Journal of Alzheimer's Disease 19 (2010) 1123–1139
DOI 10.3233/JAD-2010-1312
IOS Press

Review Article

Neuronutrition and Alzheimer's Disease

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Accepted 20 April 2009

Abstract. Alzheimer's disease (AD) is a complex neurological disorder resulting from both genetic and environmental factors with the latter being particularly important for the sporadic form of the disease. As such, diets rich in saturated fatty acids and alcohol, and deficient in antioxidants and vitamins appear to promote the onset of the disease, while diets rich in unsaturated fatty acids, vitamins, antioxidants, and wine likely suppress its onset. In addition, evidence suggests that diets rich in polyphenols and some spices suppress the onset of AD by scavenging free radicals and preventing oxidative damage. Metal ions are known to catalyze the production of free radicals and induce mental retardation or dementia, and several studies have also identified metals such as Pb, Fe, Al, Cu, and Zn in AD pathogenesis. While specific metal chelators have been tested for therapy, they have not been very successful, probably due to their late administration, i.e., after brain damage has been triggered. Since several dietary polyphenols are known to chelate metals, their routine use may also be protective against the onset of AD. In this review, we summarize beneficial dietary techniques in the fight against AD.

Keywords: Antioxidants, caloric restriction, diet, homocysteine, lipid, neurodegeneration, nutrients, oxidative stress, polyphenols, vitamins

INTRODUCTION

Alzheimer's disease (AD) is the most common form of dementia and affects one in four individuals over the age of 85. It has multiple etiological factors including genetics, environmental factors, and general lifestyles [1], and its hallmark pathology includes extracellular amyloid-β protein (Aβ) deposition in the form of senile plaques, and intracellular deposits of the microtubule-associated protein tau as neurofibrillary tangles (NFT) in the AD brain [2]. The diagnosis of this disease is based on the characteristic idiopathic psychometric deficits upon clinical evaluation and is further confirmed by the postmortem presence of the characteristic lesions described above [3]. Aβ is produced from sequential proteolytic processing of a larger precursor protein (AβPP) by β-secretase. Cleavage results in a large secreted fragment sAβPPβ and a 99 aa cellular fragment (CTFβ) that includes Aβ, the transmembrane domain and the intracellular domain of AβPP [4].

Recently, there has been increasing evidence supporting the role of diet in AD [5–7]. A number of dietary factors such as saturated fatty acid consumption [8], calorie intake [9], and excessive alcohol consumption [10] have been reported to increase the risk of dementia and AD, and in contrast, antioxidants, fish, methionine-rich proteins, and vitamins have been identified as protective against the disease [11]. Such findings indicate that the differential prevalence of AD around the world may be linked to the global variation in diet [12]. Several cross-sectional studies indeed suggest a relationship between particular nutrients and the

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ISSN 1387-2877/10/$27.50

presence of cognitive changes [5–7], however, these need to be confirmed at an experimental level [13].

Interestingly, the same dietary pattern of risk and protection has been long accepted for metabolic syndrome and cardiovascular risk. As such, diabetes and hyperinsulinaemia are considered as important risk factors for AD [14]. Among the other risk factors, depressive illness, traumatic head injury [15], cardiovascular disease [16,17], smoking [18,19], and stroke [20,21] are significant issues that may be related to the same risk factors. Further, the ε4 allele variant of apolipoprotein E (ApoE) has been associated with increased risk in sporadic and familial AD [22]. As a carrier of cholesterol, ApoE ε4 is also a risk factor in cardiovascular disease.

Oxidative stress has been suggested to play a major role in the pathology of AD [23–26] as well, and evidence for its mediation includes: 1) generation of free radicals through metal ions; 2) enhanced lipid peroxidation; 3) increased DNA and protein damage; and 4) increased tau protein phosphorylation [26]. The human body has a defense mechanism to cope with oxidative stress, or prevent the onset of oxidative stress, through endogenous antioxidants derived from enzymatic or non-enzymatic sources [27], i.e., superoxide dismutase, glutathione reductase, and catalase. The nonenzymatic sources of endogenous antioxidants include glutathione, uric acid, α-lipoic acids, acetyl L-carnitine, melatonin, and dehydroepiandrosterone. Endogenous antioxidants also include the products of reactions catalyzed by enzymes that are upregulated in response to oxidative stress (e.g., bilurubin) [27]. Dietary antioxidants and metal chelators were found to be associated with a reduced AD risk, further reinforcing the importance of dietary stress on the body's homeostasis pathways and nutritional guidelines for AD prevention.

Several studies demonstrate that diet has a definite long-term effect on general health [21,32]. Although cross-sectional studies have indicated that diet also plays a role in AD, the extended time taken for the appearance of disease pathologies makes it nearly impossible to experimentally demonstrate the specific effects of diets in AD. In this review, we attempt to define the action of presumably protective and harmful dietary habits on pathways identified as relevant to AD pathogenesis. A common theme that has emerged from the analysis is that aging and AD are associated with excesses in saturated lipids, homocysteine, oxidative stress and other toxic pathways that appear to result from reduced efficiency of clearance pathways. Thus, a general rule of AD is that moderation is key to disease prevention. However, literature also suggests that several specific additions to the diet also help in AD prevention.

We will discuss the major dietary factors involved in maintaining homeostasis and energy requirements such as calorie restriction, lipids, metal chelators, vitamins, and other special dietary supplements including red wine and spices.

CALORIC RESTRICTION AND AD

The first lesson in moderation comes from calorie restriction (CR). Energy requirements decline progressively after early adulthood, because of cessation of growth and a decrease in basal metabolic rate and physical activity. That is, the average energy requirement for an adult is 25 kcal/kg/day whereas for children it is the sum of 100 kcal/kg/day for the first 10 kg, 50 kcal/kg/day for the second 10 kg and 20 kcal/kg/day beyond 20 kg [29] It has been shown that calorie allowances are reduced by 5% per decade between 35 and 55, 8% per decade between 55 and 75 and a further 10% beyond 75 years of age, although this may vary considerably based on physical activity and other characteristics [30].

