

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

Cholinergic Drugs; **(Parasympathomimetic Drugs)**

By

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Cholinergic Drugs; (Parasympathomimetic Drugs)

- **Directly acting;**

These act by stimulating the nicotinic or muscarinic receptors.

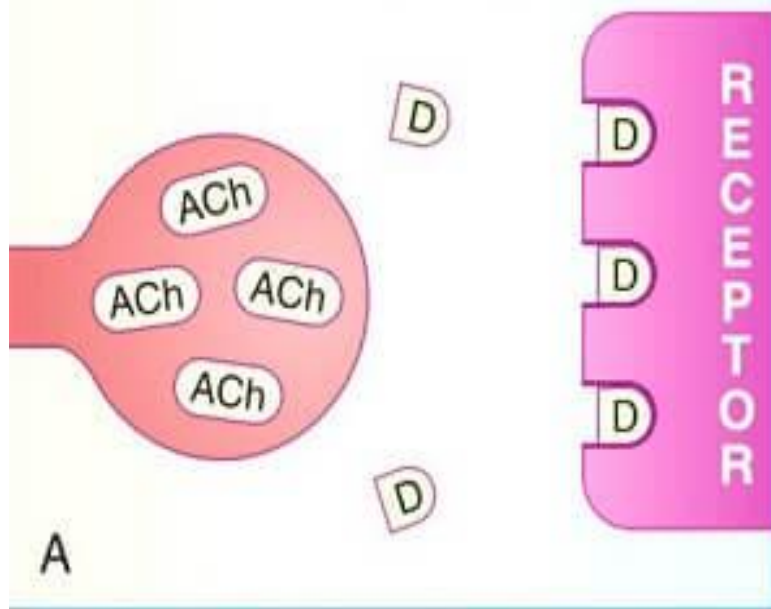
- **Indirectly acting;**

Increase the availability of Ach. to receptors

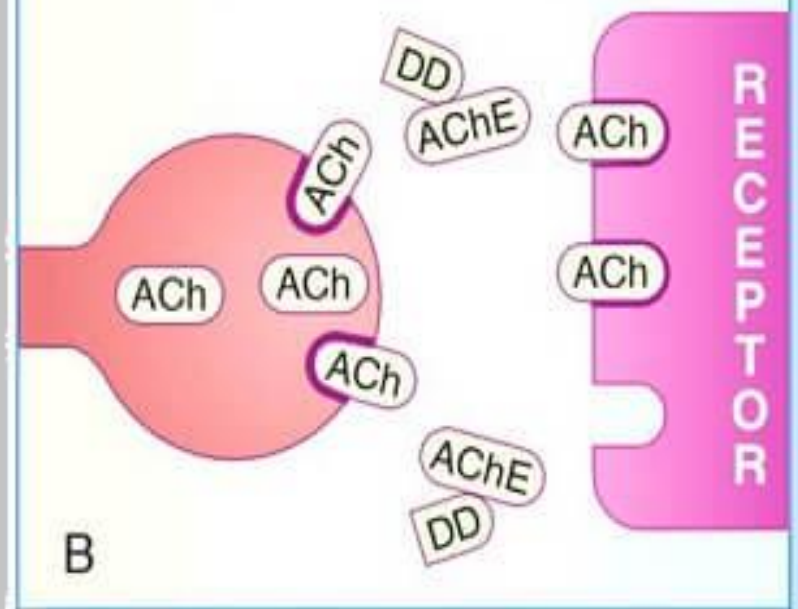
(These act as **cholinesterase inhibitors** or drugs that promote Ach. release)

Direct and indirect parasympathomimetic drugs

Direct-acting parasympathomimetic
(cholinergic drug)



Indirect-acting parasympathomimetic
(cholinesterase drug)



Cholinomimetic drugs

Direct acting

Muscarinic

Choline Esters;

Acetylcholine
Methacholine
Carbachol
Bethanechol.

Alkaloids;

Pilocarpine
Lobeline
Cevimeline
Varenicline
Arecoline
Muscarine.

Nicotinic

Alkaloids;

Nicotine

Indirect acting

Organophosphates
Very long acting

Carbamates;
Intermediate acting

Edrophonium
Short acting

Direct-acting Cholinomimetics;

Muscarinic

Choline Esters;
Acetic acid esters;
Acetylcholine
Methacholine.
Carbamic acid esters;
Carbachol
Bethanechol

Natural Alkaloids;
Quaternary Compounds;
Muscarine.

