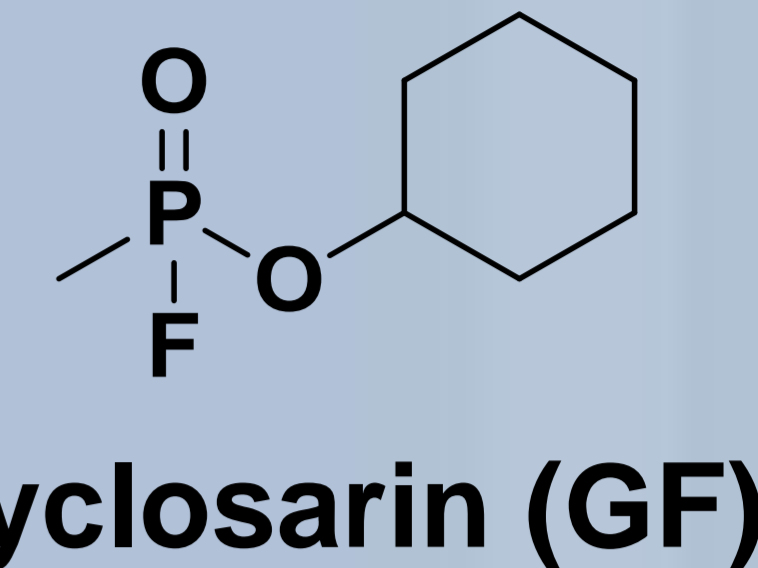
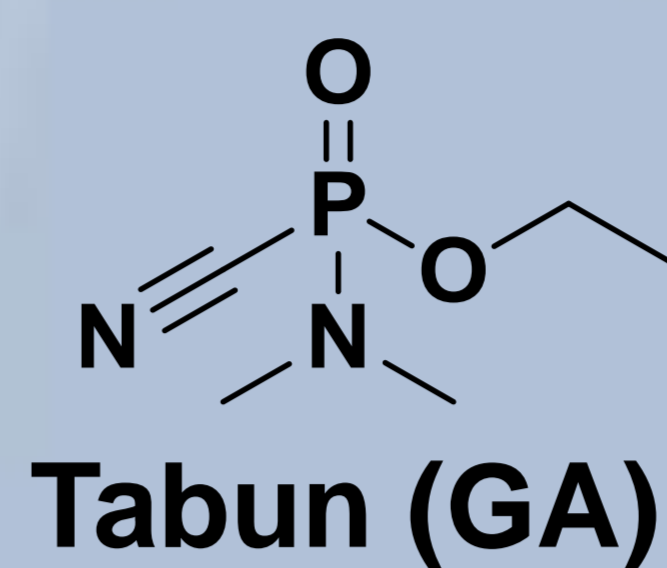
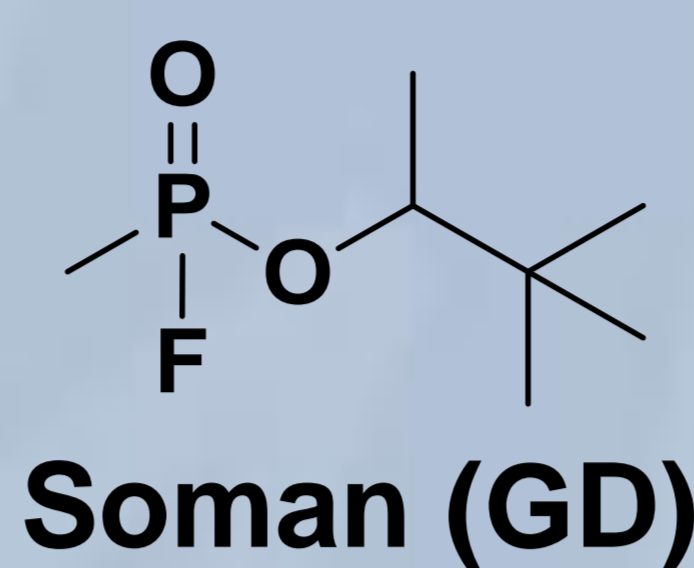
