Published in final edited form as:
J Neurochem. 2008 August ; 106(4): 1503–1514. doi:10.1111/j.1471-4159.2008.05454.x.

METABOLIC SYNDROME AND THE ROLE OF DIETARY LIFESTYLES IN ALZHEIMER'S DISEASE

Giulio Maria Pasinetti[1] and **Jacqueline A. Eberstein**[2]

1*Center of Excellence for Research in Complementary and Alternative Medicine in Alzheimer's Disease, Department of Psychiatry, The Mount Sinai School of Medicine*

2*Controlled Carbohydrate Nutrition, LLC.*

Abstract

Since Alzheimer's disease (AD) has no cure or preventive treatment, an urgent need exists to find a means of preventing, delaying the onset, or reversing the course of the disease. Clinical and epidemiological evidence suggests that lifestyle factors, especially nutrition, may be crucial in controlling AD. Unhealthy lifestyle choices lead to an increasing incidence of obesity, dyslipidemia and hypertension — components of the metabolic syndrome. These disorders can also be linked to AD. Recent research supports the hypothesis that calorie intake, among other nongenetic factors, can influence the risk of clinical dementia. In animal studies, high calorie intake in the form of saturated fat promoted AD-type amyloidosis, while calorie restriction via reduced carbohydrate intake prevented it. Pending further study, it is prudent to recommend to those at risk for AD — e.g., with a family history or features of metabolic syndrome, such as obesity, insulin insensitivity, etc. — to avoid foods and beverages with added sugars; to eat whole, unrefined foods with natural fats, especially fish, nuts and seeds, olives and olive oil; and to minimize foods that disrupt insulin and blood sugar balance.

Keywords

Alzheimer's disease; calorie restriction; diet; ketogenic diet; metabolic syndrome; diabetes; obesity; insulin

Alzheimer's disease (AD) is a growing public health concern with potentially devastating effects, especially among the elderly population. Ever since the first description of clinical dementia by Alois Alzheimer in 1907, the disease has increased exponentially worldwide. At present, 4 million Americans are affected with AD, with an estimated annual health care cost of almost 100 billion dollars. With the expected increase in the population of people over the age of 65, it is estimated that the total incidence of AD will quadruple by 2050 (Brookmeyer et al., 1998).

Currently, AD has no cure or preventive treatment. Research on drugs to prevent it or to slow its progression may pay off at some point in the distant future. Meanwhile, an urgent need exists to find a means of preventing, delaying the onset, or reversing the course of AD. Since the disease typically strikes very late in life, for some people delaying its symptoms could be just as good as a cure. It is now widely accepted that delaying the onset of AD by just five

Corresponding author: Giulio Maria Pasinetti, M.D., Ph.D., The Mount Sinai School of Medicine, One Gustave L. Levy Place, Box 1230, New York, NY 10029, Tel: 212-659-8716, E-mail: giulio.pasinetti@mssm.edu .

years can cut its incidence in half (www.alz.org/national/documents; www.alz.org/national/documents)

Clinical and epidemiological evidence suggests that lifestyle factors, especially nutrition, may be crucial in controlling AD. Evidence supporting a direct link between nutrition and AD neuropathology continues to grow, as the disease's mechanistic pathways are defined and biochemical functions scrutinized. We, among others, have recently reported experimental dietary regimens that may promote, attenuate, or even partially reverse features of AD (Wang et al., 2005; Qin et al., 2006a; Qin et al., 2006b).

AD amyloid neuropathology as a target for therapeutic dietary lifestyle factors

AD is characterized by extracellular amyloid-β (Aβ) plaques and intracellular neurofibrillary tangles composed of abnormally hyperphosphorylated microtubular protein tau in the brains of these patients. The disease manifests clinically as a progressive loss of cognitive abilities. It is also well recognized that Aβ exists in multiple assembly states, which have different physiological or pathophysiological effects. Although the classical view is that Aβ is deposited extracellularly, emerging evidence from transgenic mice and humans indicates that this peptide can also accumulate intraneuronally, which may contribute to disease progression (LaFerla et al., 2007).

While currently no cure exists for AD, even delaying AD onset by a few years would lead to significant reductions in disease prevalence and, consequently, its burden on health care systems. A long-recognized hallmark of AD is the accumulation of neurotoxic Aβ peptides and their deposition into extracellular Aβ plaques in the brain (Selkoe, 2001). Aβ species with different amino and carboxy termini are generated from the ubiquitously expressed amyloid precursor protein (APP) through sequential proteolysis by β- and γ-secretases (Haass et al., 1992; Shoji et al., 1992; Busciglio et al., 1993). A third proteolytic enzyme, α-secretase, may reduce Aβ generation by cleaving APP within the Aβ peptide sequence (Vassar and Citron, 2000). In the twenty years since the APP gene was cloned, evidence continues to accumulate that supports a seminal role for Aβ in AD. In addition, other factors linked to AD, including Apolipoprotein E, insulin-degrading enzyme, and presenilins, all affect Aβ metabolism.

Aβ neuropathology and mitochondrial energy metabolism in AD pathogenesis

Recent evidence links a potential pathogenetic role of Aβ neuropathology in AD with mitochondria pathogenesis, ultimately playing a pivotal role in the onset and possibly in the progression of clinical dementia (Bubber et al., 2005). Mitochondria, in the presence of elevated Aβ peptides, increase the formation of reactive oxygen species (ROS) which act as damaging agents and as signaling molecules. Interestingly, inhibition of energy metabolism alters the processing of the amyloid precursor protein (APP) and induces potentially amyloidogenic Aβ fragments (Gabuzda et al., 1994). Moreover, highly reactive ROS are capable of unleashing mechanisms involving the liberation of cytochrome c, which leads to neuronal apoptosis (Picklo and Montine, 2007; Vina et al., 2007), a feature of the AD brain.

Consistent with these observations, a recent genome-wide microarray study of the AD brain found a strong association between the decreased expression of mitochondrial gene products involved in mitochondrial oxidative phosphorylation (OXPHOS) and glucose metabolism as a function of the progression of clinical dementia (Qin et al., 2008). In line with this observation, recent positron emission tomography studies demonstrated that (mitochondrial) glucose utilization is also reduced in the brain of patients with AD, supporting the hypothesis that

glucose hypometabolism in AD-afflicted brains might ultimately result in increased steady-state concentrations of cerebral glucose (Haley et al., 2006).

This evidence is quite interesting, especially in view of recent evidence from our laboratory suggesting that, in an *in vitro* model of AD-type amyloidogenesis, the predicted elevation of amyloidogenic Aβ peptides coincides with hyperglycemic culture conditions in a dose-dependent manner (Qin et al., 2008). This evidence strongly associates abnormal brain glucose metabolism with abnormal OXPHOS mitochondria in the AD brain and possibly provides further evidence supporting a causal role for hyperglycemic conditions associated with metabolic syndrome as risk factors in AD (Craft and Watson 2004; Craft et al., 2007; Jagust et al., 1991; Minoshima et al., 1995). Although evidence exists that hyperglycemia in type 2 diabetes causes up to a fourfold increase in neuronal glucose levels (Tomlison and Gardiner, 2008), the molecular mechanisms through which impaired glucose metabolism/mitochondrial oxidative phosphorylation contributes to AD amyloid neuropathology is currently the subject of intensive investigation (Lin and Beal, 2006), especially in respect to the potential role of dietary lifestyle factors (discussed below) in the prevention of AD dementia.

We also note, however that recent studies suggest that the antioxidant diet in aged beagles although not decreasing Aβ-amyloid neuropathology may enhance cognitive performance (Head et al., 2008), further supporting the hypothesis that control of mitochondrial OXPHOS activities among other factors, might be also further exploited as novel therapeutic targets for the beneficial role of certain dietary life style factors involved in the prevention of clinical dementia independent from AD Aβ amyloid neuropathology (Smith et al., 2000).

Metabolic syndrome as a risk factor for AD: The role of obesity

Much epidemiological evidence indicates that type 2 diabetes (a non-insulin dependent form of diabetes mellitus, NIDDM) is associated with a two- to threefold increased relative risk for AD, independent of the risk for vascular dementia (Leibson et al., 1997; Stolk et al., 1997; Kilander et al., 1998; Forette et al., 1998; Grant, 1999; Skoog et al., 1996; Pyorala et al., 2000; Meyer et al., 2000; Petot et al., 2003). High calorie intake and diets high in sugar and refined flour are major health concerns in the Western diet; along with sedentary lifestyles, they have been linked to an increased relative risk of AD. These unhealthy lifestyle choices have led to the growing incidence of obesity and altered insulin receptor (IR) signaling due to hyperglycemic condition, also known as IR-insensitivity, among other conditions. This complex of symptoms is generally known as metabolic syndrome (Torpy et al., 2006). While, until lately, metabolic syndrome was recognized for its aggravating role in several diseases — in particular, cardiovascular disorders — recent evidence strongly suggests metabolic syndrome as a major risk factor for AD dementia.

