhibition of norepinephrine release and sympathetic system (negative feedback).
  - β2
    Stimulation of it lead to: Increase Release of norepinephrine (NE) & sympathetic stimulation (positive feedback).
- POST-SYNAPTIC
  - A1 , B1 , B2 , B3

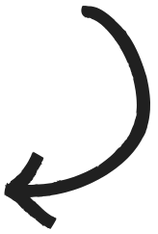


Effects of Post-Synaptic Receptors

α1	β1	β2	β3
Excitatory in function except in GIT (inhibitory)	Excitatory in function	Inhibitory in function	----------
Present in smooth muscles	Present Mainly in heart and juxtaglomerular cells of the kidney	Present in smooth muscles	Present in adipose tissue
Contraction of radial Muscle of eye mydriasis. (Active mydriasis)	Increase heart rate Tachycardia (Chronotropic effect)	Relaxation of skeletal muscles and coronary blood vessels(vasodilation)	Increase lipolysis which lead to increase free fatty acids
Contraction of pregnant uterus (pre-mature delivery)	Increase force of contraction (Inotropic effect)	Relaxation of uterus (Delay premature labor)	
Vasoconstriction of skin & peripheral blood vessels which increases peripheral resistance then lead to hypertension	Increase conduction velocity (Dromotropic effect)	Relaxation of bronchial smoothmuscle	
Contraction of sphincters in GIT & urinary bladder	Increase blood pressure	Relaxation of urinary bladder	
Relaxation of GIT muscles (constipation)		Relaxation of GIT muscles (constipation)	
Increase blood glucose level by: glycogenolysis hyperglycemia	Increase renin release (this is an enzyme produced by the kidney in response to stretch receptors found in blood vessels, its function is increase BP by convert angiotensinogen to angiotensin i then ACE convert angiotensin i to angiotensin ii , and it is in juxtaglomerular cells of the kidney) ACE inhibitors decrease BP	Increase blood glucose level by ↑ Glucagon release from Pancreas ↑ liver and muscle glycogenolysis Hyperglycemia	
		Tremor of skeletal muscle	

All Sympathetic Actions





Mydriasis (dilatation of eye pupil) α1
Increase heart rate β1
Increased blood pressure
Bronchodilation β2
Inhibit peristalsis of GIT and secretion α1 β2
Relaxation of GIT muscles (constipation)
Relaxation of urinary bladder β2
Relaxation of the uterus (Delay premature labor) β2
Increase conversion of glycogen to glucose (hyperglycemia)

Classification of sympathomimetics

They are classified according to : Action & Chemistry & Selectivity

1) ACTION

DIRECT ACTING

Direct stimulation of adrenergic receptors

e.g: adrenaline, noradrenaline, isoprenaline, salbutamol, phenylephrine, dopamine, dobutamine, clonidine, methoxamine, terbutaline.

usually natural

DUAL ACTING MIXED

Direct and indirect stimulation of adrenergic receptors

e.g : ephedrine, pseudoephedrine.

INDIRECT ACTING

1) ↑ NA release from pre-synaptic adrenergic nerve endings.

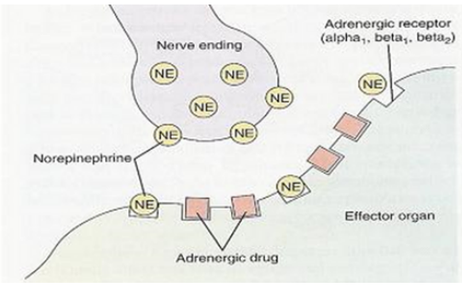
E.g: amphetamine, tyramine.

2) Inhibit NA uptake increase its availability in synapse.

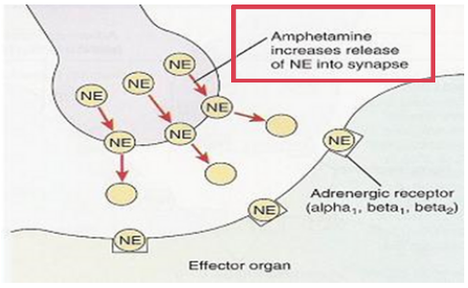
E.g: Cocaine & antidepressants.

يحافظ على وجود NA في sunaptic spaceال

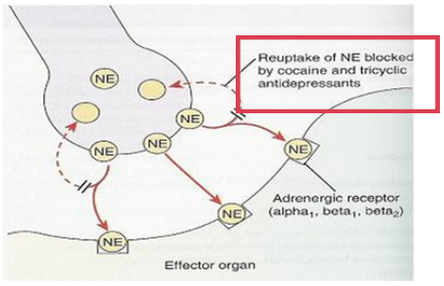
help it survive -



Direct Acting
E.g. Noradrenaline



Indirect Acting
E.g. Amphetamine



Indirect Acting
E.g. Cocaine

2) CHEMISTRY

CATECHOLAMINES

- Have catechol ring
- Water soluble (polar)
- Not effective orally
- Poor penetration into CNS
- Inactivated by COMT & MAO in GIT
- Short half-life

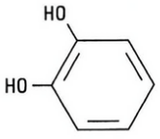
E.g:
Adrenaline, noradrenaline, dopamine, dobutamine, Isoprenaline.