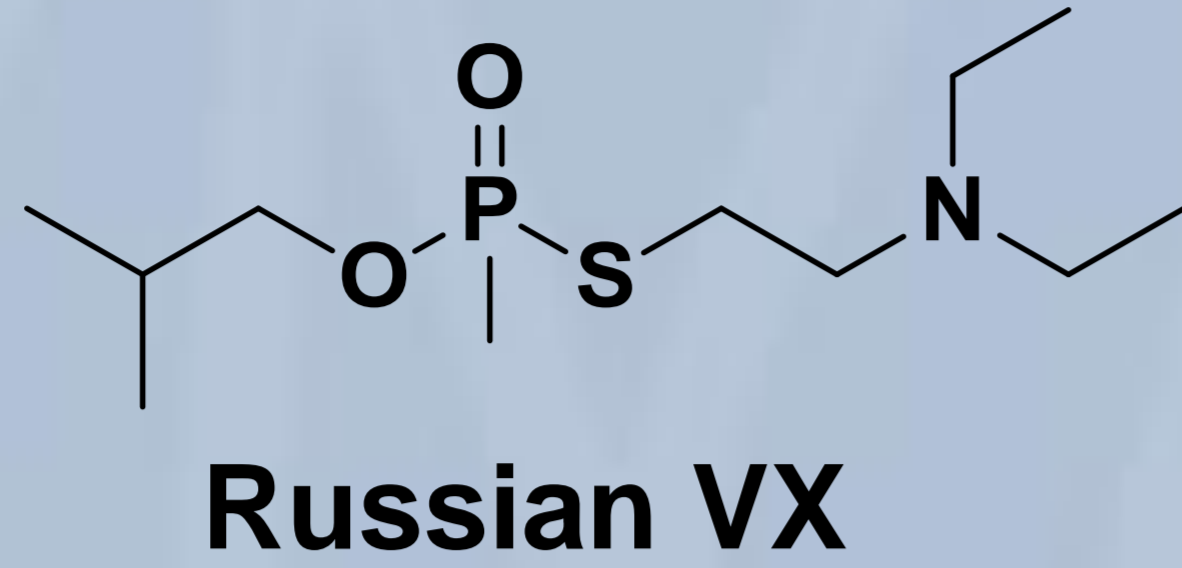
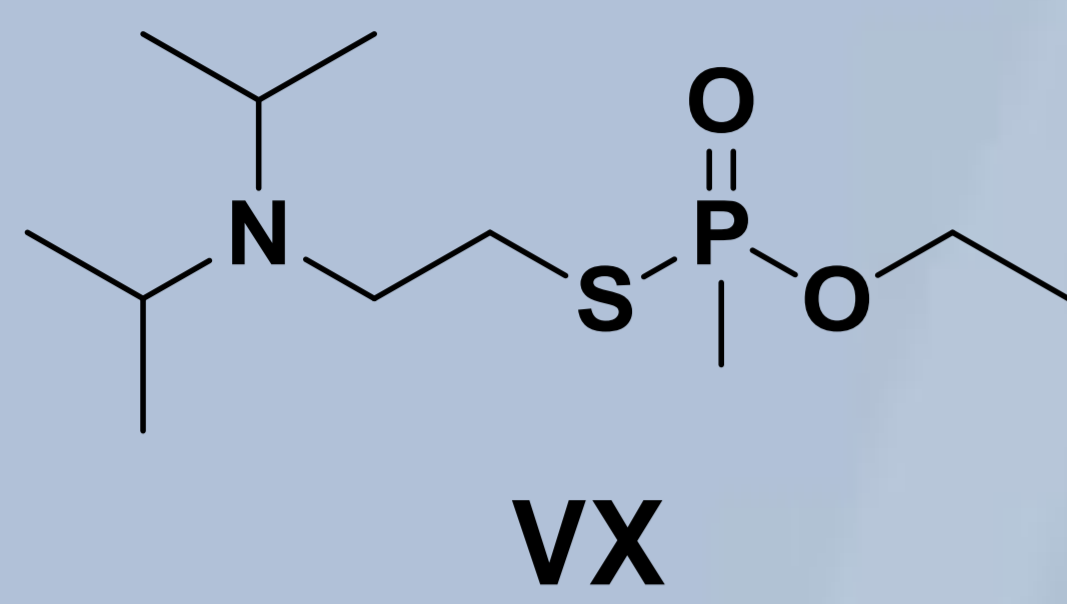


