Chronological Primacy of Oxidative-Induced Neuronal Damage in the Pathogenesis of Alzheimer's Disease

Selim F. Estefan[1], Aziza B. Shalby[1*] and Hanaa H. Ahmed[1]

[1]*Department of Hormones, National Research Centre, Cairo, Egypt.*

Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

Review Article

ABSTRACT

Alzheimer's disease (AD) is associated with hallmark pathologies including extracellular Aβ protein deposition in extracellular senile plaques and vessels, and intraneuronal tau deposition as neurofibrillary tangles.

The current study comprises the oxidative modifications associated with the pathological lesions of neuronal damage characterized AD. The repeated exposure to aluminum and heavy metals, mutations in a number of chromosomes and genes, diabetes, cardiovascular diseases, obesity and brain injury, are the major causes for these modifications.

There is clearly a need for the identification and development of panels of biomarkers for accurate diagnosis and early detection of sporadic AD. Thus, a collection of the most globally manifested expeditious diagnostic tools for early detection of AD is outlined in this review. Also, a survey of the vast clinically approved therapeutic modalities for restricting and even treating the symptoms of AD is summarized. These arguments provide useful information in both understanding pathogenesis as well as accessing the novel treatment approaches for AD.

*Corresponding author: Email: drazizanrc@yahoo.com;

1. INTRODUCTION

1.1 Historic Perspective of Alzheimer's Disease

Alzheimer's disease (AD) was only named in the early twentieth century by German psychologist Alois Alzheimer, but the history of AD may have started well before that. Dementia was first documented by ancient Egyptian physicians around two thousand BC. Also, Ancient Egyptian history, the Maxims of the Ptah Holy describes a form of AD. In the Greco-Roman period mental deterioration was considered by most as an inevitable consequence of aging, and that aging itself had come to be considered a disease process.

The Franciscan friar Roger Bacon [1214 –1294] wrote the work Methods of Preventing the Appearance of Senility, in which he commented that "in the posterior part [of the brain] occurs oblivion and memory concerning which Haly Regalis speaks in his first theoretical tratise, saying that old age is the home of forgetfulness" and that "An injury to the reasoning faculty happens in the middle part of the brain. . . . An injury to the imagination occurs in the anterior part of the brain" [1].

Chaucer [ca. 1343– 1400] commented on the inevitability of dementia: "with old folk, save dotage, is namore" [2], and Shakespeare [1564 –1616] made numerous keen descriptions of dementia through his characters in several plays, most famously in *Hamlet* and *King Lear*. Shakespeare may have been more medically astute than medical writers of the time, as he not only took note of age-related cognitive decline, but also made clear distinctions between senile decay and "plain madness," and commented on both the cognitive and the affective changes that accompany senile dementia. Then, Roman physician, Claudius Galen, who lived from 130 to 200 A.D., recounts symptoms of age-related forgetfulness in his journals. And in fourteenth century in England, there was even a verbal test to check for forgetfulness.

Esquirol [1772–1840] gave names to newly identified subtypes and categories of mental disorders [3,4]. By introducing systematic clinical observation and exact description using precise terminology into psychiatry, Esquirol established the foundation of modern classification of mental disease [4]. Esquirol characterized the difference succinctly in one of his most widely quoted statements, that "A man in a state of dementia is deprived of advantages which he formerly enjoyed; he was a rich man who has become poor [4].

Essentially, from the time of the ancient Greeks and Romans to the 19th century, no sweeping progress in the conceptualization of senile dementia had been made. The broad concept of dementia underwent some gradual refinement with the categorization of different conditions in which dementia is found, and the narrower concept of senile dementia (Amentia senilis) established itself as a medical entity. Abnormalities in the brain were suspected as the source of dementia or mental aberration, and anatomists scrutinized the brain's gross appearance (color, texture, size of pineal, appearance of meninges, blood vessels, color of fluid emanating from the tissue) in search of an anatomical correlate of dementia, but to little avail. Brain atrophy accompanying Amentia senilis was not yet remarked upon, possibly due to the heterogeneity of disorders which continued to be united in this medical entity[1].

Alois Alzheimer [1864 –1915] and Otto Binswanger [1852–1929] both extensively described this arteriosclerotic brain atrophy in the 1890's. By this time, atheromatous degeneration of blood vessels with accompanying stroke had generally become accepted as a necessary precursory event for the development of senile brain atrophy and senile dementia. In 1907, using the Bielschowsky stain on the case that made him famous, Alois Alzheimer described a startling new pathology in the brain of a recently deceased woman who died a few years after developing a clinically unusual dementia at age 51. The novel neuropathological feature that Alzheimer observed consisted of tangles of fibrils within the cytoplasm of neurons, which were stained in sharp definition by the silver impregnation. In addition to the marked neurofibrillary tangles and accompanying neuronal degeneration, Alzheimer also noted the widespread presence of plaque pathology in the brain of this woman, similar to the pathology extensively described in senile dementia by Fischer [1].

A recurrent issue which was fiercely debated for numerous decades was the question of whether Alzheimer's disease was really a unique disease entity from senile dementia. In his 1963 review on dementia, McMenemey [5] summarizes researchers' attempts to establish clinical and pathological criteria which would clearly delineate the two diseases.

While Alzheimer's disease was recognized as a troublesome disorder already in the early 1900s, today it has become a major medical problem nearing catastrophic levels; increased longevity has led to a steadily increasing population of individuals over age 65, and thus there are ever greater numbers of individuals at risk for, and afflicted with, this disease. Alzheimer's disease is today recognized as the fourth or fifth leading cause of death in the U.S., and is among the most intensely researched areas of science. In Egypt, a study that was carried out in Assiut governorate in 1998, recorded the prevalence of AD and other dementing disorders as a case per 100 population over the age of 60 and the age-specific prevalence tends to be doubled every 5 years [6].

1.2 Pathological Feature of Alzheimer's Disease

AD is a neurodegenerative disorder characterized clinically by progressive memory loss and subsequent dementia, and neuropathologically by senile plaques, neurofibrillary tangles and synapses loss [7]. The abnormal accumulation of extracellular amyloid-beta peptide (Aβ) and the intracellular neurofibrillary tangles (NFTs) are believed to be responsible for the neuronal loss and the degeneration of the cholinergic system [8]. Other essential abnormalities are gliosis, chronic inflammation and excitotoxicity [9]. The vast majority of patients diagnosed with AD also have cerebral amyloid angiopathy (CAA) [10].

