Direct & indirect agonists (muscarinic agonists) (parasympathomimetics)

By

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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)

Cholinergic receptors

- **Muscarinic: peripheral cholinergic receptors**

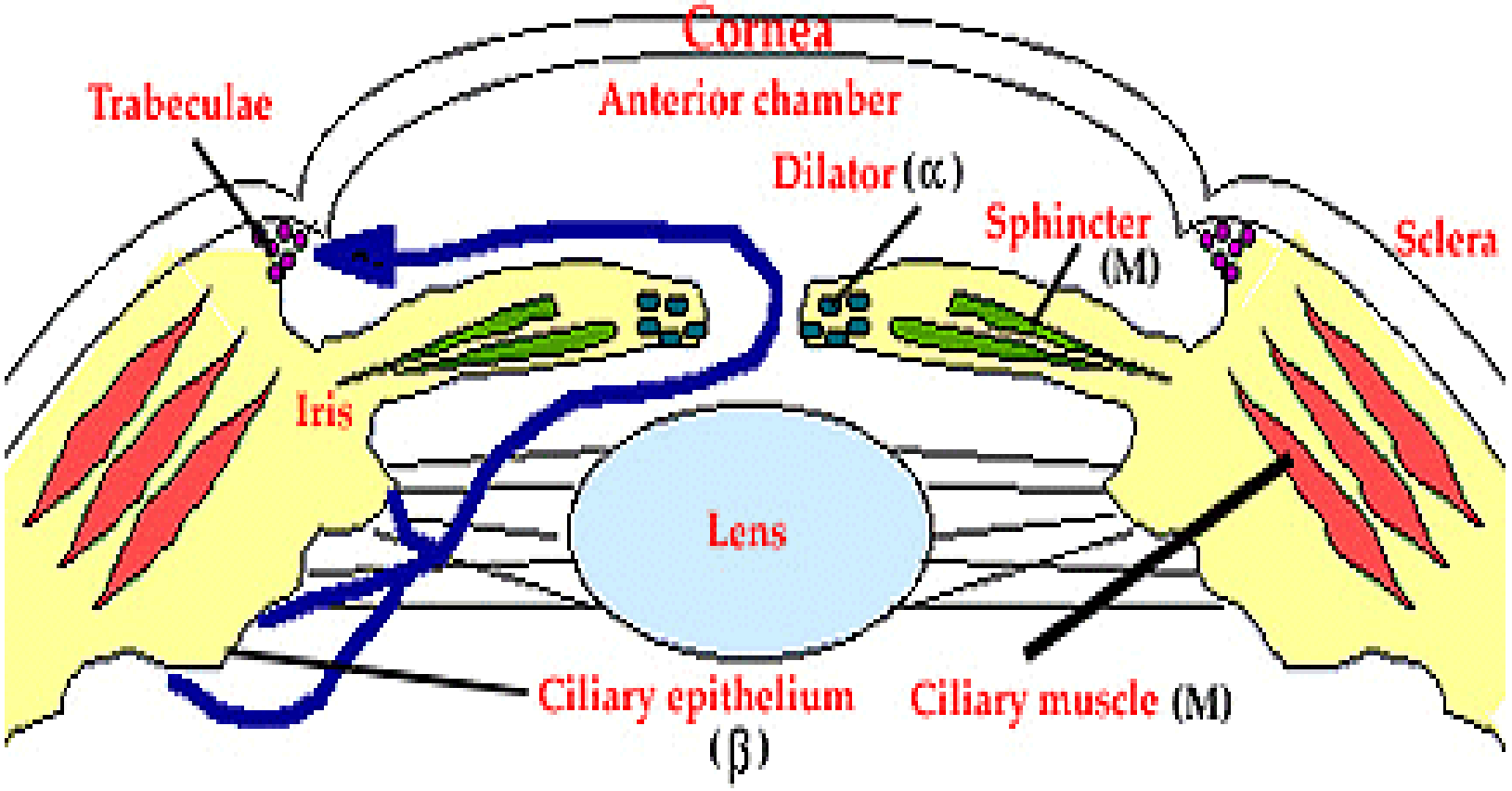
- **Nicotinic : central cholinergic receptors**
- **Nm:** muscular: muscle contraction: increasing intracellular Na+.
- **Nn:** neural: increase intracellular Na+
- 1- CNS stimulation
- 2- increase secretion of suprarenal gland
- 3- stimulation of autonomic ganglia

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.