Obesity has received a large amount of attention as a risk factor for AD (Craft and Watson, 2004; Craft et al., 2007; Whitmer et al., 2007; Fewlass et al., 2004). Indeed, growing evidence suggests a possible association between obesity in middle age, as measured by body mass index (BMI) and skinfold thickness, and risk of dementia later in life (Whitmer et al., 2007). For example, obese participants (BMI greater than or equal to 30) in this study had a 35 percent greater risk of dementia compared with those of normal weight (BMI ranging from 18.6 to 24.9). The study concluded that obesity in middle age increased the risk of future dementia independently of comorbid conditions. Finally, consistent with this evidence, Balakrishnan et al. (2005) investigated the association between plasma Aβ levels, BMI and fat mass (FM). They found that certain molecular indexes recently implicated in inflammation processes, cardiovascular disorders, and hyperglycemic conditions in type 2 diabetes — which in turn are major risk factors in AD — contribute to the association between BMI/FM and plasma Aβ

content, further linking obesity mechanistically with the onset, and possibly the progression, of AD dementia.

More recently, obesity has been further linked mechanistically to AD pathogenesis based on abnormal metabolism of the obesity-related protein leptin (Fewlass et al., 2004). Leptin, a peptide hormone secreted by adipose tissue, exhibits a wide range of central and peripheral actions. Among other functions, it was proposed that leptin's participation in diseases such as obesity is due, at least in part, to its impaired transport across the blood-brain barrier (BBB) (Dietrich et al., 2007). Interestingly, leptin was shown to attenuate β-secretase processing of APP in neuronal cells, possibly through mechanisms involving altered lipid composition of membrane lipid rafts. Most strikingly, chronic administration of leptin to AD-transgenic animals reduced the brain Aβ load, suggesting its therapeutic potential in AD (Fewlass et al., 2004). Consistent with this evidence, Dietrich et al. (2007) demonstrated that circulating leptin is transported into the brain by binding to the lipoprotein receptor megalin at the choroid plexus epithelium. In line with this hypothesis, attenuation of megalin expression in physiological and pathological conditions, such as during aging or in AD dementia, correlates with poor entry of leptin into the brain (Dietrich et al., 2007). Collectively, this information provides support to the hypothesis that pharmacological manipulation of leptin might be developed into a novel therapeutic strategy for AD.

The role of diabetogenic dietary lifestyles and altered IR signaling in AD: Experimental approaches and therapeutic implications

Experimental evidence suggests that abnormalities in insulin metabolism in diabetic conditions mechanistically influence the onset of AD via their influence on the synthesis and degradation of amyloidogenic Aβ peptides. For example, insulin itself may significantly promote Aβ accumulation by accelerating amyloid precursor protein (APP)/Aβ trafficking from the trans-Golgi network, a major cellular site for Aβ generation, to the plasma membrane (Gasparini et al., 2001). Moreover, elevated levels of circulating insulin in diabetic conditions may also provoke amyloid accumulation by directly competing with Aβ for the insulin-degrading enzyme (IDE), thereby limiting Aβ degradation by IDE. Accumulating evidence has shown that, under diabetic conditions, impairments in certain IR-responsive cellular signaling pathways may also mechanistically promote AD-related neuropathology and cognitive deterioration (Phiel et al., 2003; Ho et al., 2004; Cao et al., 2007; Li et al., 2007; Craft, 2007). Building on this observation, a recent hypothesis suggested that, regardless of diabetic or nondiabetic status, impaired insulin signaling in the brain may be a common underlying cause for sporadic AD (Steen et al., 2005). Cellular insulin signaling is initiated by the coupling of extracellular insulin with the IR in the plasma membrane, leading to IR activation and subsequent promotion of cellular IR-signaling processes (Taniguchi et al., 2006). Despite the central role of IR activation in cellular IR-signaling processes, there is limited and conflicting information on the regulation and activity of IR in the brains of subjects with sporadic AD. In particular, Frolich et al. (1998) reported significantly increased IR-binding activity in the brains of subjects afflicted with sporadic AD. In contrast, Steen et al. (2005) and Rivera et al. (2005) observed that AD is associated with significantly reduced IR content and IR activity in the brain. While this evidence tentatively suggests that abnormal carbohydrate metabolism might play an important role in AD through mechanisms that involve Aβ peptide generation, experimental studies also suggest that insulin resistance may promote AD amyloid neuropathology in Tg2576 mice, possibly by limiting Aβ degradation via competition with insulin for degradation by IDE (Farris et al., 2003).

While insulin has received major attention for its potential role in amyloid neuropathology, recent evidence also suggests a role for insulin in normal memory function, supporting the hypothesis that insulin, by itself, affects many mechanisms related to neuronal activity and

cognitive function. Chronic hyperinsulinemia and insulin resistance, or reduced insulin effectiveness, may negatively influence memory (Luchsinger et al., 2004a). Hoyer (2002) proposed that low concentrations of circulating insulin in the central nervous system — along with reduced IR expression and subsequent altered downstream signaling — would ultimately lead to reduced levels of acetylcholine and a corresponding decrease in cerebral blood flow.

We recently explored the role of experimental type 2 diabetes in a mouse model of AD amyloid neuropathology. We found that a diabetogenic diet resulting in hyperglycemic and hyperinsulinemic conditions coincided with increased amyloidogenic $A\beta_{1–40}$ and $A\beta_{1–42}$ peptide levels and AD-type Aβ neuropathology in the brains of AD mice (Ho et al., 2004). Moreover, the increased AD-type amyloid burden also coincided with a significant potentiation of cognitive deterioration (Ho et al., 2004). Further exploration of the apparent interrelationship of insulin resistance to brain amyloidosis revealed a functional decrease in IR–mediated signal transduction in the brain (Ho et al., 2004). Collectively, these studies strongly suggest that one mechanism through which diet-induced insulin resistance in AD mice can significantly promote AD-type amyloidosis in the brain is the impairment of IR signaling, which results in elevation of γ-secretase activities. The studies suggest that hyperglycemic conditions associated with experimental type 2 diabetes conditions may further contribute to AD-amyloid neuropathology by attenuating the degradation of Aβ peptide pathways associated with IDEs (Scheme 1) (Ho et al., 2004; Zhao et al., 2006).

Consistent with our finding, Li et al., (2007) examined whether AD-type neuropathology and cognitive deterioration occurred in two rat models with spontaneous onset of type 1 and type 2 diabetes; they found that endogenous Aβ peptides, phospho-tau accumulation, and neurodegeneration are primarily features of rats with hyperglycemic type 2 diabetic rather than with type 1 insulin-independent diabetes insipidus. The severity of AD-type neuropathologic changes was greater in the type 2 diabetic model and appeared to be associated with hypercholesterolemic conditions. A more recent study also suggests that a hyperglycemic condition may also exacerbate intra-cerebral administration of Aβ peptides, with respect to spatial learning and memory function, relative to control normoglycemic mice (Huang et al., 2007). Finally, a recent study suggests that intake of sucrose-sweetened water induces insulin resistance and exacerbates memory deficits and amyloidosis in a transgenic mouse model of AD neuropatholgy (Cao et al., 2007). However, we also note that vascular factors could also contribute and predict the rate of progression in AD (Mielke et al., 2007). Thus, despite the exciting evidence from experimental rodent models of AD-type neuropathology further discussed below suggesting a pathogenetic role of Aβ in the onset and progression of AD dementia, Aβ amyloidosis might not be both necessary and/or sufficient to explain the development of AD clinical dementia, under certain conditions (Hayden et al., 2006).

Collectively, these studies suggest that controlling certain cardiovascular risk factors e.g. hyperglycemic conditions by engaging in healthy dietary lifestyles might prove to be an effective way to curtail the risk of developing AD through the control of either Aβ dependent or independent brain pathogenetic mechanisms as further discussed below.

Calorie restriction (CR) as a potential preventative dietary lifestyle factor in AD

Recent studies support the hypothesis that calorie intake, among other non-genetic factors, influences the relative risk for AD clinical dementia. Most remarkably, while, as discussed above, high calorie intake may promote AD neuropathology, recent experimental evidence strongly supports the hypothesis that CR (primarily via reduced carbohydrate intake) can prevent it (see below). This exciting evidence is consistent, in part, with current epidemiological studies suggesting that obesity and diabetes are associated with a more than

fourfold increased risk for developing AD. Clarifying the mechanisms through which calorie intake may ultimately influence AD neuropathology, and eventually discovering future "mimetics" capable of recapitulating "anti-Aβ activities" will provide new avenues for the design of healthy dietary lifestyle therapeutic strategies for the treatment of AD and, possibly, other neurodegenerative disorders. The preventive effects of calorie reduction on the etiology of mild cognitive impairment (MCI), which are cases at high risk for developing AD cognitive decline, are supported in part by recent epidemiological evidence suggesting that individuals who habitually consume fewer calories demonstrate a reduced incidence of AD (Luchsinger et al., 2002; Gustafson et al., 2003).

