Drugs modifying cholinergic transmission

By

Dr.Nashwa Abo-Rayah

Assistant prof. (clinical &experimental pharmacology)

Mu'tah University- Faculty of Medicine

OBJECTIVES

- 1- **The main neurotransmitter in the parasympathetic nervous system**
- 2- **Cholinergic receptors**
- 3- **definition of parasympathomimetic drugs**
- 4- **choline esters**
- 5- **cholinomimetic alkaloids**
- 6- **anticholinestrases**
- 7- **organophosphate poisoning**
- 8- **Alzihymer's disease**
- 9- **Myasthenia gravis**

The main neurotransmitter in the parasympathetic nervous system:

ACETYLCHOLINE

Cholinergic neuron (ACH is neurotransmitter): sites of acetylcholine:

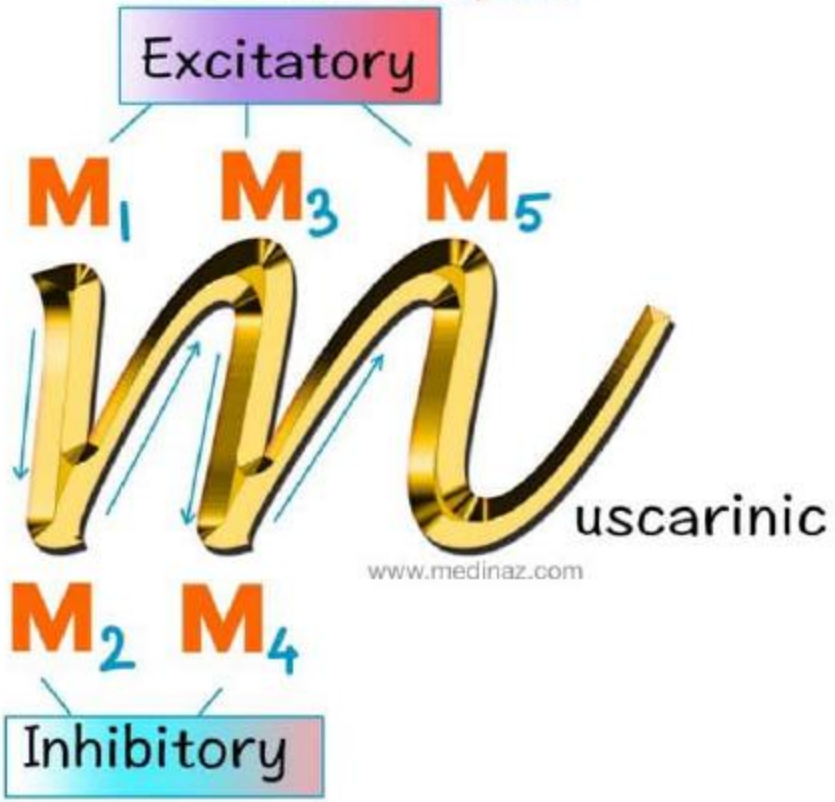
1- parasympathetic nerve endings
2- some sympathetic nerve fibers (sympathetic cholinergic):
-preganglionic fibers terminating in the adrenal medulla
-Sweat glands: except sweat glands in palms and forehead which receive sympathetic adrenergic nerve fibers.
3- autonomic ganglia (both parasympathetic and sympathetic)
4- postganglionic fibers of the parasympathetic division, - voluntary muscles of the somatic system (neuromuscular junction)
5- CNS: many functions especially memory (pathogenesis of Alzheimer disesse)

Is acetylcholine inhibitory or excitatory neurotransmitter?

- **Excitatory:**
- M1,3,5 receptors: increasing intracellular calcium ion
- Nicotinic receptors: increasing intracellular sodium ion
- **Inhibitory:**
- M2,4: increasing potassium ion efflux.

Easy way to Remember

Muscarinic receptors



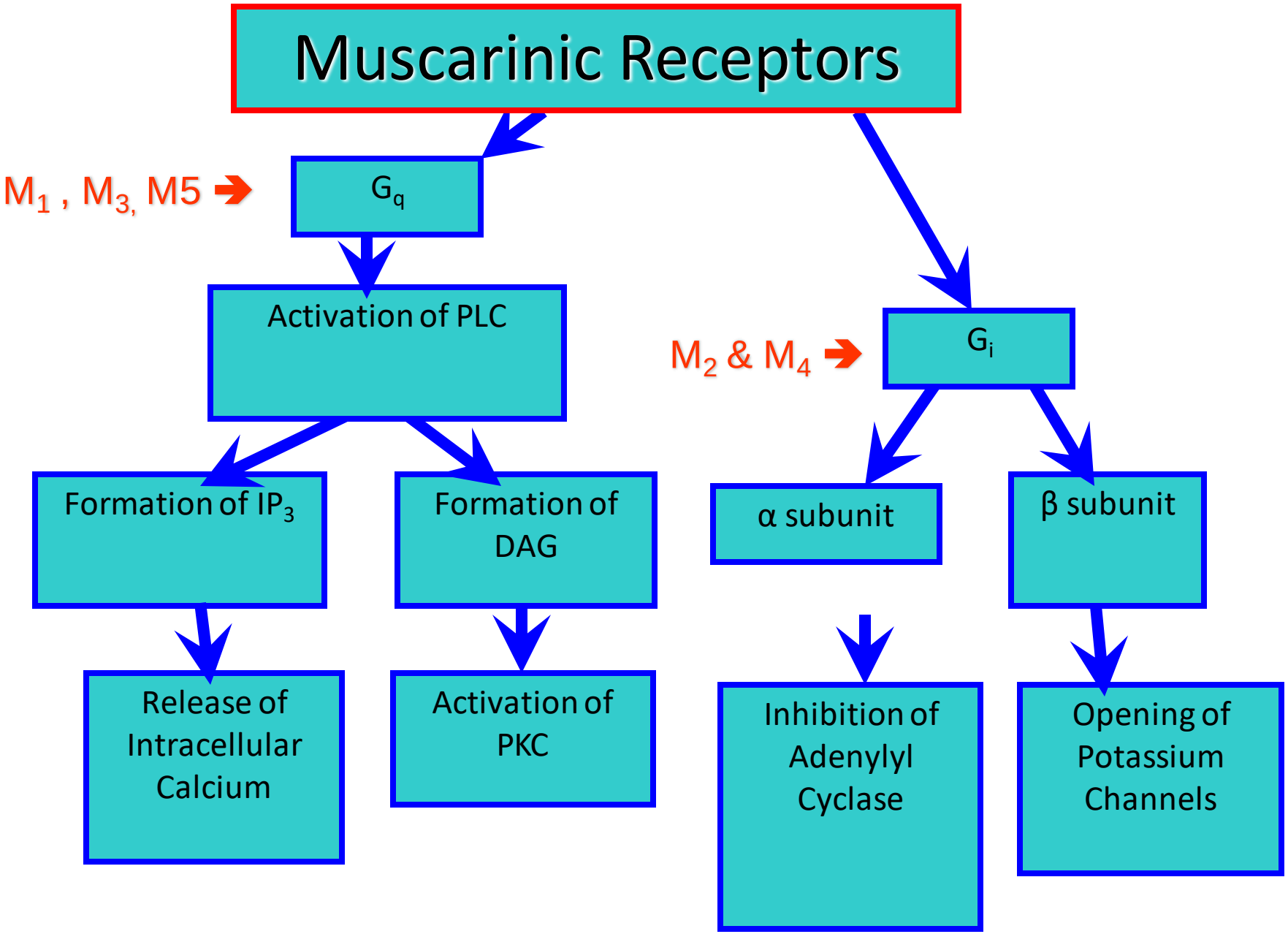
Cholinergic receptors

- **Muscarinic: peripheral cholinergic receptors**

- **Nicotinic : central cholinergic receptors**
- **Nm:** muscular: muscle contraction: increasing intracellular Na+.
- **Nn:** neural: increase intracellular Na+
- 1- CNS stimulation
- 2- increase secretion of suprarenal gland
- 3- stimulation of autonomic ganglia

