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 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.

Results and Conclusions
- 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.

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

References
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Acknowledgements
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Figure 1. Proposed mechanism for irreversible "aging" of AChE by an OP.
Figure 2. Beginning structure of apoprotein simulation colored by secondary structure.
Figure 3. Beginning structure of soman-adducted simulation colored by secondary structure.
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, isolated residues of main door. In yellow, catalytic triad of active site.
Figure 7. Distance plot across gorge of soman-adducted simulation reveals more drastic gorge fluctuations, supported by visual observation of principle modes of movement.
Figure 8. Distance plot across gorge of soman-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: 483Å³.
Figure 10. Tunnel predicted by MOLE corresponds to side door in apoprotein. Cavity (green) volume: 483Å³.
Figure 11. Tunnel predicted by MOLE corresponds to main gorge in soman-adducted protein. Cavity (green) volume: 483Å³.
Figure 12. Tunnels predicted by MOLE reveal opened side door while main gorge opening is closed in adducted protein. Cavity (green) volume: 1118Å³.

Table 1. Root Mean Square Inner Product (RMSIP) calculations comparing non-aducted simulation to OP-aducted simulations

<table>
<thead>
<tr>
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<th>APO-AChE</th>
<th>Soman-AChE</th>
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<tr>
<td>APO-AChE</td>
<td>0.628</td>
<td>0.362</td>
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<tr>
<td>Soman-AChE</td>
<td>0.527</td>
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Figure 13. Distance plot across gorge reveals side doors open while main gorge is closed and also suggests gorge volume is not necessarily correlated with main door configuration.

Table 1: RMSIP calculations comparing non-aducted simulation to OP-aducted simulations.