# ANTICHOLINESTERASES

# INDIRECT ACTING CHOLINOMIMETICS

# CHOLINESTERASE INHIBITORS

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**AP Pharmacology**

SOURCES:
BERTRAM G. KATZUNG BASIC & CLINICAL PHARMACOLOGY 15TH EDITION
GOODMAN AND GILMAN'S THE PHARMACOLOGICAL BASIS OF THERAPEUTICS 13TH EDITION.

# LEARNING OBJECTIVES

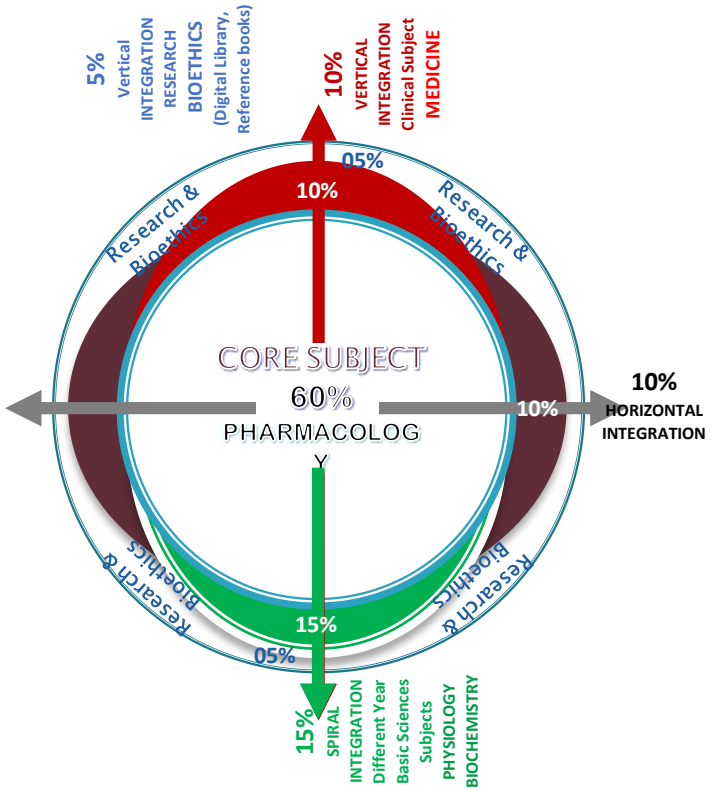
- At the end of this session, students will be able to:

- ✓ Classify indirectly acting cholinomimetics.
- ✓ Discuss mechanism of action.
- ✓ Describe the organ system effects produced by these drugs.
- ✓ Enumerate uses and adverse effects of cholinomimetics.

# MOTTO AND VISION

- To impart evidence based research oriented medical education
- To provide best possible patient care
- To inculcate the values of mutual respect and ethical practice of medicine

**Prof. Umar's Clinically Oriented Integration Model**
**For Basic Sciences Interactive Lectures**




| 3rd Year Pharmacology LGIS | | |
|---|---|---|
| Core Subject – 60% | | |
| Pharmacology | | |
| Horizontal Integration – 10% | | |
| Same Year Subjects | • | Pathology (10%) |
| Vertical Integration – 10% | | |
| Clinical Subjects | • | Medicine (10%) |
| Spiral Integration – 15% | | |
| Different Year Basic Sciences Subjects | • | Physiology (10%) |
| | • | Biochemistry (5%) |
| Vertical Integration – 05% | | |
| Research & Bioethics | | |

# PRE LECTURE ASSESSMENT

1. Which of the following condition limits the use of muscarinic agonists:

a) Bronchospasm
b) ↑ Intraocular pressure
c) Loss of memory
d) Muscles weakness
e) Xerostomia

2. A 45-year-old male patient presents with complaints of dry mouth, blurred vision and difficulty in swallowing. Upon examination, he shows signs of decreased salivation and pupillary dilation. The doctor decides to treat the patient with a drug that increases acetylcholine levels in the synaptic cleft by inhibiting acetylcholinesterase.Which of the following drugs, acting indirectly, would be most appropriate for this patient?

A) Atropine

B) Neostigmine

C) Physostigmine

D) Tropicamide

3. Which of the following cholinergic is used in treatment of Alzheimer's disease;

a) Acetylcholine
b) Bethanechol
c) Edrophonium
d) Galantamine
e) Physostigmine

4. A 45-year-old male presents to the emergency department with difficulty breathing, excessive salivation, and muscle weakness after being exposed to an organophosphate pesticide while working in the fields. On examination, he has pinpoint pupils, bradycardia, and muscle fasciculations. The physician suspects poisoning with an anticholinesterase agent.Which of the following is the most appropriate initial treatment for this patient?

