

MEETING ABSTRACTS

MODIFICATIONS OF CHOLINESTERASE STRUCTURE AND FUNCTION IN COVALENT ORGANOPHOSPHATE CONJUGATES VISUALIZED IN 2D, 3D AND VR

Zihan Zheng, Wanlu Yu, Jacqueline Rohrer, Alexandria Tran and Zoran Radić

Presenting author: Zoran Radić

Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California at San Diego, La Jolla, CA 92093-0650, USA

Backbone conformations in hundreds of PDB deposited cholinesterase (ChE) X-ray structures show surprising similarity with typical variability of $\sim 1\text{\AA}$ or less among native and liganded acetylcholinesterases (AChEs; 3.1.1.7) and as low as $\sim 2\text{\AA}$ between AChEs and butyrylcholinesterases (BChEs; 3.1.1.8). The largest backbone deviations are observed in their covalent conjugates with organophosphate (OP) inhibitors. Those deviations are likely to influence approach, binding and reaction efficacy of nucleophilic oxime reactivators of ChEs the only true antidotes of OP intoxicated individuals and therefore need to be considered in structure based design of improved oxime antidotes.

We developed a novel, reference point based principle for overlay-independent pairwise comparison of liganded and non-liganded C α conformations from respective PDB structures and encoded it in JAVA based computer algorithm for quick analysis. Comparisons are based on differences in distances between each C α pair based on differences in the angle between center of mass, reference point and each of C α in the comparison, revealing a subset of C α in two structures that maintains their relative positions in the 3D space best and that can be used as tethering points for overlay of compared structures.

Using NanoPro (Nanome Inc.) VR software, we visualized results of pairwise structure analyses creating .pdb format 3D graphs to identify interaction matrices between amino acids revealed upon ligand binding.

Structure comparisons will be paralleled to OP inhibition and oxime reactivation parameters for some of analyzed ChE-OP-oxime systems to emphasize the importance for complete molecular target template characterization in the structure based antidotes design.

Keywords: organophosphates; oxime reactivators; backbone conformation; 3D structure; VR

Acknowledgement

This work was supported by the CounterACT Program, NIH, Office of the Director, Grant R21 NS098998 from NINDS.