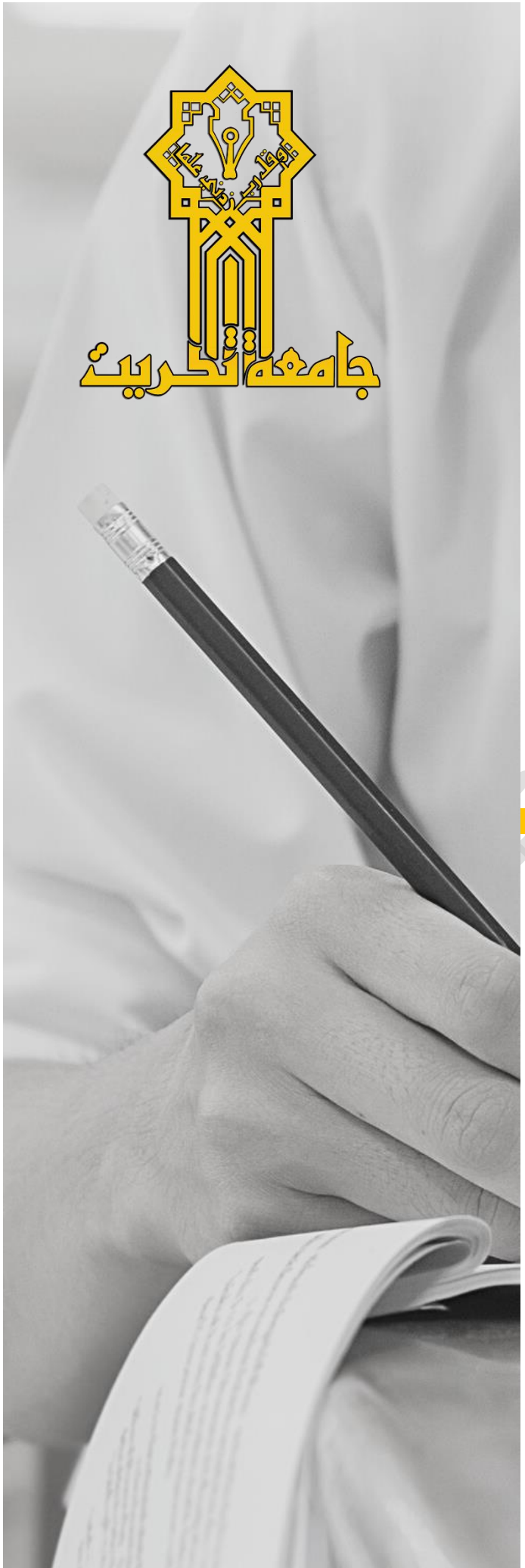

Tikrit University
College of Veterinary Medicine

Adrenergic

Subject name: Adrenergic

Subject year:2023\2024

