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Review

The potential role of nutritional components in the management of Alzheimer's Disease

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Abstract

Epidemiological evidence linking nutrition to the incidence and risk of Alzheimer Disease is rapidly increasing. The specific nutritional deficiencies in Alzheimer patients may suggest a relative shortage of specific macro- and micronutrients. These include omega-3 fatty acids, several B-vitamins and antioxidants such as vitamins E and C. Recent mechanistic studies in cell systems and animal models also support the idea that nutritional components are able to counteract specific aspects of the neurodegenerative and pathological processes in the brain. In addition, it has been shown that several nutritional components can also effectively stimulate membrane formation and synapse formation as well as improve behavior and cerebrovascular health. The suggested synergy between nutritional components to improve neuronal plasticity and function is supported by epidemiological studies as well as experimental studies in animal models. The ability of nutritional compositions to stimulate synapse formation and effectively reduce Alzheimer Disease neuropathology in these preclinical models provides a solid basis to predict potential to modify the disease process, especially during the early phases of Alzheimer Disease.

Keywords: Alzheimer; Nutritional intervention; Synapse formation

Contents

1. Introduction

The increase in life expectancy and progressive aging of the total population may be our biggest challenge in health care for the next few decades. Quality of life at older age is strongly linked to cognitive function and impairment of cognitive function can be influenced by numerous factors, one of the most obvious, yet under-recognized, being the role of nutrition. Just like other organs in the body, the brain is acutely sensitive to what we eat or drink. In fact, most of the brain is constructed and maintained from what we eat. The dry weight of the brain is composed of about 60% fat (O'Brien and Sampson, 1965), and the fats from our diet directly affect the structure and composition of cell membranes (Bourre, 2006b; Clandinin et al., 1992). The electrical signaling between neurons as well as the constant restructuring of interconnected neurons also makes it the most

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energy demanding organ of the body, the main brain fuel being glucose, again for an important part secured by dietary intake (Simpson et al., 2007).

Alzheimer Disease is the most prevalent form of dementia, i.e. diseases showing severe loss of cognitive ability, during aging. Alzheimer Disease is a heterogeneous neurodegenerative disorder, clinically characterized by progressive and irreversible cognitive deficits and behavioral alterations that affect memory and learning ability, activities of daily living and quality of life, already in an early stage of the disease. The prevalence of Alzheimer Disease is only 1% above the age of 60 but increases dramatically to 40% above the age of 85. In addition to the increased life expectancy, also the association between nutrition and life style disorders may add to the predicted global burden of Alzheimer Disease considerably as well (Greenwood and Winocur, 2005; Weih et al., 2007). Based on the fact that the underlying pathologies may start years before the cognitive and behavioral impairments are clinically evident, application of the knowledge on preventive nutritional strategies warrants early identification of the disease to be able to intervene and delay, or even prevent its onset.

There is a growing interest in the role of nutrition in aging diseases such as dementia, in particular sporadic or late-onset Alzheimer Disease. The evidence to date supports a contribution of food and food components particularly in the prevention of and risk on Alzheimer's Disease. Older people may already be at nutritional risk because of changes in taste and smell, impaired digestion, absorption or utilization of nutrients due to chronic diseases or drug-nutrient interactions (Gillette Guyonnet et al., 2007). Although epidemiological studies sometimes report conflicting results, specific associations between nutritional components and the risk for Alzheimer Disease have been found, especially in frail elderly people at risk of deficiencies. These include the potential protective effects of, for instance, specific polyunsaturated fats, B-vitamins and antioxidants (Bourre, 2004; Weih et al., 2007). These macro- and micro-nutrients are dietary components that can influence brain structure and function (Bourre, 2006a,b).

Nutritional intake may provide specific nutrients that can be used as building blocks for membrane and synapse formation and neurotransmitter production but can also directly influence the availability of nutrients, energy and oxygen to the brain. The neuronal loss, amyloid and Tau protein pathology in the Alzheimer brain, as well as possible dysfunction of the cerebrovascular system and energy metabolism may act together to accelerate the downhill cascade in cognitive and behavioral function. The potential of nutrition for neuronal maintenance rather than as an energy substrate is illustrated by the increasing evidence that nutrients not only stimulate neural plasticity but also ameliorate the ongoing neurodegenerative process and show the ability to reduce the pathological burden in the brain. With the limited therapeutic utility of current pharmacological treatments for Alzheimer Disease, the question arises what nutrition may contribute to our toolbox to address the specific needs of the Alzheimer patient. We advocate that a multi-nutrient composition specifically targeting membrane formation has the capacity to modulate all of these processes and may provide a useful way, in conjunction with the pharmaceutical route, to treat the Alzheimer patient effectively.

