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MEETING ABSTRACTS

COMPUTATIONAL ANALYSIS OF REACTION MECHANISMS FOR OPTIMIZATION OF BUTYRYLCHOLINESTERASE-BASED CATALYTIC BIOSCAVENGERS AGAINST ORGANOPHOSPHORUS AGENTS

Sofya Lushchekina [1], Bella Grigorenko [1,2], Alexander Nemukhin [1,2], Sergei Varfolomeev [1,2], Patrick Masson [3]
Presenting author: Sofya Lushchekina

[1] N.M. Emanuel Institute of Biochemical Physics of Russian Academy of Sciences, Kosygina str. 4, Moscow 119334, Russia
[2] Lomonosov State University, Chemistry department, Moscow 119991, Russia
[3] Kazan Federal University, Neuropharmacology Laboratory, Kremlevskaya str, 18, Kazan 420008, Russia

Catalytic bioscavengers are second generation bioscavengers. These biopharmaceuticals can be used to degrade toxic organophosphorus agents (OPs) on the skin for decontamination or in the bloodstream for pre-treatment and post-exposure treatment of OP poisoning. Because degradation has to be fast, their catalytic efficiency has be as high as possible (k_{cat}/K_m>106 $M^{-1}min^{-1}$). To be of interest, the catalytic activity of certain enzymes, in particular self-reactivating ChEs, has to be increased by several orders of magnitude. This can be reached by computer-redesign, directed evolution of existing enzymes, and combinational strategies.

Rational design of novel ChE-based catalytic bioscavengers requires a better understanding of chemical mechanisms of inhibition, aging of conjugate, and spontaneous reactivation. Kinetic studies, X-ray crystallography and molecular modeling, in particular QM/MM calculations, present valuable insights into specific reaction routes, role of specific amino acids and obstacles against effective reactivation of phosphylated ChEs.

Introducing new functional groups surrounding the phosphylated serine should create a stable H-bonded network susceptible to activate and orient water molecule, stabilize transition states, and intermediates. Direction of nucleophilic attack of water molecule on phosphorus atom may determine whether dephosphylation is favored over aging. Mutations of key residues surrounding human BChE active site, creating new reaction pathways, have been considered. QM/MM calculations suggest that introduction of a histidine, directing attack of water molecule from apical position competes with the aging reaction, while axial direction of water attack does not. Secondary mutations for stabilizing imidazolium upon activation of water molecule lead to lower energy barrier of reactivation reaction [1].

Keywords: catalytic bioscavengers; organophosphorus compound; butyrylcholinesterase; reaction mechanism

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