

Review Article

Caloric Intake, Dietary Lifestyles, Macronutrient Composition, and Alzheimer' Disease Dementia

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Received 1 December 2010; Accepted 12 May 2011

Academic Editor: Mikko Hiltunen

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Alzheimer's disease is a devastating neurodegenerative condition currently affecting over 5 million elderly individuals in the United States. There is much evidence suggesting that certain dietary lifestyles can help to prevent and possibly treat Alzheimer's disease. In this paper, we discuss how certain cardiovascular and diabetic conditions can induce an increased susceptibility for Alzheimer's disease and the mechanisms through which this occurs. We further discuss how the consumption of certain foods or food components can help to reduce one's risk for Alzheimer's disease and may possibly be developed as a therapeutic agent.

1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by a progressive decline in memory functions, which has become a growing public health concern. This condition of clinical dementia was first described by Alois Alzheimer in 1907, and ever since, the incidence of AD has increased exponentially. There are presently 5 million Americans affected with AD, and the estimated annual health care cost is almost 100 billion dollars. Further, due to the expected increase in the number of individuals 65 years or older, it has been estimated that the total incidence of AD will quadruple by the year 2050 [1].

As there is presently no cure for this devastating condition, there is an urgent need to find a means of preventing, delaying the onset, or reversing the course of AD. Recent research has provided evidence that certain dietary lifestyle choices can help to prevent Alzheimer's disease. This area of research has been quite exciting in light of the fact that delaying the onset of AD by just five years could cut its incidence in half.

In this paper, we first discuss the major pathological features of AD clinical dementia, followed by an examination of research on certain dietary factors that have been found to influence AD. These dietary factors include calorie, fat, and

glucose/sugar intake, in addition to the inclusion of foods like fish, certain fruits and vegetables, plant extracts, spices and red wine, or polyphenol-rich foods in one's diet.

AD is pathologically characterized by the depositions of beta-amyloid aggregates in extracellular spaces and cerebral vasculatures as well as intracellular depositions of aggregated tau protein [2]. The "amyloid cascade hypothesis" is a popular model of AD pathogenesis and most of the autosomal dominant familial AD cases are caused by mutations in the amyloid precursor protein (APP), presenilin 1, or presenilin 2, which lead to increased generation of beta-amyloid ($A\beta$) peptides. However, the majority of the AD cases are sporadic. Cause(s) of sporadic AD are largely unknown. Multiple risk factors may contribute to the onset of sporadic AD. These risk factors include genetic risk factor such as the apolipoprotein E (APOE) genotype, as well as nongenetic and environmentally modifiable factors, including dietary, cardiovascular risk factors, physical and intellectual activities, and environment factors. As such, these factors have been generally considered as potential targets of intervention for AD prevention and therapy.

1.1. Alzheimer's Disease Neuropathology. AD is characterized in the brain by accumulated extracellular β -amyloid ($A\beta$) plaques and intracellular neurofibrillary tangles composed of

abnormally hyperphosphorylated microtubular tau proteins. The manifestation of AD clinically is a progressive loss of cognitive abilities, including deficits in memory and planning. Neurotoxic $A\beta$ is known to exist in multiple assembly states, which often result in varying pathophysiological effects. Additionally, although $A\beta$ is classically understood to be deposited extracellularly, there is new evidence in mice and humans that $A\beta$ peptides can also accumulate intraneuronally [3]. $A\beta$ species are generated from the ubiquitously expressed amyloid precursor protein (APP) through sequential proteolysis by β - and γ -secretases [4–6]. Although the 40-amino acid form of $A\beta$ ($A\beta_{1-40}$) is considered to be the major secreted species in AD, the 42-amino acid form of $A\beta$ ($A\beta_{1-42}$), which contains two additional residues at its carboxyl terminus, is thought to initiate AD pathogenesis [7]. In addition, tau proteins in the brain (most particularly hyperphosphorylated tau), which aggregate into paired helical filaments and deposit as intracellular neurofibrillary tangles, [8, 9], are also considered to be a major pathology associated with Alzheimer's disease. Researchers posit that abnormal hyperphosphorylation of tau leads to the sequestration of normal and hyperphosphorylated tau in microtubules, leading to alternations in the healthy functioning of tau in the brain (including changes in axon transport and microtubule stability and polymerization [10, 11]). As $A\beta$ species and tau neurofibrillary tangles are the major hallmarks of AD neuropathology, research on therapies or preventions for AD are often geared toward attenuating or treating these neuropathologies.

In addition to $A\beta$ and tau pathologies, mitochondrial functions also play a major role in AD clinical dementia [12]. Mitochondria regulate energy metabolism in cells and contribute largely to cell life or death (apoptosis). In the presence of increased $A\beta$ content in the brain, mitochondria increase the generation of reactive oxygen species (ROS), which function as damaging agents and as signaling molecules. Highly reactive ROS, in fact, unleash a mechanism involving the liberation of cytochrome c, leading to neuronal apoptosis [13, 14]. In human AD patients, positron emission tomography (PET) imaging assessments have suggested that the AD brain is characterized by impaired mitochondrial glucose metabolism, leading to neuronal hyperglycemic conditions [15]. In light of this evidence, controlling mitochondrial glucose/energy metabolism in the brain has also been of high interest to AD researchers for the prevention and treatment of AD.