2. Neuropathology in Alzheimer Disease

In the brain, Alzheimer Disease is associated with progressive synaptic and neuronal loss, in particular of basal forebrain cholinergic neurons. In addition, the Alzheimer brain shows accumulation and spreading of two pathological features, i.e. intraneuronal neurofibrillary tangles consisting of phosphorylated Tau protein, and extra cellular senile plaques consisting of amyloid-β. The etiology of the disease is still unknown but current hypotheses focus on the synaptic and neuronal loss and the role of amyloidogenic and/or Tau proteins as well as the contribution of oxidative stress, mitochondrial and vascular dysfunction and insulin resistance in disease onset. Scientific interest in the significance of each of these pathological features also as a potential therapeutic target has boomed during the past decade.

Tau is a neuronal protein present in axons and dendrites where it promotes tubulin polymerization and stabilizes microtubules and thus contributes to cell structure and cellular transport (Himmler et al., 1989). In addition, Tau is involved in axonal growth as indicated by the fact that neurons treated with Tau antisense in vitro are unable to grow axons (Caceres and Kosik, 1990). Hyperphosphorylation of Tau as present in neurofibrillary lesions characteristic in Alzheimer Disease, prevents Tau from binding to microtubules causing destabilization of cell structure thereby likely contributing to loss of axons, dendrites and synapses (Buee et al., 2000).

Amyloid beta (Abeta) is generated by sequential proteolytic cleavage of the transmembrane amyloid precursor protein (APP) by membrane bound enzymes, called secretases. The resulting length of the Abeta protein is dependent on initial cleavage of the extracellular domain generating the amyloidogenic end products Abeta1-42 and Abeta1-40 when cleaved by β- and γ-secretase, or the shorter non-amyloidogenic p3 fragment produced by α- and γ-secretase (Slack and Wurtman, 2007; Zinser et al., 2007). The Abeta1-42 end product in free form is highly neurotoxic, and forms aggregates that appear to be the predominant species in senile plaques (Iwatsubo et al., 1994; Zinser et al., 2007). Also, the ratio between soluble Abeta1-42 and 1-40 in cerebrospinal fluid correlates directly with the age of onset of Alzheimer Disease (Duering et al., 2005).

It has been proposed that soluble Abeta may present an interesting candidate as an initial trigger in the neuropathological cascade, although it is highly likely that other elements of Alzheimer's neuropathology contribute to the progressive nature of the disease (Walsh and Selkoe, 2004). Indeed, the degree and distribution of both the amyloid- and neurofibrillary pathology show a correlation with the stage of disease (Small et al., 2006) and, for instance, in triple transgenic mice expressing both plaques and tangles, reduction of both soluble Abeta and Tau, but not of soluble Abeta alone, attenuates the observed cognitive decline (Oddo et al., 2006).

The exact mechanisms whereby these pathological features preferentially induce basal forebrain cholinergic cell loss are not fully understood. Basal forebrain cholinergic neurons innervate

the hippocampus and neocortex that also show the highest densities of plaques and tangles and are central to the loss of cognitive function in Alzheimer's Disease. It has been shown that Abeta peptides have acute negative effects on acetylcholine synthesis and release and are neurotoxic on the longer term. Conversely, activation of cholinergic receptors alters the processing of APP as well as the phosphorylation of Tau protein in favor of non-amyloidogenic and non-hyperphosphorylation, respectively (Kar et al., 2004; Slack and Wurtman, 2007). The toxic effects of Abeta, that can induce an increase in excitability under current-clamp conditions, appear to be selective for cholinergic neurons (Jhamandas et al., 2001). Tau appears to be essential for the Abeta-induced neurotoxicity linking the two pathological features mechanistically to the loss of cholinergic neurons and cognitive function in Alzheimer Disease (Rapoport et al., 2002). The current evidence supports a mechanism whereby normal cholinergic innervation participates in the non-amyloidogenic maturation of APP, whereas the amyloidogenic related peptides depress the activity of cholinergic neurons. A shift in the balance between these two may be a key factor in early targeting of cholinergic neurons in Alzheimer Disease (Kar et al., 2004). Indeed, the density of terminals containing the acetylcholine synthesizing enzyme choline acetyl transferase in the neocortex shows a negative correlation with the severity of dementia and is already altered early in the disease process (Davies and Maloney, 1976; Kar et al., 2004).

