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Review Article

Diet, nutrients and metabolism: cogs in the wheel driving Alzheimer's disease pathology?

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Abstract

Alzheimer's disease (AD), the most common form of dementia, is a chronic, progressive neurodegenerative disease that manifests clinically as a slow global decline in cognitive function, including deterioration of memory, reasoning, abstraction, language and emotional stability, culminating in a patient with end-stage disease, totally dependent on custodial care. With a global ageing population, it is predicted that there will be a marked increase in the number of people diagnosed with AD in the coming decades, making this a significant challenge to socio-economic policy and aged care. Global estimates put a direct cost for treating and caring for people with dementia at $US604 billion, an estimate that is expected to increase markedly. According to recent global statistics, there are 35·6 million dementia sufferers, the number of which is predicted to double every 20 years, unless strategies are implemented to reduce this burden. Currently, there is no cure for AD; while current therapies may temporarily ameliorate symptoms, death usually occurs approximately 8 years after diagnosis. A greater understanding of AD pathophysiology is paramount, and attention is now being directed to the discovery of biomarkers that may not only facilitate pre-symptomatic diagnosis, but also provide an insight into aberrant biochemical pathways that may reveal potential therapeutic targets, including nutritional ones. AD pathogenesis develops over many years before clinical symptoms appear, providing the opportunity to develop therapy that could slow or stop disease progression well before any clinical manifestation develops.

Key words: Alzheimer's disease: Diet: Nutrients: Lipids: Metabolism

Alzheimer's disease (AD), the most common form of dementia, is a chronic, progressive neurodegenerative disease that manifests clinically as a slow global decline in cognitive function, including deterioration of memory, reasoning, abstraction, language and emotional stability, culminating in a patient with end-stage disease, totally dependent on custodial care[1,2]. The greatest risk factor for AD is age and so with an ageing population, it is predicted that there will be a marked increase in the number of AD cases in the coming decades, in both the developed and developing world[3,4].

In the UK, 850 000 people are expected to have dementia by 2015, and recent estimates from the Alzheimer's society (UK) state that only 44 % of dementia cases receive a diagnosis. In Australia, approximately 300 000 people are suffering from dementia, with this number expected to be close to 1 million by 2050[5]. Current estimates put a direct cost of $AUD3·2

Abbreviations: AA, arachidonic acid; Aβ, β-amyloid; AD, Alzheimer's disease; ADAM-10, A disintegrin and metalloproteinase domain-containing protein 10; APP, amyloid precursor protein; BACE, β-site amyloid precursor protein-cleaving enzyme; BBB, blood–brain barrier; BDNF, brain-derived neurotrophic factor; CNS, central nervous system; EGCG, epigallocatechin-3-gallate; IR, insulin resistance; PC, phosphatidylcholine; PE, phosphatidylethanolamine; PEMT, phosphatidylethanolamine-*N*-methyltransferase; PLP, pyridoxal-5′-phosphate; SAH, *S*-adenosylhomocysteine; SAMe, *S*-adenosylmethionine; SIRT1, silent mating type information regulation 2 homologue 1; SREBP, sterol regulatory element-binding protein; THA, tetracosahexaenoic acid.

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billion to the healthcare system in Australia, with a predicted increase to $AUD6 billion within the next 5 years[6]. This represents a major economic burden to an already stretched healthcare budget. According to the Alzheimer's Association in the USA, unpaid care by family members and caregivers in 2009 represented $144 billion. Globally, it is expected that the incidence of AD will quadruple by 2050; according to these estimates, one in eighty-five individuals will be suffering from AD by 2050[2].

Currently, there is no cure for AD; while current therapies may temporarily ameliorate symptoms, death usually occurs approximately 8 years after diagnosis. These alarming statistics emphasise the importance of gaining a greater understanding of the pathophysiology of AD. Attention is now being directed to the discovery of biomarkers, which may not only facilitate pre-symptomatic diagnosis, but also provide an insight into aberrant biochemical pathways that may reveal potential therapeutic targets, including nutritional targets, which could slow or stop disease progression well before any clinical symptoms manifest. The present review provides a detailed discussion of the myriad of integrated nutritional factors probably contributing to the pathogenesis of AD. Specific emphasis is placed on abnormal lipid metabolism.

Hallmarks of disease

The causes and factors leading to disease progression are poorly understood; however, AD pathology is characterised by the presence of β-amyloid (Aβ) deposits and neurofibrillary tangles in the cerebral cortex and sub-cortical grey matter. There is much debate in the literature as to which of these hallmarks are causative and which result from other pathophysiological processes. Multiple factors have been implicated in the aetiology and pathogenesis of AD. These factors include genetic defects, abnormal lipid metabolism, energy metabolism deficits and mitochondrial defects, inflammation, abnormal amyloid precursor protein (APP) processing, deficiency of neurotrophic factors, glutamate excitotoxicity, free radical-induced neuron degeneration, and trace element toxicity, all of which are influenced by diet and nutrition. It is unlikely that any of these factors are isolated, but when combined with imbalances in neurotransmitters and hormones as well as impaired hepatic metabolic and detoxification pathways, a complex web of dysfunctional biochemistry is established, resulting in characteristic AD pathology[7].

Amyloid plaques

Amyloid plaques are a characteristic feature of AD and contain aggregates of Aβ, a 4 kDa peptide of thirty-nine to forty-three amino acids normally found in the brain, albeit at low concentrations[8]. Aβ is a protein fragment cleaved by the action of secretase enzymes from its larger parent protein called APP. APP is located in the plasma (outer) membrane of brain cells, including neurons, glial cells and the endothelial cells of the blood–brain barrier (BBB). APP is an abundant protein in the central nervous system (CNS), which is also ubiquitously expressed in the peripheral tissues such as epithelium, muscle and circulating cells[9].

APP undergoes proteolytic cleavage by enzymes termed BACE (β-site amyloid precursor protein-cleaving enzyme) and α- and γ-secretases. These enzymes act via two competing pathways that depend on the localisation of APP to specific membrane domains and feedback loops controlling gene transcription for the appropriate enzymes (reviewed in Krishnaswamy *et al.*[10]).

One product of APP cleavage is Aβ, of which two main isoforms are secreted; $A\beta_{40}$ and $A\beta_{42}$ consisting of forty and forty-two amino acids, respectively. $A\beta_{42}$ accounts for approximately 10 % of secreted Aβ, but is the main form found in amyloid plaques, suggesting a more pathological role for $A\beta_{42}$ due to its ability to aggregate and polymerise into amyloid fibrils more readily than $A\beta_{40}$[8]. An overproduction or reduced clearance of Aβ is considered a key component of AD, and alterations in Aβ kinetics may contribute to the induction of inflammation, oxidation and neurotoxicity, turning a physiologically relevant protein into a potentially toxic one[11]. Whether Aβ is the cause of AD or its deposition merely represents a protective response to some other pathophysiological process is an intense subject of debate[12].

Neurofibrillary tangles

Affected areas of the AD brain have significantly lower neuronal numbers, and the remaining neurons possess reduced numbers of dendrite branches and synaptic densities. Neurofibrillary tangles arise within individual neurons as deposits of abnormal fibrils, the primary constituent of which is the microtubule-associated protein tau. The tau protein in neurons is normally bound to microtubules, which provide structural integrity and are involved in intracellular transport[13]. Phosphorylation of tau is part of the normal process of assembly of microtubules, conferring stability. However, in AD, tau becomes hyper-phosphorylated or glycosylated, thereby weakening its affinity for microtubules. Once dissociation occurs, tau forms the filamentous double helical structures that characterise the paired helical filaments of neurofibrillary tangles. The tangles adversely affect neuronal function and result in loss of intracellular communication[14–16]. The phosphorylation and dephosphorylation of tau, as with other proteins, is tightly regulated by various kinases and phosphatases. Dysregulation of these processes, as occurs with defects in insulin and other signalling pathways, may contribute to the accumulation of neurofibrillary tangles.