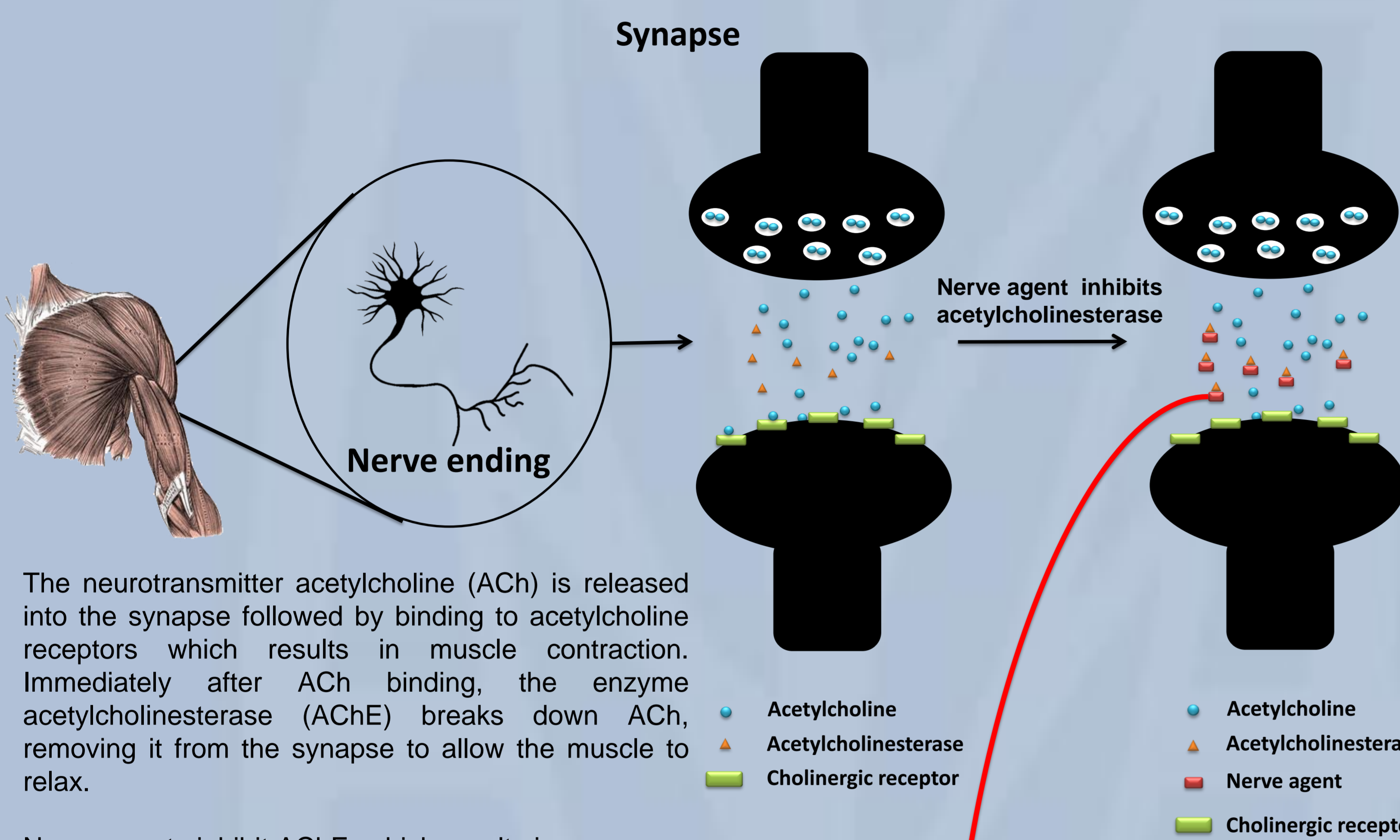


Organophosphorus (OP) Nerve Agents and their Countermeasures

Examples of nerve agents:



Mechanisms



The neurotransmitter acetylcholine (ACh) is released into the synapse followed by binding to acetylcholine receptors which results in muscle contraction. Immediately after ACh binding, the enzyme acetylcholinesterase (AChE) breaks down ACh, removing it from the synapse to allow the muscle to relax.

Nerve agents inhibit AChE, which results in an excess of ACh and over-stimulation of the neuromuscular junction. SLUDGE syndrome followed by paralysis and death results.

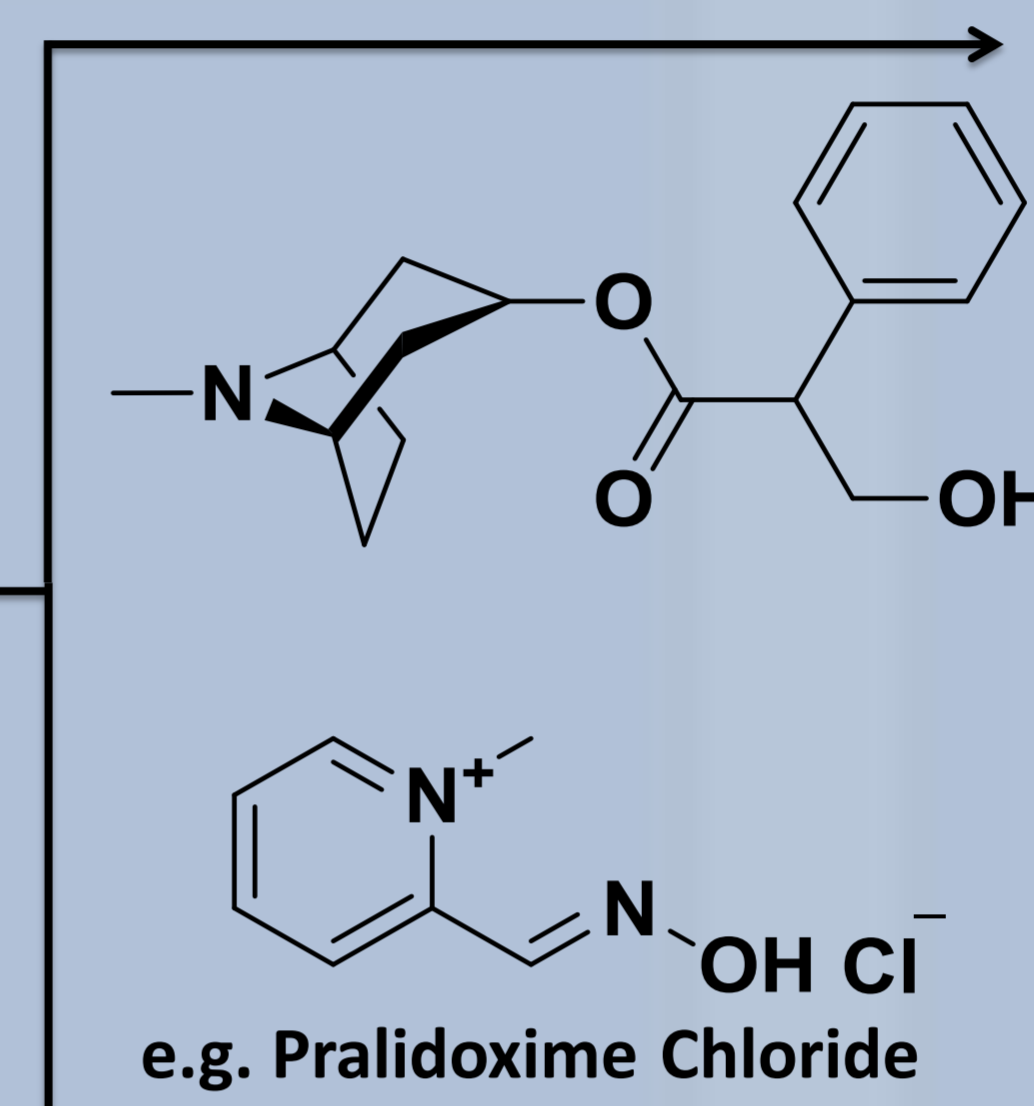
Soman (GD) adduct
Non-aged soman (GD) conjugate of *Torpedo californica* acetylcholinesterase
(Protein Data Bank structure 2WFZ)