A) Atropine
B) Pralidoxime (2-PAM)
C) Physostigmine
D) Epinephrine
E) Naloxone

5. A 60-year-old male with a history of myasthenia gravis presents to the emergency department with worsening weakness, double vision, and difficulty swallowing. He reports that his dose of pyridostigmine (an acetylcholinesterase inhibitor used to manage myasthenia gravis) has been recently increased. He appears to be fatigued, and his respiratory rate is elevated.Which of the following is the most likely cause of his symptoms?

a) Cholinergic crisis
b) Mysthenia crisis
c) Organophosphate poisoning
d) Acute stroke
e) Drug overdose

6. What does the term "aging" refer to in the context of organophosphate poisoning?

A) The process by which the organophosphate molecule undergoes chemical breakdown, reducing its toxicity.
B) The irreversible binding of the organophosphate to acetylcholinesterase, making it harder to reverse with pralidoxime.
C) The process by which acetylcholinesterase becomes more sensitive to organophosphate agents over time.
D) The acceleration of the body's ability to metabolize organophosphate compounds.
E) The gradual improvement in acetylcholinesterase activity due to aging of the nerve terminals.

7. A middle age farmer while spraying pesticide suffered diarrhea, urination, miosis, lacrimation,bronchoconstriction, bradycardia, salivation, sweating, muscle weakness & seizures. Which of the following chemical antagonist is used in this medical emergency?

a) Atropine
b) Carbachol
c) Donepezil
d) Paralidoxime
e) Rivastigmine

8. The mechanism of action of neostigmine in the management of myasthenia gravis?

A) Neostigmine blocks acetylcholine receptors at the neuromuscular junction.
B) Neostigmine inhibits acetylcholinesterase, increasing acetylcholine availability at the neuromuscular junction.
C) Neostigmine increases the release of acetylcholine from presynaptic nerve endings.
D) Neostigmine enhances the binding of acetylcholine to nicotinic receptors at the neuromuscular junction.
E) Neostigmine decreases the sensitivity of muscle cells to acetylcholine.

7. A 60-year-old male with glaucoma presents to the ophthalmology clinic for routine follow-up. His (IOP) has been difficult to control with topical medications, and his physician is considering adding another agent. The physician prescribes carbachol.Which of the following is the most likely mechanism of action of carbachol in the treatment of glaucoma?

A) Carbachol inhibits the production of aqueous humor by the ciliary body.
B) Carbachol increases the production of aqueous humor by the ciliary body.
C) Carbachol promotes contraction of the ciliary muscle, increasing the outflow of aqueous humor.
D) Carbachol blocks the receptors in the trabecular meshwork, reducing resistance to aqueous humor outflow.
E) Carbachol directly stimulates alpha-adrenergic receptors to reduce aqueous humor

8. What is the primary role of pralidoxime in the treatment of organophosphate poisoning?

A) Pralidoxime acts as a competitive inhibitor of acetylcholinesterase, reducing the breakdown of acetylcholine.
B) Pralidoxime regenerates acetylcholinesterase by breaking the bond between the organophosphate and the enzyme.
C) Pralidoxime increases the release of acetylcholine from nerve endings to counteract the effects of poisoning.
D) Pralidoxime inhibits muscarinic receptors to reverse the symptoms of poisoning.
E) Pralidoxime blocks the binding of organophosphates to muscarinic receptors in the peripheral tissues.

# CLASSIFICATION ON THE BASIS OF STRUCTURE

## REVERSIBLE

### ALCOHOLS

Edrophonium(Quaternary)