NON-CATECHOLAMINES

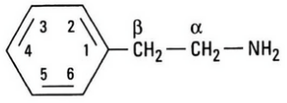
- Lack catechol ring
- Lipid soluble
- Effective orally
- Cross well BBB
- Prominent CNS effects
- Not inactivated by COMT in gut wall
- Long half-life

E.g:
Ephedrine, amphetamine, phenylephrine, salbutamol, ritodrine.

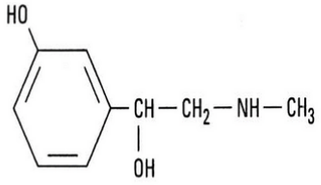
444: OH group make it polar



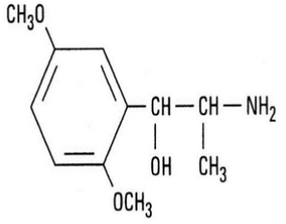
Catechol



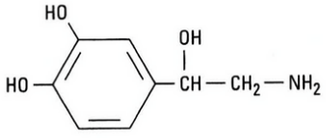
Phenylethylamine



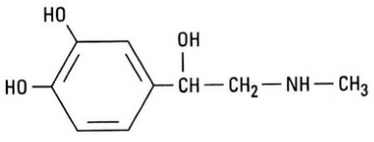
Phenylephrine



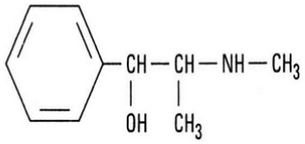
Methoxamine



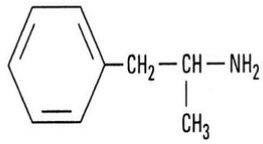
Norepinephrine



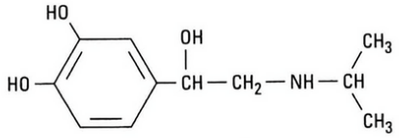
Epinephrine



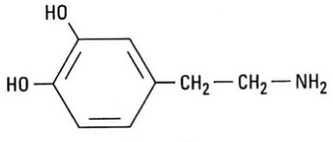
Ephedrine



Amphetamine

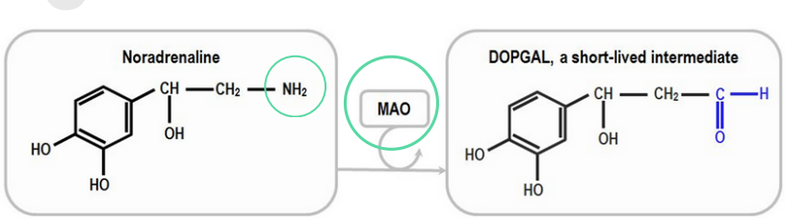


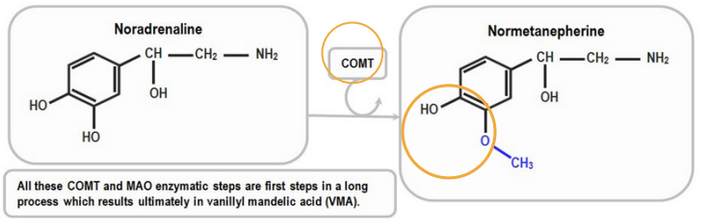
Isoproterenol



Dopamine

Some examples of noncatecholamine sympathomimetic drugs.





MAO works on the amine and converts it, COMT works on the catechol ring and converts it (a catechol ring is the benzene ring with two OH attached).

3) ACCORDING TO SPECTRUM OF ACTION

NON-SELECTIVE ADRENERGIC AGONISTS

Adrenaline (α1, α2 , β1 , β2, β3)

Noradrenaline (α1, α2 , β1)

Isoprenaline (β1, β2, β3)

Dopamine (D1, β1, α1)

SELECTIVE AGONISTS

Phenylephrine - Midodrine (α1)

α-Methyldopa - Clonidine - Brimonidine (α2)

Dobutamine (β1)

Salbutamol - Terbutaline - Ritodrine (β2)

Adrenaline (α1 α2 β1 β2 β3)

classification min 0:01 - 6:30
Adrenaline min 6:31 to the end of the video

Overview	Natural, Catecholamine. Fast onset of action & Short duration of action. Direct Action/ Non-selective **α1 α2 β1 β2 β3.**
Administration	Not effective orally (inactivated by intestinal enzymes). Given parenterally (I.V, S.C), inhalation.
Action	**Heart**: Inotropic, chronotropic (increase HR), dromotropic (β1). **Blood Pressure**: ↑ Systolic (β1) (α1) ↓ Diastolic (β2). **Blood vessels (Vascular smooth muscle cells)**: - Vasoconstriction of blood vessels in skin + peripheral (α1) - Vasodilation of blood vessels of skeletal muscles and coronaries (β2). **Eye**: Mydriasis (α1) → no effect on accommodation. **Lung**: Bronchodilation (β2). **GIT**: ↓ motility (β2) / contract sphincter (α1). **Urinary bladder**: - Relaxation of detrusor muscle (β2). - Contraction of sphincter (α1). **Pregnant Uterus:** Relaxation (tocolytic) effect (β2) (Tocolytic action means relaxation of pregnant uterus). **CNS**: Little (Since it's a catecholamine, it has poor BBB penetration) headache, tremors (trembling or shaking because of vasodilation) & restlessness. **Metabolism**: ↓ insulin (α2) ↑ glucagon (β2). ↑ liver glycogenolysis + ↑ skeletal muscle glycolysis (β2) ↑ Adipose lipolysis (β3).