- Tertiary Compounds;**
1. Pilocarpine. (from pilocarpus Jaborandi)
 2. Lobeline
 3. Cevimeline
 4. Arecoline (from Areca Catechu --- betel nut)

Nicotinic

N_N-
Acetylcholine
Nicotine,
Varenicline
Lobeline,
Carbacol

N_M--
Succinylcholine
(initially),
Carbacol

Choline ester properties;

Choline esters	Susceptibility to Cholinesterase	Muscarinic Receptors	Nicotinic Receptors
ACh.	++++	+++	+++
Methacholine	+	++++	None
Carbachol	-/+	++	+++
Bethanichol	-/+	++	None

Differences between PNS stimulation and direct acting cholinomimetics on CVS;

Parasympathetic discharge

- **Bradycardia**
- Vasodilation and ↓ BP is not a Parasympathomimetic response.

Direct acting cholinomimetics

- **Tachycardia**
- **Vasodilation & ↓ BP** via release of EDRF from endothelium (uninnervated muscarinic receptors on the endothelial cells)
- Baroreceptor reflex—strong sympathetic discharge – **tachycardia**

Differences between PNS stimulation and direct acting cholinomimetics on CVS

Parasympathetic discharge

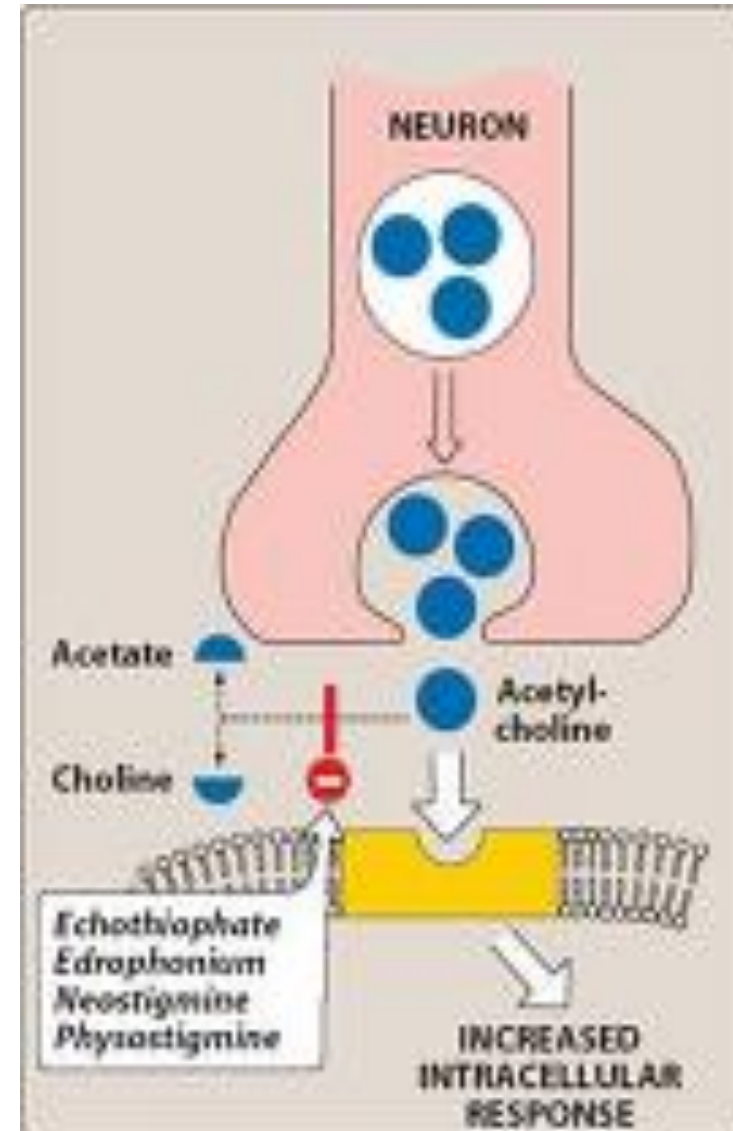
- No effect on sweat glands.

Direct acting cholinomimetics

- **Thermoregulatory sweating---**
sympathetic cholinergic effect.