### CARBAMATES

**Tertiary Amines**

Physostigmine

**Quaternary Amines**

Neostigmine

Pyridostigmine

# CONTINUED….

**OTHERS**

Tacrine

Donepezil

Rivastigmine

Galantamine

# IRREVERSIBLE

## ORGANOPHOSPHATES

**Therapeutic use**

Echothiophate

**Insecticides**

Malathion

Parathion

**Nerve gases**

Tabuin

Sarin

Soman

# CONTINUED….

## CARBAMATES

Carbaryl

Propoxur

# CLASSIFICATION ON BASIS OF DURATION OF ACTION

**SHORT ACTING** (5-10MINS)

- Edrophornium

**INTERMEDIATE ACTING** (3-6HRS)

- Neostigmine
- Physostigmine
- Pyridostigmine

**LONGER ACTING** (6-8HRS)

- Donepezil
- Tacrine

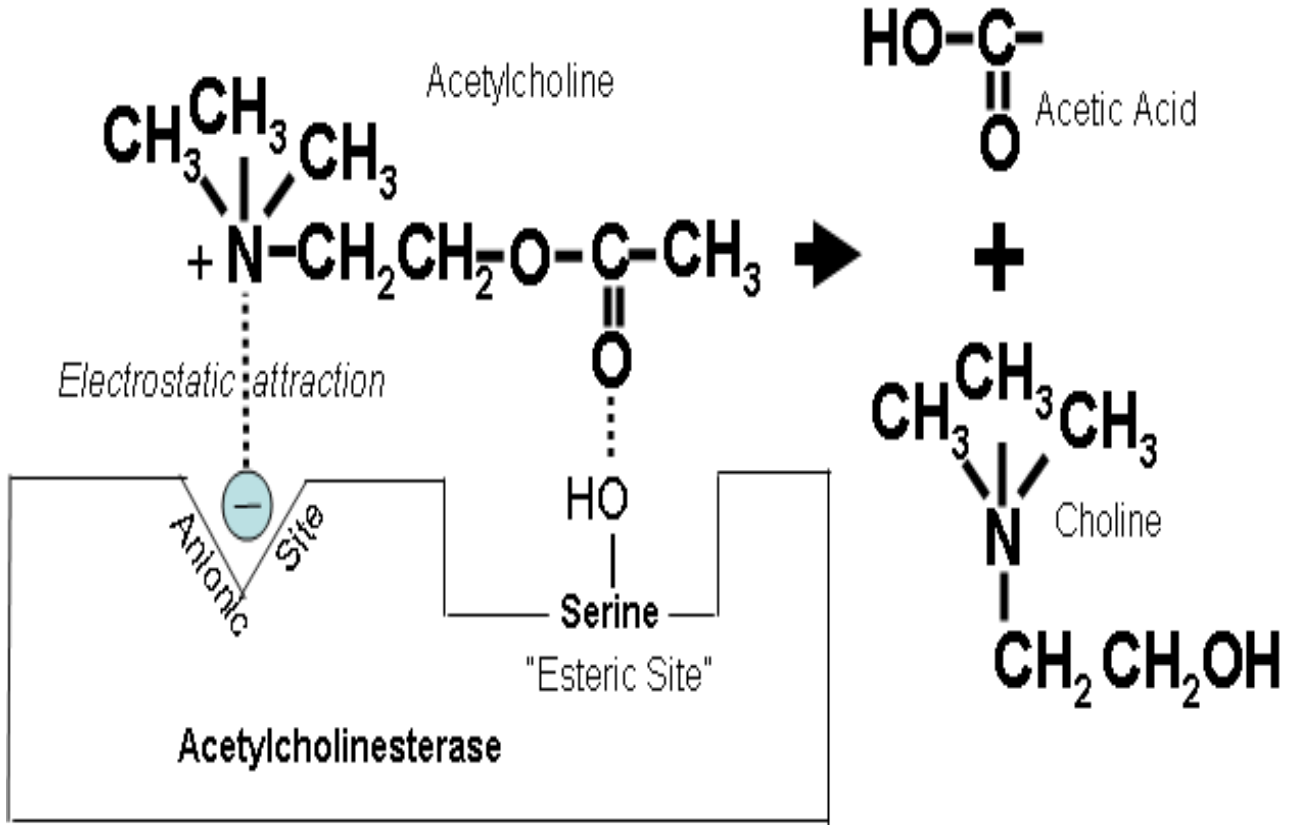
**VERY LONG ACTING** (IRREVERSIBLE)

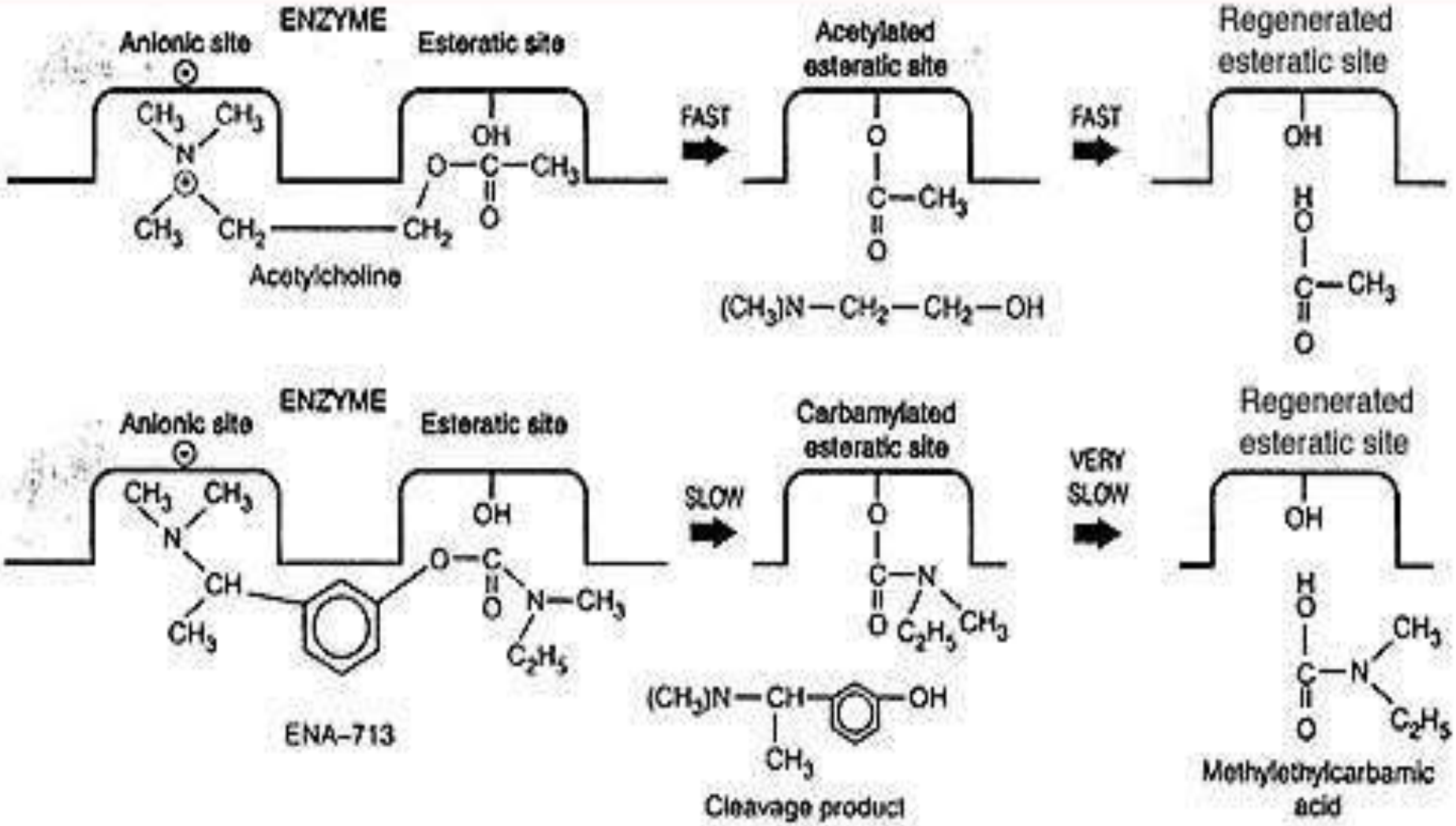
- Insecticides
- War Gases
- Ecothiopate