Although evidence supports a potential neuroprotective role for calorie reduction in neurodegeneration (Mattson, 2003), until recently there was no information on whether reduced calorie intake could attenuate AD neuropathology. Based on this consideration, we explored whether a clinically applicable weight reduction/calorie reduction regimen could attenuate the AD-type phenotype and found, for the first time, that calorie intake restriction based on an approximately 30 percent reduction of carbohydrate content in a mouse model of AD may prevent AD-type neuropathology through mechanisms associated with longevity (Wang et al., 2005).

Most importantly, in more recent studies consistent with the evidence from Tg2576 mice, discussed above, our laboratories confirmed this evidence by showing that a similar 30 percent calorie reduction in squirrel monkeys coincides with a significant reduction in $A\beta_{1-40}$ and $A\beta_{1-42}$ peptide content in the brain (Qin et al., 2006a). In view of the fact that several studies of squirrel monkeys have been successfully used to provide important human physiological and biological information at the organism, tissue, cellular, and molecular levels, these studies in squirrel monkeys strongly support the hypothesis that clinically applicable calorie reduction regimes might prevent amyloid neuropathology in humans, possibly preventing mild MCI and AD.

Although these studies are encouraging, and tentatively suggest that changes in dietary lifestyle such as lowering calorie intake might beneficially influence AD, we note that malnutrition remains a general problem among the elderly. Hence, dietary recommendations in AD may need to be made according to the needs of such comorbidities as type 2 diabetes and cardiovascular diseases.

Sirtuins at the crossroads of the promotion of longevity and the prevention of AD amyloid neuropathology following calorie restriction

Sirtuins, also known as silent information regulators, are class III histone deacetylases (HDAC) that catalyze deacetylation reactions in an NAD^+-dependent manner (Qin et al., 2006b). Sirtuins regulate important cell functions by deacetylating histone and nonhistone targets. Activation of sirtuin extends lifespan and promotes longevity and healthy aging in a variety of species, potentially delaying the onset of age-related neurodegenerative disorders.

Based on this consideration, we tested the hypothesis whether promotion of the NAD^+-dependent sirtuin, SIRT1, mediated deacetylase activity — a mechanism by which CR influences AD-type amyloid neuropathology — and found that it did (Qin et al., 2006b). Most interestingly, we found that the predicted attenuation of Aβ content in the brain during CR can be reproduced in mouse neurons *in vitro* by manipulating cellular SIRT1 expression/activity, ultimately promoting the nonamyloidogenic α-secretase processing of the APP, which precludes the generation of Aβ peptides. These results demonstrate, for the first time, a role for SIRT1 activation in the brain as a novel mechanism through which CR may influence AD amyloid neuropathology. The study provides a potentially novel pharmacological strategy for

AD prevention and/or treatment. We also note that, in mammalian systems, sirtuin activators may also protect against axonal degeneration, polyglutamine toxicity, and microglia-mediated Aβ toxicity, suggesting the potential therapeutic value of sirtuins for patients with AD (Gan, 2007). SIRT1 was recently shown to play a protective role against microglia-dependent Aβ toxicity through inhibition of NF-kappa B signaling (Chen et al., 2005).

Dietary phytonutrients and food supplements: A role in the prevention of AD dementia?

An unprecedented consumer demand has arisen for foods or food constituents that help prevent or manage health conditions, including AD (Howes et al., 2003; ANON 2003; Anekonda et al., 2005). In 2002, 8 percent of consumers indicated that they had purchased food products aiming to prevent an undesirable health condition, and 50 percent of consumers reported purchasing foods to manage or treat conditions.

Much of this consumer demand for therapeutic food products is for foods containing polyphenols. Over 35 thousand plant species currently used for medicinal purposes around the world possess more than 4 thousand polyphenolic structures (Macheix et al., 1990; Maclennan et al., 2002; Manach et al., 2005; Williamson and Manach, 2005). These dietary polyphenolics provide numerous health benefits, such as anti-inflammation and antioxidation (Duncan et al., 2003; Nijveldt et al., 2001; Williams et al., 2004). Evidence is mounting that grape-derived polyphenols may beneficially influence AD amyloid neuropathology (Dai et al., 2006). Mounting evidence also shows that moderate consumption of red wine (which contains these grape-derived polyphenols) may causally attenuate AD amyloid pathogenesis and cognitive deterioration in preclinical models of AD (Wang et al., 2006) and reduce the incidence of AD (Luchsinger et al., 2004b). However, because polyphenolic compositions and bioactivities vary considerably due to plant-growth environments, there are problems with the preparation of grape-derived polyphenolics (and other dietary polyphenolics) (McGraw and Furedi, 2005). For the same reason, there are also issues that complicate the harvest, storage, and processing/preparation of certain dietary sources of polyphenols (Anekonda et al., 2005).

These limitations have recently inspired a diverse group of interdisciplinary scientists with expertise in AD and nutritional-botanical sciences to design a series of studies with the ultimate goal of isolating and identifying bioactive natural compounds capable of providing beneficial AD-modifying activities, as discussed below.

Fish and fish oil

Epidemiological and animal studies have suggested that dietary fish or fish oil rich in omega-3 fatty acids, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), may affect psychiatric and behavioral symptoms in AD (Morris et al., 2003; Young and Conquer, 2005). Lim et al. (2005) used a transgenic AD-type mouse to evaluate the impact of DHA on AD neuropathology. They found that DHA-enriched diets significantly reduced total AD-type amyloid neuropathology by more than 70 percent when compared with low-DHA or control chow diets. The results suggest that DHA could be protective against AD-type amyloid deposition in the brain and could eventually prevent downstream neurodegenerative conditions. Hashimoto et al. (2005) showed that DHA suppressed increases in the levels of lipid peroxide and ROS in the cerebral cortex and hippocampus of Aβ-infused rats, suggesting that DHA increases antioxidative defenses. Further, the authors were of the opinion that DHA is a possible therapeutic agent for ameliorating learning deficiencies due to AD. Although a number of epidemiologic studies reported that higher intake of omega-3 fatty acids (largely associated with fish consumption) is protective against Alzheimer's disease (AD), other human studies reported no such effect (Arendash et al., 2007; Freund-Levi et al., 2007).

Plant extract and spices

Various parts of plants, including leaf, fruit, outer bark, root, etc., are used to enhance memory in traditional Asian medicine. Since plant products are known to enhance memory, various laboratories are working on mouse models of AD to observe which plant extracts decrease the severity of disease. Most recently, Niidome et al. (2007) reported that mulberry leaf extract may protect hippocampal neurons against the neurotic effect of $A\beta_{1-42}$-induced cell death in a concentration-dependent manner. *Ginkgo biloba* has been shown to improve age-related memory deficits; most interestingly, recent evidence showed that the *Ginkgo biloba* extract scavenges NO with neuroprotective properties (Bastianetto et al., 2000; Luo et al., 2002).

The *Ginkgo biloba* extract EGb761 exhibited neuroprotective effects in several mouse models (Defeudis, 2002), as well as maintaining and improving cognitive function in AD patients (Oken et al., 1998; Le Bars et al., 2003). Finally, recent *in vitro* studies indicate that the ginkgo extract's activity is due to inhibition of Aβ-induced free radical generation and occurs in a dose-dependant manner (Yao et al., 2001). Because free cholesterol may be involved in the generation of neurotoxic Aβ peptides, Yao et al. (2004) examined the ginkgo extract EGb761 in relation to cholesterol and amyloidogenesis. Exposure of PC12 cells to EGb761 decreased the processing of APP, ultimately precluding the generation of neurotoxic Aβ peptides.

Recently, curcumin, a polyphenolic yellow pigment used in turmeric spice in Indian curries and food preservation has received much attention for its potentially beneficial role in AD dementia and neuropathology. Interestingly, the prevalence of AD in populations that are between the ages of 70 and 79 is 4.4-fold less in India than in the USA (Ganguli et al., 2000). The compound is neuroprotective against Aβ toxicity *in vitro* (Shishodia et al., 2005), while also being anti-amyloidogenic (Aksenov and Markesbery, 2001; Ringman et al., 2005). Furthermore, aged transgenic mice with high amyloid plaque loads that were either fed or injected with curcumin had less brain amyloid load and plaque burden, and fewer curcumin-labeled plaques (Yang et al., 2005). To evaluate whether curcumin could beneficially influence amyloid neuropathology in a mouse model of AD-type neuropathology, Lim et al. (2001) tested different doses of dietary curcumin on inflammation, oxidative damage, and plaque pathology. Curcumin significantly lowered oxidized proteins and interleukin-1β, a proinflammatory cytokine elevated in the brains of these mice, strongly supporting a further link between inflammation and AD neuropathology.