Interestingly, there is a direct link between the function of cholinergic neurons, the cerebrovascular system and amyloid pathology. The cholinergic neurons in the basal forebrain project to cortical blood vessels directly (Vaucher and Hamel, 1995), and this innervation is reduced most prominently in the temporal lobe in Alzheimer Disease (Tong and Hamel, 1999). Acetylcholine is known as a potent vasodilator, likely acting via the muscarinic receptors (Luiten et al., 1996), and stimulation or inhibition of cholinergic neurons affects cerebral blood flow (Claassen and Jansen, 2006). Amyloid deposits are also found around cortical vessels suggesting that cholinergic deficits promote vascular Abeta deposits that consequently contribute to brain hypoperfusion or vice versa, that chronic hypo-perfusion due to cholinergic dysfunction can contribute to vascular deposition of amyloid protein.

The normal aging process is generally associated with a gradual loss of neurons, a lower ability of the brain to create new synapses and various biochemical changes at the membrane level. The latter influences axonal signal transduction, regulation of membrane bound enzymes, ion channel structure as well as maintenance of various receptors (Yehuda et al., 2002). The aging cellular membrane is characterized by higher levels of cholesterol, decreased cholesterol turnover and decreased levels of poly unsaturated fatty acids (PUFAs). This may be related to poor uptake of PUFAs over the blood-brain-barrier, decreased incorporation into the membrane and/or reduced enzymatic activity (Yehuda et al., 2002).

Also, cerebral blood flow decreases with aging and is associated with a loss of endothelial function, the decline being more pronounced in Alzheimer Disease patients (Zhu et al., 2007). Endothelial cells form a critical component of the blood-brain barrier and are actively involved in the transport of nutrients from the blood to the brain (Simpson et al., 2007). Thus, dysfunction of endothelial cells and the blood-brain barrier may contribute to inadequate supply of nutrients and energy to the brain. Indeed, hypertension leading to increased blood-brain barrier permeability in cortex and hippocampus was associated with increased amyloid deposition in two mouse models (Gentile et al., 2007). Also, reduced brain glucose metabolism has been reported in patients with mild cognitive impairment, the preclinical or prodromal stage of Alzheimer Disease, and inhibition of energy metabolism may increase amyloidogenic processing of APP (Velliquette et al., 2005). Brain metabolism in aging may be further compromised by other factors. Normal functioning of the endothelial cells, for instance, can be disturbed by elevated levels of homocysteine (Austin et al., 2004), which also reduces cerebral expression of the glucose transporter Glut-1 (Lee et al., 2005). Interestingly, there is a strong overlap between pathogenesis of cerebro- and cardiovascular disease with respect to the role of lipids. Both low PUFAs as well as high levels of cholesterol and saturated fatty acids are associated with atherosclerosis, obesity and also represent established risk factors for Alzheimer's Disease, stroke and vascular dementia (Horrocks and Yeo, 1999; Mielke and Lyketsos, 2006).

It is clear that none of the currently developed preclinical animal models resemble the full clinical phenotype of Alzheimer Disease (van Dooren et al., 2005). Also, we should keep in mind that most transgenic animals and models of Abeta toxicity represent only a small part of the total Alzheimer's pathology and do not mimic the disease process of Alzheimer Disease in terms of timing, speed and sequence of events. Interestingly, most, if not all of the current developed single and multiple transgenic animal models as well as all preclinical animal models representing risk factors for Alzheimer Disease share one basic pathological feature, that is, axon pathology. The loss of synapses links the current tauopathy, the amyoid cascade as well as cholinergic-vascular hypotheses to, for instance, cardiovascular risk factors such as the apolipoprotein E4 allel (Adalbert et al., 2007; Buttini et al., 2002; Fryer et al., 2005; Sorrentino and Bonavita, 2007), elevated homocysteine (Seshadri et al., 2002), and insulin resistance (Martins et al., 2006). The early, central and well recognized loss of synaptic connectivity provides a clear rationale and target for intervention. The potency of nutrients to support brain function and neural plasticity in general and the relevance of this to counteract and or prevent the synaptic loss and reduce the neuropathological burden in the brain in Alzheimer Disease is discussed in more detail below.

