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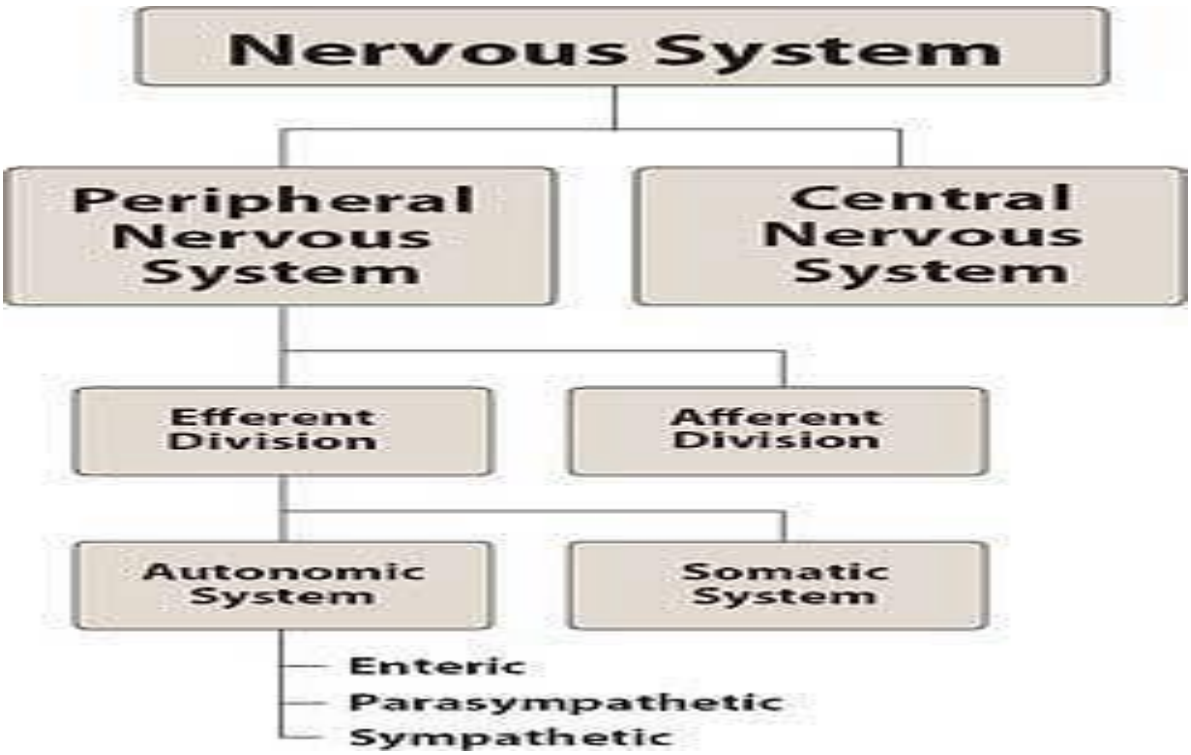
Drugs acting on the autonomic nervous system and somatic nervous system

Organization



1. **Somatic nervous system :**
   Its innervate skeletal muscle
   Axon originate from spinal cord and release neurotransmitter Ach at neuromuscular junction
   Its voluntary
   Have no ganglia
2. **autonomic nervous system :**
   Regulate the activity of

-smooth muscle

-cardiac muscle

- exocrine glands

2 neuron involved in the transmission process.

1st originate from the CNS and synapse in ganglia

2nd innervate the target tissue .

