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**REVIEW ARTICLE**

# Nutrition and Alzheimer's disease: pre-clinical concepts

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Alzheimer's disease (AD) is a progressive condition characterized by neurodegeneration and the dense deposition of proteins in the brain. There is no cure for AD and current treatments usually only provide a temporary reduction of symptoms. There is thus a strong unmet need for effective preventative and therapeutic strategies and the potential role for nutrition in such strategies is rapidly gaining interest. An Alzheimer's brain contains fewer synapses and reduced levels of synaptic proteins and membrane phosphatides. Brain membrane phosphatide synthesis requires at least three dietary precursors: polyunsaturated fatty acids, uridine monophosphate (UMP) and choline. Animal studies have shown that administration of these nutrients increases the level of phosphatides, specific pre- or post-synaptic proteins and the number of dendritic spines – a requirement for new synapse formation. These effects are markedly enhanced when animals receive all three compounds together. This multi-nutrient approach in animals has also been shown to decrease amyloid beta protein (A$\beta$) plaque burden, improve learning and memory through increased cholinergic neurotransmission and have a neuroprotective effect in several mouse models of AD. Whether these potential therapeutic effects of a multi-nutrient approach observed in animal models can also be replicated in a clinical setting warrants further investigation.

## Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by progressive impairment of episodic memory leading to global dementia. Various pathogenic mechanisms have been proposed to underlie AD, including the accumulation of amyloid beta protein (A$\beta$) forming neuritic plaques, and the somatodendritic build-up of hyperphosphorylated tau protein forming neurofibrillary tangles [1]. The brains of people with AD are also deficient in cholinergic neurons and, generally, in synapses. Synapse loss tends to be greatest in the medial temporal lobe and the hippocampus, a locus of memory formation.

Knowledge of the neurotransmitter deficits in AD has led to the development of drugs which provide a temporary amelioration of symptoms in some patients. Research is ongoing to develop drugs which may suppress amyloid plaque development [2]. Thus there remains a strong unmet need for effective therapeutic strategies, which may or may not be based on modifying neurotransmitter metabolism, the formation of A$\beta$ or hyperphosphorylated tau.

Diet and nutrition have increasingly been recognized as potentially-important factors influencing the susceptibility to and natural history of AD [3,4] and a potential role for nutrition in the management of AD seems likely [5,6]. This mini-review describes the pre-clinical evidence that specific nutrients may have therapeutic utility in AD – particularly affecting the synthesis and integrity of brain membranes. It focuses on the roles of supplemental docosahexaenoic acid (DHA), uridine-5′-monophosphate (UMP) and choline in promoting the synthesis of neuronal membranes and thereby enhancing synaptic transmission in the mammalian brain [7,8].

## Lipids and synaptic function

Accelerated loss of neuronal membranes is a common finding in people with AD [9]. Post-mortem ultrastructural investigations of the brains of people with AD have consistently demonstrated a decline in synaptic density in the neocortex and dentate gyrus which does not appear to be related to the ageing process. Recent transmission electron microscopic analysis of the total number of synapses in the outer molecular layer of the human dentate gyrus revealed a strong

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reduction in number of synapses in people with early AD, compared with age-matched controls [10]. Importantly, this reduction in the number of synapses was significantly correlated with Mini-Mental State scores and cognitive tests involving delayed recall. Synaptic loss is also a common event in most preclinical models of AD [11].

Neuronal membranes consist for the main part of phosphatides such as phosphatidylcholine, phosphatidyletanolamine, phosphatidylserine, and phosphatidylinositol. These phosphatides are embedded with cholesterol and are pierced by a variety of proteins, including ion-channels, receptors and enzymes, which are essential for neurotransmission. The membrane lipids and their peroxidation products are important participants in central nervous system function via such roles as signal transduction molecules and neuronal structural components.

Essential fatty acids, which must be obtained from the diet, are critically important for the structural integrity of neuronal membranes [12]. The most abundant fatty acid in the brain is DHA, an omega-3 polyunsaturated fatty acid (PUFA) that is present in approximately 30–40% of the phospholipids of the cerebral cortex gray matter and photoreceptor cells of the retina [13]. DHA is particularly concentrated in synaptic membranes [14] and in myelin sheaths [15]. Human and animal studies have demonstrated the essential role of DHA in the normal maintenance of brain functions, including synaptic plasticity, neurotransmission and vision [16,17]. For example, DHA is responsible for optimal membrane–protein interaction in signal transduction [18], enhancing expression of genes such as synuclein [19] and is essential for brain development and synaptogenesis [20].

