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Nutrients, age and cognition

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Abstract — Our knowledge about the influence of nutritional supplements on human cognition, especially in the elderly, rests largely on animal behavioural research and neurochemical experiments in vitro, while only a few epidemiological studies and even fewer controlled experiments in humans are reported. This is an inherent problem, due partly to the difficulty of conducting controlled nutritional experiments in humans, but may also partly be due to the gap between the research disciplines of nutritional and neurobehavioral experimental science. Learning objectives — The aim of this paper is to discuss some new findings in this line of research, and to stress the importance of the need to start bridging the gap between disciplines by identifying possible human experimental models of altered cognitive function, which can elucidate the specific mechanisms of action through which nutritional supplements may enhance cognitive performance in humans in vivo. These experimental models are important because the research in this field is mostly based on epidemiological studies, which describe associations between nutrients and cognitive functions. Contrary to epidemiological studies, experimental models mimic associations between nutrients and cognition by manipulating their presumed mechanisms of action and can eventually explain the causal nature of found associations. © 2002, Elsevier Science Ltd. All rights reserved.

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Introduction

During the search for cognitive-enhancing nutritional supplements, one cannot ignore comparing efficacy and side-effects of nutritional supplements with registered medicines. In most Western European countries and in the USA, the first three medicinal drugs have recently been registered for the indication of Alzheimer’s Disease (AD). These concern the cholinesterase inhibitors tacrine (1), donepezil (2) and rivastigmine (3). Furthermore, clinical trials are now, just as we predicted 5 years ago (4), moving from AD towards investigating the pharmacological treatment of the less severe condition of mild cognitive impairment (MCI). Whilst one would demand more clinical efficacy and tolerate more side-effects of medicinal drugs if the disease condition is more severe, such as in AD, one would tend to accept less side-effects of nutritional supplements in MCI. However, one would still demand proof of efficacy and as few side effects as possible. This is precisely where the need for demonstrating the efficacy of nutritional supplements comes in. If effective nutritional supplements or optimally composed diets could be identified, one would prefer nutritional treatments over prescription medicine. This is simply because less side effects are expected in nutritional treatments that improve or at least maintain optimal cognitive performance in adulthood and ageing.

Some researchers argue that the concept of MCI – or memory complaints in elderly people – is a stage of normal ageing, whereas others see it as an early stage of dementia (5). We found a higher frequency of the ApoE4 genotype (37.8% with at least one E4 allele) in 119 elderly subjects with MCI who fulfilled the criteria for age-associated memory impairment (AAMI), when compared to 87 matched controls (22%) (6). The frequency of at least one E4 allele of the AAMI population is in between the control population and the allele frequency of approximately 45% in Alzheimer’s Disease populations in other studies. The frequency of the ApoE4 genotype may be objective evidence of memory impairment in AAMI. This places AAMI somewhere between normal ageing and dementia of the Alzheimer’s type.

In a recent review of epidemiological and experimental studies, we concluded that several nutrients – such as beta-carotene, alfa-tocopherol, Folate rather than vitamin B12 and Ginkgo biloba – or indices of nutritional status are associated with cognitive functioning (7). The magnitude of nutrient effects on cognitive performance was considered to be small but not to be very different from that of registered medicinal or investigational cognition-enhancing or anti-dementia drugs. In this paper, we will shortly review results of recent research (i.e. 1998–2001) into the influence of nutrients on cognitive functioning, and highlight possible human experimental models, which might be used in future studies to elucidate the brain mechanisms underlying nutrient-induced effects on cognitive performance.
Recent findings

