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Review Article

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) pledges, 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, γ-secretase inhibitors (GSI) and modulators (GSM), *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) pledges, 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 ons*et* 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 dementias 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].

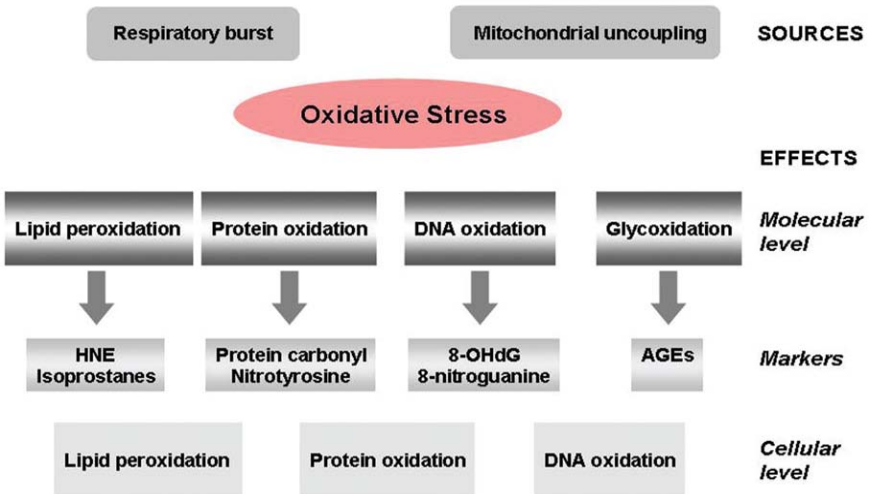

Fig. 1: Effect of oxidative stress in lipid peroxidation and protein modification in AD [82]

Role of oxidative stress in AD

Oxidative stress results due to an imbalance between the production and quenching 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, temporal cortex, amygdala, parahippocampal gyrus in AD. Oxidative amendments in proteins occur which are the outcome of direct ROS attack or from reaction with glycation, glycoxidation, and lipid peroxidation product binding [76, 77]. Oxidative impairment of DNA/RNA has been reported in AD. Oxidative impairment of DNA can cause DNA double strand disruptions, DNA/DNA or DNA/protein crosslinking, and base alteration (see in figure1). It has been reported that high levels of DNA breakdowns were established in the hippocampus and cerebral cortex in AD [78,79]. 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].

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 [83]. 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 mitochondrial dysfunction is a prominent and primary feature of AD [86]. Furthermore, mitochondrial dysfunction results in diminished features of mitochondrial function in AD [87]. Dysfunctional mitochondria cause high levels of ROS that may be noxious for neurons [88]. Moreover, ROS treats mitochondria as a target triggering oxidation of its constituents such as mtDNA, lipids, and proteins which finally results in mitochondrial worsening [89]. Declined calcium uptake and increased calcium burden leads to calcium deregulation and enlarged intracellular calcium in the brain [90-92]. Furthermore, mitochondrial dysfunction has been reported to modify the levels of numerous enzymes which contain pyruvate dehydrogenase and α-ketoglutarate dehydrogenase ATP-citrate lyase, and acetoacetyl-CoA thiolase. Reduced levels of these enzymes results in diminish production of acetyl-coA which causes deficit cholinergic expressions in AD patients [93-100]. ROS action on mitochondria generate toxic products like hydroxynonenal which facilitate the self-assembly of tau proteins into helical filaments which are reported to be present in AD [101].

Cholinergic hypothesis

There is a prominent and inconsistent insufficiency of acetylcholine. The functional basis of the cholinergic shortage is the atrophy and worsening of subcortical cholinergic neurons, mainly those in the basal forebrain (nucleus basalis of Meynert), that provide cholinergic innervation to the entire cerebral cortex. The selective insufficiency of acetylcholine in AD, results in dementia in AD, has given rise to "cholinergic hypothesis," which recommends that a lack of acetylcholine is critical in the origin of the signs of AD. In AD, there is not only damage of cholinergic neurons but also the cortical and hippocampus areas that receive cholinergic input [102].

Signs and symptoms of AD

Neuropsychiatric symptoms such as apathy, depression, violence, anxiety, sleep interruption, and psychosis are now recognized as the main symptoms of AD that are expressed to variable degrees during the progression of the disease [103] and finally results in Alzheimer's dementia.