The brain is generally well-protected against external blood-borne influences by the blood–brain barrier (BBB). However, cerebral fatty acid composition is extensively modulated by dietary lipids [21] and DHA is taken up by the brain in preference to other fatty acids [22]. This has significant implications as it is well established that omega-3 fatty acid levels (including DHA) are significantly lower in the plasma [23,24] and brain [25] of patients with AD, compared with controls, and increasing dietary intake of DHA is associated with reduced risk of AD in the general population [26–28].

Phosphatidylcholine (PC) is the most abundant phospholipid in neuronal membranes [29]. Its synthesis in brain utilizes, besides glucose, three dietary compounds obtained from the circulation: choline; a pyrimidine such as uridine; and a PUFA such as DHA [30]. Each of these compounds crosses the BBB [31–34] and synthesis of PC is restricted by the availability of substrates and rate-limiting enzymes involved in the

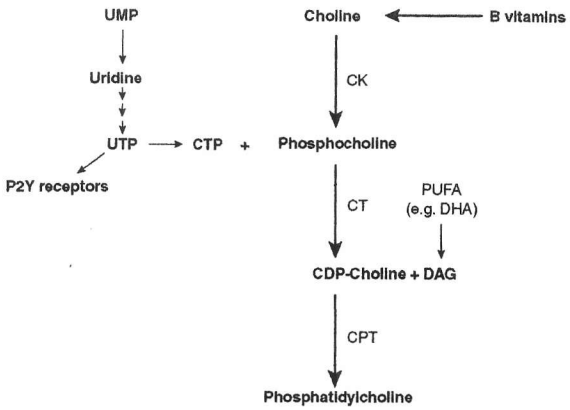


**Figure 1** Biosynthesis of phosphatidylcholine (PC). Uridine readily enters the brain yielding UTP that can be converted to CTP. CTP then reacts with phosphocholine to form CDP-choline, which combines with DAG [preferentially species containing omega-3 polyunsaturated fatty acid (PUFA) like docosahexaenoic acid (DHA)] to form PC. In rats, cytidine is the major circulating pyrimidine; in humans and gerbils the primary circulating pyrimidine is uridine. CK, choline kinase; CT, CTP: phosphocholine cytidylyl transferase; CPT, CDP-choline: 1, 2-diacylglycerol choline phosphotransferase.

cytidine diphosphate (CDP)-choline cycle or Kennedy cycle, which mediate PC synthesis (Fig. 1) [35]. Choline is phosphorylated to form phosphocholine through the action of choline kinase, a low-affinity enzyme that is unsaturated with choline at normal brain choline levels [36,37]. Uridine is phosphorylated by uridine-cytidine kinase [38] to uridine triphosphate (UTP), which is further transformed by the enzyme CTP synthetase to cytidine triphosphate (CTP) [39] – the usual rate-limiting precursor in phosphatidylcholine synthesis [40]. To complete the cycle, phosphocholine and CTP combine to form cytidine- 5′-diphosphocholine (CDP-choline) and together with diacylglycerol (derived from DHA) yield PC. The PC-synthesizing enzymes are all low-affinity (i.e. unsaturated with substrate at normal levels) and precursors must be obtained from the circulation; hence increasing plasma levels of all three can affect the overall rate of PC synthesis in the brain [41]. Phosphatidycholine can also be formed by the methylation of another membrane phospholipid, phosphatidylethanolamine. This methylation requires the conversion of methionine to homocysteine to free-up the necessary methyl-group. Homocysteine is converted back to methionine in the presence of folic acid and cobalamin. Decreases in these B-vitamins have been observed in AD patients and have been associated with cognitive decline. These deficiencies might hamper the biosynthesis of membrane phospholipids and in this way play a role in neuronal membrane degeneration. We therefore hypothesize that increased dietary intake

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of B-vitamins might stimulate neuronal PC formation. Based on this capacity for PC biosynthesis, several animal studies have investigated the effect of supplementing the diet with nutrients to promote neuronal membrane biosynthesis.

## Nutrients increase membrane synthesis and synapse formation

Experimental studies in gerbils have demonstrated that dietary supplementation with uridine (as its monophosphate, UMP) increases plasma and brain uridine levels with a subsequent increase in brain levels of CDP-choline, the immediate precursor to PC [42]. Further *in vitro* and *in vivo* studies have demonstrated that formation of neuronal membranes is promoted by increasing the availability of UMP and choline, resulting in an increase in the number and size of axonal neurites [43,44]. This effect is mediated in part by a direct action of uridine and its phosphorylated metabolites (e.g. UTP) on brain P2Y2 receptors, and is blocked by drugs that antagonize those receptors [43].

Importantly, when animals receive DHA as well as uridine and choline, the neuromodulatory actions are markedly enhanced [7,8,41,45]. For example, gerbils fed a choline-containing diet in which UMP, DHA or a combination were supplemented for four weeks, exhibited a 13–22% rise in PC with uridine and choline alone, and by 45% with the combination of uridine, choline and DHA, suggesting a synergistic effect of the nutrients [7].

