RECENT ADVANCES IN ALZHEIMER’S DISEASE: CAUSES AND TREATMENT

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ABSTRACT
Alzheimer’s disease (AD) is a destructive neurodegenerative disorder characterized by progressive memory defeat and impairment in behavior, language, and visuospatial skills. Neuropsychiatric symptoms such as apathy, depression, aggression, agitation, sleep disruption, and psychosis are now recognized as core symptoms of AD that are expressed to varying degrees throughout the course of disease. The neuro pathological features of AD comprise extracellular senile plaques constituted of β-amyloid (Aβ) plaques, intracellular neurofibrillary tangles (NFTs), and cerebral atrophy; others include apolipoprotein E, oxidative stress, mitochondrial dysfunction and cholinergic hypothesis. Anti-amyloid therapy is available for the treatment of Alzheimer’s disease, others are anticholinergic therapy, and therapy for mitochondrial dysfunction, β-secretase (BACE1) inhibitors, Glial modulating drugs includes RAGE receptor antagonists, TNF-α antagonists, neuroprotective drugs such as antioxidants, phosphodiesterase inhibitors, PPARγ agonists, and anti-tau or tau modulators like microtubule stabilizers, kinase inhibitors. This review includes discussion on neurobiological mechanisms and newly developed compounds which have lesser side effects and are proving more efficient for treatment of Alzheimer’s disease.

Keywords: Alzheimer’s disease, Alzheimer causes and treatment

INTRODUCTION
Alzheimer’s disease (AD) is a critical neurodegenerative illness characterized by memory loss and diminished performance, language, and visuospatial skills [1]. Epidemiological data show that the occurrence of AD increases with age and doubles every 5 y after 65 y of age [2, 3]. There were about 26.6 million cases of AD in the world in 2006 and it is predictable that the worldwide dominance of AD will grow fourfold to 106.8 million by the year 2050 [4]. The neuropathological features of AD involve extracellular senile plaques constituted of β-amyloid (Aβ) plaques, intracellular neurofibrillary tangles (NFTs), and cerebral atrophy [5]. Aβ, produced from the proteolytic administration of amyloid precursor protein (APP), has been projected to have a causative role in the generation of AD and this Accumulated Amyloid-β can provoke euro-toxicity by generating oxidative stress and inflammation in the brain [6, 7].

Causative factors
Both non-modifiable and modifiable risk factors are involved in AD. Non-modifiable factors include age which is one of the important risk factors, genes, family history, Down’s syndrome while modifiable factors include cognitive engagement, diet/nutritional supplement intake, physical activity level, type 2 diabetes, alcohol consumption, mood disorders, hypertension, hypercholesterolemia, and smoking [8-11].

Genetic factors
Alzheimer’s disease happens in both familial and an irregular form, also recognized as early onset or late onset Alzheimer’s disease (LOAD), respectively [12]. Early-onset domestic AD is generally produced by autosomal dominant variations in the genes for amyloid precursor protein (APP), presenilin 1 and presenilin 2. This form of AD accounts for around 2–5% of all AD cases [13]. The apoE4 allele is the single verified heritable factor in the progress of together the early and late-onset practices of AD. This factor rises vulnerability to AD however it is neither essential nor adequate for the progress of this disease. In late-onset irregular form, greater the number of the apoE4 alleles, the greater the possibility of AD and the lesser the age of onset. The risk influence of the occurrence of the apoE4 allele declines with age. Usually, around 15-20% of AD cases could be recognized to this risk [14].

Vascular factors
Smoking
Smoking is a well-recognised cardiac risk factor and facilitates oxidative stress, inflammation and atherosclerosis which are identified as the risk factors for neurodegeneration [15]. Oxidative stress promotes augmented β-secretase cleavage of APP and abnormal tau phosphorylation. It may openly enable the amyloidogenic pathway involved in Aβ oligomer invention and extracellular fibrillar Aβ aggregation, as well as abnormal tau phosphorylation [16].

Alcohol
It is well predictable that alcohol abuse causes alcohol dementia. In heavy consumers, alcohol causes injuries in the brain. Light to adequate alcohol intake is found to be closely associated with brain atrophy and volume loss [17, 18].

Obesity
It has been showed that being obese contributes to dementia and cerebral decay. Obesity leads to dementia, cerebral damage and consistent neurological modifications [19].

Blood pressure and management of hypertension
High blood pressure is one of the most significant manageable risk factors for stroke, which in turn can result in vascular dementia. It has been reported that there is a close relationship between AD and hypertension [20]. It has been recently proved that antihypertensive drugs have a protective effect against the progress of dementia and AD [21-23]. The antihypertensive remedy may protect against dementia and AD by decaying the atherosclerotic process, reducing the number of atherosclerotic scratches and improving cerebral perfusion [24].

