Adrenergic Agonists

•Red : important
•Black : in male / female slides
•Pink : in female's slides only
•Blue : in male's slides only
•Green: Females doctor notes
•Grey: Males doctor notes/ extra explanation

OBJECTIVES:

- By the end of this lecture , you should be able to:

✓ classify adrenergic agonists according to chemical

✓ structure, receptor selectivity and mode of action.

✓ Discuss pharmacodynamic actions, ADRs, indications and contraindication of adrenergic agonists.

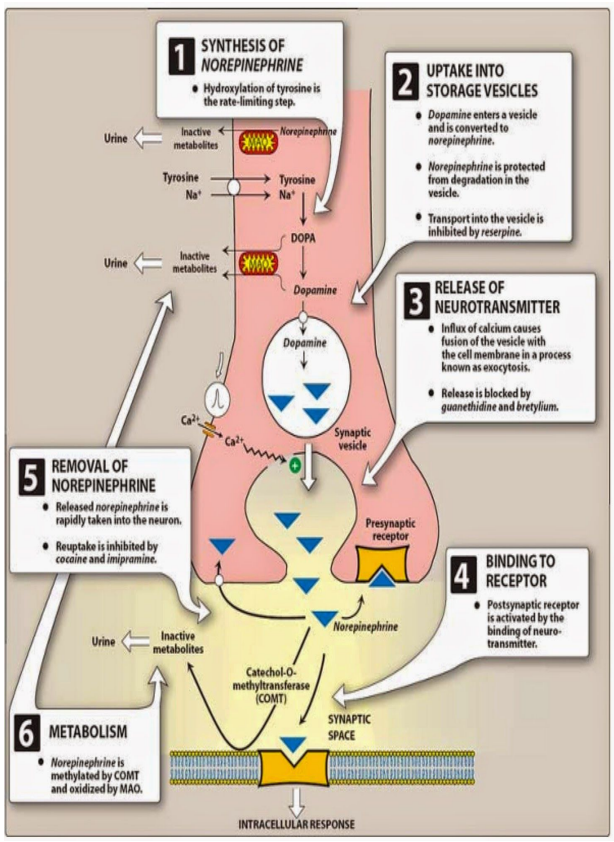
Editing File

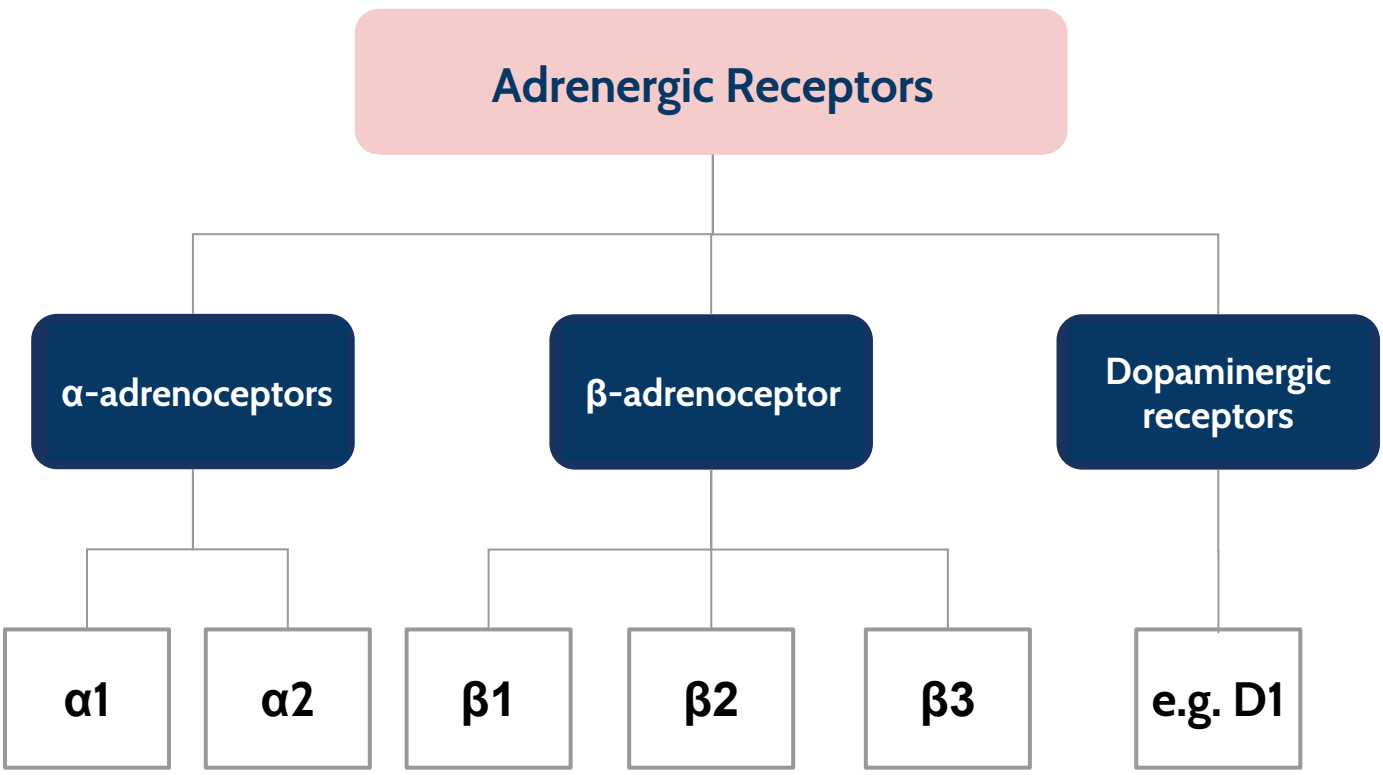
Neurotransmission at adrenergic neurons

Adrenergic transmission:

1) Synthesis of norepinephrine
(hydroxylation of tyrosine → rate limiting step)
2) Storage of norepinephrine in vesicles
3) Release of norepinephrine
4) Binding to post-synaptic receptors
5) Ending of action by:

- Neuronal reuptake into neuron
- Monoamine oxidase (MAO) in neuronal mitochondria
- Catechol-O-methyltransferase (COMT) in synaptic space





VERY IMPORTANT TO ACQUIRE AN ADEQUATE UNDERSTANDING OF THE LECTURE

<table>
<tr><th>α1</th><th>β2</th><th>β1</th><th>β3</th></tr>
<tr><td colspan="4">Post-synaptic located in tissue
(meaning it is mediated by a neuron which received a signal from a preganglionic neuron by synapsis)</td></tr>
<tr><td>excitatory in function
(cause contraction)
except in GIT</td><td>inhibitory in function
(cause relaxation)</td><td>excitatory in function, present mainly in heart, juxtaglomerular cells of the kidney</td><td>In adipose tissue</td></tr>
<tr><td colspan="2">Present mainly in smooth muscles</td><td rowspan="8">↑ heart rate: chronotropic effect (Tachycardia)

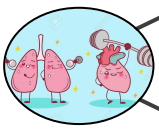
↑ force of contraction :
+ inotropic effect
Increase cardiac output
↑ conduction velocity:
+ dromotropic effect
(via A.V. node)(dromotropic effect means an effect in the speed of conduction of electrical impulses)

↑ blood pressure

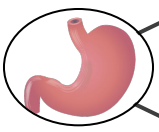
↑ renin release
(this is an enzyme produced by the kidney in response to stretch receptors found on blood vessels, its function is to increase blood pressure)</td><td rowspan="8">↑ lipolysis

