

Abstract

Title: Cholinesterases inhibited by novichok agents – in silico study of reactivation possibilities

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Abstract: Substances known as Novichok agents are banned chemical warfare agents, which were developed in Soviet Union between the 1970s and the 1980s. They were brought to the public attention very recently – they were used to poison a double agent named Skripal in 2018 and again in 2020 to poison Russian politician Navalny. It is the 4th generation of nerve agents which cause cholinergic syndrome by irreversible inhibition of acetylcholinesterase (AChE), manifesting symptoms such as depression of bronchial tubes, cramps or even paralysis of respiratory muscles and depression of the respiratory control centre in the brain. Victim then dies of asphyxiation unless antidotes are administered as soon as possible.

Treatment of nerve agents induced poisoning is based on reactivating AChE by oxime compounds which bind themselves with the toxic substance by nucleophilic attack on electropositive point of the nerve agent, releasing acetylcholinesterase that can continue with function of acetylcholine hydrolysis. The task was to choose potential reactivators (ligands) of AChE and using them to: i) find out if the ligand can sterically reach close enough to the novichok agent bound in the active site of AChE; ii) to determine ligands with the highest affinity to that specific position.

Study was done using computational methods which helped us to visualise active or blocked site of AChE and to determine affinity values. Specifically we used molecular docking (faster method but less accurate) for rough sieve of chosen ligands which was followed by more sophisticated method – molecular dynamics which predicts the movement of atoms and molecules in time.

Using modern computational methods we chose ligands which could be able to reactivate acetylcholinesterase inhibited by novichoks. The chosen ligands (with the highest affinity) will continue to be tested *in vitro*.

Keywords: Novichok agents, nerve agents, acetylcholine, acetylcholinesterase, reactivators, molecular docking, molecular dynamics