Diabetes mellitus
It has been reported that there is an increased risk of vascular dementia in persons with diabetes [25-27]. Binding of insulin or IGF-1 causes a conformational variation of the receptor leading to their autophosphorylation on definite tyrosine residues on the β-subunit resulting in activation of the insulin receptor substrate-1 (IRS-1) [28, 29]. The latter, in turn, stimulates two main signaling pathways: initially the PI3K pathway, which is involved in the preservation of...
synaptic plasticity and memory consolidation [30], Aβ-induced memory loss [31], and synthesis of nitric oxide (NO), which in turn plays a role in learning and memory practices [32]; and second pathway contains the MAPK cascade, which is accountable both for the induction of several genes essential for neuronal and synapse development, conservation and healing processes, as well as serving as a modulator of hippocampal synaptic plasticity that motivates learning and memory [33].

Hypercholesterolemia and statin therapy

High total serum cholesterol levels in medium age are involved to be a risk factor for the progress of AD at a later age [34, 35]. High total cholesterol in medium age is a risk factor for the progress of AD and additional dementia 20 y later but declining serum cholesterol levels in late medium age may be due to continuing disease progress and may characterize a sign for later AD and other dementias [36]. Statins have been reported to decline the production of β-amyloid. Statins also have several other effects that may be valuable for the CNS and thus, may smaller the risk of AD [37, 38].

Nutritional factors

Consumption of antioxidants such as vitamin E and vitamin C decreases the risk of developing AD. It has been reported that diet rich in saturated fats and cholesterol increases the risk of AD [39-41]. Antioxidants in turn decrease the oxidative stress and amyloid beta-peptide (Aβ) accumulation [42, 43]. Antioxidants, vitamins, polyphenol, polyunsaturated fatty acids, fish, fruits, vegetables, tea, and light to moderate intake of alcohol are useful for AD, while trans-fatty acids, saturated fatty acids, carbohydrates, and whole-fat dairy are harmful to AD [44].

Psychosocial factors

It was found that psychosocial factors and a vigorous lifestyle during life may decline the risk of dementias including AD [45].

Education and socioeconomic status

The risk for dementia is minor for those with higher education, occupational achievement, intelligence or IQ and cerebrally exciting leisure events [46]. Lower education is tied to enlarged risk of dementia and AD [47, 48]. It has been reported that a poor social network or a lack of social commitment are related with reduced cognitive functions and dementia [49]. The risk of dementia is also higher in elderly individuals with increased social segregation and less numerous and inadequate contacts with families and friends. Individuals with low neuroticism joined with high extraversion had a lower risk of dementia [50]. Low levels of social commitment in late life and declined social commitment from medium to late life are associated with a two-fold increase in the risk of the progress of dementia and AD later in life [51, 52].

Physical and mental activity

It has been reported that midlife physical activity may be linked with a reduced risk of AD or vascular dementia in later life [53]. Physical activity is assumed to enrich cognitive function by increasing cardiac suitability and cerebral perfusion and probably by stimulating neurogenesis [54]. Numerous activities necessitating mental exertion such as reading, social and traditional activities, indicate a defensive effect against dementia and AD [55, 56]. It has been proved recently that complex cerebral activity across lifecycle leads to reduced hippocampal atrophy [57].

Pathophysiology of AD

Two of the symbol neuro pathologic outcomes in AD are extracellular amyloid and neuritic plaques and intracellular neurofibrillary tangles.

Amyloid-β and tau proteins

According to the amyloid theory, Aβ peptide massing in patient's brain is the crucial event leading to the progress of AD. It has been reported in the in-vitro studies that the incubation of the Aβ peptide with cells in culture persuades a neurotoxic consequence characterized by oxidative stress, apoptosis, and injury to membrane and cytoplasmic proteins, mitochondrial DNA, and lipids [58, 59]. Amyloid plaques are mainly formed by accretion of insoluble Aβ peptides, while neurotic plaques are composed of insoluble Aβ peptides in deteriorated neurites (dendrites, axons, or telodendria), and some comprise hyper phosphorylated tau proteins (p-tau) [60].

In AD, the tau protein undertakes oligomerization and forms paired helical filaments (PHFs), which then leads to the progress of NFT [61]. It has been reported that tau persuades mitochondrial dysfunction, leading to severe energy dysfunction and the generation of ROS and reactive nitrogen species (RNS) [62], disturb the integrity of biological membranes and leads to synaptic failure [63], which is characterized by synaptic degradation, and neuronal loss [64, 65].