As discussed above, mitochondria-generated ROS are proposed to be involved in the apoptotic mechanism of Aβ-mediated neurotoxicity. Finally, recent evidence also shows that aged garlic extract not only suppressed the generation of ROS but also attenuated caspase-3 activation, DNA fragmentation, and PARP cleavage and eventually protected against Aβ-induced apoptosis (Peng et al., 2002). These findings further suggest that garlic compounds can reduce apoptosis, possibly by enhancing the endogenous antioxidant defenses.

The potential beneficial role of fruit polyphenols in AD

Lau et al. (2005) and Lau et al. (2007) reported that polyphenolic compounds found in fruits such as blueberries may exert their beneficial effects through signal transduction and neuronal communication. Furthermore, they showed that short-term blueberry supplementation increases hippocampal plasticity. Interestingly, recent evidence also suggests that pomegranates contain very high levels of antioxidant polyphenolic substances. Hartman et al. (2006) observed that mice treated with pomegranate juice had significantly (approximately 50 percent) less accumulation of soluble $A\beta_{1-42}$ and amyloid deposition in the hippocampus than control mice. Quercetin is one of the major flavonoids found in many fruits and vegetables. Heo and Lee (2004) investigated the protective effects of quercetin on hydrogen-peroxide-induced neurodegeneration. Results showed that cell viability was clearly improved with

quercetin, which showed a higher protective effect than vitamin C. They also observed that quercetin decreased oxidative-stress-induced neuronal cell membrane damage more than vitamin C. Finally, a recent study further confirmed that polyphenol-rich fruits, such as bananas, oranges, and apples, may protect against oxidative stress in an *in vitro* model of AD (Heo et al., 2008).

The benefits of moderate consumption of red wine in the prevention of AD

Another important component of the typical Mediterranean diet that was recently implicated as a healthy dietary lifestyle for the prevention of AD is the moderate consumption of red wine. Interestingly, recent experimental evidence found that moderate consumption of red wine, in the form of Cabernet Sauvignon, significantly attenuated AD-type cognitive deterioration and amyloid neuropathology in a mouse model of AD (Wang et al., 2006). The study found that regular consumption of wine over seven months significantly reduced AD-type changes in the brains of mice bred to have AD type symptoms. This supports epidemiological evidence suggesting that moderate wine consumption, one glass per day for women and two for men, may help reduce the relative risk for AD clinical dementia (Luchsinger et al., 2004b; Russo et al., 2003; Savaskan et al., 2003). Based primarily on this evidence, current studies are focused on identifying natural compounds in wines or other foods, including grapes, that might be neuroprotective.

Resveratrol, a naturally occurring polyphenol found mainly in grape skins and red wine, markedly lowers the levels of secreted and intracellular Aβ peptides. Savaskan et al. (2003) showed that resveratrol maintains cell viability and exerts an antioxidative action by enhancing the intracellular free radical scavenger glutathione. Tea represents another large family of plants containing high amounts of polyphenols that may confer a variety of health benefits. Recently, it has been hypothesized that tea consumption may also reduce the risk of age-related neurodegenerative pathologies. Considering the deleterious role of Aβ in the etiology of AD, Bastianetto et al. (2006) investigated green and black tea extracts and flavan-3-ols (present as monomers and dimers in green and black forms, respectively) against the toxicity induced by Aβ-derived peptides using primary cultures of rat hippocampal cells. Both green and black tea extracts displayed neuroprotective action against Aβ toxicity. These effects were shared by gallic acid (the most potent flavan-3-ol), epicatechin gallate, and epigallocatechin gallate (EGCG). Interestingly, EGCG and gallic acid inhibited Aβ aggregation and/or the formation of Aβ-derived diffusible neurotoxin ligands. Catechin gallates contribute to the neuroprotective effects of both green and black teas. Moreover, the protective effect of EGCG is likely to be associated, at least in part, with its inhibitory action on the formation of Aβ fibrils/oligomers. The authors hypothesized that not only green but also black teas are benefit the AD-afflicted brain. The primary target of existing drugs for the treatment of AD is the inhibition of the enzyme acetylcholinesterase. Okello et al. (2004) reported that both green and black teas inhibited human acetylcholinesterase.

Accumulation of iron at sites where neurons degenerate in Parkinson's disease (PD) and AD is thought to play a major role in the oxidative-stress-induced process of neurodegeneration. The main polyphenol constituent of green tea, EGCG, possesses iron-chelating, radical-scavenging and neuroprotective properties, offering potential therapeutic benefits. Lin et al. (2007) used a human neuronal cell line, MC65, and conditional expression of an APP protein fragment (APP-C99) to investigate the protection mechanism of EGCG and, excitingly, found that treatment with EGCG may, through the promotion of the nonamyloidogenic processing of APP, significantly reduce and even ultimately prevent the generation of neurotoxic Aβ peptides in the brain.

The role of dietary homocysteine in AD

Recent epidemiologic studies of different sample populations have suggested that the risk of AD may be increased in individuals with high-calorie diets and in those with increased homocysteine levels. Dietary restriction and supplementation with folic acid can reduce neuronal damage and improve behavioral outcomes in mouse models of AD (Mattson, 2003). Animal studies have shown that the beneficial effects of dietary restriction result, in part, from increased production of neurotrophic factors and cytoprotective protein chaperones in neurons. By keeping homocysteine levels low, folic acid can protect cerebral vessels and can prevent the accumulation of DNA damage in neurons caused by oxidative stress and facilitated by homocysteine. Emerging data suggest that high-calorie diets and elevated homocysteine levels may render the brain vulnerable to neurodegenerative disorders (Mattson, 2003). However, two recently published papers provide conflicting results on the benefits of using supplementation with folic acid to lower homocysteine levels and its impact on cognitive function. A two-year trial on 276 healthy, older people (65 and older) lowered homocysteine but failed to improve cognitive function in these healthy subjects (McMahon et al., 2006). A three-year study supplementing folic acid significantly improved certain aspects of cognitive function that tend to decline with age in people between 50 and 70 years of age (Durga et al., 2007). However, more research in this area is required. Until then, it is certainly reasonable to recommend, especially to people at risk for AD, inclusion in their diets of foods high in folic acid. These include leafy green vegetables, lentils, and unrefined whole grains.

Dietary lifestyles: Recommendations for the prevention of metabolic syndrome and AD dementia

Based in part on the evidence discussed in this review article, it appears possible that in the near future we might consider employing dietary intervention in preventative and possibly therapeutic strategies for AD. However, we want to point out that if modifications of dietary lifestyle prove to be helpful in either the prevention or treatment of AD, patients will have to undertake a permanent lifestyle change. Just as with many other chronic disorders, temporary changes in diet are not usually of any long-term benefit. We note that better long-term compliance with any lifestyle change is more likely if choices are available that address food preferences, satiety, availability of foods, and other factors. We must not make the mistake of thinking that one size fits all.

A diet that emphasizes whole foods and avoids refined and heavily processed foods will decrease exposure to added sugars, refined grains devoid of nutritional benefit, and manufactured trans fats. None of these foods should be a part of a healthy diet for any member of our population. Luckily, lifestyle changes that may have positive effects on AD will favorably impact a variety of chronic health conditions relating to obesity. An effective treatment will not only address AD but will also normalize weight, improve the components of metabolic syndrome, and treat or prevent diabetes and cardiovascular disease; it could revolutionize preventive care.

The Mediterranean diet, which is rich in healthy oils — especially fish containing omega-3 fatty acids, and unrefined whole foods — while decreasing the intake of other animal proteins and lowering saturated fats, has also shown benefits for treating AD. The moderate intake of red wine, also associated with a Mediterranean-type diet, provides important nutrients that may play a role in ameliorating AD (Wang et al., 2006). Mediterranean-type diets do not have to contain excessive quantities of carbohydrate foods but do contain primarily those foods high in nutrients, such as polyphenols and other foods with antioxidant effects, to protect from ROS, which detrimentally affect mitochondrial and energy metabolism activities.

In recent years, a plethora of studies on low-carbohydrate ketogenic diets have been published. None of the studies that looked at numerous factors supported the many theories that these dietary plans are dangerous. No study has demonstrated damage to kidney or liver function or loss of bone mass. Such diets have also performed better than, or at least as well as, other diets with similar long-term weight loss results (Gardner et al., 2007).

For those with no clinical experience with low-carbohydrate diets, one significant group of findings related to cardiovascular risk factors presented rather surprising results. Virtually every study has demonstrated that such diets provide significant improvements in triglyceride and HDL levels as compared to low-fat, calorie-restricted diets (Feinman and Volek, 2006). Since no good therapy exists to increase HDL levels to lower cardiovascular risk, controlling both the quality and quantity of carbohydrate foods should be considered a viable choice. It appears that even natural saturated fats, as compared to manufactured trans fats, behave in a positive way, especially when restricting carbohydrates. Postprandial lipids and a number of other atherogenic markers are improved (Forsythe et al., 2008). Individuals with dangerous small, dense LDLs (pattern B) have been shown to shift their LDL particle size to the safer pattern A (Krauss et al., 2006; Seshadri et al., 2004; Westman, 2006). When consuming foods with a lower glycemic load, as happens with low-carbohydrate diets, inflammatory markers have improved even when compared to people on diets providing a lower fat intake (Forsythe et al., 2008). In subjects with type 2 diabetes, controlling both the quality and quantity of carbohydrate foods leads to better insulin sensitivity, better glycemic control and, most importantly the need for fewer medications (Gutierrez et al., 1998; Volek and Feinman, 2005).