The relevance of these increases in phospholipid synthesis has been demonstrated in *in vitro* cell culture experiments [43]. Studies in nerve growth factor (NGF) differentiated PC-12 cells have shown that incubation with uridine significantly increases the number of neurites per cell in a dose-dependent manner. This was accompanied by increased neurite branching and elevated levels of the neurite protein neurofilament M and neurofilament 70. Importantly, uridine treatment also increased intracellular levels of CTP, suggesting that the effects on neurite outgrowth were mediated by enhanced PC synthesis. Effects of uridine on neurite outgrowth were replicated in cocultures of hippocampal embryonic neurons (E18) and astrocytes (M. Verheijen, pers. com. [46]). In addition, others have found that incubating PC12 cells with DHA promoted, whilst the n-6 PUFA arachidonic acid suppressed, NGF-induced neurite outgrowth [47]. Fujii *et al.* have also shown that enriching the medium (using cells obtained from the dorsal root ganglia of mice) with vitamin B complex (vitamin B1, B6 and B12) increases neurite outgrowh [48].

These observations have been confirmed *in vivo* by Sakamoto *et al.* [8] using gerbils whose standard choline-containing diets were supplemented with DHA or a combination of DHA and UMP. Oral supplementation with DHA (or eicosapentaenoic acid, another omega-3 fatty acid, but not by the omega-6 fatty acid arachidonic acid) was shown to substantially increase the number of dendritic spines in the hippocampus, and this effect was almost doubled when animals were co-supplemented with UMP (Fig. 2). The increase in dendritic spines was accompanied by parallel increases in membrane phosphatides and levels of the pre- and post-synaptic proteins syntaxin-3, PSD-95 and synapsin-1 (but not in those of a ubiquitous structural protein beta-tubulin) indicating an increase in quantity of synaptic membrane [41]. The supplementation of all three nutrients in the diet has also been shown to improve hippocampus-dependent cognitive behaviours in rats reared in a socially deprived environment [45].

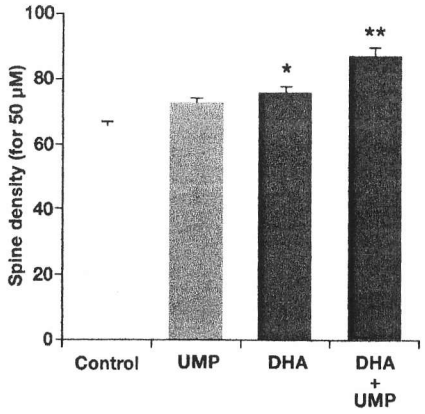


**Figure 2** Docosahexaenoic acid (DHA)-induced dendritic spine formation in adult gerbil hippocampus is enhanced by co-supplementation with UMP. Animals received UMP (0.5%), DHA (300 mg/kg) or both daily for 4 weeks; control gerbils received neither. Animals supplemented with DHA exhibited a significant increase in spine density (by 19%, $*P = 0.004$ vs. control); those receiving both DHA and UMP exhibited a greater increase (by 36%, $**P < 0.001$ vs. control or by 17%, $P = 0.008$ vs. DHA). $n$ = 20–25 neurons from 4 animals per group. One way ANOVA followed by Tukey's test. Reprinted with permission from Sakamoto *et al.* [8].

Dendritic spines mediate most excitatory connections in the brain and are thought to directly reflect the number of excitatory synapses in the central nervous system. Hence, oral DHA may promote neuronal membrane synthesis to increase the number of synapses, particularly when co-administered with UMP to a choline-containing diet.

## Nutrients improve learning and memory

Membrane PC is also an important source of choline in the biosynthesis of acetylcholine, a major neurotransmitter

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involved in learning and memory [49]. Microdialysis studies in freely moving rats have shown that administration of UMP increases acetylcholine levels in the striatum and striatal extracellular fluid in both aged and young rats [50]. Importantly, no effects on acetylcholinesterase activity were observed, indicating that the effect was a result of increased synthesis of acetylcholine. These findings are important as the pathophysiology of AD involves the preferential loss of cholinergic neurons in the basal forebrain. The behavioural relevance of these data is underlined by studies of rats reared under impoverished environmental conditions [51]. In these studies, exposure of rats to an impoverished environment leads to impaired hippocampal-dependent learning and memory which could be prevented upon supplementation with UMP. Similarly, concomitant administration of uridine and choline improved selective attention and spatial learning (as assessed by the five-choice serial reaction time task and the Morris water maze, respectively) in spontaneously hypertensive rats (SHR), which exhibit a well-defined cognitive deficit (Fig. 3A) [52]. Administration of DHA has also been reported to improve Morris water maze learning in APP/PS1 transgenic mice (Fig. 3B) [53]. In this model, reducing dietary intake of omega-3 fatty acids was shown to result in an 80–90% loss of the p85alpha subunit of phosphatidylinositol 3-kinase and in the post-synaptic actin-regulating protein drebrin. Treatment of omega-3 PFA-restricted mice with DHA protected against these effects, thereby improving cognitive function.