Diagnosis of AD

The occurrence and distribution of amyloid plaques and NFT in the brain is used to found the finding of 'definitive' AD and stage the illness [104]. In clinical settings, the diagnosis of AD, is mainly based on medical history, somatic and neural examinations, and neuropsychological evaluation [105]. Patients with minor cognitive damage should be monitored for cognitive and functional decay because of their increased risk for dementia. The NINCDS-ADRDA conditions for the diagnosis of possible AD or the DSM-III-R conditions for dementia of the Alzheimer type should regularly be used. Structural neuroimaging and magnetic resonance imaging are suitable in the initial evaluation of patients with dementia. [106-108].

Recent advances in treatment of AD

Anti-amyloid therapy

Anti-amyloid 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; or (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]

Compound	Target/Treatment	Current phase
ANI-1792	Vaccine-active immunization	Interrupted at phase I (severe side effects such as meningoencephalitis)
CAD-106	Vaccine-active immunization	Phase I (ongoing)
Bapineuzumab	Beta-amyloid monoclonal antibody	Phase III (ongoing)
Solanezumab	Beta-amyloid monoclonal antibody	Phase III (ongoing)
Ponezumab	Beta-amyloid monoclonal antibody	Interrupted at phase II (no efficacy)
Gantenerzumab	Beta-amyloid monoclonal antibody	Phase I (ongoing)
Crenezumab	Beta-amyloid monoclonal antibody	Phase I (ongoing)
Semagacestat	Gamma-secretase inhibitor	Interrupted at phase III (no efficacy and risk for skin cancer)
Avagacestat	Gamma-secretase inhibitor	Phase II (ongoing)
GRL-834	Beta-secretase inhibitor	Ongoing
TAK-070	Beta-secretase inhibitor	Ongoing
CHF-5074	Non-steroid anti-inflammatory agent	Ongoing
DAPT	Prototypal Gamma-secretase inhibitor	Ongoing
Curcumin	Anti-amyloid aggregator	Ongoing

***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 neurotoxic 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 Aβproteolysis [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 andMRK-560 131have been recently developed [129, 130]. While different (GSM) such as avagacestat (BMS-708163), begacestat and NIC5-15 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 glycogen synthase kinase 3 beta (GSK3β) and protein phosphate 2 (PP2A) augments tau hyper phosphorylation and NFT generation [132]. Lithium, valproate, NP-031112 (NP-12) and epothilone D (BMS-241027) decreases tau phosphorylation and prevent reversed features of tauopathy [133-136].

Therapy for mitochondrial dysfunction

Latrepirdine (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 (COGNEXS), donepezil (ARICEPTS), rivastigmine (EXELON), and galantamine (REMINYLS) [141].

Table 2: Overall pharmacologic treatments other than anti-amyloid therapy under research for Alzheimer's disease [142-144]

Pharmacologic treatment	Agent under research
Neurotransmitter-based	
Acetylcholine	ST 101, AF 267B, ABT 089, AZD 3480, MEM 3454, EVP-6124, Posiphen, Huperzine
Serotonin	5-HT_4 partial agonists, 5-HT_{1A} agonists/antagonists, 5-HT_6 antagonists
Norepinephrine/Dopamine:	MAO A and MAO B inhibitors
GABA:	GABA-B antagonists
Glutamate:	AMPA potentiator
Glycine:	Partial agonists
Glial modulating drugs:	
Direct glial target:	G and GM CSF, Nitro flurbiprofen, ONO-2506, Tacrolimus
RAGE receptor antagonist:	TTP 488
TNF-α antagonist:	Enbrel
Neuroprotection:	
Antioxidants:	Vitamin C and E, alpha lipoic acid, CoQ10
Miscellaneous:	PDE inhibitors, PPARγ agonists and insulin, SIRT1 activators, Growth factors (BDNF and NGF), Dimebon
Anti-tau or tau modulators:	
Microtubule stabilizers:	NAP (AL-108) and Methylene blue (Rember)
Kinase inhibitors (GSK-3α, GSK-3β, CDK 5)	Lithium, AZD-1080, Minocycline
	PDE-4 inhibitors, immunotherapies

[GABA, gamma-amino butyric acid; RAGE, receptor for advanced glycation end products; TNF, tumor necrosis factor; GSK, glycogen synthase kinase; CDK, cyclic-dependent kinase; 5-HT (4, 1A and 6), 5-hydroxytryptamine (receptor subtypes); MAO (A and B), monoamine oxidase (A and B subtypes); AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; PPAR, peroxisome proliferator-activated receptors; SIRT1, sirtuin (silent mating type information regulation 2 homolog)-1; BDNF, brain-derived neurotrophic factor; NGF, nerve growth factor; NAP, neuronal microtubule-interacting agent (a peptide of eight amino acids, NAPVSIPQ); PDE, phosphodiesterase]

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, DSM-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

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