It is quite common for those on a very low carbohydrate diet to spontaneously lower their calorie intake without actively counting calories. This likely occurs because of the satiety effects of a higher protein and natural fat intake. If a lifelong dietary change must take place to address the risk of AD, then hunger control must be a prime consideration, or the diet simply will not be followed (Nichols-Richardson, 2005). When controlling carbohydrates one is able to concentrate on an adequate protein intake, a quantity of low-glycemic vegetables and fruits, natural fats from all sources including fish, nuts and seeds, avocado, olives and olive oil.

Summary

Our studies, and recent work by others, support existing epidemiological evidence indicating that calorie intake is positively associated with increased incidence of AD. These findings raise the possibility that changes in dietary regimens may be used in the future as preventative measures aimed at delaying the onset of AD amyloid neuropathology. Investigations in experimental mouse models of AD-type amyloid neuropathology are of great potential benefit in terms of public health. They provide insights into possible interventions aimed at preventing or ameliorating conditions associated with aging, obesity, and diabetes, all of which indicate a high risk of developing AD dementia.

We want to point out, however, that decisions about diet recommendations in AD can be a complex endeavor and must, of course, be a healthy diet. Recommendations should be made on the basis of combined evidence from prospective epidemiological studies, and, ultimately, controlled clinical studies. While we believe that the ultimate evidence to support such recommendations should come from controlled clinical studies, we are also aware of the potential limitations of this approach. For example, we point out that, in view of the chronic nature of AD dementia and its relatively long latency period, it may be difficult to execute appropriate clinical studies over a long enough time and with large enough samples to draw accurate and repeatable conclusions. Despite these limitations, however, we believe that the recent prospective studies identifying increased calorie intake as a risk for AD offer

practitioners enough evidence to prudently address the dietary issues facing their patients at risk for AD. We also believe that a diet rich in protein (especially fish), non-starchy vegetables, low glycemic fruits, and natural fats; low in foods with added sugars (especially high fructose corn syrup) and processed foods; and with moderate wine intake will be beneficial in normalizing insulin and blood sugar pathology, will provide a variety of antioxidant nutrients, will improve brain function, and may possibly prevent AD.

Acknowledgments

The studies discussed in this manuscript related to GMP are supported, in part, by NIA AG02219 and MERIT Review grant from the Department of Veterans Affairs; they are also supported, in part, by grants from the Atkins Foundation, the New York Wine and Grape Foundation, Polyphenolics, Inc., and Humanetics Corporation. JE is a consultant for the Veronica Atkins Foundation.

References

Aksenov MY, Markesbery WR. Changes in thiol content and expression of glutathione redox system genes in the hippocampus and cerebellum in Alzheimer's disease. Neurosci. Lett 2001;302:141–145. [PubMed: 11290407]

Alzheimer’s Association. Alzheimer’s disease Facts and Figures. 2007. http://www.alz.org/national/documents

Anekonda T, Reddy HP. Can herbs provide a new generation of drugs for treating Alzheimer’s disease? Brain Res. Rev 2005;50:361–376. [PubMed: 16263176]

ANON. Health & Wellness Trends Report. Harleyville, Pa: Natl. Marketing Inst.; 2003.

Arendash GW, Jensen MT, Salem N Jr. Hussein N, Cracchiolo J, Dickson A, Leighty R, Potter H. A diet high in omega-3 fatty acids does not improve or protect cognitive performance in Alzheimer's transgenic mice. Neuroscience 2007;149(2):286–302. [PubMed: 17904756]

Balakrishnan K, Verdile G, Mehta PD, Beilby J, Nolan D, Galvao DA, Newton R, Gandy SE, Martins RN. Plasma Aβ1-42 correlates positively with increased body fat in healthy individuals. J. Alzheimers Dis 2005;8:269–282. [PubMed: 16340084]

Bastianetto S, Ramassamy C, Doré S, Christen Y, Poirier J, Quirion R. The Ginkgo biloba extract (EGb 761) protects hippocampal neurons against cell death induced by β-amyloid. Eur. J. Neurosci 2000;12 (6):1882–1890. [PubMed: 10886329]

Bastianetto S, Yao ZX, Papadopoulos V, Quirion R. Neuroprotective effects of green and black teas and their catechin gallate esters against β-amyloid-induced toxicity. Eur. J. Neurosci 2006;23(1):55–64. [PubMed: 16420415]

Brookmeyer R, Gray S, Kawas C. Projections of Alzheimer's disease in the United States and the public health impact of delaying disease onset. Am. J. Public Health 1998;88:1337–1342. [PubMed: 9736873]

Bubber P, Haroutunian V, Fisch G, Blass JP, Gibson GE. Mitochondrial abnormalities in Alzheimer brain: mechanistic implications. Ann. Neurol 2005;57(5):695–703. [PubMed: 15852400]

Busciglio J, Yeh J, Yankner BA. β-Amyloid neurotoxicity in human cortical culture is not mediated by excitotoxins. J. Neurochem 1993;61:1565–1568. [PubMed: 8377009]

Cao D, Lu H, Lewis TL, Li L. Intake of sucrose-sweetened water induces insulin resistance and exacerbates memory deficits and amyloidosis in a transgenic mouse model of Alzheimer disease. J. Biol. Chem 2007;282:36275–36282. [PubMed: 17942401]

Chen J, Zhou Y, Mueller-Steiner S, Chen LF, Kwon H, Yi S, Mucke L, Gan L. SIRT1 protects against microglia-dependent amyloid-β toxicity through inhibiting NF-kappaB signaling. J. Biol. Chem 2005;280:40364–40374. [PubMed: 16183991]

Confronting the Burgeoning Alzheimer’s disease crisis: new frontiers. http://www.alz.org/national/documents.

Cook DG, Leverenz JB, McMillan PJ, Kulstad JJ, Ericksen S, Roth RA, Schellenberg GD, Jin LW, Kovacina KS, Craft S. Reduced hippocampal insulin-degrading enzyme in late-onset Alzheimer's

disease is associated with the apolipoprotein E-epsilon4 allele. Am. J. Pathol 2003;162:313–319. [PubMed: 12507914]

Craft S. Insulin resistance and Alzheimer's disease pathogenesis: potential mechanisms and implications for treatment. Curr. Alzheimer Res 2007;4:147–152. [PubMed: 17430239]

Craft S, Watson GS. Insulin and neurodegenerative disease: shared and specific mechanisms. Lancet Neurol 2004;3:169–178. [PubMed: 14980532]

Dai Q, Borenstein AR, Wu Y, Jackson JC, Larson EB. Fruit and vegetable juices and Alzheimer's disease: the Kame Project. Am. J. Med 2006;119(9):751–759. [PubMed: 16945610]

Defeudis FV. Bilobalide and neuroprotection. Pharmacol Res 2002;46(6):565–568. [PubMed: 12457632]

Dietrich MO, Spuch C, Antequera D, Rodal I, de Yebenes JG, Molina JA, Bermejo F, Carro E. Megalin mediates the transport of leptin across the blood-CSF barrier. Neurobiol Aging. 2007[Epub ahead of print].

Duncan AM, Phipps WR, Kurzer MS. Phyto-oestrogens. Best Pract. Res. Clin. Endocrinol. Metabol 2003;17:253–271.