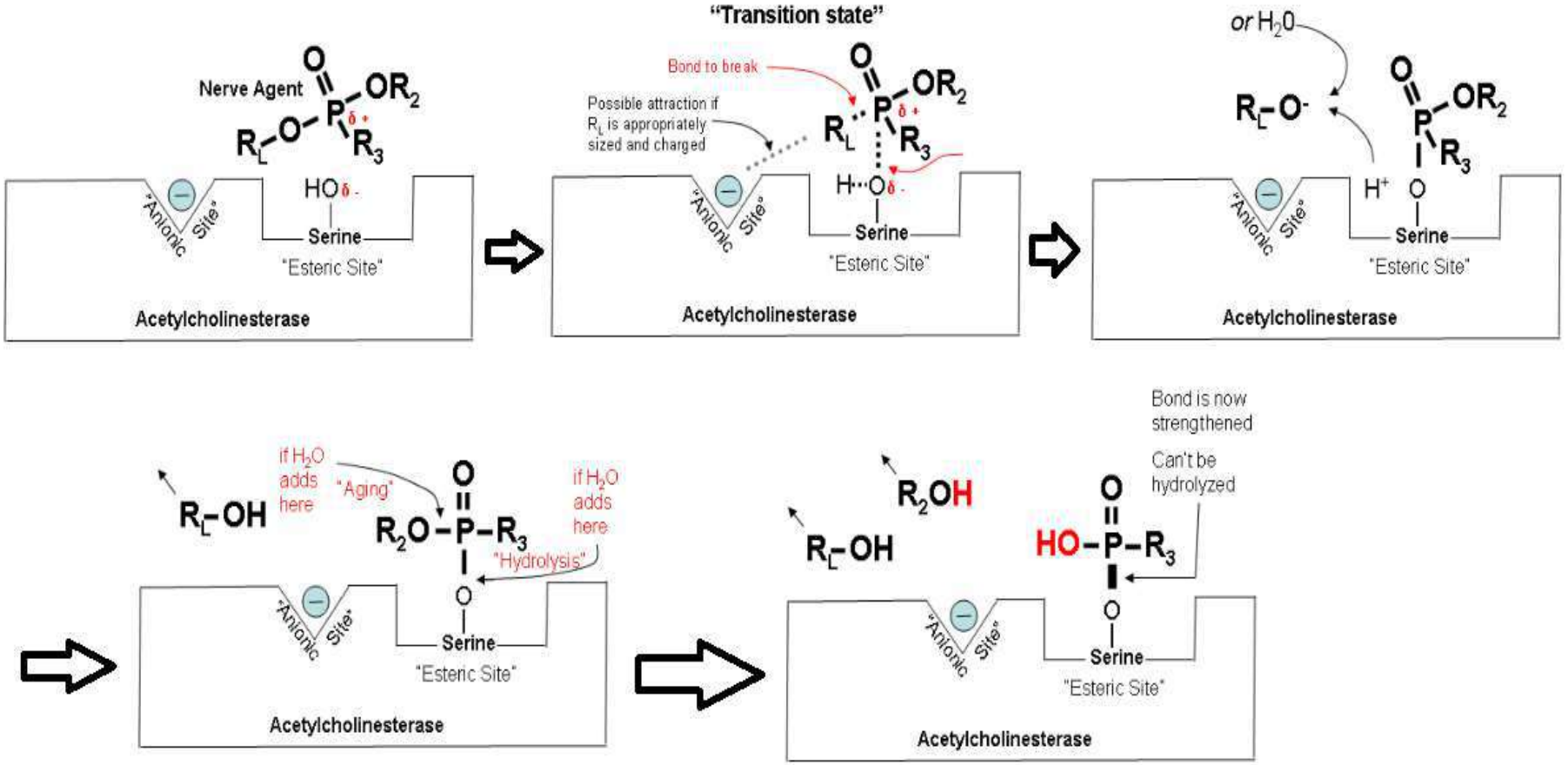
# PHARMACOKINECTICS

| | |
|---|---|
| **Indirect-acting, alcohol** | |
| Edrophonium | Highly polar; used IV<br>Duration: 5–10 min |
| **Indirect-acting, carbamate** | |
| Neostigmine | Moderately polar but orally active<br>Duration: 2–4 h |
| Pyridostigmine | Moderately polar but orally active<br>Duration: 4–8 h |
| Physostigmine | Lipid soluble; can be used topically in the eye<br>Duration: 2–4 h |

| Indirect-acting, organophosphate | |
|---|---|
| Parathion | Highly lipid-soluble |
| Malathion | Highly lipid-soluble but metabolized to inactive products in mammals and birds |
| Sarin, tabun, others | Like parathion but more rapid action |


Acetylcholine
Electrostatic attraction
Anionic Site
Serine
"Esteric Site"
Acetylcholinesterase
Acetic Acid
Choline


ENZYME
Anionic site
Esteratic site
Acetylcholine
FAST
Acetylated esteratic site
(CH3)N—CH2—CH2—OH
FAST
Regenerated esteratic site
ENZYME
Anionic site
Esteratic site
ENA-713
SLOW
Carbamylated esteratic site
(CH3)N—CH—OH
CH3
Cleavage product
VERY SLOW
Regenerated esteratic site
Methylethylcarbamic acid


Nerve Agent
"Anionic Site"
Serine
"Esteric Site"
Acetylcholinesterase
"Transition state"
Bond to break
Possible attraction if $R_L$ is appropriately sized and charged
or $H_2O$
Bond is now strengthened
Can't be hydrolyzed
if $H_2O$ adds here
"Aging"
"Hydrolysis"