Use

Locally:

➢ **Haemostatic (control bleeding)**

Nasal packing epistaxis (nasal bleeding) & in dental practice.

➢ **Combined with local anesthetic to:**

↓ Absorption of the local anesthetic and toxicity & ↑ duration of action.

↓ Bleeding from the incision (vasoconstriction reduce blood flow also reduce diffusion of anesthetic to the tissue so it decrease the toxicity).

Systemically:

➢ **In acute asthma**

S.C or inhalation as emergency bronchodilation (β2) + ↓ mucosal edema (α1).

(Selective β2 are better in asthma by inhalation). to reduce side effects

➢ **Anaphylactic shock (Hypersensitivity reactions)**

Is the drug of choice as it is the physiological antagonist of histamine

↑ BP & bronchodilation

➢ **Cardiac arrest (i.v.)**

Not Best choice, selective β1 are better.

physiological antagonist two drugs act on different receptors to produce opposing actions in body, so tend to cancel each other's effect.
Histamine: Vasodilatation (↓ BP) & bronchoconstriction
Adrenaline: Vasoconstriction (↑ BP) & bronchodilation.
Special thx to 444 foundation team <3

ADR

- Tachycardia, palpitation, arrhythmias
- Headache, anxiety, restlessness, weakness and tremors.
- Hypertension → cerebral hemorrhage and pulmonary edema.
- Coldness of extremities → tissue necrosis (Vasoconstriction of skin vessels α1)

contraindication

- Arrhythmia, coronary heart diseases (CHD), Ischemic heart disease
- Hypertension, peripheral arterial disease.
- Hyperthyroidism (it increase thyroid hormone)
- Closed-angle glaucoma (ciliary relaxation decrease filtration angle) lead to increase Intraocular Pressure

Noradrenaline

Overview	It is naturally released from postganglionic adrenergic fibers. Catecholamine, non-selective agonist.
Receptors	Mainly on α adrenoceptors (α1, α2, β1) Weak action on β2.
Administration	ONLY administered by I.V may cause necrosis using IM or SC.
Action	• Severe vasoconstriction (α1). • Reflex bradycardia due to severe Vasoconstriction. • Increase force of contraction (inotropic effect) but decrease heart rate.
Use	• **Locally** haemostatic with local anesthetic. • **Systemically** hypotensive states (in septic shock “hypotension” if fluid replacement and inotropes fail).

-noradrenaline min 0.01 - 11:00
- Dopamine min 11:10
-Dobutamine min 26:21
-beta 2 agonists min 31:30
- Isoprenaline min 42:01
- selective alpha min 44:26
- Clonidine min 54:00

Isoprenaline

Overview	• Synthetic, direct acting catecholamine. • Longer effect (no reuptake -no destruction by **MAO**-).
Receptors	Non-selective β agonist (β1, β2, β3).
Administration and use	• Parenteral used mainly in cardiac arrest. • Inhalation rarely in acute attack of asthma.
Action	• **β1:** - Inotropic effect - Chronotropic effect - Increase cardiac output • **β2:** - Vasodilation of blood vessels of skeletal muscles and coronaries -Bronchodilation - Relaxation of uterus - Hyperglycemia • **β3:** - Lipolysis
Uses	• Used mainly in cardiac arrest (Parenteral). • Rarely in acute attack of asthma (inhalation).
Contraindication	Contraindicated in hyperthyroidism & CHD (Congenital heart disease)

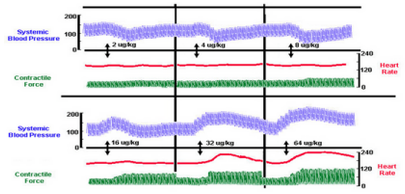
Dopamine

Overview

- It is a Natural CNS neurotransmitter, a precursor to norepinephrine in noradrenergic nerves.
- Direct acting catecholamine.

Receptors

D1 > β1 > α1
(in order, depending on dose)



Administration

Given parenterally by infusion

Action

- **Low dose** (Dopaminergic Receptor D1):

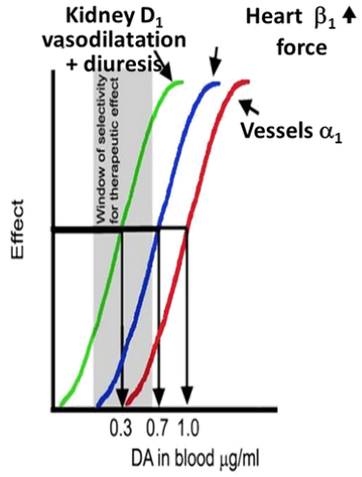
Vasodilatation of mesenteric, coronary and renal blood vessels (Thus improves blood flow to viscera) Has diuretic action.

