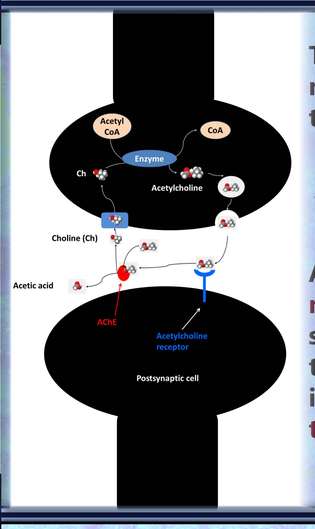
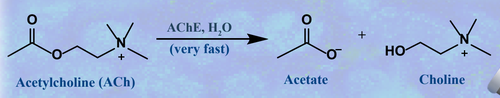
Acetylcholinesterase Inhibition

created by Sofía Sola Sancho and Maria Hemme

Acetylcholinesterase



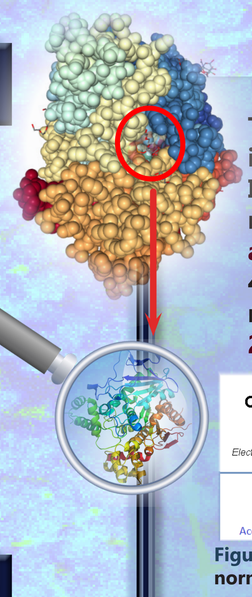
The primary **toxicity** of organophosphorus nerve agents results from the **inhibition** of the **enzyme Acetylcholinesterase (AChE)**.



AChE is responsible for breaking down the **neurotransmitter acetylcholine (ACh)**. This switches a nerve signal from on to off. If the enzyme is **inhibited**, ACh **accumulates** in the synapse and the signal **continues to transmit**.

Figure 1: Life Cycle of ACh.

Binding Site



The AChE **active site** is buried deep within the enzyme. It contains three amino acid residues **crucial for catalytic activity**: serine 200, histidine 440 and glutamate 327. The nerve agent binds to **serine 200**.

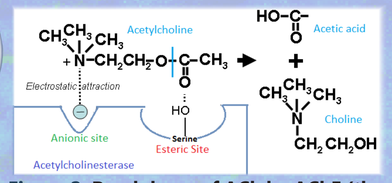


Figure 2: Breakdown of ACh by AChE (the normal function of the enzyme).

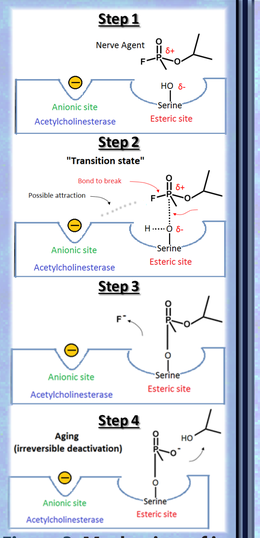
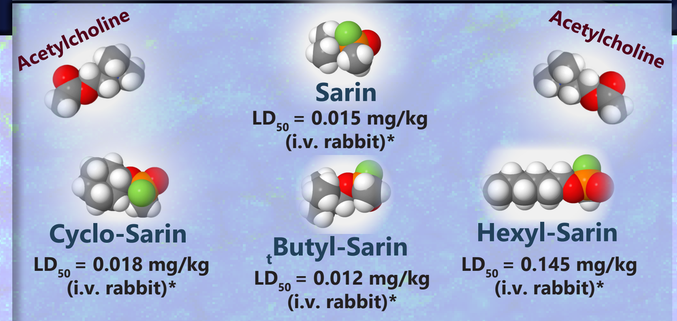
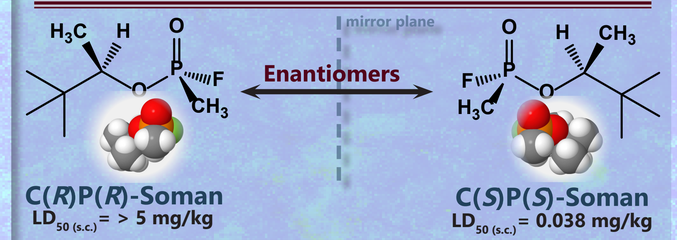


Figure 3: Mechanism of inhibition of AChE by Sarin.

Nerve Agent Molecular Shape and Size



Toxicity of an organophosphorus nerve agent depends on the ability to access the AChE binding site. **Size, shape and hydrophobicity** of the nerve agent exerts an effect. As alkyl substituents increase in size and degrees of freedom, toxicity decreases.



The **spatial orientation** (shape) of the molecule also matters, as illustrated by toxicity differences across the four stereoisomers of Soman.

* = Black, R. M., & Harrison, J. M. (2009). The Chemistry of Organophosphorus Chemical Warfare Agents. PATAI'S Chemistry of Functional Groups. doi:10.1002/9780470682531.pat0070

Effects and Symptoms

Inhibition of AChE in muscarinic synapses (neuromuscular system) induces **cholinergic crisis**. Nicotinic synapses (central nervous system, e.g. brain) are also effected.

Symptoms include **sweating, salivation, miosis (pinpoint pupils), paralysis, respiratory failure, seizures** and eventually **death**.

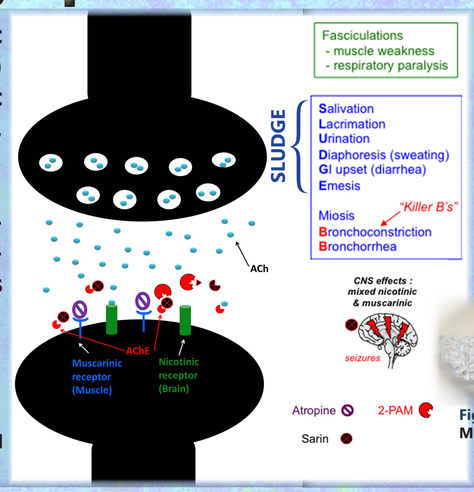
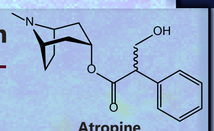


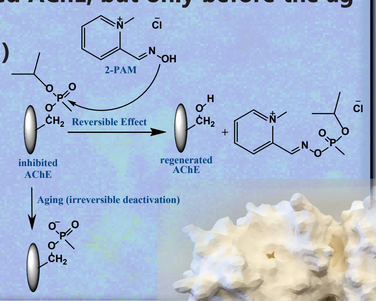
Figure 4: Inhibition of AChE by Sarin and Treatment with Atropine and 2-PAM.

Treatment

Atropine blocks the action of ACh at **muscarinic receptors** and treats **SLUDGE**.



Oximes such as **2-PAM** (pralidoxime) can reactivate inhibited AChE, but only before the aging process.
(Fig. 3, Step 3)



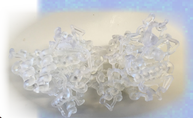


Figure 5: printed 3D Model of AChE

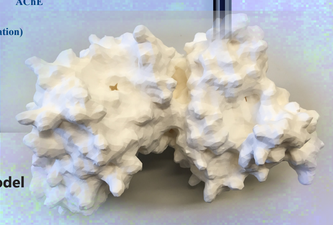


Figure 6: printed 3D Model of the AChE surface

OPCW @opcw @opcw_st /opcwonline /opcwonline /company/opcw /opcw