2. Obesity and the Metabolic Syndrome in AD

High-fat diets and sedentary lifestyles have become major concerns throughout the world. They have led to a growing incidence of obesity, dyslipidemia, high blood pressure, and hyperglycemic conditions, known collectively to be components of metabolic syndrome [16]. These health conditions are well known to develop along with, or be precursors of, atherosclerosis, cardiovascular disease, and diabetes. Recent studies have found that most of these disorders can also be linked to an increased risk of AD. Of note, accumulating evidence suggests a mechanistic link between cholesterol

metabolism in the brain and the formation of amyloid plaques in AD development [17, 18].

Epidemiological studies have demonstrated that individuals with obesity and diabetes have a fourfold increased risk for AD. Health risks associated with obesity, including evidence that obesity may causally promote the AD degenerative process, are of high concern for public health. By the beginning of the twenty-first century, the fraction of Americans considered to be obese reached "epidemic" levels, according to a study published in [19]. This study, carried out between 1991 and 1998, observed a steady increase in weight in all 50 states, across genders, age groups, races, and educational levels, and occurring regardless of smoking status. This study found that obesity had increased from 12.0% in 1991 to 17.9% in 1998. Likewise, national survey data has shown that between 1976–1980 and 1988–1994, the age-adjusted prevalence of obesity increased by 8 percentage points, from 14.5% to 22.5%, in the US adult population ages 20–74 years [20].

Several major studies have been conducted in humans to explore the relationship between obesity and the brain. Recently, Pannacciulli and colleagues [21] explored the association between body fat and regional alterations in brain structure using voxel-based morphometry (VBM) imaging (based on high-definition 3D magnetic resonance imaging [MRI]). Compared to lean subjects, obese individuals were found to have significantly lower gray matter density in the postcentral gyrus, frontal operculum, putamen, and middle frontal gyrus, indicating differences in the brain regulation of taste, reward and behavioral control. Additionally, Whitmer and colleagues [22] evaluated the possible association between obesity (as measured by body mass index (BMI) and skinfold thickness) in middle age and risk of dementia in later life in a large scale, multiethnic population-based cohort. Findings revealed that obese individuals (BMI > 30) in middle age had a 35% higher risk for dementia compared to normal weight individuals (18.6 < BMI < 24.9), independent of other comorbid conditions. Additionally, Balakrishnan and colleagues [23] investigated the association between blood plasma $A\beta$ levels (which promote AD development), BMI, and fat mass (FM) in healthy adults and found significant correlations of BMI and FM with plasma $A\beta_{1-42}$ levels and also noted that the presence of certain proteins known to play a role in inflammation, cardiovascular disease, and type 2 diabetes strengthened these correlations.

Researchers have also investigated the role of leptin, a protein hormone secreted in fat cells associated with obesity (which regulates appetite and metabolism), in AD pathogenesis. In pathological conditions of aging, such as in AD, it has been demonstrated that the transport of leptin across the blood brain barrier (BBB) is significantly impaired, in particular, by the downregulation of megalin, a protein to which leptin must bind in order to enter the brain [24]. Leptin has also been shown to reduce β -secretase activity in neuronal cells, possibly by altering the lipid composition of membrane rafts, and thereby affecting $A\beta$ generation. In fact, chronic administration of leptin actually reduced $A\beta$ load in the brains of AD transgenic mice, suggesting the potential

of leptin as a treatment for AD [25] and providing further support for the hypothesized link between obesity and AD.

3. Calorie Intake and Caloric Restriction

Research has demonstrated that caloric intake (among other nongenetic factors) influences one's risk for AD, and, accordingly, that curbing obesity/calorie intake might play an important role in delaying the AD degenerative process. Clarifying the mechanisms through which caloric intake may ultimately influence AD neuropathology, and how caloric restriction (CR) may exert anti- β -amyloidogenic activities, may provide new avenues for designing preventive and/or therapeutic lifestyle strategies for AD and other neurodegenerative conditions.

The hypothesized preventive effects of CR on the development of mild cognitive impairment (MCI) or AD are supported by epidemiological evidence indicating that individuals who habitually consume fewer calories have a reduced incidence of AD [26, 27]. Additionally, studies have demonstrated that CR is one method by which one can mitigate the risk factor presented by elevated plasma homocysteine levels (which increase with age) for AD. Specifically, as high homocysteine levels render neurons to be more vulnerable by impairing DNA repair mechanisms (and thereby promoting cell death), lowering homocysteine levels through CR could potentially help to maintain the brain's neuroprotective abilities and help prevent against AD [28].

Halagappa and colleagues [29] tested the hypothesis that two different dietary energy restriction regimens—40% calorie restriction (CR) and intermittent fasting (IF)—could protect against cognitive decline in a transgenic mouse model of AD and found that both regimens ameliorated age-related cognitive impairments but could not directly link the observed effects to $A\beta$ and tau pathologies. Further, Wu and colleagues [30] investigated the effects of CR for 4 months on different AD phenotypes in another mouse model, finding that CR diets improved cognitive impairments in treated mice based on improved scores on assessments of novel object recognition and contextual fear conditioning memory. Further histological and biochemical analyses revealed that CR actually attenuated ventricle enlargement, caspase-3 activation and astrogliosis and reduced the induction of tau hyperphosphorylation. Importantly, DNA microarray analysis in this study also demonstrated that CR could increase the expression of neurogenesis-related genes and decrease the expression of inflammation-related genes in the hippocampus of the mice, indicating that CR could induce neuroprotective activity in the brain.