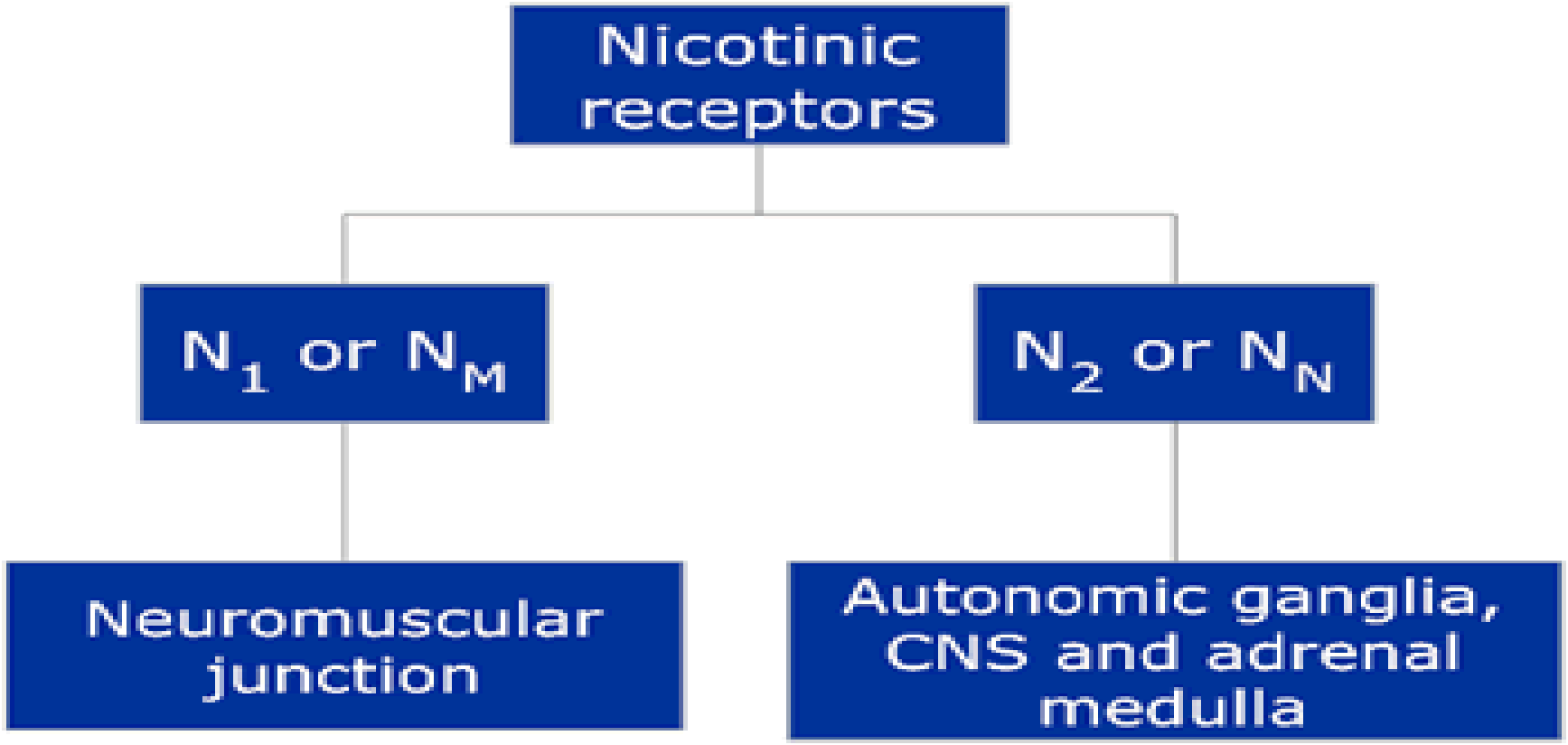
Muscarinic receptors

Characteristic	M_1 (neutral)	M_2 (cardiac)	M_3 (glandular/ smooth muscle	M_4	M_5
Site	CNS, smooth muscles in Glands: gastric, salivary, endothelium	Heart: atria: SAN Presynaptic	Exocrine glands: gastric, salivary, etc. Smooth muscle: GI tract, eye Blood vessels: endothelium(not innervated???	Presynaptic CNS	CNS
physiological action	CNS excitation Gastric secretion Increase release of EDRF	Cardiac inhibition Control of acetylcholine release (-ve feed back)	Gastric, salivary secretion; GI smooth muscle contraction; Ocular accomodation; Vasodilatation	Presynaptic inhibition of neurotrans mitter release	CNS stimulation
Agonist (non-selective)	ACh; Carbachol; (Oxotremorin e,	As M_1	As M_1	As M_1	As M_1
Antagonist (non-selective except those in italics)	Atropine; Dicycloverine (dicyclomine); Ipratropium; *Pirenzepine;*	Atropine Ipratropium *Gallamine*	Atropine Ipratropium	Atropine Ipratropiu m	Atropine Ipratropium


Muscarinic Receptors
M1 , M3, M5
Gq
Activation of PLC
Formation of IP3
Formation of DAG
Release of Intracellular Calcium
Activation of PKC
M2 & M4
Gi
α subunit
β subunit
Inhibition of Adenylyl Cyclase
Opening of Potassium Channels

