Novel Nucleophiles to Negate Nerve Gases

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Paraoxonase 1 (PON1) is a calcium-dependent hydrolase that is found associated with high-density lipoprotein (HDL) particles in the blood. PON1 naturally hydrolyzes organophosphates (OP's), including nerve agents, but most OP's, including all the nerve agents, are poor substrates. In this talk I will describe my group's modeling work to develop small-molecule nucleophiles that can enhance the ability of PON1 to detoxify nerve agents. The modeling was part of a joint experimental-computational effort, which led to the discovery of novel pyridinium oximes that were shown to enhance the ability of PON1 to degrade nerve agent surrogates. These compounds appear to work through the rather novel mechanism of enhancing enzyme activity by binding into the active site of the protein once the substrate is bound and then directly taking part in the enzymatic hydrolysis reaction.

PON1 is a lipid-bound protein, but the only crystal structures available are for a recombinant form of the enzyme that was made soluble in water. Therefore, a pertinent question is the extent to which the interaction of the enzyme with the lipid layer affects the structure and function of the enzyme. PON1 was known to have both an open and a closed conformation. Our modeling provided evidence for a second, previously unknown, open conformation for PON1. In addition, the modeling revealed a possible explanation for the known reactivity differences between the Q192 and R192 isoforms of the human enzyme. Finally, we showed that the binding pocket of the recombinant PON1 was substantially smaller than that of the human PON1. This difference has serious implications for the substrate specificity of the enzyme.