## Nutrients and amyloid precursor protein processing

According to the amyloid hypothesis of AD, accumulation of A$\beta$ in the brain is the primary influence driving AD pathogenesis [54]. Because of the role of dietary omega-3 fatty acids in membrane fluidity, it has been suggested that they may alter enzymatic activity of the secretase enzymes involved in the processing of the amyloid precursor protein [55]. *In vitro* studies using ovarian hamster cells transfected with human APP have shown that, on incubation with increasing dosages of DHA, changes in the omega-3/omega-6 ratio of neuronal membranes (as DHA is incorporated into the membrane) correlated with a decrease in cellular amyloid beta (A$\beta$) production [56]. The potential of DHA to prevent both production and accumulation of A$\beta$-peptide has been demonstrated in a number of animal studies. Dietary supplementation of DHA in APP transgenic mice significantly reduced amyloid plaque burden by 40% in the hippocampus and parietal cortex in aged transgenic animals (Fig. 4) [57] as well as

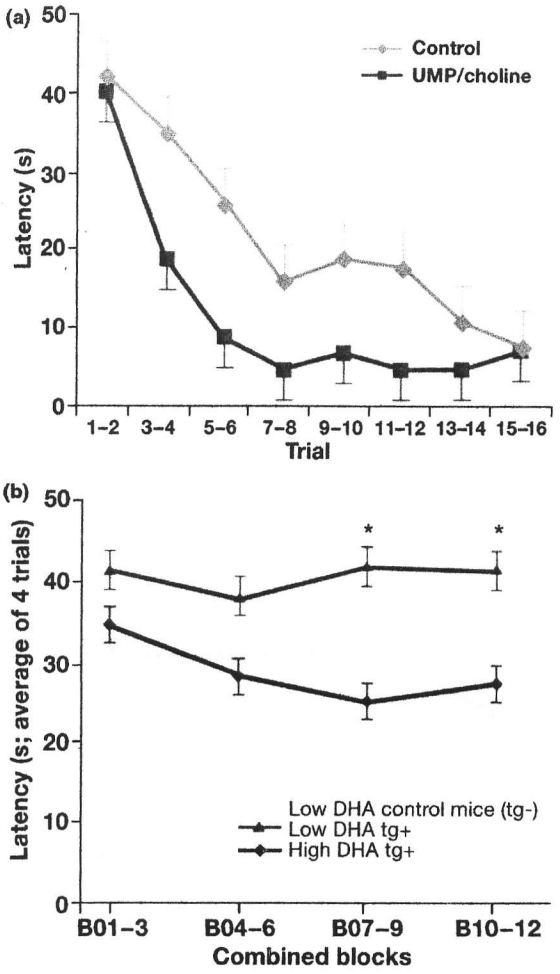


**Figure 3** Effects of uridine/choline on Morris water maze latency parameters in (a) SHR [52] and (b) APP/PS1 transgenic mice [53]. (a) UMP/choline supplementation decreased escape latency in comparison to the control condition ($n$ = 8 in each group) between trials 3–10 of a 16-trial task. Adapted from de Bruin *et al.* [52]. (b) Aged transgenic Tg2576 (Tg+) mice fed a depleted-DHA diet displayed increased escape latency in comparison to transgene-negative control (Tg-) mice fed the same diet. This impairment was reversed in Tg+ mice fed a DHA-enriched diet, with a significant treatment effect observed during blocks 7–9 and 10–12 ($P < 0.005$; $n$ = 6 in each group). Adapted from Calon *et al.* [53].

decreasing the number of activated microglia in the hippocampus [58].

Inclusion of DHA into the diet of rodent models of AD has also been shown to increase exploratory activity in APP/PS1 transgenic mice [58] and improve spatial cognition learning ability in A$\beta$-infused rats [32,59]. Most recently, a study in a double-transgenic APP/PS1 mouse model of AD found that, compared with a normal diet, mice receiving a diet enriched with DHA, UMP, choline and minerals showed a reduction in A$\beta$ plaques which was accompanied by an attenuation of

