Informing Drug Design: Human Acetylcholinesterase Response to Organophosphate Poisoning

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Abstract
Acetylcholinesterase (AChE) is a target enzyme of organophosphate (OP). Current treatments for OP poisoning, i.e. oximes, have limited success, especially without pre-treatment. This study uses molecular dynamic analysis to shine light on structure and dynamical fluctuations of free AChE and OP-inhibited AChE. Knowledge gained by the study of OP inhibition of acetylcholinesterase should guide future drug designs of more effective antidotes.

Background
• AChE is a serine protease that breaks down the neurotransmitter acetylcholine to terminate neurotransmission.
• AChE is present in all nerve synapses, neuromuscular junctions, and RBCs.
• OPs are commonly found oil additives, pesticides, and chemical weapons, which can target and inhibit AChE.

Methods
1. NAMD, Scalable Molecular Dynamics: Parallel molecular dynamics code for high-performance simulation
2. Essential Dynamics Analysis: Covariance matrix of positional fluctuations of the Ca atoms analyzed reveal principle directions of large concerted motions used to assess dynamical similarity
3. VMD, Visual Molecular Dynamics: displaying, animating and analyzing biomolecular systems (Solvent Accessible Surface Area, Distance Plots, Modes of Motion Comparison)
4. MOLE: Rapid and fully automated location and characterization of channels, tunnels, and pores in molecular structures

Results and Conclusions
• Minimal conformational differences between initial structures of simulations.
• Simulations adequately sampled essential subspace.
• Apoprotein simulation compared with soman-adducted simulation show low similarity of overall motions.
• Adducted simulation revealed more rigid fluctuations when compared with apoprotein.
• Side door to active site revealed in both apoprotein and adducted simulations.
• MOLE analysis reveals side doors open while main gorge is closed and also suggests gorge volume is not necessarily correlated with main door configuration.

References

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