Indirectly acting agonists; (Indirect Cholinomimetics) (anticholinesterases);

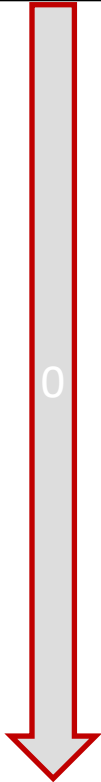
- Ach. is **metabolized** by ChE.
- The enzyme occur in **two forms**.
True ChE (present in synapse)
Pseudo ChE (present in blood)
- **Anticholinesterases inhibit both enzymes.**
- **↑ concentration, $t_{1/2}$ & action of Ach.**
- **Have both muscarinic & nicotinic effects.**
- **Do not have effect at uninnervated sites (vascular endothelium).**



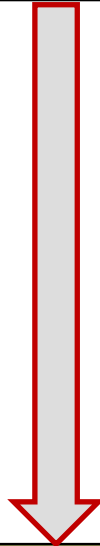
Anticholinesterases;



Indirect acting Cholinomimetics;



**Irreversible anticholinesterases;
Organophosphates.
Very long acting. 100 hrs.**



**Reversible Anticholinesterases;
Carbamates, Intermediate acting. 2-8 hrs.**

Edrophonium, Reversible, Short acting. (2- 10 mins)

Reversible Anticholinesterases;

- ***Alcohols;***

- Edrophonium. *Short acting (2-10 min)*
 - bearing quaternary ammonium group,

- ***Carbamates; Intermediate acting (2-8 hrs);***

- Neostigmine,
- Pyridostigmine,
- Rivastigmine,
- Donepezil,
- Ambenonium
- Carbaryl (insecticide)
- Physostigmine
- Distigmine
- Tacrine
- Galantamine
- Demecarium

Reversible drugs (most are Carbamates)

a) With N^{3+} (cross BBB)

- **Alkaloids:**
 - Galantamine, Physostigmine
- **Synthetic drugs:**
 - Donepezil, Rivastigmine, Tacrine

b) With N^{4+} (do not cross BBB)

- Demecarium, Edrophonium (Tensilon[®])
- Neostigmine, Pyridostigmine

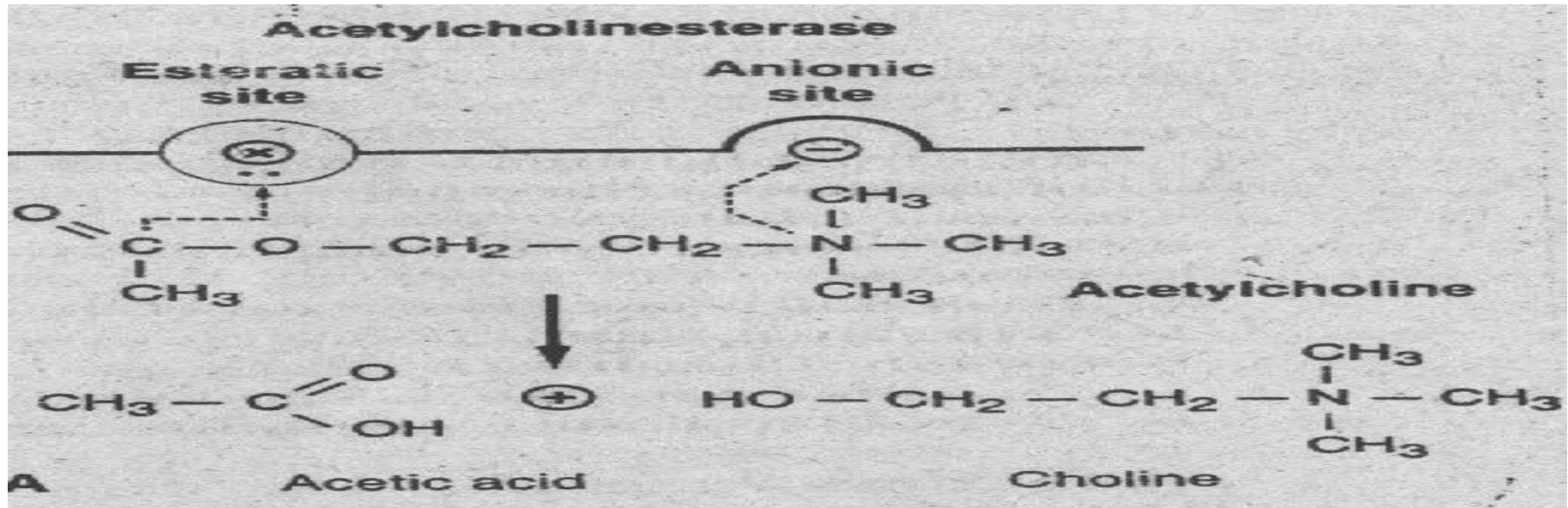
Reversible Anticholinesterases;