↑ free fatty acids</td></tr>
<tr><td>Contraction of pregnant uterus</td><td>Relaxation of the uterus (Delay premature labor)
also called tocolytic effect</td></tr>
<tr><td>Vasoconstriction of skin & peripheral blood vessels → increased peripheral resistance (resistance to blood flow due to constriction of blood vessels)→ hypertension. Agonists used as nasal decongestants.</td><td>Relaxation of skeletal & coronary blood vessels (vasodilatation)</td></tr>
<tr><td colspan="2">Relaxation of GIT muscles & urinary bladder's muscles.
Contraction of GIT sphincter (constipation) & urinary bladder's sphincter urinary retention</td></tr>
<tr><td>Contraction of radial muscle of eye causes active mydriasis,
(dilation of pupil, cholinergic agents have no effect on this muscle)</td><td>.Relaxation of bronchial smooth muscles (bronchodilation)
.Tremor of skeletal muscles</td></tr>
<tr><td colspan="2">Increase blood glucose level (hyperglycemia), by:</td></tr>
<tr><td>.↑ glycogenolysis</td><td>.↑ glucagon release from pancreas
.↑ liver & muscle glycogenolysis</td></tr>
<tr><td colspan="2"></td></tr>
<tr><td colspan="2"></td></tr>
<tr><th colspan="2">α2</th><th colspan="2">β2</th></tr>
<tr><td colspan="4">Pre-synaptic</td></tr>
<tr><td colspan="2">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)</td><td colspan="2">Increase release of norepinephrine (Positive feedback mechanism)</td></tr>
</table>

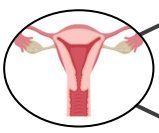
Adrenergic Agonists "sympathomimetics" actions:



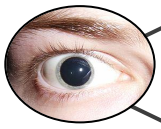
-Increase heart rate
-Bronchodilation



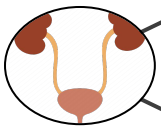
Inhibit peristalsis of GIT and secretion + Relaxation of GIT muscles (constipation)



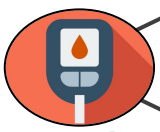
Relaxation of the uterus (Delay premature labor) tocolytic



Mydriasis
(dilatation of eye pupil)



Relaxation of urinary bladder



Increase conversion of glycogen to glucose (hyperglycemia)

Because sympathetic system have high effect in metabolism

Classification of Adrenergic agonist: according to:

❖ Chemistry:

Catecholamines	Non-Catecholamines
Rapidly acting Have short half-life, due to rapid degradation by MAO (Monoamine Oxidase) & COMT (Catechol-O-MethylTransferase) in GIT	Delayed action Have Long half-life, because they resist degradation by MOA & COMT in GIT
Have catechol ring water soluble (polar) ,thus not effective orally and have Poor penetration to CNS	**Lack catechol ring** Lipid soluble , thus Effective orally and Cross BBB well , have Prominent CNS effects
Parenterally administered	Orally administered
Natural: Adrenaline, Noradrenaline, Dopamine Synthetic: Isoprenaline.	e.g. Ephedrine, amphetamine, phenylephrine.

❖ Mode of action:

Direct-Acting	Indirect-Acting	Dual-Acting (Mixed)
Stimulate adrenergic receptors directly e.g. adrenaline,noradrenaline, dopamine, isoprenaline, phenylephrine, clonidine, dobutamine, salbutamol, methoxamine	**Stimulate adrenergic receptors by:** ↑noradrenaline release from presynaptic adrenergic nerve endings. e.g. amphetamine, Tyramine **Or** Inhibit uptake of noradrenaline e.g. Cocaine & antidepressants	**Direct and indirect stimulation of adrenergic receptors (mixed)** e.g. ephedrine, pseudoephedrine

❖ Spectrum of action: ★

Non-selective adrenergic agonist:	selective adrenergic agonist:
• Adrenaline (α1, α2 , β1 , β2, β3) • Noradrenaline (α1, α2 , β1) • Isoprenaline (β1, β2, β3) • Dopamine (D1, β1, α1) • Ephedrine	• Phenylephrine (α1) • α-Methyldopa - clonidine (α2) • Dobutamine (β1) • Salbutamol, terbutaline, ritodrine (β2)