Dietary excess is known to influence the onset and progress of age related diseases like diabetes, obesity and vascular diseases, and actually has been shown to reduce life-spans [31–33]. CR known to reduce the production of reactive oxygen species in animals by modulating neuroinflammation and oxidative stress [34–36], and CR is reported to have neuroprotective effects in young rodent models of neurodegenerative disease [37,38]. Furthermore, CR activates intercellular neurotrophic signaling mechanisms and thus provides neuroprotection [39]. Recent studies strongly suggest a link between diets and AD leading to the notion that CR may delay or prevent AD [9,40–43]. There is still a debate about whether CR works to increase life span, and by extension, other benefits in humans, although the bad effects of dietary excess remain unchallenged [44]. Nevertheless, data from population based studies suggest that a lower calorie intake leads to a lowered risk of AD and PD [9,37,45].

CR is known to induce neuroprotective molecules that have a role in resistance of neurons to oxidative, metabolic, excitotoxic and apoptotic insults [44,46–48]. CR is known to induce expression of several different neurotrophic factors, like brain derived neurotrophic factor (BDNF) in brain cells [43]. Rats maintained on

CR show increased levels of BDNF in neurons in cerebral cortex, hippocampus, and striatum [48,49]. BDNF has been reported to have role in enhancing memory and learning, and protects neurons against oxidative and metabolic insults and is also known to stimulate neurogenesis [48,49]. Studies also show reduced levels of brain-derived neurotrophic factors in patients with AD and PD [50,51]. There is a substantial amount of data accumulating in favor of increase in life span by stimulating silent mating type information regulation-2. The silent mating type information regulation-2 is required in some species for enhanced life span [52]. CR has also been demonstrated to be capable of reducing the amyloid and NFT lesion load of animal models suggesting that it may directly affect the pathogenesis of AD [53,54]. However, there is a need for more data generation on calorie restriction and its benefits to the brain. The mechanism by which CR modulates AD is not clear, however, it is postulated that CR increases synaptic plasticity, anti-inflammatory mechanisms, and induces neuroprotective factors [55]. CR was shown to protect the age-related loss of neurons in AD [56]. They also observed that CR could reduce the enlargement of ventricles, caspase activation and astrogliosis [56]. From the above findings it indicated that CR could increase neurogenesis [57] but, before a consensus is reached, an analysis and quantification of the long-term effects of CR in adults is necessary [55].

Before rushing to advocate CR as a treatment paradigm, it is important to recognize that the treatment may be too late and even be counterproductive. AD patients commonly develop abnormal eating behaviors [58] that include anorexia nervosa and bulimia nervosa [59]. Studies indicate that dietary intake of nutrients is poor in older adults who convert to early stage AD, as compared to their cognitively intact counterparts [60]. Indeed, weight loss may be an early indicator of AD prior to dementia [61].

It is important to emphasize that little is known about the factors correlated with eating difficulties in AD. Riviere and colleagues [59] conducted a one-year investigation to understand the factors responsible for adverse eating behavior among AD patients living at home with caregivers. This study involved 224 patients and their caregivers. Eating difficulties were assessed using the eating "Dependency Scale and Averse Eating Behavior Inventory". The study found two significant associations which include: i) eating difficulties and age of the caregivers and ii) severity of the disease and psychological function of the patients [59]. They analyzed the data using the regression analysis and found positive correlation between adverse eating behavior and initial caregivers burden. There was, however, an inverse correlation between memory impairment and adverse eating behaviors. Thus, both cognitive impairment and family stress can help in predicting that AD patients living at home develop adverse eating behaviors.

LIPIDS AND AD

Lipids have two major functions in the cell: they are reservoirs of chemical energy stored as fat and they are the structural components of cell membranes. Lipids also act as signaling molecules through steroid hormones and eicosanoids. Lipid metabolism plays a key role in AD through the ApoE ε4 allele, one of the genetic risk factors for AD [62–65]. The transport of lipid in blood, brain and cerebrospinal fluid is modulated by ApoE [64,66]. There is also an important association between dietary factors and ApoE polymorphisms, which gives a clue as to why we should consider dietary fat uptake patterns in different populations [67]. There is a hypothesis that one dose of ε4 allele in the brain increases AD risk by 2–3 times, two doses of the ε4 allele provides a 12–15 times higher risk [68,69].

An interesting study has been conducted to assess the risk factors throughout adult life based on a life history questionnaire; it includes medical, occupation, activity level, education, smoking and dietary habit questions [70]. The investigation obtained lifestyle patterns for three age groups: 20–39, 40–59 and 60 + or 5 years prior to AD diagnosis for cases. They indicated that healthy controls with the ApoE ε4 allele consumed less total and saturated fat between the ages of 20 and 60 years than those without the ε4 allele [70]. The consumption of higher fat through diet during mid-life may therefore reduce the risk for AD than for those without the ε4 allele. This may indicate a protective effect of the ApoE ε2 allele and ε3 allele due to the modulating effects of ApoE on LDL cholesterol level [71,72]. The intake of non-hydrogenated unsaturated fats, low intake of hydrogenated and saturated fats, and high intake of n-3 polyunsaturated fatty acids from fish or vegetable sources may lower the risk of vascular dementia as well [73].