In accordance with this line of work, we initiated a series of studies to investigate whether AD pathogenesis can be prevented by reducing calorie intake to levels appropriate for cardiac health. At the beginning of this endeavor, although evidence had supported a possible neuroprotective role of CR in neurodegeneration, there had been no information regarding whether CR could attenuate AD neuropathology until recently.

We explored whether a clinically acceptable weight reduction/CR regimen, based on an approximately 30%-reduced carbohydrate intake, could attenuate AD neuropathology and possibly mitigate preexisting amyloid neuritic pathology (by a reduction in plaque size) resulting in the recovery of amyloid-associated neuritic dystrophy as a function of time in Tg2576 AD-type mice [31]. In this study [32], 3-month old Tg2576 mice, which developed AD-type amyloid neuropathology at 8–10 months of age, were fed with a daily low-carbohydrate (low-carb) diet for 9 months, resulting in 30% lower caloric intake compared to age- and gender-matched control mice fed *ad libitum* (AL) with a standard laboratory rodent diet (dietary content of protein, fat, cholesterol, vitamins, and minerals were identical across both mice groups). We found that the low-carb/CR diet in mice resulted in body weight stabilization, 3-fold lower ependymal fat pad weight, and improved glucose tolerance responses compared to the AL-fed mice at 9 months of age. This finding was consistent with clinical evidence indicating that low-carb/CR diets considerably improve abnormal glucose control and obesity [33–35], which are risk factors for diabetes and AD [27, 36]. Moreover, when examined for AD-type neuropathology, we found that the CR intervention almost completely prevented cortical and hippocampal AD-type amyloid plaque (lower $A\beta_{1-40}$ and $A\beta_{1-42}$ concentrations) development relative to the AL-fed group. We next proceeded to explore APP processing and $A\beta$ peptide generation in the CR- and AL-fed mice, and, consistent with our previous evidence, we confirmed decreased levels of $A\beta_{1-40}$ and $A\beta_{1-42}$ in CR-fed compared to AL-fed mice. Further investigation revealed that γ -secretase activity had no involvement in the anti-amyloidogenic activity observed but that α -secretase activity (which promotes the nonamyloidogenic processing of APP) likely played a role in the observed benefits of CR treatment in mice. As α -secretase cleavage of APP is known to involve the release of a soluble and neuroprotective form of APP (sAPP α), it is possible that CR may not only promote a non-amyloidogenic pathway in the brain, but also may promote brain repair activities as a result of sAPP α neurotrophic function [37].

Current therapeutic approaches to AD are aimed at preventing the generation of amyloidogenic $A\beta$ peptides, and for this reason, β - and γ -secretase activities required for the formation of $A\beta$ peptides are central targets in the development of therapeutic agents in AD [38]. However, it has been difficult for scientists to find safe and selective β - and γ -secretase inhibitors, as these activities are vital in the processing of other cellular substrates [38]. Our studies collectively revealed that CR dietary intervention benefitted AD mice by promoting α -secretase activity, and thereby inhibiting the generation of high molecular weight $A\beta$ peptides.

3.1. Sirtuins (SIRT1) in CR-Mediated AD Prevention. Sirtuins are class III histone deacetylases (HDAC) known as silent information regulators, which serve to catalyze deacetylation reactions in an NAD(+)-dependent manner. Often called “longevity” genes, sirtuins regulate important cell functions by deacetylating histone and nonhistone targets. Activation of sirtuins is known to extend lifespan by promoting healthy

aging in a variety of species and by protecting crucial tissues in the body, including those in the heart and brain. In mammalian systems, sirtuin activators protect against axonal degeneration, polyglutamine toxicity, and microglia-mediated $A\beta$ toxicity, suggesting the potential therapeutic value of sirtuin activation in patients with AD [39]. SIRT1 has been found to protect against microglia-dependent $A\beta$ toxicity by inhibiting NF- κ B signaling in the brain [40].

In 2006, we reported for the first time that promotion of SIRT1-mediated deacetylase activity may be a mechanism through which CR influences AD-type amyloid neuropathology. CR by 30% reduced carbohydrate intake was found to prevent amyloid neuropathology in young-adult Tg2576 mice, which may have been mediated in part through mechanisms involving activation of mammalian SIRT1 [41]. Consistent with this evidence in Tg2576 mice, we confirmed this finding in a new animal model by showing that a similar 30% CR regimen in squirrel monkeys coincided with a significant reduction in $A\beta_{1-40}$ and $A\beta_{1-42}$ peptide content in the brain, which inversely correlated with the elevation of SIRT1 protein concentrations, relative to AL-fed monkeys [42]. In view of the fact that several studies in squirrel monkeys have been successfully used to provide important human physiological and biological information at organism, tissue, cellular, and molecular levels, these studies in squirrel monkeys strongly support our hypothesis that clinically applicable CR regimens in humans might be effective in preventing amyloid neuropathology and possibly MCI and AD.