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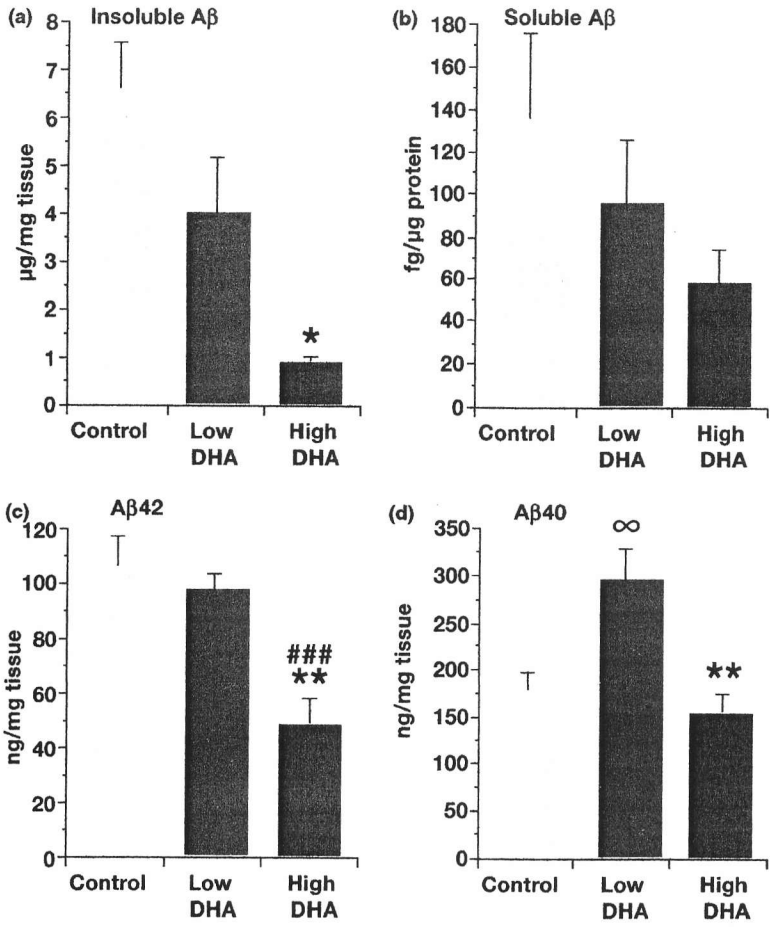


**Figure 4** Detergent-insoluble amyloid (total A$\beta$, A$\beta$42, and A$\beta$40) is reduced in cortex of mice fed DHA-enriched diets. (a) Detergent-insoluble amyloid measurements in cortex, $^{*}P < 0.05$ compared with low-DHA group. (b) Soluble amyloid measurements in cortex. (c) A$\beta$42 measurements in cortex, $^{**}P < 0.01$ compared with low-DHA group; $^{\#\#\#}P < 0.001$ compared with control diet group (d) A$\beta$40 measurements in cortex, $^{\infty}P < 0.01$ compared with control group; $^{**}P < 0.01$ compared with low-DHA group. Error bars represent SE. Reprinted with permission from Lim *et al.* [57].

neuronal damage [60]. Importantly, mice receiving these dietary enhancements as individual supplements did not demonstrate significant changes in A$\beta$ plaques or brain cell damage, suggesting that a multi-nutrient diet is more effective than a single-nutrient enriched diet.

Further studies in a mouse model of AD have demonstrated the neuroprotective benefits of a multi-nutrient enriched diet. Infusion of A$\beta$ into the lateral ventricles of mice has been shown to reduce choline acetyl-transferase levels by 30–40% and reduce locomotor activity in the open field. This decrease in choline acetyltransferase activity can be completely restored when mice receive the multi-nutrient enriched diet (including: DHA, EPA, UMP, choline, phospholipids, antioxidant and B vitamins) and behavioural deficits are normalized [61].

## Conclusions

It is clear that dietary supplementation with specific nutrients has beneficial effects in animal models of AD. A striking feature of the role of the nutrients discussed in this review is the apparent synergistic effects of multiple nutrients on AD pathophysiology and cognitive function. Specifically, the neuromodulatory actions of DHA, uridine and choline in promoting new neuronal membrane and synapse formation are markedly enhanced when animals receive all three compounds together [7,8,41,62]. As nutrients may have additive effects and may interact to produce their beneficial effect, combining multiple nutrients may be more effective than single nutrient supplementation.

This may also translate into clinical strategies. For example, one of the first studies to evaluate the effect of multiple nutrients in an AD population found that adherence to a Mediterranean diet (characterized by high intake of vegetables, legumes, fruits, cereals and unsaturated fatty acids and fish, and low intake of saturated fatty acids) not only reduced the risk of developing AD, but also favourably affected the course of the disease [3,4]. Superior adherence to a Mediterranean diet was associated with lower mortality in AD and led the authors to suggest a possible dose–response effect.