A relationship between reduced risk of AD and a diet rich in docosahexaenoic acid (DHA) and omega-3 essential polyunsaturated fatty acid was reported [74]. Furthermore, a possible role for DHA in preventing lipid peroxidation and in reducing the accumulation

of Aβ in the cortico-hippocampal region in the mouse model was hypothesized [75]. It has also been shown that DHA plays a role in the expression of signal transduction molecules [76]. Additionally, DHA is known to stimulate the expression of transthyretin, a protein involved in the transport of thyroxin. Transthyretin has an affinity for Aβ and possibly stimulates the clearance mechanism of Aβ [77]. These observations support the need for further research to understand the therapeutic potential of DHA in AD.

Cholesterol is present in specialized membranes of myelin and in the membranes of neuronal and glial cells present in the brain (approximately 25% of the total cholesterol of the human body) [78–82]. Alterations in the metabolism of cholesterol are reported to be associated with age [83–88] and have been shown to play a role in the pathogenesis of AD [89–91]. Recent reports show a link between cholesterol and AβPP processing pathways [92,93]. An increase in dietary cholesterol levels increase secreted AβPP derivatives, namely sAβPPα and sAβPPβ in mouse brain and modulate the levels of major secreted Aβ forms Aβ_{40} and Aβ_{42} [92, 94] Recent studies suggest that β- and γ-secretase may be regulated by isoprenoid that are synthesized in the cholesterol biosynthesis pathway in addition to cholesterol [95,96].

Transgenic mouse models over expressing human AβPP and maintained on a diet rich in saturated fats and cholesterol have shown an increased accumulation of Aβ alone or in combination with other AD-related proteins [97]. Additionally, the dietary fats (saturated fat, hydrogenated fat and cholesterol) are reported to be involved in the impairment of memory and hippocampal pathology in the rat brain [98]. Conversely, inhibition of cholesterol synthesis reduces amyloid load.

Though the etiology of AD is still elusive, reports have strongly linked the role of cholesterol and ApoE in AβPP processing. Elevated levels of saturated fatty acids in AD and its role in hyperphosphorylation of tau were reported [99]. To examine free fatty acid induced hyperphosphorylation of tau, they studied primary rat cortical neurons in untreated (control) and treated neurons with 0.2 mM of either palmitic or stearic acids for 24 h. The findings indicated that astroglia-mediated oxidative stress is found to be involved in free fatty acid-induced hyperphosphorylation of tau in primary neurons. Further, it was reported that saturated fatty acids might induce aggregation of tau, as well as Aβ [99]. A study indicated that higher intake of saturated fatty acids may be a risk factor for AD [100]. However, the question is whether or not a higher intake of polyunsaturated fatty acids and monounsaturated fatty acids will reduce the risk for AD. A word of caution is the quantity of uptake of polyunsaturated fatty acids and monounsaturated fatty acids, and their link to atherogenesis. As an example, a high intake of linoleic acid, which is n-3 polyunsaturated fatty acids, may increase the susceptibility of LDL cholesterol to oxidation leading to atherogenesis [101]. The recent report suggests that diet rich in omega-3 fattyacids or use of fish oil supplements (DHA and EPA), did not protect against AD. But the dietary fish may contain nutrients, other than DHA and EPA, that may provide some protection against AD [102].

In conclusion, lipids have a complex relationship with AD. Some appear to be protective whereas others such as cholesterol appear to be harmful. The relationship is however even more complex, with some of the effects of cholesterol attributable to intermediates in cholesterol biosynthesis such as isoprenoids. Interestingly, the relationship between AD and cholesterol epidemiology is complex with almost no difference between normal controls and AD. However, high levels of cholesterol in middle age has been linked to higher risk for AD in later life [103]. Further complicating the picture is the finding that high cholesterol late in life is actually linked to a reduction in AD risk [104], suggesting that AD is likely linked to a rapid loss of cholesterol with age [105].

METAL CHELATORS IN AD

The brain is rich in unsaturated fatty acids, and thus it is prone to oxidative stress. Redox-active metals such as Fe and Cu are involved in the production of reactive oxygen species in the brain, and the levels of Fe and Cu are high in brain tissues. Oxidative stress is a process leading to the production of reactive oxygen species, where it causes molecular damage leading to altered biological functions [106]. Moreover, Fe and Cu are implicated in the formation of oxygen free radicals and damage tissue in AD brain [107]. Fe accumulates in NFTs as well as in Aβ deposits [108]. Aluminum (Al) also accumulates in NFT-containing neurons [109,110] and is found to stimulate Fe-induced lipid peroxidation [111]. There are reports on increased levels of Zn (II), Fe (III), and Cu (II) in the neuropil and senile plaques in the AD brain [112]. Al is also known to aggravate the free radical damage already initiated by Fe [113].

Interestingly, metals such as Cu (II) appear to facilitate the cholesterol-mediated increase in amyloid pathology [114]. Early exposure to Pb is also implicated in increased amyloidosis by increasing AβPP expression [115]. Several dietary spices are known to act as metal chelators and may therefore be protective against dementia [116].

VITAMIN E AND AD

The body's defensive system against oxidative stress includes molecules called antioxidants that are also known as free radical scavengers. There is still a debate regarding the role of reactive oxygen species related to neuronal damage. Considering that oxidative stress can be a primary event, the role of dietary antioxidants in combating oxidative stress in AD is discussed below. Additionally, the dysregulations of metabolic pathways in the aged brain will lead to reduced synthesis of defense molecules to combat oxidative stress. The major questions still to be understood are: What are the regulatory molecules of the metabolic pathways in aged brain that are susceptible to oxidative damage? What are the homeostatic mechanisms make neurons resistant to oxidative damage?

Studies have reported the role of antioxidants in lowering the risk of stroke and AD [117–120]. The change in the concentration of antioxidants in neurodegeneration may be a primary or secondary event in relation to dietary intake [120]. Studies have established a relationship between the plasma concentration of antioxidants and cognition [121,122]. Studies indicate that the various antioxidant supplements could be effective in reducing oxidative stress [123,124].