- **Intermediate dose (β1):**

+ve inotropic (increase contractility).
+ve chronotropic (increased heart rate).

- **High dose (α1):**

Vasoconstriction
On heart → inotropic, chronotropic effect.
On BP → according to the dose:
First ↓ BP due to (D1)
Then ↑ increase BP due to (β1) followed by (α1) effect.



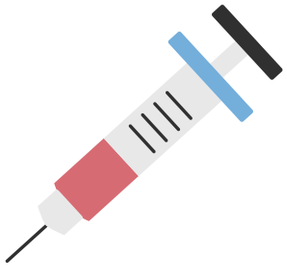
Use

- **Cardiogenic shock:**

septic, hypovolemia or cardiogenic (I.V infusion)
↑ BP & CO (β1) without causing renal impairment (D1)

- **Can be given in acute heart failure (HF)** but better to use dobutamine

	Dobutamine	Phenylephrine
Overview	• Synthetic Direct acting catecholamine • Metabolized by COMT, which gives it a short duration of action.	Synthetic Direct acting NON-catecholamine Is NOT Metabolized by COMT, which gives it a longer duration of action.
Administration	IV infusion	Topically
Receptors	**Selective β1–agonist**	**Selective α1–agonist**
Action	• Positive (desirable) inotropic effect which increase heart contractility • Increases cardiac output	• Vasoconstriction • Increases systolic & diastolic blood pressure (cause hypertension) due to vasoconstriction (α1) • Reflex Bradycardia (In case of hypotensive patient we use Midodrine instead; as it has shorter duration)
Uses	• Short term management of Cardiac decompensation after cardiac surgeries. • In Acute myocardial infarction (AMI) & heart failure.	• Nasal decongestant (topically) • Nasal drops : allergic rhinitis and cold • Vasopressor agent: hypotension & terminate atrial tachycardia (reflex bradycardia). • Local Hemostatic with local anesthesia • Mydriatic : In ophthalmic solutions to facilitate eye examination. **Adverse effect :** Hypertension
Midodrine	peaks in 20 min, duration 30 min, used mainly In **hypotensive states.**	



ADRENERGIC STIMULANTS
DIRECT ACTING SYMPATHOMIMETICS
NASAL & OCULAR DECONGESTANTS

- PHENYLETHYLAMINES
  - Phenylephrine
  - Pseudoephedrine
  - Methoxamine
- IMIDAZOLINE
  - Naphazoline
  - Oxymetazoline HCI (Afrin)
  - Xylometazoline HCI (Otrivine)

Focus on selective drug

Selective β2 agonists

	Salbutamol	Ritodrine	Terbutaline
Overview	• non catecholamines • **Administration:** orally or by inhalation or injection.	• non catecholamines • **Administration:** orally or by injection	Direct acting
Action	Produce Bronchodilation	tocolytic drug (relaxation of uterus).	Bronchodilator and Tocolytic
Use	Acute attack of Asthma & COPD	premature labor	