Involuntary

The autonomic nervous system subdivided into

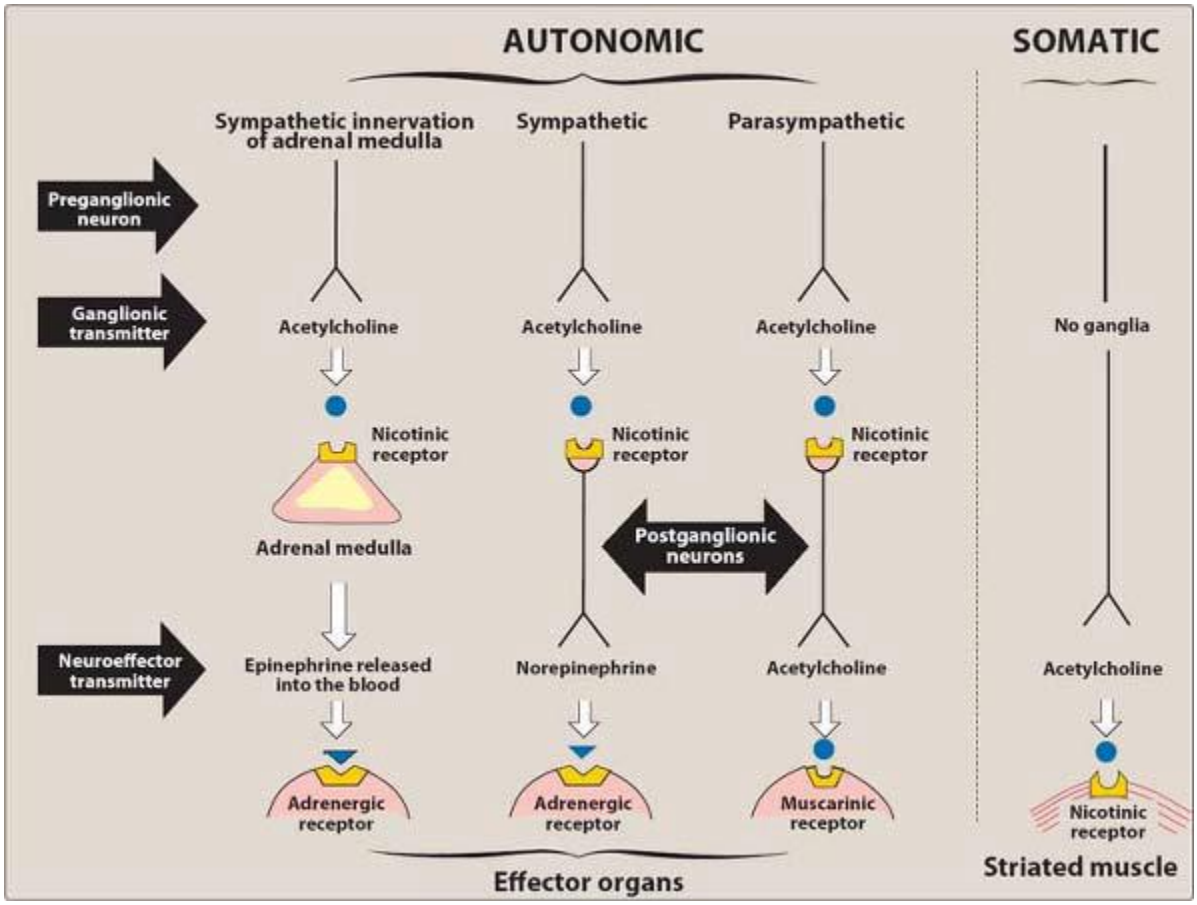
1- Sympathetic N.S.

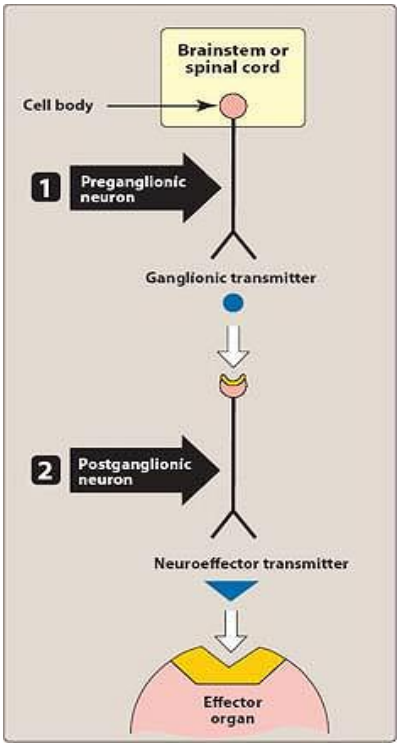
2- Parasympathetic N.S.