Collectively, our studies on CR in AD mice and in squirrel monkeys revealed that certain experimental CR dietary regimens may promote, attenuate, or even partially reverse features of AD [32, 41, 42]. In our studies, we found that high caloric intake, in particular of saturated fat, promotes AD-type β -amyloidosis and that reducing carbohydrate intake may actually prevent it, possibly through SIRT1-mediated response mechanisms.

4. The Role of Insulin in AD

Insulin and insulin signaling have been suggested to play a role the pathophysiology of AD [43, 44]. In population-based studies, individuals with type 2 diabetes mellitus are at an increased risk for cognitive impairment, dementia, and neurodegeneration. Mechanisms through which diabetes presents a risk factor include glycemia, insulin resistance, oxidative stress, advanced glycation endproducts, inflammatory cytokines, and microvascular and macrovascular disease [45]. The principal defect in type 2 diabetes is insulin resistance, leading to insulin deficiency. The islet of Langerhans (in the pancreas) in type 2 diabetes is characterized by β -cell loss and islet amyloid derived from islet amyloid polypeptide (IAPP) [46–48], a protein co-expressed and secreted with insulin by β -cells. As with $A\beta$ peptides, IAPP spontaneously forms into amyloid aggregates in an aqueous environment [49]. Additionally, as with AD, the incidence of type 2 diabetes strongly increases with age. Borderline diabetes is also associated with increased risks of dementia and AD, independent of whether one develops diabetes in later life, and may

interact with severe systolic hypertension to multiply one's risk for Alzheimer's disease [50]. These findings implicate a close biological relationship between type 2 diabetes and AD.

In addition to complications affecting the eyes, kidneys, heart, blood vessels and nerves, diabetes mellitus is associated with damage to the central nervous system (CNS) and cognitive deficits [51, 52]. Impairments in learning and memory have been documented in both types 1 and 2 diabetes. CNS deficits range from moderate to severe, depending on the quality of glycemic control, and involve mainly verbal memory and complex information processing [53–55]. Furthermore, it has been shown that insulin affects several brain functions including cognition and memory, and several studies have established links between insulin resistance, diabetes mellitus and AD [56]. Recent evidence indicates that insulin regulates the metabolism of $A\beta$ and tau proteins [57–59]. It has also been suggested that desensitization of neuronal insulin receptors and certain signaling events in AD could lead to reduced acetylcholine levels and cerebral blood flow, resulting in chronic and increasing deficits in oxidative metabolism [60]. Additionally, insulin is known to facilitate the hepatic clearance of plasma $A\beta_{1-40}$ by intracellular translocation of low-density lipoprotein receptor-related protein 1 (LRP-1) to the plasma membrane in hepatocytes [61].

Alzheimer's disease (AD) is associated with major impairments in insulin and insulin-like growth factor (IGF) gene expression and signaling in the brain, which increase with severity of dementia and deficits in energy metabolism and acetylcholine homeostasis. This coexistence of insulin/IGF deficiency and resistance in the brain suggests that AD may represent a brain-specific form of diabetes (i.e., type 3 diabetes). This hypothesis is supported by findings from de la Monte and colleagues [62] in an experimental animal model in which intracerebral streptozotocin (ic-STZ) was used to deplete brain, and not pancreatic, insulin. The ic-STZ treatment produced brain-specific insulin depletion and insulin resistance and was associated with progressive neurodegeneration sharing many features in common with AD. They demonstrated that early treatment with peroxisome-proliferator activated receptor agonists can effectively prevent ic-STZ-induced neurodegeneration and its associated deficits in learning and memory and that the observed effects were mediated by increased binding to insulin receptors, reduced levels of oxidative stress and tau phosphorylation, and increased choline acetyltransferase expression in the brain, suggesting potential therapeutic efficacy of insulin sensitizing agents in AD.

4.1. Diabetogenic Diets and AD Amyloid Pathology. There is *in vitro* evidence that insulin itself may significantly promote the generation of extracellular amyloidogenic $A\beta$ peptides through mechanisms that involve accelerated APP/ $A\beta$ trafficking from the trans-Golgi network (a major cellular site for $A\beta$ generation) to the plasma membrane [63]. While this evidence tentatively suggests that abnormal carbohydrate metabolism might play an important role in AD through mechanisms that involve $A\beta$ peptide generation, experimental studies also suggest that insulin resistance may promote AD amyloid neuropathology in Tg2576 mice, possibly by

limiting A β degradation via competition with insulin for degradation by the insulin-degrading enzyme (IDE) [64], a zincmetallopeptidase that preferentially cleaves proteins with a propensity to form β -pleated sheet-rich amyloid fibrils, such as monomeric A β peptides [64].

Recent evidence suggests a role for insulin even in normal memory function, thereby supporting the hypothesis that insulin by itself affects mechanisms related to neuronal activity and cognitive function. Of particular interest to our research group, chronic hyperinsulinemia and insulin resistance, or reduced insulin effectiveness, has been demonstrated to negatively influence memory [65, 66]. For example, Hoyer [60] proposed that low concentrations in circulating insulin in the CNS, along with reduced expression of insulin receptors and subsequent altered downstream signaling in AD, would ultimately lead to reduced levels of acetylcholine and a corresponding decrease in cerebral blood flow.