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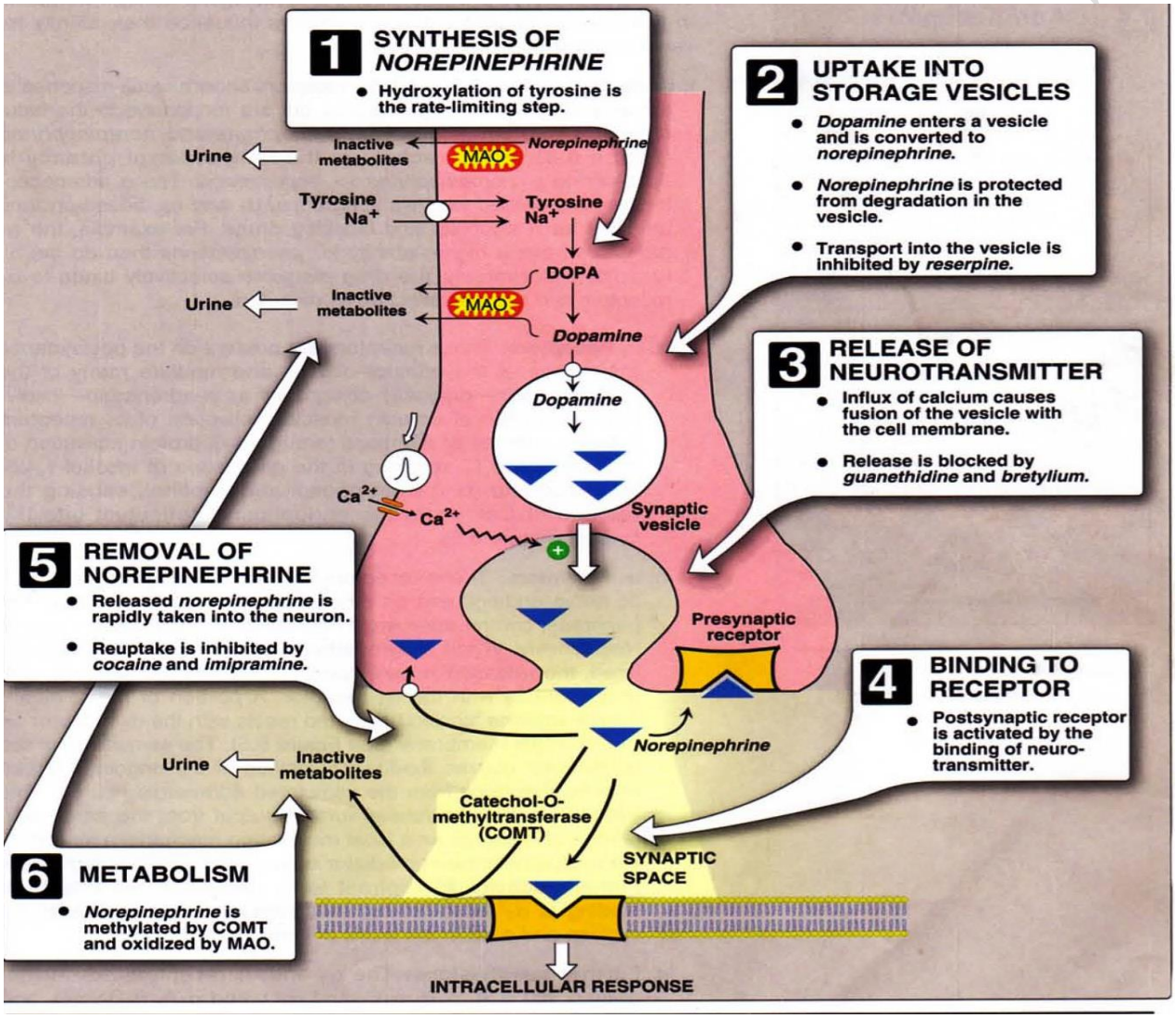
SCAN ME

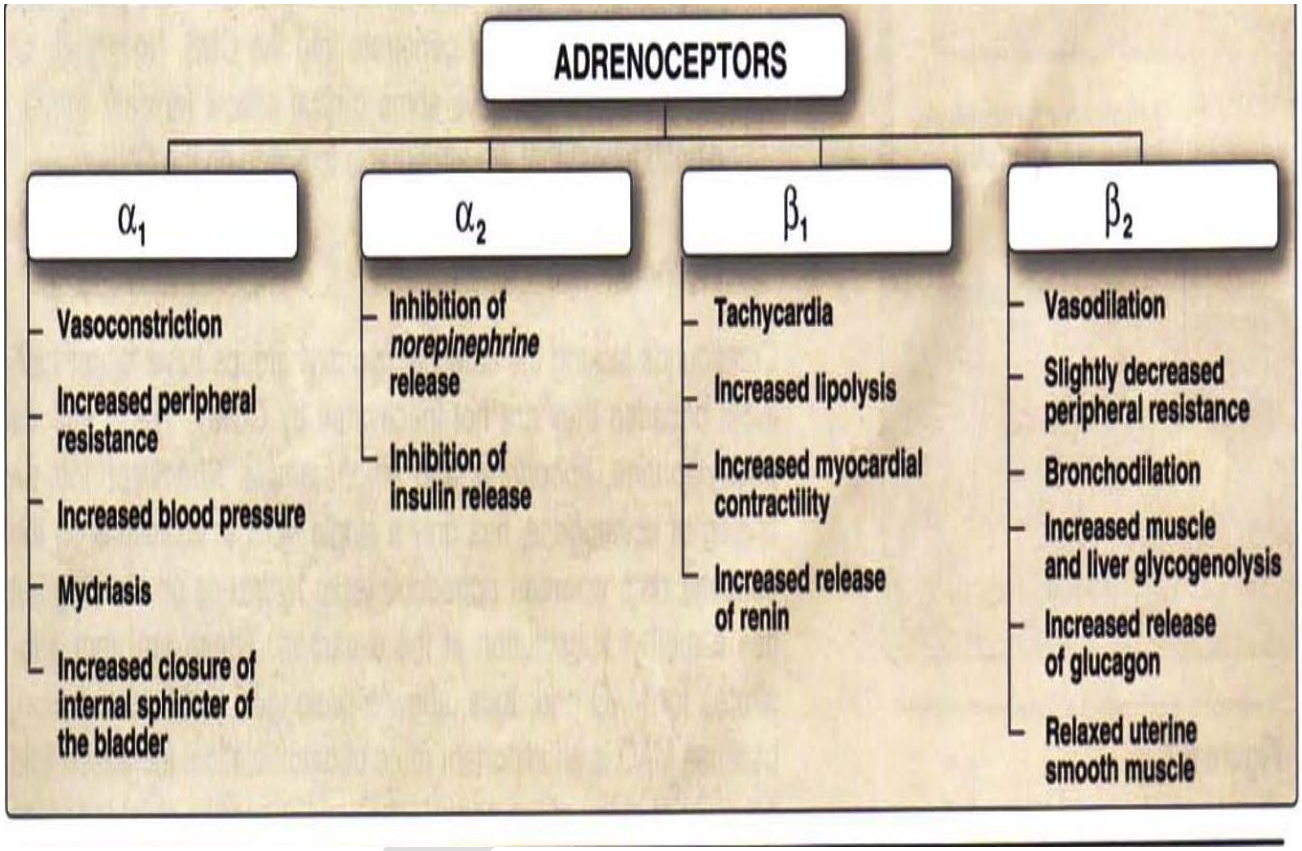
Adrenergic agonists
(sympathomimatics)

