Hadad **developing reagent solution** to deadly nerve agent exposure

Scientists at The Ohio State University (OSU) are working to develop a drug that will regenerate a critical enzyme that "ages" after a person is exposed to deadly chemical warfare agents. To help develop a more effective antidote to organophosphorus (OP) nerve agents, Christopher Hadad, Ph.D., professor of chemistry, is combining findings from the biochemical studies of his partners with synthetic and computational organic chemistry his research team is conducting at OSU and the Ohio Supercomputer Center.

OP nerve agents inhibit the ability of an enzyme called acetylcholinesterase (AChE) to turn off the messages being delivered by acetylcholine (ACh), a neurotransmitter, to activate various muscles, glands and organs. After exposure to OP agents, AChE undergoes a series of reactions, culminating in an "aging" process that inhibits AChE from performing its critical biological function. Without the application of an effective antidote, neurosynaptic communication continues unabated, resulting in uncontrolled secretions and muscle spasms, which, if untreated, result in death.

Conventional antidotes to OP nerve agents block nerve agent activity by introducing oxime compounds, which have been the focus of several studies. These compounds attach to the phosphorus atom of the nerve agent, after the OP is bound to AChE, and then split it away from the AChE enzyme, allowing the AChE to engage with receptors and finally relax the tissues.

However, in some cases, the combined nerve agent/AChE molecule undergoes a process called aging, in which groups of single-bonded carbon and hydrogen atoms called alkyl groups are removed from the molecule, and a phosphonate residue is left behind in the AChE active site. Relatively unstudied in nerve agents, this "dealkylation" process, makes the nerve agent/AChE molecule unreceptive to oxime treatments – an unfortunate situation, considering that certain nerve agents (e.g., soman) can undergo aging within minutes of exposure to AChE.

Hadad is studying compounds that would return an appropriate alkyl group to the aged nerve agent/AChE molecule, thus allowing treatment with oximes to provide for complete recovery. The project is focusing on numerous common OP nerve agents, which take on a similar molecular structure upon aging.

"Computational studies of the interaction of the alkylating compounds with AChE were used to provide insight for the design of selective reagents," Hadad explained. *"Ligand-receptor docking, followed by molecular dynamics simulations of the interactions of alkylating compounds with aged OP-AChE, was carried out in conjunction with experimental studies to investigate the binding of alkylating compounds to AChE. These results were then used to suggest interactions that aided in the orientation of alkylating compounds for maximal efficacy."* ■

Project lead: Christopher Hadad, The Ohio State University
Research title: Design of an alkylating agent with specificity for acetylcholinesterase to reactivate the aged enzyme following nerve agent exposure
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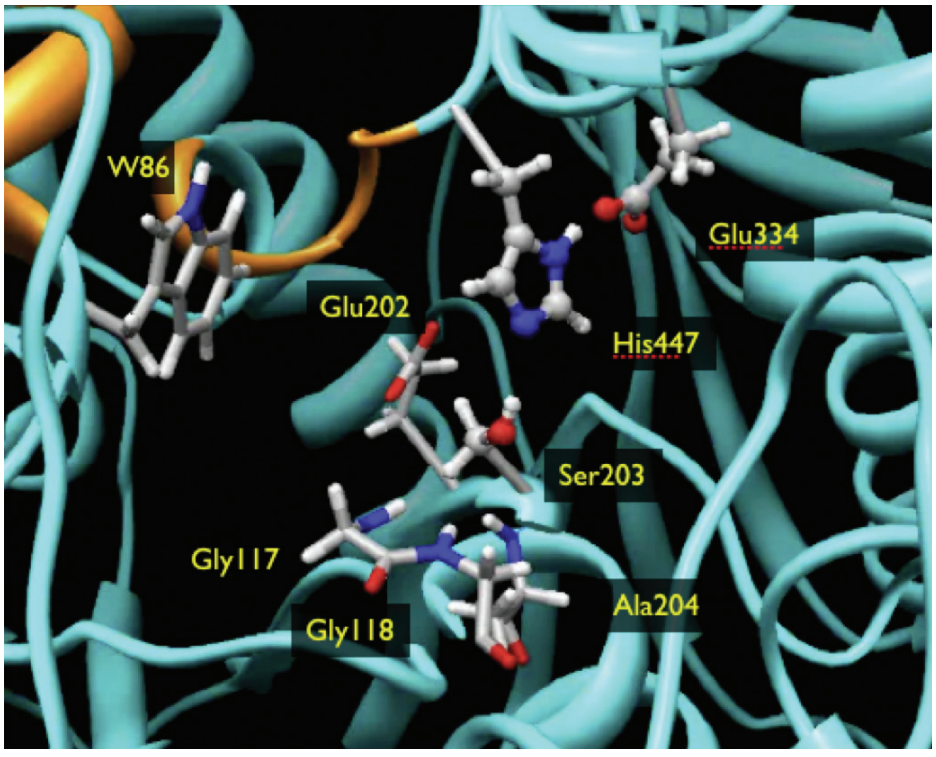

left: Preliminary simulations conducted by Christopher Hadad identify catalytic amino acid residues and other critical binding residues in the active site of AChE.