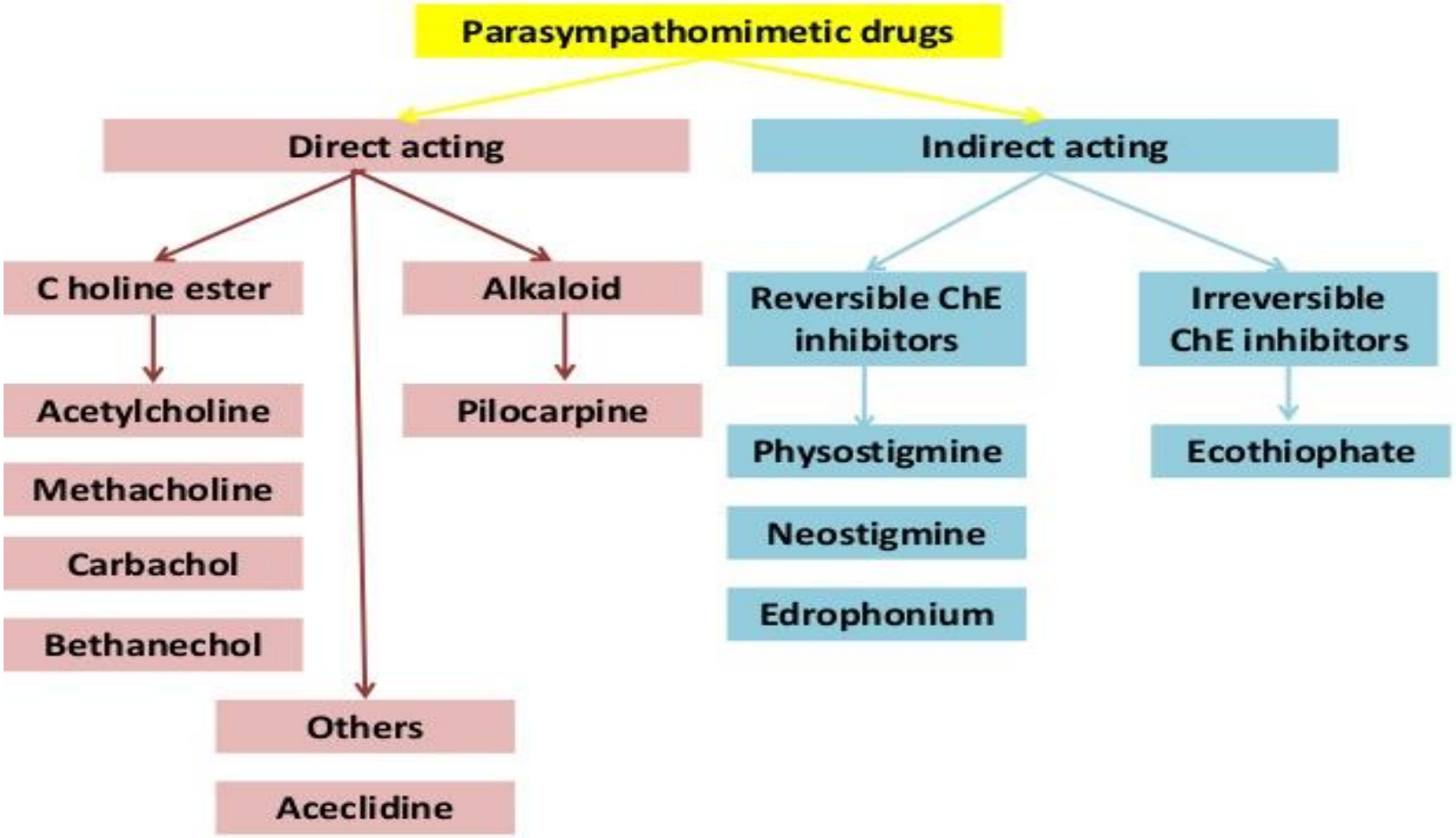
M_1 and M_3	G_q coupled	↑ phospholipase C →↑ IP_3, DAG, Ca^{2+}
M_2	G_i coupled	↓ adenylyl cyclase →↓ cAMP
N_N and N_M	No 2nd messengers	activation (opening) of Na/K channels

Table II-2-2. Cholinergic Receptor Mechanisms



parasympathomimetics=Cholinomimetics= Parasympathetic stimulants or agonists:

- Drugs that promote cholinergic transmission
- Drugs when administered give an effect similar to stimulation of parasympathetic nervous system.


Parasympathomimetic drugs
Direct acting
Indirect acting
C holine ester
Alkaloid
Acetylcholine
Pilocarpine
Methacholine
Carbachol
Bethanechol
Others
Aceclidine
Reversible ChE inhibitors
Irreversible ChE inhibitors
Physostigmine
Ecothiophate
Neostigmine
Edrophonium

Pharmacological Action of ACh & Cholinomimetics:

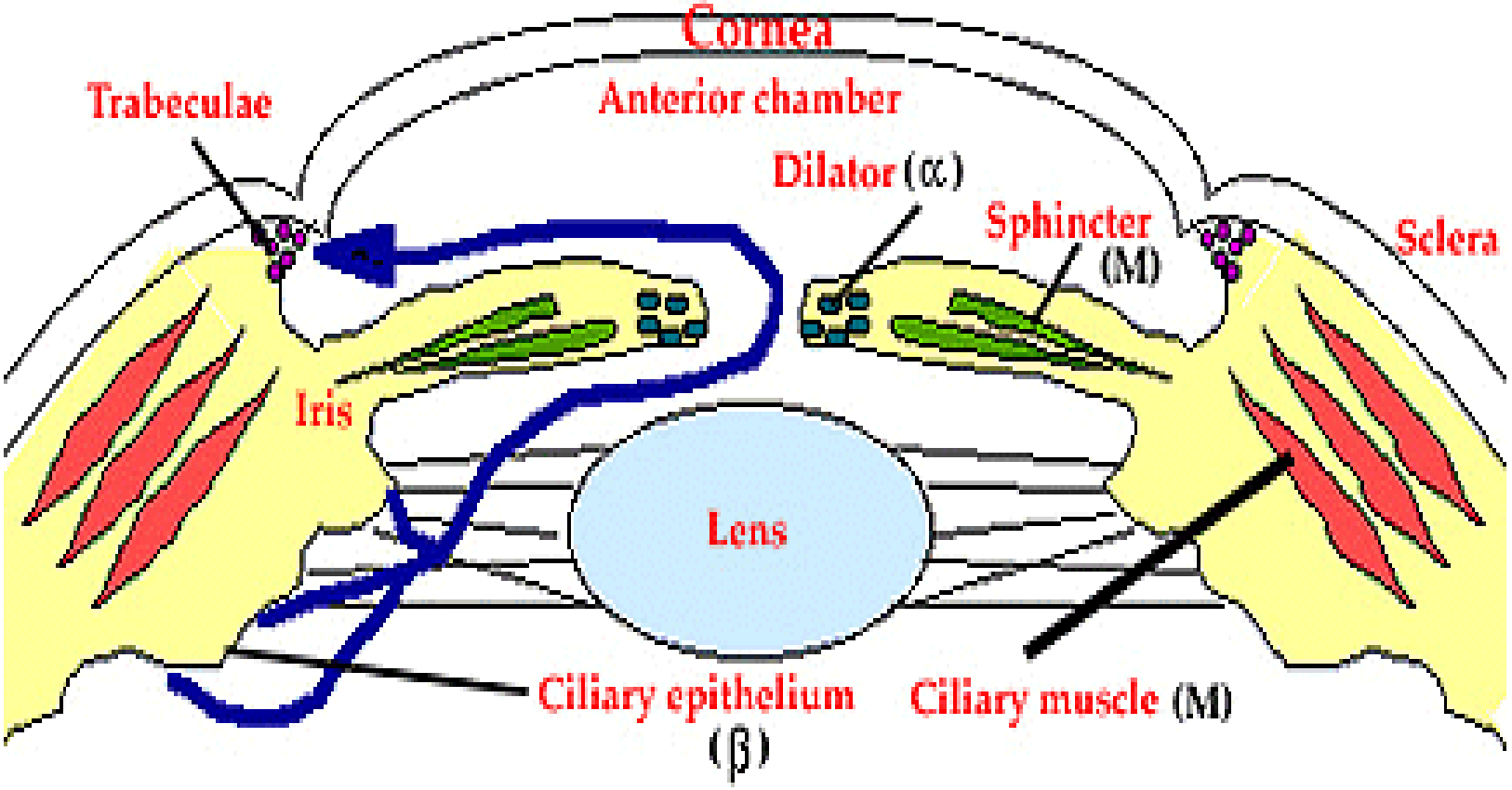
(A) Muscarinic actions

- **Heart: M2**
- Decrease in heart rate (sinus bradycardia): -ve chronotropic.
- Increase atrial conductivity
- Decrease in conductivity in A VN (-ve dromotropic) .
- No direct effect on ventricles

- **Blood Vessels**: Vasodilatation of arterioles and venueles .
- **Blood pressure:** Hypotension
- **Bronchi:** Bronchoconstriction
- **Respiratory secretion**: increase ciliary movement. Increase secretion

- **GIT:**
- Stimulation of the Motility of the smooth muscles of wall of GIT
- Sphincters: relaxation
- GIT Secretions: stimulation.
- **GENITOURINARY:**
- Detrusor muscle: stimulation.
- Sphincter: relaxation
- Trigone: urethral sphincter relaxation. This results in promotion of micturition.