- ***Selective for CNS --- Used in Alzheimer's Disease;***
 - Donepezil,
 - Rivastigmine,
 - Galantamine,
 - Tacrine.

Irreversible anticholinesterases;

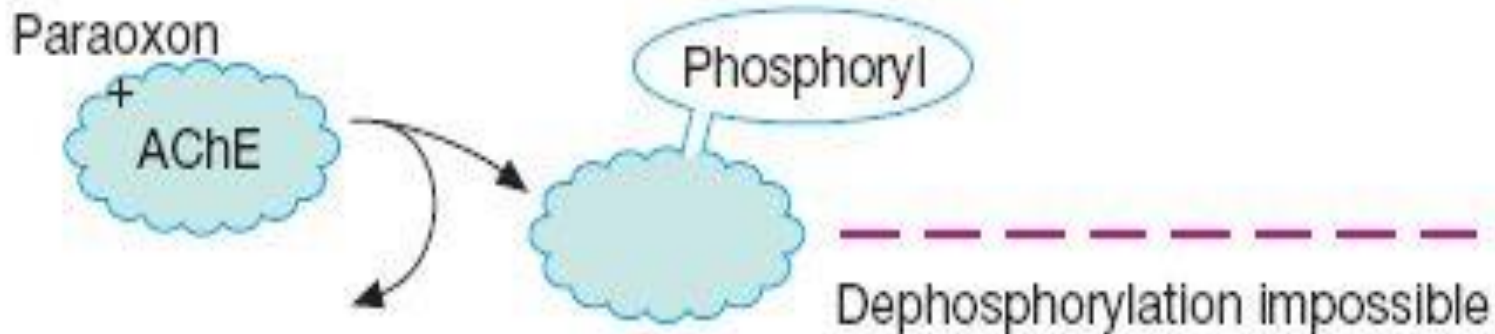
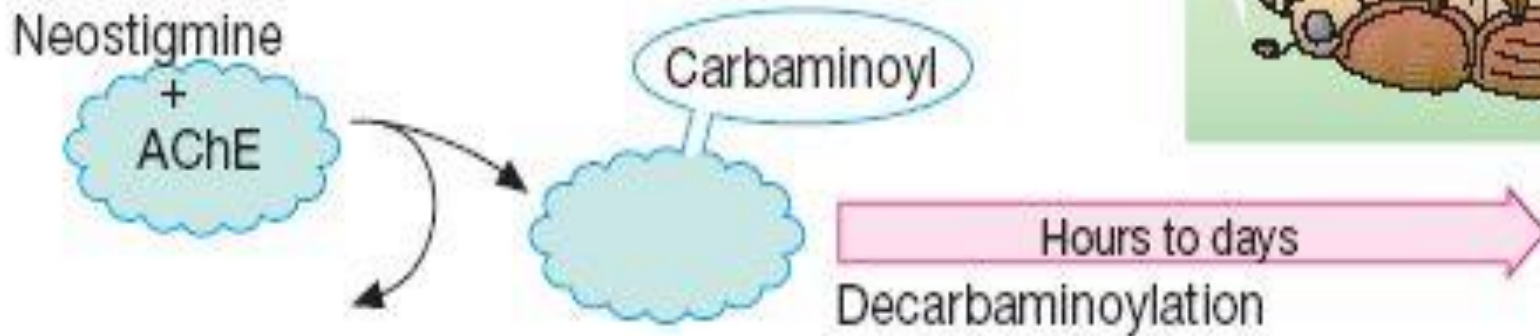
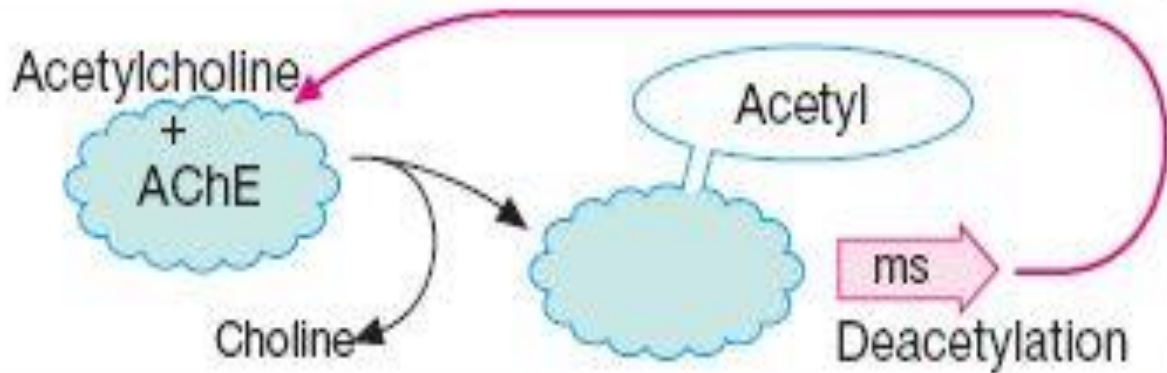
- **Phosphoric acid esters;**
 - Organophosphates (10,000-----50,000)
- **Very long acting (1 week)**
- **Used as pesticides & “nerve gas”**
- Highly lipid soluble, except **echothiopate**.
- **Sarin, Soman, Tabun** extremely potent nerve gases.
- Paraoxon, Malaixon
- Difluorophosphate
- Thiophosphate insecticides;
 - **Parathion & Malathion**(Sulfur containing Phosphate Prodrugs)

