Inhibition of AChE

A Terrorist Target and a Potential Contributor to Gulf war Syndrome

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On March 20th, 1995, a terrorist attack on the Tokyo subway involved the release of the nerve gas Sarin (isopropylmethylphosphonofluoridate) in five carriages on three subway lines (Okumura et al., 1996). Sarin is a potent inhibitor of AChE with an estimated lethal dose in humans of 1 mg. Like DFP, sarin forms an essentially irreversible phosphoryl–serine enzyme intermediate. In the subway attack, 12 people died and 5,000 were injured, with over 600 sufficiently injured to warrant hospital care. The most common symptoms were breathing difficulties, ocular pain, nausea and vomiting, and headaches, with death due to respiratory failure. These symptoms reflect the roles of the cholinergic system in the control of muscle contraction (notably the intercostal muscles and diaphragm used for breathing), and in parasympathetic and central nervous system functions (including the brainstem control of respiratory function, see Table 1). In severe cases red blood cell AChE activity was reduced by more than 80%, and in some cases took more than two months to return to normal levels.

Emergency workers in the Tokyo attack.

Treatment of victims, in the more affected cases, involved artificial ventilation to sustain breathing, and administration of atropine to inhibit muscarinic receptors, thereby reducing cholinergic transmission at parasympathetic and CNS synapses. Pyridine oximes, such as pralidoxime or PAM-2, have been developed as an antidote for organophosphorus poisoning (Jokanovic & Stojilikovic, 2006). These drugs are powerful nucleophiles that reactivate AChE by displacing the phosphoryl moiety from the catalytic serine to form a phosphorylated oxime, thus regenerating the serine residue.

Reactivation of phosphorylated AChE with pralidoxime and formation of reactivated enzyme and phosphorylated oxime.

A more insidious case of low-level poisoning has been suggested to contribute to 'Gulf War syndrome.' More than a quarter of all U.S. veterans from the 1990–1991 Persian Gulf war report having a chronic illness with symptoms including fatigue; sleep disturbance; pain; cognitive and mood defects; and gastrointestinal, respiratory and skin problems. These processes are all influenced by central or peripheral cholinergic systems. Epidemiological studies have linked the incidence of symptoms with exposure to AChE inhibitors (Golomb, 2008), although this interpretation remains controversial.

Personnel deployed to the Persian Gulf in this period (about 700,000 in total) could have encountered these inhibitors in several ways:

Pyridostigmine, as given to US service personnel in the first Gulf War.

- An estimated 250,000 personnel received the carbamate AChE inhibitor pyridostigmine bromide as a protective agent against possible nerve agent exposure in the battlefield.
- Both carbamate and organophosphorus pesticides were used extensively to prevent insect-transmitted diseases.
- Demolition of munitions depots may have resulted in low-level organophosphorus exposure if they contained nerve agents.

References

Golomb, B. A. (2008). Acetylcholinesterase inhibitors and Gulf War illnesses. *Proceedings of the National Academy of Sciences of the United States of America*, *105*, 4295–4300.

Jokanovic, M., & Stojilikovic, M. P. (2006). Current understanding of the application of pyridinium oximes as cholinesterase reactivators in treatment of organophosphate poisoning.

European Journal of Pharmacology, *553*, 10–17.

Okumura, T., Takasu, N., Ishimatsu, S., Miyanoki, S., Mitsuhashi, A., & Kumada, K., et al. (1996). Report on 640 victims of the Tokyo subway sarin attack. *Annals of Emergency Medicine*, *28*, 129–135.