1.3 Risk Factors for Alzheimer's Disease

The main risk factors for AD are age, age-related diseases such as cardiovascular disease, diabetes, obesity, low educational levels, head trauma and repeated exposure to aluminum and heavy metals such as cupper, iron and zinc [11,12]. Aluminum is a prooxidant induced its neurotoxicity *via* free radical production and stimulation of Aβ oxidation. Moreover, aluminum has been shown to be colocalized with both the amyloid plaques and the neurofibrillary tangles in AD [13,14].

1.4 Pathogenesis of Alzheimer's Disease

A growing body of evidence indicates that oxidative stress occurs early in the development of AD, principally before the formation of the hallmark pathologies; neurofibrillary tangles and senile plaques [15]. Researchers from Mayo Clinic (USA) linked late onset of AD to a locus on chromosome 10 that affects processing of the amyloid protein to form the amyloid plaques in the brain. Furthermore, genetic analyses of families with early-onset AD have revealed mutations in chromosome 21, within Aβ sequence, in addition to mutations within presenilin 1 and 2 genes. Most of these mutations lead to increased production of Aβ 1-42 and its oligomeric forms [16]. Thus, there is increasing consensus that the production and accumulation of A*β* peptide is central to the pathogenesis of AD [17,18].

Aβ peptides, derived from proteolytic cleavage of amyloid precursor protein (APP), are thought to be a pivotal toxic species in the pathogenesis of AD [19]. Proteolytic processing of APP occurs through two different pathways, a non-amyloidogenic pathway and an amyloidogenic pathway [20].

In the nonamyloidogenic pathway, the cleavage of APP is initiated by α-secretase in the middle of Aβ peptide, thus inhibiting the generation of Aβ [21]. During this cleavage, a soluble ectodomain of APP (sAPPα) is released and a 10 kDa C-α terminal fragment (α-CTF) remains within the membrane [22]. The soluble ectodomain of APP is known as a neurotrophic and neuroprotective peptide [23]. Also, a further action of γ-secretase on C-α terminal fragment (α-CTF) generates a nonamyloidogenic peptide p3 [21]. At least 30% of APP is processed by this pathway [24]. However, in the pathological amyloidogenic pathway, Aβ is produced by the cleavage of APP *via* the action of two aspartyl proteases, β- and γ-secretases [21]. Beta-secretase cleaves the APP, thereby generating the N-terminal Aβ peptide [20]. The remaining membrane bound C-β terminal fragments (β-CTF) of APP are substrates for γ-secretase. Cleavage of β-CTF at different sites by γ-secretase leads to the formation of Aβ that varies in its length [20] and are released into extra- or intracellular space [10]. In both pathways, APP intracellular domain (AICD) is released into the cytosol where it participates in gene transcription. The main variants are 40 and 42 amino acids long and are called Aβ [1–40] and Aβ [1–42], respectively [20]. Under normal conditions, about 90% of secreted Aβ peptides are Aβ40, which is a soluble form of the peptide that only slowly converts to an insoluble β-sheet configuration and thus can't be eliminated from the brain. In contrast, about 10% of secreted Aβ peptides are Aβ42 species that are highly fibrillogenic and deposited early in individuals with AD [24].

The apolipoprotein E *ε* 4 genotype, a major genetic risk factor for AD, leads to accelerated deposition of amyloid, and the generation of antiamyloid antibodies in humans with AD [25]. Apolipoprotein E (APOE) genotype influences the average age at which AD pathology begins and thus may account for the risk of dementia onset that occurs later [26]. Alternate hypotheses regarding the pathophysiology of AD place great emphasis on the potential role of tau-protein abnormalities, heavy metals, vascular factors, or viral infections [27].

Elevated brain homocysteine level is involved in iron dysregulation/oxidative stress cycle that has a central role in the pathogenesis of AD [28]. Also, hydrogen sulphide (H_2S), a neuromodulator agent, is severely reduced in AD as a result of reduced activity of the enzyme cystathionine-β-synthase (CβS) which is the source of H_2S in the brain. Thiol derived amino acids such as homocysteine are electron donors in mixed function oxidation system, acting with the transition metals iron and copper, and thus by interfering with iron sequestration, *in vivo*, increases in redox-active iron in AD neurons with concomitant

oxidative stress and subsequent accumulation of amyloid in the brain. Therefore, AD is often associated with abnormal localization of iron regulatory proteins (IRP's) [29]. Specifically, alteration of IRP-2 might be directly linked to impaired iron homeostasis, leading to neurofibrillary tangles, senile plaques and neuropil threads in AD patients.

Oxidative stress, the direct result of the imbalance between the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS), and intracellular antioxidant defences, is invariably involved in the onset of neurological pathologies such as AD, Parkinson's disease, and amyotrophic lateral sclerosis [30,31]. The major species responsible for oxidative stress is the overproduction of ROS and RNS, due to mitochondrial dysfunction [32]. ROS which include superoxide anion radical and hydroxyl radicals are involved in the damage of lipids, DNA, and protein modifications. Minor modifications of the nucleic acid bases are repaired through base excision repair involving DNA glycosylase and Apurinic/apyrimidinic (AP) endonuclease. These enzymes are located in the nuclei and mitochondria. The progression of AD is associated with the diminished expression of these DNA repair enzymes [33,34]. The accumulation of the oxidatively damaged nucleic acids and proteins leads to the onset and progression of neurological pathologies characterizing AD [35].