3. Nutrition, nutritional deficiencies and Alzheimer Disease risk

The epidemiological evidence supports the idea that Alzheimer patients could benefit from nutritional intervention, although conflicting results have been reported. Alzheimer patients appear to be (subclinical) deficient in specific nutrients, and low intake of these nutrients has been associated with increased risk to develop Alzheimer's Disease. Since there are

indications that the prevalence of protein-energy malnutrition does not differ between Alzheimer's patients in the early stages and the general elderly population (Bedard et al., 2000; Faxen-Irving et al., 2002; Saletti et al., 2000; Sandman et al., 1987), this indicates that Alzheimer Disease patients may have very specific nutrient needs that could very well be a consequence of the disease process itself or may also reflect the net result of low intake of specific nutrients and/or reduced bioavailability of specific nutrients to the brain. Additionally, the individual genetic make-up, but also the contribution of specific risk factors or co-morbidities such as cardiovascular disease, high blood pressure and insulin resistance could further drive the need for higher intake of specific nutrients. When this specific need is not adequately met by the diet the emerging nutritional deficiency may accelerate the disease process.

Plasma levels of omega-3 fatty acids appear to be directly associated with cognitive function and are found to be lower in Alzheimer Disease patients (Conquer et al., 2000; Tully et al., 2003). Also, phospholipid (PL) fatty acid profiles in the brains of Alzheimer patients are altered (Soderberg et al., 1991). In contrast, high intake of omega-3 PUFAs has been associated with a reduced risk to develop Alzheimer Disease (Kalmijn, 2000; Kalmijn et al., 1997; Kalmijn et al., 2004; Solfrizzi et al., 2006a; Solfrizzi et al., 2006b; van Gelder et al., 2007). Several lines of evidence suggest that omega-3 PUFAs may also be able to improve the availability of nutrients to the brain by altering vascular components such as brain blood supply, and blood-brain barrier integrity and transporter efficiency (de Wilde et al., 2002; de Wilde et al., 2003; Hooijmans et al., 2007; Ximenes da Silva et al., 2002).

Epidemiological evidence indicates that antioxidants or vitamins such as folate also represent potentially beneficial nutritional components in Alzheimer Disease. Intake of vegetables, in particular the intake of the antioxidant vitamins C and E, has been linked to a lower risk of Alzheimer Disease (Engelhart et al., 2002). Studies in a rat model show that Abeta induced lipid peroxidation could be reduced by feeding vitamin E in rats (Montiel et al., 2006). Despite clear and promising results in animal studies, the use of these nutrients in clinical studies have to date, demonstrated unclear or only minor benefits (Sano et al., 1997). Furthermore, decreasing homocysteine, does not necessarily leads to improved performance in demented patients (Eastley et al., 2000; Sommer et al., 2003), despite the fact that high plasma homocysteine, which reflects low B-vitamin status, is associated with increased risk for Alzheimer Disease. Interestingly, recent data from the Rotterdam study suggest that cognitive performance is linked to folate status regardless of homocysteine levels (de Lau et al., 2007).

In addition to specific nutritional deficiencies, dietary excess has also been linked to Alzheimer Disease. Cohort studies show that high caloric and high saturated fatty acids intake and obesity also increases Alzheimer Disease risk. Diets that reduce caloric intake to address obesity or excess body fat, however, are often unbalanced in that these reduce the intake of carbohydrate, but increase those of fats and proteins. Even when evaluating the normal dietary intake we have to realize that our dietary habits have changed substantially during the past few decades. For instance, dietary intake of omega-6 linoleic acid has gradually increased due to the use of corn-fed cattle and plant fats in nutritional products and now exceeds omega-3 α-linolenic acid fatty acids by a factor four to ten as reflected in breast milk composition measurements (Ailhaud and Guesnet, 2004).

High total fat intake, in particular that of omega-6 saturated fatty acids are associated with poor cognitive performance and present a risk factor for Alzheimer Disease (Kalmijn et al., 1997; Luchsinger et al., 2002; Morris et al., 2003a,b; Ortega, 2006). The brain is extremely rich in PUFAs, particularly omega-3 fatty acids, and on average 1 out of every three fatty acids is a PUFA of dietary origin (Bourre, 2006b). A higher ratio of omega-6 to -3 PUFA is also associated with decreased insulin sensitivity and Diabetes Mellitus Type II (Harris, 1996). One mechanism linking the intake of high total fat and saturated fat intake to cognitive impairment and dementia may be through the development of insulin resistance (Greenwood and Winocur, 2005). Alzheimer's patients show reduced expression of insulin receptors in the brain (Hoyer, 2002; Steen et al., 2005), and diet-induced insulin resistance was accompanied by amyloid accumulation in a transgenic mouse model (Ho et al., 2004). Recent studies in knock out mice for the neuron-specific insulin receptor support the notion that insulin resistance in the brain may contribute to the development of dementia although the insulin resistance by itself is not sufficient to induce neurodegenerative changes (Schubert et al., 2004).