Based on this evidence, and the fact that type 2 diabetes appears to be associated with an increased relative risk for AD [60, 63, 65–67], we recently explored in our laboratory the role of experimental type 2 diabetes in a Tg2576 mouse model of AD amyloid neuropathology. We found that a diabetogenic diet, resulting in elevated circulating levels of insulin, promoted amyloidogenic A β_{1-40} and A β_{1-42} peptide generation and amyloid plaque burden in the brain of Tg2576 mice. This also corresponded with increased γ -secretase activities and decreased IDE activities. Moreover, the increased AD-type amyloid neuropathology also coincided with increased impairments in spatial memory function [68]. Further exploration of this interrelationship between insulin resistance and brain amyloidosis revealed a functional decrease in insulin receptor- (IR-) mediated signal transduction in the brain, as suggested by decreased IR β -subunit (IR- β Y^{1162/1163}) autophosphorylation and reduced phosphatidylinositol 3 (PI3)-kinase/pS⁴⁷³-AKT/protein kinase- (PK-) B in these same brain samples [68]. This study collectively suggests that diet-induced insulin resistance in AD mice may significantly promote AD-type amyloidosis in the brain through mechanisms involving the elevation of γ -secretase activity as a result of impaired IR signaling and also that type 2 diabetes may contribute to AD amyloid pathology by attenuating the degradation of A β peptide pathways associated with IDEs.

Interestingly, a later study by Li and colleagues [69] explored whether AD-type pathological changes in the brain occur in two experimental rat models which develop type 1 and type 2 diabetes. They found accumulations of β -amyloid and phosphor-tau in these mice and that these pathologies were associated with neurite degeneration and neuronal loss. Changes in the rat model of type 2 diabetes were more severe and appeared to be associated with insulin resistance and possibly hypercholesterolemia. Additionally, Huang and colleagues [70] found that compared to normal mice, a mouse model of hyperglycemia was more vulnerable to β -amyloid oxidative stress. These findings further support the role of insulin and insulin resistance in AD neuropathology and provide evidence that preventing diabetic conditions may in turn help to prevent AD dementia.

5. Hypertension and AD

Several studies have demonstrated an association between high blood pressure and AD [71–73]. It has been suggested that hypertension can increase one's risk for AD by potentially causing cerebrovascular disease or changes in blood vessel walls (which could lead to hypoperfusion, ischemia, and hypoxia), among other conditions, which can potentially initiate the pathological degenerative AD process. Additionally, subclinical AD has also been suggested as a risk factor for high blood pressure; thus, similar biological mechanisms may be involved in the pathogenesis of these two conditions [74].

The relationship between cognitive function and antihypertensive drug therapy has been investigated in several studies of hypertensive elderly human patients. For example, Guo and colleagues [75] found that a combination of certain calcium channel and β -adrenergic blockers used as antihypertensive agents protected elderly individuals from developing AD. Similarly, other studies have demonstrated that certain calcium channel blockers, such as dihydropyridine [76] and nitrendipine [77], decreased the incidence of AD in hypertensive individuals. Further, it has also been found that antihypertensive drugs that are K⁺-sparing diuretics, in particular, reduce the risk of AD in elderly individuals with hypertension [78]. Moreover, it was demonstrated that antihypertensive agents that cross the BBB and affect the rennin-angiotensin-aldosterone system (including perindopril or losartan), or brain calcium metabolism (like nitrendipine), provide additional protection against cognitive decline in addition to blood pressure control. All of these studies suggest a neuroprotective effect of certain antihypertensive agents.

In light of these findings, animal studies in our laboratory have shown that the application of certain antihypertensive drugs can improve cognition in animal models of AD. We conducted a high-throughput drug screening of 55 commercially available antihypertensive drugs and found 7 candidate agents that significantly reduced AD-type A β accumulation in the brains of Tg2576 mice. Of these 7 drugs, we found that valsartan, an angiotensin receptor blocker, attenuated the oligomerization of A β into high-molecular-weight (HMW) oligomeric peptides (known to be involved in cognitive deterioration) *in vitro* and reduced the content of soluble HMW oligomeric A β in the brain in preventive studies. Additionally, we also found that valsartan, delivered at a dose 2-fold lower than the equivalent clinical dosage used in humans for hypertension, significantly attenuated the development of A β -mediated cognitive deterioration [79]. Another *in vitro* study in this line of investigation revealed that the antihypertensive drugs furosemide, nitrendipine, and candesartan cilexetil prevented A β_{1-40} and A β_{1-42} oligomerization and that furosemide in particular dissociated preaggregated A β_{1-42} oligomers; follow-up studies revealed that short-term treatment with furosemide in Tg2576 mice resulted in reduced A β content in the brain [80]. Most recently, we have investigated the potential beneficial effects of carvedilol, a nonselective α/β -adrenergic receptor blocker used to treat hypertension, on AD pathogenesis and treatment in two AD

mouse models. We found that chronic oral treatment with carvedilol significantly attenuated brain contents of oligomeric A β and cognitive deterioration in two mouse models of AD (the Tg2576 model of β -amyloidosis and TgCRND8 model of tauopathy), which coincided with improvements in neuronal transmission and the maintenance of less stable "learning" thin dendritic spines (associated with learning and memory functions) in the brains of these AD mice [81]. A related study in our laboratory investigated the benefits of carvedilol in AD on an electrophysiological parameter of learning and memory, long-term potentiation (LTP), as assessed in the TgCRND8 mouse model [82]. In this *ex vivo* study, hippocampal slices from carvedilol-treated TgCRND8 mice chronically treated with carvedilol showed improved basal neurotransmission and improved LTP, relative to slices from nontreated TgCRND8 mice, indicating that carvedilol improves neuroplasticity in this mouse model of AD.