Aβ accumulation in AD induces oxidative stress through several mechanisms, including stimulation of nitric oxide synthase (NOS) activity [36]. NO synthase mediated NO radical formation through converting L-arginine to L-citrulline. NO caused brain lesion development and further progression of brain pathology and dementia [37]. Peroxynitrite is a powerful oxidant produced as a result of diffusion limited reaction of superoxide anion $^{\cdot}O_2^{-}$ with nitric oxide. Peroxynitrite causes the nitration of tyrosine residues so that nitrotyrosine immunoreactivity is increased in the neuronal cytoplasm of the cerebral cortex within regions of neurodegeneration in AD brains [38]. Also, AD induces oxidative stress by stimulating the hydrogen peroxide (H_2O_2) generation in isolated neocortex mitochondria, decreasing the activities of catalase and glutathione peroxidase in mitochondria [39]. Hence, it is thought that oxidative stress may be an underlying mechanism in AD, and agents that prevent oxidative damage may be particularly efficacious in the treatment of AD [40].

Cell dysfunction and cell death in nuclear groups of neurons, responsible for maintenance of specific transmitter systems, lead to deficits in acetylcholine, norepinephrine, and serotonin [41]. AD is characterized by a dysfunction of central cholinergic systems. Acetylcholine (Ach) is the only classical neurotransmitter that, after release into the synaptic cleft, is inactivated by enzymatic hydrolysis. Acetylcholinesterase (AchE) was identified as the enzyme responsible for termination of cholinergic transmission by cleavage of Ach to acetate and choline. AchE is found in cholinergic synapses in the brain as well as in autonomic ganglia, the neuromuscular junction, and the target tissues of the parasympathetic system [42,43].

Excitotoxicity is also considered to play an important role in the pathogenesis of AD. It is triggered by excessive stimulation of glutamate receptors (e.g. N-methyl-D-aspartate NMDA) due to the increased release or a decreased uptake of excitatory amino acids, mostly glutamate [43]. Many investigations using cultured cortical neurons demonstrated that Aβ induced cell damage by increasing glutamate release [44]. The Aβ and excessive glutamatergic tone may act synergistically in a reinforcing manner to induce oxidative stress [45].

Alteration in the precisely regulated calcium homeostasis is one of the known causes of neuronal malfunction. Moreover, calcium dysregulation is considered to be capable of

eliciting increased Aβ formation and tau phosphorylation in the brain [13]. Calcium/calmodulin-dependent protein kinase II phosphorylates tau at the site of its interaction with microtubules (Green and Peers, 2001). The increase in the cytosolic calcium concentration induces transient phosphorylation of APP leading to an increased production of intracellular Aβ [46]. Amyloid-β oligomers have been shown to rapidly elevate intracellular calcium levels in human neuroblastoma cells and increase general membrane permeability and membrane conductance [47]. Amyloid-β triggers calcium release from endoplasmic reticulum (ER) stores by ryanodine receptor [48]. Cytosolic calcium concentration can be additionally increased by the formation of cation selective ion channels by Aβ [49]. Moreover, the mechanism by which Aβ disrupts intracellular calcium homeostasis is related to its ability to form reactive oxygen species that may induce membrane lipid peroxidation [50]. These events cause the alteration in membrane properties and affect the function of membrane transporters and ion channels leading to an elevation of intracellular calcium levels [51]. These observations strongly suggest the existence of a positive feedback loop between Aβ generation and an elevated level of calcium ions in the cytosol [52]. Additionally, the increase in intracellular calcium results in overload of Ca^{2+} in mitochondria, causing mitochondrial dysfunction manifested by increased production of ROS, deficiencies in key enzymes of energy metabolism and glucose utilization, most consistently α-ketoglutarate dehydrogenase and pyruvate dehydrogenase with consequent reduction in glucose transport activity for the cerebral vessels [53], release in cytochrome *c*, and eventually apoptosis that observed in AD patients brain [54].

In recent years, a number of studies have investigated the potential role of various metal ions in the pathogenesis of AD [55] and there was an Egyptian study carried out at Alexandria University Hospital in 1993 revealed a significant increase in serum aluminum level in patients with AD. This study supports the hypothesis that aluminum may be implicated in AD etiology and pathogenesis [56]. Also, neurofibrillary degeneration found in rabbits following aluminum exposure supported the implication of Al in the formation of neurofibrillary tangles in the brain [57] as Al could induce miss folding and self-aggregation of highly phosphorylated cytoskeletal proteins such as neurofilaments or microtubule associated proteins which are implicated in AD [58].

Aluminum is found associated with amyloid-beta in the brains of AD patients [59]. This is because of the ability of Al (III) to interact with acidic groups of the peptides, and to bind these peptides with one another [60]. Also, Al causes the conformational change of Aβ peptides into the beta-sheet structure *in vivo* and *in vitro* [61].

AD involves a progressive mental deterioration manifested by cognitive impairments. The relationship between occupational Al exposure and the possible impairment of cognitive performance was also assessed [62]. Al inhibits long-term potentiation, causes synaptic structural abnormalities, thereby resulting in profound memory loss [63]. Some epidemiological studies indicated that occupational Al exposure can produce behavior impairments [64].

Aluminum is a potent cholinotoxin [65] as it could reduce cholinergic function [66]. It causes apoptotic neuronal loss *in vivo* as well as *in vitro* [63]. The neuronal loss is considered as a characteristic symptom of AD [67].

Oxidative stress induced neuronal damage has been shown to be one of the important mechanisms indicating the association of Al with the etiology of AD [68]. Aluminum is a nonredox active metal which is capable of increasing the cellular oxidative milieu by

potentiating the pro oxidant properties of transition metals such as iron and copper [69]. An aspect of the biochemistry of this non redox active metal is its prooxidant activity, which might be explained by the formation of an Al (III)-superoxide radical anion complex [70]. It has been shown that chronic aluminum exposure is involved in the impairment of mitochondrial electron transport chain (ETC) and the increased production of ROS [71]. ROS interact with all biological macromolecules, including lipids, proteins, nucleic acids, and carbohydrates. The resulting stress increases neuronal death, which contributes to the neuropathology associated with several neurodegenerative diseases [72]. Also, Al induced depletion of glutathione (GSH) and reduction in the activity of glutathione peroxidase (GPx), glutathione S-transferase (GST) and catalase (CAT) [73].

1.5 Diagnosis of Alzheimer's Disease

Even though there is a large literature demonstrating altered levels of a range of biomarkers in patients with AD, attempts to identify a single biomarker specific to AD have failed [74].

