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Recent advances in the neurobiology and neuropharmacology of Alzheimer's disease

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ABSTRACT

Alzheimer's disease (AD) is an age-related neurodegenerative disorder characterized by progressive deterioration of cognitive functions. The pathological hallmarks are extracellular deposits of amyloid plaques and intracellular neurofibrillary tangles of tau protein. The cognitive deficits seen are thought to be due to synaptic dysfunction and neurochemical deficiencies. Various neurochemical abnormalities have been observed during progressive ageing, and are linked to cognitive abnormalities as seen with the sporadic form of AD. Acetylcholinesterase inhibitors are one of the major therapeutic strategies used for the treatment of AD. During the last decade, various new therapeutic strategies have shown beneficial effects in preclinical studies and under clinical development for the treatment of AD. The present review is aimed at discussing the neurobiology of AD and association of neurochemical abnormalities associated with cognitive deterioration and new therapeutic strategies for the treatment of AD.

1. Introduction

Alzheimer's disease (AD) is an age-related progressive neurodegenerative disorder that causes both physical and mental decline gradually resulting in death [1–2]. According to World Alzheimer's report 2015, the number of people with AD and other forms of dementia worldwide was estimated to be 46.85 million; will likely double by 2030 and could possibly rise to three times the current level by 2050 [3–4]. Every year approximately 7.7 million new cases of dementia are reported [5]. Pathologically AD has been characterized by loss of cholinergic neurons, extracellular deposition of β-amyloid (Aβ) protein due to abnormal processing of amyloid precursor protein (APP), intracellular neurofibrillary tangles (NFT) formation of hyperphosphorylated tau protein, gliosis, and loss of neurons [6–7]. Further, extracellular depositions of Aβ and intracellular formation of tau tangles have been well documented to play a major role in oxidative stress, excitotoxicity, neuro-inflammation and neurotransmitter deficits as shown in Fig. 1 [8–9].

Cholinergic neurons synthesize acetylcholine (ACh), which plays a major role in learning and memory [10]. AD has been characterized by the loss of cholinergic neurons in both the cortical and hippocampal regions [11–12]. Besides this, AD has been also reported to alter the function of serotonergic, glutamatergic dopaminergic and adrenergic neurons [13–14].

Clinically, only acetylcholinesterase inhibitors (AChEIs) (donepezil, rivastigmine, galantamine and huperzine) along with N-methyl-D-aspartate (NMDA) receptor antagonists such as -memantine have been used to provide symptomatic relief during AD [3,15–16]. However, these agents were not able to prevent or slow the progression in neurodegenerative processes [4,17–18]. During the last decade, various new therapeutic strategies showed beneficial effects and are under clinical development for the treatment of AD [19–20]. One of the major revolutionary approaches in the drug design strategy based on the multi-target directed (MTD) ligand has been reported as new hope in the treatment of multi-factorial disease like AD. This is due to classic drug design based around the "one molecule one target" directed ligand strategy, which was found to be ineffective in the treatment of multi-factorial diseases like AD [21–22]. A memantine heterodimer, more specifically the molecule 7-methoxytacrine has been studied based on the multi-target directed ligand theory for the treatment of AD [22]. The aim of this review is to give an overview of the pathological hallmarks and synaptic abnormalities including neurotransmitter deficits, and their association with cognitive abnormalities, and new therapeutic strategies for the treatment of AD.

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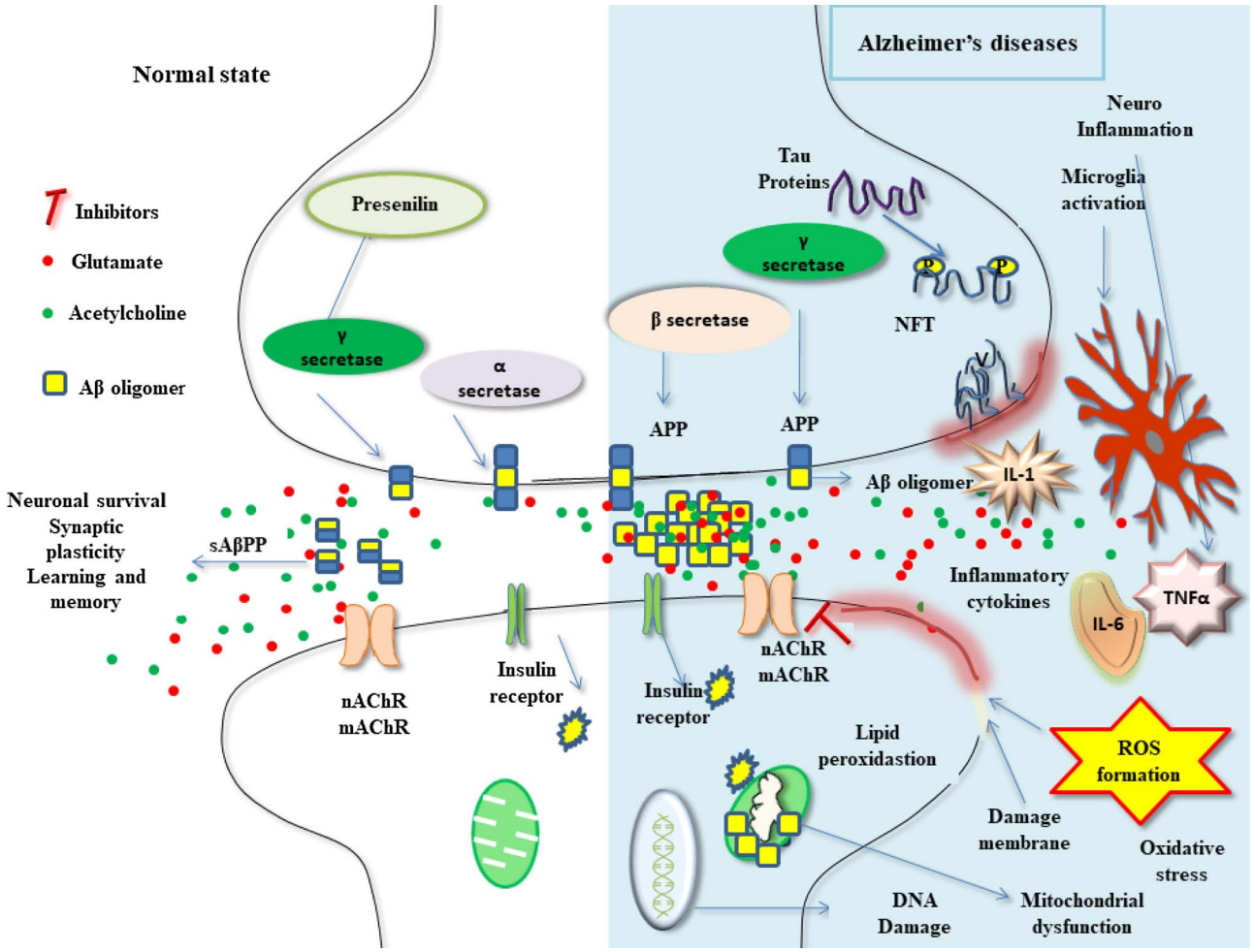