Abnormal lipid metabolism

Abnormal lipid metabolism is emerging as a very important pathophysiological process in the development of AD. This is logical as the adverse effects of abnormal lipid metabolism on neuronal biochemistry are numerous, affecting membrane lipid composition and a myriad of cellular signals generated by lipid mediators. The link between AD and lipid metabolism was firmly established when carriage of the APOEε4 allele was identified as a major risk factor for AD[17]. Lipidomic studies

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have identified specific lipid changes in AD, including phospholipids, sphingomyelins, cholesterol and ceramides. Also, lipid metabolism has been intimately connected to processing of APP, leading to increased generation of Aβ[18–20]. These studies have also demonstrated the relevance of particular lipid alterations, such as ceramides, to general metabolic dysfunction and insulin resistance (IR)[21]. Diet and lifestyle factors generate signals to a complex network of hormones and transcription factors that orchestrate metabolism by sensing cellular energy requirements and influencing anti-ageing and pro-survival proteins, such as the sirtuins and AMP kinase. There are many integrated factors that derail normal lipid metabolism such as abnormal hormone signalling, inflammation, oxidation, altered neurotransmitters and abnormal hepatic metabolic pathways, all of which are profoundly influenced by diet nutrient status.

In recent years, numerous reports have highlighted the strong relationship between dementia and metabolic disorders that include dyslipidaemia, obesity, diabetes, CVD and hypertension (reviewed in Farooqui *et al.*[22], Frisardi & Imbimbo[23], Craft[24], Merlo *et al.*[25], Luchsinger[26] and Moreira[27]). While the mechanisms that underpin this association are beyond the scope of this article, it is important to emphasise that the aforementioned conditions rarely occur in isolation; the complex network of metabolic dysfunction that is associated with these conditions has been shown to influence many aspects of AD pathogenesis and neurodegeneration.

Insulin resistance

Poor diet and lifestyle choices can result in the development of IR, which often precedes the development of metabolic disease. IR is the failure of insulin to affect glucose disposal in muscle and adipose tissue as well as the failure to inhibit gluconeogenesis in the liver, resulting in elevations of blood glucose. Due to the tight relationship between glucose and lipid homeostasis, lipid abnormalities will also co-exist. When IR develops, increased circulating NEFA result from increased adipose tissue lipolysis as insulin normally inhibits hormone-sensitive lipase. The increased NEFA delivered to the liver eventually lead to increased hepatic VLDL secretion (elevated plasma TAG) and increased plasma cholesterol. A 'lipotoxic' state results from abnormal accumulation of TAG and fatty acids in the muscle and liver, which exacerbates IR by inhibiting insulin receptor substrate cascades[28–30]. Additionally, the increased expression of the inflammatory cytokine TNF-α by adipose tissue in obesity both impairs phosphorylation of the insulin receptor and enhances the release of NEFA[31,32]. Insulin has also been shown to induce the expression of fatty acid desaturase in monocytes, and may provide an explanation of the increased inflammation promoted by postprandial hyperinsulinaemia when the dietary *n*-6:*n*-3 ratio is high, resulting in the production of inflammatory eicosanoids from *n*-6 fatty acids[33]. Systemic inflammation is a key contributor to AD, particularly with respect to vasculature and integrity of the BBB[34].

Insulin is required for blood glucose regulation in both the periphery and the brain. When peripheral IR develops, metabolic dysfunction results and brain insulin signalling is altered, affecting glucose utilisation, Aβ and tau pathology, vasculature, mitochondrial function, inflammation, oxidation, neuronal maintenance and plasticity[24,35–37]. A neurodegenerative cycle consisting of AD pathogenesis, IR and inflammation has often been described. The components of this cycle have elevated ceramide levels as a common factor, suggesting that these toxic lipids may represent the link between all these pieces of the AD puzzle[38,39] (see Fig. 1).

Diet and nutrition

Dietary habits and nutritional status are emerging as key components of chronic degenerative diseases, including AD. This is further compounded by the fact that AD is an age-related disorder with a general decline in digestive function, absorptive capacity and assimilation of nutrients.

Atrophic gastritis is common in older people and can affect absorption of key nutrients such as vitamin B_{12} and folate[40,41], which have been associated with hyperhomocysteinaemia and increased risk of AD[42,43]. Atrophic gastritis can also affect protein absorption and, therefore, the supply of essential amino acids, such as tryptophan and tyrosine, which are required for the synthesis of neurotransmitters such as serotonin and catecholamines[44].

There is an age-related decline in metabolic rate, coupled with a decrease in physical activity; elderly people tend to eat less and may consume inadequate micronutrients. Additionally, co-morbidities often exist, requiring pharmaceutical agents that may further compromise nutrient status. The well-established risk factors for developing AD are elevated cholesterol and dyslipidaemia, obesity, diabetes, hypertension, depression, CVD and cerebrovascular disease (reviewed in Polidori *et al.*[45] and Patterson *et al.*[46]), all of which are biochemically connected and are influenced by diet and possible nutrient deficiencies.

An increase in AD incidence has been reported in populations who have a high intake of saturated fat, *trans*-fatty acids, refined sugar, processed foods, and total energy[47]. High fish consumption is inversely correlated with the development of dementia, and moderate alcohol consumption appears to offer a protective effect[47–49].

Many studies have confirmed the link between high-fat/high-sugar diets and declining cognitive function, strongly suggesting a role for IR and diet-induced endocrine abnormalities[35,50–52]. Diets that contain high saturated fat, cholesterol, added sugar, including high-fructose maize syrup, and high-glycaemic load foods contribute to dyslipidaemia[53,54]. Animal studies have shown that a diet high in fat and refined sugar influences brain structure and function via the regulation of neurotrophins[55]. Until recently, it was assumed that the adverse effects of such diets on AD were a direct result of the negative influence on insulin sensitivity, metabolism and cardiovascular health. While these are major contributing factors, these studies have shown a direct effect of such diets on the brain. Recent studies have also shown that hippocampal neurogenesis is adversely affected by high intakes of SFA[56,57].

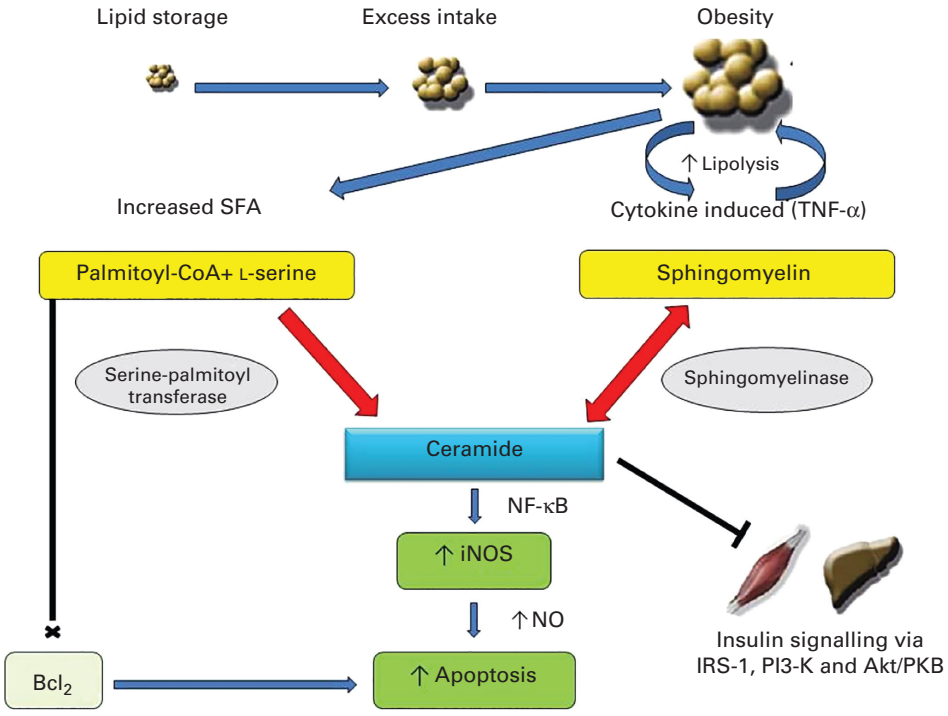

Fig. 1. Ceramides – the toxic intermediate linking metabolic dysfunction, inflammatory cytokines and insulin resistance? When adipose tissue exceeds its storage capacity, adipokines increase inflammation that increases ceramides. This inhibits insulin signalling, further increasing lipolysis and increasing the release of fatty acids for ceramide synthesis. Ceramide promotes apoptosis and elevated SFA inhibit the B-cell lymphoma 2 (Bcl_2) anti-apoptotic protein family of anti-apoptotic proteins. iNOS, inducible nitric oxide synthase; IRS-1, insulin receptor substrate-1; PI3-K, phosphatidylinositol-3 kinase; Akt/PKB, Akt also known as protein kinase B, a serine/threonine-specific protein kinase. A colour version of this figure can be found online at http://www.journals.cambridge.org/bjn

