Rescuing Acetylcholinesterase from Nerve Agent Inhibition: Protein Dynamics Driven Drug Discovery

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Abstract

Severe morbidity and mortality consequences result from irreversible inhibition of human acetylcholinesterase by organophosphates (OPs). Oxime-based reactivators are currently the only available treatments but lack efficacy in the central nervous system (CNS) where the most damage occurs. Computational docking and molecular dynamics (MD) simulations reveal complex structural barriers that may reduce oxime efficacy. These results may guide future drug designs of more effective countermeasures.

Background

- AChE is a serine protease that breaks down the neurotransmitter acetylcholine.
- AChE is present in all nerve synapses, neuromuscular junctions, and RBCs.
- OPs are commonly found oil additives, pesticides, and chemical weapons which can inhibit AChE function causing "runaway" neurotransmission and cholinergic crisis.

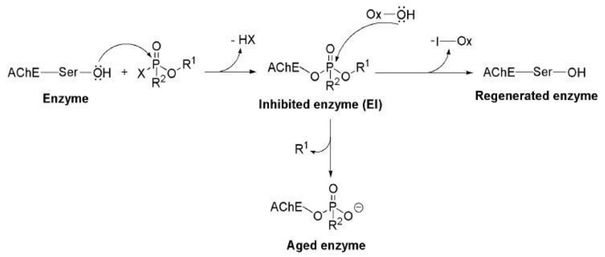

Figure 1. Inhibition, reactivation, and aging of Acetylcholinesterase.

- Oximes are currently the only available treatment for OP poisoning. Their value is a matter of debate. Better countermeasures are needed. No single compound is effective across a wide range of OPs and most lack efficacy within the CNS.
- MD analysis was performed to elucidate protein-protein and protein-ligand interactions to aid rational design of therapeutics to reactivate inhibited AChE.

Methods

1 VMD, Visual Molecular dynamics
Displaying, animating, and analyzing biomolecular systems

2 AutoDock Vina
Open source program for predicting the preferred orientation, binding affinity between two molecules

3 NAMD, Scalable Molecular Dynamics
Parallel molecule dynamics code for high-performance simulation

Results and Discussion

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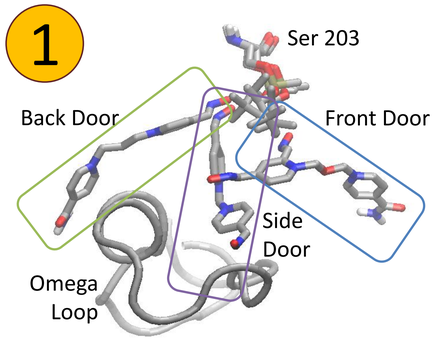

Figure 2. Composite image of three docked oximes representing the three major access points to the active site. HLO7 is docked into the front door, MM40 is docked into the side door, and KO27 is docked into the back door.

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- Hlo7 preferred by front and side doors as well as being the most commonly docked structure. K027 preferred by back door.
- Weakest affinities found at smallest (acute) angles.

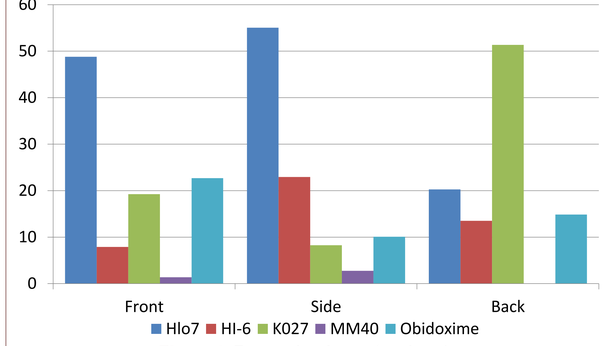

Figure 3. Percent by door of each oxime.

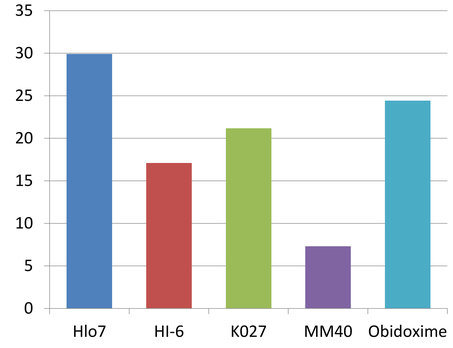

Figure 4. Percent oxime of total identified.

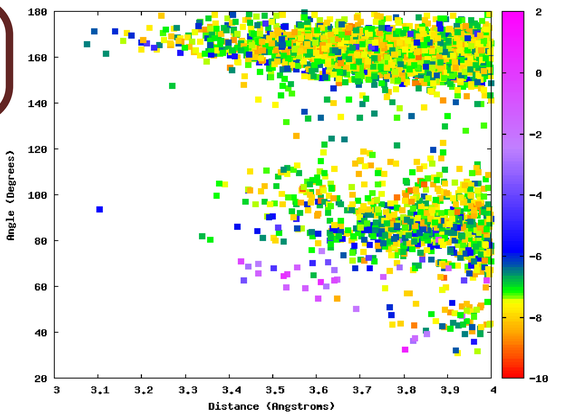

Figure 5. Plot of distance (from oxime oxygen to adduct phosphorous), angle (formed between adduct oxygen and phosphorous and oxime oxygen), and affinities calculated during docking.

- Three major docking positions identified- front (main gorge), side, and back door.
- Highest average angle observed in front door (gorge).
- Highest average affinity observed in the back door.

	Distance	Angle	Affinity
Hlo7	3.802298296	146.2569	-7.957222222
HI-6	3.864258654	149.2588	-7.466504854
K027	3.83685908	149.7995	-7.500784314
MM40	3.835454085	133.3407	-7.301136364
OBDO	3.823793324	145.1391	-7.175510204

Table 1. Distance, angle, and affinity averages by oxime.

	Distance	Angle	Affinity
Front	3.79088284	163.8014	-7.518556701
Side	3.83372096	105.1306	-7.258715596
Back	3.827483693	128.9129	-7.735135135

Table 2. Distance, angle, and affinity averages by door.

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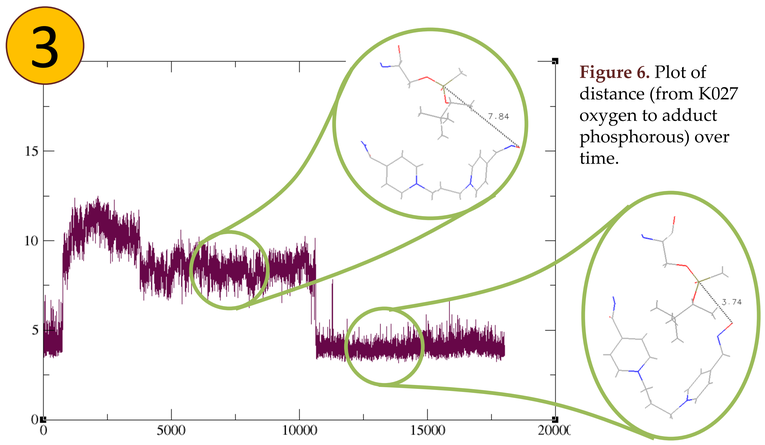

Figure 6. Plot of distance (from K027 oxygen to adduct phosphorous) over time.

- Two major conformations of K027-protein complex observed.
- Oximes tended to spend more time at 7-10Å away from OP phosphorous. (Data not shown)
- Further analysis required to determine reaction energetics.

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References

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