Muscarinic receptors

Characteristic	M_1	M_2 (cardiac)	M_3 (glandular/ smooth muscle	M_4	M_5
Site	1-CNS, 2-smooth muscles in Glands: gastric, salivary	1-Heart: atria: SAN 2-Presynaptic	1-Exocrine glands: gastric, salivary, etc. 2-Smooth muscle: GI tract, eye 3-Blood vessels: endothelium(not innervated???	1.Presynaptic 2.CNS	CNS
physiological action	CNS excitation Gastric secretion	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	As M_1	As M_1	As M_1	As M_1
Antagonist	Atropine *Pirenzepine;*	Atropine Ipratropium	Atropine Ipratropium	Atropine Ipratropium	Atropine Ipratropium


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

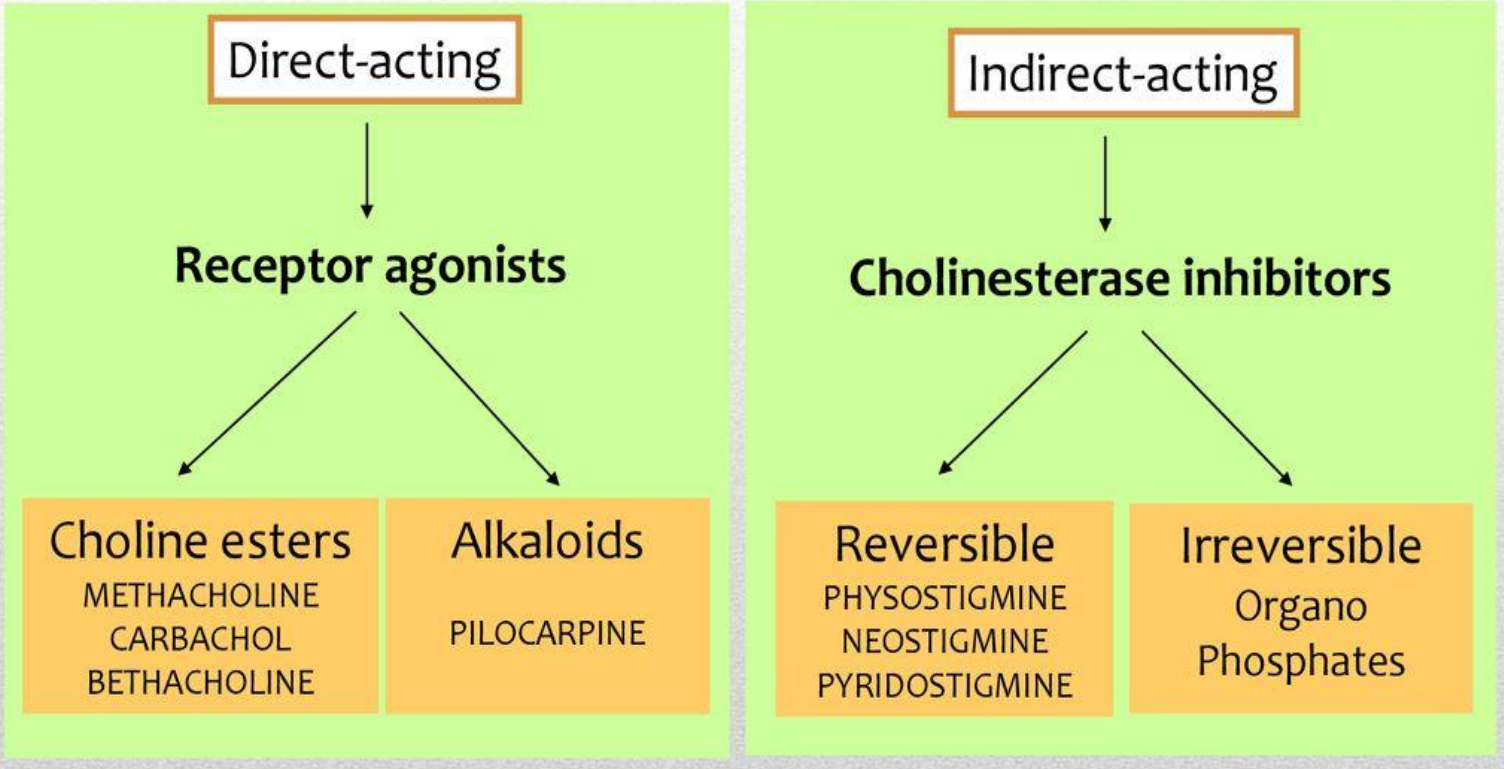
M_1 and M_3	G_q coupled	↑ phospholipase C →↑ IP_3, DAG, Ca^{2+}
M_2	G_i coupled	↓ adenylyl cyclase →↓ cAMP
N_N and N_M	No 2nd messengers	activation (opening) of Na/K channels