Neuronal plasticity is the brain's ability to compensate for challenges by influencing synapse formation and neurite growth. A high-fat/high-sugar diet has been shown in animals to decrease brain plasticity via the regulation of brain-derived neurotrophic factor (BDNF)[55], a major mediator of neuronal plasticity and a contributor to learning and memory capabilities[58,59]. Animals that learn a spatial memory task faster have been shown to have more BDNF mRNA and protein in the hippocampus, and after feeding a high-fat/high-sugar diet for 2 months, the hippocampal levels of BDNF were reduced and the animals demonstrated reduced spatial learning performance[55].

In contrast to the standard Western diet, characterised by high fat, high refined sugar, low fibre and high salt, the Mediterranean diet has been shown to reduce the risk for AD[60,61]. This eating style consists of high intakes of nutrient-dense, high-fibre foods such as vegetables, legumes, fruits and cereals. The intakes of high-fibre, non-refined carbohydrates contribute to a low-glycaemic load eating plan that helps to prevent IR and dyslipidaemia. Intakes of meat, dairy products and poultry (and, therefore, SFA and cholesterol) are low to moderate, and intake of fish and seafood is moderately high. Unsaturated fat intake in the form of monounsaturated fats from olive oil and *n*-3 fats from fish and seafood is high. Dairy products are consumed mainly in the form of cheese or yogurt, and there is regular consumption of red wine, usually with meals[60,62].

The Mediterranean-style diet also contains numerous nutrients and plant phytochemicals that are anti-inflammatory, antioxidant and beneficial to health. For example, low dietary intake of antioxidants may contribute to increased oxidative stress, a feature of AD[47,63]. Some of these nutrients and plant phytochemicals are now being shown to have a powerful influence on gene transcription factors, such as SIRT1 (silent mating type information regulation 2 homologue 1) that influence energy homeostasis, lipid metabolism and possibly longevity[64–68]. A meta-analysis involving twelve studies with a total of over 1·5 million people, followed for a period of 3–18 years, has shown that a greater adherence to the Mediterranean eating style was associated with a reduced risk of mortality and morbidity, including AD[69]. The beneficial effects were observed in many markers of coagulation and inflammation, including homocysteine, C-reactive protein, IL-6, white cell count and fibrinogen. Blood lipids and blood pressure were also positively affected, all of which are risk factors for both CVD and AD[70].

Key macronutrients

Dietary fatty acids

Apart from dietary fatty acids being an energy-generating nutrient, the amount and type of fat is important for determining disease risk due to the diverse function of lipids in general; the structure and function of which is influenced by the fatty acids they contain. Fatty acids consumed affect plasma cholesterol levels differently due to the impact on the LDL receptor, the activity of which is regulated by the sterol content of the cell via sterol regulatory element-binding proteins (SREBP)[44].

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High saturated fat intake, particularly palmitic acid, is strongly associated with the development of dyslipidaemia, IR, obesity, diabetes, vascular disease and metabolic abnormalities, which as mentioned previously are all risk factors for AD[71–73]. Saturated and *trans*-fatty acid intakes are positively correlated with increased cholesterol levels and unfavourable shifts in LDL:HDL ratios[74–76]. Excess palmitic acid can also up-regulate ceramide production, which is considered a major contributor to dyslipidaemia and IR[38,77]. Emerging evidence suggests an association between IR and ceramides, where toxic ceramides may be the intermediate that links excess dietary SFA and inflammatory cytokines with IR[39]. This proposed relationship is depicted in Fig. 1. Additionally, studies have shown elevated ceramides in AD brain tissue[78,79]. Moreover, the ganglioside monosialotetrahexosylganglioside (a sialylated glycoceramide) is thought to accelerate Aβ pathology by promoting the formation of insoluble fibrils[80], and abnormal sphingolipid metabolism has been shown to enhance tau pathology[81,82].

IR results in an atherogenic lipid profile that also includes a decrease in LDL particle size, reduced HDL and a postprandial accumulation of TAG-rich remnant lipoproteins. This has implications for vascular abnormalities in the brain.

Trans-fatty acids. Dietary *trans*-fatty acids are known to contribute to dyslipidaemia and associated increased disease risk[83], and have been linked to brain ageing and impaired cognition[84,85]. *Trans*-fatty acids alter membrane fluidity and responses of various membrane receptors through their incorporation into membrane phospholipids. As fatty acids are ligands for nuclear receptors, such as PPAR, liver X receptor and SREBP, regulation of gene transcription can be altered[86–88], directly modulating metabolic and inflammatory responses in an adverse way.

PUFA. Unsaturated fatty acids are competitive substrates for the enzymes involved in PUFA metabolism[44]. PUFA are converted via the action of cyclo-oxygenase and lipoxygenase enzymes to prostaglandins, leukotrienes, thromboxanes and other metabolites that are important mediators of cellular function; the signalling molecules generated, therefore, are partly influenced by dietary intakes[89]. Signalling molecules derived from *n*-6 PUFA are more inflammatory, atherogenic and pro-thrombotic than those derived from the *n*-3 series[44]. α-Linolenic acid is the precursor for the important EPA and DHA; DHA is the most abundant PUFA in the CNS[90].

Deficiency of essential fatty acids is rare; however, conversion of α-linolenic acid by the action of elongase and desaturase enzymes to the longer-chain PUFA is affected by hormone imbalances, diet and nutrient deficiencies[91–93]. High intakes of *n*-6 fatty acids, including arachidonic acid (AA), typically found in meat can elevate pro-inflammatory eicosanoids and up-regulate pro-inflammatory cytokines. Levels of non-enzymatically derived isoprostanes, which are vasoconstrictive, are also elevated in AA-enriched diets[94]. Conversely, diets enriched in DHA from fish and fish oil are more anti-inflammatory, anti-thrombotic and vasodilatory, and have neuroprotective effects in terms of synaptic function and plasticity via the generation of docosanoids[89,95]. The ratio of dietary AA:DHA would appear to influence several diseases, including AD, and may be important in designing nutrition-based strategies for disease prevention[96]. The brain relies on a supply of AA and DHA from the periphery, which are delivered via plasma lipoproteins and lysophospholipids. Unesterified AA and DHA can also enter the brain where they are esterified into the sn-2 structural position of phospholipids following activation by long-chain fatty acyl-CoA synthase[44].