Durga J, van Boxtel MP, Schouten EG, Kok FJ, Jolles J, Katan MB, Verhoef P. Effect of 3-year folic acid supplementation on cogniyive function in older adults in the FACIT trial: a randomized, double blind, controlled trial. Lancet 2007;369:208–216. [PubMed: 17240287]

Farris W, Mansourian S, Chang Y, Lindsley L, Eckman EA, Frosch M, Eckman CB, Tanzi RE, Selkoe DJ, Guenette S. Insulin-degrading enzyme regulates the levels of insulin, amyloid-β protein, and the β-amyloid precursor protein intracellular domain in vivo. Proc. Natl. Acad. Sci. U S A 2003;100:4162–4167. [PubMed: 12634421]

Feinman RD, Volek JS. Low carbohydrate diets improve atherogenic dyslipidemia even in the absence of weight loss. Nutr. Metab. (lond) 2006;3:24. [PubMed: 16790045]

Fewlass DC, Noboa K, Pi-Sunyer FX, Johnston JM, Yan SD, Tezapsidis N. Obesity-related leptin regulates Alzheimer's Aβ. FASEB J 2004;18:1870–1878. [PubMed: 15576490]

Forette F, Seux ML, Staessen JA, Thijs L, et al. Prevention of dementia in randomised double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial. Lancet 1998;352:1347–1351. [PubMed: 9802273]

Forsythe C, Phinney S, Fernandez ML, Quann EE, Wood RJ, Bibus DM, Kraemer WJ, Feinman RD, Volek JS. Comparison of low fat and low carbohydrate diets on circulating fatty acid composition and markers of inflammation. Lipids 2008;43(1):65–77. [PubMed: 18046594]

Freund-Levi Y, Basun H, Cederholm T, et al. Omega-3 supplementation in mild to moderate Alzheimer's disease: effects on neuropsychiatric symptoms. Int. J. Geriatr. Psychiatry 2007;23(2):161–169. [PubMed: 17582225]

Frolich L, Blum-Degen D, Bernstein HG, et al. Brain insulin and insulin receptors in aging and sporadic Alzheimer's disease. J. Neural. Transm 1998;105:423–438. [PubMed: 9720972]

Gabuzda D, Busciglio J, Chen LB, Matsudaira P, Yankner BA. Inhibition of energy metabolism alters the processing of amyloid precursor protein and induces a potentially amyloidogenic derivative. J. Biol. Chem 1994;269(18):13623–13628. [PubMed: 8175797]

Gan L. Therapeutic potential of sirtuin-activating compounds in Alzheimer's disease. Drug News Perspect 2007;20:233–239. [PubMed: 17637936]

Ganguli M, Chandra V, Kamboh M, et al. Apolipoprotein E polymorphism and Alzheimer disease: The Indo-US cross-national dementia study. Arch. Neurol 2000;57:824–830. [PubMed: 10867779]

Gardner CD, Kiazand A, Alhassan S, Kim S, Stafford RS, Balise RR, Kraemer HC, King AC. Comparison of the Atkins, Zone, Ornish, and LEARN Diets for change in weight and related risk factors among overweight premenopausal women. JAMA 2007;297:969–977. [PubMed: 17341711]

Gasparini L, Gouras G, Wang R, Gross RS, Beal MF, Greengard P, Xu H. Stimulation of beta-amyloid precursor protein trafficking by insulin reduces intraneuronal beta-amyloid and requires mitogen-activated protein kinase signaling. J. Neurosci 2001;21:2561–2570. [PubMed: 11306609]

Grant WB. Dietary Links to Alzheimer's Disease: 1999 Update. J. Alzheimers Dis 1999;1:197–201. [PubMed: 12214118]

Gustafson D, Rothenberg E, Blennow K, Steen B, Skoog I. An 18-year follow-up of overweight and risk of Alzheimer disease. Arch. Intern. Med 2003;163:1524–1528. [PubMed: 12860573]

Gutierrez M, Akhavan M, Jovanovic L, Peterson CM. Utility of a short-term 25% carbohydrate diet on improving glycemic control in type 2 diabetes mellitus. J. Am. Coll. Nutr 1998;17:595–600. [PubMed: 9853539]

Haass C, Koo EH, Mellon A, Hung AY, Selkoe DJ. Targeting of cell-surface β-amyloid precursor protein to lysosomes: alternative processing into amyloid-bearing fragments. Nature 1992;357:500–503. [PubMed: 1608449]

Haley AP, Knight-Scott J, Simnad VI, Manning CA. Increased glucose concentration in the hippocampus in early Alzheimer's disease following oral glucose ingestion. Magn. Reson. Imaging 2006;24(6): 715–720. [PubMed: 16824966]

Hartman RE, Shah A, Fagan AM, Schwetye KE, Parsadanian M, Schulman RN, Finn MB, Holtzman DM. Pomegranate juice decreases amyloid load and improves behavior in a mouse model of Alzheimer's disease. Neurobiol. Dis 2006;24(3):506–515. [PubMed: 17010630]

Hashimoto M, Hossain S, Agdul H, Shido O. Docosahexaenoic acid-induced amelioration on impairment of memory learning in amyloid β-infused rats relates to the decreases of amyloid β and cholesterol levels in detergent-insoluble membrane fractions. Biochim Biophys Acta 2005;1738(1–3):91–98. [PubMed: 16427803]

Hayden KM, Zandi PP, Lyketsos CG, et al. Vascular risk factors for incident Alzheimer disease and vascular dementia: the Cache County study. Alzheimer Dis Assoc Disord 2006;20(2):93–100. [PubMed: 16772744]

Head E, Pop V, Vasilevko V, et al. A Two-Year Study with Fibrillar β-Amyloid (Aβ) Immunization in Aged Canines: Effects on Cognitive Function and Brain Aβ. J. Neurosci 2008;28(14):3555–3566. [PubMed: 18385314]

Heo HJ, Choi SJ, Choi S-G, Shin D-H, Lee JM, Lee CY. Effects of Banana, Orange, and Apple on Oxidative Stress-Induced Neurotoxicity in PC12 Cells. J. Food Sci. 2008[Epub ahead of print]

Heo HJ, Lee CY. Protective effects of quercetin and vitamin C against oxidative stress-induced neurodegeneration. J. Agric. Food Chem 2004;52(25):7514–7517. [PubMed: 15675797]

Ho L, Qin W, Pompl PN, et al. Diet-induced insulin resistance promotes amyloidosis in a transgenic mouse model of Alzheimer’s disease. FASEB J 2004;12:902–904. [PubMed: 15033922]

Howes MJ, Perry NS, Houghton PJ. Plants with traditional uses and activities, relevant to the management of Alzheimer’s disease and other cognitive disorders. Phytother. Res 2003;17:1–18. [PubMed: 12557240]

Hoyer S. The aging brain. Changes in the neuronal insulin/insulin receptor signal transduction cascade trigger late-onset sporadic Alzheimer disease (SAD). J. Neural Transm 2002;109:991–1002. [PubMed: 12111436]

Huang HJ, Liang KC, Chen CP, Chen CM, Hsieh-Li HM. Intrahippocampal administration of A β (1–40) impairs spatial learning and memory in hyperglycemic mice Neurobiol. Learn. Mem 2007;87:483–494.

Jagust WJ, Seab JP, Huesman RH, Valk PE, Mathis CA, Reed BR, Coxson PG, Budinger TF. Diminished glucose transport in Alzheimer's disease: dynamic PET studies. J. Cereb. Blood Flow. Metab 1991;11 (2):323–330. [PubMed: 1997504]

Kilander L, Nyman H, Boberg M, Hanson L, Lithell H. Hypertension is related to cognitive impairment: a 20-year follow-up of 999 men. Hypertension 1998;31:780–786. [PubMed: 9495261]

Krauss RM, Blanche PJ, Rawlings RS, Fernstrom HS, Williams PT. Separate effects of reduced carbohydrate intake and weight loss on atherogenic dyslipidemia. Am. J. Clin. Nutr 2006;83:1025–1031. [PubMed: 16685042]

LaFerla FM, Green KN, Oddo S. Intracellular amyloid-β in Alzheimer's disease. Nat. Rev. Neurosci 2007;8:499–509. [PubMed: 17551515]

Lau FC, Shukitt-Hale B, Joseph JA. The beneficial effects of fruit polyphenols on brain aging. Neurobiol. Aging 2005;26(1):128–132. [PubMed: 16194581]

Lau FC, Shukitt-Hale B, Joseph JA. Nutritional intervention in brain aging: reducing the effects of inflammation and oxidative stress. Subcell. Biochem 2007;42:299–318. [PubMed: 17612057]

Le Bars PL, Velasco FM, Ferguson JM, Dessain EC, Kieser M, Hoerr R. Influence of the severity of cognitive impairment on the effect of the Gnkgo biloba extract EGb 761 in Alzheimer's disease. Neuropsychobiology 2002;45(1):19–26. [PubMed: 11803237]

Leibson CL, Rocca WA, Hanson VA, Cha R, Kokmen E, O'Brien PC, Palumbo PJ. Risk of dementia among persons with diabetes mellitus: a population-based cohort study. Am. J. Epidemiol 1997;145:301–308. [PubMed: 9054233]

Li L, Holscher C. Common pathological processes in Alzheimer disease and type 2 diabetes: a review. Brain Res. Rev 2007;56:384–402. [PubMed: 17920690]

Li ZG, Zhang W, Sima AA. Alzheimer-like changes in rat models of spontaneous diabetes. Diabetes 2007;56:1817–1824. [PubMed: 17456849]

Lim GP, Chu T, Yang F, Beech W, Frautschy SA, Cole GM. The curry spice curcumin reduces oxidative damage and amyloid pathology in an Alzheimer transgenic mouse. J. Neurosci 2001;21:8370–8377. [PubMed: 11606625]

Lim GP, Calon F, Morihara T, Yang F, Teter B, Ubeda O, Salem N Jr. Frautschy SA, Cole GM. A diet enriched with the omega-3 fatty acid docosahexaenoic acid reduces amyloid burden in an aged Alzheimer mouse model. J. Neurosci 2005;25(12):3032–3040. [PubMed: 15788759]