	Location	**Neurotransmitters**	**nerve**	**Receptors**
Sympathetic	Thoracolumbar portion of the spinal cord	Epinephrine Norepinephrine	Adrenergic neurons 1-Preganglionic N. release Ach into nicotinic R. OF postganglionic N. 2-postgangilonic N. release NE into the effectors tissue	α 1 α 2 β 1 β 2 β 3
Parasympathetic	Crainosacral portion of the spinal cord	Acetylcholine	Cholinergic neurons 1-Preganglionic N. release Ach into nicotinic R. OF postganglionic N. 2-postgangilonic N. release Ach into the effectors tissue	M1-M5 Nn Nm

Neurotransmitter :

Is a chemical substance transmit impulse across junctions such as synapse


AUTONOMIC
SOMATIC
Sympathetic innervation of adrenal medulla
Sympathetic
Parasympathetic
Preganglionic neuron
Ganglionic transmitter
Acetylcholine
Acetylcholine
Acetylcholine
No ganglia
Nicotinic receptor
Nicotinic receptor
Nicotinic receptor
Adrenal medulla
Postganglionic neurons
Neuroeffector transmitter
Epinephrine released into the blood
Norepinephrine
Acetylcholine
Acetylcholine
Adrenergic receptor
Adrenergic receptor
Muscarinic receptor
Nicotinic receptor
Effector organs
Striated muscle


Brainstem or spinal cord
Cell body
1
Preganglionic neuron
Ganglionic transmitter
2
Postganglionic neuron
Neuroeffector transmitter
Effector organ

The adrenergic receptors

α 1	α 2	β 1	β 2	β 3
1- Found in the blood vessels :vasoconstriction 2- Uterus: contraction 3- Eye : contraction of radial M. leading to mydraisis 4- GIT and bladder : Wall → relaxation Sphincters → contraction 5- Sweat gland of palm and forehead : increase sweating 6- Salivary gland :↑ salivation	90% of these receptor found presynaptically in the brain : decrease NE release	Found in the heart : increase heart rate leading to tachycardia	1- Lung :bronchodilation 2- Blood vessels of skeletal muscle :vasodilation 3- Coronary artery : vasodilation 4- Liver : ↑ glycogenolysis → ↑glucose in blood 5- Make the N. receptor more sensitive to Ach 6- ↑ the intracellular K → hypokalimaia	Found in adipose tissue → lipolysis

Notes :

1- Most organs are innervated by both division of the ANS (dual innervation)
2- Some organs are supplied by one division
   - Iris sphincter M. (circular M.) : supply by parasympathetic M3 receptors
   - Iris dilator M. (radial M.): supply by sympathetic α 1receptors
   - Pilomotor M. : supply by sympathetic α 1receptors (hair erection)
3- Thermoregulatory sweat gland : supply by sympathetic fiber but through M3 receptors
4- Adrenal medulla : supply by sympathetic fiber through nicotinic receptors
5- Blood vessels : are innervated by sympathetic indirect non – innervated by parasympathetic
   - Direct acting : innervated by sympathetic α 1 receptors → vasoconstriction
   - Indirect acting: non innervated parasympathetic M3 receptors → vasodilation via the nitric oxide .

Enteric nervous system (NANC nerve)

Is the division of the nervous system which innervated the intestine (local control system) , the co-transmitter (ATP ,purins,histamine , serotonin and nitric oxide) responsible for the activity of these system .

The comparison between sympathetic and parasympathetic system according to their pharmacological effects

Sympathetic	Parasympathetic
Tachycardia	Bradycardia
Vasoconstriction	Vasodilation
↑ BP	↓BP
↓ renal blood flow	↑ renal blood flow
↓ urine out put	↑ urine out put
Brochodilation	Brochconstrction
↓GIT motility and secretion	↑GIT motility and secretion

Adrenergic agonist (sympathomimetic)

These drugs can be classified according to their mode of action :

1-direct acting :drugs that acting directly on the adrenergic receptors

2-indirect acting :drugs that release NE from the nerve ending .

