Tittle: Development of novel cholinesterase modulators

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Abstract

The enzyme acetylcholinesterase (AChE) is a key component in cholinergic synapses and at the neuromuscular junctions. Its physiological function is essential in humans, as well as in animal species, including insects. In pathological conditions, AChE is also involved in various disorders such as Alzheimer's disease (AD) or myasthenia gravis. The significance of the enzyme has also been demonstrated by its successful use as a target in insecticides. In addition, it is the key mediator in the manifestation of symptoms of intoxication after exposure to Chemical warfare agents (CWA) (Nerve agents; NA). Herein, I report my study of three different aspects of this enzyme: as an anti-AD target; as an insecticidal target; and as an enzyme to be reactivated after intoxication by organophosphorus compounds (OPCs).

Since the introduction of tacrine in 1993 as an anti-AD drug, much attention has been paid to the development of novel AChE inhibitors; some, such as donepezil, have been successfully marketed. At present, there is still a need for efficient drugs against AD. As AD is a multifactorial disorder, it believed that it cannot be treated by simply targeting one pathological condition. Therefore, the so-called multi-target directed ligands (MTDLs) have been developed to overcome this limitation. Within this thesis, the development of two families of MTDLs is described.

Specifically targeting harmful insect species (e.g., those responsible for vector-borne diseases) and not beneficial ones, such as honey bees or other animals, appears to be an almost impossible task. However, AChE is considered as one of the most promising targets, even though currently used insecticides have very poor selectivity. Two series of insecticides have been discovered and are reported herein. The ones with the highest efficacy also proved to have very promising selectivity towards insect AChE.

AChE reactivators represent the only available causal protection against OPC intoxication. At present, there is no reliable enzyme reactivator that would ensure sufficient protection. Within this work, three series of AChE reactivators were prepared. Based on a survey of the literature, some of them exert the most promising reactivation profiles yet to be presented.

Keywords: nerve agent, acetylcholinesterase, reactivator, oxime, synthesis, *in vitro*