# Organ system effects

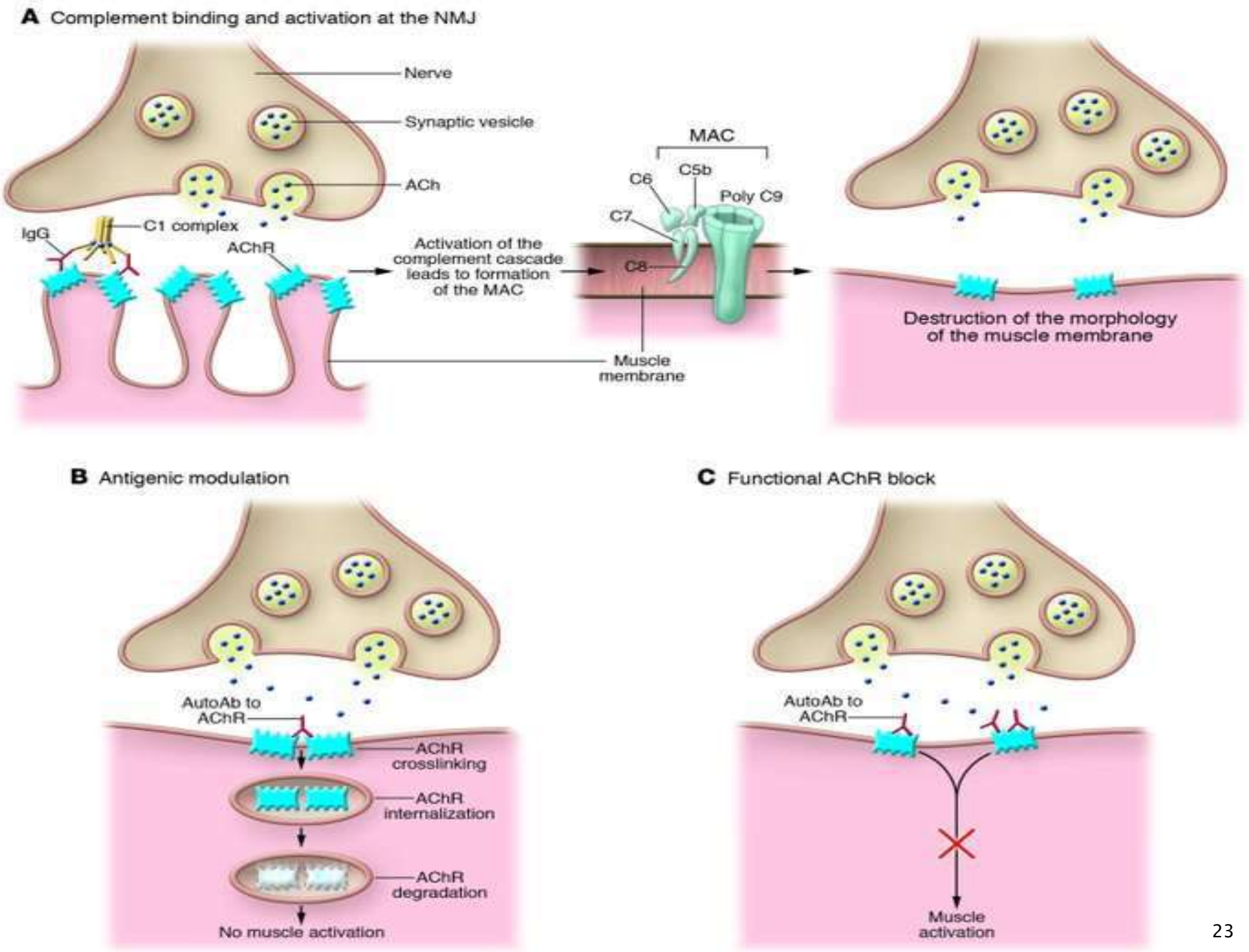
- G.I.T
- URINARY BLADDER
- EXOCRINE GLANDS
- LUNGS
- C.V.S
- SKELETAL MUSCLES

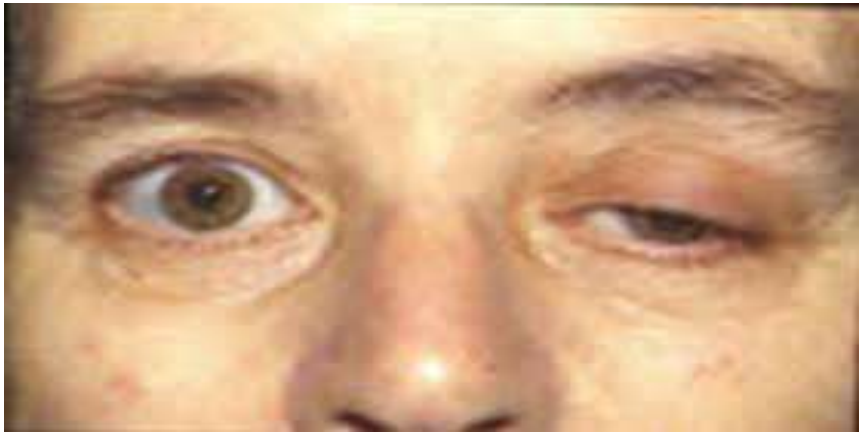
# Therapeutic Uses of Inhibitors of Acetylcholinesterase

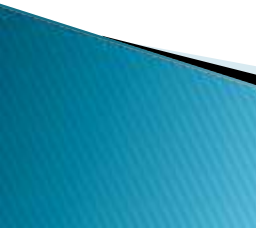
1. Glaucoma (wide angle)
2. Atony of the bladder or GIT (after surgery).
3. Intoxication by antimuscarinic agents, tricyclic antidepressants (TCA's) or phenothiazines (use physostigmine)
4. Recovery of neuromuscular function after competitive blockade of Nm receptor of skeletal muscle fibers
5. Myasthenia gravis

# MYASTHENIA GRAVIS

- Definition
- MOA
- Signs and symptoms
- Diagnosis
- Difference between myasthenic crisis and cholinergic crisis
- Management

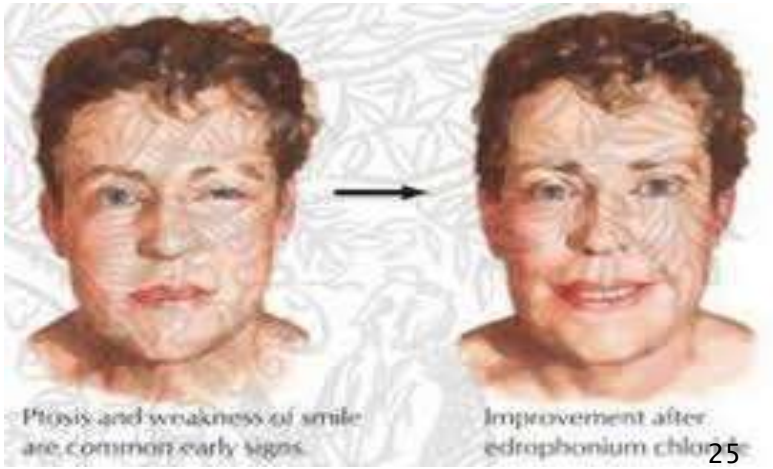

A Complement binding and activation at the NMJ
Nerve
Synaptic vesicle
ACh
C1 complex
IgG
AChR
Activation of the complement cascade leads to formation of the MAC
MAC
C6
C5b
Poly C9
C7
C8
Muscle membrane
Destruction of the morphology of the muscle membrane
B Antigenic modulation
AutoAb to AChR
AChR crosslinking
AChR internalization
AChR degradation
No muscle activation
C Functional AChR block
AutoAb to AChR
Muscle activation





# DIAGNOSIS

- **EDROPHONIUM** is used as diagnosis for myasthenia gravis.(Tensilon test)
- 2mg dose is injected iv after baseline muscle strength has been measured.
- If nothing untoward happen in 45 secs, an additional 8mg may be injected.
- If the patient has myasthenia gravis, an improvement in muscle strength that lasts about 5mins can usually be observed.