There is a clear unmet medical need for novel approaches to the management of AD. Whilst there are

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limitations in applying the findings of pre-clinical models to the clinic, the growing evidence from pre-clinical studies indicates that a combination of nutrients is more effective than single nutrients, and thus a multi-nutrient approach appears to be a promising clinical approach in the management of AD. A multi-nutrient intervention would represent a completely novel approach to AD management. Whether the potential therapeutic effects of combined nutrients observed in animal models can also be replicated in a clinical setting warrants further investigation.

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## Conflicts of interest

PJ Kamphuis is an employee of Danone Research; RJ Wurtman is a professor at MIT, which owns patents and has filed patent applications relating to the uses of compounds described in this review to increase synapse formation and to treat diseases associated with the loss of synapses. RW is also a paid consultant to Danone on scientific matters.

## References


1. Blennow K, de MJ, Zetterberg H. Alzheimer's disease. *Lancet* 2006; **368:** 387–403.
2. Cummings JL. Treatment of Alzheimer's disease: the role of symptomatic agents in an era of disease-modifying therapies. *Rev Neurol Dis* 2007; **4:** 57–62.
3. Scarmeas N, Luchsinger JA, Mayeux R, Stern Y. Mediterranean diet and Alzheimer disease mortality. *Neurology* 2007; **69:** 1084–1093.
4. Scarmeas N, Stern Y, Tang MX, Mayeux R, Luchsinger JA. Mediterranean diet and risk for Alzheimer's disease. *Ann Neurol* 2006; **59:** 912–921.
5. Steele M, Stuchbury G, Munch G. The molecular basis of the prevention of Alzheimer's disease through healthy nutrition. *Exp Gerontol* 2007; **42:** 28–36.
6. Gillette Guyonnet S, Abellan Van Kan G, Andrieu S, *et al.* IANA task force on nutrition and cognitive decline with aging. *J Nutr Health Aging* 2007; **11:** 132–152.
7. Wurtman RJ, Ulus IH, Cansev M, Watkins CJ, Wang L, Marzloff G. Synaptic proteins and phospholipids are increased in gerbil brain by administering uridine plus docosahexaenoic acid orally. *Brain Res* 2006; **1088:** 83–92.
8. Sakamoto T, Cansev M, Wurtman RJ. Oral supplementation with docosahexaenoic acid and uridine-5′-monophosphate increases dendritic spine density in adult gerbil hippocampus. *Brain Res* 2007; **1182:** 50–59.
9. Nitsch RM, Blusztajn JK, Pittas AG, Slack BE, Growdon JH, Wurtman RJ. Evidence for a membrane defect in Alzheimer disease brain. *Proc Natl Acad Sci U S A* 1992; **89:** 1671–1675.
10. Scheff SW, Price DA, Schmitt FA, Mufson EJ. Hippocampal-pal synaptic loss in early Alzheimer's disease and mild cognitive impairment. *Neurobiol Aging* 2006; **27:** 1372–1384.
11. Spittaels K, Van den Haute C, Van Dorpe J, *et al.* Prominent axonopathy in the brain and spinal cord of transgenic mice overexpressing four-repeat human tau protein. *Am J Pathol* 1999; **155:** 2153–2165.
12. Bourre JM, Dumont O, Piciotti M, *et al.* Essentiality of omega 3 fatty acids for brain structure and function. *World Rev Nutr Diet* 1991; **66:** 103–117.
13. Lauritzen L, Hansen HS, Jorgensen MH, Michaelsen KF. The essentiality of long chain n-3 fatty acids in relation to development and function of the brain and retina. *Prog Lipid Res* 2001; **40:** 1–94.
14. Bazan NG, Scott BL. Dietary omega-3 fatty acids and accumulation of docosahexaenoic acid in rod photoreceptor cells of the retina and at synapses. *Ups J Med Sci Suppl* 1990; **48:** 97–107.
15. Ansari KA, Shoeman DW. Arachidonic and docosahexanoic acid content of bovine brain myelin: implications for the pathogenesis of multiple sclerosis. *Neurochem Res* 1990; **15:** 7–11.
16. Yehuda S, Rabinovitz S, Carasso RL, Mostofsky DI. The role of polyunsaturated fatty acids in restoring the aging neuronal membrane. *Neurobiol Aging* 2002; **23:** 843–853.
17. McCann JC, Ames BN. Is docosahexaenoic acid, an n-3 long-chain polyunsaturated fatty acid, required for development of normal brain function? An overview of evidence from cognitive and behavioral tests in humans and animals *Am J Clin Nutr* 2005; **82:** 281–295.
18. Litman BJ, Mitchell DC. A role for phospholipid polyunsaturation in modulating membrane protein function. *Lipids* 1996; **31:** S193–S197.
19. Barcelo-Coblijn G, Kitajka K, Puskas LG, *et al.* Gene expression and molecular composition of phospholipids in rat brain in relation to dietary n-6 to n-3 fatty acid ratio. *Biochim Biophys Acta* 2003; **1632:** 72–79.
20. Green P, Glozman S, Kamensky B, Yavin E. Developmental changes in rat brain membrane lipids and fatty acids. The preferential prenatal accumulation of docosahexaenoic acid. *J Lipid Res* 1999; **40:** 960–966.
21. Angulo-Guerrero O, Oliart RR. Effects of dietary polyunsaturated fatty acids on rat brain plasma membrane fatty acid composition. *Arch Latinoam Nutr* 1998; **48:** 287–292.
22. Horrocks LA, Yeo YK. Health benefits of docosahexaenoic acid (DHA). *Pharmacol Res* 1999; **40:** 211–225.
23. Conquer JA, Tierney MC, Zecevic J, Bettger WJ, Fisher RH. Fatty acid analysis of blood plasma of patients with Alzheimer's disease, other types of dementia, and cognitive impairment. *Lipids* 2000; **35:** 1305–1312.
24. Tully AM, Roche HM, Doyle R, *et al.* Low serum cholesteryl ester-docosahexaenoic acid levels in Alzheimer's disease: a case–control study. *Br J Nutr* 2003; **89:** 483–489.
25. Soderberg M, Edlund C, Kristensson K, Dallner G. Fatty acid composition of brain phospholipids in aging and in Alzheimer's disease. *Lipids* 1991; **26:** 421–425.
26. Grant WB, Campbell A, Itzhaki RF, Savory J. The significance of environmental factors in the etiology of Alzheimer's disease. *J Alzheimers Dis* 2002; **4:** 179–189.
27. Morris MC, Evans DA, Bienias JL, *et al.* Consumption of fish and n-3 fatty acids and risk of incident Alzheimer disease. *Arch Neurol* 2003; **60:** 940–946.
28. Kalmijn S, van Boxtel MP, Ocke M, Verschuren WM, Kromhout D, Launer LJ. Dietary intake of fatty acids and fish in relation to cognitive performance at middle age. *Neurology* 2004; **62:** 275–280.