As discussed above, also the increase in membrane cholesterol with age, but hypercholesterolemia as a risk factor more particular, may contribute to loss of neuronal functionality. Indeed, genetic polymorphisms in apolipoprotein E, decreasing transport of cholesterol over the blood-brain barrier, are strongly linked with the age of onset of Alzheimer's disease. Increased membrane cholesterol results in stimulation of Abeta cleavage from APP, conversely Abeta can decrease cholesterol synthesis suggesting a tight link between lipid homeostasis and APP processing (Zinser et al., 2007). Animals fed diets high in cholesterol show increased production of Abeta whereas cholesterol-lowering drugs reduce circulating Abeta levels (Fassbender et al., 2001; Refolo et al., 2000; Refolo et al., 2001). Yet, cholesterol depletion also activates Abeta production indicating that cholesterol needs to be present within the membrane in an optimal amount to support normal functioning (Abad-Rodriguez et al., 2004).

Thus the development of late-onset Alzheimer's Disease appears to be complex and supports the notion that multiple pathways can be involved. These may interact to initiate and/or accelerate the cascade of events.

4. Benefits of nutritional components in Alzheimer Disease

Our interest in the potential of nutrition in neurodegenerative diseases such as Alzheimer Disease, has been initiated by our long standing research interest in the role of nutrition in brain development. The importance of, for instance, PUFAs in infant milk formulas to stimulate brain development and improve cognitive function in infants is now well established (Fleith and

Clandinin, 2005). Research within our own laboratory in collaboration with several academic groups during the past 10 years has led to the development of a nutritional composition that is currently being tested in a double-blind active controlled multicenter, multi-country clinical trial in early Alzheimer's Disease patients. Our strong believe in the potential of a multi-nutrient approach rather than that of a single nutrient, to stimulate neural plasticity and thereby improve cognitive function, is supported by several lines of evidence as discussed below. Fundamental to this is our hypothesis that the, perhaps modest, modulatory effect of each nutrient could have a clinically relevant potential when used in combination. A focus on membrane formation and membrane composition and integrity as the primary target for nutritional intervention is supported by the fact that it can be substantially modulated by nutrition, but also that several studies report loss of membrane early during the disease process (Mielke and Lyketsos, 2006; Mulder et al., 1998; Pettegrew et al., 2001; Pettegrew et al., 1988; Svennerholm and Gottfries, 1994). Furthermore, the membrane loss may be associated with the disease stage (Pratico et al., 2002). Axon pathology including synaptic loss or even dysfunction is a common event in most, if not all, preclinical models that display the hallmarks of Alzheimer pathology, but also in early Alzheimer Disease in humans (Adalbert et al., 2007; Scheff et al., 2007; Selkoe, 2002; Spittaels et al., 1999; Tsai et al., 2004).

The formation of new neuronal membrane, but also maintenance of membrane composition are highly dynamic processes that occur continuously throughout life and for which precursors and essential building blocks are needed, largely provided via the diet. For example, membrane lipids may act as (cofactors for) second messengers or as precursors for the production of for instance cytokines and prostaglandins. Homeostasis of membrane lipids in neurons is essential to prevent loss of synaptic plasticity, cell death and neurodegeneration (Mielke and Lyketsos, 2006; Pfrieger, 2003). Approximately 20% of the fat in our brains is made from essential omega-3 and omega-6 fatty acids that cannot be synthesized by the body and for which we are dependent on dietary intake. PUFAs are structural components of phospholipids which form the primary constituents of neuronal membranes. PUFAs of the omega-3 series include the longer chain ($\geq$C20) compounds eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), and their biosynthetic precursor, the C18 α-linolenic acid. PUFAs of the omega-6 series include the C18 precursor linoleic acid and the long chain PUFA (C20) arachidonic acid. Changes in brain lipids due to an increased or decreased synthesis or metabolism may result in homeostatic dysregulation and eventually neurodegeneration (Mielke and Lyketsos, 2006). The omega-3 and omega-6 fatty acids positively influence both function and fluidity of the membrane by altering membrane composition. In contrast, saturated fatty acids accumulate in neuronal membranes but instead increase membrane stiffness and thickness. The brain is also one of the most cholesterol-rich organs of the body and contains almost 25% of total body cholesterol. Cholesterol is concentrated within lipid rafts in the neuronal cell membrane and is involved in the formation and maintenance of synaptic connections (Pfrieger, 2003). Although cholesterol is synthesized locally and transport over the blood-brain barrier is limited, brain cholesterol homeostasis is not completely independent of blood cholesterol (Dietschy and Turley, 2004). Both excess of dietary cholesterol and dietary lipids, in particular PUFAs, affect neuronal membrane fluidity but also the cholesterol content of membranes (Stillwell et al., 2005; Yehuda et al., 2002).