3- MAO inhibitors : drugs that destroy the monoamino oxidase enzyme thus prolong the action of catecholamine

Also can be classified these drug according to their chemistry into :

1- Catecholamine

Dopamine

Norepinephrine

Epinephrine

It's have essential properties :

1- not absorbed orally ,

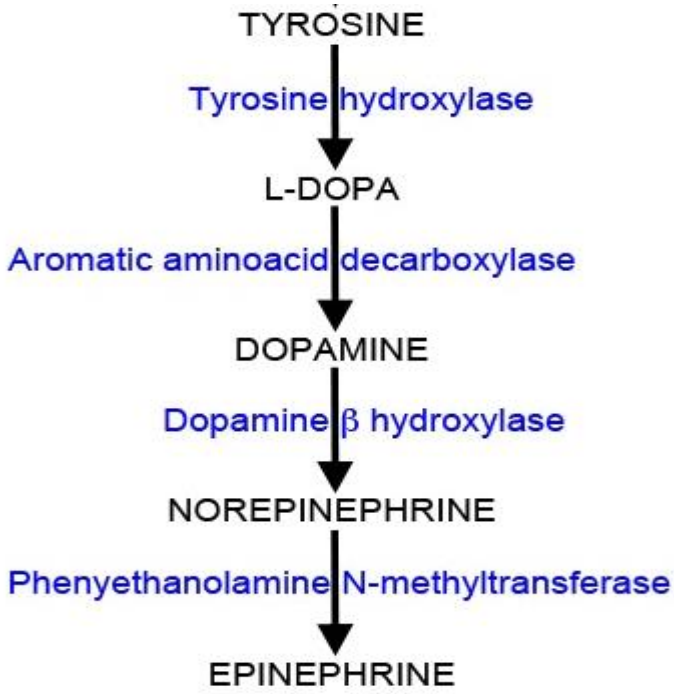
2-not cross BBB,

3-inhibited by MAO and COMT ,

4- short acting

Catecholamine :

Biosynthesis



Epinephrine (adrenaline)

Discovered in 1895 in suprarenal gland

Synthsis in 1904

1-chemistry

2-pharmacokinetic

3-pharmacodynamic (mechanism of action)

4-uses

5-adminstration

6-adverse effect

7-Contraindication

1- Chemistry of adrenaline : adrenaline is natural in the body and contain catecholamine ring .
2- Pharmacokinetic :

Absorption :

- Not absorb orally
- In the skin cause vasoconstriction
- Eye :very low absorption because the tear contain MAO
- Can absorb well by inhalation

Distribution

Reach all the body except brain , brain have adrenaline but injectable adrenaline can not cross the BBB.

Metabolism

I. **Tissue uptake mechanism** : remove the drug from the receptor site thereby decreasing the NO. of receptor being occupied and decrease the response

Uptake 1: is the uptake the drug from the receptor into the presynaptic neurons. coccaine produce sympathomimetic effect by blocking uptake 1.

Uptake 2: is the uptake of catecholamine into the effector cell which contain :

MAO –MONOAMONOOXIDASE

COMT –catechol-o-methyl transferase

These 2 enzyme metabolize catecholamine into inactive product

Metanephrine and vaniline mandilic acid VMA which can be detected in the plasma and urine , these end product increased in :

1.stress

2.adrenaline injected

3.pheochromocytoma .

Note :80% of adrenaline into the vesicles by uptake 1 and uptake 2

20% of adrenaline is metabolized by COMT in the nerve space and MAO inside the nerve terminals

II. The liver and kidney which are rich in MAO and COMT inactivate circulating catecholamine

Administration:
S/C
IV……RISK ……dangerous arrhythmia
IM

Mechanism of action
Is potent agonist of α 1, α 2, β 1, β 2 and β 3.
Pharmacological effects
Heart : tachycardia → β 1
Blood pressure: ↑BP→ α 1
Lung :bronchodilation → β 2

CNS : X

EYE : mydriasis →↓IOP

Uterus : contraction → α 1

Relaxation → β 2

Depending on the state of estrus cycle , pregnancy and species

Liver :↑glycogenolysis

Spleen : contraction → α 1 leading to ↑RBC in dogs .

