Informing Drug Design: Human Acetylcholinesterase Response to Organophosphate Poisoning

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Award No. 0952013

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.

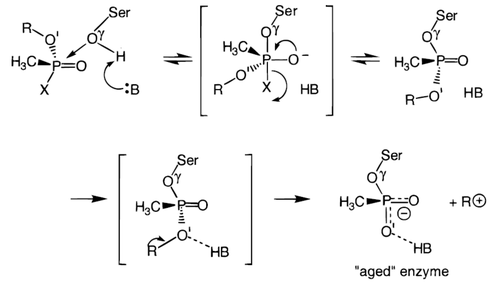

Figure 1. Proposed mechanism for irreversible "aging" of AChE by an OP.

- 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

Results and Conclusions

1

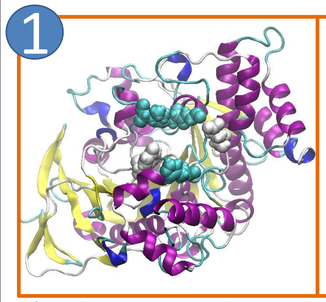

Figure 2. Beginning structure of apoprotein simulation colored by secondary structure.

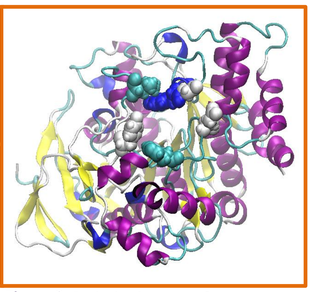

Figure 3. Beginning Structure of soman-adducted simulation colored by secondary structure.

2

	APO-AChE	Soman-AChE
APO-AChE	0.628	0.362
Soman-AChE		0.527

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

- 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.

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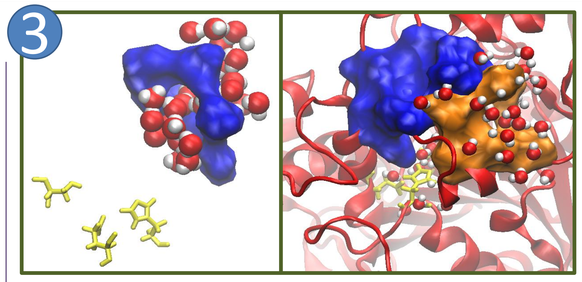
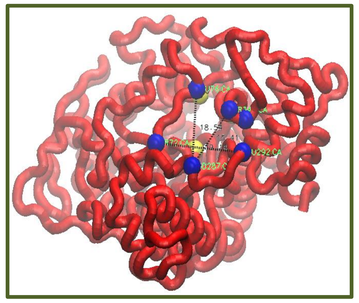


Figure 4. Entrance to Active Site of Apoprotein. In blue, main gorge opening. In yellow, catalytic triad of active site.

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.

- Adducted simulation revealed more rigid fluctuations when compared with apoprotein.
- Side door to active site revealed in both apoprotein and adducted simulations.



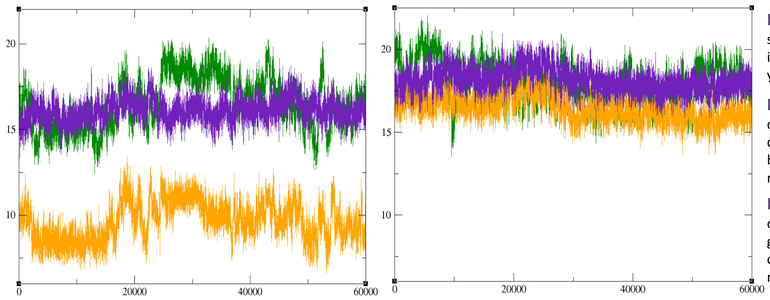


Figure 6. Main door opening in soman-adducted simulation. In blue, isolated residues of main door. In yellow, catalytic triad of active site.

Figure 7 . Distance plot across gorge of apoprotein simulation reveals more drastic gorge fluctuations, supported by visual observation of principle 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.

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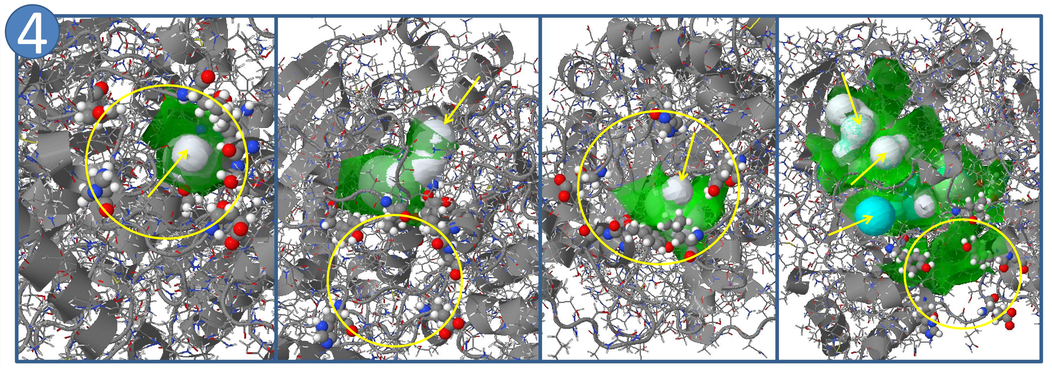

Figure 9. Tunnel predicted by MOLE corresponds to main gorge in apoprotein. Cavity (green) volume: 483 A^3

Figure 10. Tunnel predicted by MOLE reveals opened side door in apoprotein. Cavity (green) volume: 704 A^3

Figure 11. Tunnel predicted by MOLE corresponds to main gorge in adducted protein. Cavity (green) volume: 483 A^3

Figure 12. Tunnels predicted by MOLE reveal opened side and back doors while main gorge opening is closed in adducted protein. Cavity (green) volume: 1351 A^3

- MOLE analysis reveals side doors open while main gorge is closed and also suggests gorge volume is not necessarily correlated with main door configuration.

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Acknowledgements

This material was based upon work supported by the S.D. Bechtel, Jr. Foundation and by the National Science Foundation. Any opinions, findings or recommendations expressed in this material are those of the authors and do not necessarily reflect the views of the S.D. Bechtel, Jr. Foundation or the National Science Foundation. This project has also been made possible with support of the National Marine Sanctuary Foundation. The STAR program is administered by the Cal Poly Center for Excellence in Science and Mathematics Education (CESaME) on behalf of the California State University (CSU). This work is performed under the auspices of the U.S. Department of Energy by Lawrence Livermore National Laboratory under Contract DE-AC52-07NA27344. IM# 568308