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Review article

Therapeutic strategies for Alzheimer's disease in clinical trials

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ABSTRACT

Alzheimer's disease (AD) is considered to be the most common cause of dementia and is an incurable, progressive neurodegenerative disorder. Current treatment of the disease, essentially symptomatic, is based on three cholinesterase inhibitors and memantine, affecting the glutamatergic system. Since 2003, no new drugs have been approved for treatment of AD. This article presents current directions in the search for novel, potentially effective agents for the treatment of AD, as well as selected promising treatment strategies. These include agents acting upon the beta-amyloid, such as vaccines, antibodies and inhibitors or modulators of γ- and β-secretase; agents directed against the tau protein as well as compounds acting as antagonists of neurotransmitter systems (serotoninergic 5-HT_6 and histaminergic H_3). Ongoing clinical trials with Aβ antibodies (solanezumab, gantenerumab, crenezumab) seem to be promising, while vaccines against the tau protein (AADvac1 and ACI-35) are now in early-stage trials. Interesting results have also been achieved in trials involving small molecules such as inhibitors of β-secretase (MK-8931, E2609), a combination of 5-HT_6 antagonist (idalopirdine) with donepezil, inhibition of advanced glycation end product receptors by azeliragon or modulation of the acetylcholine response of α-7 nicotinic acetylcholine receptors by encenicline. Development of new effective drugs acting upon the central nervous system is usually a difficult and time-consuming process, and in the case of AD to-date clinical trials have had a very high failure rate. Most phase II clinical trials ending with a positive outcome do not succeed in phase III, often due to serious adverse effects or lack of therapeutic efficacy.

Contents

Abbreviations: ACh, acetylcholine; AD, Alzheimer's disease; ADAM, disintegrin and metalloproteinase domain; ADAS-cog, Alzheimer's Disease Assessment Scale-cognitive; ADCS ADL23, Alzheimer's Disease Cooperative Study – Activities of Daily Living Scale; ADCS-CGIC, Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change; APH-1, anterior pharynx defective protein 1; API, Alzheimer's Prevention Initiative; APOE ε4, apolipoprotein E ε4; APP, amyloid precursor protein; ARIA, amyloid-related imaging abnormalities; Aβ, amyloid beta protein; BACE1, beta-site amyloid precursor protein cleaving enzyme 1; BBB, blood–brain barrier; CNS, central nervous system; CSF, cerebrospinal fluid; CTF, C-terminal fragment; DIAN, Dominantly Inherited Alzheimer's Network; GSK-3β, glycogen synthase kinase 3 beta; IVIG, intravenous immunoglobulin; MMSE, Mini Mental State Examination; MRI, magnetic resonance imaging; MTC, methylthionium chloride; NFTs, neurofibryllary tangles; NGR1, neuregulin 1; NMDA, N-methyl-D-aspartate; NPI, neuropsychiatric inventory; NTB, Neuropsychological Test Battery; PEN-2, presenilin enhancer 2; PS1, presenilin 1; RAGE, receptor for advanced glycation end products; Th1, T-helper type 1; Th2, T-helper type 2; ZBI, Zarit Burden Interview; α7-nAChR, alpha7 nicotinic acetylcholine receptor.

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Introduction

Alzheimer's disease (AD) is an irreversible and neurodegenerative brain disorder. It is the most common form of dementia, affecting 4–8% of the elderly population worldwide [1,2]. AD is characterized by relatively slow, chronic but progressive neurodegeneration and impairment in cognition accompanied by abnormal behavior and personality changes, ultimately leading to full dementia. Incidence increases with age, affecting an estimated 35 million patients worldwide [3]. As the average age of the population increases, the incidence of AD is expected to more than triple by 2050, reaching over 115 million. This disorder is usually diagnosed in people aged 65 (about 95%) and older, and is classified on the basis of patient age [4]. When diagnosed in the elderly, the disease is typically referred to as late-onset AD – in contrast to early-onset AD (accounting for 1–5% of all cases), where initial symptoms can be observed between 30 and 65 years of age [5].