Notably, the level of vitamin E in plasma of AD patients is 18.65 ± 3.62 mmol/L compared to age-matched controls 30.03 ± 12.03 mmol/L [125,126]. It has been shown that long term feeding of rats (from 6 to 15 months of age; F344 rats) with a supplemented AIN–93 diet (strawberry or spinach extract (1–2% of the diet) or vitamin E (500 IU), have protected against age-related changes in cognitive functions. Furthermore, the supplemented diet could prevent the onset of age related deficits in several indices, including cognitive behavior and performance with the Morris water maze [125,126]. However, Petersen and colleagues [127] indicated that vitamin E had no beneficial effect in patients with mild cognitive impairment [127]. In a double blind study [127], subjects with mild cognitive impairment were given 2000 IU of vitamin E daily, 10 mg donepezil daily, or a placebo for three years. The overall rate of progression from mild cognitive impairment to full clinical AD was 16% per year, and, importantly, there was no difference between subjects on the placebo and subjects who received vitamin E over a period of three years. These studies disagree on the validity of vitamin supplements to AD patients and, thus, more research is essential to understand further.

Researchers across the globe are interested in elucidating the protective potential of vitamin E and vitamin C against AD [128]. In another major study, AD patients were given 2,000 IU of vitamin E per day, a dose that exceeds the recommended daily allowance of vitamin E. They found that a higher dose of vitamin E is able to delay the admission to a nursing home by six months, compared to those taking a placebo [128]. The question is to understand the quantity of vitamins required in reducing the risk of AD and safety of vitamin E at higher concentrations. Further, the dietary supplements of vitamin E fail to provide better results compared to dietary intake of vitamin E [129]. If the supplements are less beneficial than dietary vitamin E, what is the main reason for such a difference? The probable reason might be the composition of the diet, which has a cumulative and synergistic effect in the vitamin bioavailability. The apparent protection provided by dietary vitamins E and C could be by synergy due to other substances in fruits and vegetables, such as flavonoids, which have both anti-inflammatory and antioxidant properties [130].

Ultimately, the clinician should diagnose the plasma concentration of antioxidants at a particular point of AD grading and make a decision on recommending the use of vitamin E supplements.

VITAMINS AND HOMOCYSTEINE INTERRELATIONS

Hyperhomocysteine levels induce neurologic abnormalities such as cerebral atrophy, and seizures, etc. [131]. A deficiency of vitamins is found to elevate the concentration of homocysteine, which is implicated in vascular mechanisms leading to AD [131,132]. Vitamins like folate, B6, and B12 have been involved in the biosynthesis of amino acids, which contain sulphur, methionine, and cystein [133]. Folate and vitamin B12 are involved in biosynthesis of methionine from its precursor homocysteine, whereas B6 has a role to play in the conversion of homocysteine to cysteine. The levels of homocysteine in the blood are elevated with ageing

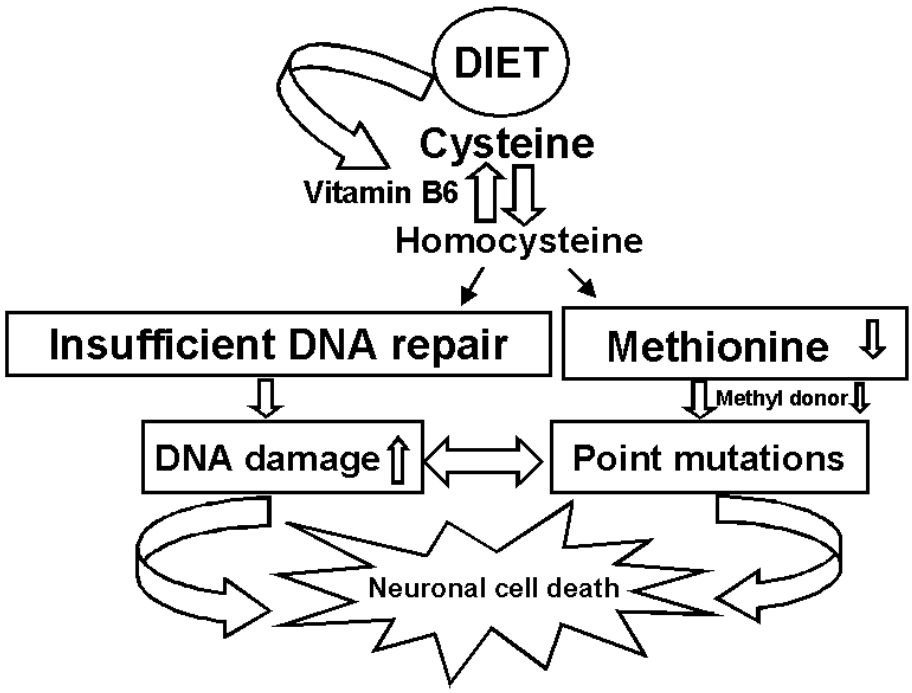

Fig. 1. The role of homocysteine in AD. Vitamin B6 acts as a cofactor in the maintenance of homeostasis between homocysteine and cysteine. Any imbalance in the vitamin B6 levels alters the balance between homocysteine to cysteine. The higher levels of homocysteine are a risk factor for AD. The higher homocysteine levels may cause insufficient DNA repair leading to accumulation of DNA strand breaks. This may lead to neuronal cell dysfunction.