- Inhalation toxicity
- Dermal toxicity
- Neurological complications

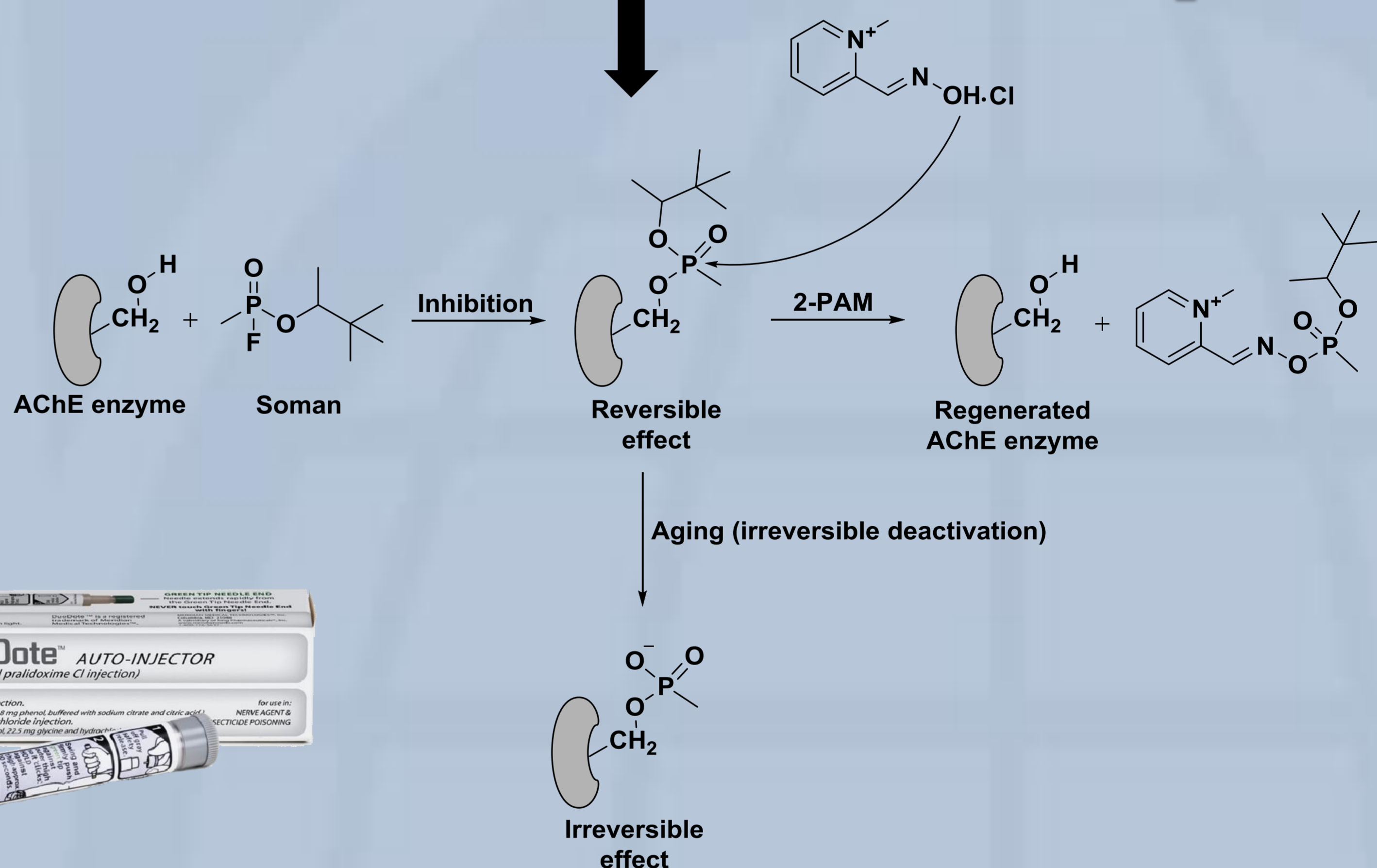
Nerve agent countermeasures
Atropine and Pralidoxime Chloride auto injector