Low DHA levels may reflect inadequate intakes and/or the presence of abnormal biochemical pathways involving this compound. While DHA can be obtained from dietary sources, an adequate supply to the brain also relies on peroxisomal production. The elongation and desaturation of fatty acids occurs in the endoplasmic reticulum or microsomes; however, the conversion of EPA to DHA requires a final additional step that only occurs in peroxisomes[97]. EPA undergoes two further elongation steps and a final δ-6 desaturation step occurs in the endoplasmic reticulum to yield tetracosahexaenoic acid (THA). This very-long-chain fatty acid is transported to the peroxisome for a final β-oxidation step to remove two carbons and yield DHA[98]. This additional step is suggested as a reason for inefficient conversion of the essential fatty acid α-linolenic acid to DHA, and why additional dietary intakes of DHA may be required to meet the needs of the brain. A recent study of AD patients has shown deficient liver biosynthesis of DHA; higher levels of THA, and lower expression of peroxisomal D-bifunctional protein (required for the conversion of THA to DHA) were detected in these individuals[99]. Any accumulation of very-long-chain fatty acids such as THA can adversely affect mitochondrial function[100], with mitochondrial dysfunction and oxidative stress thought to be central to AD pathogenesis. Abnormal elongase and desaturase enzyme activity could be present in AD, resulting in a lower than normal production of longer-chain PUFA. This may then have multiple consequences including reduced membrane fluidity and an imbalance in PUFA-derived signalling molecules such as eicosanoids and docosanoids. Δ6-Desaturase acts as a gateway for the flow of fatty acids into the elongation and desaturation pathways; the activity of this enzyme may be influenced by dietary intakes of fatty acids, various nutrients such as Zn, Mg and vitamin B_6[91] and metabolic hormones[101,102]. Furthermore, insulin is known to affect the activity of both Δ5- and Δ6-desaturases[92] and by reducing the supply of long-chain PUFA to the brain, may represent an additional mechanism by which metabolic dysfunction and associated IR could contribute to AD.

DHA and EPA are important in maintaining normal plasma TAG levels as they regulate the activity of various nuclear receptors resulting in a repartitioning of fatty acids away from storage as TAG and towards oxidation. These receptors include liver X receptor, hepatocyte nuclear factor 4α, farnesoid X-activated receptor, and PPAR. Each of these receptors is, in turn, regulated by SREBP-1c[103]. Both EPA and DHA reduce SREBP-1c, which is the main genetic switch controlling lipogenesis, and thereby reduces the amount of NEFA available for VLDL synthesis. EPA and DHA are highly unsaturated and are prone to peroxidation, which stimulates the degradation of ApoB, required for VLDL synthesis, and their presence in lipoproteins may also enhance postprandial chylomicron clearance by stimulating lipoprotein lipase activity[103].

Dietary carbohydrates

The amount and type of dietary carbohydrate has a significant impact on lipid profiles and the risk of developing AD risk factors such as CVD and type 2 diabetes. Long term consumption of high glycaemic load, refined carbohydrates and simple sugars can lead to IR and the metabolic syndrome[54,104].

In 1992, the US Department of Agriculture recommended that no more than 40 g of extra sugars should be added to a standard 8368 kJ (2000-calorie)-a-day diet. The liver rapidly absorbs and metabolises fructose, and exposure to large amounts of fructose leads to lipogenesis and TAG accumulation. Fructose is phosphorylated by fructokinase to fructose-1-phosphate, which is then metabolised to triose phosphates, glyceraldehydes and dihydroxyacetone phosphate. A key factor of fructose metabolism is that the entry of fructose via fructose-1-phosphate bypasses regulation by allosteric inhibition of phosphofructokinase by citrate and ATP, which is the main rate-controlling step in glycolysis[105]. In this way, fructose continually gets converted to fat.

Fructose conversion to glycerol-3-phosphate esterifies with NEFA to form TAG. The accumulation of TAG contributes to reduced insulin sensitivity, hepatic IR and impaired glucose intolerance[106]. As mentioned above fructose has been shown to up-regulate lipogenesis[107]. Glucose and insulin directly regulate lipogenesis as insulin controls SREBP expression that regulates fatty acid and cholesterol synthesis by the activation of pathways involving enzymes such as 3-hydroxy-3-methyl-glutaryl-CoA reductase and fatty acid synthase.

Animal models have been used to investigate the relationship between chronic ingestion of simple sugars and neurogenesis[108]. This study has shown that sugar (either sucrose or fructose) feeding to rats reduced the number of newly mature neurons in the dentate gyrus, the most prolific neurogenesis region of the hippocampus, with the number of apoptotic cells also being significantly increased. Interestingly, when the feeds contained either glucose or fructose, enhanced proliferation of new neurons was observed, probably resulting from an attempt to compensate for the increased apoptosis. The authors of this study have also suggested that the observed elevated TNF-α levels reduced the survival of new neurons by promoting apoptosis and impairing BBB function. Elevated inflammatory cytokines and TAG can both compromise the integrity of the BBB[109]. Studies have shown that the adipokines leptin and gut-derived ghrelin stimulate adult neurogenesis in the regions of the hippocampus, hypothalamus and brain stem that regulate feeding, and the vagus nerves connecting the brain and gut[110–113]. A compromised BBB can also prevent the delivery of neuroprotective leptin and ghrelin to the hippocampus, and reduce neurogenesis[108]. These elegant animal studies have shown that these effects appear to be related to fructose and sucrose ingestion and are not seen with glucose only. The down-regulated hippocampal neurogenesis also appears to be independent of glucose levels, insulin, insulin-like growth factor-1 and cortisol. Fructose is thought to be metabolised mainly by the liver and kidney; however, it now appears that fructose affects neuronal function and neurogenesis[114]. This may provide a plausible link between increased fructose consumption in sweetened foods and drinks and the escalating rates of obesity and metabolic disease, which are risk factors for the development of AD.

Key micronutrients

Specific nutrient deficiencies in the elderly may exacerbate existing pathology in the brain, particularly in the presence of other risk factors[115]. The formation and maintenance of neurons relies on an adequate supply of the building blocks and cofactors required for normal functioning of biochemical and neurotransmitter pathways, all of which must be obtained from the diet[116]. In addition, mitochondrial decay due to oxidation is a feature of brain ageing and neurodegenerative disease and an adequate supply of nutrients that protect mitochondrial enzymes and mitochondrial membranes is crucial to support cellular energy generation and prevent neurological decline[117].

Vitamins, minerals and other metabolites act as critical cofactors for the synthesis of mitochondrial enzymes and other pathways, and, therefore, diets that supply inadequate amounts of micronutrients can accelerate mitochondrial decay and neurodegeneration[118]. Nutrients supporting mitochondrial function include B vitamins, vitamin C, cysteine, ubiquinone (co-enzyme Q10), α-lipoic acid, sulphur, Fe, Cu, Zn, Mn and Mg[118]. Deficiencies of several nutrients have been linked to dementia, including vitamins A, B, D and E, Mg, Zn and essential fatty acids.

There have been several studies that have examined the status of various nutrients in AD and mild cognitive impairment, a condition which often but not always precedes AD[119–122]. Several interventional clinical trials of nutrient supplementation have also been conducted to examine the effect on cognition[47,123–128]. These studies have provided inconsistent and sometimes conflicting results, which may be explained by poor study design, heterogeneous populations in terms of stage of disease and the complexities of nutrient interventions in an elderly population who have significant neurodegeneration.

Various nutrients influence lipid metabolism and also have specific effects on lipid-related AD pathology. The importance of methylation pathways in phospholipid, sphingolipid and sterol metabolism is discussed below, as dietary intakes of vitamins B_6, B_{12} and folate influence these pathways. Additionally, methylation is a crucial facilitator of epigenetic modifications controlling gene expression, and can be adversely affected. Abnormal methylation pathways can also elevate plasma homocysteine levels, a risk factor for developing AD.

Water-soluble vitamins

B vitamins. The B vitamins are interconnected and intimately involved with lipid, carbohydrate and protein metabolism via their role as co-enzymes in mitochondrial ATP generation. The metabolism of vitamin B_6 (pyridoxine) depends on both vitamins B_2 (riboflavin) and B_3 (niacin). Synthesis of niacin

from tryptophan requires the activated form of vitamin B_6 (pyridoxal-5′-phosphate, PLP) to act as a cofactor for the enzyme kyureninase[44,129]. In AD the activity of tyrosine hydoxylase, which catalyses the conversion of tyrosine to L-dopa (the precursor for dopamine), has been shown to be reduced in key regions of the brain[130]. In addition, *in vitro* studies have shown that the redox co-enzyme NADH can increase the activity of tyrosine hydroxylase and dopamine in cells by 6-fold[131]. Vitamin B_5 (pantothenic acid) is the precursor to CoA, which forms the key intermediate acetyl-CoA, the molecule that links the metabolism of lipids, proteins and carbohydrates together and is the gateway to energy generation via ATP in the tricarboxylic acid/oxidative phosphorylation cycle[44]. Due to the crucial role of the B vitamins in cell biochemistry and mitochondrial function, it is clear that any dietary or lifestyle factor that reduces their availability, including poor absorption, excess alcohol consumption and medication use, increases the risk of neurological damage.