Phospholipids constitute the backbone of neuronal membranes and are required for proper functioning of membrane proteins such as enzymes and receptors. The different classes of phospholipids present in the membrane, vary with respect to composition of the fatty acid groups and hydrophilic polar ends of the molecules, phosphatidylcholine (PC) being the most prominent membrane phosphatide. Formation of neuronal membrane is driven by the Kennedy pathway (Kennedy and Weiss, 1956), and restricted by rate limiting enzymes and the availability of substrates (Araki and Wurtman, 1998; Wurtman et al., in press). The most important component in neuronal communication, the synapse, consists of phospholipids that are very rich in DHA. Synthesis of phospholipids is regulated by availability of three critical precursor pools, i.e. choline, cytidine triphosphate (CTP) and diacylglycerol. The latter preferentially uses PUFAs to build new membrane. Brains of Alzheimer patients not only show an altered phospholipid fatty acid composition and reduced DHA and arachidonic acid levels (Soderberg et al., 1991), but also contain fewer and smaller synapses (Selkoe, 2002; Terry et al., 1991), reduced levels of membrane phosphatides (Nitsch et al., 1992) and synaptic proteins (Coleman et al., 2004), whereas levels of phosphatide breakdown products are increased and brain levels of choline appear to be reduced in the brains of Alzheimer Disease patients (Nitsch et al., 1992).

In a series of elegant studies Wurtman and coworkers showed that the nucleotide uridine, a precursor for the Kennedy cycle, adequately increases blood and brain uridine also increases levels of CDP-choline, an immediate precursor to PC (Cansev et al., 2005). The increases in plasma and brain uridine and the intermediate steps in the Kennedy pathway following oral intake of uridine monophosphate (UMP), a uridine source, were all time dependent. The rise in plasma, but not that in brain uridine was also dose dependent indicating that administrating an uridine source accelerates phosphatide synthesis very effectively.

In vitro, levels of PC increase following incubation with DHA, EPA or arachidonic acid, but not after incubation with saturated or mono-unsaturated fatty acids (Richardson and Wurtman, 2007). Likewise, in vivo supplementation of DHA or EPA (but not of arachidonic acid increases brain phosphatide formation in gerbils (Cansev and Wurtman, 2007b). More interestingly also levels of pre- and post-synaptic proteins were increased indicating an increase in synaptic membrane (Cansev and Wurtman, 2007b). Oral administration of the nucleotides uridine and cytidine also promote the synthesis of new synapses (Wurtman et al., in press).

The fact that availability of precursors is the limiting step in controlling the overall rate of phosphatide synthesis and formation of new membrane is illustrated by the fact that combining membrane building blocks, i.e. an uridine source, choline and the omega-3 fatty acid DHA, has additive effects on the formation of new membrane in vivo (Cansev and Wurtman, 2007b; Wurtman et al., in press; Wurtman et al., 2006). Daily administration of DHA, UMP and choline increased levels of all major PL classes

significantly in various brain regions to levels much more effectively than found after DHA or UMP alone. The increase in membrane phospholipids was also seen following the combination of UMP, choline and EPA, but not with the omega-6 fatty acid arachidonic acid (Cansev and Wurtman, 2007b). Moreover, the changes in brain phosphatide levels were associated with parallel increases in levels of pre- and post-synaptic proteins (Cansev and Wurtman, 2007b; Wurtman et al., 2006). The increase in synaptic protein markers supports the functional potential of the newly formed membrane. Indeed, other studies from this lab also demonstrate an increase in dendritic spine density in the hippocampus following oral DHA and UMP in adult gerbils (Sakamoto et al., 2007). The increase in dendritic spines was accompanied by increases in membrane phosphatides and synaptic proteins. Length and width of the dendritic spines were not affected, only the number of dendritric spines was increased. Again the increase in spine density was higher following the combination than of each ingredient alone. The effect was already apparent after 1 week and remained during the entire treatment period of 4 weeks.