Fig. 1. Neurobiology of Alzheimer's disease.
APP: Amyloid precursor protein; Aβ oligomer: Amyloid β oligomer sAβPP: Soluble amyloid β precursor protein; ROS: Reactive oxygen species; IL-1: Interleukin-1; IL-6: Interleukin-6; TNFα: Tumor necrosis factor α; NFT: Neurofibrillary tangles; nAChR: Nicotinic acetylcholine receptor; mAChR: Muscarinic acetylcholine receptor; DNA: deoxyribonucleic acid.

2. Neurobiology of Alzheimer's disease

2.1. Amyloid hypothesis

Amyloid plaques, formed due to abnormal proteolytic cleavage of APP, have been reported to play a dominant role in the pathogenesis of AD [23]. APP is a type 1 membrane protein with a short cytoplasmic region and extracellular domain that was firstly identified in 1987. APP is synthesized in the endoplasmic reticulum, transported through secretary vesicles, and cleaved in the Golgi complex by N- and O-linked glycosylation pathways [24–26]. Within the Golgi complex, either by α, β- and γ-secretases cleave APP through either of two distinct metabolic pathways [27]. The first major cleavage is reportedly driven by α-secretase in between Lys16 and Leu17 of APP, resulting in the formation of a soluble ectodomain of APP (sAPPα), which may have neuroprotective effects [24]. Whereas, β- and γ-secretases dependent proteolytic cleavage of APP give rise to the formation of Aβ peptides fragments ranging in length from 39 to 43 amino acids. These Aβ peptide fragments have been found to play a large role in the amyloid plaque characteristic of AD pathology. The most predominately formed fragments are $A\beta_{1\text{-}40}$ and $A\beta_{1\text{-}42}$ as shown in Fig. 2 [28–29].

$A\beta_{1\text{-}40}$ is soluble, less neurotoxic, and predominantly found in the healthy brain, while $A\beta_{1\text{-}42}$ is highly neurotoxic, has a greater propensity to aggregate and predominantly found in brains with AD pathology [30–31]. Recently, $A\beta_{1\text{-}43}$, a new proteolytic cleaved product, has been reported to potentially contribute to Aβ formation [32]. Interestingly, $A\beta_{1\text{-}43}$ is highly amyloidogenic, neurotoxic, and deposits earlier than the other two cleavage products [33–34]. Furthermore, amyloid peptide deposits have also been reported to interact with the neuronal membrane, resulting in pore formation and an excessive influx of ions that further lead to neuronal loss and progression of AD [35].

2.2. Tau hypothesis

In 1907, the NFT hypothesis was first described by Alois Alzheimer, whereas the correlation between NFT and AD, and the structural composition of these tangles were characterized in 1968 and 1988 respectively [36–37]. Tau is a soluble microtubule protein present in neuronal cells that plays a dominant role in axonal growth and neuronal development by stabilizing the micro-tubular assembly [38–39]. Under normal conditions, balance between microtubule-associated phosphatase and kinases have been reported to maintain both phosphorylation and de-phosphorylation states of tau [40]. Under pathological conditions, up regulation of kinases and down regulation of phosphatase results in hyper-phosphorylation of tau protein that generates double helical insoluble filaments and tangled clumps, known as NFT, which lead to neuronal degeneration and synaptic dysfunction as shown in Fig. 3 [41–42]. NFT form inside the neuronal cell body during the progression of AD and are relatively insoluble protein complexes that survive even after the death of affected neuronal cells, where they may released extracellularly. Following the release, these extracellular NFT are reportedly engulfed by astrocytes and microglia cells [43].