Vitamin B_1 (thiamin). Subclinical thiamin deficiency is not uncommon, particularly in the elderly[132] or those with high alcohol consumption as alcohol interferes with the active transport of thiamin out of the intestinal cells[44]. Numerous thiamin-dependent processes have been shown to be significantly reduced in the AD brain[133,134], and deficiency has been associated with dementia[135]. The effects of thiamin deficiency on neurological function can be explained in part by considering the enzymes that use thiamin as a cofactor. The thiamin-dependent enzymes transketolase, pyruvate dehydrogenase and α-keto-glutarate dehydrogenase have crucial roles in glucose metabolism and energy generation, and reductions in enzyme activity can result in nerve cell damage[136]. A reduction in transketolase also decreases the availability of reducing substances such as NADPH via the pentose phosphate pathway, which is required for lipid synthesis and the removal of reactive oxygen species. A reduction in pentoses, required for nucleic acids, co-enzymes and polysaccharides, is also observed, which can further compromise cellular function[136]. Thiamin deficiency also leads to increased lactic acid in the brain, and is probably a result of reduced pyruvate entering the tricarboxylic acid cycle due to diminished pyruvate dehydrogenase activity. The reduction in α-keto-glutarate dehydrogenase activity may contribute to the decreased levels of several neurotransmitters such as γ-amino butyric acid, glutamate and aspartate[137]. This suggests that *N*-methyl D-aspartate receptor-mediated excitotoxicity may be involved in neuronal damage observed with thiamin deficiency, although this is yet to be established. Any cause of inadequate ATP production in neurons will result in an inability to pump the neurotransmitter glutamate out of the synaptic gap which will, therefore, continue to stimulate the neuron. ATP is required to control Na and Ca pumps, the balance of which is critical for nerve conduction. It has been shown that brain tissue of Alzheimer's patients contains reduced activities of thiamin-dependent enzymes, such as α-keto-glutarate dehydrogenase[134,138–140]. Increased levels of cerebrospinal fluid phosphorylated tau, a biomarker of AD, have been observed in cases of thiamin deficiency[141]. It has also been shown in both cellular and animal models that thiamin deficiency induced oxidative stress promotes amyloidogenic processing of APP and Aβ accumulation by regulating BACE1 maturation[142,143]. However, the relationship between thiamin deficiency and AD in humans needs further clarification.

Vitamin B_2 (riboflavin) and vitamin B_3 (niacin). Riboflavin is a precursor of the co-enzymes FMN and FAD, which are crucial redox cofactors in mitochondrial ATP generation and other biochemical pathways[117]. There is substantial evidence that oxidative stress is a contributing factor in both the development and progression of AD[144,145]. Riboflavin is vital in reducing oxidised glutathione (a major intracellular antioxidant) and restoring its antioxidant capacity[146]. FAD is also a co-enzyme for methylene tetrahydrofolate reductase (MTHFR) that converts homocysteine to methionine and xanthine oxidase and that produces uric acid[117]. Elevated homocysteine and low levels of reduced glutathione and uric acid are linked to both ageing and cognitive decline[147–149].

Niacin or nicotinic acid is required for the formation of the ubiquitous mitochondrial redox co-enzymes NAD and NADP, and severe deficiency of niacin or its precursor tryptophan causes pellagra, of which dementia is a main feature[44]. Although the exact mechanism linking niacin deficiency and dementia has not been established, niacin has been shown to be important for DNA synthesis and repair, myelination and dendritic growth, cellular Ca signalling, and acts as a potent antioxidant in the brain mitochondria[150–153]. Niacin has been included in preparations used in trials, where improvements in cognitive test scores have been reported[154], and a large prospective study using FFQ to estimate niacin intake concluded that dietary niacin may protect against AD and age-related cognitive decline[153]. However, further research into the role of specific nutrients to improve cognition is required as studies using FFQ have limitations, particularly in the elderly.

Vitamin B_6 (pyridoxine), vitamin B_{12} (cobalamin) and folate. Vitamin B_6 depletion has been implicated in mood disorders, depression and decline in cognitive function, and may contribute to AD disease progression[155]. It has been estimated that approximately 10% of the US population consumes less than half the RDA of vitamin B_6[156] and poor vitamin B_6 status is generally common in the elderly population[155]. PLP is the active form and is involved in amino acid metabolism of neurotransmitters such as γ-amino butyric acid, serotonin, dopamine and noradrenalin. Taurine synthesis from cysteine also has a PLP-dependent step and taurine is a neuromodulatory compound[44]. PLP is a co-enzyme for several enzymes in one-carbon metabolism and *trans*-sulphuration. These reactions are crucial in providing methyl groups for the remethylation of homocysteine, a process that also requires adequate vitamin B_{12} and folate.

As mentioned previously, methylation reactions in the brain are critical and, therefore, an adequate supply of methyl groups provided by folic acid, vitamin B_{12} and SAMe (*S*-adenosylmethionine) is vital. The elderly may be compromised by dietary deficiency, poor absorption and inadequate inter-conversion of folates as occurs with polymorphisms in

the *MTHFR* gene. The importance of vitamin B_{12} has been described in relation to methylation reactions, which is also crucial for the production and maintenance of myelin; demyelination is thought to be one mechanism via which vitamin B_{12} deficiency affects CNS function[146]. Additionally, adenosylcobalamin, a metabolite of vitamin B_{12} acts as a mitochondrial cofactor for the production of succinyl-CoA. This is important for converting odd-chain fatty acids (not normally present in cell membranes) from propionate to succinate for oxidation in the tricarboxylic acid cycle. This conversion is inhibited with vitamin B_{12} deficiency and can result in odd-chain fatty acids being incorporated into myelin, therefore affecting nerve transmission[157]. Folate status also appears to be associated with the tissue levels of DHA, which are concentrated in neural tissue and affect receptor function and cell signalling[158]. Animal studies have shown that concentrations of DHA in platelets, erythrocytes and intestinal phospholipids are increased in rats fed supplemental folate[159]. Furthermore, animal studies have demonstrated that dietary folate deficiency causes depletion of DHA in neural tissue[160]. When there is folate sufficiency however, the increases in DHA observed are likely to be due to the efficient transfer of methyl groups from SAMe to phosphatidylethanolamine (PE) to form phosphatidylcholine (PC). Conversion of PE to PC that occurs in the liver is catalysed by phosphatidylethanolamine *N*-methyltransferase (PEMT), the conversion of which relies on methyl transfer and PC is critical for mobilisation of DHA from the liver into the plasma[158].

Homocysteine, choline and methylation pathways

Homocysteine is a sulphur-containing amino acid that exists at a critical biochemical intersection in the ubiquitous methionine cycle, the function of which is to generate one-carbon methyl groups for transmethylation reactions and synthesise cysteine and taurine[146] (see Fig. 2). Methionine is converted to SAMe, which is the most important methyl donor in the body and is critical for stabilising many macromolecules such as myelin and DNA. Methylation of DNA is an epigenetic modification that controls gene expression, including the highly methylated APP gene[161]. Methylation via SAMe is involved in the synthesis of numerous compounds including PC, melatonin, serotonin, noradrenalin, co-enzyme Q10 and carnitine[162]. Additionally, SAMe is a crucial component of both phase I and phase II detoxification pathways in the liver, providing the methyl group directly. Furthermore, a balanced methionine cycle is required to supply taurine for bile acid synthesis and cysteine for both sulphur conjugation and for the formation of glutathione, which is both an antioxidant and a vital phase I and II component[162]. All these processes are crucial for normal neurological and metabolic function.

