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Water structure changes in oxime-mediated reactivation process of phosphorylated human acetylcholinesterase

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Abstract

c 2018 The Author(s). The role of water in oxime-mediated reactivation of phosphylated cholinesterases (ChEs) has been asked with recurrence. To investigate oximate water structure changes in this reaction, reactivation of paraoxon-inhibited human acetylcholinesterase (AChE) was performed by the oxime asoxime (HI-6) at different pH in the presence and absence of lyotropic salts: a neutral salt (NaCl), a strong chaotropic salt (LiSCN) and strong kosmotropic salts (ammonium sulphate and phosphate HPO42−). At the same time, molecular dynamic (MD) simulations of enzyme reactivation under the same conditions were performed over 100 ns. Reactivation kinetics showed that the low concentration of chaotropic salt up to 75 mM increased the percentage of reactivation of diethylphosphorylated AChE whereas kosmotropic salts lead only to a small decrease in reactivation. This indicates that water-breaker salt induces de-structuration of water molecules that are electrostricted around oximate ions. Desolvation of oximate favors nucleophilic attack on the phosphorus atom. Effects observed at high salt concentrations (>100 mM) result either from salting-out of the enzyme by kosmotropic salts (phosphate and ammonium sulphate) or denaturing action of chaotropic LiSCN. MDs simulations of diethylphosphorylated hAChE complex with HI-6 over 100 ns were performed in the presence of 100 mM (NH4)2SO4 and 50 mM LiSCN. In the presence of LiSCN, it was found that protein and water have a higher mobility, i.e. water is less organized, compared with the ammonium sulphate system. LiSCN favors protein solvation (hydrophobic hydration) and breakage of elelectrostricted water molecules around of oximate ion. As a result, more free water molecules participated to reaction steps accompanying oxime-mediated dephosphorylation.

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