**Daria Ahtyamova**
Kyiv National University of Technologies and Design
Scientific supervisor – PhD Maria Chernets

## CHOLINESTERASE INHIBITOR: PHARMACOLOGICAL APPLICATION

Alzheimer's disease (AD) is a progressive neuro-degenerative disorder which was first described by German psychiatrist and neuropathologist Alois Alzheimer in 1906. AD is the fourth leading cause of death in people over 65 years old worldwide [1]. AD is the leading cause of dementia amongst the aging population. Although many factors have been involved in AD, its etiology is not completely clear. This devastating disorder is generally connected with the gradual memory loss, specified by a reduction of acetylcholine level in the cortex hippocampus of the brain due to hyperactivation of cholinesterases (acetylcholinesterase (AChE) and butyrylcholinesterase (BChE)) [2]. Trial data suggest a reduced emergence of behavioral and psychiatric symptoms among patients treated with cholinesterase inhibitors.

AChE and BChE are a part of the serine hydrolase family. They destroy choline-based structures and participate in neurotransmission like AChE degradation by AChE/BChE or in detoxification of xenobiotics like cocaine, salicylic acid, and others by BChE. Violation in AChE neurotransmission - main factor to the manifestation of symptoms related to diseases like myasthenia gravis, Parkinson's disease, AD, glaucoma, etc.

Tacrine, the first dual inhibitor of both cholinesterases approved by Food and Drug Administration (FDA) in 1993, was withdrawn from the pharmaceutical market due to its poor oral bioavailability, the necessity of multiple day-doses, and a number of serious side effects. Tacrine was prohibited due to its poor oral bioavailability, the need of plural day-doses, and some of serious side effects such as hepatotoxicity, vomiting, diarrheal disease, urinary incontinence, and potential carcinogenicity [2].

Today, THA assist as a useful foundation for the structure of novel agents potentially useful for AD treatment. One such substance, namely 7-methoxytacrine (7-MEOTA), exhibits an intriguing profile, retaining AChE inhibition properties and concomitantly having suppressed hepatotoxicity [2]. The results of some development of previous studies have shown that both tacrine and 7-MEOTA are capable of binding to the peripheral anionic site (PAS), as well as to the AChE catalytic anionic site (CAS), depending on the structure of the second attached fragment. Significant role plays a length of the alkyl chain in ensuring of proper contact with both crucial sections of the enzyme.

Different important class of AChE inhibitors presents Huprines, designed by merging two fragments of the known AChE inhibitors-THA and huperzine A. Some parts of this compound family are more potent human AChE inhibitors than the parent compounds. The most promising are so-called huprines X and Y [3].

Today approved drugs for the treatment of mild or moderate AD stages are donepezil, rivastigmine, and galantamine. They provide symptomatic treatment by improving cholinergic neurotransmission via inhibition of AChE to improve the quality of life of AD patients. Though they share the same mechanism of effect, they differ in terms of their route of administration and pharmacologic effects, which can impact their safety and bioavailability. Rivastigmine, available in both oral and transdermal patch formulations, is a slowly reversible dual inhibitor of acetyl and butyryl cholinesterase, selective for the G1 isoform of acetylcholinesterase. Despite its unique features, it was associated with a higher incidence of side effects compared to other drugs [2].

A research has demonstrated clinical benefits of sustained cholinesterase inhibition with rivastigmine in AD and Parkinson's disease dementia (PDD). Rivastigmine is a unique cholinesterase inhibitor with both AChE and BuChE inhibitory activity, unlike donepezil and galantamine that selectively inhibit AChE. Scientists suggest that the dual inhibition of AChE and BuChE may afford additional medication potential of rivastigmine in subcortical dementias (subcortical PDD) with benefits on cognition and behavioral symptoms [4].

Furthermore, evidence shows that acetylcholine plays a role in suppression of cytokine release through a "cholinergic anti-inflammatory pathway" which raises questions about the role of these inhibitors in the immune system. Several review covers research and discussion of the role of the inhibitors in modulating the immune response using as examples the commonly available medicine, donepezil, galantamine, huperzine, neostigmine and pyridostigmine. Great attention is given to the cholinergic anti-inflammatory pathway, a well-described link between the central nervous system and terminal effector cells in the immune system.

Due to the complex pathogenesis of AD, currently, there is no ideal drug for the prevention or treatment of AD. Thus, the treatment of AD remains a challenge in the pharmaceutical community. And today AChE inhibitors like tacrine and donepezil the only drugs against of AD.

REFERENCES

1. Tacrine-propargylamine derivatives with improved acetylcholinesterase inhibitory activity and lower hepatotoxicity as a potential lead compound for the treatment of Alzheimer's disease. [Electronic resource] // Journal of Enzyme Inhibition and Medicinal Chemistry. – 2015. – Mode of access: – https://www.ncbi.nlm.nih.gov/pubmed/25792506 – Title of the screen

2. Identification of New Chromenone Derivatives as Cholinesterase Inhibitors and Molecular Docking Studies. [Electronic resource] // Journal Medicinal Chemistry. – 2018. – Mode of access: https://www.ncbi.nlm.nih.gov/pubmed/29473519 – Title of the screen

3. Development of 2-Methoxyhuprine as Novel Lead for Alzheimer's Disease Therapy. [Electronic resource] // 2017 – Mode of access: https://www.ncbi.nlm.nih.gov/pubmed/28788095 – Title of the screen

4. Rivastigmine: the advantages of dual inhibition of acetylcholinesterase and butyrylcholinesterase and its role in subcortical vascular dementia and Parkinson's disease dementia. [Electronic resource] // Clinical Interventions in Aging. – 2017. – Mode of access: https://www.ncbi.nlm.nih.gov/pubmed/28458525 – Title of the screen