Adrenergic neurons release norepinephrine as the neurotransmitter, these neurons are found in the central nervous system(CNS), and also in the sympathetic nervous system where they serve as links between ganglia and the effectors' organs.the adrenergic drugs affect receptors that are stimulated by norepinephrine or epinephrine,.

Drugs that partially or completely mimic the action of noradrenaline and adrenaline

The natural synthetic path is tyrosine --- dope----- dopamine---- noradrenaline---- adrenaline




ADRENOCEPTORS
α1
Vasoconstriction
Increased peripheral resistance
Increased blood pressure
Mydriasis
Increased closure of internal sphincter of the bladder
α2
Inhibition of norepinephrine release
Inhibition of insulin release
β1
Tachycardia
Increased lipolysis
Increased myocardial contractility
Increased release of renin
β2
Vasodilation
Slightly decreased peripheral resistance
Bronchodilation
Increased muscle and liver glycogenolysis
Increased release of glucagon
Relaxed uterine smooth muscle

Classification of sympathomimetics drugs:-

1-by structure:- adrenergic drugs are derivative of beta- phenylethylamine

a- catecholamines:- (adrenaline, noradrenaline, isoprenaline, and dopamine) rapid onset of action , brief duration of action Have short half-life, due to rapid degradation by MAO & COMT, are polar---- not penetrate into CSF , not administered orally.

