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Recent progress in multifunctional metal chelators as potential drugs for Alzheimer's disease

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ABSTRACT

Alzheimer's disease (AD) is a chronic and irreversible neurodegenerative illness, which involves the progressive deterioration of intellectual functions and behavioral disorders. Several therapeutic approaches have been proposed, but only four acetylcholinesterase inhibitors and one *N*-methyl-D-aspartate receptor antagonist have been approved by the US Food and Drug Administration, which have quite limited effectiveness and that mostly provide palliative therapy. The complex pathology of this multifaceted disease and the possible interconnections among numerous intervening factors have led to the development of several multi-target candidate drugs. This review describes the most recent progress in multifunctional compounds containing a biometal (Fe, Cu, Zn) chelating unity for potential AD prevention/therapy. The importance of including a chelating moiety in these anti-AD drug candidates is associated with the recognized roles played by metal dyshomeostasis and related oxidative stress in AD pathogenesis, particularly by preceding or inducing the hallmark pathologies of this disease (neurofibrillary tangles, senile plaques, and reactive oxygen species). This review focuses on recent approaches based on the combination or fusion of different functions in a unique molecular entity, including chelating moieties, with various types of donor atoms and denticity in several scaffolds, i.e., 8-hydroxyquinolines, beta-aminopyridines and other diamino-based chelators, phenol-amino derivatives, amino/hydroxyl chalcones, 3-hydroxy-4-pyridinones, flavonoids, and hydroxyanthraquinones.

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1. Introduction

Alzheimer's disease (AD) is one of the most prevalent and devastating forms of dementia that affects the elderly population worldwide. Due to increases in the life expectancy of humans, studies suggest that there will be an exponential rise in the number of AD cases (the total estimated prevalence in 2050 may be 13.8 million), thereby necessitating the development of an effective treatment for this frontline health problem [1]. In the brain, neurons connect and communicate at synapses, where neurotransmitters carry information from one cell to another. AD disrupts this communication network in the brain by destroying synapses and killing neurons. The main symptoms of AD are impaired cognition and profound irreversible memory loss. The etiology of AD is multifactorial and its pathophysiology is complex, involving disturbances and imbalances in various mechanisms, which ultimately lead to neuronal death. The two main pathological hallmarks of AD are senile plaques deposited around neurons and neurofibrillary tangles, which are twisted fibers inside neurons [2], where they are associated with protein misfolding, thereby leading to the extracellular aggregation of amyloid-β (Aβ) peptides and intracellular aggregates of tau protein, respectively. However, other major pathological features also play important roles in the progress of the disease, including enhanced brain oxidative stress and the disruption of metal homeostasis [3]. Another prominent and consistent feature of AD is the disturbance of neurotransmitters, especially acetylcholine (cholinergic) deficit due to its hydrolysis by acetylcholinesterase (AChE). Despite decades of research to understand the etiology and pathogenesis of AD and develop new drugs, there are still no effective drugs for AD treatment. At present, the only US Food and Drug Administration (FDA)-approved drugs for the treatment of AD patients are four AChE inhibitors (AChEIs), (tacrine (TAC), donepezil, rivastigmine, and galanthamine) and one *N*-methyl-D-aspartate (NMDA)-receptor antagonist (memantine). These drugs can only modulate some neurotransmitters and ameliorate symptoms (improved patient memory) over a limited time window (1–2 years) and in mild situations, but they cannot alter the course of the disease [4]. The complexity of this disease pathology and its incomplete understanding are significant factors that have hindered the discovery and development of effective therapeutic agents. A number of novel strategies based on modifying the disease's progress have also been pursued and one of the major developments has focused on amyloid-based therapeutics, either by preventing Aβ production *via* different pathways (*e.g.*, amyloid precursor protein (APP)-cleaving enzymes, such as the aspartic proteases β- and γ-secretases), or by targeting Aβ and its aggregates for clearance or disaggregation. However, none of the drugs targeted at reducing the amyloidal load have passed clinical trials. Moreover, perturbations in the brain of AD patients, such as metallostasis with high concentrations of the triad of biometal ions (Cu, Fe, and Zn) and elevated oxidative stress levels as a consequence, have been implicated in various upstream events related to AD.

