MMSL
Military Medical
Science Letters
Since 1925

Mil. Med. Sci. Lett. (Voj. Zdrav. Listy) 2018, 87(supplementum 1)
ISSN 2571-113X (Online)

MEETING ABSTRACTS

PHENYLTETRAHYDROISOQUINOLINE-BASED TRIAZOLE COMPOUNDS ARE HIGH-AFFINITY POTENTIAL REACTIVATORS OF NERVE AGENT-INHIBITED HUMAN ACETYLCHOLINESTERASE

Nikolina Maček Hrvat [1], Jarosław Kalisiak [2], Antonio Zandona [1], Goran Šinko [1], Zoran Radić [3], K. Barry Sharpless [2], Palmer Taylor [3] and Zrinka Kovarik [1]
Presenting author: Nikolina Maček Hrvat

[1] Institute for Medical Research and Occupational Health, HR-10000 Zagreb, Croatia
[2] Skaggs Institute for Chemical Biology, The Scripps Research Institute, La Jolla, CA 92037, USA
[3] Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California at San Diego, La Jolla, CA 92093-0650, USA

Ten phenyltetrahydroisoquinoline-based compounds synthesized using alkyne+azide [3+2] building block cycloaddition were tested as potential reactivators of human acetylcholinesterase (hAChE) inhibited by different organophosphates. Computational docking indicated molecule phenyltetrahydroisoquinoline moiety association with the hAChE peripheral anionic binding site (Trp286, Tyr337 and Tyr341). Therefore, stabilization near the gorge opening seemed to control the general orientation of the pyridinium ring with its attached aldoxime group inserted into the internal gorge of the hAChE active center. All of the oximes were tested *in vitro* as potential reactivators of sarin-, cyclosarin-, tabun- and VX-conjugated hAChE and potent reactivators were identified, especially with the cyclosarin-hAChE conjugate. Nevertheless, in order to acquire results applicable to reactivation in vivo, compounds should be tested at concentrations higher than 10μM, which proved limiting due to the concomitant reversible inhibition of unconjugated hAChE. High oxime affinity was observed for hAChE, but not for human butyrylcholinesterase, where an aromatic peripheral site is absent. Therefore, we tested the oximes as reversible inhibitors of hAChE. All of the compounds potently inhibited hAChE with dissociation inhibition constants in nM range. To further explore potential for safe antidotal activity, we tested oxime cytotoxicity on the human neuroblastoma SH-SY5Y cell line. No cytotoxicity was observed at studied concentrations. In conclusion our study has shown that likely binding poses of an oxime in the hAChE active center do not always ensure enhanced enzyme activity for *in vivo* reactivation. Very high affinity of a candidate oxime for unconjugated hAChE may prove counterproductive for reactivation in tissue.

Keywords: nerve agent; oxime reactivators; cholinesterases; reversible inhibitor; cytotoxicity

Acknowledgement

This work was supported by the Croatian Science Foundation (4307) and the NIH CounterACT Program U01 NS 5058048.