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Invited review

Acetylcholinesterase inhibitors as Alzheimer therapy: From nerve toxins to neuroprotection

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ABSTRACT

Acetylcholinesterase is a member of the α/β hydrolase protein super family, with a significant role in acetylcholine-mediated neurotransmission. Research in the modulators of AChEs has moved from a potent poison (Sarin, Soman) in war times to the potent medicine (physostigmine) in peaceful times. Natural anti-AChE includes carbamates, glycoalkaloids, anatoxins derived from green algae; synthetic anti-AChE includes highly poisonous organophosphates used as nerve gases and insecticides. Recently, the role of anti-AChE was reassessed from neurotoxins to neuron-protective in the diseases characterized by impaired acetylcholine-mediated neurotransmission like Alzheimer's disease (AD). So, the AChE has been proven to be the most viable therapeutic target for the symptomatic treatment of AD. This review article gives a spectrum of strategies to design AChE inhibitors used in the Alzheimer therapy.

1. Introduction

Research is motivated and funded mostly for the short term goals which vary with time. Acetylcholinesterase (AChE) inhibitor physostigmine was used in glaucoma in 1876 by physician Dr Ludwig Laqueur, unknowingly about the mechanism of action of the drug [1]. Later on AChE inhibitors were utilized as pesticide and most of the research was dedicated to its selective pesticidal action [2]. With the eruption of war the selectivity of these agents was rather misused to develop Sarin as the first nerve gas and later on during the war whole research funding was concentrated on the nerve gases and finding their antidotes. Hence, AChE inhibitors mainly phosphates as nerve gas and oximes as antidotes came into the existence [3–5]. The post war era saw the scarcity of food and hence the funding went into crop growth and crop protection (pest management). The average population age was less and growth was the need of the hour, hence this era saw the development of pesticides for crops. Further, this era saw the development of biological drugs (immunization) for longevity as most of deaths accounted due to infections (bacterial, malaria etc.) and many synthetic agents came into existence [6]. The major breakthrough in the research came with the advent of recombinant DNA technology and view of looking at a disease changed to a molecular level [7]. With an average population growing older the prevalence of disorders of old age increased and hence in the present era the major funding is targeted at older age disorders and hence Alzheimer research came to front-stage. With concentration on Alzheimer, the history was revisited by Dr. Graeber in 1997 to study and characterize the disease [8]. Along with AChE inhibitors, several other therapies are also used for the management of Alzheimer's disease including Tau-based therapies, dealing with oxidative stress, targeting cellular Ca^{2+} handling, anti-inflammatory therapy, amyloid targeted strategies (β-Secretase inhibitors and γ-Secretase modulators). Among these therapies, inhibition of β-Secretase causes the reduction of Aβ level along with blockage of all harmful downstream steps in the pathogenesis of AD whereas γ-Secretase modulators (GSMs) have been shown to selectively lower Aβ42 production without affecting total Aβ levels [9,10]. Although targeting amyloid seems to be favorable strategy but no BACE inhibitors or GSMs have reached market till date. With the approval of an acetylcholinesterase inhibitor i.e. Tacrine as an agent for Alzheimer by US-FDA, major funding and research was concentrated in this thrust area [11]. This review highlights journey through time in the research of therapies targeted towards Alzheimer with special emphasis on AChE inhibitors.

2. Alzheimer's disease

Dementia is a loss of brain function that occurs with certain diseases. Dementia usually first appears as forgetfulness. Dementia symptoms include difficulty with many areas of mental function

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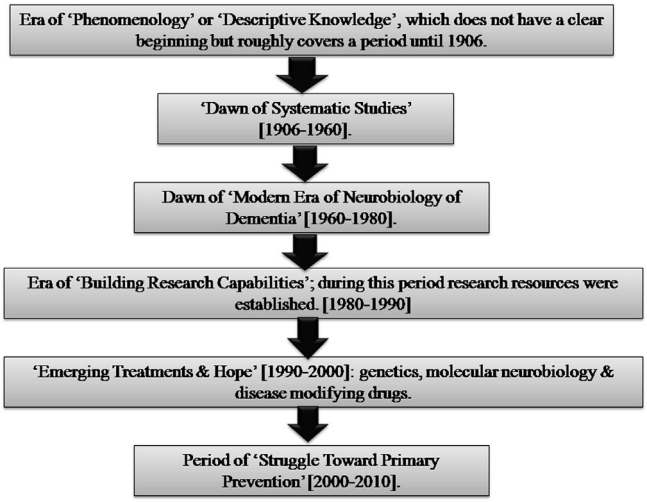

Fig. 1. Schematic representation of journey of Alzheimer's disease.