- **EYE:**
- Twitches of upper eye lid (Nicotinic action).
- Stimulation of constrictor pupillae muscle (miosis).
- Spasm of ciliary muscle muscle (accomodation to near vision).
- Improvement of Aqueous humour drainage (decrease
- I.O.P).
- **Exocrine Glands:**
- Stimulation of all exocrine glands.
- Sweat glands --------- Sweating.
- Lacrymal glands ------ tears.
- Salivary glands ------- salivation.
- Bronchial and gastrointestinal gland

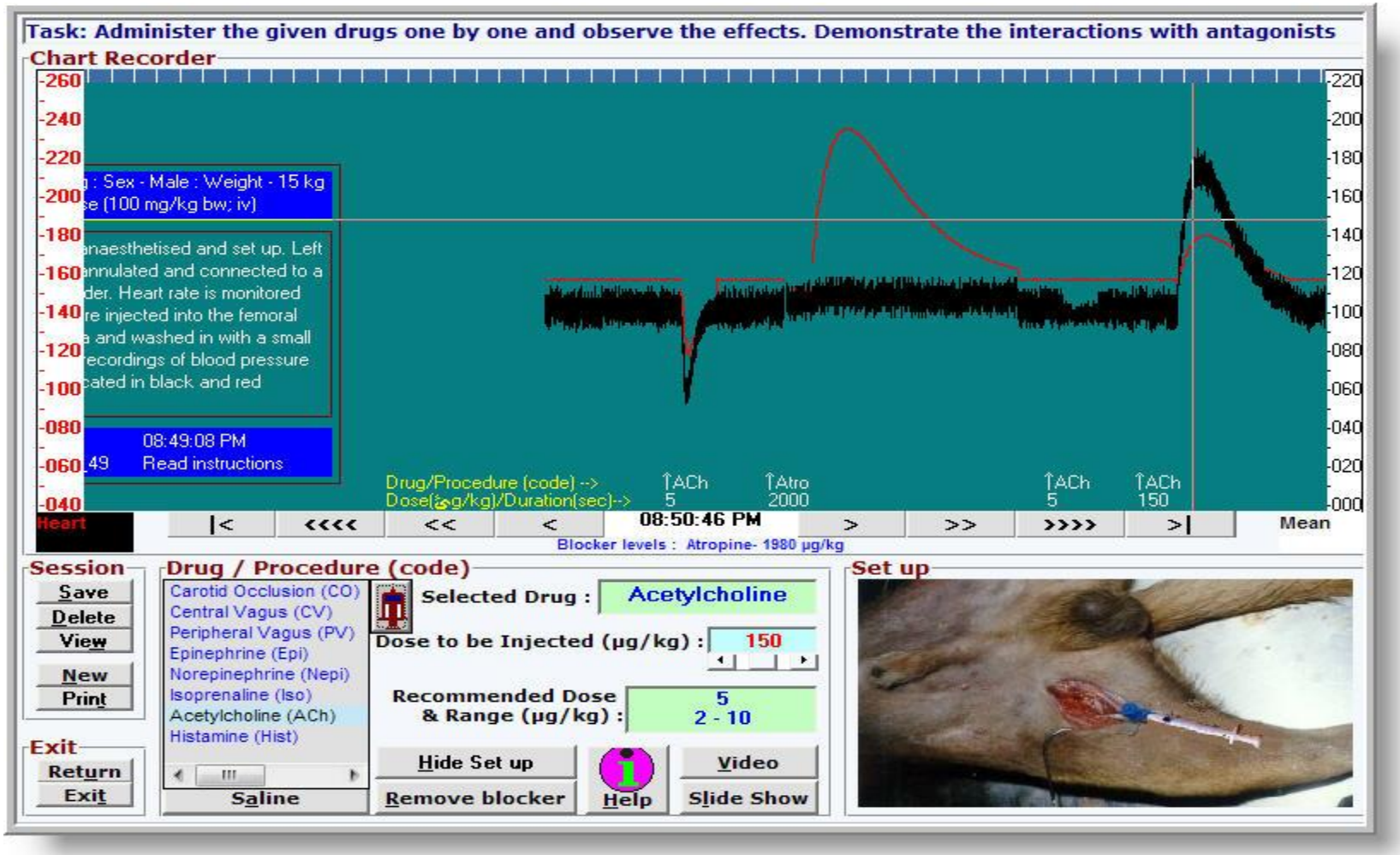

Cornea
Trabeculae
Anterior chamber
Dilator (α)
Sphincter (M)
Sclera
Iris
Lens
Ciliary epithelium (β)
Ciliary muscle (M)

(B) Nicotinic Actions:

- **1-Skeletal muscle**: Fasiculation and twitichs
- **2- Adrenal medulla**: Release of adrenaline and noradrenaline.

- **3-Autonomic ganglia:**
- **1- Small dose of ACH** produces a decrease in blood pressure (hypotension) of short duration. This effect is mediated through stimulation of muscarinic receptors. This hypotensive effect is blocked after injection of atropine.
- **2- Large dose of ACH after injection of atropine:** produces an increase instead of a decrease in the blood pressure. This effect is due to:
- a- Stimulation of sympathetic ganglia resulting in the release of adrenaline and noradrenaline .
- b- Stimulation of the adrenal medulla resulting in the release of adrenaline and noradrenaline

Acetylcholine reversal

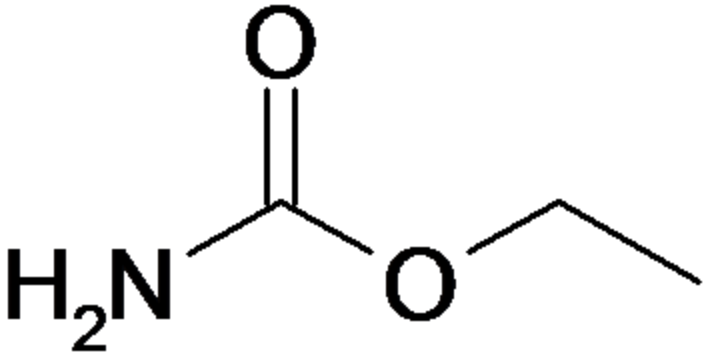


I- Choline esters

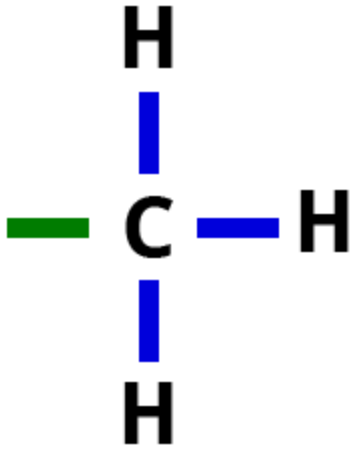
- 1) Actylcholine.
- 2) Methacholine.
- 3) Carbachol.
- 4) Bethacholine (bethanechol)

General properties:

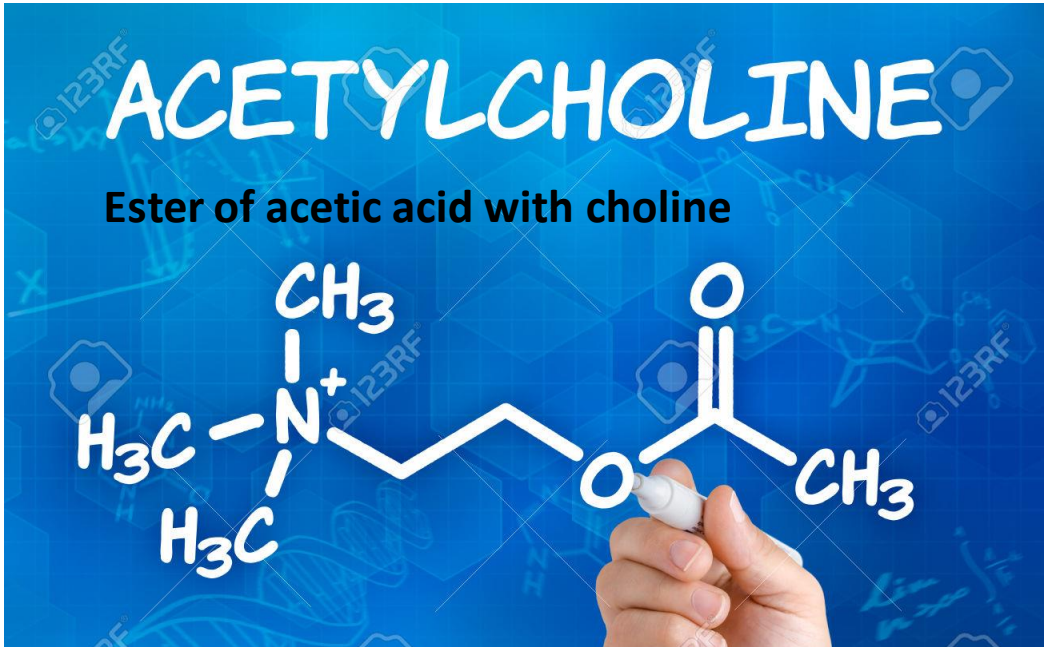
- l- Presence of the B- methyl group (methacholine, bethanechol) reduces the potency of these drugs at the nicotinic receptors .
- 2- The carbamic acid esters (carbachol,bethanechol) are completely resistant to hydrolysis by cholinesterase enzyme and have longer duration of action.
- 3- They are effective orally & parentrally.
- 4- They are more selective in their actions.

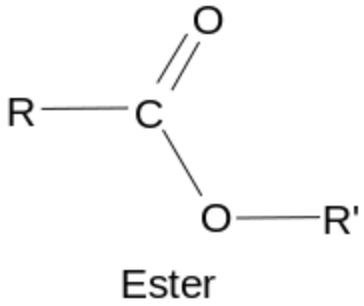


Carbamic acid ester



Methyl group





Pharmacological Differences of Choline Esters

	A.Ch.	Methacholine	Carbachol	Bethacholine
Chemistry	Ester of acetic acid with choline	Methyl derivative of A. Ch.	Carbonic acid ester of A.Ch.	Methyl derivative of carbachol.
Absorption from GIT	Nil	Partial	Complete	Complete
Duration	Very short	Intermediate	Long	Long
Hydrolysis	True Ch E Pseudo Ch E	True Ch E		
Nicotinic action	+++		+++	-------
Muscarinic action	++++	++++	++++	++++
Administ.	Parentral	Parentral	Locally in Eye	Orally
Uses	------	CVS	Glaucoma	GIT, Urinary T .

Clinical Uses of Cholinesters:

- l) Postoperative urine retention without obstructions (stone, constriction or enlarged prostate) e.g. bethacholine
- 2) Postoperative paralytic ileus or gastric atony e.g. bethacholine.
- 3) Open angle glaucoma.
- 4) Alternative with mydriatics to break adhesions between iris & lens.
- 5) Treatment of paroxysmal supraventricular tachycardia because they produce M2 mediated bradycardia.
- 6) Diagnosis of intermittent type of pheochromocytoma. Carbachol augments nicotinic receptor mediated adrenaline release from suprarenal gland. Increase in blood pressure by 30 mmHg systolic and to 15 mm Hg diastolic is diagnostic for pheochromocytoma
- 7) Treatment of xerophthalmia, xerostomia due to autoimmune parotitis and conjunctivitis) (SjOgren syndrome) (pilocarpine &cevimeline)

Choline Esters- Uses

- Acetylcholine not used because of its transient & non-selective action
- Others rarely used nowadays
- Bethanechol has been used in
  - Postoperative paralytic ileus & gastric atony
  - Postoperative/postpartum nonobstructive urinary retention
  - Neurogenic bladder atony
  - Congenital megacolon, and
  - Gastroesophageal reflux
- Methacholine was occasionally used to terminate paroxysmal supraventricular tachycardia (PSVT)

Contraindications of Cholinesters:

- 1) Angina pectoris (due to hypotension and coronary insufficiency).
- 2) Bronchial asthma (due to bronchoconstriction and increase in bronchial secretions
- 3) Hyperthyrodism (due to cardiac arrhythmia).
- 4) Peptic ulcer (due to ↑ gastric motility and secretions).
- 5) gastrointestinal and urinary hypotonia with organic obstruction

II- Pilocarpine (cholinomimetic alkaloid)

•It is a tertiary amine alkaloid which possesses muscarinic activity.

• Its action is similar to methacholine. It causes initial increase in blood pressure due to adrenaline release from suprarenal gland as a result of stimulation of nicotinic receptors in suprarenal gland followed by decrease due to M receptor mediated vasodilatation.

• When applied locally in the eye produces miosis and fall in intraocular pressure .

• It can be blocked by the muscarinic blocker (atropine) .

•It is resistant to hydrolysis by both pseudo & true-cholinesterase

Clinical Uses of Pilocarpine:

- 1) Glaucoma (open angle type) 1 % drops.
- 2) Alternative with mydriatics to break adhesions between iris and lens.
- 3) It is topically applied to promotion of hair growth in case of alopecia.
- It acts by increasing blood flow of the scalp by local vasodilatation .
- 4) In treatment of atropine over-dosage.
- 5) sjugreen syndrome

MUSCARINIC AGONISTS

Drug	Activity	AChE Hydrolysis	Clinical Uses
ACh	M and N	+++	Short half-life—no clinical use
Bethanechol	M	–	Rx—ileus (postop/neurogenic), urinary retention
Methacholine	M > N	+	Dx—bronchial hyperreactivity
Pilocarpine, cevimeline	M	–	Rx—xerostomia, glaucoma (pilocarpine)

Table II-2-3. Properties of Direct-Acting Cholinomimetics

III-Anticholinesterases

III-Anticholinesterases

Reversible

(Weak bond)

Produce transient carbamylation of the enzyme

Teriary amine

Physiostigmine

Quaternary amines

Neostigmine

Amenonium

Pyridostigmine

Irreversible

(Usually toxin)