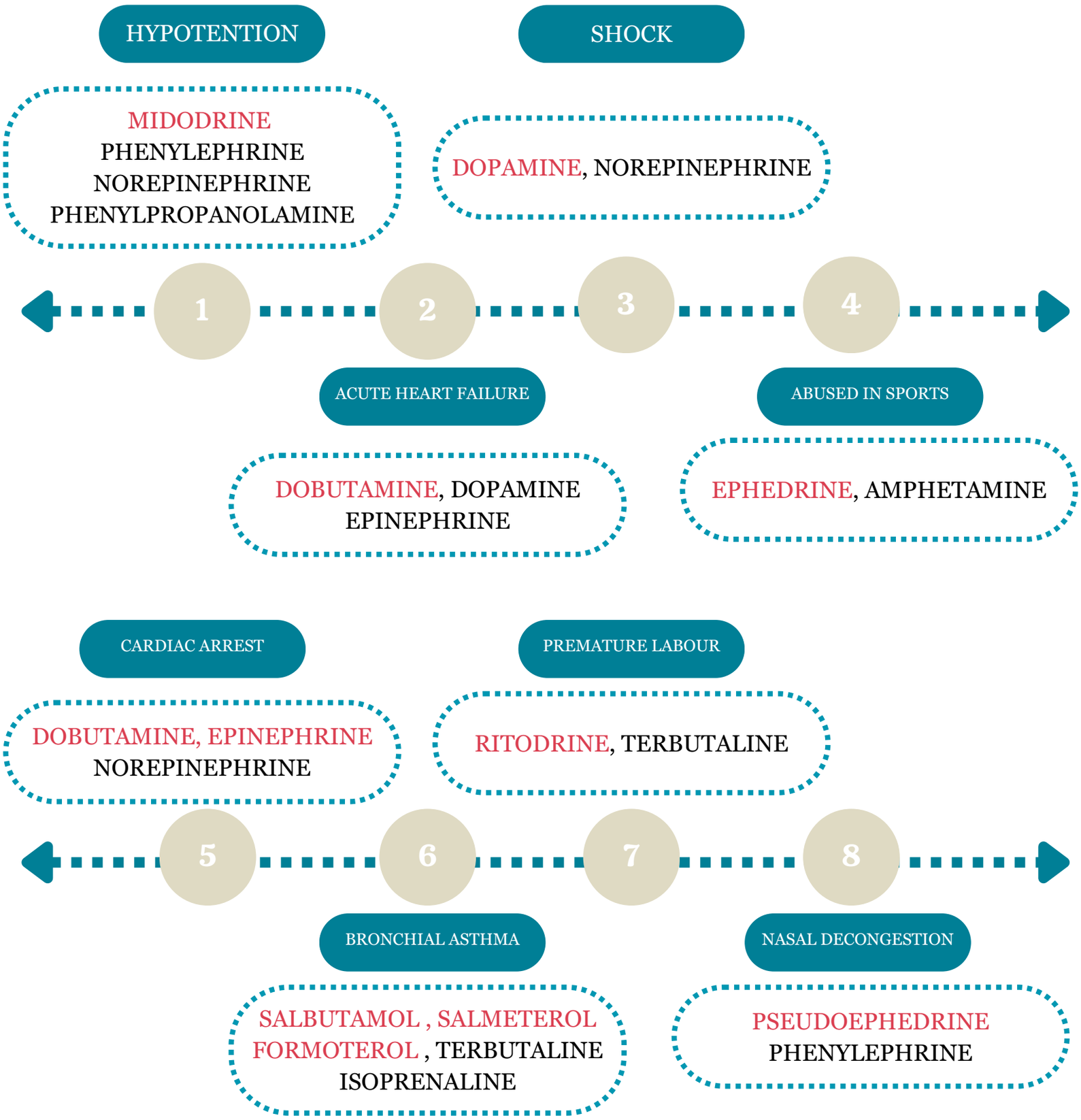
Selective α2 Agonist (presynaptic)

	Clonidine	Brimonidine
Overview	Synthetic, Direct acting. **Administration:** orally or patch	
Action	• Acts centrally (α2) at nucleus tractus solitarius to lower sympathetic outflow to heart & vessels. • Inhibits sympathetic vasomotor centers*. **Presynaptic (α2) agonists**	Reduce aqueous humor production by the ciliary body).
Use	As antihypertensive in essential hypertension to lower BP.	Used in glaucoma

	Indirect Acting Sympathomimetics	Dual Acting Sympathomimetics	
	Amphetamine	Ephedrine	Pseudoephedrine
 amphetamine min 0:01 - 9:00 Dual min 22:00 **Classification**	Synthetic, Non-catecholamine. Exerted mostly unchanged (Increases with acidification of urine).	Plant alkaloid, synthetic, Non-catecholamine.	———————
Administration	Orally; since they're Non-catecholamines. Enzymes can't destroy them -> Longer duration.		———————
Action	Acts Indirectly, it depletes vesicles from stored NE leading to tachyphylaxis.	Directly on receptors. Indirectly by releasing NE from adrenergic endings → depletes stores. Tachyphylaxis.	————————

Effect	• **CNS stimulant effects;** mental alertness, wakefulness, concentration & self-confidence followed by depression & fatigue on continued use. • E**uphoria** → Causes abusing. • ↓ **Weight** by: ↓appetite & ↑energy expenditure.	**CNS stimulant effects** (less than Amphetamine)	- **Vasoconstriction**, mainly Nasal vessels → reducing nasal congestion.
count..Use	No more therapeutically used. (induces psychic & physical dependence and psychosis).	No more therapeutically used, but Athletes abuse (prohibited during games).	- As nasal & ocular decongestant. - In flu remedies.
Receptor	**α & β**	α & β	----------