- When **ACh** reacts with ChE, reaction occurs at anionic and esteratic sites.

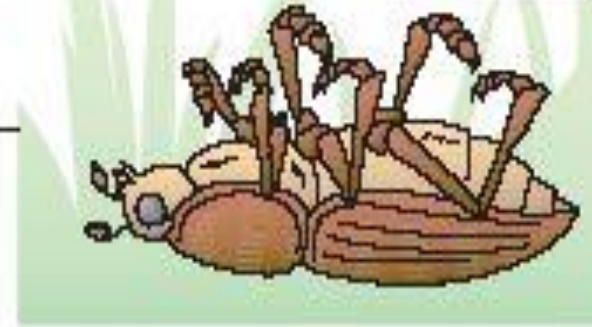


- Reversible anticholinesterases** react at the anionic site.
- Irreversible anticholinesterases** cause phosphorylation of cholinesterase at esteratic site only.

ACh Metabolism by Cholinesterase; Entire Process occurs in **100-150 u. sec.**
Deacetylation is the rate limiting step.



Nitrostigmine =
Parathion =
E 605

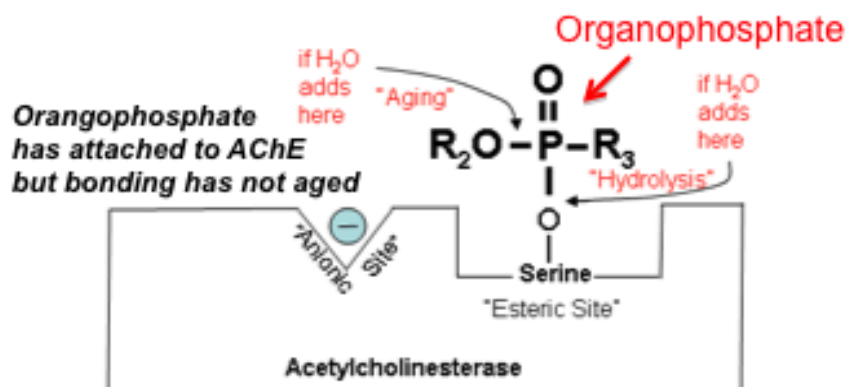


Mechanism of action of Organophosphate poisoning;