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29. Sastry PS. Lipids of nervous tissue: composition and metabolism. *Prog Lipid Res* 1985; **24:** 69–176.
30. Kennedy EP, Weiss SB. The function of cytidine coenzymes in the biosynthesis of phospholipides. *J Biol Chem* 1956; **222:** 193–214.
31. Cornford EM, Braun LD, Oldendorf WH. Carrier mediated blood-brain barrier transport of choline and certain choline analogs. *J Neurochem* 1978; **30:** 299–308.
32. Hashimoto M, Hossain S, Shimada T, *et al.* Docosahexaenoic acid provides protection from impairment of learning ability in Alzheimer's disease model rats. *J Neurochem* 2002; **81:** 1084–1091.
33. Spector AA. Plasma free fatty acid and lipoproteins as sources of polyunsaturated fatty acid for the brain. *J Mol Neurosci* 2001; **16:** 159–165.
34. Li JY, Boado RJ, Pardridge WM. Cloned blood-brain barrier adenosine transporter is identical to the rat concentrative Na+ nucleoside cotransporter CNT2. *J Cereb Blood Flow Metab* 2001; **21:** 929–936.
35. Araki W, Wurtman RJ. How is membrane phospholipid biosynthesis controlled in neural tissues? *J Neurosci Res* 1998; **51:** 667–674.
36. Spanner S, Ansell GB. Choline kinase and ethanolamine kinase activity in the cytosol of nerve endings from rat forebrain. *Biochem J* 1979; **178:** 753–760.
37. Millington WR, Wurtman RJ. Choline administration elevates brain phosphorylcholine concentrations. *J Neurochem* 1982; **38:** 1748–1752.
38. Suzuki NN, Koizumi K, Fukushima M, Matsuda A, Inagaki F. Structural basis for the specificity, catalysis, and regulation of human uridine-cytidine kinase. *Structure* 2004; **12:** 751–764.
39. Genchev DD, Mandel P. CTP synthetase activity in neonatal and adult rat brain. *J Neurochem* 1974; **22:** 1027–1030.
40. Ross BM, Moszczynska A, Blusztajn JK, Sherwin A, Lozano A, Kish SJ. Phospholipid biosynthetic enzymes in human brain. *Lipids* 1997; **32:** 351–358.
41. Cansev M, Wurtman RJ. Chronic administration of docosahexaenoic acid or eicosapentaenoic acid, but not arachidonic acid, alone or in combination with uridine, increases brain phosphatide and synaptic protein levels in gerbils. *Neuroscience* 2007; **148:** 421–431.
42. Cansev M, Watkins CJ, van der Beek EM, Wurtman RJ Oral uridine-5′-monophosphate (UMP) increases brain CDP-choline levels in gerbils. *Brain Res* 2005; **1058:** 101–108. Epub 2005 Aug 2029.
43. Pooler AM, Guez DH, Benedictus R, Wurtman RJ. Uridine enhances neurite outgrowth in nerve growth factor-differentiated PC12 [corrected]. *Neuroscience* 2005; **134:** 207–214.
44. Wang L, Pooler AM, Albrecht MA, Wurtman RJ. Dietary uridine-5′-monophosphate supplementation increases potassium-evoked dopamine release and promotes neurite outgrowth in aged rats. *J Mol Neurosci* 2005; **27:** 137–145.
45. Cansev M, Wurtman RJ, Sakamoto T, Ulus IH. Oral administration of circulating precursors for membrane phosphatides can promote the synthesis of new brain synapses. *Alzheimer's Dement* 2008; **4:** S153–S168.
46. De Wilde MC, Groenendijk M, Kamphuis PJ, Broersen LM. Effects of dietary lipids and other nutrients on membrane and synapse formation. Proc. 8th Dutch ENP Meeting, p. 71.