Lin CL, Chen TF, Chiu MJ, Way TD, Lin JK. Epigallocatechin gallate (EGCG) suppresses β-amyloid-induced neurotoxicity through inhibiting c-Abl/FE65 nuclear translocation and GSK3β activation. Neurobiol. Aging. 2007[Epub ahead of print]

Lin MT, Beal MF. Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases. Nature 2006;443:787–795. [PubMed: 17051205]

Luchsinger JA, Tang M-X, Shea S, Mayeux R. Calorie intake and the risk of Alzheimer disease. Arch. Neurol 2002;59:1258–1263. [PubMed: 12164721]

Luchsinger JA, Tang M-X, Shea S, Mayeux R. Hyperinsulinemia and risk of Alzheimer's disease. Neurology 2004a;63:1187–1192. [PubMed: 15477536]

Luchsinger JA, Tang M-X, Siddiqui M, Shea S, Mayeux R. Alcohol intake and risk of dementia. J. Am. Geriatr. Soc 2004b;52:540–546. [PubMed: 15066068]

Luo Y, Smith JV, Paramasivam V, Burdick A, Curry KJ, Buford JP, Khan I, Netzer WJ, Xu H, Butko P. Inhibition of amyloid-β aggregation and caspase-3 activation by the Ginkgo biloba extract EGb761. Proc. Natl. Acad. Sci. U S A 2002;99(19):12197–12202. [PubMed: 12213959]

Macheix, JJ.; Fleuriet, A.; Billot, J. Fruit Phenolics. Boca Raton, FL. USA: CRC Press, Inc; 1990.

Maclennan KM, Darlington CL, Smith PF. The CNS effects of *Ginkgo biloba* extracts and ginkgolide B. Prog. Neurobiol 2002;67:235–257. [PubMed: 12169298]

Manach C, Williamson G, Morand C, Scalberg A, Remesy C. Bioavailability and bioefficiency of polyphenols in humans: I. Review of 97 bioavailability studies. Am. J. Clin. Nutr 2005;81(1):230S–242S. [PubMed: 15640486]

Mattson MP. Will caloric restriction and folate protect against AD and PD? Neurology 2003;60:690–695. [PubMed: 12601113]

McGraw JB, Furedi MA. Deer browsing and population viability of a forest understory plant. Science 2005;307:920–922. [PubMed: 15705851]

McMahon JA, Green TJ, Skeaff CM, Knight RG, Mann JI, Willaims SM. A Controlled Trial of Homocysteine Lowering and Cognitive Performance. NEJM 2006;354:2764–2772. [PubMed: 16807413]

Meyer JS, Rauch G, Rauch RA, Haque A, Crawford K. Cardiovascular and other risk factors for Alzheimer's disease and vascular dementia. Ann. N.Y. Acad. Sci. USA 2000;903:411–423.

Mielke MM, Rosenberg PB, Tschanz J, et al. Vascular factors predict rate of progression in Alzheimer disease. Neurology 2007;69:1850–1858. [PubMed: 17984453]

Miller BC, Eckman EA, Sambamurti K, et al. Amyloid-beta peptide levels in brain are inversely correlated with insulysin activity levels in vivo. Proc. Natl. Acad. Sci. USA 2003;100:6221–6226. [PubMed: 12732730]

Minoshima S, Frey KA, Foster NL, Kuhl DE. Preserved pontine glucose metabolism in Alzheimer disease: a reference region for functional brain image (PET) analysis. J. Comput. Assist. Tomogr 1995;19(4):541–547. [PubMed: 7622680]

Morris MC, Evans DA, Bienias JL, Tangney CC, Bennett DA, Wilson RS, Aggarwal N, Schneider J. Consumption of fish and n-3 fatty acids and risk of incident Alzheimer's disease. Arch. Neurol 2003;60:940–946. [PubMed: 12873849]

Nichols-Richardson SM, Coleman MD, Volpe JJ, Hosig KW. Perceived hunger is lower and weight loss is greater in overweight premenopausal women consuming a low-carbohydrate/high-protein vs high-carbohydrate/low-fat diet. J. Am. Diet. Assoc 2005;105:1433–1437. [PubMed: 16129086]

Niidome T, Takahashi K, Goto Y, et al. Mulberry leaf extract prevents amyloid β-peptide fibril formation and neurotoxicity. Neuroreport 2007;18(8):813–816. [PubMed: 17471072]

Nijveldt RJ, van Nood E, van Hoorn DE, Boelens PG, van Norren K, van Leeuwen PA. Flavonoids: A review of probable mechanisms of action and potential applications. Am. J. Clin. Nutr 2001;74:418–425. [PubMed: 11566638]

Okello EJ, Savelev SU, Perry EK. In vitro anti-β-secretase and dual anti-cholinesterase activities of Camellia sinensis L. (tea) relevant to treatment of dementia. Phytother. Res 2004;18(8):624–627. [PubMed: 15476306]

Oken BS, Storzbach DM, Kaye JA. The efficacy of Ginkgo biloba on cognitive function in Alzheimer disease. Arch. Neurol 1998;55(11):1409–1415. [PubMed: 9823823]

Ono K, Naiki H, Yamada M. The development of preventives and therapeutics for Alzheimer's disease that inhibits the formation of β-amyloid fibrils (fAβ), as well as destabilize preformed fAβ. Curr. Pharm. Des 2006;12(33):4357–4375. [PubMed: 17105432]

Peng Q, Buz'Zard AR, Lau BH. Neuroprotective effect of garlic compounds in amyloid-β peptide-induced apoptosis in vitro. Med. Sci. Monit 2002;8(8):BR328–BR337. [PubMed: 12165737]

Petot GJ, Traore F, Debanne SM, Lerner AJ, Smyth KA, Friedland RP. Interactions of apolipoprotein E genotype and dietary fat intake of healthy older persons during mid-adult life. Metabolism 2003;52:279–281. [PubMed: 12647263]

Phiel CJ, Wilson C, Lee VM, Klein PS. GSK-3alpha regulates production of Alzheimer's disease amyloid-beta peptides. Nature 2003;423:435–439. [PubMed: 12761548]

Picklo MJ Sr. Montine TJ. Mitochondrial effects of lipid-derived neurotoxins. J. Alzheimers Dis 2007;12:185–193. [PubMed: 17917163]

Pyorala M, Miettinen H, Halonen P, et al. Insulin resistance syndrome predicts the risk of coronary heart disease and stroke in healthy middleaged men: the 22-year follow-up results of the Helsinki Policemen Study. Arterioscler. Thromb. Vasc. Biol 2000;20:538–544. [PubMed: 10669654]

Qin W, Haroutunian V, Katsel P, Cardozo CP, Ho L, Buxbaum JD, Puigserver P, Pasinetti GM. PGC-1α decreases in the brain of Alzheimer's disease as a function of dementia. 2008(submitted)

Qin W, Chachich M, Lane M, Roth G, Bryant MR, Ottinger MA, Mattison J, Ingram D, Gandy S, Pasinetti GM. Calorie restriction attenuates Alzheimer's disease type brain amyloidosis in Squirrel monkeys (Saimiri sciureus). J. Alzheimers Dis 2006a;10:417–422. [PubMed: 17183154]

Qin W, Yang T, Ho L, et al. Neuronal SIRT1 activation as a novel mechanism underlying the preservation of Alzheimer's disease amyloid neuropathology by calorie restriction. J. Biol. Chem 2006b; 281:21745–21754. [PubMed: 16751189]

Ringman JM, Frautschy SA, Cole GM, Masterman DL, Cummings JL. A potential role of the curry spice curcumin in Alzheimer's disease. Curr. Alzheimer Res 2005;2:131–136. [PubMed: 15974909]

Rivera EJ, Goldin A, Fulmer N, Tavares R, Wands JR, de la Monte SM. Insulin and insulin-like growth factor expression and function deteriorate with progression of Alzheimer's disease: link to brain reductions in acetylcholine. J. Alzheimer Dis 2005;8:247–268.

Russo A, Palumbo M, Aliano C, Lempereur L, Scoto G, Renis M. Red wine micronutrients as protective agents in Alzheimer-like induced insult. Life Sci 2003;72(21):2369–2379. [PubMed: 12639702]

Savaskan E, Olivieri G, Meier F, Seifritz E, Wirz-Justice A, Müller-Spahn F. Red wine ingredient resveratrol protects from β-amyloid neurotoxicity. Gerontology 2003;49(6):380–383. [PubMed: 14624067]

Selkoe DJ. Alzheimer's disease results from the cerebral accumulation and cytotoxicity of amyloid β-protein. J Alzheimers Dis 2001;3:75–80. [PubMed: 12214075]

Seshadri P, Iqbal N, Stern L, Williams M, Chicano KL, Daily DA, McGrory J, Gracely EJ, Rader DJ, Samaha FF. A randomized study comparing the effects of a low-carbohydrate diet and a conventional diet on lipoprotein subfractions and C-reactive protein levels in patients with severe obesity. Am. J. Med 2004;117:398–405. [PubMed: 15380496]

Shishodia S, Sethi G, Aggarwal BB. Curcumin: getting back to the roots. Ann. N.Y. Acad. Sci. USA 2005;1056:206–217.