Apolipoprotein E

The Apolipoprotein E (Apo E) is a significant protein involved in preserving the structural and functional integrity of synapses and membranes [66]. There are three iso forms: ApoE2 (Cys112, Cys158), ApoE3 (Cys112, Arg158), and ApoE4 (Arg112, Arg158) [67]. The E4 allele confers an augmented risk; however the e2 allele decreases the risk. ApoE4 may increase the intracellular reprocessing of APP, which could raise Aβ production [68]. Modifications in complement signaling pathways may affect microglia function resulting in reduced capability to phagocytize apoptotic cells and clear beta-amyloid [69].

Sources of oxidative stress:

- Lipid peroxidation
- Protein oxidation
- DNA oxidation
- Glycolysis

Effects of oxidative stress:

- Molecular level
- Cellular level

Fig. 1: Effect of oxidative stress in lipid peroxidation and protein modification in AD [82]
Role of oxidative stress in AD

Oxidative stress results due to an imbalance between the production of reactive oxygen species (ROS) and their scavenging by antioxidants. Enhanced ROS assembly or decreased antioxidant system leads to oxidative imbalance and cause ROS overproduction [71,73]. The process of aging is also related with augmented oxidative stress [74]. It has been reported that oxidative stress plays a vital role in the pathogenesis of AD leading to neuronal dysfunction and cell loss [75]. As lipid peroxidation is significantly augmented in AD. Lipid peroxidation is the process in which lipids are attacked by ROS through a free radical chain reaction mechanism to produce lipid peroxidation products. It has been reported that the 4-hydroxynonal levels are considerably raised in the hippocampus, entorhinal cortex, and thalamus. Moreover, oxidative stress results due to an imbalance between the production of free radicals from oxygen species [70]. Enhanced ROS assembly or decreased antioxidant system leads to oxidative imbalance and cause ROS overproduction [71-73]. The process of aging is also related with augmented oxidative stress [74]. It has been reported that oxidative stress plays a vital role in the pathogenesis of AD leading to neuronal dysfunction and cell loss [75]. As lipid peroxidation is significantly augmented in AD. Lipid peroxidation is the process in which lipids are attacked by ROS through a free radical chain reaction mechanism to produce lipid peroxidation products. It has been reported that the 4-hydroxynonal levels are considerably raised in the hippocampus, entorhinal cortex, and thalamus. Moreover, oxidative stress results due to an imbalance between the production of free radicals from oxygen species [70].

Mitochondrial dysfunction

Mitochondria are responsible for ATP production, signaling pathway and cell activities. They are also involved in apoptosis and in dynamic movements essential for precise respiratory activity and metabolic efficiency through fusion/fission [85]. Dysfunctional mitochondria are less effective producers of ATP but more effective producers of ROS, signifying the main source of oxidative imbalance as detected in AD [84, 85]. It has been reported that an increase of oxidative biomolecule products and reduction in antioxidant levels or antioxidant enzyme action leads to AD [80]. The decreased plasma levels of antioxidants such as albumin, bilirubin, uric acid, lycopene, vitamin A, vitamin C, and vitamin E has been reported in AD patients [81].

Antioxidant therapy

Antioxidant therapy involves the uses of drugs (see in table 1) with a different mechanism of actions: (i) Enhance the clearance of Aβ; (ii) Prevent the production of Aβ; (iii) Inhibit the accumulation of Aβ [109]. Active and passive immunization results in decreased levels of intracerebral Aβ burden by inducing humoral reaction against the Aβ peptide leading to its clearance from the brain [110].

Table 1: Newer compounds targeted to anti-beta-amyloid treatment [111-120]

<table>
<thead>
<tr>
<th>Compound</th>
<th>Target/Treatment</th>
<th>Current phase</th>
</tr>
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<tbody>
<tr>
<td>AN1-1792</td>
<td>Vaccine-active immunization</td>
<td>Interrupted at phase II (no efficacy) (ongoing)</td>
</tr>
<tr>
<td>CAD-106</td>
<td>Vaccine-active immunization</td>
<td>Phase I (ongoing)</td>
</tr>
<tr>
<td>Bapineuzumab</td>
<td>Beta-amyloid monoclonal antibody</td>
<td>Phase II (ongoing)</td>
</tr>
<tr>
<td>Solanezumab</td>
<td>Beta-amyloid monoclonal antibody</td>
<td>Phase III (ongoing)</td>
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<tr>
<td>Ponezumab</td>
<td>Beta-amyloid monoclonal antibody</td>
<td>Phase I (ongoing)</td>
</tr>
<tr>
<td>Gantenerumab</td>
<td>Beta-amyloid monoclonal antibody</td>
<td>Interrupted at phase II (no efficacy)</td>
</tr>
<tr>
<td>Crenezumab</td>
<td>Beta-amyloid monoclonal antibody</td>
<td>Phase I (ongoing)</td>
</tr>
<tr>
<td>Semagacestat</td>
<td>Gamma-secretase inhibitor</td>
<td>Interrupted at phase III (no efficacy)</td>
</tr>
<tr>
<td>Avagacestat</td>
<td>Gamma-secretase inhibitor</td>
<td>Phase II (ongoing)</td>
</tr>
<tr>
<td>GRL-834</td>
<td>Beta-secretase inhibitor</td>
<td>Ongoing</td>
</tr>
<tr>
<td>TAK-070</td>
<td>Beta-secretase inhibitor</td>
<td>Ongoing</td>
</tr>
<tr>
<td>CHF-5074</td>
<td>Non-steroid anti-inflammatory agent</td>
<td>Ongoing</td>
</tr>
<tr>
<td>DAPT</td>
<td>Prototypical Gamma-secretase inhibitor</td>
<td>Ongoing</td>
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<tr>
<td>Curumin</td>
<td>Anti-amyloid aggregtor</td>
<td>Ongoing</td>
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β-Secretase (BACE1) inhibitor