Vitamins

No association was found between self-reported anti-oxidant nutritional supplement use (vitamin A, C, E, beta-carotene, zinc, or selenium) and cognitive function after correction for age, education and gender (8). In AD patients, lowered plasma levels of vitamin C were found to be proportionally related to the degree of cognitive decline (9). The authors contended that the nutritional status of these patients was normal, hence the declined concentrations of vitamin C could be due to oxidative stress associated with the disease. Smith et al. (10) showed in a double-blind placebo-controlled study in 205 (110 female and 95 male) elderly subjects, that a 12 month anti-oxidant supplementation, including beta carotene, alpha-tocopherol and ascorbic acid, had little effect on mental performance. There were only 4 significant differences of 117 analyses, and these could have been expected by chance. Morris et al. (11) studied the association between use of vitamin E and vitamin C and the incidence of Alzheimer’s Disease in a prospective study of 633 volunteers of 65 years and older. The results indicated that none of the 27 vitamin E supplement users and none of the 23 vitamin C supplement users had Alzheimer’s Disease after a follow-up period of 4.3 years. Based upon the incidence of the non-users, corrected for age, sex, education and follow-up interval, an incidence of 2.5 and 3.2 for the E- and C-users respectively would be expected. This suggests that use of vitamin E and vitamin C supplements may lower the risk of Alzheimer’s Disease. The Honolulu-Asia Aging Study (12) did not show a protective effect of Vitamin E and C supplements of Alzheimer’s Disease. This study showed a protective effect of these vitamins for vascular dementia and for mixed/other dementia in 3,385 men who used vitamin E and C supplements in 1988 during a dementia prevalence survey carried out in 1991 to 1993. However, there was a positive association between use of either vitamin E or C supplements in 1988 and cognitive test performance between 1991 and 1993. The authors suggest that vitamin E and C supplements may protect against vascular dementia and may improve cognitive function in the elderly. Previous studies suggested that low concentrations of folate are related to poor cognitive function and to neurodegeneration as in dementia. A report from the so called ‘nun study’ concluded that among 30 elderly Catholic sisters who lived in one convent, ate from the same kitchen, and were highly comparable for a wide range of environmental and lifestyle factors, low serum folate was strongly associated with atrophy of the cerebral cortex (13). Homocysteine on the other hand has been associated with reduced cognitive function. However, no support was found for this association in a random sample of 702 community-dwelling respondents aged 55 years or over (14). To determine if long-term, high-dose vitamin supplementation could reverse cognitive malfunction in older people, a longitudinal study was performed in 20 non-vitamin-deficient elderly females with a Folstein mini mental state examination score indicating cognitive malfunctions, relating the 12-month outcome to baseline values. No improvement in cognitive malfunction was noted despite elevation of blood vitamins levels. Administration of a high-dose vitamin and mineral supplement for 1 year did not improve cognitive malfunction in non-vitamin-deficient elderly in this study (15). In a study with 70 elderly male subjects, lower concentrations of vitamin B12 and folate and higher concentrations of homocysteine were associated with poorer spatial copying skills (16). Recently, McCaddon et al. (17) showed that thirty patients suffering from senile dementia of the Alzheimer type had significantly higher plasma levels of homocysteine than thirty healthy elderly controls. Homocysteine and vitamin B12 plasma levels were interrelated with cognitive scores. In another study, higher plasma concentrations of homocysteine were also found in patients with vascular dementia or minor cognitive impairment and also in patients with senile dementia of the Alzheimer type (18). Vitamin B12 and folate are both involved in the conversion from homocysteine to methionine (19), which is indirectly involved in the maintenance of the myelin sheath. This mechanism might explain the association between the higher plasma concentrations of homocysteine, the lower concentrations of vitamin B12 and folate, and reduced cognitive function. The high homocysteine plasma concentrations might, on the other hand, influence cognitive performance in the elderly, due to its excitotoxicity. High concentrations of homocysteine may induce high concentrations of homocysteic acid and cysteine sulphonic acid, which act as endogenous agonists of NMDA receptors (20). It has been shown that supplementation with a mixture of B-vitamins, with or without antioxidants, lowered homocysteine concentrations compared to placebo in a randomized double-blind placebo-controlled trial of 132 healthy men (21), whereas antioxidants alone induced a non-significant increase of homocysteine concentrations compared to placebo. This decrease of homocysteine concentrations, induced by supplementation of B-vitamins, is a promising finding that might trigger researchers to further explore the influence of vitamin B12 and folate supplementation on cognitive performance. Recently, Ravaglia et al. found no relationship between homocysteine, B vitamins and reduced cognitive function, measured with the Mini Mental State Examination (MMSE) and a battery of neuropsychological tests, in 56 healthy cognitively-normal elderly subjects (22). In another recent study with 156 elderly volunteers Budge et al. (23) showed that the cognitive performance scores on the cognitive section of the Cambridge Examination for Mental Disorders of the Elderly were inversely related to
homocysteine concentrations, which was independent of age, gender, IQ and depression. However, they found no association between homocysteine concentrations and Mini Mental State Examination (MMSE) scores. According to the authors, this last result may be caused by the small number of volunteers. The results of the above mentioned vitamin studies are not consistent, which makes it difficult to draw a conclusion about the neuroprotective effects of vitamins at this stage. The anti-oxidative effects of vitamin E and C supplements and the effects of the B vitamins on cognitive function need to be confirmed in long-term placebo-controlled studies.