Biomarkers currently under investigation for the early diagnosis of AD include: brain volume or activity measurements derived from neuroimaging techniques, such as positron emission tomography (PET) or magnetic resonance imaging (MRI) and chemical indices detected in various body fluids [75]. Decreased $A\beta_{1-42}$ and increased phospho-tau protein levels in the cerebrospinal fluid (CSF), when measured together, exhibit sensitivity and specificity in the range 80% -90%, and are currently the most accurate chemical neurodiagnostics of sporadic AD [75]. Other candidate chemical biomarker of the disease currently and commercially available is CSF and urinary F_2 –isoprostanes [75].

The serum protein-based algorithin biomarkers can be combined with clinical information to accurately classify AD patients [74]. These markers consistently distinguished AD cases from controls in significant analysis of microarray, logistic regression and Wilcoxon analyses, suggesting the existence of an inflammatory-related endophenotype of AD that may provide targeted therapeutic opportunities for this subset of patients. The serum brain derived neurotrophic factor (BDNF) levels are significantly different between AD rat model and controls suggesting that serum BDNF are a useful marker for AD disease status [76].

AD7C-NTP (neural thread protein 41-kD) is a brain protein that is selectively elevated in AD disease and is associated with the pathologic changes of AD, and over expression of AD7C-NTP is associated with the cell death similar to that found in the AD brain [77]. Urinary AD7C-NTP is validated as a sensitive biomarker for AD and has significant clinical usefulness [78].

The ultra high-sensitivity nanoparticle-based bio-barcode assay was used to measure the concentration of Aβ-derived diffusible ligands (ADDLs), a potential soluble pathogenic AD's disease marker in the CSF of AD patients [79]. This method can be used to measure the concentration of the pathogenic ADDL in CSF at clinically relevant concentrations and proved that the elevated levels of ADDLs correlate with the presence of AD disease. This method points toward a potential reliable detection method for diagnosing AD faster, higher throughput, and less expensive than current imaging techniques.

AD can be linked to characteristic alterations in serum autoantibody expression profiles, and by using only 10 autoantibody diagnostic biomarkers, AD patients serum samples were readily distinguished from non-demented control (NDC) sera with a sensitivity of 96% and a specificity of 92.5% [80]. This approach proved to be useful for AD diagnosis throughout the

full course of the disease, and may also be useful for early detection, perhaps including patients with mild cognitive impairment (MCI) and pre-symptomatic disease [80].

Recent research has shown that when the exosomes, present in the cerebral spinal column, contain high levels of tau and other proteins, that gives an indicator of advanced stages of AD and may become revolutionary in diagnosing AD in its early onset.

1.6 Potential Therapeutics for Alzheimer's Disease

There is no cure or effective therapy for reducing a patient's amyloid burden or preventing amyloid deposition in AD [16]. However, there was some recent sort of treatments which showed an appreciable improvement in AD patients.

Positron emission tomography (PET) scans have shown that patients with AD treated with genetically engineered tissue expressing nerve growth factor protein (NGF), inserted directly into their brains, and realized a decrease in the rate of cognitive decline and an increase in the brain's uptake of glucose, a sign of increased brain activity. Also, the evaluation of Mini-Mental Status Examination (MMSE) suggested an improvement in the rate of cognitive decline and amyloid toxicity due to this type of treatment [81]. Also, the treatment with exosome-mediated (siRNA) delivery produced a knockdown of BACE1, a therapeutic target in AD in wild-type mice [82]. Moreover, the protein produced by K^+-Cl^- co transporter 2 (KCC2) gene which is a member of the K^+-Cl^- co transporter gene family has been found to prevent exitotoxicity and protect neurons from death in neurodegenerative disease such as AD [83].

Another type of recent treatment for AD is called cysteine protease inhibitors CA074Me and E64d which were selected to inhibit β-secretase activity in the secretory vesicles that produced β-amyloid [84]. That treatment of APP mice model, expressing the wild type WT β-secretase site, with these inhibitors resulted in marked improvement in memory deficit accompanied by the reduction in amyloid plaque load, depletion in Aβ-40 and Aβ-42, and a decrease in the C-terminal β-secretase fragment derived from APP. The notable efficacy of these inhibitors provides support for CA074Me and E64d as potential therapeutic agents for AD patients [84].

Both atorvastatin and semavastatin may be associated with a decreased risk for AD disease. Statin action is related to the drug's ability to activate α-secretase-cleaved soluble Alzheimer amyloid precursor protein ectodomain (sAPP $_\alpha$). Statins also inhibit the isoprenoid pathway thus modulating the activities of the Rho family of small GTPase-RhoA,B and C. Rho proteins, in turn, exert many of their effects *via* Rho-associated protein kinases ROCKs. They suggest that the Rho/ROCK1 protein phosphorylation pathway might be involved statin-stimulated shedding on sAPP $_\alpha$ [85].

Epidemiologic studies revealed that long-term use of a select of nonsteroidal anti-inflammatory drugs (NSAID) such as dapsone, meclofenamic acid and enantiomers of flurbiprofen reduced the risk for development of AD and lowered Aβ-42 levels to greatest extent by targeting γ-secretase. These drugs are excellent candidates for clinical testing to lower Aβ-42 levels in AD patients [86].

The effect of another type of anti-inflammatory agent called nattokinase (Natto) on growth factors in the brain of AD rat model has been studied. A remarkable improvement in the biochemical parameters of the brain reflected by a decreased transforming factor-β (TGF-β)

level with a significant increase in brain derived neurotrophic factor (BDNF) and vascular endothelial growth factor (VEGF) levels has been detected. Moreover, histological examination of brain tissue sections of the treated rats showed improvement in the brain morphological structure and disappearance of most of the amyloid plaques [87].

Adenosine receptor (AR) signaling has been found to modulate the blood brain barrier (BBB) permeability *in vivo* and AR activation could facilitate the entry of intravenously administered macromolecules including large dextrans and antibodies to β-amyloid [88]. Treatment with a broad-spectrum AR agonist (Lexiscan) allowed the intravenously administered anti-β-amyloid to enter the CNS and bind β-amyloid plaques in a transgenic mouse model of AD disease. *In vitro* study, a selective AR activation resulted in neuronal changes including a decreased transendothelial electrical resistance, increased actinomyosin stress fiber formation, and alterations in tight junction molecules [88]. These findings aid in drug delivery and treatment options for neurological diseases such as AD.

