European Journal of Pharmacology 815 (2017) 364–375

Contents lists available at ScienceDirect

European Journal of Pharmacology

journal homepage: www.elsevier.com/locate/ejphar

The present and future of pharmacotherapy of Alzheimer's disease: A comprehensive review

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ARTICLE INFO

Keywords:
Alzheimer's disease
Acetylcholine
Dementia
Nutraceuticals
Phytoconstituents

ABSTRACT

Alzheimer's disease (AD) is a generalized term used for the loss in memory and other intellectual abilities on levels serious enough to interfere with daily life. It accounts for 60–80% of dementia cases. The characteristic features include aggregation of Amyloid-Beta (Aβ) plaques and Tau Protein Tangles in the nervous tissue of brain. Another important aspect associated with development of AD is the decrease in levels of Acetylcholine (ACh) in brain. The conventional pharmacotherapy of AD employs the use of compounds that inhibit the enzyme acetylcholinesterase (e.g. donepezil, rivastigmine) thereby elevating the levels of Acetylcholine in nervous tissue of brain. Lately, another drug has come into picture for treatment of AD i.e.memantine. It is a Glutamatergic antagonist that protects the nervous tissue against glutamate mediated excitotoxicity. However, both these classes of drugs provide only the symptomatic relief. There has been a desperate need arising since the past few decades for evolution of a drug that could treat the underlying causes of AD and thereby halt its development in susceptible individuals. There are several plants and derived products which have been employed for their benefits against the symptoms and complications of AD. Some novel drugs having the potential to moderate AD are under clinical trials. This review presents a comprehensive overview of the existing and the upcoming potential treatments for AD.

1. Introduction

Alzheimer's disease (AD) was first described by a German neuropathologist Alois Alzheimer in 1906. Alzheimer's disease (AD) was recognized as the most prevalent form of dementia among geriatric persons by the commencement of 21st century. Over 47.5 million people globally were estimated to be living with dementia in 2016. By 2030, the figure is being speculated to rise to 75.6 million (World Health Organization, 2016). AD is a neurodegenerative disorder that generally appears in mid to late adulthood. It is associated with a progressive and rather irreversible decline in memory various other cognitive capabilities. In AD, there is neuronal destruction and deterioration of neural connections in the cerebral cortex region of the brain along with a substantial loss of brain mass (Perl, 2010). AD is invariably progressive and lethal within 5–10 years of its onset (Dwyer et al., 2009). Death usually ensues due to complications of the chronic illness. It is one of the top five most common causes of mortality in population of the United States (Centers for Disease Control and Prevention, 2017). In some rare cases, it appears in people in their 40s and 50s, but otherwise it is a disease of old age. Based on clinical, population-based studies, about 200,000 people under 65 years of age are suffering from AD. In contrast, around 5 million of those over 65 years of age have AD. As per speculations, a new case of AD is expected to be developed every 33 s, by 2050 (Alzheimer's Association, 2014).

AD is characterized by the presence of two neuropathological hallmarks i.e. extracellular Aβ plaques and intracellular Tau neurofibrillary tangles (NFTs). The plaques constitute chiefly of the neurotoxic peptide amyloid (Aβ), which forms after the sequential cleavage of a large precursor protein *i.e.* APP by two enzymes, namely, β-secretase (commonly known as BACE1) and γ-secretase (involving four proteins, including presenilin). However, Aβ is not formed if APP is first acted upon and cleaved by the enzyme α-secretase instead of β-secretase. NFTs comprise mainly of the protein tau which is a microtubule associated protein (MAP) *i.e.* it binds microtubules in cells to facilitate the neuronal transport system. In the development of AD, Tau uncouples from microtubules and aggregates into tangles thereby inhibiting transport and resulting in microtubule disassembly. It also depends on the phosphorylation of Tau (Nisbet et al., 2015).

The actual causes at play behind the development of AD are still not well defined. However, certain factors like anomaly in the phosphorylation of tau protein, alterations in calcium metabolism, oxidative stress, neuro-inflammation, abnormal energy metabolism and protein

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http://dx.doi.org/10.1016/j.ejphar.2017.09.043
Received 2 August 2017; Received in revised form 20 September 2017; Accepted 28 September 2017
Available online 01 October 2017
0014-2999/

processing *i.e.* undesired Aβ formation and aggregation, are considered to be important factors in the pathogenesis of AD (Butterfield et al., 2002; Habibyar et al., 2016; Hardy and Selkoe, 2002). A relatively recent mitochondrial dysfunction hypothesis for pathogenesis of AD proposes that AD brain mitochondrial dysfunction leads to amyloidosis, cell cycle re-entry, and tau phosphorylation (Swerdlow et al., 2014).

Evidence exists suggesting involvement of both cholinergic and glutamatergic neurochemical systems in the etiology of AD. Acetylcholine (ACh) is an essential neurotransmitter responsible for cognitive functions and learning. In the brains of patients suffering from AD, it is decreased both in concentration and function. This deficit and other presynaptic cholinergic limitations, like loss of cholinergic neuronal network and reduced acetylcholinesterase activity, validate the cholinergic hypothesis of AD. Another neurochemical hypothesis for development of AD is the N-Methyl d-aspartate (NMDA) mediated glutamatergic hypothesis. Glutamate is an excitatory neurotransmitter which acts on NMDA receptors, which are pivotal in learning and memory. However, in some circumstances, over stimulation of NMDA receptors by glutamate causes neuronal damage due to excitotoxicity (Francis, 2005).