47. Ikemoto A, Kobayashi T, Watanabe S, Okuyama H. Membrane fatty acid modifications of PC12 cells by arachidonate or docosahexaenoate affect neurite outgrowth but not norepinephrine release. *Neurochem Res* 1997; **22:** 671–678.
48. Fujii A, Matsumoto H, Yamamoto H. Effect of vitamin B complex on neurotransmission and neurite outgrowth. *Gen Pharmacol* 1996; **27:** 995–1000.
49. Ulus IH, Wurtman RJ, Mauron C, Blusztajn JK. Choline increases acetylcholine release and protects against the stimulation-induced decrease in phosphatide levels within membranes of rat corpus striatum. *Brain Res* 1989; **484:** 217–227.
50. Wang L, Albrecht MA, Wurtman RJ. Dietary supplementation with uridine-5′-monophosphate (UMP), a membrane phosphatide precursor, increases acetylcholine level and release in striatum of aged rat. *Brain Res* 2007; **1133:** 42–48.
51. Teather LA, Wurtman RJ. Chronic administration of UMP ameliorates the impairment of hippocampal-dependent memory in impoverished rats. *J Nutr* 2006; **136:** 2834–2837.
52. De Bruin NM, Kiliaan AJ, De Wilde MC, Broersen LM. Combined uridine and choline administration improves cognitive deficits in spontaneously hypertensive rats. *Neurobiol Learn Mem* 2003; **80:** 63–79.
53. Calon F, Lim GP, Yang F, *et al.* Docosahexaenoic acid protects from dendritic pathology in an Alzheimer's disease mouse model. *Neuron* 2004; **43:** 633–645.
54. Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. *Science* 2002; **297:** 353–356.
55. Wolozin B. A fluid connection: cholesterol and Abeta. *Proc Natl Acad Sci U S A* 2001; **98:** 5371–5373.
56. de Wilde MC, Leenders I, Broersen LM, Kuipers AAM, van der Beek EM, Kiliaan AJ *The Omega-3 Fatty Acid Docosahexaenoic Acid (DHA) Inhibits the Formation of Beta Amyloid in CHO7PA2 Cells.* Program Number 730.11, New Orleans, LA: Society for Neuroscience Meeting, 2003.
57. Lim GP, Calon F, Morihara T, *et al.* A diet enriched with the omega-3 fatty acid docosahexaenoic acid reduces amyloid burden in an aged Alzheimer mouse model. *J Neurosci* 2005; **25:** 3032–3040.
58. Oksman M, Iivonen H, Hogyes E, *et al.* Impact of different saturated fatty acid, polyunsaturated fatty acid and cholesterol containing diets on beta-amyloid accumulation in APP/PS1 transgenic mice. *Neurobiol Dis* 2006; **23:** 563–572.
59. Hashimoto M, Tanabe Y, Fujii Y, Kikuta T, Shibata H, Shido O. Chronic administration of docosahexaenoic acid ameliorates the impairment of spatial cognition learning ability in amyloid beta-infused rats. *J Nutr* 2005; **135:** 549–555.
60. Broersen L, De Wilde M, Leenders I, *et al.* Reduced beta-amyloid plaque burden and neurodegeneration in APP/PS1 transgenic mice following multi-nutrient dietary intervention. *Soc Neurosci Abstr.* 2007: 157.116/U127.
61. van der Beek EM, Kuipers A, Broersen L, Leenders I, Kamphuis P, De MC *Dietary Intervention Improves Cholinergic Function.* Program No. 467.13, Atlanta, GA: Society for Neuroscience Meeting, 2006.
62. Wurtman RJ, Cansev M, Sakamoto T, Ulus IH. Oral administration of circulating precursors for membrane phosphatides can promote the synthesis of new brain synapses. *Alzheimer's Dement* 2008; **4:** S153–S168.


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