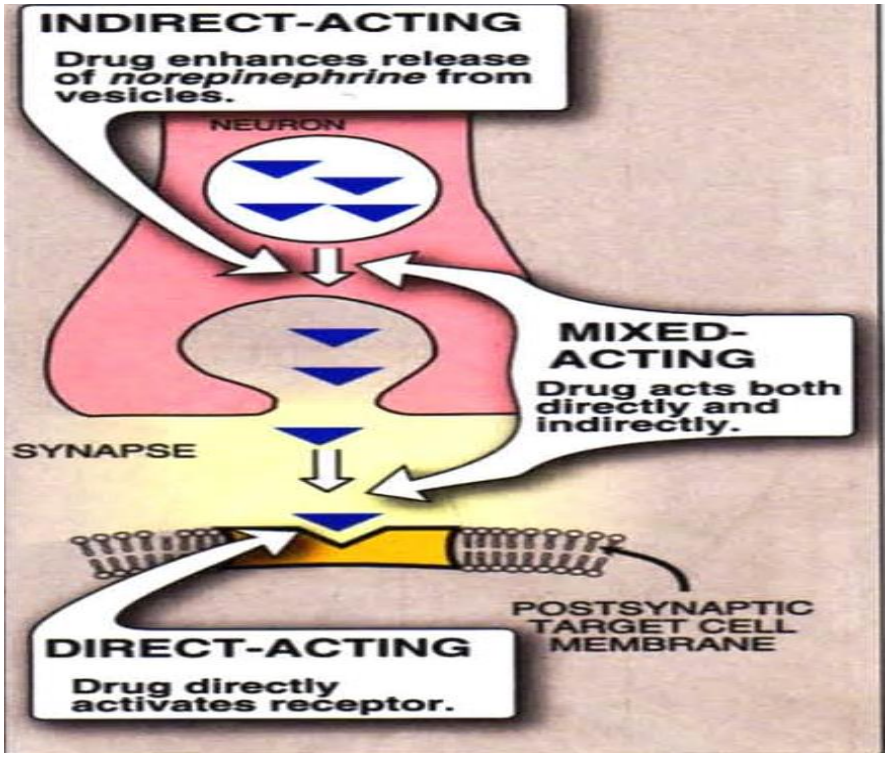
b-non- catecholamines:-(phenylephrine, methoxamine, clonidine, amphetamine, ephedrine) long duration of action because they resist degradation by MOA &COMT in GIT , all can be administered orally , lipid solubility--- penetrate into CSF.

2-by mode of action may be classified as:-

a- direct acting drugs:-(noradrenaline, isoprenaline, methoxamine, metaramine, dopamine and phenyephrine) bind to adrenergic receptor--- second messengers ---- response.

b- Indirectly acting drugs: (amphetamine, ephedrine, and tyramine) causing a release of noradrenaline from stors at nerve endings.

c- Mixed- acting drugs (direct and indirect) e.g. ephedrine, metaraminol.



Chatecholamines:-

1- Adrenaline(epinephrine)

Is synthesized from tyrosine in the adrenal medulla, pharmacological actions(alpha-1, beta-1,beta-2 actions).

1- Cardiovascular effects:- includes

a- Beta-1 stimulation ---- increase the heart rate, increase force of contraction, increase CO, and increase velocity of impulse conduction.

b- Alpha effects--- constriction of arteriols in skin, mucous membranes and viscera.

c- Beta-2 stimulation----- dilates vessels going to liver and skeletal M.

NOT| at low doses------- Beta effect (vasodilator) on the vascular system
high doses ----- Alpha effects(vasoconstriction) are strongest

2- Respiratory system :- powerful bronchodilator(Beta-2-action) relives all known allergic or histamine (bronchonstriction).

3- GIT: sphincters: contraction(alpha effects)
Wall: relaxation (alpha and Beta)

4- Eye: cilia body Bv constriction (alpha effect) ----- decrease IOP (glaucoma).
Redial M of iris------constriction(alpha effects)

5- Uterus: variable(contraction alpha), relaxation Beta

6- Metabolic effects:-
↑ glycogenolysis in liver (Beta-2)
↑ glucagon release (beta-2)
↓insulin release (alpha -2)------ hyperglycemia
↑lipolysis (beta)

7- CNS:- restlessness , anxiety, fear

Pharmacokinetics:- routes of administration(S.C. , I.M.) more rapid absorption, IV in small doses
Inhalation as 1% aerosol in asthma,
Rapid onset , brief duration of action , metabolites by enzymatic COMT , excreted in the urine.

Therapeutic uses:- 1- acute attack of asthma**.**

2- Hypersensitivity reaction (adrenalin acts as physiological antagonist the release of histamine).
3- In anesthetics: local anesthetic solution usually , the effect of the drug is to greatly increase the duration of the local anesthesia
4- Glaucoma: 2% adrenalin solution may be used to reduce IOP.
5- heart block

Adverse effects

1- CNS disturbances
2- Hemorrhage :- cerebral hemorrhage due to marked increase BP.
3- Cardiac arrhythmia, 4- pulmonary odema.

Interactions:-

1- Hyperthyrodisim: epinephrine may have enhanced cardiovascular action in patients with hyperthyroidism.
2- Cocaine: prevent active uptake of extracelluar epinephrine and norepinephrine --- hypertensive crisis

Precautions and contraindications:-

1- Hyperthyroidism,2- hypertensive,3-elderly, 4- infiltration with local anesthetics into finger--- gangrene.