It is becoming increasingly clear that the complex pathology of AD may be responsible for the lack of an effective pharmacological treatment. Therefore, to develop the next generation of therapies, the focus has shifted toward searching for molecules that exhibit multitarget properties to combat the multifactorial nature of the disease. This review provides a brief overview of the current therapeutics and the multifactorial nature of AD, before describing and discussing the most recent strategies based on the development of metal-chelating multi-target drugs with potential applications in AD.

2. Current therapies and main AD targets

2.1. FDA-approved AD drugs

Among the five FDA-approved AD therapies, four (TAC, donepezil, rivastigmine, and galanthamine) are inhibitors of AChE, a serine-protease responsible for the degradation (by hydrolysis) of the neurotransmitter acetylcholine. The mechanism of AChE hydrolysis involves a catalytic triad of amino acid residues (Asp, His, and Ser) located in the active site of the enzyme at the bottom of a narrow cavity. This cavity is lined with several key aromatic amino acid residues, specifically the peripheral anionic binding site (PAS) and the catalytic anionic binding site (CAS), which are located at the entrance and in the middle of the cavity, respectively. Several drugs have been approved as AChEIs, which have different structures associated with diverse interactions within the active site as well as mechanisms of action. TAC was the first and most potent AChEI to be approved by the FDA in 1993 [5], but it is now used rarely due to its hepatotoxic effects [6]. Subsequently, three more AChEIs were approved for AD, i.e., donepezil [7], rivastigmine [8], and galanthamine [9].

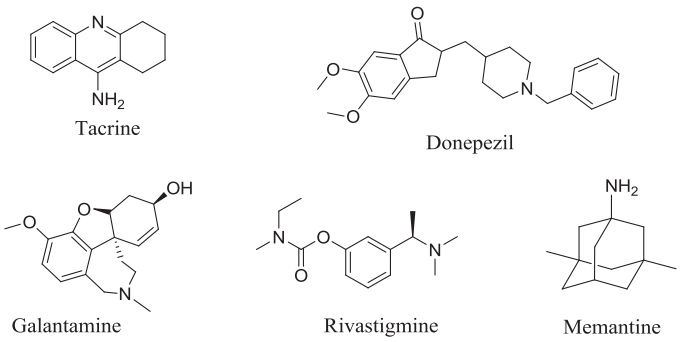

Fig. 1. Structural formulae of FDA-approved drugs for treating AD, including AChEIs and memantine.

The only approved non-cholinergic drug is an NMDA receptor antagonist (memantine), which restores the Aβ-induced Ca^{2+} imbalance (intracellular accumulation of Ca^{2+}) with a concomitant decrease in neuronal death [10]. In 2014, a combination of donepezil and memantine (10:14 or 10:28) (Fig. 1 and Table 1) has also been used. However, these FDA approved drugs only provide short-term (6–12 months) amelioration of the cognitive and behavioral symptoms in mild forms of AD, and they do not treat the underlying disease or delay its progression.

Since the approval of memantine in 2003, several hundred promising drugs have been developed and tested, but they have failed clinical trials [11]. In addition to cholinergic recovery, researchers have been searching for other AD targets, such as misaggregated Aβ and tau proteins [12], as well as the dysregulation of oxidative stress.

2.2. Drug targets for AD

Over the last 30 years, in addition to targeting and stimulating the cholinergic function, researchers have made remarkable progress in understanding the healthy function of the brain and the problems that lead to AD.

Table 1
Medications approved by the US Food and Drug Administration (FDA) for treating the symptoms of Alzheimer's disease.

Drug name	Brand name	Approved for	Approved in
Tacrine	Cognex	All stages/discontinued	1993
Donepezil	Aricept	All stages	1996
Rivastigmine	Exelon	All stages	2000
Galanthamine	Razadyne	Mild to moderate	2001
Memantine	Namenda	Moderate to severe	2003
Donepezil with memantine	Namzaric	Moderate to severe	2014

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