Pilomotor muscles : contraction → α 1.

Uses

1- Anaphylactic shock IM.
2- Acute bronchial asthma S.C,IM or inhalation
3- Cardiac arrest
4- Prolong the effect of local anesthetic .
5- Treatment of the open angle glaucoma

Adverse effects

1- ↑BP and cerebral hemorrhage
2- Tremors
3- Tachycardia
4- Acute heart failure

5- Acute pulmonary edema
6- Gangrene of fingers

Contraindication

1. Hypertensive patient
2. Cardiovascular problem
3. Large dose of local anesthetic
4. Cardiac outflow obstruction
5. Hyperthyroidism

Noradrenaline

Mechanism of action: its potent agonist on α 1, α 2 and β 1 receptors

90% on α 1----------10% on β 1

Uses : acute hypotension

Administration : not SC or IM or IV but only intravenous infusion because of tissue necrosis .

Dopamine

Dopamine receptors:

D1→ Renal, mesenteric and coronary circulation → vasodilation

D2→CNS

D3→CNS

D4→Heart and CNS

D5→LYMPHOCYTE

MECHANISM OF ACTION

Low dose →activate D1 →Vasodilation

Intermediate dose →activate β 1→ increase cardiac output

Large dose → activate α 1 →vasoconstriction

Uses

Shock state with impaired tissue perfusion

Administration

IVI only

Dopamine	***Dobutamine***
Natural cat	Synthetic cat
D1 >β 1>α 1	β 1
Septic shock	Cardiogenic shock

Beta agonist

1- Selective beta 2 agonist
2- Selective beta 1 agonist →dobutamine
3- Non selective beta agonist →isoprenaline Its synthetic cat act on β1 and β 2

Selective β 2 agonist

-Salbutamol

-Retordine

-Terbutaline

-Salmetrol

-zilpaterol

- Its non-catecholamine
- Taken orally
- Have long duration
- Not destroyed by MAO and COMT

USES

1-bronchial asthma

2- uterine relaxation (retodrine)

Adverts effects

T→Tachycardia

T→ Tremors

T→Tolerance

H→ Hypokalemia

Alpha agonist

α 1 agonist

phenylpherine , methoxamine (non cat)

act as vasopressor

administration

1.injectabel

2.eye drop

3.nasal drop

4. tablet

Uses

1. Red eye
2. Nasal decongestion

Adverse effect :

1.rebound congestion

2.strok hypertension

3. atrophic rhinitis .

Alpha 2 agonist

Xylazine , medotimidine , detomidine , clonidine , tizanidine

Chemistry : its non cat

Mechanism of action :

Agonist on α 2 receptors which decrease the secretion of adrenaline peripherally and centrally because the drug is not cat .

Clinical uses

1- Sedation
2- Anesthesia
3- Muscle relaxation
4- Analgesia
5- Emetic in cat
6- Hypertension
7- Treat withdrawal syndrome

Adverse effect

S→ Sedation , dry mouth

S→ Sudden withdrawal lead to sever hypertension

S→ Salt and water retention

Tizanidine :act specially on the α 2 receptor in the spinal cord leading to muscle relaxation so it used in muscle spasm .

Indirect sympathomimetic

Can be divided into

-indirect

-mixed acting

1- indirect acting

- **Amphetamine** : its synthetic drug , not catecholamine ,absorbed orally
  Act on the nerve ending promote adrenaline release and inhibit the uptake leading to accumulation of NE,E,D and serotonin in the synaptic space

Effects

- CNS stimulation
- Anorexia
- Euphoria
- Hallucination

Adverse effect :

- -physical dependence
- insomnia
- -nervousness
- -headache
- -Seizure

Notes :

