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Review Article

Role of Enzyme Inhibition to Slow Down the Progression of Alzheimer's Disease

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Abstract

Alzheimer's diseaseis a chronic neurodegenerative disease affecting population of 45-60 years age and is thought to be one of the most troublesomemedicalillnesseswhich financially drain the healthcare budget of the developed and under-development countries at same rate. The drug development programs which are under clinical trials aimatcholinergic system deficiency, β-secretase inhibitors, γ-secretaseinhibitors,butyrylcholinesterase inhibitors and neprilysin are discussed. As the rate of cases of Alzheimer's disease are rising enormously wordwide, the unfulfilled need for disease-modifying pharmacotherapy continues. In spite of these struggles, development of effective therapeutics for the devastating disease has proved to be awfully problematic and many of the clinical trials have faced unsatisfactory results.

Key words: alzheimer's disease; neurodegenerative disease; therapeutic agents; butyrylcholinesterase; neprilysin; pharmacotherapy; anti-oxidants; anti-inflammatory agents; natural products; devastating disease

Introduction

According to the WHO, this terrible disease affects approximately 44 million individuals globally. Vascular dementia and Alzheimer's disease-related dementia are more common in Western Europe and rare in Sub-Saharan Africa (Uddin, Al Mamun et al. 2019).

Extracellular β-amyloid protein buildup, known as senile plaques, compensates for neuron loss (El-Amouri, Zhu et al. 2008;Greig, Utsuki et al. 2001; McCabe-Sellers, Frankel et al. 2003; El-Amouri, Zhu et al. 2008).

Histological examination of Alzheimer's patients' brains indicates the existence of neurofibrillary tangles and senile plaques, whereas histochemical analysis reveals a considerable amount of aberrant amyloid protein in these plaques (McCabe-Sellers, Frankel et al. 2003). Amyloid plaques are exclusive to Alzheimer's disease, although neurofibrillary tangles are also prevalent in other illnesses.

Secretases:

β-Amyloid protein is a normal metabolite that helps neurons develop and repair (Haass, 2004).

β-Secretase/BACE:

Recent studies demonstrate that the amount and activity of BACE increase up to two times normal in Alzheimer's patients, suggesting that a higher level of BACE initiates or accelerates the disorder (Vassar, Kovacs et al. 2009).

It hydrolyzes β-site amyloid precursor protein and forms β-amyloid in the endosomes of brain neurons. A clinically effective β-secretase inhibitor should be able to pass the blood-brain barrier (Haass 2004; Menting and Claassen, 2014).

β-secretase inhibitors attach to β-secretase or BACE using non-covalent bonds, making them reversible. The inhibitor's inhibitory property is determined by BACE's affinity for APP and the inhibitor, resulting in a competitive inhibition. BACE's affinity for the inhibitor correlates with lower β-amyloid formation. Increase the amount of covalent reactions between BACE and the inhibitor to achieve optimum affinity for the inhibitor (Menting and Claassen, 2014).

γ-Secretase:

Reducing γ-secretase activating protein (GSAP) in the cell line may lead to less β-amyloid formation and accumulation in senile plaques (He, Luo et al. 2010).

Butyrylcholinesterase:

Acetylcholinesterase (AChE) is found in a healthy person's brain at a higher level (80%) than butyrylcholinesterase (BuChE), and it is thought to serve a modest role in controlling acetylcholine (ACh) levels. Butyrylcholinesterase (BuChE) levels and activity increase in Alzheimer's patients' brains, while acetylcholine (ACh) levels remain constant or decline. As a result, the two enzymes indicated above are likely to be implicated in the control of acetylcholine (ACh) levels and serve as reliable therapeutic targets, up to 50%, for improving cholinergic function by stabilizing cognitive function.

According to recent research, butyrylcholinesterase (BuChE) may have a significant role in the course of Alzheimer's disease, in addition to regulating acetylcholine (ACh) levels. Experimental studies have also shown that the use of butyrylcholinesterase (BuChE) and cholinesterase (ChE) inhibitors, as well as donepezil, rivastigmine, and memantine, has strong therapeutic benefits in Alzheimer's disease by inhibiting both acetylcholine (ACh) and butyrylcholinesterase (Greig, Utsuki et al. 2001).

Neprilysin:

The β-amyloid protein has two forms: monomers and oligomers. When single unit monomers are joined, the resulting aggregates or assemblies are referred to as oligomers, and the process is known as oligomerization. Neprilysin (NEP) is an enzyme that breaks down β-amyloid. It helps degrade two forms of β-amyloid and regulates its levels in the brain. Recent investigations reveal that two types of β-amyloid peptide assembly [soluble (e.g., monomers and oligomers) and insoluble (e.g., fibrils] are present in nearly equal proportions and maintain equilibrium. This means that changing any of their metabolisms will disrupt their equilibrium, slowing disease progression. Neprilysin (NEP) may thus have an important role in reducing the progression of Alzheimer's disease (El-Amouri, Zhu et al. 2008).

Conclusion

Enzyme inhibition is critical in Alzheimer's disease treatment and may delay its progression. While existing medicines mostly rely on cholinesterase inhibition to regulate symptoms by boosting acetylcholine levels, recent research into alternative enzyme targets provides hope for more complete therapy techniques. Cholinesterase inhibitors have been shown to be beneficial in relieving symptoms and increasing cognitive function in Alzheimer's patients, but they do not stop disease progression. Research on enzyme inhibitors that target amyloid beta formation and other disease pathways has the potential to change the course of the disease. However, many of these ideas are still in the experimental phase and require further confirmation. The future of Alzheimer's treatment may include a combination of enzyme inhibitors and other therapeutic techniques, such as lifestyle changes, disease-modifying medications, and innovative therapeutics that target distinct parts of AD pathogenesis. As research progresses, personalized medicine approaches can help adapt enzyme inhibition medicines to unique patient profiles, enhancing efficacy and reducing side effects. To summarize, enzyme inhibition is an important component of Alzheimer's disease treatment. While existing medicines can help with symptoms, further study is needed to find techniques that will eventually slow or stop the disease's course.

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