Collectively, these studies suggest a clear link between hypertensive conditions and AD and, importantly, that anti-hypertensive agents may benefit AD. In turn, these studies also indicate that taking dietary precautions to prevent hypertension may, in turn, reduce one's risk for AD.

6. The Link between Dietary Choices and AD

A large area of research in the field of neurodegeneration has been focused on the role of specific foods and food components in the neurodegenerative process. Luchsinger et al. [65, 66] posited that taking nutritional supplements alone (e.g., carotenoids versus carrots) might not be as effective as whole foods in providing nutrients, perhaps because the *interaction* of nutrients within whole foods or certain dietary patterns might contribute largely to any food's benefit. As an example, one study [83] demonstrated that plant-based low-fat diets might be superior to low-fat diets containing little plant-based food intake (e.g., lower consumption of fruits, vegetables, nuts, etc.), even if the two diets have identical contents of fat, protein, carbohydrates, and cholesterol. The authors further noted that the beneficial effect of low-density lipoprotein (LDL) cholesterol in one's diet should not be underestimated.

One food of high interest in the AD prevention field has been fish. For example, researchers have investigated the benefits of certain omega-3 fatty acids found in fish and fish oils, specifically docosahexaenoic acid (DHA) and eicosapentaenoic acid, which have been shown to affect psychiatric and behavioral symptoms in AD, as demonstrated in animal studies and in human epidemiological studies [84, 85]. In this line of research, Lim and colleagues [86] demonstrated that DHA-enriched diets significantly reduced AD-type amyloid neuropathology by approximately 70%, including a decrease in A β_{1-42} levels, compared to low-DHA or control diets, in a mouse model of AD. Moreover, Hashimoto and colleagues [87] studied the effects of DHA on AD-type pathology following 12 weeks of DHA administration and found that DHA treatment led to a decreased number of working memory errors in A β -infused rats in addition to an increase in corticohippocampal DHA levels and in the molar ratio of DHA/arachidonic acid, suggesting that DHA

treatment attenuated impaired spatial cognition and learning abilities. They further demonstrated that DHA suppressed increases in levels of lipid peroxide and reactive oxygen species in the cerebral cortex and hippocampus of these A β -infused rats, which suggested that DHA may also increase antioxidative defenses. These findings collectively demonstrated DHA's potential as a therapeutic agent in AD.

Another area of interest to researchers has been the benefits of certain plant extracts and spices in AD. In traditional Asian medicine, various leaves, fruits, barks, roots, and so forth have been used as agents to improve memory functions. In Ayurvedic medicine (a traditional system of Indian medicine), for example, *Bacopa monnieri*, *Centella asiatica*, *Withania somnifera*, *Glycyrrhiza glabra*, *Acorus calamus*, and *Embllica officinalis* have been considered to enhance one's memory. Based on this notion, various laboratories have tested some of these memory-enhancing compounds in mouse models of AD. Mulberry leaf, for example, has been shown to inhibit A β_{1-42} fibril formation and protect hippocampal neurons from A β_{1-42} -induced cell death in a concentration-dependent manner [88]. Additionally, in a screening of 27 herbs for their ability to protect A β_{1-42} -induced neuronal death, *Curcuma aromatica* and *Zingiber officinale* (ginger) extracts were found to most effectively protect neurons. Several other herbs were also found to be neuroprotective (such as *Ginkgo biloba* (Ginkgo), *Polygonatum* sp. (King Solomon's seal), *Cinnamum cassia* (Chinese cinnamon), and *Rheum coreanum* (Korean rhubarb)), but did not exert as potent effects [89].

Ginkgo biloba extract in particular has been heavily investigated for its use as a preventive and therapeutic agent in AD. It has been shown to exhibit neuroprotective effects in several mouse models [90] and improve cognitive function in AD patients [91, 92]. Several studies have demonstrated the mechanisms by which Ginkgo biloba extract may benefit AD. For example, it has been shown to improve age-related memory deficits and A β -peptide burden, act as a nitric oxide scavenger [93, 94], and regulate APP metabolism toward the α -secretase pathway [95]. Ginkgo biloba extract has also been shown to inhibit A β -induced free radical generation in a dose-dependent manner [96]. Further, Yao and colleagues [97] examined a specific Ginkgo biloba extract EGb761 in relation to cholesterol and amyloidogenesis and found that EGb761 treatment reduced APP and A β generation coincidental with decreased levels of free circulating cholesterol in *in vivo* (in rats) and *in vitro* studies. Moreover, Lee and colleagues [98] investigated ginkgolides A and B for their effect on A β -modulated acetylcholine release from hippocampal brain slices and found that ginkgolide B may produce anti-amnesic effects by mitigating A β peptides' inhibitory effect on cholinergic transmission. These studies have provided evidence supporting further investigation of Ginkgo biloba extract in AD.