Researchers from the University of Sheffield used lasers to fabricate intricate scaffolds from a commonly used polymer, polylactic acid (PLA). These synthetic biocompatible materials degrade in the human body to form lactic acid that can easily be removed leaving the regenerated tissue behind in the required size, shape and structure. Also, these materials had the ability to effectively harness the growth of neuronal cells. Therefore, the fabrication of these scaffolds is considered as a vital step in the process of tissue engineering but these scaffolds need to be fine-tuned when used in the treatment of AD [89].

Hormone therapy also took part in the treatment of AD as it has been found that estradiol or dehydroepiandrosterone (DHEA) administration in a rat model of AD produced marked improvement in the histological feature of the brain with a complete disappearance of amyloid plaques [90].

Natural therapy has been also participated in the treatment of AD. When a naturally derived grape seed polyphenolic extract was administered in Tg2576 mice, expressing high molecular weight (HMW) Aβ oligomers, this polyphenolic preparation significantly attenuated AD - type cognitive deterioration coincidently with a reduced HMW soluble oligomeric Aβ in the brain. Therefore, it has been concluded that grape seed-derived polyphenolics may be useful agents to prevent or attenuate AD in humans [34]. Moreover, the extracts of both blackcurrants and boysenberries containing anthocyanins and polyphenolics can protect against AD by influencing the gene expression in learning and memory areas in the brain, that in turn activates cell signaling pathways which help neuronal cells to communicate with each other [91].

The effect of dietary omega-3 polyunsaturated fatty acid; docosahexaenoic acid (DHA) on amyloid precursor protein (APP) processing and amyloid burden has been studied. DHA enriched diets has been found to reduce Aβ-42 levels and markedly deplete total Aβ by 70% when compared with low-DHA or control diets. [92]. Thus, it has been suggested that dietary DHA could be protective against β-amyloid production, accumulation, and potential downstream toxicity [92].

Treatment of AD rat model with a combination of coenzyme Q_{10}, vitamin B complex and lecithin resulted in marked regression in the neurological damage as indicated through histopathological examination of the brain tissue of the treated rats [62]. Also, treatment of AD rat model with a combination of vitamin E, acetyl-L-carnitine (ALC) and α-lipoic acid (LA) restored the biochemical markers represented by total homocysteine (tHcy), insulin, insulin-

like growth factor-1 (IGF-1), interleukin 1β (IL-1β) and tumor necrosis factor- α (TNF- α) to near normal levels as compared to those achieved by using the AD drug "donepezil". These findings provide evidence for the importance of dietary supplements in delaying the progression of age-related neurodegenerative diseases such as AD [93].

2. CONCLUSION AND OUTLOOK

In conclusion, AD is a fast growing world-wide epidemic disease. Aβ protein plays a pivotal role in disease onset and progression and the secondary consequences of Aβ generation and deposition, that include tau hyperphosphorylation and neurofibrillary tangle formation, oxidation, inflammation, and excitotoxicity, also, contribute to the disease process. Reducing tau hyperphosphorylation, limiting oxidation and excitotoxicity, and controlling inflammation might be beneficial disease-modifying strategies.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Berchtold NC, Cotman CW. Evolution in the conceptualization of dementia and Alzheimer's disease: Greco-Roman period to the 1960s. 1998;19(3):173-189.
2. Torack R. The early history of senile dementia. In: Reisberg, B., eds. Alzheimer's Disease. New York: The Free Press. 1983:23–28.
3. Hunter R, Macalpine I. Three Hundred Years of Psychiatry (1535–1860): A history presented in selected English texts. Hartsdale, New York: Carlisle Publishing; 1982.
4. McGrew RE. Encyclopedia of Medical History. USA: Roderick E. McGrew; 1985.
5. McMenemey WH. Alzheimer's disease. J. Neurol. Psych. 1940;3:211–240.
6. Farrag A, Farwiz HM, Khedr EH, Mahfouz RM, Omran SM. Prevalence of Alzheimer's disease and other dementing disorders: Assiut-Upper Egypt study. Dement Geriatr Cogn Disord. 1998;9(6):323-328.
7. Aluise CD, Robinson RA, Beckett TL, Murphy MP, Cai J, Pierce WM, Markesbery WR, Butterfield DA. Preclinical Alzheimer's disease: brain oxidative stress, amyloid- beta peptide and proteomics. Neurobiol. Dis. 2010;39:221-228.
8. Mattson MP. Pathways towards and away from Alzheimer's disease. Nature. 2004;430:631-639.
9. Pereira C, Agostinho P, Moreira PI, Cardoso SM, Oliveira CR. Alzheimer's disease-associated neurotoxic mechanisms and neuroprotective strategies. Curr. Drug Targets CNS Neurol. Disord. 2005;4:383-403.
10. Holtzman DM. In vivo effects of Apo E and clusterin on amyloid-beta metabolism and neuropathology. J Mol Neurosci. 2004;23(3):247-254.
11. Mayeux R. Epidemiology of neurodegeneration. Annu Rev Neurosci. 2003;81-104.
12. Mattson MP. Gene-diet interactions in brain aging and neurodegenerative disorders. Ann Intern Med. 2003;139(5 Pt 2):441-444.
13. Christen Y. Oxidative stress and Alzheimer disease. Am. J. Clin. Nutr. 2000;71(2):6215-6295.
14. Lynch T, Cherny RA, Bush AI. Oxidative process in Alzheimer's disease: the role of A beta-metal interaction. Exp. Gerontol. 2000;35(4):445-451.

15. Lee HG, Perry G, Moreira PI, Garrett MR, Liu Q, Zhu X, Takeda A, Nunomura A, Smith MA. Tau phosphorylation in Alzheimer's disease: pathogen or protector? Trends Mol Med. 2005;11(4):164-169.

16. Sigurdsson EM, Scholtzova H, Mehta PD, Frangione B, Wisniewski T. Immunization with a nontoxic/nonfibrillar amyloid-beta homologous peptide reduces Alzheimer's disease-associated pathology in transgenic mice. Am J Pathol. 2001;159(2):439-447.

17. Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science. 2002;297:353-356.

18. Wollen KA. Alzheimer's disease: the pros and cons of pharmaceutical, nutritional, botanical, and stimulatory therapies, with a discussion of treatment strategies from the perspective of patients and practitioners. Altern Med Rev. 2010;15(3):223-244.

19. Randall AD, Witton J, Booth C, Hynes-Allen A, Brown JT. The functional neurophysiology of the amyloid precursor protein (APP) processing pathway. Neuropharmacology. 2010;59:243-267.

20. Hartman T, Kuchenbecker J, Grimm MOW. Alzheimer's disease: the lipid connection. J. Neurochem. 2007;103:159-170.

21. Walsh DM, Selkoe DJ. $A\beta$ oligomers: a decade of discovery. J. Neurochem. 2007;101:1172-1184.

22. Hemming ML, Selkoe DJ. Amyloid-β protein is degraded by cellular angiotensin converting enzyme (ACE) and elevated by an ACE inhibitor. J. Biol. Chem. 2005;280:37644-37650.

23. Chow VW, Mattson MP, Wong PC, Gleichmann M. An overview of APP processing enzymes and products. Neuromol. Med. 2009;12:1-12.

24. Pakaski M, Kalman J. Interactions between the amyloid and cholinergic mechanisms in Alzheimer's disease. Neurochem. Int. 2008;53:103-111.

25. Hock C, Konietzko U, Streffer JR, Tracy J, Signorell A, Müller-Tillmanns B, Lemke U, Henke K, Moritz E, Garcia E, Wollmer MA, Umbricht D, de Quervain DJ, Hofmann M, Maddalena A, Papassotiropoulos A, Nitsch RM. Antibodies against beta-amyloid slow cognitive decline in Alzheimer's disease. Neuron. 2003;38:547-554.

26. Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, Roses AD, Haines JL, Pericak-Vance MA. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science. 1993;261(5123):921-923.

27. Cummings JL. Alzheimer's disease. New England journal of medicine. 2004;351(1):56-67.

28. Dwyer BE, Raina AK, Perry G, Smith MA. Homocysteine and Alzheimer's disease: a modifiable risk? Free Radic Biol Med. 2004;36(11):1471-1475.

29. Smith MA, Wehr K, Harris PL, Siedlak SL, Connor JR, Perry G. Abnormal localization of iron regulatory protein in Alzheimer's disease. Brain Res. 1998;788(1-2):232-236.

30. Cente M, Filipcik P, Mandakova S, Zilka N, Krajciova G, Novak M. Expression of a Truncated Human Tau Protein Induces Aqueous-Phase Free Radicals in a Rat Model of Tauopathy: Implications for Targeted Antioxidative Therapy. J Alzheimers Dis. 2009;17(4):913-20.

31. Reddy VP, Zhu X, Perry G, Smith MA. Oxidative stress in diabetes and Alzheimer's disease. J Alzheimers Dis. 2009;16(4):763-774.

32. Zhu X, Su B, Wang X, Smith MA, Perry G. Causes of oxidative stress in Alzheimer disease. Cell Mol Life Sci. 2007;64(17):2202-2210.

33. Nakabeppu Y, Tsuchimoto D, Ichinoe A, Ohno M, Ide Y, Hirano S, Yoshimura D, Tominaga Y, Furuichi M, Sakumi K. Biological significance of the defense mechanisms against oxidative damage in nucleic acids caused by reactive oxygen species: from mitochondria to nuclei. Ann N Y Acad Sci. 2004;1011:101-111.

34. Wang X, Su B, Zheng L, Perry G, Smith MA, Zhu X. The Role of Abnormal Mitochondrial Dynamics in the Pathogenesis of Alzheimer's Disease. J Neurochem. 2008a;109(Suppl 1):153–159.

35. Stadtman ER. Protein oxidation in aging and age-related diseases. Ann N Y Acad Sci. 2001;928:22-38.

36. Ali AK, Banks WA, Kumar VB, Shah GN, Lynch JL, Farr SA, Fleegal-Demotta MA, Morley JE. Nitric Oxide Activity and Isoenzyme Expression in the Senescence-Accelerated Mouse P8 Model of Alzheimer's Disease: Effects of Anti-Amyloid Antibody and Antisense Treatments. J Gerontol A Biol Sci Med Sci. 2009;64(10):1025-1030.

37. Seyidova D, Aliyev A, Rzayev N, Obrenovich M, Lamb BT, Smith MA, de la Torre JC, Perry G, Aliev G. The role of nitric oxide in the pathogenesis of brain lesions during the development of Alzheimer's disease. In Vivo. 2004;18(3):325-333.

38. Smith MA, Richey Harris PL, Sayre LM, Beckman JS, Perry G. Widespread peroxynitrite-mediated damage in Alzheimer's disease. J Neurosci. 1997;17(8):2653-2657.

39. Kaminsky YG, Kosenko EA. Effects of amyloid-beta peptides on hydrogen peroxide-metabolizing enzymes in rat brain in vivo. Free Radic Res. 2008;42(6):564-573.

40. Nivsarkar M, Banerjee A, Padh H. Cyclooxygenase inhibitors: a novel direction for Alzheimer's management. Pharmacol Rep. 2008;60(5):692-698.

41. Pappas BA, Bayley PJ, Bui BK, Hansen LA, Thal LJ. Choline acetyltransferase activity and cognitive domain scores of Alzheimer's patients. Neurobiol Aging. 2000;21:11-17.

42. Soreq H, Seidman S. Acetylcholinesterase –new roles for an old actor. Nature Rev Neurosci. 2001;2:294-302.

43. Naik RS, Hartmann J, Kiewert C, Duysen EG, Lockridge O, Klein J. Effects of rivastigmine and donepezil on brain acetylcholine levels in acetylcholinesterase-deficient mice. J Pharm Pharm Sci. 2009;12(1):79-85.

44. Ban JY, Cho SO, Jeon SY, Bae K, Song KS, Seong YH. 3,4- Dihydroxybenzoic acid from Smilacis chinae rhizome protects amyloid-beta protein-induced neurotoxicity in cultured rat cortical neurons. Neurosci. Lett. 2007;420:184-188.