Amphetamine derivatives→ **methylphenidate** uses in attention deficit – hyperactivity syndrome

modafinil: used in narcolepsy

cocaine : its plant alkaloids inhibit reuptake of E used as local anesthetic

toxicity of cocaine treated by benzodiazepame

2- mixed acting sympathomimetic

Ephedrine: act on the α and β receptor and stimulate the release of adrenaline from the nerve ending

Chemistry : its natural from plant alkaloid , its non cat

Effects: CNS stimulation

Pseudoephedrine : available as eye drop and nasal drop to treat congestion

Notes : ephedrine cause urinary retention because it stimulate α 1and β 1 receptor in the bladder and contraction of the sphincter and because it have long duration of action (8h) unlike adrenaline which is catecholamine remain in the body for few min.

adrenergic blockers

Alpha adrenergic blocker :

- α 1 and α 2 nonselective blocker (phenoxybenzamine , phentolamine)
- selective α 1 blocker prazosin
- selective α 2 blocker yohimbine
- ergot alkaloids

non selective α 1 and α 2 blocker:

phenoxybenzamine :

its blocker to α receptors , its bind to receptors irreversibly by covalent bond .

long acting 4days

uses

1- In pheochromocytoma with propranolol (which block β 1 and β 2).
2- In dog and cat reduce hypertonus at urethral sphincters
3- In horse: treat laminitis and secretory diarrhea.

Adverse effect :

1- ↓BP with reflex tachycardia.
2- Failure of ejaculation.
3- Miosis
4- Not use in horse with colic

Phentolamine

It's a competitive **α 1 and α 2** receptors antagonist .

selective α 1 blocker:

prazosin

its act by block α 1 receptors

effects

1-vasodilation

2- direct relaxation of smooth muscle of blood vessels

3- Don't affect RBF

5- ↓BP and lipid profile (cholesterol and triglyceride)

Uses :

1- Hypertensive patient with renal disease
2- Acute heart failure
3- Urine retention in benign prostate hypertrophy

Adverse effect :

F→ First dose syncope

F→ Fluid retention

U→ Urine incontinence

Selective α 2 blocker

Yohimbine

Is competitive α 2 receptors antagonist .

Pharmacological effects:

1- CNS stimulation
2- ↑ BP by increasing parasympathetic tone
3- ↑ HR

Adiminstration : IV and IM .

USES : reverse the effect of α 2 agonist .

Ergot alkaloids

Natural	**Semisynthetic**
Ergotamine	Dihydroergotamine
Ergometrine	Methylergometrine
Ergotoxin (very toxic)	Dihydroergotoxin
	Bromocriptine

Note : all ergot alkaloids stimulate vomiting center

Caffeine increase the absorption

Drug	Properties	Effect	Uses
Ergotamine	Partial agonist for α 1 and 5HT receptor	Vasoconstriction of cerebral blood vessels	Migraine
Ergometrine	Agonist α 1	Vasoconstriction and uterine contraction	Post-partum hemorrhage
Dihydroergotoxin	Antagonism of α 1	Vasodilation of cerebral blood vessels	Cerebral insufficiency
Bromocriptine	Dopamine receptor agonist	↓ prolactin secretion	Treat Parkinson Treat hyperprolactinemia

Beta blocker

1- β 1 and β 2 blockers :propranolol , nadolol, satolol and timolol
2- β 1 blockers: atenolol , esmolol ,metoprolol
3- β 1 blocker with direct vasodilator : carvedilol and labetalol

pharmacokinetics :

1- absorbed well
2- extensive first pass metabolism

	Nonselective beta blockers	**Selective beta blockers**
1	Propranolol	atenolol
2	Lipophilic	Hydrophilic
3	CNS effect	no
4	↑ distribution	↓ distribution
5	Need liver metabolism to be more water soluble	no
6	Short duration	Long duration
7	Multiple dose	One tablet daily

Pharmacodynamics

1- heart : decrease HR
2- Decrease blood pressure
3- Bronchial constriction
4- Eye: decrease intraocular pressure

5- CNS : beta2 presynaptic → ↓ NE release → sedation →depression

Beta blocker with special effect

1- Propranolol: membrane stabilization action so it have local anesthetic effect and antiarrhythmic action .
2- Pindolol: partial agonist---no brady cardia
3- Esmolol: very short acting use during surgery to prevent arrhythmia .
4- Labetalol: beta and alpha 1 blocker ----pheochromocytoma .
5- Carvidolol : antioxidant action .