and age is one of the risk factor for AD [134]. The factors like folic acid and caloric intake are also known to modulate the plasma homocysteine [134]. There is an inverse relationship between plasma folic acid and homocysteine, and dietary folic acid is found to lower homocysteine levels. Additionally, calorie restriction is also found to decrease homocysteine levels, but the magnitude of the effect is moderate [135]. There are higher homocysteine levels in the patients with deficient enzyme cystathione β synthase, which is involved in catabolism of cystein. A study has shown that in mice fed in a diet with reduced levels of folic acid, there is hipppocampal pyramidal neuronal degeneration [136]. This may be because of the elevated levels of homocysteine in mice due to low folic acid. Also, administration of homocysteine into the brain is found to enhance neuronal degeneration [137], and elevated levels of homocysteine induce accumulation of DNA damage in neurons [135,136,138]. This may be because increased homocysteine induces a deficiency of methyl donors, which has implication on uracil misincorporation and oxidative damage to DNA bases [136, 138]. A link between levels of homocysteine and gene expression was also reported and increased homocysteine leads to decrease in the levels of methyl donors, causing hypomethylation of PS1 promoter [139]. It is likely to alter the gene expression as gene silencing is mediated by the methylation of the promoter [139]. Figure 1 represents the details of homocysteine and neuron cell death. A number of studies suggest that homocysteine can increase amyloid load in transgenic mice [140]. All the above events provide insights into the relationship between dietary intake of vitamins and homocysteine and their effect in neuronal cell death. We therefore hypothesize a relationship between vitamins, homocysteine and neuronal dysfunction. The increased levels of homocysteine in AD patients are a risk factor. Higher homocysteine levels cause insufficient DNA repair and point mutations, which leads to the accumulation of DNA damage and cell death. A reduction in the levels of homocysteine can be brought about by increasing cysteine levels in the body through the use of vitamin B6, which acts as a cofactor in the transformation of homocysteine to cysteine or by recycling it back to methionine using vitamin B12 and folate. Indeed, a deficiency in vitamin B12 leads to a form of dementia that resembled AD in clinical presentation and can be reversed by diet.

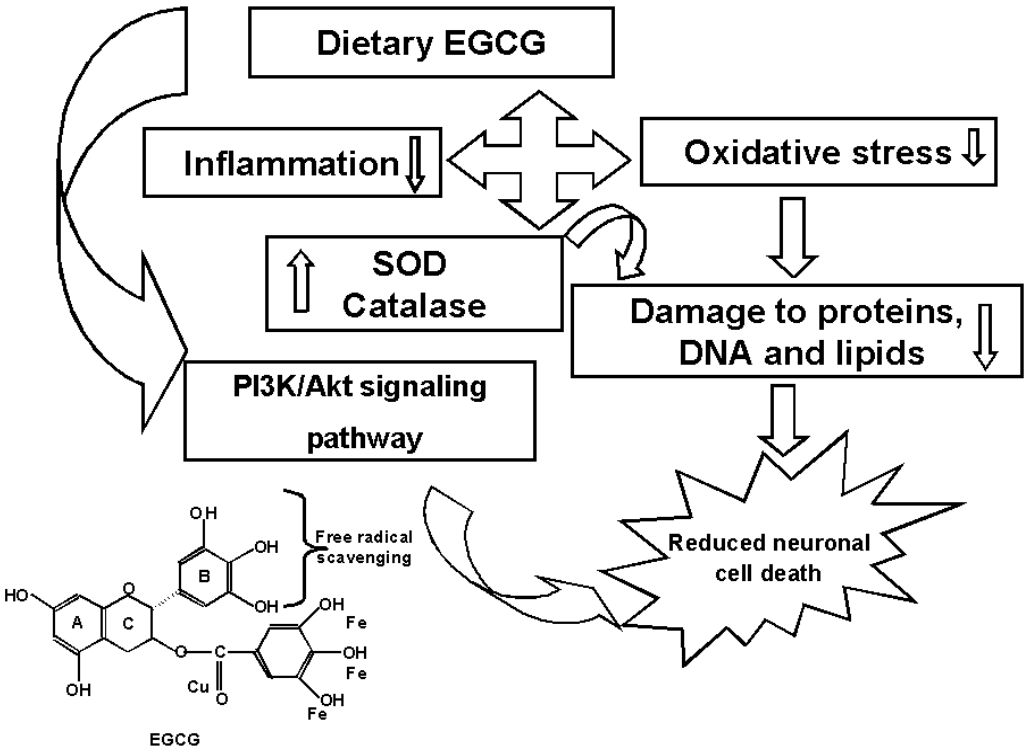

Fig. 2. EGCG's mode of action. Environmental factors such as metals cause oxidative stress, leading to protein, lipid, and DNA damage. EGCG is known to chelate transition metals like Fe and Cu, thereby preventing oxidative stress. EGCG also acts as an anti-inflammatory molecule and increases the activity of SOD and catalase. EGCG induces the PI3K/Akt-signaling pathway, and this pathway has a pivotal role in neuronal cell survival.

DIETARY POLYPHENOLS AND AD

Polyphenols are natural substances that are present in plants, and their quantities vary in leaves, flowers, vegetables, and fruits. Considerable amounts of these compounds, moreover, are present in olive oil and red wine [141]. Among the polyphenols, flavonoids occupy the largest group [27]. The major component of green tea flavanoids, EGCG, for instance, has recently been shown to have neuroprotective functions such as antioxidation, iron chelation, and anti-inflammation [142]. Specifically, the abundant phenolic hydroxyl groups on the aromatic ring confers the antioxidant activity, and the 3-OH group is essential for iron chelating activity of these compounds [143,144]. Similarly, the Mega Natural grape seed polyphenolic extract (GSPE), derived from grape seed, significantly inhibits oligomerization of Aβ and restores the cognitive deterioration [145]. These trends ultimately provide a clue that polyphenols can be good intervention molecule for neurodegeneration.