Direct acting Adrenergic Agonists

Adrenaline

(always know the actions of the receptors, and which receptors the drug acts on. This helps in guessing the probable actions of the drug)

Receptor	Non-selective **α1; α2; β1 ; β2; β3** Adrenaline has a more dominant action on β2 receptors, followed mainly by α1 and β1, remembering their respective actions is helpful in studying this drug's effects.
overview	Natural catecholamine. It has fast onset & Short duration of action
Administration	Given I.V, S.C, inhalation. Not effective orally (inactivated by intestinal enzymes)
Action	**Heart:** inotropic,chronotropic,dromotropic (β1) **Blood pressure:** • ↑systolic (β1) (α1) (systolic: the phase of heartbeat when the heart contracts and pumps blood) ↓diastolic (β2) (diastolic: the phase of heartbeat when the heart relaxes and allows the chambers of the heart to be refilled with blood) "vasorelaxation" **Vascular:** •Vasoconstriction of blood vessels in skin + peripheral (α1) •Vasodilatation of blood vessels of skeletal muscles and coronaries (β2) **Eye:** mydriasis (α1) → no effect on accommodation (ciliary muscle of the eye action) **Lung:** bronchodilatation (β2) (a prominent β2 receptor agonist effect, we advise you to keep it in mind) **GIT:** ↓motility (β2) / contract sphincter (α1) **Bladder:** •relaxation of detrusor muscle (β2) •contraction of sphincter (α1) **CNS:** little (rare), headache, tremors & restlessness (due to vasoconstrictor effects, less oxygen to brain cells) **Pregnant uterus:** relaxation tocolytic effect (β2) (relaxation of uterus "suppresses contractions" to prevent premature labor) **Metabolism:** •↓ insulin (α2),↑ glucagon (β2) •↑ liver glycogenolysis +skeletal muscle glycolysis (β2) •↑ adipose lipolysis (β3)

Direct acting Adrenergic Agonists

Indication

Locally

- **Haemostatic (control bleeding):** By vasoconstriction
  - Nasal pack (stuffing) in epistaxis and in dental practice.
- **combined with local anesthetic to:**
  - ↓ absorption of L.A. & ↑ duration of action
  - ↓ side effects of local anesthetic
  - ↓ bleeding from the incision

Systemically

- **In acute asthma (status asthma)** S.C.,inhalation,emergency bronchodilatation (β2) + ↓mucosal edema (α1)
- **Anaphylactic shock (Hypersensitivity reactions)** is the drug of choice as it is the **physiological antagonist of histamine** (histamine is a vasodilator and decreases blood pressure) (↑BP & bronchodilation)
- **Cardiac arrest (i.v.)**

ADRs

- Tachycardia, palpitation, arrhythmias, angina pains (chest pains) . (TAAP)
- Headache, weakness, tremors, anxiety and restlessness
- Hypertension → cerebral hemorrhage and pulmonary edema ينفجر الشريان ويحصل النزيف
- Coldness of extremities → tissue necrosis (due to vasoconstriction = reduced blood flow = necrosis)
- Nasal stuffiness: rebound congestion if used as decongestant

Contraindications

- coronary heart diseases (CHD), Ischemic heart disease (angina)
- Arrhythmia, Myocardial infarction
- Hypertension, peripheral arterial disease
- Hyperthyroidism (adrenaline has similar effects to thyroid gland hormones, such as increased metabolism rate and tachycardia therefore injecting adrenaline will only intensify the effects making them unwanted)
- Closed-angle glaucoma (ciliary relaxation ↓filtration angle) →↑ IOP (remember that iris sphincter muscle " aka: constrictor pupillae, circular muscle of iris" decreases IOP when contracted)