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



Pharmacological Action of ACh & Cholinomimetics:

(A) Muscarinic actions

- **Heart: M2**
- Decrease in heart rate (sinus bradycardia): -ve chronotropic.
- 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

(B) Nicotinic Actions:

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

I- Choline esters

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

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) methacholine: its therapeutic uses are limited by its adverse cardiovascular effects, such as bradycardia and hypotension, the only medical use now is methacholine challenge test.

II- Pilocarpine (cholinomimetic alkaloid)

- **Pharmacological properties:**
- It is a tertiary amine alkaloid
- Only muscarinic activity.
- It is resistant to hydrolysis by both pseudo & true-cholinesterase

Clinical Uses of Pilocarpine: & cevimeline

- 1) Glaucoma (open angle type) 1 % drops.
- 2) Treatment of xerophthalmia, xerostomia due to autoimmune parotitis and conjunctivitis) (SjOgren syndrome)

Cholinergic OD Side Effects

DUMB BELS

D iarrhea

U rination

M iosis/muscle weakness

B ronchorrea

B radycardia

E mesis

L acrimation

S alivation/sweating

Contraindications of direct parasympathomimetics

- 1) Bronchial asthma (due to bronchoconstriction and increase in bronchial secretions
- 2) gastrointestinal and urinary hypotonia with organic obstruction
- 3) Peptic ulcer (due to ↑ gastric motility and secretions).

III-Anticholinesterases

III-Anticholinesterases

(Weak bond)
Produce transient inhibition of the enzyme

Reversible

Irreversible

(Usually toxin)
Produces permanent phosphorylation of the enzyme

Teriary amine	**Quaternary amines**	**Organophosphoruscompunds**
Physiostigmine	Neostigmine	war gases: taban, sarine
	Amenonium	Insecticide: Parathione
	Pyridostigmine	Topical eye drops: echothiophate

Physostigmine	Neostigmine
Natural (physostigma venenosum)	Synthetic
Tertiary amine	Quaternary amine
Good oral absorption	Poor oral absorption
Good tissue penetration	Poor tissue penetration
Crosses BBB, CNS effects	Does not cross BBB: No CNS effects
Main indication—glaucoma	Myasthenia gravis
Used in atropine poisoning	Used in curare poisoning