The diagnosis of AD involves asking some questions from the patient and his/her friends or relatives. Scanning and imaging techniques, such as Computed Tomography (CT), Magnetic Resonance Imaging (MRI), or Positron Emission Tomography (PET) of the brain may be carried out depending upon the need, severity of symptoms and the gravity of the situation. However, definite diagnosis of AD can be made only after death, by connecting clinical data with an analysis of brain tissue in an autopsy (NIH National Institute on Aging, 2017a).

The symptoms of AD get worse with time, although the pace at which the disease progresses is variable. Alterations in the brain related to AD commence years before any related clinical manifestations emerge. This period, spanning over a few years, is known as preclinical AD. The progression of AD occurs in three stages, namely Mild AD (early-stage), Moderate AD (middle-stage) and Severe AD (late-stage). The symptoms associated with each stage are given in Fig. 1 (Alzheimer's Association, 2017).

2. Treatment

AD is quite complex, and it is improbable for any one drug or other intervention to successfully treat it. Current pharmacotherapeutic approaches are based on aiding the sufferers to preserve mental abilities, manage behavioral manifestations, and delay the progression and thereby slow down the appearance of symptoms of disease. All the existing treatments work by regulating the levels of certain neurotransmitters in brain, mainly ACh and glutamate. They may be helpful in the maintenance of thinking, cognitive functions, and communication skills and may relieve certain behavioral issues to some extent. But these approaches don't treat the underlying cause of the disease. They are not effective for all types of patients of AD and may be helpful only to some extent, both in terms of efficacy and time. Several drugs are being marketed under the approval of the U.S. Food and Drug Administration (US-FDA) to provide symptomatic relief in AD (NIH National Institute on Aging, 2017b)

2.1. Conventional pharmacotherapy of AD

The existing drugs employed in treatment of AD can be broadly classified as:

a. Acetylcholinesterase inhibitors: Rivastigmine, Donepezil, Galantamine, Tacrine.
b. NMDA antagonist (glutamate inhibitor): Memantine

2.1.1. Acetylcholinesterase inhibitors

These drugs show a dose-dependent alleviation in symptoms of AD, with varying magnitude of cholinergic side effects on the systemic level. The early research into this category of agents included tacrine (tetrahydroaminoacridine), physostigmine and velnacrine. However, out of all these compounds of interest only tacrine could be taken forward to elaborate clinical trials. In turn, it saw a commercial launch in the USA and some parts of Europe. In the coming times, newer drugs like donepezil and rivastigmine followed the suit and the prescription of tacrine was discontinued (McGleenon et al., 1999).

In AD affected individuals, the activity of the acetylcholinesterase gets augmented and leads to the increased breakdown of acetylcholine and causes the diminished levels of acetylcholine in the brain. The enzyme is also partially involved in the formation of amyloid plaques and neurofibrillary tangles. Acetylcholinesterase also acts as a promoter that helps β-amyloid peptide fragments to aggregate by forming complexes with the growing fibrils. The formed complexes are more cytotoxic than β-amyloid fibrils alone (Alvarez et al., 1998, 1997; Singh et al., 2013). These drugs attempt at elevating the fallen levels of acetylcholine in the brain of the patients suffering from mild to moderate AD by inhibiting the enzyme acetylcholinesterase that it responsible for metabolic breakdown of acetylcholine, thereby increasing its level. They are usually well tolerated in the most of the patients (Tabet, 2006).

2.1.2. NMDA antagonist (glutamate inhibitor)

Glutamate is one of the chief neurotransmitters in the brain of mammals which plays a role in the excitatory postsynaptic transmission through various ionotropic and metabotropic glutamate receptors. Glutamate-gated channels and a group of G-protein coupled receptors

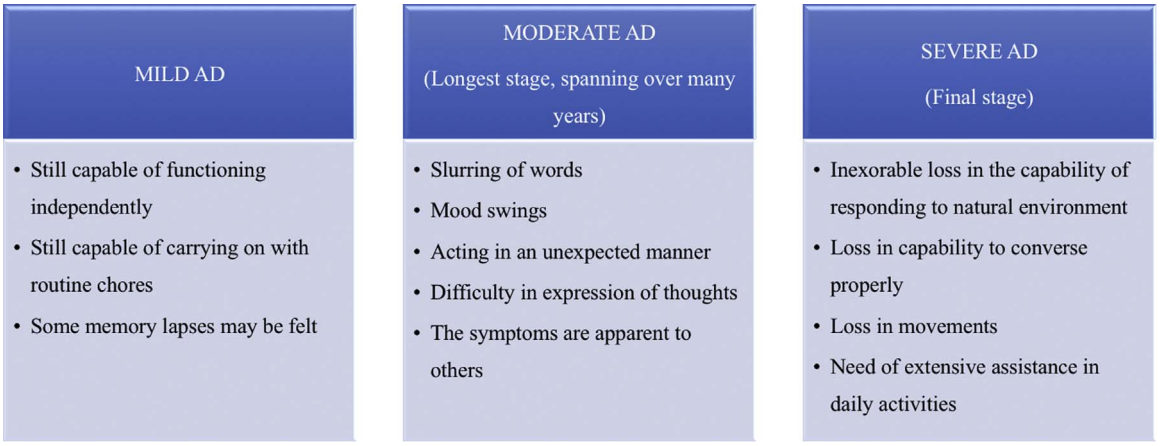

Fig. 1. Stages of AD progression and associated symptoms.