Direct acting Adrenergic Agonists

	Noradrenaline (Norepinephrine)	Isoprenaline
overview	Catecholamine non-selective agonist	Think of this drug as a synthetic adrenaline, has very similar effects • Synthetic direct acting catecholamine. • shows no reuptake nor breakdown by MAO which leads to longer action.
Administration	• only administered by I.V • may cause necrosis using IM or SC	• Parenteral in cardiac arrest • inhalation rarely in acute attack of asthma
Receptor	mainly on α adrenoceptors (α1, α2, β1, weak action on β2).	non-selective β agonist It Acts on β1, β2, β3
Pharmacological Action	• Severe vasoconstriction (α1) • Increase force of contraction but decrease H.R. • Reflex bradycardia due to severe vasoconstriction (baroreceptors in blood vessels detect change in pressure of blood vessels due to sympathetic stimulation, this triggers a parasympathetic stimulation "vagus nerve" to restore the blood vessels to their dilated appropriate diameter, hence the tone will be maintained)	β1 : • + inotropic effect • + chronotropic effect • increase cardiac output β2 : • Vasodilatation of blood vessels of skeletal muscles and coronaries • Bronchodilatation • Relaxation of uterus • Hyperglycemia β3 : • lipolysis
Indication	**Locally**: as a local haemostatic with local anesthetic to reduce tachycardia & irritability, but as side effect, may produce necrosis & sloughing of the skin **Systemically**: hypotensive states : • in spinal anesthesia (especially in birth via C-section) • in septic shock (hypotension) if fluid replacement and inotropics fail. (fluid replacement is a therapeutic way to compensate for the slowing and loss of adequate blood circulation during anesthesia for example. this can be compensated by giving IV fluids. However, at times this does not work and we might need the heart to increase its activity by the use of stimulants of heart activity like adrenaline, this way the circulation can return back to normal)	**Uses:** • Used mainly in cardiac arrest (Parenteral). • Rarely in acute attack of asthma (inhalation). **Contraindications:** • In hyperthyroidism & Congestive heart disease CHD

Direct acting Adrenergic Agonists

	Dopamine	Dobutamine	Phenylephrine
overview	• Natural catecholamine & CNS neurotransmitter. • direct acting. • Released from postganglionic adrenergic fibres.	• Synthetic catecholamine. • direct acting. • Metabolized by COMT, thus has a short duration	• Synthetic **non catecholamine** • direct acting • has prolonged duration of action, since it's Not inactivated by COMT
Administration	Given parenterally by infusion	IV	Orally
Receptor	**D1 > β1 > α1** (in order)	Selective **β1**–agonist	selective **α1**
Pharmacological Action	D1: **Low dose:** • **Vasodilatation** of mesenteric, coronary, renal blood vessels. Thus improves blood flow to viscera. • **Diuresis** (increase excretion of urine) • **Decrease BP** β1: **intermediate dose:** • +ve inotropic • +ve chronotropic effects • **Increase BP** α1: **high dose:** • Vasoconstriction	• **On heart:** +ve Inotropic with little chronotropic effect. as it increases cardiac output and heart contractility. • **On BP:** Hardly any effect; β1 & β2 counterbalance + no α1. (since β1 agonists increase BP, and β2 decrease it by vasodilatory effect)	• ↑ increased both systolic & diastolic blood pressure (hypertension) due to vasoconstriction (α1) • Reflex Bradycardia due to↑BP **Adverse effects:** Hypertension. Thus, another drug is more preferable to produce hypertension that doesn't last for long. This drug is **Midodrine**. It peaks in 20 min, duration 30 min only.
Uses	**- Drug of choice in treatment of shocks**: **septic**, **Hypovolemic** (after fluid replacement), **cardiogenic** (I.V) It increases the BP & CO by β1 receptor but **without causing renal impairment (D1)** - Can be given in acute heart failure (HF) **but Dobutamine is better.**	• short term management of Cardiac decompensation after cardiac surgery, in acute myocardial infarction (AMI) & heart failure. • It does not increase oxygen demand which made it preferred.	**- Systemically:** Vasopressor (anti-hypotensive) agent in hypotension & terminates atrial tachycardia by its reflex bradycardia action. **- Topically:** • **Haemostatic** with Local anesthesia. • **Mydriatic** (in ophthalmic solutions to facilitate eye examination). • **Nasal decongestant** "vasoconstriction" topically, nasal drops in allergic rhinitis, cold.