Uses :

1- Hypertensive patient .
2- Ischemic heart disease .
3- Supraventricular arrhythmia
4- Hyperthyroidism
5- Glaucoma (betaxolol)
6- Pheochromocytoma .(timolol).

Adverse effects:

1- Fatigue due to ↓COP and ↓ blood supply of skeletal muscle
2- Bronchoconstriction .
3- Bradycardia
4- Peripheral ischemia.

Adrenergic neuron blocker

α - methyldopa

mechanism of action : its act by enter in the NE synthesis as a false substrate which result in α - methylnorepinephrine (false transmitter) which act on α 2 receptor .

uses : treatment hypertensive pregnant

clonidine

reserpine

mechanism of action :

this drug facilitate the NE release from the nerve ending and prevent reuptake 2 to the vesicle which result in destroyed by MAO leading to depletion of NE , D and 5HT .

direct acting parasympathomimetics

1- Acetylcholine

Mechanism of action :

Its stimulate muscsrinic and nicotinic receptors

Note : Ach have no therapeutic uses because of :

- Short duration →destroyed by ChE enzyme rapidly during second .
- Non-selective drug .

Antagonism : atropine is specific antagonist at muscarinic receptor .

Cholinergic receptor

Receptors	M1	M2	M3	Nm	Nn
Site	Gastric	Cardiac	Glandular	Skeletal m.	Ganglia
effect	↑HCl from the parietal cells	↓ HR (Bradycardia)	1- Bv. Non innervated receptors →vasodilator 2-contraction of wall of stomach and relaxation of sphincters 3-gland (aquas gland) ↑ secretion 4-eye :miosis ↓ IOP		

Direct acting parasympathomometic : acting on M and N receptors

Indirect acting parasympathomometic: drugs that prevent destroy of Ach by pseudocholinesterase and true cholinesterase

Note : the difference between them

	True cholinesterase	Psuedocholiesterse
1	CNS, NMJ,RBC	PLASMA , liver
2	Specific for ChE	NON specific , it can metabolize heroin , procaine ans succinylcholine
3	Metabolize Ach in synapse	Metabolize Ach in blood stream
4	Essential for life	Non .

Direct acting parasympathomometic:

1- Carbachol : its agonist on M and N receptors , have resistance to ChE so its have long duration of action 2-3h .

Use as eye drop to treat glaucoma .

2- Bethanecol : its agonist on M receptors only , have resistance to ChE.

Uses :

1- SC to treat the distention of the U.B.
2- SC to treat GIT and uterine atony .

Precaution :

1- oraganic obstruction .

2- bronchial asthma .

3- Pilocarpine : agonist on M and N receptors used in glaucoma .

Side effects

D→ diarrhea ,

U→ uresis

M→ miosis

L→ lacrimation

E→ emesis . excitation of CNS

S→ Salivation

Indirect parasympathomimetic

- Reversible - Indirect parasympathomimetic (carbamylation)
- Irreversible - Indirect parasympathomimetic (phosphorylation)→ organophosphorus compound .
- **Reversible - Indirect parasympathomimetic (carbamylation)**
  This group of drug inhibit the ChE enzyme by carbamylation .
  1- Physostigmine
  2- Neostigmine
  3- Pyredostigmine
  4- Edrophonium .

Physostigmine	**Neostigmine**
Plant alkaloids	Synthetic
Tertiary amine	Quaternary amine
Cross BBB	NOT
High lipid soluble (polar)	Not absorb orally(not polar)
Have CNS effect	Not
Uses :	Uses :
1- Glaucoma 2- Ruminal atony 3- In myasthenia gravis 4- Treat toxicity of atropine	1- Urine retention 2- Paralytic ileus 3- Ruminal atony 4- Myasthenia gravis 5- Muscle relaxant poisoning

Note :

1- in case of poisoning with physostigmine use atropine as antidote
2- Neostigmine have 2 mechanism to treat myasthenia gravis
- ChE inhibitor →↑Ach
- Direct acting on NMJ →Nm receptor .