Communication in the central nervous system is not only dependent on optimal connections between neuronal components but also on adequate supply and release of neurotransmitters. The rate of synthesis of neurotransmitters such as acetylcholine is also dependent on dietary intake of precursors (Cansev and Wurtman, 2007a; Fernstrom, 1981; Wurtman et al., in press). Synthesis of acetylcholine is controlled by dietary intake of choline (Cohen and Wurtman, 1976), but choline can also be made available from membrane phospholipids, i.e. PC, when dietary supply falls short (Ulus et al., 1989). Choline supplementation increases acetylcholine release and protects against the stimulation-induced decrease in membrane phosphatide levels in slices from rat striatum (Ulus et al., 1989). As is the case for membrane formation, the rate of transmitter synthesis is largely driven by precursor availability, since the rate limiting enzymatic step in acetylcholine production is not saturated at normal brain precursor concentrations (Cansev and Wurtman, 2007a; Wurtman et al., in press). The increase in the membrane precursor CDP-choline following supplementation of uridine sources, however, is not affecting acetylcholine synthesis or release in slice preparations (Ulus et al., 2006). In fact, supplementation of UMP on a normal choline containing diet background has been shown to increase acetylcholine levels and release in the striatum of aged rats in vivo using microdialysis, suggesting direct improvement of cholinergic function (Wang et al., 2007). This is of particular importance since the pathological cascade that underlies the loss of cognitive function, preferentially involves loss of cholinergic neurons in the basal forebrain. Indeed, chronic supplementation of UMP ameliorated impairment of hippocampal dependent memory in impoverished rats (Teather and Wurtman, 2006), and in our lab the combination of UMP and choline improved performance in several cognitive tests in spontaneous hypertensive rats (De Bruin et al., 2003). The above cited studies strongly support the potential use of nutritional membrane building blocks to support the capability of the brain to form new neurites and functional synapses. Also, the combination of these building blocks appears to be much more effective than each of these alone.

Thus, optimal neuronal function requires adequate intake and delivery of the specific nutrients to the brain to provide the building blocks for the maintenance of cell membranes in general and of synapses more specifically as well as for the communication between cells. Adequate supply of nutrients to the brain is, in turn, critically dependent on cerebrovascular function and optimal functioning of the blood-brain barrier. Compromised cerebrovascular function, for instance as a result of hyperhomocysteinemia or oxidative stress, can be targeted through respectively B-vitamin and antioxidant supplementation. In parallel to reducing homocysteine levels, B-vitamin supplementation reduces endothelial damage in brain microvasculature (Lee et al., 2005) and can improve endothelium dependent vasodilatation (Chambers et al., 2000). Also, supplementation of antioxidants can reduce markers for endothelial activation and preserve endothelium-mediated vasodilatation (Aminbakhsh and Mancini, 1999).

Improvement of neuronal function may also occur simply via reduction of the neuropathological impact. Amyloidogenic processing of APP may preferentially occur in cholesterol-rich lipid rafts within the membrane, whereas non-amyloidogenic processing of APP by α-secretase occurs in the non-raft regions of membranes (Cordy et al., 2006). Non-amyloidogenic processing of APP can be stimulated by altering membrane composition providing omega-3 fatty acids, most preferably DHA, that is build into the phospholipid domain and retained at the expense of other fatty acids (Stillwell et al., 2005). DHA enriched diets have indeed been shown to reduce Abeta production and/or improve cognitive function in several preclinical models for Alzheimer's Disease, including transgenic mouse models as well as rat models of Abeta toxicity (Calon et al., 2004; Cole et al., 2005; Hashimoto et al., 2002; Hashimoto et al., 2005; Lim et al., 2005; Oksman et al., 2006). DHA has previously shown to effectively lower Abeta production in transgenic mice as reported in studies from several laboratories (Cole et al., 2005; Lim et al., 2005; Oksman et al., 2006). Yet, plaque burden was reduced in only one study using aged transgenic mice following three months DHA enriched diet (Lim et al., 2005), but not in several other studies which started dietary intervention at a much younger age (Hooijmans et al., 2007; Oksman et al., 2006). Such an age dependent effect was also reported for the antioxidant vitamin E. Eight months intervention in young, 5 months old animals effectively lowered plaque burden in the hippocampus and cortex, but 6 months intervention starting at 14 months of age did not (Sung et al., 2004). Especially diet context with respect to fat composition and omega-6 to -3 ratio may be crucial since it was shown that DHA was effective in lowering intraneuronal Abeta (and Tau) up to 9 months after start of the intervention in a triple transgenic mouse, whereas combining DHA with arachidonic acid and other n-6 fatty acids diminished its effectiveness (Green et al., 2007).