Summary for uses of sympathomimetics

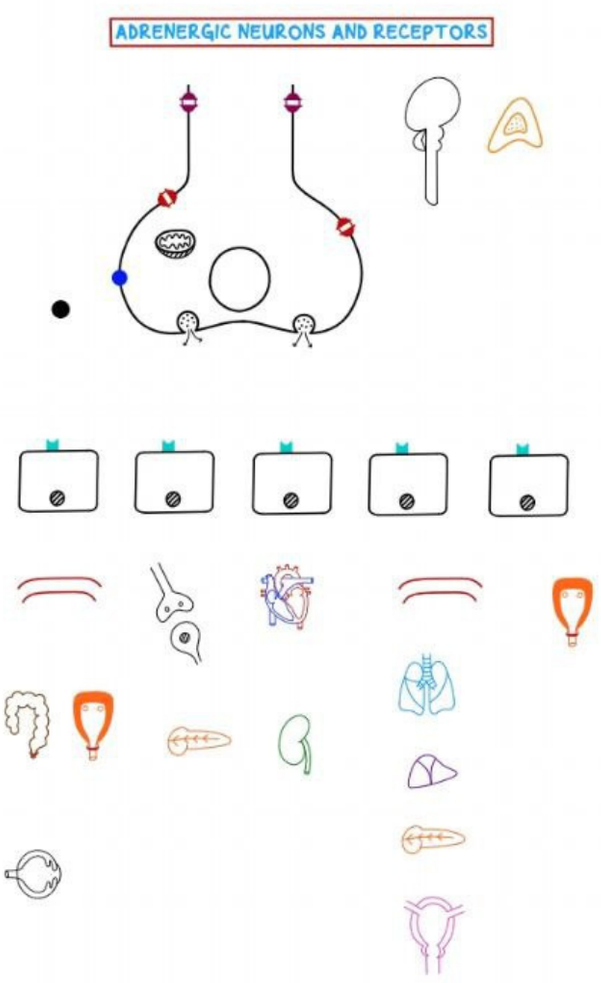


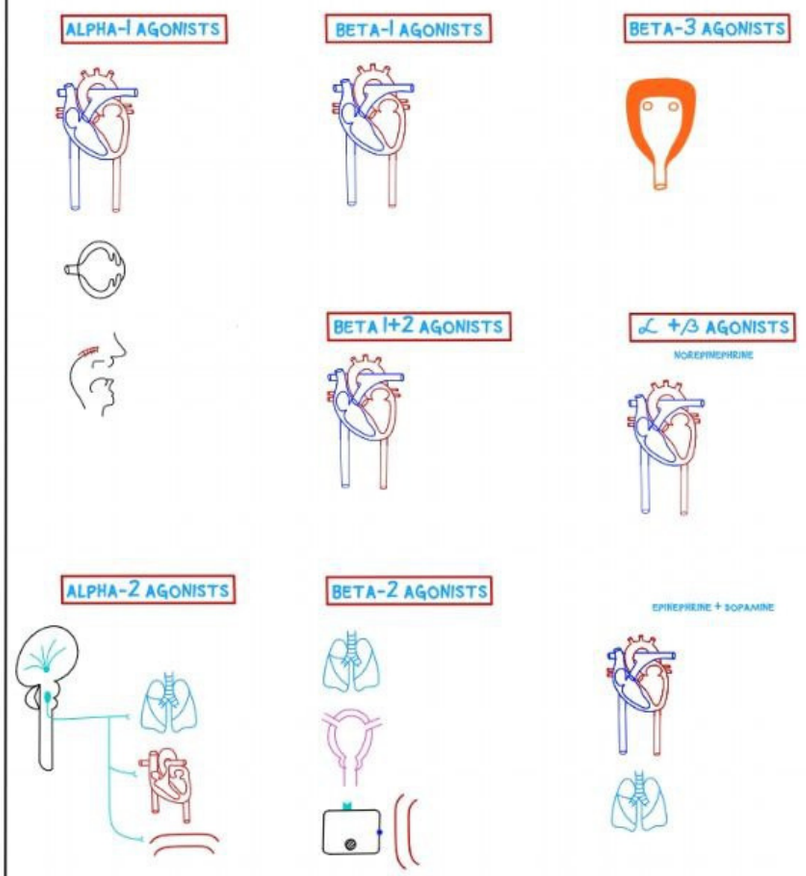
Summary

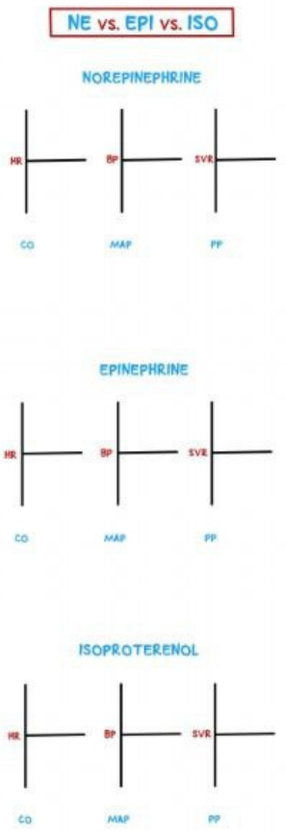
Drug	Receptor	Uses
Adrenaline	α1, α2, β1,β2, β3	-Combined with local anesthetic-Haemostatic (Stops bleeding)-In acute asthma-Anaphylactic shock-Cardiac arrest
Noradrenaline	α1, α2, β1,weak β2	-local haemostatic with local anesthetic to reducetachycardia.-in septic shock (after fluid replacement)
Isoprenaline	β1, β2, β3	-cardiac arrest (preferred)-Rarely in acute attack of asthma
Dopamine	D1 > β1 > α1(in order)	-Treatment of shocks: septic, Hypovolemic (after fluidreplacement), cardiogenic (I.V)
Dobutamine	β1	- Short term management of Cardiac decompensation.- Acute myocardial infarction(AMI) & heart failure.
Phenylephrine	α1	- Vasopressor (anti-hypotensive)- Haemostatic with Local anesthesia.- Mydriatic- Nasal decongestant
Salbutamol	β2	- Acute attack of asthma & COPD.
Ritodrine	β2	-Treat premature labor.
Terbutaline	β2	__
Clonidine	α2	-Antihypertensive
Brimonidine	α2	-Glaucoma treatment
Amphetamine	__	No more used therapeutically
Ephedrine	__	No more therapeutically used but is abused by athletes
Pseudoephedrine	__	- Nasal & ocular decongestant- In flu remedies.