Fig. 2. Factors involved in Alzheimer's disease progression.

including language, memory dysfunction, perception, emotional behavior or personality and Cognitive skills (such as calculation, abstract thinking, or judgment). Most types of dementia are nonreversible (degenerative). Nonreversible means the changes in the brain that are causing the dementia cannot be stopped or turned back [12,13].

Alzheimer's disease (AD) is the major cause of dementia, and is a multifaceted neurodegenerative disorder characterized at a molecular level by protein misfolding and aggregation, oxidative stress, mitochondrial abnormalities, and neuroinflammatory processes [14,15]. It is characterized by a gradual onset and progression of deficits in more than one area of cognition, including episodic memory, mood and behavior changes, language, praxis and attention, and the most common early symptom is difficulty in remembering newly learned information [16,17]. Brain area involved is the basal forebrain, cortex and amygdala, which are the areas involved in learning, memory, attention and emotional regulation. There are two forms of AD: Sporadic AD and Familial AD (FAD), Sporadic AD is characterized by a severe progressive decline in cognition and increased neuronal cell death, and Familial AD (FAD) develops much faster and is caused by mutations in components of the amyloid pathway such as Amyloid Precursor Protein (APP), apolipoprotein E4 (ApoE4), presenilin-1 and presenilin-2 (PS1 and PS2) and sortilin-related receptor 1 (SORL1) [18,19].

3. History of AD

AD is named after a German physician, Alois Alzheimer, who first described it in the early 20th century on November 4, 1906 in Tubingen (Wilkins, 1969). In 1901, Alois Alzheimer, a doctor at the state asylum in Frankfurt, studied a patient Auguste D, 51-year-old woman with symptoms of cognition and language deficits, auditory hallucinations, delusions, paranoia and aggressive behavior. After the death of the patient in 1906, Alois Alzheimer working with Emil Kraepelin carried out the post-mortem of the brain and came to know that her brain exhibited arteriosclerotic changes, senile plaques, and neurofibrillary tangles and he subsequently published the observations in 1907 [20]. In 1910, Kraepelin coined the term 'Alzheimer's disease' – a term still used to refer to the most common cause of senile dementia.

In 1950s, increasing interest in theories and general ideas along with the development of molecular biology lead to the formation of genetic code concept [21]. In 1959, it was widely accepted that AD was exclusively a rare pre-senile disorder [22]. In 1963, Terry studied histologic pattern of the tangles and plaque [23]. Plaques were interpreted to be: amyloid fibrillar core, surrounded by unmyelinated dystrophic axons and dendrites containing filaments, dense bodies and paired helical filaments (PHF) [24]. In 1976, Dr Robert Katzman reviewed the frequency and mortality of AD and highlighted the need for focused research in this area [25]. As with increased population age the prevalence of AD increased and was bound to increase even further. Epidemiologists, clinical neurologists, radiologists, psychiatrists, and psychologists quickly became active in developing better diagnostic methods for AD [26].

The prolonged history of scientific efforts to characterize better the clinical features of dementia perhaps can be described in the context of six arbitrarily defined epochs (Fig. 1). Factors affecting disease progression are summarized in Fig. 2 [27–29].

4. Pathogenesis of AD

The exact cause of the Alzheimer's disease is still uncertain, but in general the following hypothesis has been put forward on the basis of the various causative factors (Fig. 3).

4.1. Cholinergic hypothesis

Degeneration of neurons has been associated with loss of memory function. The discovery of a link between the clinical symptoms of the disease (memory loss) and specific cholinergic deficits in the brains of people with AD, by Peter Davies in 1976, was a landmark because it opened the door for modern neurochemistry [30]. In this hypothesis deficiency of a critical neurotransmitter, acetylcholine, in brain was observed either due to decreased production of neurotransmitter or amplified acetylcholinesterase activity [31]. This decreased level of the neurotransmitter causes impairment of the cholinergic neurotransmission leading to the loss of intellectual abilities. This hypothesis generally implies that the cholinergic augmentation will improve the cognition in AD.

4.2. Amyloid hypothesis

Histological studies of the brain of the person with AD indicated the presence of plaque, which lead to exclusive study of these objects. In 1984, building block of amyloidogenic peptide was found to