3- Neostigmine +atropine to treat block M receptors .
4- Edrophonium : more selective on NMJ but have short duration of action so it uses for diagnosis myasthenia gravis .
5- Pyredostigmine more selective on NMJ , not need atropine to block M receptors .

Irreversible - Indirect parasympathomimetic (phosphorylation)→ organophosphorus compound .

1- Insecticide , malathion , parathion .
2- Ecothiophate
3- Nerve gases ---- sarin and soman
   - These compound have very rapid of absorption (skin , orally and inhalation)

- These compound make covalent bond with the enzyme
- Complete inhibition occur in 12 h.
- 3h 50% of enzyme inhibited …….aging of the enzyme .

Signs of poisoning

DUMBELSS

Muscle twitches

Treatment :

1.atropine

2. pralidoxime

3. diazepam

Cholinergic antagonist

Muscarinic receptor antagonist :

1- Atropine
2- Hyoscine (scopolamine).
3- Glycopyrrolate
4- Pirenzepine
    - Act as selective M1 receptor antagonists
    - Used to treat peptic ulcer
    - It reduce gastric acid secretion and reduce muscle spasm
    - Not cross blood brain barrier

Atropine sulfate :

Mechanism of Action

Its competitive antagonize Ach at muscarinic receptors .

Therapeutic uses:

- Preanesthetic to reduce salivary and respiratory secretion .
- Treat renal and bilary colic .
- Treat anti – ChE Toxicity.
- Treat mashroom toxicity .

- ----------

Ganglionic blocker :

It's a type of drugs that inhibits transmission between preganglionic and postganglionic neurons in the ANS by acting as nicotinic receptors antagonist .

1- **Nicotine** : is an agonist Ach , but in high doses it block ganglia .
2- **Hexamethonium** : it blocks Ach at the ganglia and cause ↑HR and ↓GIT motility .
3- **Botulinum toxin** (**BTX**) or **Botox** is a neurotoxic protein produced by the bacterium *Clostridium botulinum* and related species. It prevents the release of the neurotransmitter acetylcholine from axon endings at the neuromuscular junction and thus causes flaccid paralysis. The toxin is also used commercially in medicine, cosmetics and research.

Muscle relaxant :

Classification

1- Agent acting on NMJ

-competitive non- depolarizing agents : curare

-depolarizing agent: succinylcholine .

2- centrally acting M relaxant :xylazine , diazepam .

3- local anesthesia as lidocaine .

4- direct acting M relaxant as dantroline.

competitive non- depolarizing agents

agent antagonize N receptors at NMJ causing muscle relaxation .

- Tubocurarine
- Aminoglycosides
- Pancuranium
- Gallamine

depolarizing agent

succinylecholine (Ach-ch)

agent depolarizing muscle membrane after stimulation of N receptors causing muscle relaxation .

note

1- metabolize by pseudocholiesterase in plasma and liver .

2- has short duration of action in horses because high level of pseudocholiesterase

3- dangerous in ruminant because of low level of pseudocholiesterase .

4- ChE inhibitors potentiate the action of succinylecholine .

5- not cross BBB.

6- It ↑HR and BP because the release of adrenaline

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centrally acting M relaxant :xylazine , diazepam, tizanidine

it act on brain stem and has hypnotic effects .

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direct acting M relaxant

dantroline : it inhibit muscle contraction by preventing release of calcium from sarcoplasmic reticulum .act as antagonize to ryanodine receptors .

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local anesthetic

It block the voltage – gated Na channels in the neuronal cell membrane .

lidocaine for example

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clinical uses of muscle relaxant :

1- general anesthesia

2- chemical restraint for wild animal

3- strychnine poisoning

4- muscle disorder

Handbook of Veterinary Pharmacology Second edition by Walter H. Hsu