Development of novel acetylcholinesterase reactivators – antidotes against nerve agents

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Keywords: *Reactivator, oxime, nerve agent, antidotes*

Introduction

Nerve agents (NA) are extremely toxic compounds originally developed as pesticides in Germany. However, during World War II the pesticide research was diverted for the development of chemical warfare agents. Among them, sarin, soman, cyclosarin and tabun are the most known members of this group of toxic chemicals (Figure 1). Their acute toxicity results from the irreversible inhibition of acetylcholinesterase (AChE, EC 3.1.1.7) through phosphylation of its catalytic serine. Accumulation of neurotransmitter acetylcholine (ACh) at cholinergic synapses ensues, leading to nervous and respiratory failures. Depending on the NA, administered dose and time of the administration, intoxicated organism could die within minutes.[1]

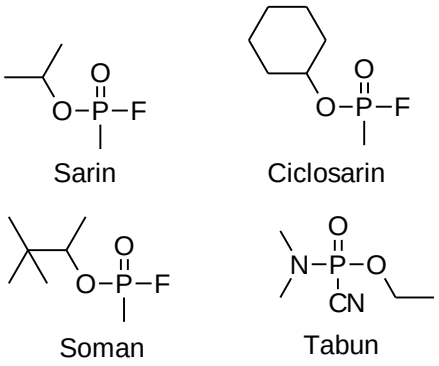

Figure 1. Structures of nerve agents.

Results and Discussion

There are several commercially available oximes – pralidoxime, trimedoxime, obidoxime, MMB4 or HI-6 – on the market. However, their reactivation potency, if broad-spectrum applicability is considered, is limited. Due to this fact, novel oximes are searched for. In 2007, novel oxime K203 was developed as a new reactivator for treatment of tabun-inhibited AChE (Figure 2).[2] The design of this compound originated from many promising compounds prepared as reactivators of tabun-inhibited AChE (K027, K048, K074 and K075). Mentioned compounds were synthesized and published within the last decade.[3] Oxime K203 showed excellent results in reactivation of tabun-inhibited AChE *in vitro,* exceeding all previously tested oximes (including trimedoxime and obidoxime).[2] Furthermore, its toxicity was lower compared to commercial oximes. The following *in vivo* evaluation highlighted oxime K203 as a lead compound in case of tabun poisoning.[4]

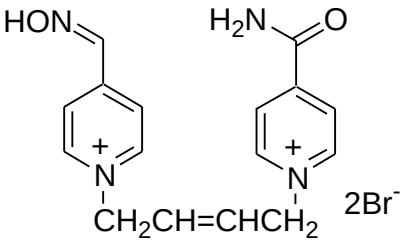

Figure. 2. Structure of oxime K203.

Conclusions

According to all the conducted studies, oxime K203 could not be designated as a universal, so called broad-spectrum, reactivator. However, it still remains the most promising oxime for treatment of tabun intoxications. Although there were further attempts via changing the K203 structure (by introduction of other functional groups), later compounds have not yet overlapped K203 in the reactivation potency against tabun. In future, there will probably be a quite different approach how to get the universal reactivator – a combination of two structurally different ractivators with a different range of reactivation activities. This should be more investigated in further studies.

Acknowledgements

CAPES/CNPq/IME/Ministério da Defesa

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