The link between elevated homocysteine and AD risk has been firmly established in several studies[147,163,164], and homocysteine levels are also correlated to vitamin B_6, B_{12} and folate status[165–167]; however, the exact mechanisms underlying the elevated homocysteine, connected metabolites and AD, remain to be fully elucidated. It is probable that

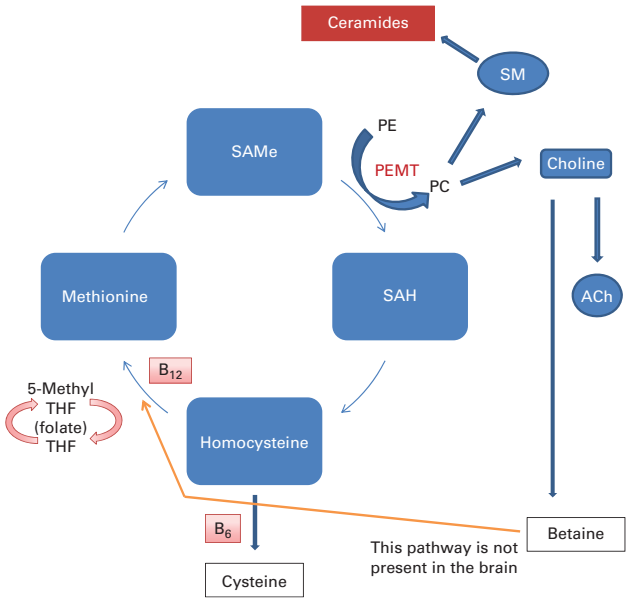

Fig. 2. Methylation pathway depicting interaction with phospholipids and sphingolipids. After donating the methyl group, *S*-adenosylmethionine (SAMe) is converted into homocysteine via *S*-adenosylhomocysteine (SAH). Homocysteine is then broken down by one of three pathways. First, it can be converted back to methionine by accepting a methyl group from methylcobalamin (vitamin B_{12}), and second, it can be converted to methionine by accepting a methyl group from trimethylglycine (betaine), or third, it can be converted to cysteine and taurine via serine and activated vitamin B_6[146]. The catabolism of homocysteine depends on an adequate supply of vitamin B_6, folate and vitamin B_{12}. The majority of the essential nutrient choline is present in phosphatidylcholine (PC) and sphingomyelin (SM), major components of all cell membranes. Additionally, PC and SM are precursors for the signalling molecules ceramide, platelet-activating factor and sphingophosphorylcholine[265]. Choline is required for the synthesis of the neurotransmitter, acetylcholine, and as it is oxidised to trimethylglycine, plays a crucial role as a methyl donor in the methionine/homocysteine pathway. PE, phosphatidylethanolamine; PEMT, phosphatidylethanolamine methyltransferase; ACh, acetylcholine; B_6, vitamin B_6; B_{12}, vitamin B_{12}; THF, tetrahydrofolate. A colour version of this figure can be found online at http://www.journals.cambridge.org/bjn

elevated homocysteine promotes AD by more than one mechanism, and while homocysteine serves as a surrogate marker for nutrient status (which when deficient can promote neurological damage in its own right), evidence suggests that homocysteine has direct actions on the brain. Cerebral microangiopathy has been demonstrated in stroke-associated hyperhomocysteinaemia[168]; endothelial dysfunction, oxidative damage and neuronal DNA damage are all reported consequences of elevated homocysteine[169–171]. There also appears to be an enhancement of Aβ-mediated neurotoxicity and apoptosis when homocysteine levels are elevated[172,173], and homocysteic acid, which is a metabolite of homocysteine, is possibly an *N*-methyl D-aspartate agonist itself, causing excitotoxicity and apoptosis[174,175].

The conversion of *S*-adenosylhomocysteine (SAH) to homocysteine is a reversible reaction, and so elevated homocysteine can also lead to an increase in SAH which is a potent inhibitor of methyltransferase enzymes (including PEMT required for PC production), further reducing the capacity of SAMe to participate in methylation reactions. This adversely affects numerous biochemical processes[176]. The APP gene is

highly methylated and decreased methylation may increase expression leading to increased Aβ production[161,177]. A link between elevated SAH and PUFA metabolism has also been established in AD[178]. The connection between homocysteine and lipid metabolism has been further highlighted as homocysteine-induced endoplasmic reticulum stress interferes with phospholipid metabolism. This has the effect of activating SREBP associated with increased expression of genes involved in cholesterol and TAG uptake and intracellular accumulation of cholesterol[179]. A regulatory feedback circuit has been identified, where SREBP-1 controls the production of SAMe and therefore PC production, which is dependent on methylation reactions, thereby giving merit to the notion that nutritional or genetic factors limiting the production of SAMe or PC, may activate SREBP-1 and contribute to metabolic dysfunction[180]. The inhibition of methyltransferase enzymes by SAH is very important in the brain as the alternate pathway for homocysteine catabolism via trimethylglycine (betaine) has no activity[42] (see Fig. 2). CNS cells cannot export SAH and therefore conversion to homocysteine and extracellular transport is the only way to remove SAH, causing a subsequent rise in plasma homocysteine. This raises the possibility that SAH could be the toxic metabolite, at least in some tissues[176], and suggests why the question of elevated homocysteine and increased disease risk has been difficult to answer with certainty.

Dietary fat and cholesterol are transported to the liver via chylomicrons and then packaged into VLDL in the liver for delivery to other tissues. PC is an essential component of these lipoproteins, and deficiency of choline and PC results in fat accumulation in the liver. Requirement for choline depends on the status of other methyl group donors such as folate and SAMe. When dietary choline is inadequate, the liver has a back-up pathway to provide choline from PE via a three-step methylation pathway involving SAMe, a reaction catalysed by PEMT[181]. Deficiencies of nutrients involved in this pathway could reduce the availability of choline. Interestingly, oestrogen induces endogenous synthesis of choline by up-regulating PEMT, which may put postmenopausal women at risk of choline deficiency, when dietary choline intakes are inadequate and oestrogen levels are declining[182]. Additionally, disturbed choline transport is suggested to play a role in various neurological disorders, including AD[183]. Loss of cholinergic neurons is a feature of AD and various choline transporters have been investigated as potential targets for increased choline delivery to the neurons for acetylcholine synthesis[183–185]. Studies have shown that one of the choline transport systems in erythrocytes is abnormal in patients with AD[186].