Noradrenalin(Noerpinephrine)

Has directly stimulating alpha adrenergic receptor .it has some direct stimulating Beta -1 on heart but non on the lung (B2receptor) .

Norepinephrine is directly metabolized to dopamine and is primary used in the treatment of hypotension and shock.

Therapeutic uses:-

1- As a presser agents (shocked patients)
2- As topical homeostatic
3- Mixed with local anesthetics.

Precautions:-0

1- May cause cerebral hemorrhage or gangrene of fingers
2- Sudden cessation of infusion may lead to marked fall in BP.

Isoproterenol:-

Has Beta-1, Beta-2 effects

Produce stimulation of heart to increase its rate and force of contraction causing increased cardiac output----- useful in the treatment of atrioventricular block or cardiac arrest

Its also dilates the artioles of skeletal M--------(B2)

Was used by inhalation in acute asthma-------(B2)

Increase blood sugar and increased lipolysis (not clinically)

Non-catecholamines:-

1- Predominantly alpha- stimulants

A -pressor agents:-

Used in some hypotensive states, following sympathectomy,

- **Phenylepherine:** has also minimal Beta-1 effects
- -it's a vasoconsntraction that rises both systolic and diastolic blood pressures
- - causes reflex bradycardia
- Its used topically on the nasal mucous M and in ophthalmic solution for mydriasis.
- Large doses can cause hypertensive headache and cardiac irregularities.

Mthoxamine:

- It's a direct acting synthetic adrenergic drug that binds to alpha receptor(1&2)
- Has no Beta -1 effects
- Its raises blood pressure by stimulating alpha-2 receptors in the arteriols, causing vasoconstriction , this causes an increase in total peripheral resistance because of its effects on the vagus
- -its used clinically to relieve attacks of (paroxysmal supraventricular tachycardia,)
- also used to overcome hypotension during surgery .

B- Nasal decongestants:

e.g. naphlazoline, xylometzoline, tetrahydrazoline, phenylephrine,pseudoephedrine

used in:

1- Mild nasal allergies
2- Sever nasal allergies
3- Relief of nasal congestion associated with common cold, vasomotor rhinitis

Prolonged used of topical decongestants may damage nasal cilia and may cause nasal obstruction, local decongestants should be avoided in children under 2 year

C- Selective Alpha-2 agonist

Useful in treatment of hypertension. Include:

1-**Clonidine**:- used in essential hypertention to lower blood pressure because of its action in the CNS.

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- 2-**Methyldopa(aldomet**)

2- Predominantly Beta –Stimulants

a- Beta-1 selective drugs include

Dubutamine:- has also some alpha- effects , has greater inotropic than chronotropic effect ---- increased CO with less reflex tachycardic

Useful in shock and low output heart failure.

b- Bta-2 selective agonists

Salbutamol

Given orally, inhalation, injection

Has also some Beta -1 effect--- tachycardia

Used in asthma and premature labor. Causes hypokalamia, tachycardia

Terbutaline:- has longer duration of action , give orally or S\C

Used asthma and premature labor.

Albuterol(similar trbutaline)

Salmeterol (slow onset, long duration)

INDIRECT-ACTING ADRENERGIC AGONISTS

Indirect-acting adrenergic agonists (IAAA) cause the release, inhibit the reuptake, or inhibit the degradation of epinephrine or norepinephrine. They potentiate the effects of epinephrine or norepinephrine produced endogenously, but do not directly affect postsynaptic receptors

IAAA	Receptor specificity	Features
Amphetamine	**β_1, α_1 and CNS**	*Its actions are mediated primarily through an increase in nonvesicular release of catecholamines such as dopamine and norepinephrine from nerve terminals. *It can increase blood pressure significantly by α_1 agonist action on the vasculature, as well as β_1 stimulatory effects on the heart. *It can be abused by addicts.
Tyramine	Adrenoreceptors	* Tyramine can enter the nerve terminal and displace stored norepinephrine. The released catecholamine then acts on adrenoceptors. *It is important because it is found in fermented foods, such as aged cheese. *Normally, it is oxidized by MAO in the gastrointestinal tract, but, if the patient is taking MAOIs, it can precipitate serious vasopressor episodes. *Not used clinically.
Cocaine	α_1 agonist actions and β	*It can be abused by addicts. *It can block the sodium-chloride (Na^+/Cl^-)-dependent norepinephrine transporter required for cellular uptake of norepinephrine into the adrenergic neuron. Consequently, norepinephrine accumulates in the synaptic space, resulting in enhanced sympathetic activity and potentiation of the actions of epinephrine and norepinephrine.