**Nutritional status**

In a study into diet composition and cognitive function in elderly males in Finland, Italy and The Netherlands the ‘Health Diet Indicator’ (HDI), defined according to the guidelines of the World Health Organisation (WHO), was used. A higher HDI means that a person’s diet is more in accordance with the WHO guidelines. In 4 of the 5 cohorts that were studied a lower prevalence of cognitive decline (MMSE < 24) was associated with an increased HDI (24). This indicates the importance of the effects of a nutritionally healthy diet.

**Wine and other alcohol containing beverages**

Interesting reports of epidemiological studies into the association of wine consumption with the incidence of AD have been reported. A 4-fold lowered relative risk for AD was found in subjects categorized as moderate drinkers (3–4 glasses wine/day), compared to non-drinkers (25). These results could not be confirmed in another study, because when the data were corrected for whether or not subjects were living in a nursing home, the association disappeared, putatively because wine consumption in elderly nursing homes is kept low (26). A possible mechanism for the protective effect of wine is provided by the antioxidative properties of polyphenoles which are most prominent in red wine. These effects are independent of alcohol and can also occur in alcohol-free red wine (27). In the aforementioned epidemiological studies the difference between consumption of white and red wines has however not been taken into account.

Not only has the association between wine consumption and the incidence of AD been studied. The relationship between alcohol consumption, which includes all types of beverages, and cognitive performance has recently been studied by several researchers. Launer et al. (28) showed in the Zutphen Elderly Study that men with cardiovascular disease or diabetes and low-to-moderate alcohol intake had a significantly lower risk of poor cognitive function, which was measured in 1990 and 1993 with the Mini-Mental State Examination, compared to abstainers. In the Framingham Heart Study the association between alcohol consumption and cognitive performance was analysed separately for men and women, since the researchers expected a different alcohol-cognition relationship for male and female drinkers (29). Test performance of moderate (>2 and ≤4 drinks/day) male drinkers performed significantly better than abstainers only on logical memory delayed-recall, whereas heavy (>4 and ≤8 drinks/day) drinkers performed better on logical memory delayed-recall, on the attention and concentration (AC) composite score, and on total composite score. Female drinkers showed superior performance compared to abstainers on more cognitive tests than male drinkers. Light (1–2 drinks/day) female drinkers performed better on logical memory delayed-recall, on the learning and memory (LIM) composite and the total composite, whereas moderate female drinkers scored significantly better than abstainers on delayed memory, word fluency, similarities and on the AC, LIM and total composites.

Thus moderate wine consumption might not only be associated with a lowered relative risk for AD, but light to moderate alcohol consumption might also influence cognitive performance. Experimental studies are necessary to confirm these associations.

**Herbal extracts**

The ingredients of ginkgo biloba, flavonoids, terpenoids and organic acids, are putative antioxidants as well. The influence of chronic oral treatment with 240 mg/day of ginkgo biloba on the clinical course of AD was investigated in a 3 month, double-blind, randomized, placebo-controlled parallel-group design in 20 outpatients. A small improvement of cognitive performance was found. However, there was no effect on the Alzheimer’s Disease Assessment Scale (ADAS) cognitive and non-cognitive subscales (30). In 1992 a meta-analysis was conducted in which the authors concluded that 8 out of 40 studies of ginkgo biloba for cerebral insufficiency were of adequate methodology, but all 8 well-controlled studies found positive effects of ginkgo (31). A remarkable ginkgo study was then carried out by this group in The Netherlands. In over 250 elderly subjects diagnosed with MCI, vascular dementia, or AD, no effects of ginkgo on a large number of cognitive tests and clinical scales were found in a double-blind, placebo-controlled, parallel-groups study (32). One of the explanations for the lack of effect of ginkgo in this very thoroughly conducted trial was that this was the first ginkgo study employing a truly identical placebo (33). Consequently the authors assertion was that most, if not all other results of previously conducted clinical trials on ginkgo biloba are based on expectancy effects (32). Another popular herbal preparation from ancient China, ginseng, is also said to enhance cognitive function. Only 4 placebo-controlled trials have been carried out in healthy volunteers so far. In three studies
Panax ginseng improved performance on tasks of mental arithmetic and abstract thinking, while eleuthero ginseng improved memory performance. Whether ginseng can actually enhance cognition in the elderly remains to be established (34). Wesnes and colleagues (35) recently studied the cognitive effects of a combination of ginkgo biloba and Panax ginseng in 256 healthy middle-aged subjects. Dosages of 160 mg b.i.d. or 320 mg o.d. were tested in a placebo-controlled, double-blind, parallel group 14-weeks study. The combination Ginkgo biloba/Panax ginseng improved significantly the Quality of Memory Index compared to placebo. The Quality of Memory Index is a combination of cognitive tests for the quality of episodic and working memory. The treatment did not influence power of attention, speed of attention and the speed of memory processes. These ginkgo biloba results are promising, but more chronic dosage studies are necessary to replicate these cognitive enhancing findings. The quality of the placebo capsule should especially be taken into account.