45. Coyle JT, Puttfarcken P. Oxidative stress, glutamate and neurodegenerative disorders. Science. 1993;262:689-695.

46. Pierrot N, Santos SF, Feyt C, Morel M, Brion JP, Octave JN. Calcium-mediated transient phosphorylation of tau and amyloid precursor protein followed by intraneuronal amyloid-beta accumulation. J. Biol. Chem. 2006;281:39907-39914.

47. Sokolov Y, Kozak JA, Kayed R, Chanturiya A, Glabe C, Hall JE. Soluble amyloid oligomers increase bilayer conductance by altering dielectric structure. J. Gen. Physiol. 2006;128:637-647.

48. Ferreiro E, Oliveira CR, Pereira C. Involvement of endoplasmic reticulum Ca2+ release through ryanodine and inositol 1,4,5-triphosphate receptors in the neurotoxic effects-induced by the amyloid-beta peptide. J. Neurosci. Res. 2004;76:872-880.

49. Mirzabekov TA, Lin MC, Kagan BL. Pore formation by the cytotoxic islet amyloid-beta peptide amylin. J. Biol. Chem. 1996;271:1988-1992.

50. Hensley K, Carney JM, Mattson MP, Aksenova M, Harris M, Wu JF, Floyd RA, Butterfield DA. A model for amyloid-beta aggregation and neurotoxicity based on free radical generation by the peptide: relevance to Alzheimer's disease. Natl. Acad. Sci. USA. 1994;91:3270-3274.

51. Deshpande A, Mina E, Glabe C, Busciglio J. Different conformations of amyloid-beta induce neurotoxicity by distinct mechanisms in human cortical neurons. J. Neurosci. 2006;26:6011-6018.

52. Bojarski L, Herms J, Kuznicki J. Calcium dysregulation in Alzheimer's disease. Neurochem. Int. 2008;52:621-633.

53. Perry G, Nunomura A, Raina, AK, Aliev, G, Siedlak SL, Harris PL, Casadesus G, Petersen RB, Bligh-Glover W, Balraj E, Petot GJ, Smith MA. A metabolic basis for Alzheimer disease. Neurochem Res. 2003;28(10):1549-1552.

54. Rego AC, Oliveira CR. Mitochondrial dysfunction and reactive oxygen species in excitotoxicity and apoptosis: implications for the pathogenesis of neurodegenerative diseases. Neurochem. Res. 2003;28:1563-1574.

55. Gomez M, Esparza JL, Cabre M, Garcia T, Domingo JL. Aluminum exposure through the diet: metal levels in APP-β transgenic mice a model for Alzheimer's disease. Toxicology. 2008;249:214-219.

56. Mohamd EM, Ahmed HH, Estefan SF, Farrag AE, Salah RS. Windows into estradiol effects in Alzheimer's disease therapy. Eur Rev Med Pharmacol Sci. 2011;15(10):1131-1140.

57. Walton JR. Aluminum in hippocampal neurons from humans with Alzheimer's disease. Neurotoxicology. 2006;27:385-394.

58. Kawahara M, Muamoto K, Kobayashi K, Mori H, Kuroda Y. Aluminum promotes the aggregation of Alzheimer's amyloid-β protein in vitro. Biochem. Biophys. Res. Commun. 1994;198:531-535.

59. Exley C. Aluminum and iron, but neither copper nor zinc, are key to the precipitation of beta-sheets of amyloid-beta 42 in senile plaque cores in Alzheimer's disease. J. Alzheimer's Dis. 2006;10:173-177.

60. Chen YR, Huang HB, Chyan CL, Shiao MS, Lin TH, Chen YC. The effect of amyloid-beta conformation on the metal affinity and aggregation mechanism studied by circular dichroism spectroscopy. J. Biochem. 2006;139:733-740.

61. Ricchelli F, Drago D, Filippi B, Tognon G, Zatta P. Aluminum triggered structural modifications and aggregation of amyloids-beta. Cell. Mol. Life Sci. 2005;62:1724-1733.

62. Ahmed HH, Shousha WG, Hussie RM, Farrag AH. Potential role of some nutraceuticals in the regression of Alzheimer's disease in an experimental animal model. Turk J Med Scin. 2011;41(3):455-466.

63. Kawahara M. Effects of aluminum on the nervous system and its possible link with neurodegenerative diseases. J. Alzheimer's Dis. 2005;8:171-182.

64. Meyer-Baron M, Schkper M, Knapp G, Van-Thriel C. Occupational aluminum exposure: evidence in support of its neurobehavioral impact. Neurotoxicology. 2007;28:1068-1078.

65. Gulya K, Rakonczay Z, Kasa P. Cholinotoxic effects of aluminum in rat brain. J. Neurochem. 1990;54:1020-1026.

66. Strong MJ, Garruto RM, Joshi JG, Mundy WR, Shafer TJ. Can the mechanisms of aluminum neurotoxicity be integrated into a unified scheme? J. Toxicol. Env. Health. 1996;48:599-613.

67. Ghribi O, Dewitt DA, Forbes MS, Herman MM, Savory J. Co-involvement of mitochondria and endoplasmic reticulum in regulation of apoptosis: changes in cytochrome c, Bcl-2 and Bax in the hippocampus of aluminum-treated rabbits. Brain Res. 2001;8:66-73.

68. Kumar V, Bal A, Gill KD. Susceptibility of mitochondrial superoxide dismutase to aluminum-induced oxidative damage. Toxicology. 2009;255:117-123.

69. Bjertness E, Candy JM, Torvik A, Ince P, Mc-Arthur F, Taylor GA, Johansen SW, Alexander J, Grønnesby JK, Bakketeig LS, Edwardson JA. Content of brain aluminum is not elevated in Alzheimer's disease. Alzheimer's Dis. Assoc. Disord. 1996;10:171-174.

70. Exley C. The aluminum amyloid cascade hypothesis and Alzheimer's disease. Subcell. Biochem. 2005;38:225-234.

71. Kumar V, Bal A, Gill KD. Impairment of mitochondrial energy metabolism in different regions of rat brain following chronic exposure to aluminum. Brain Res. 2008;1232:94-103.