Another plant extract, curcumin, a polyphenolic yellow pigment in the turmeric spice used in Indian curries and in Indian herbal medicine, has been investigated for its potential use in AD prevention and therapy. Epidemiological studies demonstrated that the prevalence of AD in individuals 70–79 years of age is 4.4-fold less in the India compared

to the U.S. [99]. The curcumin compound (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6 heptadiene-2,5 dione) has been shown to be neuroprotective against $A\beta$ toxicity *in vitro* [100], antiamyloidogenic [101, 102], and capable of reducing brain amyloid load and plaque burden [103]. Spectrophotometric studies have suggested that curcumin binds to the more readily redox-reactive metals Cu and Fe, but does not bind to Zn, and, in turn, acts as an antioxidant by chelating the redox active metal ions in the body [104]. Lim and colleagues [105] found that dietary curcumin treatment in AD mice significantly lowered levels of oxidized proteins, interleukin-1 β (a proinflammatory cytokine elevated in these mice), and insoluble and soluble $A\beta$ in the brain and reduced amyloid plaque burden by 43%–50%.

Several other spices have been investigated for their role in AD. For example, aged garlic extract has been shown *in vitro* to suppress the generation of reactive oxygen species, which are known to be involved in apoptosis as a result of $A\beta$ -mediated neurotoxicity [106], suggesting that garlic compounds may enhance antioxidant defenses in the brain. Additional *in vitro* evidence demonstrated that garlic treatment inhibits caspase-3 in a dose-dependent manner, which indicates that garlic may inhibit apoptotic neuronal death in the brain [107]. Another spice of interest to researchers has been *Crocus sativus*, or saffron, due to its unusually polar carotenoid components. Notable, certain saffron extracts have been shown to inhibit $A\beta$ fibrillogenesis [108]. Further research on these extracts may illuminate precise mechanisms of action on AD neuropathology and their potential as preventive or therapeutic agents in AD.

6.1. Fruit Juices and Wine. Polyphenols, the most abundant dietary antioxidants, have been heavily investigated for their ability to provide neuroprotection against oxidative damage in the brain. One study that propagated research on polyphenols in AD, conducted by Dai and colleagues [109], revealed that long-term fruit juice consumption can reduce one's risk for AD. The investigators suggested that the neuroprotective effects of fruit juices can be enhanced by consuming a combination of juices that are rich in phenolic compounds, which include juices derived from purple grapes, grapefruit, cranberries, and apples.

Several studies have examined the effects of certain fruit juices and extracts on AD. For example, apple juice was shown to prevent $A\beta$ -induced oxidative damage *in vitro* [110], and blueberry treatment has been found to reverse the effects of aging on motor behavior and neuronal signaling in animal models [111], possibly through mechanisms involving signal transduction, neuronal communication, and enhancement of hippocampal plasticity [112, 113]. Moreover, treatment with antioxidant-rich pomegranate juice has been shown to reduce $A\beta_{1-42}$ content and amyloid deposition in the hippocampus by approximately 50% in mice. A study conducted by Mullen and colleagues [114] examined 13 different fruit juices and reported that purple grape juice contained the highest number of individual phenolic compounds in addition to the highest concentration of total phenolics. The main components found in purple grape juice, accounting for 93% of the total phenolic content, were flavan-

3-ols, anthocyanins, and hydroxycinnamates. White grape juice, on the contrary, containing mainly hydroxycinnamates, had the lowest phenolic content of the juices examined.

Resveratrol is a naturally occurring polyphenol, found in the skin of grapes and red wine as a result of exposure to fungi or bacteria, which has been investigated for its ability to neuroprotect. Resveratrol has been demonstrated to maintain cell viability, exert antioxidant activity, exert proteasome-dependent antiamyloidogenic activity, and attenuate $A\beta$ -induced cytotoxicity in PC12 cells *in vitro* [115–117]. Importantly, resveratrol is also understood to activate the expression of sirtuins, often referred to as the “longevity gene,” in yeast [118] and in mammalian animal models of neurodegeneration [119, 120]—this resveratrol-induced sirtuin activation has been shown to promote neuroprotective activities against neuronal apoptosis. However, given recent evidence suggesting that resveratrol may not directly activate sirtuins [121], it is not quite clear if sirtuin activation plays a role in resveratrol's observed benefits in AD-type neuropathology. Further research will certainly illuminate resveratrol's bioactivity and the mechanisms through which it benefits AD.

Several studies have suggested that moderate red wine consumption reduces the incidence of AD clinical dementia [65, 66, 115, 122–124] and may even benefit the course of AD [125]. Derived from red grapes, red wine is rich in antioxidants and holds neuroprotective properties. Studies in our laboratory, using an AD mouse model, examined whether moderate consumption of the red wine cabernet sauvignon (the most polyphenol-rich red wine, likely due to increased inclusion of grape skins) reduces AD-type neuropathology and cognitive deterioration. We found that cabernet sauvignon treatment was capable of attenuating AD-type cognitive deterioration and $A\beta$ neuropathology by mechanisms involving nonamyloidogenic processing of APP, ultimately inhibiting $A\beta$ generation [126, 127].