Abbreviations: BBB, blood brain barrier; CNS, central nervous system

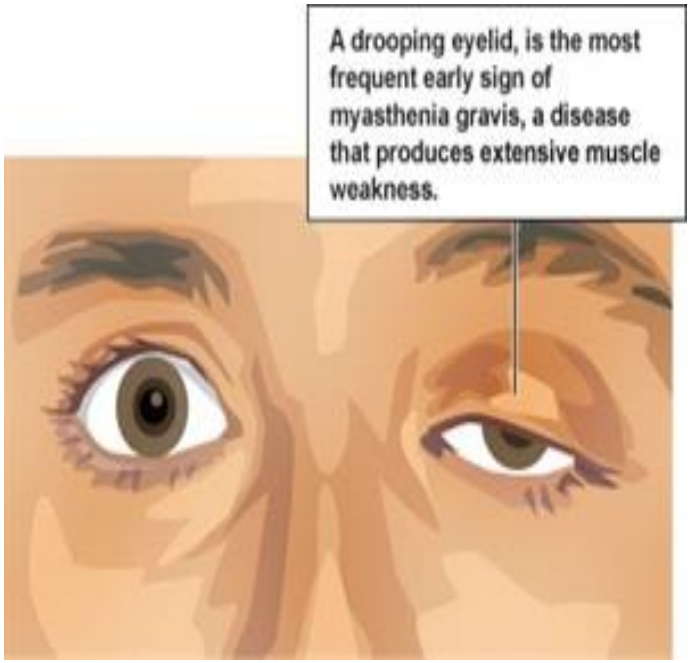
Myasthenia gravis

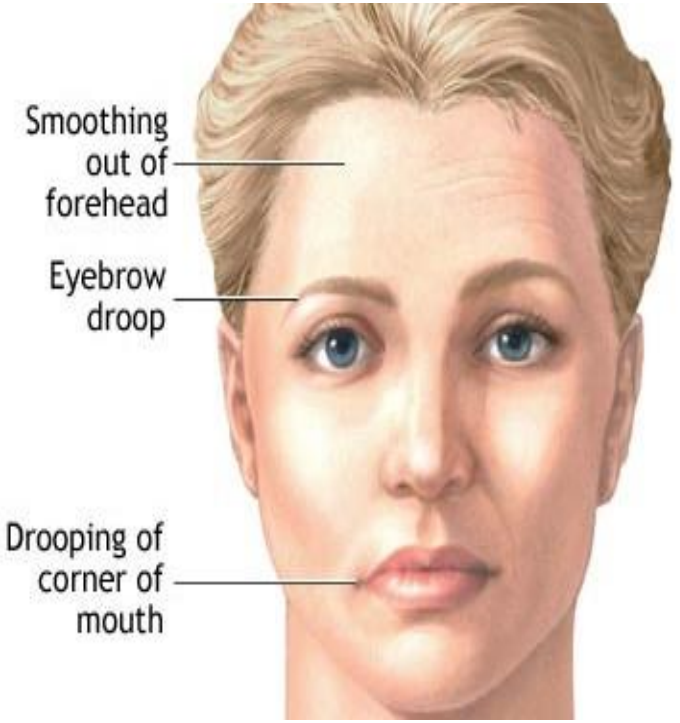
•It is an autoimmune disease (genetic) in which there is an antibody to the nicotinic Nm receptor system which impairs the responsiveness of the neuromuscular junction resulting in weakness and rapid fatigability of skeletal muscles.

•More proximal muscles are affected: ptosis, diplopia, weak mastication muscles, drop of mouth angle, dysarthria, shoulder girdle.

•Bulbar muscles (muscles are involved in speaking, swallowing, chewing, and holding the jaw in place) when affected: patient dies.

Manifestations of M.gravis





Treatment:

- **1- Anticholinesterases: e.g. neostigmine, pyridostigmine**
- An antimuscarinic agent is necessary to block the muscarinic effect of ACh especially if large doses of anticholinesterase (which drug?) are given e. g atropine.

- **2- Immunosuppressive drugs:**
- Prednisolone
- **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**