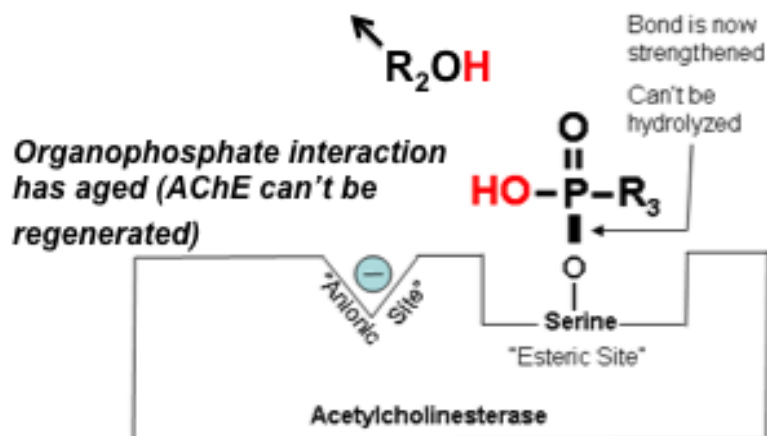
- Irreversibly bind to esteratic site of acetylcholinesterase (AChE) → establish covalent bond.
- Aging; loss of alkyl group + strengthening of covalent bond.
- Phosphorylated AChE is very stable.
- Inhibition of enzyme activity → accumulation of ACh. in the synapses and NMJ.
- Overstimulation of Cholinergic receptors.



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

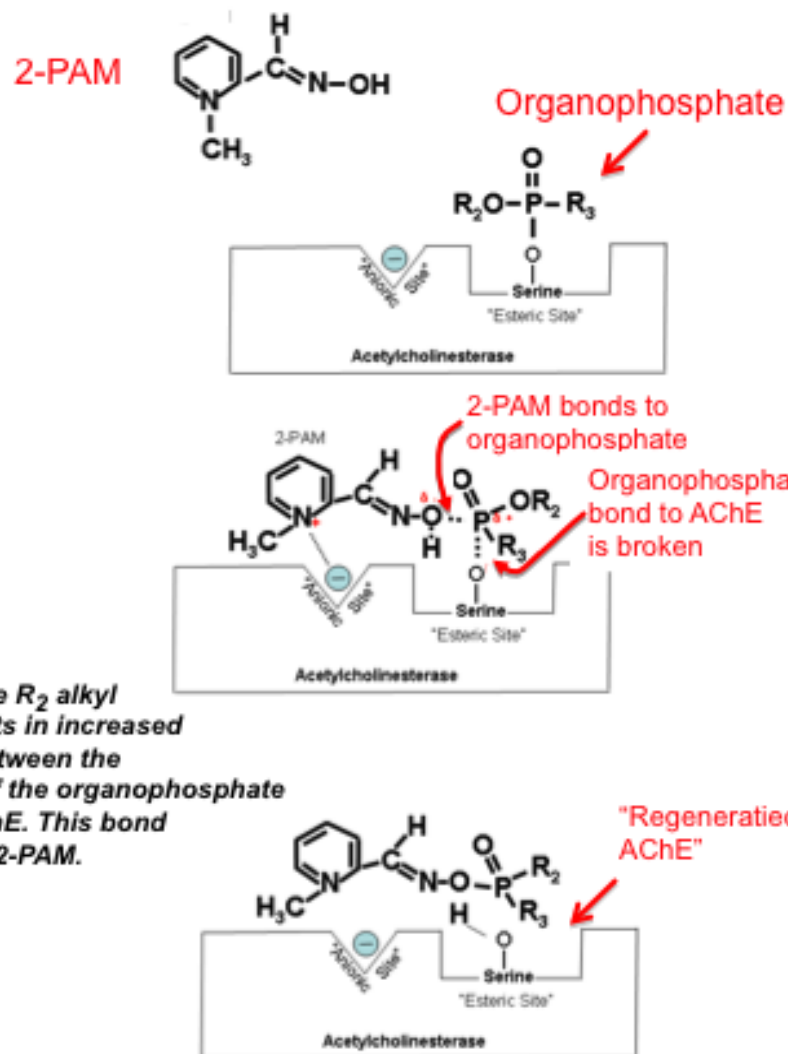


The rate of aging is unique for each organophosphate compound, and can occur over minutes to days depending on the agent



The departure of the R₂ 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



A landscape photograph featuring rolling green hills in the foreground and middle ground. The foreground is dominated by a field of bright yellow wildflowers. The sky is a deep blue, filled with soft, white, wispy clouds. The overall scene is bright and cheerful.

Thank You