The pathogenesis of AD is complex and fraught with open questions; however, it is generally accepted that, regardless of its etiology, the disease is histopathologically characterized by the presence of extracellular neuritic (senile) plaques and intracellular neurofibrillary tangles. The senile plaques are formed by the accumulation of the amyloid β protein (Aβ, Aβ-peptide) while the neurofibrillary tangles are composed of hyperphosphorylated tau protein. The role of these proteins in the patophysiology of AD is not completely clear, and many different theories have been advanced over time. Currently, it seems that such proteins represent cellular adaptation to oxidative stress. The complexity of AD indicates that many other factors may be involved in its pathogenesis [6]. This includes genetic factors, incidence of AD in the patient's family, cerebrovascular disease, traumatic brain injury, depression, hormonal disturbance, inflammation, hyperlipidemia and hyperglycemia. AD is also characterized by massive cell loss, especially of cholinergic neurons in the basal nuclei, leading to irreversible dementia [1]. Moreover, multiple neurotransmitter systems are altered in AD. Discovery of a novel anti-AD agent is, therefore, the focus of many molecular targets which include the Aβ protein, the tau protein and various neurotransmission pathways (cholinergic, glutamatergic, serotoninergic, histaminergic, dopaminergic, noradrenergic). Moreover, a number of processes involved in the pathomechanism of AD, such as excitotoxicity, oxidative stress, calcium and metal dyshomeostasis, neuroinflammation, and mitochondrial damage, are considered promising targets in the search for an effective AD treatment [5,7].

Over the years, many hypotheses have been proposed to explain the pathophysiology of AD. The earliest one, called the cholinergic deficit hypothesis, was formulated by Davies and Maloney in 1976 [8]. According to this hypothesis, many symptoms of dementia and especially learning difficulties are explainable by the lack of acetylcholine (ACh). This theory led to the introduction of the first drug, tacrine (an acetylcholinesterase inhibitor), for the treatment of AD in 1993. However, due to its very serious side effects (especially hepatotoxicity) the drug was soon withdrawn from the market. Currently, three other cholinesterase inhibitors – rivastigmine, donepezil and galantamine – are available on the market. This treatment strategy is based on the observation that the level of ACh is low in AD patients due to diminished production of choline acetyl transferase. These drugs do not represent a cure, as they do not arrest the progression of dementia, but rather lead to a temporary slowdown in the loss of cognitive function by decreasing cholinesterase activity, resulting in higher ACh levels and improved brain function. Also in use is memantine, approved in 2003 by the Food and Drug Administration (FDA) for the treatment of moderate to severe AD. It is an NMDA (*N*-methyl-D-aspartate) receptor antagonist which protects neuronal cells from glutamate-mediated excitotoxicity by blocking pathologic stimulation of NMDA receptors [9].

Unfortunately, none of the presented therapies stop the progressive loss of neurons and there is no treatment that can halt the progressive deterioration of cognitive faculties in AD patients. Consequently, the development of novel drugs with strong disease-modifying properties represents one of the greatest challenges in modern medicine [10]. Preclinical studies performed in academic as well as industrial settings focus on many potential molecular targets involved in the pathogenesis of AD [11,12]. Because of a huge attrition rate, only selected candidates are accepted onto clinical trials as potential anti-AD agents [13,14]. Due to the importance of these studies, several comprehensive reviews of anti-AD drug development prospects have been published in recent years [1,15–17]. This article presents the latest advances in the scope of the most promising anti-AD drug candidates currently undergoing clinical trials.

Therapies directed against β-amyloid

Neurotoxic Aβ is produced from the amyloid precursor protein (APP) through aggregation of soluble oligomers, leading to formation of senile plaques (fibrils), a major neuropathological marker of AD. APP is a natural membrane glycoprotein present in neurons, and is a substrate for two enzymes: α- and β-secretase. These enzymes intersect the extracellular domain of APP, generating soluble *N*-terminal peptides (APPsα and APPsβ, respectively) as well as C-terminal fragments (CTFα and CTFβ) which bond to the cell membrane. In the next step – proteolysis – the transmembrane peptides CTFα and CTFβ are cleaved inside