Tea polyphenols have been found to be potent scavengers of free radicals [146,147]. EGCG contains three heterocyclic rings, A, B, and C, and the free radical scavenging property of EGCG is attributed to the presence of trihydroxyl group on the B ring and the gallate moiety at the 3' position in the C ring. EGCG is also known to chelate transition metal ions like iron and copper [142]. There are two sites where metal ions bind to the flavonoid molecule: 1) o-diphenolic group in the 3',4'-dihydroxy positions in the B ring, and 2) keto structure 4-keto, 3-hydroxy in the C ring of flavonols [143,148]. Further, EGCG is found to have role in elevating the activity of two major antioxidant enzymes, superoxide dismutase, and catalase in the mouse striatum [149]. Finally EGCG treatment has been reported to modulate AβPP processing to Aβ [150]. The mechanisms regarding oxidative stress and its augumentation by EGCG are highlighted in Fig. 2.

WINE AND AD

A number of researchers have explored the relationship between alcoholic beverages and AD [151–155].

Studies have shown that frequent alcohol uptake in rats can result in mitochondrial dysfunction in neurons leading to neurodegeneration [156]. In contrast, it is reported that moderate alcohol uptake is related to a lower risk of clinical stroke [157]. Thus, alcohol may have paradoxical and competing effects in the brain; it lowers the risk of cerebrovascular disease and also likely acts as a neurotoxin. Researchers have shown a relationship between alcoholic drinks and AD [8,151–153,155]. A study of people aged 65 years and older showed that alcohol consumption of one to six drinks a week, regardless of the type of beverage used, lowered the risk of AD compared to abstainers [152]. In another study, people who consumed three servings of alcohol a day had a low risk of AD compared to those who were never exposed to alcohol [151]. An interesting study involving individuals aged 65 years and older found that monthly or weekly intake of wine, but not other alcoholic drinks, was associated with a lower risk of dementia including AD [155,158]. Most of the results obtained in the above studies were not statistically significant, given the small number of elderly people participating in the studies.

However, several epidemiological studies have shown that moderate wine consumption reduces the risk of developing AD [8,155,158,159]. Wine contains antioxidants such as resveratrol, a flavonoid, which is not present in beer or other spirits. Resveratrol occurs in abundance in grapes and red wine [141,160]. The beneficial effect of wine consumption on the neurodegenerative process is therefore attributed to resveratrol [141,160–162], and resveratrol was reported to reduce Aβ production in cell line HEK293 expressing wild type or Swedish-mutant AβPP695 [162]. Additionally, studies indicate the involvement of resveratrol in proteosome clearance of Aβ; decreases in its presence reduce Aβ clearance and reduce toxicity in AD brains. The proteosome is an ubiquitin activated protein quality control system that enzymatically labels, transports, and finally degrades misprocessed and misfolded protein [163]. While a number of possible functions of the proteosome in the regulation of Aβ metabolism have been ascribed to the multicatalytic complex of proteosomes [163], additional studies are needed to understand the role of the proteosome in the clearance of Aβ. There is also a need to understand whether it is specific for the monomer, oligomer, or the protofibril, and this is not clearly known.

No reduction in the activity of γ-secretase mediated-cleavages of AβPP in the presence of resveratrol was found [162]. Thus, it excludes the possibility that resveratrol lowers Aβ by promoting the proteosomal degradation of C99 (C terminal fragment of AβPP upon cleavage by BACE). Recent evidence also suggests that Aβ can be degraded by proteosome-dependent endoplasmic reticulum (ER)-associated degradation. However, ER Aβ represents a small fraction of the total Aβ produced, and it appears to be controlled by ER-associated degradation and not resveratrol. There is no clear-cut indication on the effect of resveratrol on the mechanism of clearance of Aβ levels in the neurons, although resveratrol may have an effect on key players (components) in the Aβ clearance pathway [162]. Resveratrol was also found to interact with other proteins, including members of the sirtuin family. Sirtuins are deacetylases with a role in cellular longevity [164]. It is also known that resveratrol acts as a potent activator of the human sirtuin 1 *in vitro* [165]. Moreover, activation of sirtuin1 by resveratrol has been linked to neuroprotective pathways [165]. Therefore, it would be of interest to understand whether sirtuin mediates the resveratrol-induced decrease of Aβ. However, it is not clear whether a decrease in activity of the proteosome parallels an increase of Aβ levels [166]. Further, it has been shown that resveratrol selectively activates the proteosome in the anti-amyloidogenic pathway [166].

Antioxidant effects of flavonoids also include transcriptional upregulation of antioxidant enzymes such as glutathione synthesizing enzymes. There is also a report interlinking the inhibitory effect of flavonoids on 5-lipoxygenase, which is involved in lipid peroxidation [166]. However, it seems reasonable not to recommend alcohol intake to those who are potentially at risk for abuse and addiction [167]. Figure 3 depicts the importance of resveratrol, in particular, in modulating neurodegeneration. Resveratrol favors phosphorylation in PKC, and this activates the non-amyloidogenic pathway of AβPP cleavage, which leads to reduction in Aβ release. sAβPPα, which is a product of AβPP cleavage, becomes translocated to the nucleus and may induce genes involved in neuroprotection. Resveratrol also nonspecifically stimulates the proteosome, which helps in clearing Aβ and in turn reduces neuronal cell death. The oral ingestion of resveratrol by rodents and humans showed that resveratrol absorbs readily into the system, appearing in plasma (total resveratrol which includes both modified and unmodified resveratrol) [168–173]. The major drawback in using resveratrol in modulation of neurodegeneration is its low bioavailability [174]. It has been demonstrated that mice fed with feasible dosages of resveratrol for 45 days either showed the presence of resveratrol or

