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Emergence of catalytic bioscavengers against organophosphorus agents

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ABSTRACT

Bioscavengers are an effective alternative approach for pre- and post-exposure treatments of nerve agent (NA) poisoning. Bioscavengers are natural or recombinant enzymes, reactive proteins, and antibodies that neutralize NAs before they reach their physiological targets. They are administered by injection (protein or gene delivery vector) and react with NAs in the bloodstream. Other ways of delivery can be used: inhalation for pulmonary delivery, topical creams for skin protection, etc. Operational bioscavengers must be producible at low cost, not susceptible to induce immune response and adverse effects, and stable in the bloodstream, upon storage, and under field conditions.

First generation bioscavengers, cholinesterases and carboxylesterases, are stoichiometric bioscavengers. However, stoichiometric neutralization of NAs needs administration of huge doses of costly biopharmaceuticals. Second generation bioscavengers are catalytic bioscavengers. These are capable of detoxifying organophosphates regeneratively. By virtue of high turnover, much lower doses are needed for rapid neutralization of toxicants. The most promising catalytic bioscavengers are evolved mutants of phosphotriesterases (bacterial enzymes, mammalian paraoxonases), displaying enantiomeric preference for toxic NA isomers. However, engineering of cholinesterases, carboxylesterases, prolidases and other enzymes, e.g. phosphotriesterases-lactonases from extremophiles is of interest. In particular, association of cholinesterase mutants (not susceptible to age after phosphylation) with fast-reactivating oximes leads to pseudocatalytic bioscavengers. Thus, catalytic and pseudocatalytic bioscavengers are an improvement of bioscavenger-based medical countermeasures in terms of efficacy and cost.

1. Introduction

Bioscavengers are enzymes, antibodies, and reactive proteins, that sequester and inactivate highly toxic compounds before these molecules reach their biological targets. The idea that exogenous bioscavengers could be used for protection against NAs and treatment of poisoning was introduced some 30 years ago [1]. In fact, it was known for decades that endogenous enzymes react with OPs in the body and exert some protection against OP poisoning [2]. It was also known that numerous enzymes degrade and detoxify OPs, including nerve agents (NAs) [3,4].

We must consider three types of bioscavengers: 1) stoichiometric bioscavengers that neutralize OPs in a mole-to-mole reaction; 2) pseudocatalytic bioscavengers, which are stoichiometric bioscavengers that are continuously regenerated after phosphylation in a coupled nucleophile-mediated reaction, and 3) catalytic bioscavengers for which OPs are substrates.

First studies on exogenous bioscavengers demonstrated the protective effect of stoichiometric bioscavengers [1] and catalytic bioscavengers [5]). In the past 20 years, research was dominated by the development of first generation bioscavengers, mostly human butyrylcholinesterase (BChE) as an alternative to pharmacological drugs for pre-treatment of NA poisoning [6] and post-exposure treatment [7]. However, the trend is being reversed. Several recent reviews pointed out the interest of catalytic bioscavengers [8–11]. Moreover, during the joint international conference on cholinesterases and paraoxonases there were twice as many communications about catalytic bioscavengers than about stoichiometric bioscavengers (http://tox.umh.es/12thche/index.html). The present article illustrates the advantages of catalytic bioscavengers

Abbreviations: AChE, acetylcholinesterase; BChE, butyrylcholinesterase; CaE, carboxylesterase; CSP, cresyl saligenyl phosphate; DFP, diisopropylfluorophosphate; GMP, Good Manufacturing Practice; NA, nerve agent; NTE, neuropathy target esterase; OP, organophosphorus compound; PLL, phosphotriesterase-like lactonase; PAF-AH, platelet-activating factor acetylhydrolase; PON, paraoxonase; PROL, prolidase; PTE, phosphotriesterase; QM/MM, combined quantum mechanics and molecular mechanics method; MD, molecular dynamics; TOCP, tri-*ortho*-cresyl phosphate.

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