Produces permanent phosphorylation of the enzyme

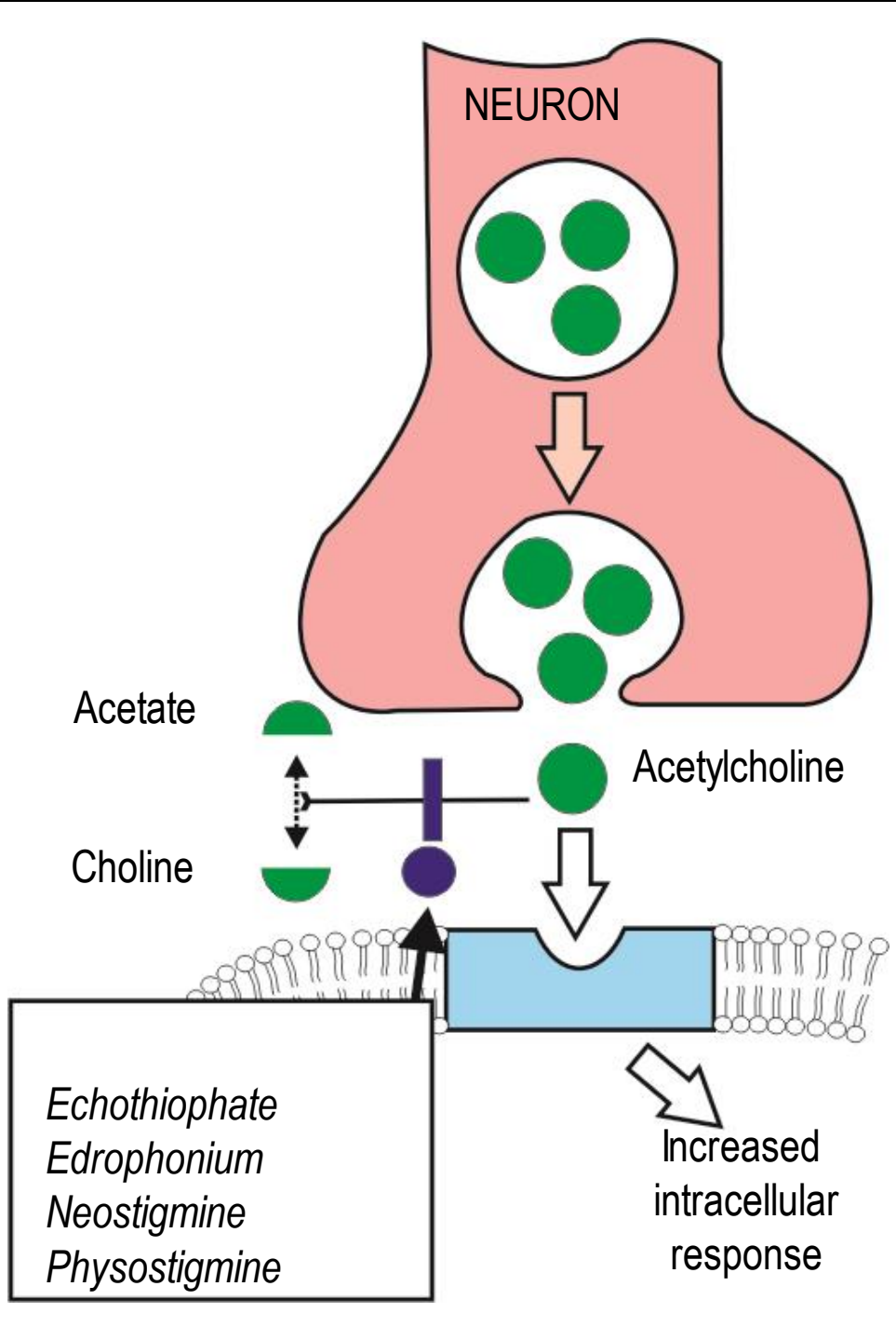
Organophosphoruscompunds

war gases: taban, sarine

Insecticide: Parathione

Topical eye drops: echothiophate

Mechanisms of action of indirect (reversible) cholinergic agonists.



Pysiostigmine (eserine)	Neostigmine
Natural plant Teriary amine	Synthetic Quaternary amine
It passes blood brain barrier	It does not pass blood brain barrier
Complete absorption from GIT	Poor absorption from GIT
It stimulates cholinergic receptors in CNS	No effect on CNS
It stimulates muscarinic receptors indirectly by inhibition of metabolic inactivation of acetyl choline	
It stimulates nicotinic receptors indirectly by inhibition of acetyl choline metabolism	They stimulate nicotinic receptors • Indirectly by inhibition of metabolic inactivation of acetyl choline • Direct stimulation of nicotinic receptors in skeletal muscles
It is used in : • Atropine poisoning .It antagonizes both central and peripheral effects of atropine • Antidote in tricyclic antidepressant poisoning because their toxic effect is	It is used in : • Treatment of myasthenia gravis • Antidote to reverse the effect of neuromuscular blockers eg D-tubocurarine. • Treatment of paralytic ileus & postoperative urinary retention ,

From physiostgmine (neo)

One charge:ionized

Muscarinic and nicotinic

Inhibits both types of the enzyme

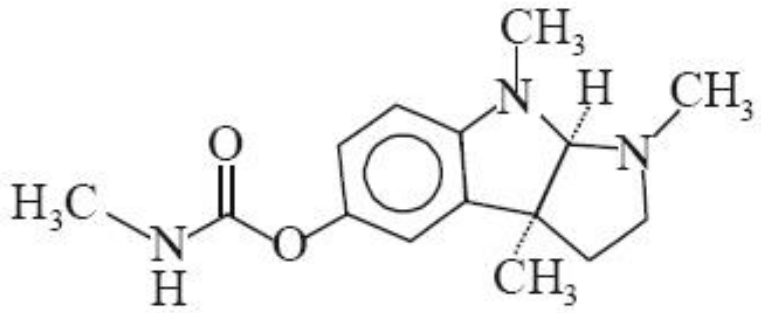
To increase Ach peripherally

1Anticholinestrase & direct stimulant of skeletal muscles

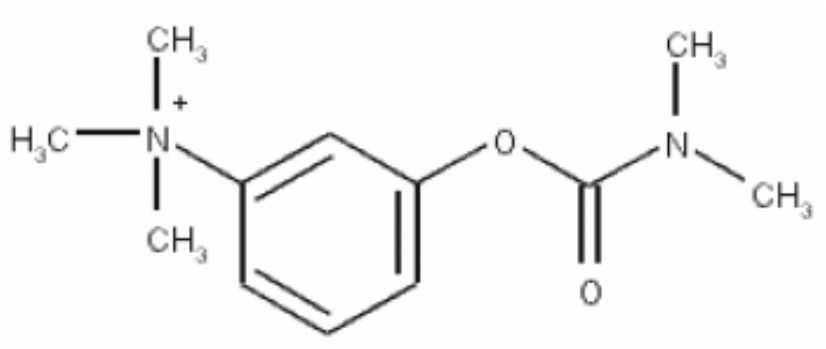
2- Administered with atropine?

due to atropine like effect • It is used in the treatment of Alzeheimer disease. • Improves memory. • It is used topically in treatment of acute and chronic glaucoma &reversion of the effect of mydriatics and to break intraocular adhesions **Dose** 0.5 % eye drops	to stimulate salivary secreation in Sjgreen disease • It is used in same indications as choline esters **Dose** 15 mg three times daily orally 0.5 mg intramuscular
Atropine (1-2 mg IV) is used in the treatment of physiostigmine poisoning to reverse cholinenergic effects of the drug Phenobarbitone may be used to reverse CNS effects	Atropine is used in the treatment of neostigmine poisoning to reverse cholinenergic effects of the drug Artificial respiration and oxygen therapy

**Main use to avoid systemic side effects, most powerful miotic



Physostigmine



Neostigmine

Neostigmine Vs Physostigmine

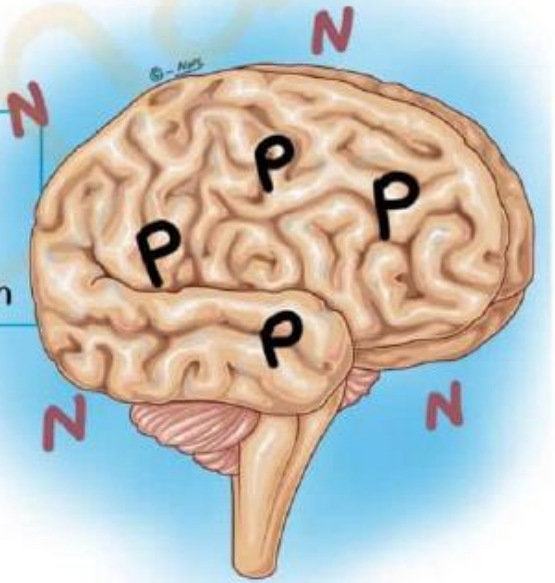
Neostigmine

Neo CNS = **No** CNS penetration

Physostigmine:

Phreely (freely)

crosses blood-brain



•Pyridostigmine is preferred over neostigmine in treatment of M.gravis?

