TOXIN MEDICAL COUNTERMEASURES - DEVELOPMENT OF NOVEL, BROAD-SPECTRUM COUNTERMEASURES FOR TOXIN EXPOSURE

Aging Of Acetylcholinesterase, The Movie: Understanding The Mechanisms Of Dealkylation Of Organophosphorus-acetylcholinesterase Adducts As A Means Of Developing New Medical Countermeasures

Julian Chen Los Alamos National Laboratory **Robert Williams** Los Alamos National Laboratory **Karissa Sanbonmatsu** Los Alamos National Laboratory **Li-Wei Hung** Los Alamos National Laboratory

Acetylcholinesterase is a crucial enzyme involved in terminating neurotransmission at cholinergic synapses by catalyzing the hydrolysis of the neurotransmitter acetylcholine. Organophosphorus compounds act as potent inhibitors of acetylcholinesterase, through the formation of a covalent adduct between the catalytic serine residue in the active site of the enzyme, leading to the accumulation of acetylcholine at the synaptic cleft. Excessive acetylcholine leads to continuous depolarization of the postsynaptic neurons, causing cholinergic and muscarinic toxicity. Despite ratification of the Chemical Weapons Convention over two decades ago, the potential for misuse of these compounds highlights the ongoing threat to military personnel and civilians.

Aging refers to a dealkylation reaction that occurs after formation of the organophosphorus-acetylcholinesterase adduct. Though a still poorly understood mechanism, loss of the alkyl group results in a highly stable, electrostatically stabilized form of the enzyme that is refractory to standard oxime-based reactivation. Aging occurs on vastly different time scales depending on both the species as well as the adduct. To study this process in detail, we are undertaking a combined experimental and computational approach to understanding how aging occurs in acetylcholinesterase. A search of the PDB reveals a very limited set of aged and non-aged acetylcholine structures that were used for comparison. Preliminary conclusions from these structures shows that global structural rearrangements are very limited, and that side-chain motions, especially around the conserved aromatic residues and the histidine of the catalytic triad, are associated with aging, although not necessarily a result of accommodation of the aged product. Time-resolved structural studies of the aging process of are underway. The results will provide experimental data to guide our molecular dynamics-based computational modeling to reveal the details of the aging process.