Beta-site APP-cleaving enzyme 1 (BACE1) is a protease responsible for cleavage of APP, resulting in generation of assembly of neurototoxic irregular Aβ[121,122]. Nuclear peroxisome proliferator activated receptor gamma (PPARγ) functions as a transcription factor which regulates gene expression [123], promotes microglia-mediated Aβendocytosis. Also it reduces inflammation response and
causes decreased cytokine excretion [124]. Thiazolidinedione can induce PPARγ to inhibit β-secretase and stimulate ubiquitination to worsen amyloid burden [125]. It has been also reported that PPARγ agonist i.e. thiazolidinedione derivatives like rosiglitazone and pioglitazone worsens AD neuropathology by reducing insulin sensitivity which helps in Aβ proteolysis [126].

**γ-Secretase inhibitors (GSI) and modulators (GSM)**

γ-secretase is a transmembrane protease responsible for cleavage of amyloid precursor protein (APP) to produce Aβ [127,128]. Different GSIs such as DAPT, L685458 and MRK-560 131 have been recently developed [129, 130]. While different GSIs such as avagacestat (BMS-708163), bagacestat and NNC-15 are under clinical trials [131].

**Kinase inhibitors**

The first class of tau inhibitors which helps in targeting tau phosphorylation and reduces tau phosphorylation by decreasing the activity of kinase enzyme. Interaction between glycosynthesis kinase 3 beta (GSK3β) and protein phosphate 2 (PP2A) augments tau hyper phosphorylation and NFT generation [132]. Lithium, valproate, NP-031112 (NP-12) and epitophine D (BMS-241027) decreases tau phosphorylation and prevent reversed features of tawopathy [133-136].

**Therapy for mitochondrial dysfunction**

Latropiridine (DIMEBON), an antihistamine which preserves mitochondrial structure and function and protects against Aβ induced apoptosis is under investigation [137,138]. Its combination with donepezil is also under investigation [139]. AC-1204 is considered to improve mitochondrial metabolism by inducing chronic ketosis, thereby releasing regional cerebral hypometabolism presented in early Alzheimer’s disease, and this agent is also under investigation [140].

**Anticholinergic therapy**

Anticholinergic therapy includes administration of cholinesterase inhibitors to treat the cholinergic deficit associated with AD. The drugs include tacrine (COGNEIXES), donepezil (ARICEPTS), rivastigmine (EXELON), and galantamine (REMYNL1) [141].

**CONCLUSION**

Herein, we have made an effort to review recent trends in AD. The molecular heredities of AD and the role of key proteins, oxidative damage, mitochondrial dysfunction and the cholinergic hypothesis that are assumed to contribute in AD pathogenesis are significant fields for advanced research. There is significant active investigation ongoing in the development of new inhibitors for BACE, kinase, and γ-secretase as targets for treatment of AD. Thus, it is hoped that all these lines of ongoing research, combined, should lead to a deeper understanding of the progressions that happen in the AD brain to permit us to preclude efficiently their incidence. Thus, we conclude that these categories of drugs discussed in this review can be potentially targeted for research and development for the treatment of AD.

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**ABBREVIATION**

AD= Alzheimer disease, NFTs= Neurofibrillary tangles, GSI= Gamma secretase inhibitors, GSM= Gamma secretase modulators, BACE1= Beta-site APP-cleaving Enzyme 1, RAGE= Receptors for Advanced Glycation End products, PPARγ= Peroxisome Proliferator-activated Receptor γ, DMS-III-R = Diagnostic and Statistical Manual, 3rd edition, revised; NINCDS-ADRDA = National Institute of Neurologic, Communicative Disorders and Stroke—Alzheimer’s Disease and Related Disorders Association.

**CONFLICT OF INTERESTS**

Declared none

**REFERENCES**


