MMSL Military Medical Science Letters Since 1925

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

MEETING ABSTRACTS

UNCHARGED REACTIVATORS OF CHOLINESTERASES INHIBITED BY ORGANOPHOSPHORUS NERVE AGENTS

N. Probst [1], A. Braïki [1], P. Warnault [1], J. Renou [1], C. Gomez [1], G. Mercey [1], T. Verdelet [1], R. Baati [2], J. Dias [3], G. Calas [3], F. Nachon [3], M. Weik [4], L. Jean [1], P.Y. Renard [1]

[1] Normandie University, COBRA, UMR 6014 and FR 3038; University of Rouen; INSA of Rouen; CNRS, 1 rue Tesniere F-76821 Mont-Saint-Aignan, Cedex, France
[2] Université de Strasbourg, UMR CNRS 7515 ICPEES, 25 Rue Becquerel, 67087 Strasbourg, France
[3] Département de Toxicologie, Institut de Recherche Biomédicale des Armées BP7391993 Brétigny/s/Orge, France
[4] Commissariat à l'Energie Atomique, Institut de Biologie Structurale, F-38054 Grenoble; CNRS, UMR5075, F-38027 Grenoble; Université Joseph Fourier, F-38000, Grenoble, France

The acute toxicity of OPNA results from irreversible inhibition of AChE (EC 3.1.1.7), a key enzyme in neurotransmission, via the formation of a covalent P–O bond at the catalytic serine. Inhibition of AChE leads to the accumulation of acetylcholine neurotransmitter (ACh) in the synaptic cleft causing among other symptoms, seizures and respiratory arrest leading to death.

The current urgency treatment of OPNA poisoning is based on the administration of a cocktail of three components: an antimuscarinic agent (e.g. atropine), an anticonvulsant drug (e.g. diazepam) and mono or bispyridinium AChE reactivator (e.g. pralidoxime, obidoxime, trimedoxime). The high nucleophilicity of these alpha-nucleophiles allows the displacement of the phosphyl group from the catalytic serine, yielding to the restoration of AChE activity.

However, reactivation of central AChE is inefficient due to the fact that positively charged pyridiniums poorly cross the brain blood barrier (BBB). Moreover pyridinium(s) oximes exhibit a quite narrow spectrum of reactivation. Despite decades of research in this field, there are no efficient and general broad-spectrum reactivators for OP-inhibited AChE.

In this context, we have developed families of new uncharged reactivators of OP-inhibited acetylcholinesterase and/or OP-inhibited butyrylcholinesterase with the potential to cross the BBB. Three new families of uncharged reactivators display *in vitro* reactivation potencies towards VX-, tabun- and paraoxon-inhibited human AChE that are superior to those of the mono- and bis-pyridinium aldoximes (e.g. 2-PAM, HI-6, obidoxime, HLö-7, TMB-4) which include those currently used in the armed forces.

Keywords: organophosphorus; AChE; reactivator; aldoxime; uncharged

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