Fat-soluble vitamins

Vitamin A (retinol, retinal and retinoic acid). Vitamin A exerts hormone-like activity via binding of its metabolite retinoic acid to nuclear receptors. This process regulates cell differentiation, proliferation and apoptosis in adults, and influences binding of many other nuclear receptors involved in a diverse number of processes, including lipid metabolism[146,187]. Studies in rats have shown that vitamin A deficiency decreases the liver content of phospholipids[188], probably as a result of lower PC synthesis and reduced availability of fatty acids. This may be explained by a low activation of the transcription factor PPARα by its coactivator retinoid X receptor, which together play pivotal roles in the regulation of genes involved in lipid metabolism[189]. This process may adversely affect liver function itself in terms of lipid metabolism and bile production, and may also affect the supply of crucial phospholipids to other organs, including the brain. Vitamin A plays key roles in α-secretase production, acetylcholine transmission and in the regulation of excessive microglial activation[190], and vitamin A insufficiency has been shown to contribute to these processes in AD[191,192]. There are two binding sites for the retinoic acid receptor just upstream from the α-secretase gene ADAM-10 (A disintegrin and metalloproteinase domain-containing protein 10), and retinoic acid has been shown to up-regulate the expression of ADAM-10[193], thereby increasing non-amyloidogenic APP processing. In animal studies, vitamin A-deficient mice have been shown to have impaired ADAM-10 transcription and the addition of vitamin A up-regulated both ADAM-10 and APP, resulting in the reduced formation of Aβ and increased formation of the neuroprotective secreted β-APP ectodomain APPsα[194]. Additionally, dietary deficiency of vitamin A in adult rats leads to an increase in the deposition of Aβ in cerebral blood vessels[195]. Retinoic acid insufficiency has also been connected to reduced production of acetylcholine transferase, which inhibits the neurotransmitter function of acetylcholine, an additional feature of AD[192]. Furthermore, as mentioned previously, inflammation is a key feature of AD, and retinoic acid is a powerful modulator of immune function by reducing Aβ-induced inflammation via suppression of IL-6 and inhibition of TNF-α, and increased production of anti-inflammatory cytokines such as IL-10. The net effect is to reduce microglial expression of inducible NO synthase and hence activation. These effects are thought to be mediated by inhibiting the translocation of NF-κB[192]. Additionally, retinol has a crucial role in mitochondria as it is an essential cofactor for protein kinase C-delta, which acts as a nutritional sensor to regulate energy homeostasis. The protein kinase C-delta/retinol complex signals the pyruvate dehydrogenase complex to increase influx of pyruvate into the tricarboxylic acid cycle to produce more ATP[196]. Therefore, vitamin A deficiency may contribute to the hypometabolism observed in the AD brain[24]. Vitamin A insufficiency can result from poor dietary intakes of vitamin A-rich foods, as well as a result of two recently identified SNP in the gene that converts the vitamin A precursor, β-carotene, to retinol (β-carotene 15,15′-monoxygenase). These SNP are present in 25–40 % of the population and result in reduced enzyme activity and conversion to retinol[197]. Individuals carrying these SNP may benefit from higher intakes of pre-formed retinol and not rely on carotenoid sources from plant foods.

Vitamin D. Vitamin D, a cholesterol metabolite, has been implicated as a factor in AD, and recently the presence of a ligand-mediated vitamin D receptor pathway in the CNS was confirmed[198]. Studies have shown lower serum

vitamin D levels in AD[199,200] and higher parathyroid hormone levels[201]. In addition, the comorbidities of osteoporosis (associated with vitamin D deficiency) and AD often exist[202,203], both conditions being provoked by inflammatory processes and IR. Reduced mRNA for the vitamin D receptor has been shown in specific hippocampal regions in AD compared with normal controls[204] and a higher frequency of vitamin D receptor polymorphisms in AD has also been reported[205]. Vitamin D may protect the structure and integrity of neurons through detoxification pathways, and 1,25-dihydroxy vitamin D_3 (the active vitamin D metabolite) inhibits inducible NO synthase, and, therefore, reduces inflammation and oxidation, preventing excessive microglial activation. Vitamin D up-regulates γ-glutamyl transpeptidase and increases glutathione synthesis, a critical intracellular antioxidant[206]. Furthermore, neurotrophins, such as the docosanoid, neuroprotectin D1, and glial-derived neurotrophic factors are proteins necessary for neuronal survival, and vitamin D up-regulates their synthesis[198]. In AD, there is loss of hippocampal cells, which has been attributed to elevated voltage-gated Ca channels, reduced Ca-buffering capacity and glucocorticoid neurotoxicity. Vitamin D is a major regulator of Ca homeostasis and can protect against excitotoxicity[198]. Insulin sensitivity and signalling is also linked to vitamin D[207]. A study of over 2000 men has shown a correlation between vitamin D levels and bioavailable testosterone[208], and low levels of testosterone in elderly men has been linked to mild cognitive impairment and AD[209,210]. Moreover, animal studies have shown that vitamin D is crucial for gonad function and the production of sex steroids[211].

Vitamin E. Vitamin E levels have been shown to be lower in AD[212], and decreasing serum levels have been associated with poor memory in the elderly[213]. In addition to accumulating in circulating lipoproteins, vitamin E is also transported in plasma by phospholipid transfer protein. Studies have shown lower cerebrospinal fluid phospholipid transfer protein activity levels in AD compared with normal healthy controls, and this may result in reduced vitamin E transport to the brain and increased oxidative stress[214,215]. In neuronal cultures, vitamin E inhibits Aβ-induced lipid peroxidation and cell death[216,217]. Apart from its role as an antioxidant, there is increasing evidence that vitamin E may regulate gene activity as gene array studies have connected vitamin E deficiency with altered gene expression in the hippocampus of rats[218]. This study showed down-regulation of 948 genes including those affecting growth hormone, thyroid hormones, insulin-like growth factor, neuronal growth factor, melatonin, dopaminergic neurotransmission and clearance of advanced glycation end products[218]. Also, genes coding for proteins related to Aβ clearance were strongly down-regulated in the presence of vitamin E deficiency[218]. In addition to protecting against lipid peroxidation and modifying gene expression, recent studies have shown that vitamin E can block intracellular accumulation of ceramides and cholesterol, providing a further role for this vitamin[219]. However, trials using supplemental vitamin E have produced conflicting results[7,47], perhaps due to the varying forms of vitamin E used; naturally occurring vitamin E is a mixture of α- and γ-tocopherols, while the commonly used commercial form (D-α-tocopherol) contains just one isomer with activity. Additionally, a single isolated nutrient is less likely to produce a positive outcome due to the synergistic nature of nutrients and the fact that dietary sources contain so many other compounds. This, however, is likely to remain a limitation with respect to many such studies and should not be considered as unique to trials of vitamin E.

Zinc: a key mineral

Zn is a cofactor for numerous enzymes involved in DNA replication, repair and transcription, and is also a cofactor for the activity of the major intracellular antioxidant enzyme, superoxide dismutase[146]. Zn deficiency is a common feature in the elderly population[220], and dietary intakes of Zn and subsequent status may be influenced by other dietary factors and nutrients, such as Cu. Brain and cerebrospinal fluid levels of Zn have been shown to be depleted in AD, and serum Zn levels are inversely correlated with senile plaque count[221]. However, a paradox exists with the role of Zn in terms of AD risk and pathology[222]. Plasma levels may indicate Zn deficiency; however, Zn homeostasis in the brain is regulated in a way that is not reflected by peripheral levels, and levels in various regions of the brain may actually be increased[223]. Despite this conflicting situation, subclinical Zn deficiency, as a risk factor for AD, is supported by several studies[224–226]. Redox metals, including Zn, Fe and Cu, are implicated in the pathophysiology of AD, by facilitating the neurotoxicity of Aβ[227,228]. The paradoxical role of Zn can be related to both its function in the mitochondria and in haem synthesis, which binds to Aβ to prevent aggregation[117,229,230]. On the one hand, high levels as occurs with excessive Zn release (flooding) in response to oxidative stress may potentiate Aβ toxicity and activate apoptotic processes[222,231], yet Zn is also involved in mechanisms attempting to neutralise oxidative stress via metalloproteins, such as superoxide dismutase[228]. The Zn situation is complex in AD, but there is no doubt that abnormal cellular Zn mobilisation occurs, and the increase in Zn concentrations observed in affected areas may reflect an increase in the amount of Zn/Cu superoxide dismutase, when, in fact, tissue Zn in unaffected areas is depleted[232]. Furthermore, insulin-degrading enzyme, which is a Zn metallopeptidase, breaks down both Aβ and plasma insulin levels, and an isoform is also found in the mitochondria[233]. Zn depletion could, therefore, reduce the activity of this enzyme and hinder the clearance of Aβ.

