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Comparative Effect of Different Group of Oximes on the Reactivity of Inhibited Acetylcholinesterase

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The use of pesticides and insecticides has increased in agricultural field and household etc for pest control, pest management and to prevent diseases caused by insects respectively over a period. Insecticides are also a category of pesticides. Some of the most abundantly used pesticides contain organophosphate compounds as basic ingredient. Organophosphate compounds are ester, amide and thiol derivatives of phosphoric acid. Such compounds are highly toxic and their accumulation in the human body can cause neuro-poisoning. They deactivate the human acetylcholinesterase (AChE) and thus stop the acetylcholine neurotransmission. Although the process is not permanent, it depends upon how much time the interaction between organophosphate compound and AChE has taken before the aging and denaturation of the enzyme starts. Before aging of the enzyme, a group of compounds known as Oximes belonging to the family of amines can be used to reactivate the human acetylcholinesterase.

Oximes are divided into four sub-categories namely: aldoximes, ketoximes, oxime esters and steroid oximes depending upon their chemical orientation. The first oxime was developed by Czech Republic in 1956. Among them, obidoxime and pralidoxime are clinically used for years and are synthesised commercially. Oximes can reactivate the human AChE by removing the phosphate attached to its residues in the catalytic active sides, phosphorylated by organophosphate compounds. In this study, the structures of oximes were obtained from previously performed experiments. The structures were then converted to 2D structures (SDF) via PubChem. The SDF files were then converted to PDB (3D) format using PyRx tool which produced a tertiary structure of the oximes which was a requirement to perform docking. As for the human AChE, the structures of inhibited AChE were downloaded from Protein Data Bank in the PDB format and cleaned using Chimera tool. After preparing the 3D structures, oximes with highest chances of reactivating the inhibited AChE were selected by observing the AChE and oxime interactions. A total of 67 oximes from different categories were selected forming more than 600 conformations of enzyme-ligand complexes. To further improve the properties, characteristics if the toxicity and metabolism of these oximes were also checked using ligplot+ and Vega ZZ.

Results:
Our results suggest that, brasofensine, caproxamine, CPCCOEt, Demexiptiline, FERb-033, Milameline, NS-2710, Noxiptiline, Perillartine, Pralidoxime and Salicylaldoxime showed very strong interaction with the receptor and thus were able to reactivate the inhibited AChE.

Conclusions:
The penetration of oximes on the hematoencephalic barrier is a very important point for their activity as antidotes against neurotoxic organophosphorus compounds. 62 This study provides evidence that neutral oximes, which possess better capacities for membrane and hematoencephalic barrier permeation, exhibit potential as reactivators of human acetylcholinesterase inhibited with paraoxon. The comparison of the activities of the different oximes with their acidities (pKa values and ΔE = E protonated -E anionic) did not reveal a clear direct correlation between these values and the respective AChE reactivating capacities. The comparison between the DE values and the reactivating capacity for 2-PAM and oximes 16 to 22, which have similar structures, displays a R 2value of 0.62, indicating that there is some correlation between ΔE and the percentage of reactivation of huAChE. Despite the fact that the oximes acidity seems not directly involved with their AChE reactivation capacity, these results suggest that there is some dependence of oxime activity on its acidity, indicating that there should exist different pathways for oxime deprotonation at the huAChE active site mostly due to their differences in structure and the substitution groups at the aromatic ring. This is evident by the observation that neutral oximes containing electron deficient substituents on their aromatic rings, especially at positions that allow direct conjugation with the oxime C = N bond, are the most effective. In addition to the capacity of an oxime to be deprotonated inside the enzyme active site,63 Future studies are needed to elucidate the nature of these other factors.

It is also necessary to carry out evaluation tests using AChE inhibited with other compounds, like chemical warfare agents to determine the potential of neutral oximes for the general treatment of intoxication with neurotoxic organophosphorus agents.