Direct acting Adrenergic Agonists

	Clonidine	Brimonidine	Salbutamol	Terbutaline	Ritodrine
Overview	Synthetic Imidazoline	Imidazoline	Synthetic non catecholamines		
Administration	Orally or patch	———	Orally, inhalation or injection	———	Orally or injection
Receptor	**Presynaptic α2 agonist** Remember: this receptor inhibits NE release	**α2 agonist**	**selective β2 agonists**		
Pharmacological action	• Acts centrally (α2) at nucleus tractus solitarius to decrease sympathetic outflow to heart & vessels. • Inhibit sympathetic vasomotor centers.	used in **glaucoma** as it reduces formation of **aqueous humor** and therefore decrease intraocular pressure (IOP)	**Bronchodilator** for **acute attacks of asthma & COPD.** N.B. Salmeterol & Formoterol act longer	**Bronchodilator** & **Tocolytic**	**Tocolytic** relaxation of uterus to treat premature labor
Uses	**Antihypertensive drug**: used in essential hypertension to lower BP.				

Indirect & Dual acting Adrenergic Agonists

Amphetamine (Indirect acting)

P.K	• Synthetic non-catecholamine. • give orally, long duration of action (not destroyed by MAO) • Excreted mostly unchanged (increases by acidification of urine)
M.O.A	It acts indirectly by releasing NE from adrenergic nerve endings. It depletes vesicles from stored NE and thus causes **Tachyphylaxis.** **Rapid tolerance**
Selectivity	Acts on **α** & **β** similar to **epinephrine** but has **CNS stimulant effects**
CNS effects	Mental alertness, wakefulness, concentration & self-confidence followed by depression and fatigue on continued use
ADRS	- Euphoria* & abuse in use - Loss of appetite & decreased weight - Increased energy expenditure *a feeling or state of intense excitement and happiness which is what cause its addiction
Extra information	Not used therapeutically anymore, because it induces psychic & physical dependence & psychosis

Ephedrine (Dual Acting)

Overview	Plant alkaloid, synthetic, non-catecholamine, dual (mixed) acting
Spectrum of Action	Non selective , Acts on α & β
Pharmacokinetics	Absorbed orally, not destroyed by MAO or COMT → prolonged action
Mechanism of action	- **Directly**: direct action on receptors → down-regulation of receptors. - **Indirectly**: Release NE from adrenergic nerve endings → depletion of stores → **Tachyphylaxis**
Action	- Facilitation of neuromuscular transmission & retention of urine - It has CNS stimulant effects (less than amphetamine)
ADRS	- Drugs of abuse by athletes and prohibited during games, thus Not used therapeutically anymore - **Bi folded effect:** activation followed by dropping; Because it depletes vesicles of stored NE and causes tachyphylaxis
Pseudoephedrine	**Dual acting ,** acts on CNS & has less pressor effects compared to ephedrine. Produces vasoconstriction in nasal passages thus **Used as nasal & ocular decongestant & in flu remedies**

Drugs Summary
(taken from the doctor's lecture)

1 Hypotension

Midodrine, Phenylephrine, Norepinephrine, Phenylpropanolamine

2 cardiogenic shock → AHF

Dobutamine, Dopamine, Epinephrine

3 shock

Dopamine, Norepinephrine

4 cardiac arrest

Dobutamine, Epinephrine, Norepinephrine

5 bronchial asthma

Salbutamol, Salmeterol, Formoterol, Terbutaline, Isoprenaline

6 premature labour

Ritodrine, Terbutaline

7 nasal decongestion

Pseudoephedrine, Phenylephrine.

