Electrophiles for Re-activation of Aged Acetylcholine Esterase

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Technology description

The Need

Organophosphorus (OP) poisons including sarin, VX, and novichoks are lethal agents of chemical warfare. Their toxicity is due to their direct inhibition of acetylcholinesterase (AChE), an enzyme that is vital to the nervous system via regulation of the neurotransmitter acetylcholine (ACh). AChE inhibition by OPs leads to death from respiratory failure due to overstimulation of ACh receptors at neuromuscular junctions. Current treatments rely on oxime-based therapeutics, which cleave the OP molecule from AChE. However, oxime therapy is only successful if treatment occurs in a brief window following exposure. If untreated, OP-bound AChE undergoes a process called “aging” and sheds the OP’s O-alkyl group. This dealkylation leaves only the phosphate remaining in the AChE active site, which permanently inhibits AChE. Once inhibited, oxime-based treatments including pralidoxime become counter-effective, increasing the state of intoxication. After aging occurs, there is no therapy to reactivate AChE.

The Technology

We have developed pyridine and pyridinium electrophiles that de-age AChE and reopen the window for oxime therapy. Since aged AChE cannot be treated by oxime therapy, our electrophiles re-alkylate aged AChE and append an alkyl to the phosphate occupying the AChE active site. This alkylation effectively de-ages the AChE. Once this occurs, AChE can be targeted by oximes and treated. In effect, these electrophiles de-age AChE by forming alkylphosphonate-AChE adducts that can be treated with conventional oxime therapy. Therefore, this technology expands the effective treatment window for organophosphate poisoning.

Application area

Reversal of neuromuscular block
Target-promoted alkylation
Biochemistry therapeutics
Biocatalysts

Advantages

Increases the effective treatment period for organophosphorus poisoning
Increases the efficacy of treatments for organophosphorus poisoning
Creates a new window for treating organophosphorus poisoning

Institution

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