So far, the approach in most clinical trials has been focused on the manipulation of a single component. This may also explain the difficulty to date to obtain solid proof of efficacy of for instance DHA in a clinical setting (Freund-Levi et al., 2006; Terano et al., 1999). There is substantial evidence, however, that a Mediterranean diet might be effective which again emphasizes the role of multiple ingredients rather than that of a single nutrient (Ortega, 2006). Adherence to a Mediterranean diet has also been associated with lower mortality in Alzheimer Disease suggesting a possible dose–response effect (Scarmeas et al., 2007). Indeed,

the nutritional components present in the Mediterranean diet that is characterized by high intake of vegetables high in antioxidants, legumes, fruits, cereals and unsaturated fatty acids, may indeed have synergistic or agonistic effects on health outcomes based on the preclinical results described above. The strength of combining nutrients is also supported by the evaluation of several intervention studies comparing single or multiple (micro) nutrients (Van Dyk and Sano, 2007). Factors of importance may include the ratio of one nutritional component to another, the preparation or even when it is eaten during the day and if or not specific components are taken at the same time. Also clinically, combinations of nutrients have indeed been found to be more effective than single components. For instance, Vitamins E+C were more effective in reducing lipoprotein oxidation than either one alone (Kontush et al., 2001). In addition, combining B-vitamins effectively reduced homocysteine levels (Stott et al., 2005), but more importantly improved memory function, attention and processing speed (Nilsson et al., 2001). B-vitamins have been shown to reduce plasma levels of Abeta (Flicker et al., 2006), and CSF levels of folate correlate with CSF phosphorylated Tau protein (Obeid et al., 2007). Interestingly, the relation between folate status and cognitive function recently appeared to be independent of homocysteine levels (de Lau et al., 2007), which may suggest that the contribution of B-vits may be directly correlated with its presumed effects at the brain level. B-vitamins play a crucial role in methylation processes important to energy metabolism in the cell. Especially membrane formation, but also neurotransmitter synthesis and release are energy demanding processes that involve methylation processes.

Combining nutritional components that are able to stimulate membrane synthesis and alter membrane composition may indeed be a promising approach as suggested by other recent findings. Studies in vascular compromised rat models showed significantly more improvement of receptor function and behavior in the group with the diet containing the highest concentration and number of brain specific nutrients including omega-3 fatty acids, phospholipids and several micronutrients (de Wilde et al., 2003; Farkas et al., 2002). The diets tested were equally effective in improving endothelial integrity and membrane composition (de Wilde et al., 2002; de Wilde et al., 2003). Interestingly, the diet improved receptor function selectively, since muscarinic M1 expression was significantly increased by the PUFA containing diet, but the increase in the serotonergic 5HT1A receptor was only significant in the group receiving the highest amount of brain specific nutrients (Farkas et al., 2002). Recent data from our lab also support the proposed additive or synergistic effects between nutritional components in animal models for Alzheimer Disease. Using a multi-nutrient intervention we observed protective ability against Abeta toxicity in the rat (van der Beek et al., 2006) as well as decreased amyloid and neurodegenerative burden in transgenic mice, while in the latter study DHA alone was ineffective (Broersen et al., 2007).

Effective treatment requires early detection of the neurodegenerative process to prevent excessive neuronal loss. This discussion has led to a proposal for revision of the current diagnostic criteria for Alzheimer Disease (Dubois et al., 2007). Although validation and evaluation of the proposed new criteria is needed, this approach clearly strives to enable earlier detection, before the full spectrum of the illness occurs to enlarge options for early treatment of Alzheimer Disease. We believe that in early stages of the disease specific nutritional approaches can certainly be effective and have considerable potential to beneficially impact the disease process. Nevertheless, even when considerable damage has already been done, the capacity of some of the brain-supportive nutrients may still be able to improve brain function or prevent further deterioration. Central to this is our assumption that stimulation of neuronal plasticity by stimulation of synapse formation using nutrient membrane building blocks may also benefit support of neuronal repair mechanisms and decrease the impact of secondary events in the neuropathological cascade due to inflammation, oxidation toxicity and apoptosis.

In conclusion, the current epidemiological evidence points to a role of nutrition in the prevention of Alzheimer Disease. The contribution of both macro- and micronutrients in this respect is supported by epidemiological data that emphasize the relevance of diet context (i.e. a multi-nutrient approach) rather than single nutrients (Ortega, 2006; Van Dyk and Sano, 2007), and also by recent findings from our lab and others. In addition, recent mechanistic studies specifically support benefits of selective nutritional components in counteracting some of the neurodegenerative and pathological processes. The potential synergy between nutritional components to stimulate neuronal plasticity and function and reduce neuropathology provides a solid basis to investigate the potential benefits of such nutrient combinations in a clinical setting. The modulating capacity of such a specifically designed nutritional approach may show disease modifying capacity rather than symptomatic, especially during the prodromal and early stage of Alzheimer's Disease.

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