6.2. Grape Seed Polyphenolic Extract. Another area of investigation of high interest in the AD field has been the potential beneficial role of grape seed polyphenolic extract (GSPE) in attenuating AD-type neuropathology and cognitive impairments. Studies in our laboratory have investigated a specific GSPE (MegaNatural), which is comprised primarily of catechin and epicatechin in monomeric, oligomeric, and polymeric forms, is readily absorbed through the intestinal mucosa due to modification of the constituent polyphenols in its preparation and has been demonstrated to be safe in animal models [128–131] and in humans with pre-hypertensive conditions [132]. In an initial investigation in a mouse model of AD [129], mice were treated for 5 months with 200 mg/kg/day GSPE in drinking water (equivalent to 1 g/day in humans, according to Food and Drug Administration criteria for converting drug dosages across species), after which *in vitro* and *in vivo* assessments were conducted at 6 (for behavior) and 10 (for neuropathology) months. *In vitro* studies revealed that GSPE prevented $A\beta$ peptides from aggregating into high molecular weight (HMW) oligomers, and *in vivo* studies showed that GSPE treatment significantly

reduced $A\beta_{1-40}$ and $A\beta_{1-42}$ peptide and HMW $A\beta$ oligomer levels and amyloid plaque burden in the brain, relative to age- and gender-matched water-treated mice. Moreover, GSPE-treated mice also performed significantly better tests of cognitive function compared to age- and gender-matched water treated mice. A follow-up mechanistic study [130] investigated *in vitro* GSPE's ability to alter the assembly of $A\beta_{1-40}$ and $A\beta_{1-42}$ oligomers and $A\beta$ -induced cytotoxicity in $A\beta$ -treated PC12 cells; these studies revealed that GSPE blocked $A\beta$ protofibril formation, preprotofibrillar oligomerization, and the structure transition from initial coil to α -helix/ β -sheet. Additionally, GSPE exerted protective activities in assays of $A\beta$ -induced cytotoxicity (prior to peptide assembly, following assembly, and just prior to peptide addition in cells). These studies collectively suggest a neuroprotective and possibly therapeutic role of GSPE in AD-type $A\beta$ neuropathology and cognitive deterioration.

To follow this line of work, we also investigated *in vitro* the potential beneficial role of GSPE on AD-type tau neuropathology [133], another major hallmark of AD. Using an *in vitro* model system, we found that GSPE treatment significantly inhibited the aggregation of tau peptides into filaments and was also capable of dissociating preformed tau aggregates. This finding suggests that GSPE treatment may attenuate deposits of tau aggregates in the AD brain.

In light of our evidence that GSPE was capable of attenuating $A\beta$ and tau pathology, we next explored GSPE bioavailability [131] to further assess its potential as an AD treatment. We found that acute oral administration of GSPE in Sprague Dawley rats led to detectable contents of catechin, epicatechin and their metabolites in the brain. Following repeated GSPE exposure, we detected accumulations of catechin, epicatechin, and gallic acid and their metabolites in the blood and similarly, catechin and epicatechin and their metabolites in the brain.

These studies, which demonstrate GSPE's ability to attenuate AD-type $A\beta$ pathology *in vivo* and *in vitro* and tau pathology *in vitro*, combined with its demonstrated safety and bioavailability, support the continued development of GSPE as a treatment for $A\beta$ - and tau-mediated neurodegeneration and cognitive impairments.

7. Conclusions and Future Trends

Collectively, epidemiological and experimental research has demonstrated that dietary choices can play a key role in the prevention of AD and dementia. For example, much of the research described here suggest that preventing and managing conditions such as diabetes, hypertension, obesity, and heart disease may in turn prevent the onset of pathological aging and dementia. Research from our laboratory and others has demonstrated that reducing calorie intake can help prevent AD and similarly, given the demonstrated relationship between diabetogenic conditions and AD, that preventing diabetes (perhaps by limiting one's glucose intake) may also decrease one's risk for AD. Moreover, studies have demonstrated that consuming foods that are rich in polyphenols, such as blueberries or grapes, may also prevent AD and cognitive deterioration, perhaps through their antioxidant

and antiamyloidogenic activities. Based on the evidence described, it seems possible that in the near future, we may be able to utilize our knowledge of AD prevention through dietary changes and work toward intensive dietary intervention(s) that might be capable of preventing or treating AD.

However, when reviewing this body of scientific literature, one must understand that this area of research is still in its infancy, and further research must be conducted before making any dietary recommendations to the general public for preventing neurodegenerative conditions of aging. For example, conditions such as AD are chronic and have a long latency period, and conducting clinical trials for dietary interventions under such circumstances, over long enough periods of time and on large enough samples to draw accurate and repeatable conclusions, would be a highly complex endeavor. Moreover, any dietary recommendations made toward this aim must always be incorporated into a general healthy diet. Future research on dietary lifestyles and their role in the prevention or treatment of dementia will certainly elucidate which diets and foods are capable of exerting neuroprotective activities, in what quantities, and by what mechanism(s) of action.

The current medical model for preventing and treating neurodegenerative conditions such as AD lacks a "whole organism" approach. For example, the onset of AD is likely a result of genomic and proteomic factors, but also psychosocial and lifestyle factors, such as nutrient intake or levels of stress. Today, Medicare and other insurers and individuals will pay billions of dollars for various surgical and medical procedures to treat chronic conditions (such as heart disease or diabetes), and yet they pay very little for integrative and preventive medicine approaches (such as alterations in diet) that can prevent or reverse many chronic conditions. By further investigating the role that dietary choices may play in AD and other dementias and diseases of aging, we will work toward the utilization of an integrative approach to medicine, taking into account all aspects of an individual's lifestyle when working toward the maintenance and curing of chronic diseases.

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