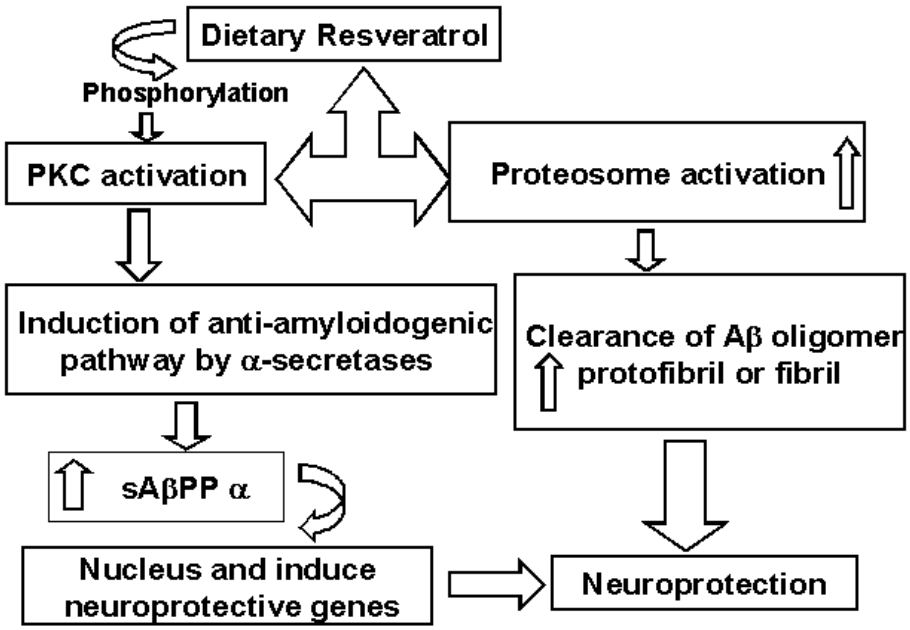

Fig. 3. The role of resveratrol in modulating neurodegeneration. Resveratrol favors phosphorylation in PKC. This activates the non-amyloidogenic pathway of AβPP cleavage, leading to reduction in Aβ formation. sAβPPα, which is a product of AβPP cleavage, may get translocated to the nucleus and may modulate the genes. Resveratrol also nonspecifically stimulates proteosomes, which helps in clearing Aβ. All these events favor neuronal cell survival.

its metabolites in the brain indicating bioavailability to brain [174].

As stated above, the Mega Natural grape seed polyphenolic extract, a commercial formulation of polyphenolics derived from grape seed, significantly inhibited oligomerization of Aβ [175]. The extract was also shown to have the ability to inhibit the cytotoxicity of Aβ_{40}/Aβ_{42} in PC12. Furthermore, the extract significantly restored the cognitive deterioration in Tg2576 transgenic mice [175].

DIETARY SPICES AND AD

The Indian diet is rich in spices including red chili, coriander, turmeric, etc. Turmeric, a yellow curry spice, is widely used as a food preservative and herbal medicine in India [176], and notably, the prevalence of AD patients in India between 70 and 79 years of age is 4.4 fold less than that of the United States [177]. We hypothesize that this is partially attributed to turmeric consumption in India as a result of its curcumin contents.

Inflammation of the brain due to injury or disease is mediated by microglia [178]. Brain inflammation is also mediated by activation of the complement system. AD involves a chronic central nervous system inflammatory response that is associated with both head injury and Aβ pathology [179]. For example, prolonged use of non-steroidal anti-inflammatory drugs, statins and ibuprofen, have reduced inflammation in the AD brain [180]. The main disadvantage of the use of non-steroidal anti-inflammatory drugs in AD is their toxicity to the gastrointestinal tract, liver, and kidney. Non-steroidal anti-inflammatory drugs are also found to inhibit cyclo-oxygenase I [181,182]. Researchers are involved in finding alternatives to non-steroidal anti-inflammatory drugs. One such phenolic antioxidant alternative is curcumin, derived from yellow curry spice, which is found to have an anti-inflammatory effect. Curcumin is a potent free radical scavenger, better than vitamin E, and it provides protection against lipid peroxidation [183] and acts as a scavenger of nitric oxide radicals [184]. Curcumin also decreases the overall insoluble amyloid plaque burden in an animal model [184]. In an intraventricular Aβ infusion rat model, dietary curcumin reduced an isoprostane index of oxidative damage, amyloid plaque burden, and Aβ-induced spatial memory deficits in the Morris water maze [185]. Studies have shown that curcumin reduces inflammation and oxidative damage in the brain of Tg2576 AβPPSw transgenic mice [186, 187]. The low, nontoxic doses of curcumin decreases the levels of soluble and insoluble Aβ and plaque

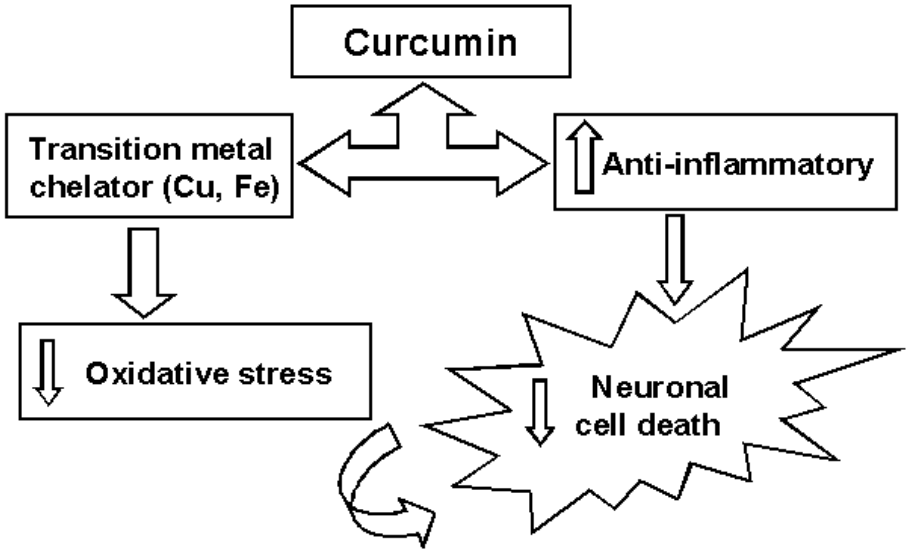

Fig. 4. The diverse effects of curcumin in combating neurodegeneration. Curcumin has multiple biological effects. It chelates transition metals (Fe and Cu) and also acts as an antioxidant and anti-inflammatory molecule. Curcumin may protect the cells from oxidative stress.