•1- more selective on skeletal muscle: no need for atropine administration (no sever muscarinic side effects)

•2- longer duration of action: 5-6 hs while neostigmine duration of action is 2 hs.

•**Edrophonium (tensilon):**

•More selective than neostigmine and pyridostigmine: *no muscarinic side effects*.

•Very Short duration of action: 5 min. → Diagnosis of M.Gravis: ***(tensilon test):*** parental edrophonium → Improvement of M.gravis symptoms e.g.ptosis.

Differential diagnosis of Maythinic crisis and cholinergic crisis: tensilon test:

Improvement of symptoms in M.crisis

Worsening of symptoms in cholinergic crisis

•**Donibezil, rivastigmine**: new drugs which are expensive.

•Anticholinestrase activity is only central

•No peripheral effects ⟹ treatment of **Alzihymer´s disease**: amnesia, dementia, loss of cognetive function due to degeneration of cholinergic neurons and accumulation of beta amyloid protein in CNS insulating neurons from each other.

Drug	Characteristics	Clinical Uses
Edrophonium	Short-acting	Dx—myasthenia gravis
Physostigmine	Tertiary amine (enters CNS)	Rx—glaucoma; antidote in atropine overdose
Neostigmine, pyridostigmine	Quaternary amines (no CNS entry)	Rx—ileus, urinary retention, myasthenia gravis, reversal of nondepolarizing NM blockers
Donepezil, rivastigmine	Lipid-soluble (CNS entry)	Rx—Alzheimer disease
Organophosphates	Lipid-soluble, irreversible inhibitors	Note: used as insecticides (malathion, parathion) and as nerve gas (sarin)

Table II-2-4. Properties of Indirect-Acting Cholinomimetics

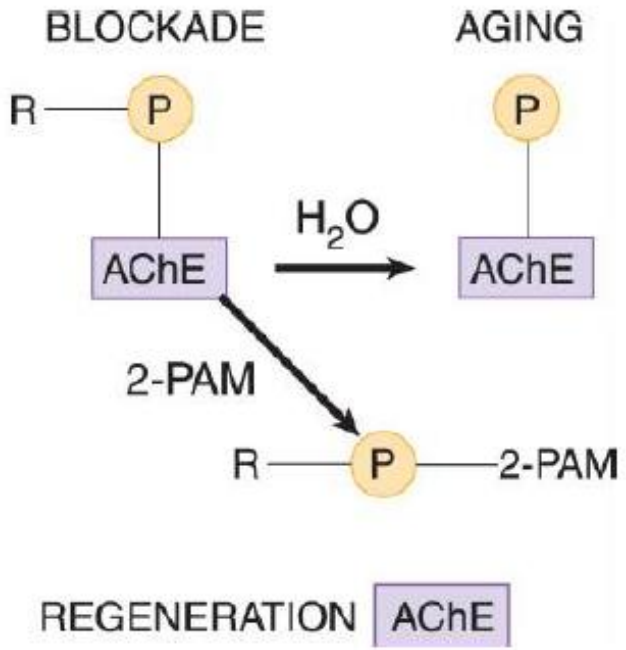
Long - acting (Irreversible) Cholinesterase Inhibitors

- **Organophosphates:**
- 1- Isoflurophate (DFP) Used in treatment of glucoma.
- 2- Echothiophate Used in treatment of glucoma: eye drops.(duration of action 2 weeks: not prefered)
- 3- Parathion Used as pesticides.
- 4- Malathion Used as pesticides.
- 5- nerve gases: sarin غاز الخردل, soman

Irreversibly Acting Cholinomimetics:

These compounds phosphorylate the esteratic site on AChE, at serine hydroxyl groups

1. phosphorylation; reversible by pralidoxime (2-PAM)
2. removal of a part of the organophosphate molecule (aging); complex no longer reversible by 2-PAM



R = leaving group
P = organophosphate

Figure II-2-2. Effects of Organophosphate on AChE

Symptoms and Signs of organophosphate poisoning:

•Rapid absorption even from skin with rapid accumulation in CNS.

•1- Nausea, vomiting, abdominal colic and diarrhea.
•2- Increase of salivation and sweating.
•3- Tightness of the chest with dyspnea.
•4- Bradycardia and hypotension.
•5- Muscle twitches and convulsions.
•6- Constricted pupil (miosis).
•7- cause of death respiratory failure: bronchoconstriction, increased bronchial secretions, inhibition of RC, paralysis of resp.muscles.

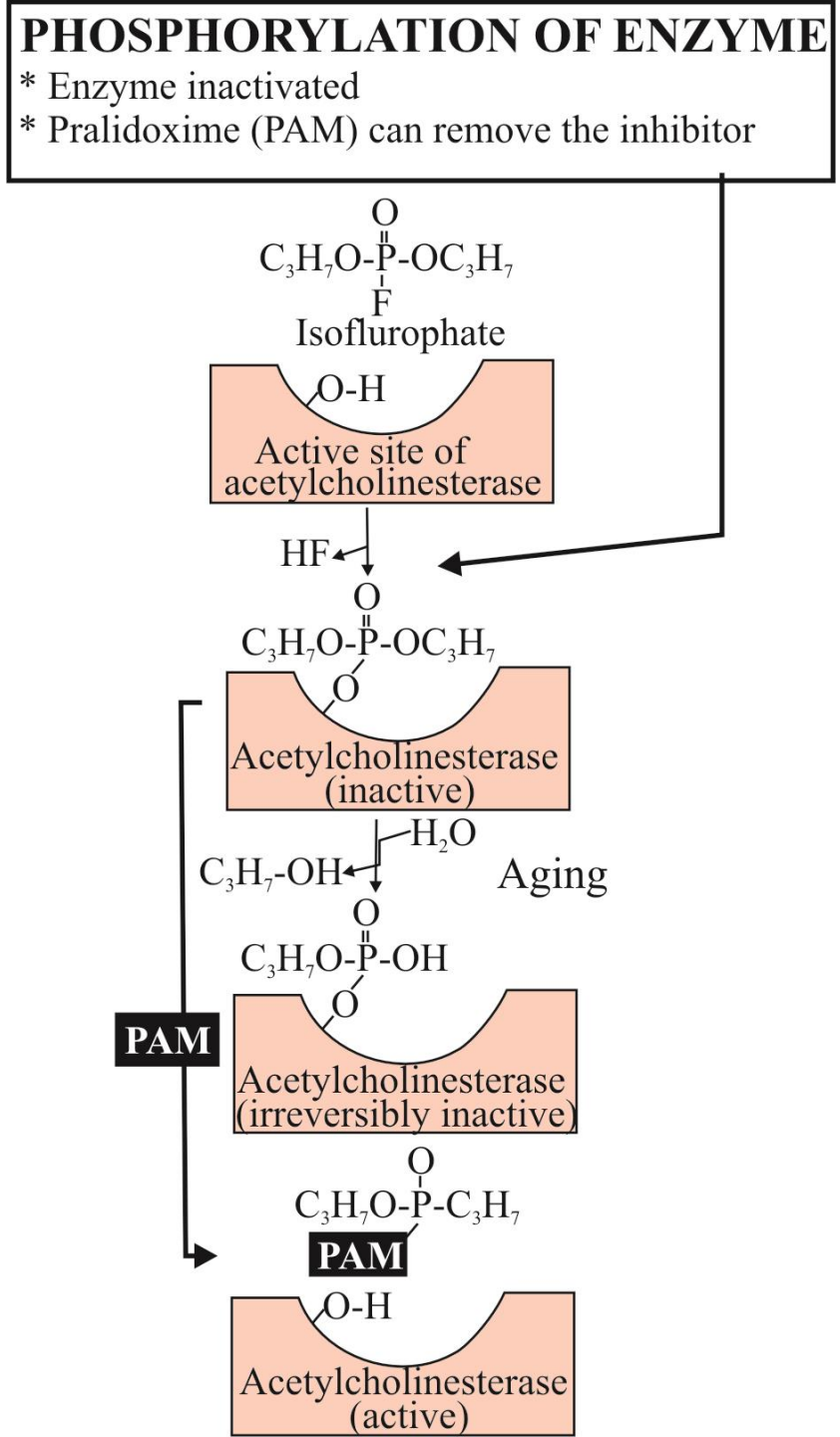
CLASSIC CLUE

AChE inhibitor poisoning: "Dumbbeelss"

- Diarrhea
- Urination
- Miosis
- Bradycardia
- Bronchoconstriction
- Emesis
- Excitation (CNS/muscle)
- Lacrimation
- Salivation
- Sweating

Covalent modification acetylcholinesterase by isoflurophate; also shown is the reactivation of the enzyme with pralidoxime.