Mixed- Acting Agonists:

Ephedrine and pseudoephedrine are mixed-action adrenergic agents. They not only release stored norepinephrine from nerve endings but also directly stimulate both α and β receptors. Thus, a wide variety of adrenergic actions ensue that are similar to those of epinephrine, although less potent. Ephedrine and pseudoephedrine are not catechols and are poor substrates for COMT and MAO. Therefore, these drugs have a long duration of action.

Ephedrine;'-

- It is plant alkaloid
- Has direct actions on alpha and beta receptors
- Readily absorbed from GIT and penetrate into CNS
- Has prolonged action but slower onset of action than adrenalin
- Eliminated unchanged in the urine
- Has peripheral effects similar to adrenaline ---- increase systolic and diastolic blood pressure (vasoconstriction, cardiac stimulation)
- Uses:
- 1- in asthma
- In heart block
- Nasal decongestant
- Presser agent
- Hypersensitivity reaction
- Mydritic

Adrenoceptor blocker(Adrenergic Antagonist)

Alpha&Beta blocking agents are divided into subgroups on the basis of their receptor selectivity.

Alpha-blocking drugs:-

Classification:- 1-irreversible long acting:-**phenoxybenzamine**

Long acting ,irreversible, alpha1-selective.

2-reversible short acting :-**phentolamine**(nonselective) &**tolazine**(slightly alpha2 selective) are competitive ,reversible blocking agents

3-alpha1-selective:-prazosin is a selective ,reversible.

4-alpfa2-selective:-yohimbine alpha-selective competitive

Pharmacokinetic:-

-these drugs all active by oral as well as parental rout.

-phentolamine&tolaoline are rarely given orally

-phenoxybenzamine ,long of action because it binds covelantly to its receptor, phentolamin duration of action2-4h when used orally, and 20-30minuts when used given parentrally.

Clinical uses:-

Non-selective alpha-blocker:-have limited clinical application , the pest application in the presurgical management of pheochromocytoma,carcinoid tumor(phenoxybenzamine).

-phentolamin used to prevent sever hypertension during surgery.

-phentolamin, yohambin used impotence

Selective alpha blocker:- prazosin and other alpha1 blocker are used

- hypertension

-use in mananagement and prevention of urinary retention in men with prostatic hyperplasia.

Adverse effects:-

-orthostatic hypotention associated with alpha1-selective

-oral administration:- nausea,vomiting

-non-selective: reflex tachycardia

Beta-Blocker drugs:-

Classification:- all of the clinically used beta-blocker are competitive pharmacologic antagonist

1-receptor-selective:- beta1 receptor selectivity (B1>B2) such as acebutolol,atenolol, esmolol,metoprolol treating with asthma-

-Butoxamine B2selective drugs

-nadolol, proponanol and timolol are typical nonselective beta blockers

-labetalol agent combined alpha-beta blocking sever hypertension

2- partial agonist activity:- pindolol, acebutolol cause some bronchodilation

NOT\timolol reduce the production of aqueous humor in the eye (treatment glaucoma)and treatment hypertensive

pharmacokinetic:-esmolol is a short acting that only used parenterally, nadolol is longest acting ,acetolol and atenolol are less lipid –soluble than and probably enter CNS

B-blocker have important organ level effects:-

-CNS:- cause sedation, reduction of anxiety

Eye;-reduce secretion of equeues humor

-airway- bronchodilator

-CVS: slow the heart rate and AV condition and reduce myocardial contractility, reduction blood pressure in hypertensive.

GIT: little effect

Reduce skeletal M. tremor , glucose release ,rennin release thyroid effect

Uses of B-blocker:-

-β -blocker widely used in the hypertension, angina, arrhythmia, heart failure(reduce mortility,and morbidity)

-oral drugs reduce tremor

-topical treatment glaucoma

I\V treatment thyrotoxicosis

Toxicity:-

-bradycardia

-AV blocker

-diminish CO

-brochospasm
-elevate blood glucose, lipid ,uric acid