Ninga Nerd illustration

If you wanna watch ninja nerd then follow with him on this template then test yourself and check answers at next slide





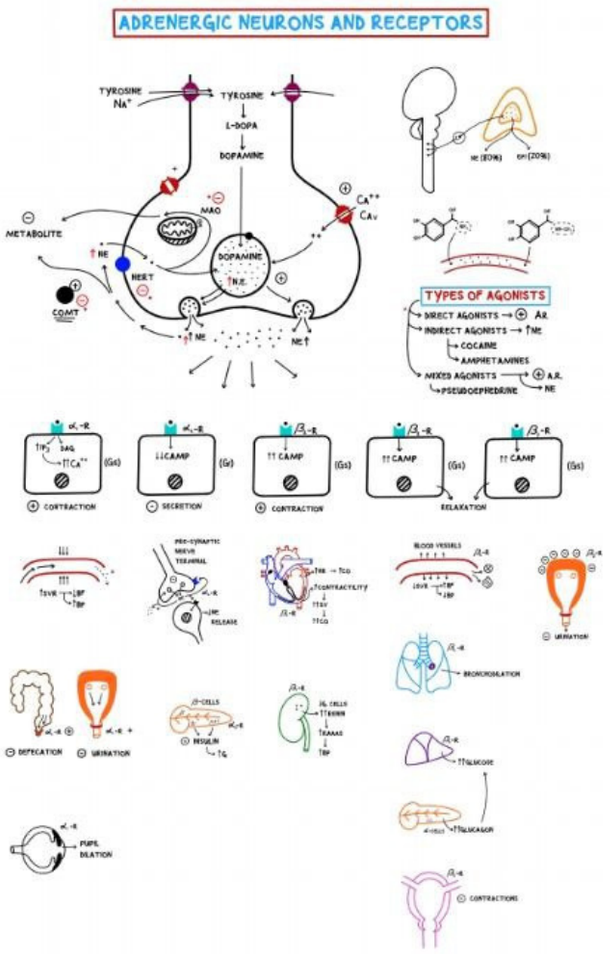


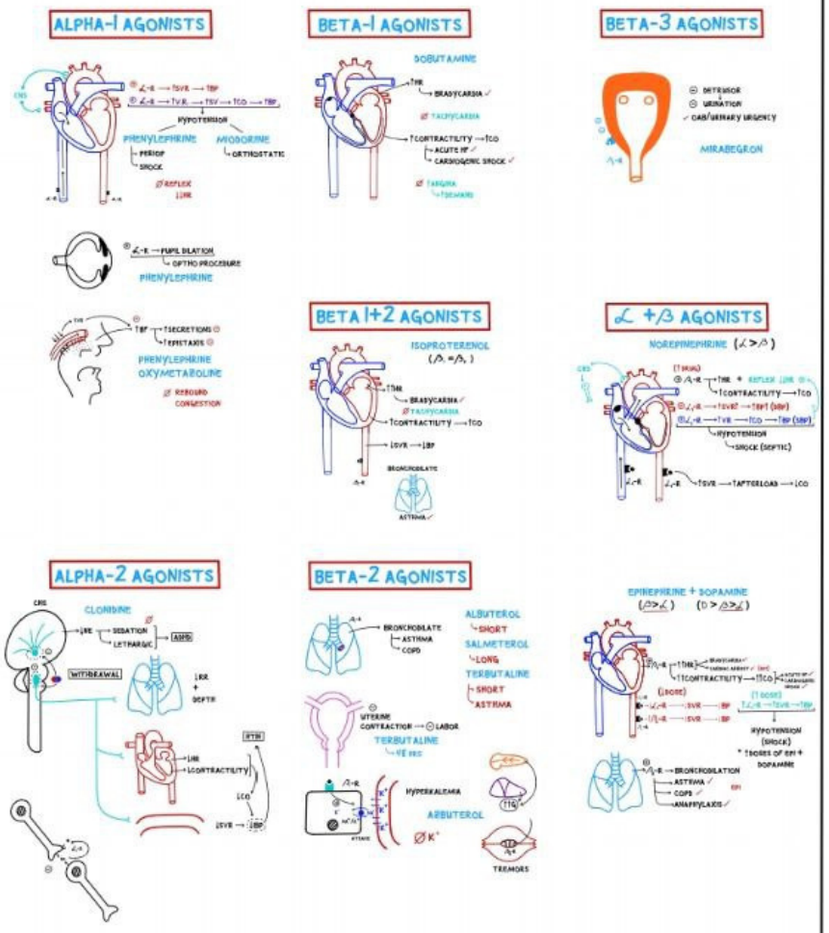
ADRENERGIC AGONISTS

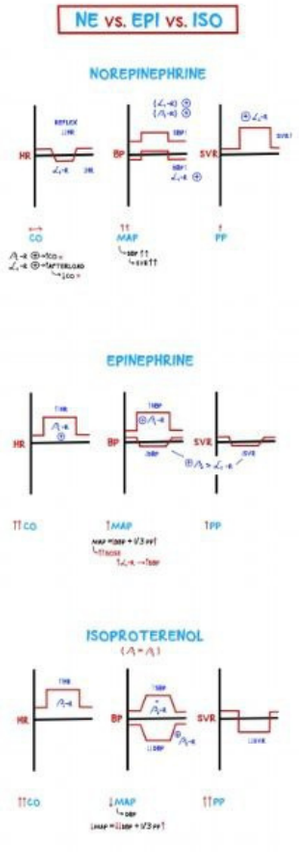
NINJA NERD

Ninga Nerd illustration

EXTRA INFO







ADRENERGIC AGONISTS

dk @drukkolorukkolo

NINJA NERD

“ study smarter , not harder “

Active recall

For Anki flash cards click the icon

Take active quizzes in our team channel to test your understanding.

click the icon to get free flash cards

summary

MCQs

1 A 62-YEAR-OLD MAN STARTED ON A NEW MEDICATION FOR THE MANAGEMENT OF HYPERTENSION. THE NEW DRUG ACTS AT PREJUNCTIONAL (A2)-AGONISTS RECEPTORS WHICH OF THE FOLLOWING MEDICATIONS WAS PRESCRIBED?

- **A** CLONIDINE
- **B** DOBUTAMINE
- **C** DOPAMINE
- **D** METAPROTERNOL

2 A 77-YEAR-OLD MAN HAS A CARDIAC ARREST WICH OF THE FOLLOWING IS THE BEST DRUG OF CHOICE?

- **A** DOPAMINE
- **B** ADRENALINE
- **C** NORADRENALINE
- **D** DOBUTAMINE

3 ALL OF THE FOLLOWING DRUG HAS DIRECT MECHANISM OF ACTION EXEPT?

- **A** DOPAMINE
- **B** PHENYLEPHRINE
- **C** ISOPRENALINE
- **D** TYRAMIEN

4 8 YEARS OLD BOY HAS AN EPISTAXIS NASAL WICH OF THE FOLLOWING IS THE BEST FRUG OF CHOICE?

- **A** ADRENALINE
- **B** DOPAMINE
- **C** PHENEYEPHRINE
- **D** TERBUTALINE

1)A 2)D 3)D 4)A

MCQs

5 WHAT DRUG WOULD THE NURSE EXPECT TO ADMINISTER IF BETA-SPECIFIC ADRENERGIC AGONIST EFFECTS ARE DESIRED TO PREVENT BRONCHOSPASM DURING ANESTHESIA?