**Lipids**

The cognition-enhancing potential of phospholipids has been studied in AD patients and in subjects with MCI. About a decade ago, a number of placebo-controlled studies were carried out with bovine cortex phosphatidylserine (PS) which was shown to improve memory in subjects with age-associated memory impairment. PS has a function in the maintenance of the membrane structure of nerve cells, thereby maintaining the conduction of nerve cells. In ageing the concentration of PS is reduced. Since the recent genesis of plant-derived soy-PS, the interest for PS as a nutritional supplement has been revived (36). Recent animal studies show that soy-PS improves aspects of memory in rats in a comparable manner with bovine PS (37). In a recently-conducted published placebo-controlled study into the efficacy of soy-PS in the treatment of subjects, fulfilling the criteria of age-associated memory impairment, 120 male and female volunteers of 58 years and older received a 12 weeks treatment of 300 mg soy-PS, 600 mg soy-PS or placebo. A neuropsychological test battery, including the visual verbal learning test, the memory scanning test, the fluency test, the Stroop colour word test, the signal detection test, the motor choice reaction time test, the concept shifting and the tower of London, was conducted at baseline, after 6 and 12 weeks of treatment and after a washout period of 3 weeks. Both dosages of Soy-PS did not influence learning and memory, choice reaction time, planning and attention (38). According to the authors the fatty acid content of PS is an important factor which should be controlled for in future studies. The fatty acid content of the PS-formulas used in animal studies differed considerably, whereas the fatty acid content is not mentioned in most human studies. This fatty acid aspect is rather important, since the administration of n-3 and n-6 essential fatty acids in a 1:4 composition has been said to improve cognition as well. A placebo-controlled study in 100 AD patients (60 treatment and 40 placebo) of -linolenic acid (n-3 polyunsaturated fatty acid; PUFA) and linolenic acid (n-6 PUFA) reported a positive effect on mood, appetite, sleep and short term memory (39). This fatty acid treatment might influence cognitive functions through the modulation of neuronal membrane fluidity (40). The relation between cognitive functions and daily fatty acid intake has also been addressed in epidemiological studies. According to Ortega et al. (41) adequate cognitive functioning in elderly (assessed with the MMSE) was associated with lower consumption of monounsaturated fatty acids (MUFA), saturated fatty acids (SFA) and cholesterol. However, in another study cognitive function was positively associated with consumption of MUFA, 80% of which were consumed through constituents of olive oil (42). According to the authors, the protective effect of MUFA could especially be associated with the antioxidant action of tocopheroles and polyphenoles in olive oil.

Results from the Rotterdam Study (43) showed that high intakes of total fat, saturated fat and cholesterol were associated with an increased risk of dementia, whereas an inverse association between fish consumption and cognitive measures. Adequate cognitive functioning in two epidemiological studies (44, 45), Wardle et al. (46) studied the effects of cholesterol-lowering dietary treatments on mood and cognitive functioning in 176 adults with raised serum cholesterol levels. In this study two cholesterol-lowering diets did not influence psychological well-being (mood and aggression), or the cognitive measures motor speed, memory and choice reaction time after 6 and 12 weeks of treatment. However, sustained attention was relatively impaired in the treated groups compared to the control group. In another study the psychological effects of treatment of hypercholesterolemia with lovastatin were investigated (47). The placebo-treated subjects showed a greater improvement on attention and psychomotor speed, compared to the lovastatin-treated subjects. The cholesterol-lowering treatment did also in this study not influence psychological well-being. These are very interesting results, since the studies show the same impairment of attentional functions after a cholesterol-lowering treatment, which is in contrast with the mentioned association between adequate cognitive functioning and lower consumption of cholesterol and other lipids (41). At this point it is unclear whether the association between cholesterol level and cognitive performance is determined by change of cholesterol level or by the levels itself.
Amino acid and protein/carbohydrate diet manipulations