Covalent bond takes 12 hours to produce complete inhibition of the enzyme: aging of the enzyme



Management of organophosphate poisoning:

Assessment of patient: ABC

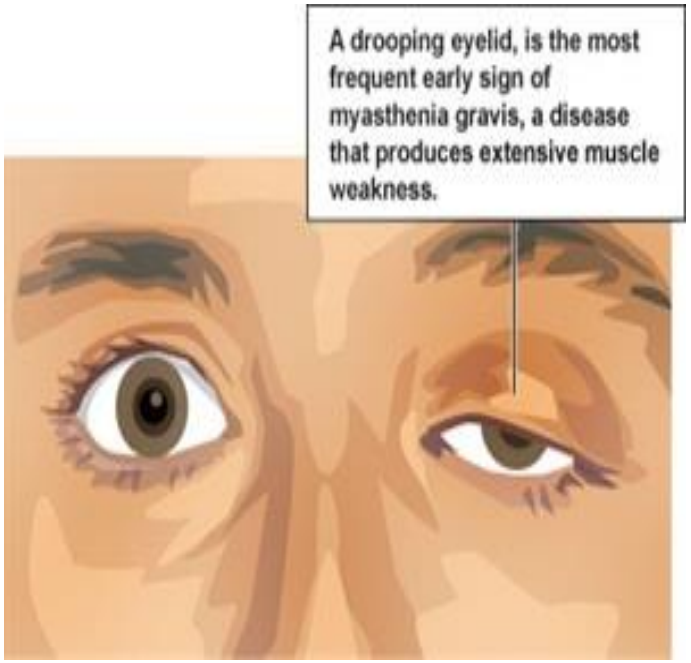
A: air way B: breathing C: circulation: pulse, BP,

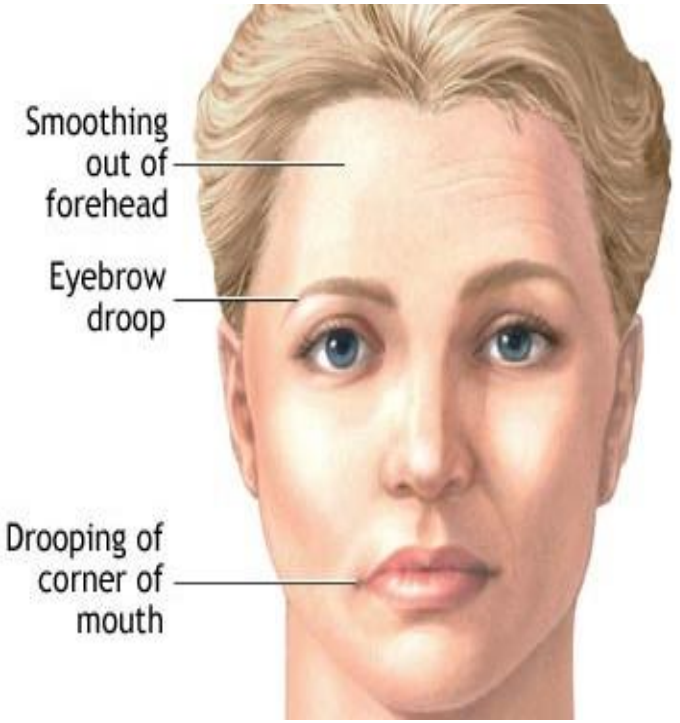
- 1- Endotrachial intubation with artificial respiration.
- 2- Atropine 2 mg I.V. repeated/5 min. until signs of atropinization appears. (dry mouth, dilated pupil and tachycardia, increase BP) FOLLOW UP FOR 24-48 hs. WHY? **Life saving drug**
- 3- diazepam (10 mg IV) preferred to barbiturates to treat convulsions.
- 4- Fresh blood transfusion.
- 5- Oximes (PAM, pralidoxime): CHOLINESTRASE REACTIVATORS: DEPHOSPHORYLATION: break the covalent bond.
- The treatment with Oximes should be within hours (2gm in 5% Dextrose 100 ml I. V. drip in 20 min.). Oximes produce their effect through:-
- a) Direct reaction with enzyme.
- b) Direct reaction with inhibited enzyme.
- c) Reactivation of inhibited enzyme.

Myasthenia gravis

- It is an autoimmune disease (genetic) in which there is an antibody to the A.Ch. nicotinic Nm receptor system which impairs the responsiveness of the neuromuscular junction resulting in weakness and rapid fatigability of skeletal muscles.
- More proximal muscles are affected: ptosis, weak mastication muscles, drop of mouth angle, shoulder girdle.
- Bulbar muscles when affected: patient dies.

Manifestations of M.gravis





- **Causes:**
- 1- Curare like substance circulating in blood.
- 2- Abnormal motor end plate poorly sensitive to A.Ch.
- 3- Decrease of ACh Concentration at nicotinic receptors at motor end plate.
- 4- Increase of ACh cholinesterase activity.
- 5- Autoimmune disease affects motor end plate.

- **Diagnosis**
- Neostigmine 1.5 mg + 0.6 mg atropine (to block muscarinic effect) are injected IM this improves muscle weakness.
- Edrophonium 2 mg IV if the first dose is without effect 8 mg are injected after 45 seconds.

Treatment:

•**1- Anticholinesterases: e.g. neostigmine, pyridostigmine** and ambenonium (Ambenonium was withdrawn from the market in the United States in 2010).why?

•Atropine, belladonna, ganglionic blocking agents (eg, mecamylamine), quinine, or quinidine decrease effectiveness of ambenonium.

•Cholinergic agents (eg, guanidine) because the risk of side effects may be increased

•**N.B. Excessive dosage of an anticholinesterase can lead to prolonged** stimulation of nicotinic receptors (Nm) by ACh resulting in a depolarizing blockade of the neuromuscular junction. Therefore, muscle weakness in myasthenia gravis can be the result of either inadequate or excessive dosage of anticholinesterases (cholinergic crisis)

•• An antimuscarinic agent is necessary to block the muscarinic effect of ACh especially if large doses of anticholinesterase are given e. g atropine or propantheline.

- **2- Immunosuppressive drugs:**
- Prednisolone, azathioprine and cyclosporine.
- **3- Thymectomy should be considered in myasthenia associated with a** thymoma (tumor of the thymus gland)
- **4- Plasmapharesis to remove circulating antibodies directed against** nicotinic receptors.
- **5- Artificial respiration in acute crises.**
- **6- Potassium chloride because it promote depolarization of skeletal** muscles.
- **7- Ephedrine due to its anti-fatigue effect via B2 mediated increase** glycogenolysis and muscle blood flow and muscle potassium


Thank you