Atropine, blocks the action of ACh at muscarinic receptors and treats SLUDGE syndrome (salivation, lacrimation, urination, diaphoresis, gastrointestinal motility, emesis)

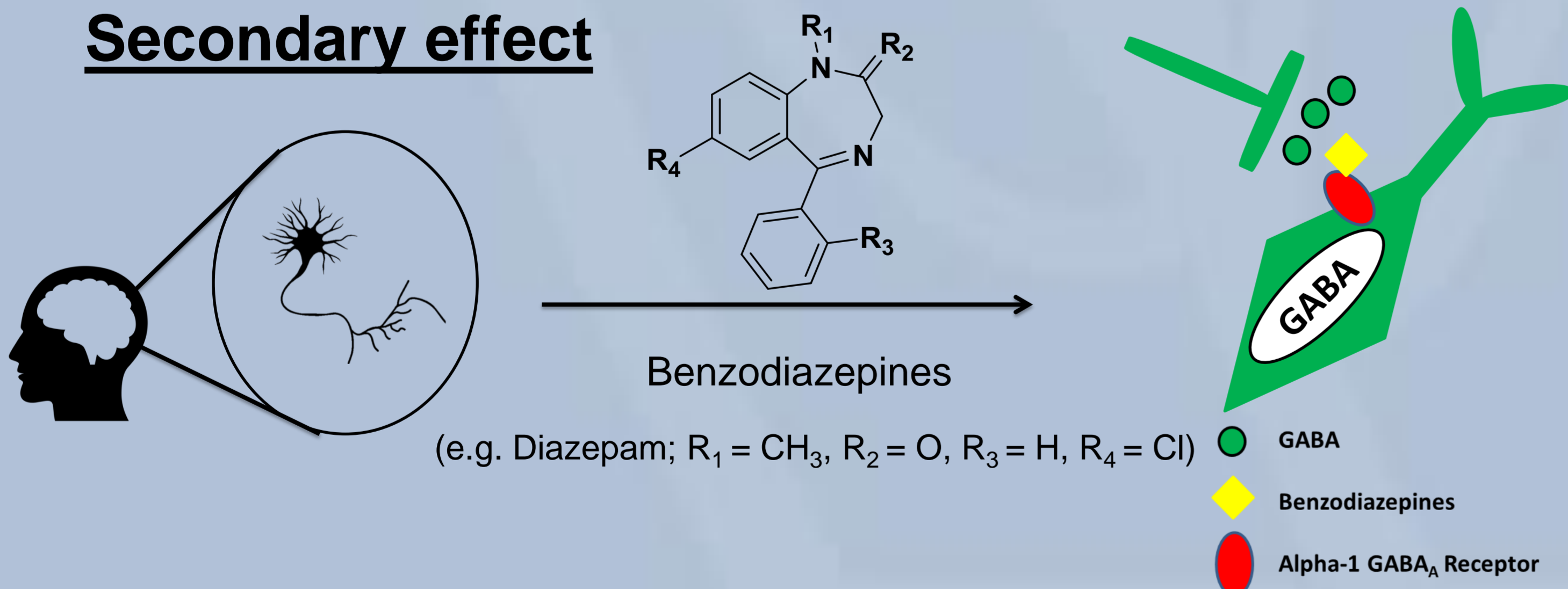


Oximes, reactivate acetyl cholinesterase before the process of aging (e.g. irreversible inhibition of the enzyme). Oximes can be co-administered with atropine, commonly used oximes include pralidoxime chloride, HI-6, trimedoxime and obidoxime