A RITODRINE **B** SALBUTAMOL **C** NAPHAZOLIN **D** ATROPIN

6 WICH OF THE FOLLOWING IS AN ADR OF ADRENALINE ?

A BRADYCARDIA **B** HYPOTENSION **C** HYPERTENSION **D** FEVER

7 A PATIENT TAKES A STIMULANT THAT PRODUCES EUPHORIA, AS WELL AS AN INCREASE IN HEART RATE AND BLOOD PRESSURE. TO EXERT ITS EFFECTS, THIS DRUG MUST BE TAKEN UP INTO NERVE TERMINALS WHERE IT STIMULATES THE RELEASE OF NOREPINEPHRINE & DOPAMINE FROM THEIR VESICULAR STORAGE SITES. THIS DRUG IS:

A AMPHETAMINE **B** COCAINE **C** NICOTINE **D** KETAMINE

8 A12-year-old boy with a peanut allergy is brought to the emergency room after accidental consumption of peanuts. He is in anaphylactic shock. Which of the following drugs is most appropriate to treat this patient?

A Norepinephrine **B** Phenylephrine **C** Dobutamine **D** Epinephrine

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

SAQs

1. **Enumerate selective beta-2 agonist?**

   Salbutamol, terbutaline, ritoderine

2. **What causes cerebral hemorrhage?**

   Adrenaline

3. **Describe the mechanism of action for dopamine ?**

   slide 15

4. **Best drug of choice in glaucoma?**

   Brimonidine

Team leaders

Ritaj Alsubaie **Raseel Aldajany**

Eyad Alzubaidi

Team members

Madaen Alarifi

Haya Alateeq

Noreen Almarabah

Janan Alsayari

Norah Alnoshan

Alanoud alnajawi

Sahar Alfallaj

Samiyah sulaiman

shaden Alotaibi

Ali Al-Abdulazem

Waleed Alanazi

Abdulaziz Sahhari

Abdulrahman Almalki

khalid Alghamdi

Abdulaziz Alanazi

Abdulrahman Alnafisah

Abdullah Alzoom

Ahmed Alabbad

Contact us at : pharmacology.444ksu@gmail.com