•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

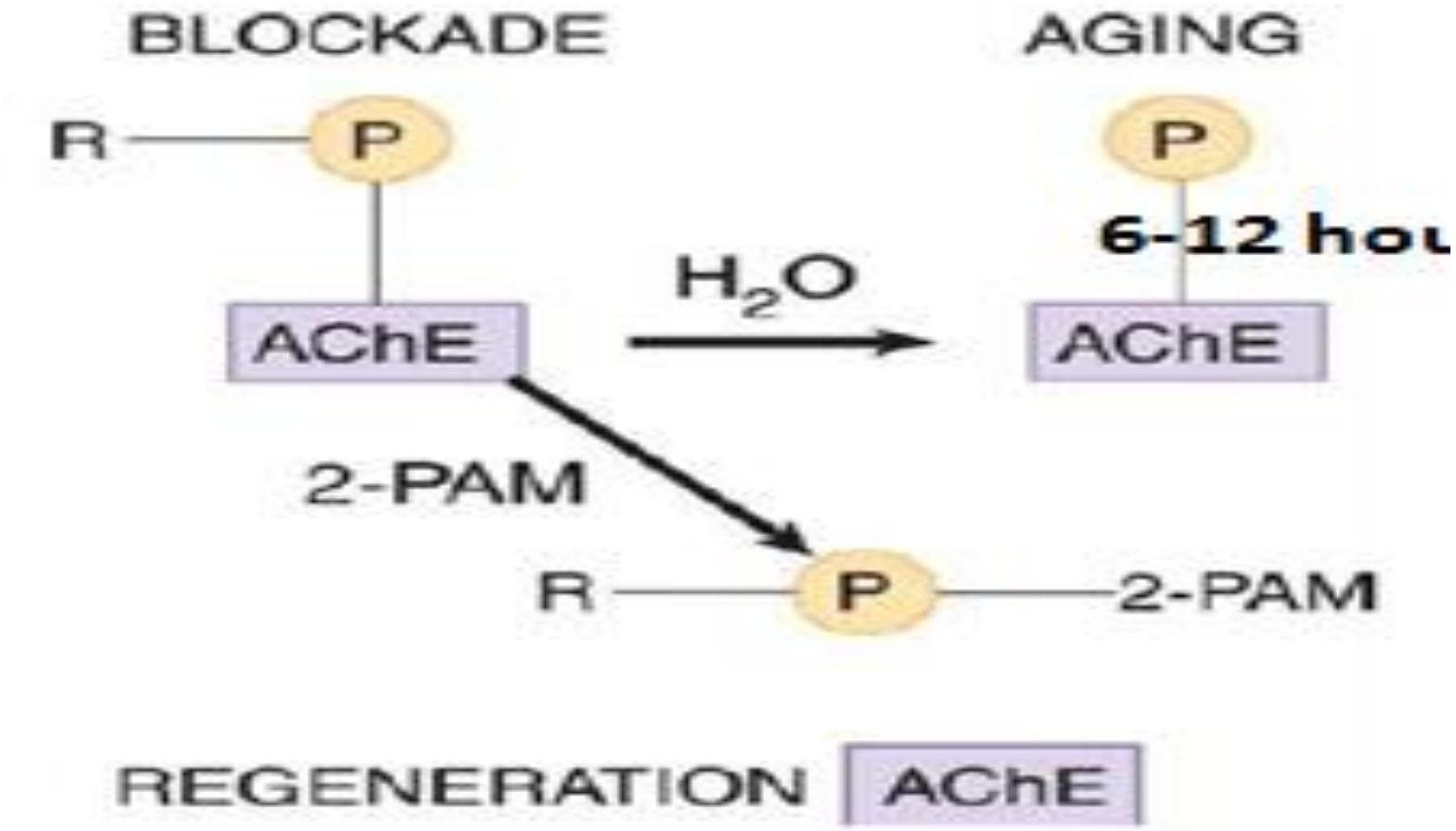
•No peripheral effects ⟹ treatment of **Alzihymer´s disease**: amnesia, dementia, loss of cognetive function due to degeneration of cholinergic neurons and accumulation of beta amyloid protein in CNS insulating neurons from each other.

Long - acting (Irreversible) Cholinesterase Inhibitors

- **Organophosphorus compounds:**
- 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

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.