72. Baydas G, Reiter RJ, Yasar A, Tuzcu M, Akdemir I, Nedzvetskii VS. Melatonin reduces glial reactivity in the hippocampus, cortex and cerebellum of streptozotocin-induced diabetic rats. Free Radic. Biol. Med. 2003;35:797-804.

73. Mahieu S, Millen N, Gonzalez M, Contini M, Del C, Elias MM. Alteration of the renal function and oxidative stress in renal tissue from rats chronically-treated with aluminum during the initial phase of hepatic regeneration. J. Inorg. Biochem. 2005;99:1858-1864.

74. O'Bryant SE, Xiao G, Barber R, Reisch J, Doody R, Fairchild T, Adams P, Waring S, Diaz-Arrastia R. Texas Alzheimer's Research Consortium. A serum protein-based algorithm for the detection of Alzheimer disease. Arch Neurol. 2010;67(9):1077-1081.

75. Schipper HM. Biological markers and Alzheimer disease: a canadian perspective. Int J Alzheimers Dis. 2010. pii: 978182.

76. Mohamd EM, Ahmed HH, Estefan SF, Farrag AE, Salah RS. Windows into estradiol effects in Alzheimer's disease therapy. Eur Rev Med Pharmacol Sci. 2011;15(10):1131-1140.

77. Munzar M, Levy S, Rush R, Averback P. Clinical study of a urinary competitive ELISA for neural thread protein in Alzheimer disease. Neurol Clin Neurophysiol. 2002;(1):2-8.

78. Ghanbari H, Ghanbari K, Beheshti I, Munzar M, Vasauskas A, Averback P. Biochemical assay for AD7C-NTP in urine as an Alzheimer's disease marker. J Clin Lab Anal. 1998;12(5):285-288.

79. Georganopoulou DG, Chang L, Nam JM, Thaxton CS, Mufson EJ, Klein WL, Mirkin CA. Nanoparticle-based detection in cerebral spinal fluid of a soluble pathogenic biomarker for Alzheimer's disease. Proc Natl Acad Sci U.S.A. 2005;102(7):2273-2276.

80. Nagele E, Han M, Demarshall C, Belinka B, Nagele R. Diagnosis of Alzheimer's disease based on disease-specific autoantibody profiles in human sera. PLoS One. 2011;6(8):e23112.

81. Tuszynski MH, Thal L, Pay M, Salmon DP U HS, Bakay R, Patel P, Blesch A, Vahlsing HL, Ho G, Tong G, Potkin SG, Fallon J, Hansen L, Mufson EJ, Kordower JH, Gall C, Conner J. A phase 1 clinical trial of nerve growth factor gene therapy for Alzheimer disease. Nat Med. 2005;11:551–555.

82. Alvarez-Erviti L, Seow YQ, Yin HF, Betts C, Lakhal S, Wood MJA. Delivery of siRNA to the mouse brain by systemic injection of targeted exosomes. NAT BIOTECHNOL. 2011;29(4)341-U179.

83. Pellegrino C, Gubkina O, Schaefer M, Becq H, Ludwig A, Mukhtarov M, Chudotvorova I, Corby S, Salyha Y, Salozhin S, Bregestovski P, Medina I. Knocking down of the KCC2 in rat hippocampal neurons increases intracellular chloride concentration and compromises neuronal survival. J Physiol. 2011;589(Pt 10):2475-2496.

84. Hook VY, Kindy M, Hook G. Inhibitors of cathepsin B improve memory and reduce beta-amyloid in transgenic Alzheimer disease mice expressing the wild-type, but not the Swedish mutant, beta-secretase site of the amyloid precursor protein. J Biol Chem. 2008;283(12):7745-7753.

85. Pedrini S, Carter TL, Prendergast G, Petanceska S, Ehrlich ME, Gandy S. Modulation of statin-activated shedding of Alzheimer APP ectodomain by ROCK. PLoS Med. 2005;2(1):e18.

86. Eriksen JL, Sagi SA, Smith TE, Weggen S, Das P, McLendon DC, Ozols VV, Jessing KW, Zavitz KH, Koo EH, Golde TE. NSAIDs and enantiomers of flurbiprofen target gamma-secretase and lower Abeta 42 in vivo. J Clin Invest. 2003;112(3):440-449.

87. Metwally F, Ahmed HH, Shalby AB, Abd El- Dayem SM, Foda FM, Zaazaa AM. Potential effect of nattokinase on brain growth factors in experimental model of Alzheimer's disease. World journal of Medical Sciences. 2012;7(2):91-99.

88. Carman AJ, Mills JH, Krenz A, Kim DG, Bynoe MS. Adenosine receptor signaling modulates permeability of the blood-brain barrier. J Neurosci. 2011;31(37):13272-80.

89. Melissinaki V, Gill A, Ortega I, Vamvakaki M, Ranella A, Fotakis C, Farsari M, Clayessens F. Direct laser writing of 3D scaffolds for neural tissue engineering applications, Biofabrication. 2011;3(4):045005.

90. Mohamed A, Cortez L, de Chaves EP. Aggregation state and neurotoxic properties of alzheimer β-amyloid peptide. Curr Protein Pept Sci. 2011;12(3):235-257.

91. Ghosh D, Mcghie TK, Fisher DR, Joseph JA. Cytoprotective effects of anthocyanins and other phenolic fractions of Boysenberry and blackcurrant on dopamine and amyloid Beta induced oxidative stress in transfected COS-7 cells. Journal of the Science of Food and Agriculture. 2007;87:2061-2067.

92. Lim GP, Calon F, Morihara T, Yang F, Teter B, Ubeda O, Salem N Jr, Frautschy SA, Cole GM. A diet enriched with the omega-3 fatty acid docosahexaenoic acid reduces amyloid burden in an aged Alzheimer mouse model. J Neurosci. 2005;25(12):3032-3040.

93. Shalby AB, Ashour MN, Ahmed HH. Possible mechanisms for the role of dietary supplements in management of Alzheimer's disease in aged rats. J. Applied Sci. Res. 2011;7:980-990.

_____