Shoji M, Golde TE, Ghiso J, et al. Production of the Alzheimer amyloid β protein by normal proteolytic processing. Science 1992;258:126–129. [PubMed: 1439760]

Skoog I, Lernfelt B, Landahl S, Palmertz B, Andreasson LA, Nilsson L, Persson G, Odén A, Svanborg A. 15-year longitudinal study of blood pressure and dementia. Lancet 1996;347:1141–1145. [PubMed: 8609748]

Smith MA, Rottkamp CA, Nunomura A, Raina AK, Perry G. Oxidative stress in Alzheimer's disease. BBA 2000;1502:139–144. [PubMed: 10899439]

Steen E, Terry BM, Rivera EJ, Cannon JL, Neely TR, Tavares R, Xu XJ, Wands JR, de la Monte SM. Impaired insulin and insulin-like growth factor expression and signaling mechanisms in Alzheimer's disease – is this type 3 diabetes? J. Alzheimers Dis 2005;7:63–80. [PubMed: 15750215]

Stolk RP, Breteler MM, Ott A, Pols HA, Lamberts SW, Grobbee DE, Hofman A. Insulin and cognitive function in an elderly population. The Rotterdam Study. Diabetes Care 1997;20:792–795. [PubMed: 9135944]

Taniguchi CM, Emanuelli B, Kahn CR. Critical nodes in signalling pathways: insights into insulin action. Nat. Rev. Mol. Cell Biol 2006;7(2):85–96. [PubMed: 16493415]

Tomlinson DR, Gardiner NJ. Glucose neurotoxicity. Nat. Rev. Neurosci 2008;9(1):36–45. [PubMed: 18094705]

Torpy JM, Lynm C, Glass RM. JAMA patient page. The metabolic syndrome. JAMA 2006;295(7):850. [PubMed: 16478914]

Vassar R, Citron M. Aβ-generating enzymes: recent advances in β- and gammasecretase research. Neuron 2000;27:419–422. [PubMed: 11055423]

Vina J, Lloret A, Valles SL, Borras C, Badia MC, Pallardo FV, Sastre J, Alonso MD. Effect of gender on mitochondrial toxicity of Alzheimer's Aβ peptide. Antioxid. Redox. Signal 2007;9:1677–1690.

Volek JS, Feinman RD. Carbohydrate restriction improves the features of metabolic syndrome. Metabolic syndrome may be defined by the response to carbohydrate restriction. Nutr. Metab. (Lond) 2005;2:31. [PubMed: 16288655]

Wang J, Ho L, Qin W, et al. Caloric restriction attenuates β-amyloid neuropathology in a mouse model of Alzheimer's disease. FASEB J 2005;19:659–661. [PubMed: 15650008]

Wang J, Zhao Z, Ho L, Seror I, Humala N, Percival S, Pasinetti GM. Moderate consumption of Cabernet Sauvignon attenuates β-amyloid neuropathology in a mouse model of Alzheimer's disease. FASEB J 2006;20:2313–2320. [PubMed: 17077308]

Westman EC, Yancy WS Jr. Olsen MK, Dudley T, Guyton JR. Effect of a low-carbohydrate, ketogenic diet program compared to a low-fat diet on fasting lipoprotein subclasses. Int. J. Cardiol 2006;110:212–216. [PubMed: 16297472]

Whitmer RA. The epidemiology of adiposity and dementia. Curr. Alzheimer Res 2007;4:117–122. [PubMed: 17430233]

Williams RJ, Spencer JP. Rice-Evans C. Flavonoids: antioxidants or signaling molecules? Free Radical. Biol. Med 2004;36:838–849. [PubMed: 15019969]

Williamson G, Manach C. Bioavailability and bioefficacy of polyphenols in humans: II. Review of 93 intervention studies. Am. J. Clin. Nutr 2005;81(1):243S–255S. [PubMed: 15640487]

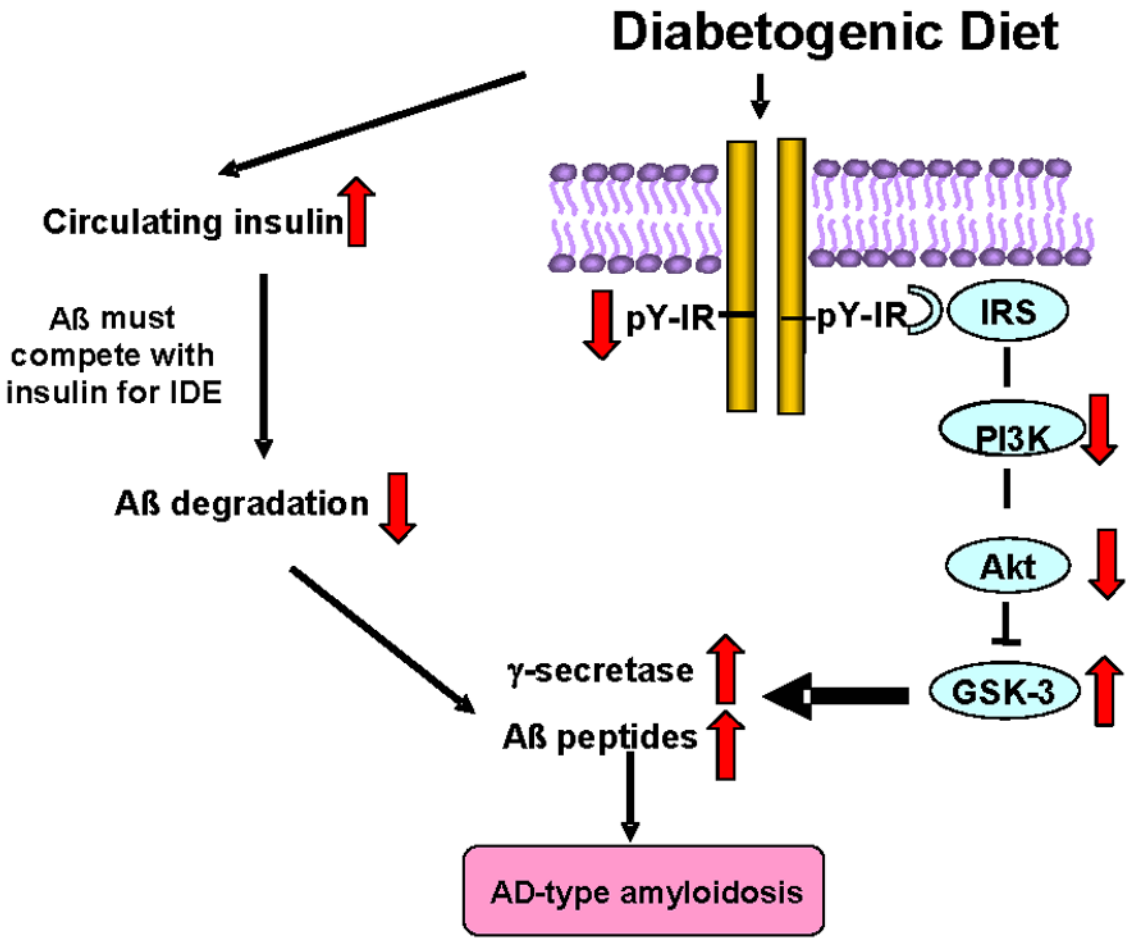
Yang F, Lim GP, Begum AN, et al. Curcumin inhibits formation of amyloid beta oligomers and fibrils, binds plaques, and reduces amyloid in vivo. J. Biol. Chem 2005;280:5892–5901. [PubMed: 15590663]

Yao Z, Drieu K, Papadopoulos V. The Ginkgo biloba extract EGb 761 rescues the PC12 neuronal cells from β-amyloid-induced cell death by inhibiting the formation of β-amyloid-derived diffusible neurotoxic ligands. Brain Res 2001;889:181–190. [PubMed: 11166702]

Yao ZX, Han Z, Drieu K, Papadopoulos V. Ginkgo biloba extract (Egb 761) inhibits β-amyloid production by lowering free cholesterol levels. J. Nutr. Biochem 2004;15(12):749–756. [PubMed: 15607648]

Young G, Conquer J. Omega-3 fatty acids and neuropsychiatric disorders. Reprod. Nutr. Dev 2005;45 (1):1–28. [PubMed: 15865053]

Zhao Z, Xiang Z, Haroutunian V, Buxbaum J, Stetka B, Pasinetti GM. Insulin degrading enzyme activity selectively decreases in the hippocampal formation of cases at high risk to develop Alzheimer's disease. Neurobiol. Aging 2006;28:824–830. [PubMed: 16769157]



Scheme 1. Hypothetical role of diabetogenic diet in AD amyloid pathogenesis
Abbreviations: IRS - insulin receptor substrate, PI3K - phosphoinositide kinase-3