BLOCKADE
AGING
R
P
P
6-12 hou
H_2O
AChE
AChE
2-PAM
R
P
2-PAM
REGENERATION
AChE

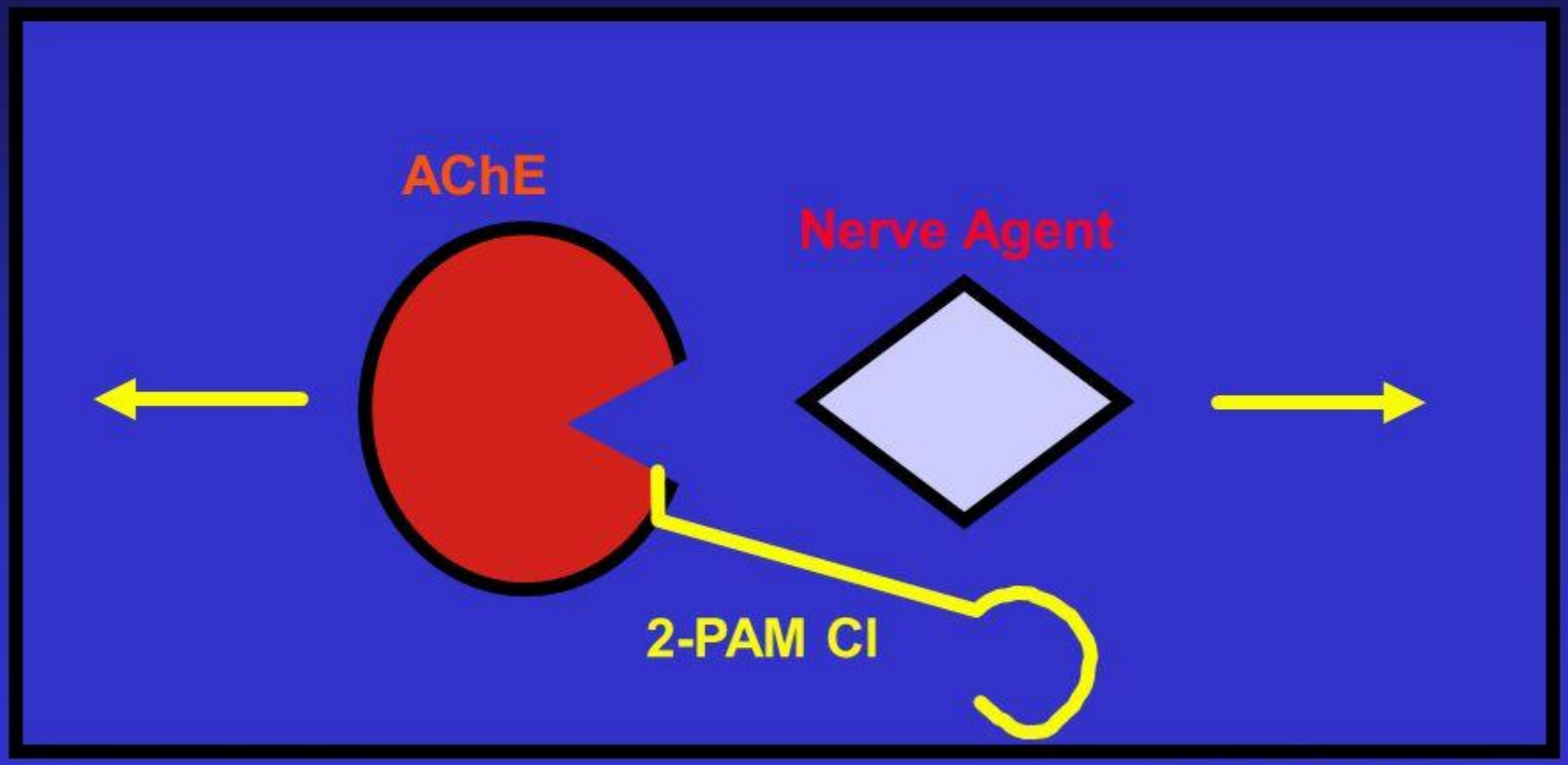
Management of organophosphate poisoning:

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- 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.)
- 3- Diazepam (10 mg IV) to treat convulsions.
- 5- Fresh blood transfusion.

ACTION OF PRALIDOXIME CHLORIDE (2-PAM Cl)



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Thank you