- Acetylcholine
- ▲ Acetylcholinesterase
- Nerve agent
- Cholinergic receptor
- ▲ Atropine
- Pralidoxime Chloride

Secondary effect

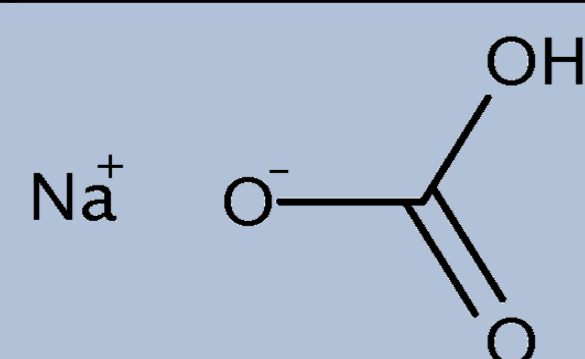


Benzodiazepines (BDZs, a class of anticonvulsants) bind to the gamma sub-unit of the GABA_A receptor. Binding results in an allosteric (structural) modification of the receptor that increases receptor activity and inhibits excessive nerve cell activity. BDZs used for this purpose include diazepam, lorazepam and midazolam.

Neuroprotective substances that bind to the GABA_A receptor such as BDZs are helpful for preventing neurological damage in the brain (atropine and oximes are targeted at muscle tissue).

Ketamine has also been studied as a neuroprotective substance.

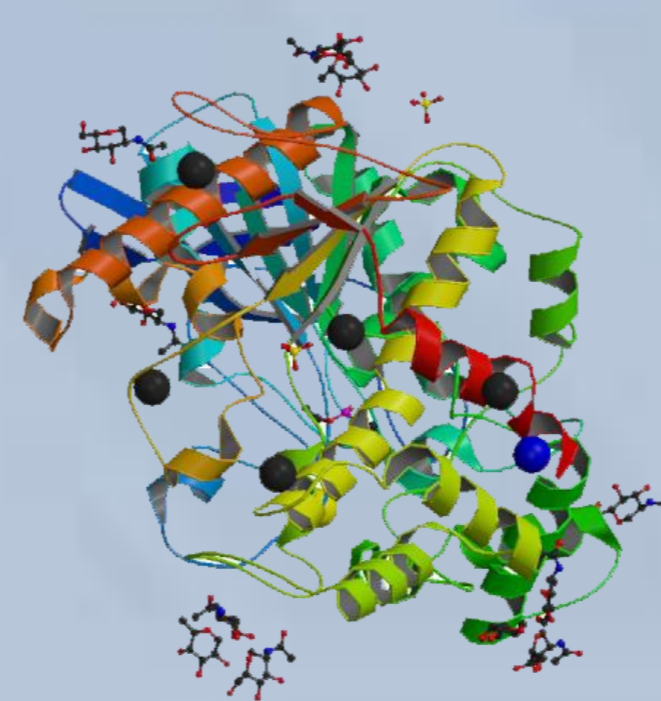
Other reported countermeasures



Sodium bicarbonate infusion has been reported to neutralize nerve agents. This is not a generally recommended procedure but there are reports of its use. *Iran J Med Sci.* 2012 Jun; 37(2): 74-91

Hemoperfusion and fresh frozen plasma can also be used to increase the excretion rate of nerve agent from the body. *Arch Toxicol.* 2014 Feb;88(2):301-7

Bioscavengers are enzymes that detoxify OPs by stoichiometric reaction or by catalytically cleaving the OPs into biologically inert products. Butyrylcholinesterase (illustrated below) represents an example of a stoichiometric bioscavenger. *Chem Biol Interact.* 2013 Dec 5;206(3):536-44



Non-aged form of human butyrylcholinesterase inhibited by the tabun analogue TA1. (Protein Data Bank structure 2WID).