## How to differentiate between
## **Myasthenic crisis & Cholinergic crisis**

### Myathenic crisis

- Skeletal muscle weakness due to untreated or inadequately treated myasthenia Gravis.
- **Neostigmine** : Improved muscle strength
- **Treatment: Give or ↑ the dose of** neostigmine

### Cholinergic crisis

Skeletal muscle **weakness due to over treated myasthenia gravis i.e.** depolarization block.

- **Neostigmine:** No effect or increase muscle weakness
- **Treatment**: Decrease the dose of neostigmine

# TREATMENT

- Indirectly acting cholinesterase inhibitors
  - ✓ Neostigmine
  - ✓ Pyridostigmine
- Corticosteriods
- Plasmapheresis
- Thymectomy

# ADVERSE EFFECTS

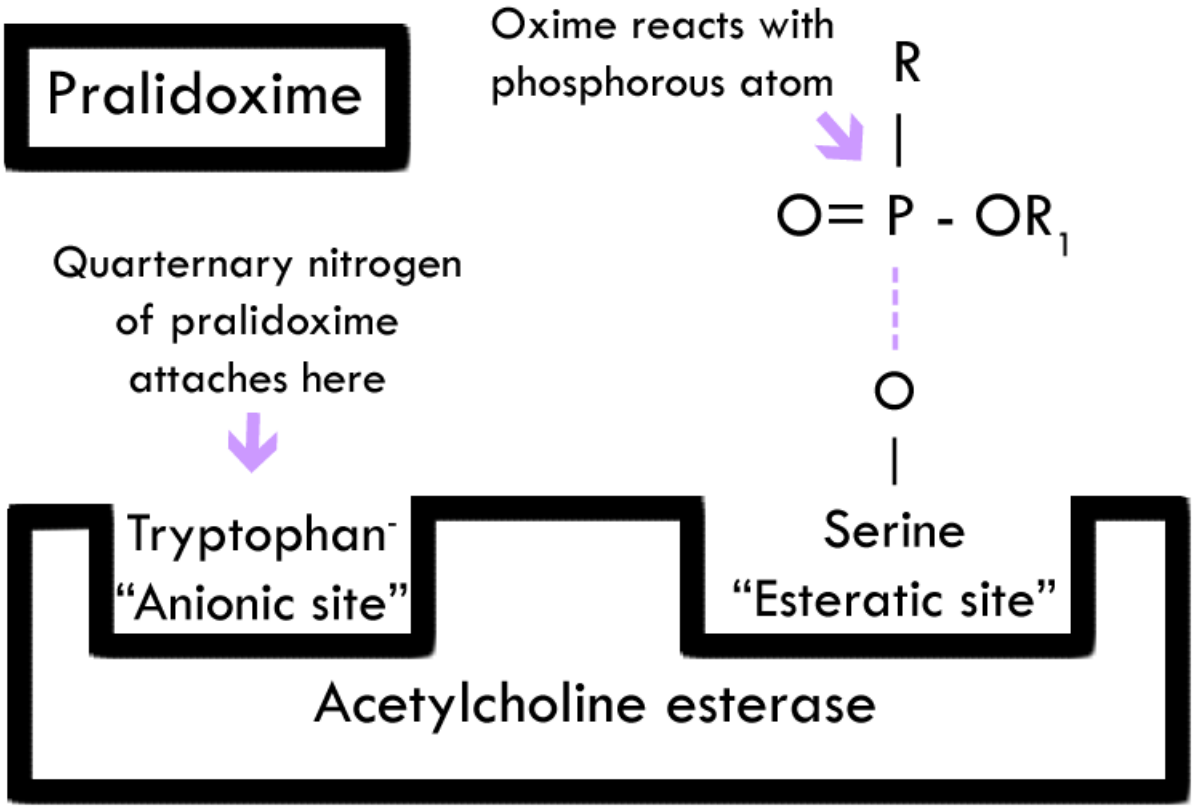
## ORGANOPHOSPHOROUS POISONING

- **Features**

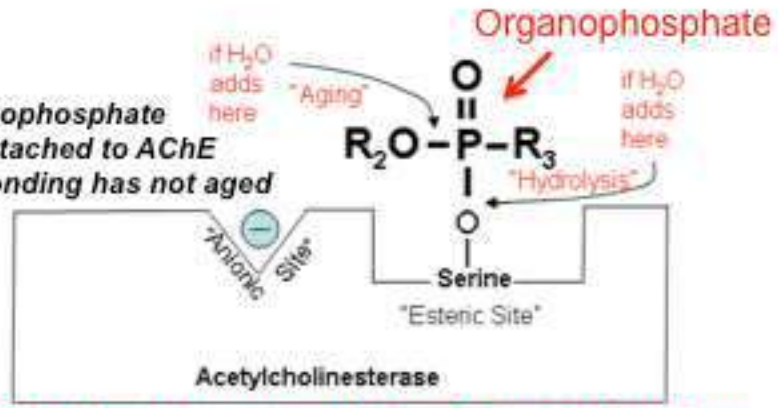
- ✓ Diarrhea
- ✓ Urination
- ✓ Muscle weakness/miosis
- ✓ Bradycardia
- ✓ Bronchoconstriction
- ✓ Emesis
- ✓ Lacrimation
- ✓ Salivation/sweating
- ✓ Convulsions , coma