8 abused in sports

Ephedrine, Amphetamine

QUIZ

MCQs:

1- which one of the following adrenergic agonists is most likely to cause CNS side effect when administered systemically?

A-Norepinephrine B-Epinephrine C-Ephedrine

2-Which one of these drugs is α2 agonist used in glaucoma ?

A-Clonidine B-Brimonidine C-Terbutaline

3-Which one of the following adrenergic agonists is commonly present in nasal sprays to treat nasal congestion?

A-Norepinephrine B-Oxymetazoline C-Dobutamine

4-Which one of the following drugs shouldn't be given in condition of Hyperthyroidism & CHD ?

A-Dopamine B-Norepinephrine C-Isoprenaline

5-What drug is specifically indicated for premature labour?

A-Formoterol B-Ritodrine C-Dobutamine

6-Both norepinephrine and epinephrine (noradrenaline & adrenaline) can be given i.v. to produce pressor responses. While both work equally well in many cases, what receptor subtype is stimulated by epinephrine, but is not stimulated by norepinephrine?

A- alpha-1 B- beta-1 C- beta-2

7-Which of the following is correct regarding responses mediated by adrenergic receptors?

A-Stimulation of α1 receptors increases blood pressure. B-Stimulation of α1 receptors reduces blood pressure. C-Stimulation of β2 receptors increases heart rate (tachycardia).

8-What is the predominant β-adrenoceptor in bronchial smooth muscle?

A- β1-adrenoceptor B- β2-adrenoceptor C- β3-adrenoceptor

9-A 15-year-old girl was treated topically with eye drops during a routine ophthalmoscopic examination. After fifteen minutes the ophthalmologist registered a moderate increase in pupillary diameter. Which of the following drugs was most likely administered to the patient?

A- Phenylephrine B-Acetylcholine C-Dobutamine

10-.A 21 year old famous athlete joined a race, after few days he under went a sudden drug level checkup and was found to have an abnormal blood result. Then he was eliminated from the race. What drug do you think he was taking?

A-Ephedrine B-Norepinephrine C-Dopamine

Answers: 1)C -2)B -3)B -4)C -5)B -6)C -7)A -8)B -9)A -10)A

QUIZ

SAQ:

1-2. A 12-year-old boy who is allergic to peanuts was brought to the emergency room after accidentally consuming peanuts contained in fast food and he is in anaphylactic shock.

Q1.What is the most appropriate drug to treat this patient ?

Q2.Which receptors do that drug effect?

Q3. A 70-year-old patient was brought to the emergency room with a blood pressure of 76/60 mmHg, tachycardia and low cardiac output. He was diagnosed with acute heart failure. What is the most appropriate drug to treat this patient ?

4-5. A 32-year-old patient came to the emergency with acute asthma attack because of the bad weather that day.

Q4.What is the most appropriate drug to treat this patient ?

Q5.Which receptors do that drug effect?

Q6.What is the mechanism of action of clonidine?

7-8.-A 67 Year-Old Woman with Sudden Cardiogenic Shock in the 7th Day after Acute Myocardial Infarction.

Q7. What drug is mainly used in this case?

Q8.How this drug Metabolized?

Q9.-Explain what receptors are affected by Dopamine at these given doses

Low dose?

Intermediate dose?

High dose ?

Answers :

1)Adrenaline. 2)Non-selectiveagonistα1,α2,β1,β2,β3.

3)Dobutamine.

4)Salbutamol. 5)Selective β2 agonists

6)Selective presynaptic α2 agonist

7)Dobutamine. 8)Metabolized by COMT

9) Low dose: dopaminergic receptors D1* - Intermediate dose: β1 receptors* - High dose: α1 receptors*

pharmacology

Team 438

GOOD LUCK

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Sources:

Team 435