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 antitoxins.

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.
- Acute cholinergic crisis, is the major manifestation of OP poisoning. Inhibition of synaptic AChE causes an accumulation of acetylcholine in the nerve synapse leading to continuous neurotransmission and possible death within minutes.
- Molecular Dynamic (MD) analysis was performed to elucidate characteristics of enzyme/adduct to aid design of more effective countermeasures of OP poisoning.

Results and Conclusions

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

- 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.

Methods

- Figure 1. Proposed mechanism for irreversible "aging" of AChE by an OP.
- Figure 4. Entrance to Active Site of Apoprotein. In blue, main-gorge opening. In yellow, catalytic triad of active site.
- Figure 5. Side Entrance to Active Site of Apoprotein. In orange, side-door opening. In blue, main-gorge closed. In yellow, catalytic triad of active site.
- Figure 6. Main door opening in soman-adducted simulation. In blue, occluded residues of main door. In yellow, catalytic triad of active site.
- Figure 7. Distance plot across gorge of apoprotein simulation reveals more erratic gorge fluctuations, supported by visual observation of principal modes of movement.
- Figure 8. Distance plot across gorge of adducted simulation reveals rigid gorge fluctuations, supported by visual observation of principle modes of movement.
- Figure 9. Tunnel predicted by MOLE corresponds to main gorge in apoprotein. Cavity (green) volume: 483 Å3.
- Figure 10. Tunnel predicted by MOLE opens and closes in apoprotein. Cavity (green) volume: 493 Å3.
- Figure 11. Tunnel predicted by MOLE corresponds to main gorge in adducted protein. Cavity (green) volume: 493 Å3.
- Figure 12. Tunnels predicted by MOLE reveal opened side and back doors while main gorge opening is closed in adducted protein. Cavity (green) volume: 111 Å3.

References

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