burden in many affected brain regions. Moreover, cell culture experiments with HEK293 cells indicated that fibrillar Aβ are destabilized by nordihydroguaiaretic acid [188]. Thus, it may be reasonable to speculate that bioactive molecules like curcumin, rosmanaric acid, and nordihydroguaiaretic acid could possibly prevent the onset of AD, not only by scavenging reactive oxygen species, but also by inhibiting fibrillary Aβ deposition in the brain.

Curcumin also protects mouse brain from oxidative stress caused by 1-methyl-4-phenyl-1, 2,3,6-tetrahydropyridine [189] and has also been reported to attenuate 3-nitropropionic acid-induced neurotoxicity [190]. In rat brain, curcumin protects against lead- and cadmium-induced lipid peroxidation as well as lead-induced tissue damage [191]. Figure 4 highlights the diverse effects of curcumin in combating neurodegeneration. Curcumin has multiple biological effects. It chelates transition metals (Fe and Cu) and acts as an antioxidant and anti-inflammatory molecule. It also acts as an antioxidant by scavenging reactive oxygen species, which will prevent oxidative damage to macromolecules, thereby reducing neuronal cell death.

DIET AND GENES IN AD

Diet-genetic interactions may play an important role in healthy aging [38]. Lifestyles include dietary patterns during early, middle, and adult life that may influence the risk of brain disorders. Genetic factors include mutations in genes like amyloid precursor protein, presenilin 1, and presenilin 2 that are risk factors and cause early onset events in AD. Research related to the effect of dietary molecules on the expression of AβPP gene and its processing to produce Aβ has not been done. The scope of the dietary molecules on AD can also be extended for stimulating Aβ clearance mechanisms of cells. APOE ε4 is the most important genetic risk factor for AD and cardiovascular diseases [192,193]. Dietary molecules may affect genes independently or through signaling molecules. APOE ε4 also been associated with cognitive decline [194,195]. The genotype APOE ε4 has a differential effect on fat consumption in different stages of human life. Importantly, there are limits to commenting on dietary-gene interactions and more data is required to arrive at conclusion.

DIETARY RECOMMENDATION FOR AD PATIENTS

Recommending a diet for AD patients must be done by careful clinical observations. To date, there is no report of a perfect diet for the different categories of AD patients such as those with initial onset, mild cognitive decline and final stage AD. A clear problem for patients even in the early stages of AD is weight loss and nutritional deficiencies as discussed earlier. Indeed weight loss may be an early predictor of the onset of

Table 1
Studies on diet and neurochemical effects

Sl No	Brain food	Active principle	Effect/function	References
1	Blueberries	flavonoids	Cognition, memory, and coordination	[197]
2	Fish	Omega-3 fatty acids (DHA and EPA)	Reduces amyloid pathology by 70% (mice)	[73]
3	Turmeric	curcumin	Antioxidant, anti-inflammatory, anti-amyloid	[186]
4	Green tea	EGCG (a polyphenol)	Antioxidant, anti-inflammatory	[142]
5	Red wine	resveratrol	Antioxidant, anti-inflammatory	[62]
6	Ginkgo biloba	flavonoids and terpenoids	Antioxidant	[198]
7	Tomato	Ferulic acid	Antioxidant	[199]
8	Amla	Vitamin C	Antioxidant	[200]
9	Meat	Vitamin E	Antioxidant	[27]
10	Fruits and vegetables	vitamin A (retinol)	Antioxidant	[27]

AD related dementia. Many of the recommendations that may be made at this late stage need to be focused towards maintaining the health of the patient. It is certainly important to examine the patient for nutritional deficiencies and identify a good healthy diet to ensure good physical health. Certain vitamins such as B12 and folic acid need to be replaced to ensure that the dementia is not partially due to this deficiency. AD patients also have altered dietary preferences and dysphagia and tend to show additional weigh loss in their late stages, where the caregiver needs to be adequately counseled to reduce frailty. Nutritional information and support of family are probably the best strategies to prevent adverse eating behavior in AD to improve the patients and caregiver's quality of life. Inadequate attention has been paid to understanding the specific alterations in food intake in AD [196]. Indeed, at present the only advice that one may provide is to ensure adequate nutrition, physical exercise, relaxing mild treatments to reduce agitation, and enrichment of environment with music, dance etc.

Prior to the onset of dementia, there is great hope that nutritional intervention may lead to improvements in general health and prevent or delay AD. Many of the promising dietary supplements are listed in Table 1. In addition, the rule of thumb appears to be high levels of physical and mental activity coupled with dietary moderation with care to ensure the lack of nutritional deficiencies. There is a need to identify the stages of progression of AD that are associated with disturbed food intake patterns; in depth research is required to further such an understanding.

ACKNOWLEDGMENTS

Our sincere thanks to Dr. V Prakash, Director, CFTRI, Mysore for his support. BNR is thankful to the University Grant Commission, India, for providing a fellowship. The authors are thankful to DBT for financial support through a research grant. We also thank NIH for grants AG022103 and AG023055.

Authors' disclosures available online (http://www.j-alz.com/disclosures/view.php?id=57).

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