Zn is intimately connected to lipid and fatty acid metabolism. The animals that are raised with *n*-3 PUFA-deficient diets demonstrate an increased expression of the Zn transporter protein (ZnT3, which loads Zn into synaptic vesicles), with an associated increased Zn level in the hippocampus and a decreased plasma Zn level[234]. Studies using neuroblastoma cell lines exposed to DHA have shown a decrease in Zn uptake and in the expression of ZnT3, and an associated reduction in apoptosis when compared with cells grown in a DHA-enriched medium[235]. Therefore, it could be speculated that in DHA-depleted cells, there is an increase

in desaturase activity (required for DHA production), for which Zn is a cofactor, in an attempt to generate additional long-chain PUFA. The interaction of Zn, DHA and vitamin D (which enhances intestinal absorption of Zn) may also provide an explanation for the beneficial effect of fish consumption as fatty fish are rich sources of all three nutrients[236]. The notion of such micronutrient synergy is supported by the systematic review of Loef *et al.*[223], who concluded that while it is not currently possible to determine whether Zn supplementation confers benefit in the context of AD prevention or treatment, animal studies have suggested that the effect of dietary Zn on cognition is contingent upon the presence of additional nutrients.

Dietary phytochemicals

Components of food are now recognised as having a profound influence on signalling pathways involving energy metabolism and synaptic plasticity, thereby influencing cognitive function. It appears that at a molecular level, these phytochemicals activate adaptive cellular stress responses, a phenomenon known as hormesis. These hormetic pathways involve transcription factors and kinases that influence the expression of genes encoding antioxidant enzymes, hepatic detoxification enzymes, protein chaperones, anti-inflammatory proteins and neurotrophic factors[67]. Examples of these hormetic pathways include SIRT1, NF-κB and nuclear factor-erythroid-2-related factor 2–antioxidant response element. The NAD-dependent deacetylase SIRT1 has been shown to attenuate amyloidogenic processing of APP, resulting in reduced production of Aβ in both cell culture and transgenic AD mouse models[237,238]. This effect is mediated by an up-regulation of the transcription of α-secretase, by deacetylating and thereby activating the retinoic acid receptor that binds to the promotor of the ADAM-10 gene. Additionally, ADAM-10 also enhances the Notch pathway that up-regulates the transcription of genes involved in neurogenesis including BDNF[239]. Activation of SIRT1 increases the gene expression of antioxidant response proteins (forkhead box O proteins), reduces inflammatory proteins (NF-κB) and increases mitochondrial biogenesis via PPARγ coactivator-1α[240]. Collectively, these effects result in reduced Aβ, reduced oxidative stress, reduced inflammation and enhanced resistance to Aβ-mediated toxicity and apoptosis.

Energy restriction[241] and *n*-3 fatty acids[242] are known to activate SIRT1. It has also been reported that dietary supplementation with *n*-3 fatty acids was effective in reversing the reduced SIRT1 expression observed in rats with traumatic brain injury (notably, in humans, traumatic brain injury is proposed to increase cerebral Aβ levels and increase AD risk in later life)[243–246]. In addition, the diet provides polyphenolic plant compounds that activate sirtuins, and may, therefore, be protective against some of the pathological processes contributing to AD. These compounds may protect against AD pathology by both SIRT1-dependent and SIRT1-independent mechanisms. These polyphenols include resveratrol[247] and its metabolite piceatannol[248] found in grapes, wine, peanuts, blueberries, bilberries and cranberries. The polyphenol fisetin found in foods such as strawberries, apples and grapes has been shown to stimulate signalling pathways that enhance long-term memory[249]. Quercetin, a polyphenol found in many foods including apples, onions, citrus fruits, green vegetables and berries, has significant anti-inflammatory and antioxidant properties and in cell cultures has been shown to attenuate Aβ production[250]. Furthermore, lutein and zeaxanthin are two carotenoids that can accumulate in retinal and brain tissue[251], and lower brain levels, as assessed by retinal pigment, have been observed in individuals with mild cognitive impairment compared with cognitively normal subjects[252].

Several other plant phytochemicals such as curcumin (the active constituent of turmeric), catechins (green tea) and anthocyanins (berries and pomegranate) have been shown to attenuate amyloid and tau pathology in addition to their general antioxidant and anti-inflammatory properties[64,253]. Curcumin has been shown to target multiple sites in the AD cascade. Redox metals such as Fe have been implicated in the aggregation and toxicity of Aβ. The structure of curcumin confers metal-chelating activity and inhibits metal-catalysed lipid peroxidation[254]. Furthermore, by the inhibition of c-Jun N-terminal kinase/activator protein-1 and NF-κB gene transcription, curcumin reduces the expression of inflammatory cytokines such as TNF-α, cyclo-oxygenase-2 and inducible NO synthase; elevations of which have been implicated in AD pathology[255,256]. In turn, the reduction in inflammatory cytokines may limit the induction of BACE, thereby reducing the amyloidogenic processing of APP[253]. However, despite the multimodal activities of curcumin, randomised placebo-controlled clinical trials of curcumin therapy conducted in early to moderate AD patients have, to date, failed, with no differences in the measures of cognition, blood Aβ, or cerebrospinal fluid Aβ and tau species observed[257,258]. Advanced cerebral pathology and limited curcumin bioavailability were cited as possible reasons for the lack of observed effects.

Studies comparing metal-associated (Cu and Zn) Aβ species demonstrated that the green tea extract epigallocatechin-3-gallate (EGCG) mitigated the toxicity of both free Aβ and metal-associated toxicity in cultured cells. In addition, aggregation of EGCG-bound Aβ species was attenuated, demonstrating anti-amyloidogenic properties of EGCG[259]. Whether EGCG can demonstrate such anti-amyloid capacity in humans, however, remains to be determined, and while oral dosing in humans has been shown to yield appreciable plasma EGCG concentrations[260], its ability to cross the BBB and enter the CNS has not been proven.

Studies in animals and cell-culture models have also shown that anthocyanins have direct effects on APP processing and reducing Aβ toxicity[261–263]. Notably, anthocyanin treatment has been shown to prevent memory impairment in a rodent model of AD, with the regulation of cholinergic neurotransmission implicated as a potential mechanism of action[264]. These promising biochemical and behavioural results suggest that additional *in vivo* and human studies are warranted.

Conclusion

The numerous integrated processes leading to the development and proliferation of AD are complex and involve genetics, epigenetics, metabolic dysfunction, hormonal circuits and toxic injury. Nutrition, by its influence on all of these contributing factors, is likely to have a profound impact on AD pathology. Therefore, understanding the effect of macro and micronutrients on neuronal biochemistry and AD pathology will provide opportunities for dietary manipulation to promote neuronal resistance to insults and reduce brain injury. The present review has highlighted some of the key nutrients involved both directly in neuronal biochemistry and indirectly by influencing peripheral metabolism, which, in turn, can promote AD pathology. Deficiencies or excesses of nutrients are unlikely to cause AD in their own right, but when combined with genetic factors and metabolic disease may accelerate existing pathology. AD pathology develops over many years before clinical symptoms appear, providing the opportunity to develop interventions, including nutritional approaches, which could slow or stop disease progression well before any clinical manifestations are apparent. Such interventions could include the use of intermittent energy restriction regimens, dietary phytochemicals and *n*-3 fatty acids to activate sirtuins, and help ameliorate poor metabolic health. Diets composed of energy-dense, nutrient-poor foods and containing high saturated fats, high simple sugars and low fibre will continue to drive metabolic disease and associated morbidities, including AD.

Micronutrient insufficiencies are often present with metabolic disease due to inadequate intakes and increased requirement as part of altered metabolism and medication use. In an ageing individual, intakes and assimilation of nutrients can be compromised, and may partly explain the conflicting results of clinical studies using nutrient interventions. In addition, many of these studies are poorly designed in terms of the stage of disease and extent of neuronal injury, and further trials need to be conducted that consider intervention before significant neurodegeneration is present. The profound impact of nutrition on the processes contributing to AD pathology cannot be denied; however, the lack of consistency in study data highlights the complexity of interpreting results from nutritional intervention trials. Future trials should account for the bioavailability of supplements used and the synergistic nature of nutrients in general: isolated nutrients are not present in food. Strategies need to be employed to reduce the predicted explosion in the number of AD cases, and as nutrition is part of the complex AD puzzle, one strategy might be the assignment of a specialist nutritionist as part of ongoing healthcare of an ageing individual, particularly in those with increased risk of developing this devastating disease.

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