## TREATMENT

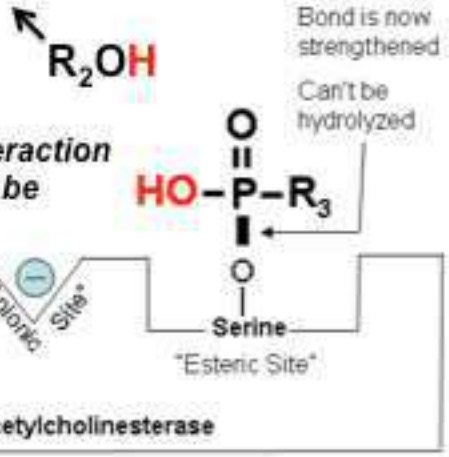
- Maintenance of vitals
- Decontamination
- Atropine
- Diazepam
- Cholinestrase enzyme regenerators
  - Pralidoxime
  - Diacetylmonoxime



## Organophosphate Aging – chemical stabilization of phosphate bond to AChE occurs over time

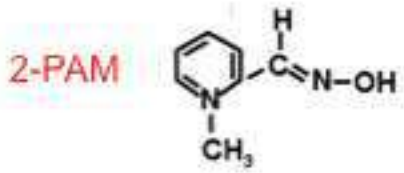


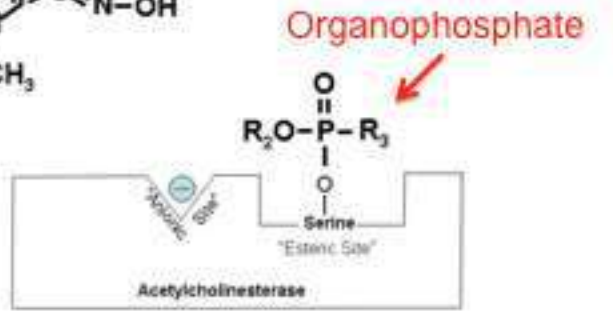

***The rate of aging is unique for each organophosphate compound, and can occur over minutes to days depending on the agent***

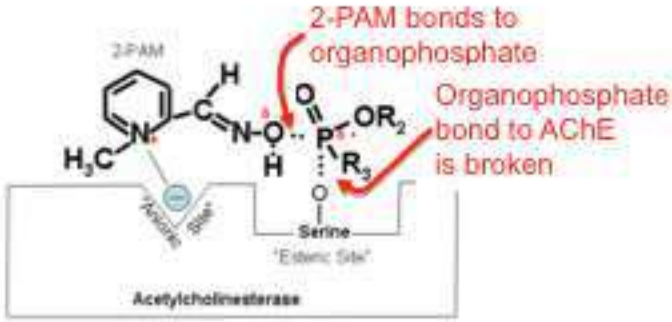


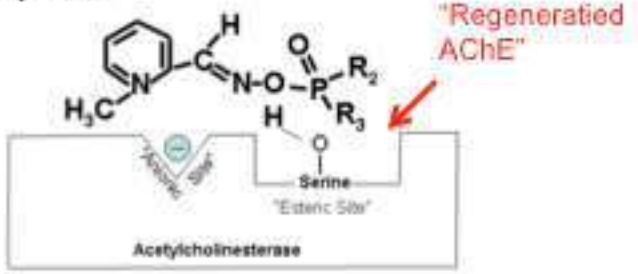

***The departure of the $R_2$ alkyl group (aging) results in increased electron sharing between the phosphate group of the organophosphate & the serine on AChE. This bond can't be broken by 2-PAM.***

## Pralidoxime (2-PAM) prevents aging & regenerates AChE




Modifed from: CDC Case Studies in Environmental Medicine
http://www.atsdr.cdc.gov/csem/csem.asp?csem=11&po=23

- **Chronic exposure**

- ✓ Triorthocresyl phosphate
- ✓ Delayed neuropathy associated with demyelination of axons

- **Intermediate syndrome**

- **Prophlaxsis of chemical warfare**

- ✓ Pyridostigmine

# RESEARCH

- Žnidaršic, N., Štrbenc, M., Grgurevic, N. and Snoj, T., 2023. Potential revival of cholinesterase inhibitors as drugs in veterinary medicine.

## ARTIFICIAL INTELLIGENCE

- Nour H, Abdou A, Belaidi S, Jamal J, Elmakssoudi A, Dakir M, Chtita S. Discovery of promising cholinesterase inhibitors for Alzheimer's disease treatment through DFT, docking, and molecular dynamics studies of eugenol derivatives. Journal of the Chinese Chemical Society. 2022 Sep;69(9):1534-51.