Serotonin syntheses in the brain depends on the tryptophan (TRP) concentration in the central nervous system. The ratio TRP to Large Neutral Amino Acids (LNAA’s) is important, because TRP competes with the other LNAA’s to pass the blood–brain barrier. Therefore, more serotonin will be synthesized in the brain not only when TRP increases but also when the total concentration of the other LNAA’s decreases. Food manipulations achieving subchronic relative supplementation or depletion of TRP are a carbohydrate-rich/protein-poor diet (CR/PP) and a protein-rich/carbohydrate-poor diet (PR/CP) respectively (48). In stress-prone subjects, CR/PP prevented a deterioration of mood and performance under uncontrollable laboratory stress conditions. The assumption was that in stress-prone subjects (HS) there is a higher risk of serotonin (5-hydroxytryptamine; 5-HT) deficiency in the brain. Consequently, carbohydrates may prevent a functional shortage of central 5-HT during acute stress, due to their stimulatory effect on brain TRP. Significant increases were found in the ratio of TRP to Large Neutral Amino Acids (LNAA) during the CR/PP diet compared with the PR/CP diet. With respect to cognitive performance, significant dietary effects were found on speed of memory scanning. It is suggested that CR/PP food in HS subjects may increase personal control, probably under the influence of higher levels of brain TRP and 5-HT (48, 49). In another study administration of alfa-lactalbumin, which is a bovine protein with a high TRP content, increased the plasma Trp/LNAA ratio, reduced cortisol and improved mood under stress in stress-vulnerable subjects (50).

The daily administration of tyrosine, a large neutral amino acid found in dietary proteins, which has received recent attention as a potential treatment for stress, has been shown to be effective in enhancing cognitive function in healthy young individuals who were physically exhausted through military training during 5 days. Supplementation with tyrosine may reduce the effects of psychosocial- and physical stress and fatigue on cognitive task performance (51). Another study indicated that tyrosine may sustain working memory in situations of high mental load (52).

Human experimental models

Experimental studies are necessary to confirm the association between different nutrients and cognitive performance in the elderly. Human experimental models of altered cognitive function, might indicate the specific mechanisms of action through which the nutrients or nutritional supplements may enhance cognitive performance. Therefore, we will now move on to briefly discuss possible human experimental models for the mentioned nutrients.

Several of the nutrients mentioned above, including the vitamins, polyphenoles in wine, tocopheroles and polyphenoles in olive oil, and flavonoids, terpenoids and organic acids in ginkgo biloba, display antioxidative properties. These antioxidants may prevent oxidative stress by acting as free radical scavengers. The hypoxia model may be a useful human experimental model to study the antioxidative actions of these nutrients. During the hypoxia condition subjects breath low-oxygen air, either through pressurized gas tubes within a normal environment, or in low pressure chambers simulating the effects of high altitude. Subsequently, controlled experiments on the acute or chronic effects of substances (e.g. antioxidants) with neuroprotective properties are carried out (53).

Phospholipids and fatty acids influence the functioning of the neuronal membranes. By altering the membrane fluidity, membrane receptor formation and function, membrane signalling, and surface membrane activity they affect the activity of the blood–brain barrier, neurotransmitters, hormones and cytokines. These effects cannot be measured in humans directly, but have to be deduced from altered measures of brain function and cognition. The administration of anaesthetic gases to human volunteers is a specific model of neuronal membrane dysfunction with its concomitant impairment of human cognition.

There are also nutrient-based human experimental models of impaired neurotransmission. Acute tryptophan depletion (ATD) might be a human experimental model to study the efficacy of nutrients or nutritional supplements which influence cognitive performance through a serotonergic pathway. During this experiment volunteers drink different amino acid mixtures on two separate test days. The tryptophan depletion mixture contains a mixture of amino acids including all long chain neutral amino acids except tryptophan. This mixture decreases plasma tryptophan concentration and consequently brain tryptophan concentrations and serotonin synthesis. The brain tryptophan decrease is probably caused by two mechanisms. The amino acids administered in the mixture stimulate protein synthesis at tissue level, which causes a decrease of plasma tryptophan, and on the other hand, tryptophan competes for the same carrier enzyme system as the other LNAA’s to pass the blood–brain barrier (54). It has been shown that elderly and Alzheimer’s Disease patients are more sensitive to the memory impairing effects of ATD (55). Consequently, if nutritional substances reverse or attenuate ATD-induced memory impairment, this can be taken as an indication of their serotonergically mediated cognition enhancing efficacy in elderly.

Acute phenylalanine/tyrosine depletion (APTD) is a comparable model that reduces dopamine function, and has similar mood lowering (56), and memory impairing effects as in ATD (57). Likewise, if nutritional substances reverse or attenuate APTD-induced cognitive impairment, this can be taken as an indication of their dopaminergically mediated cognition enhancing efficacy in elders.
Conclusions

In epidemiological studies associations have been established between nutritional status, consumption of vitamins, wine, fatty acids and cognitive decline. This does not mean however, that depletion of certain nutrients can actually be suppleted through a change in diet or through the use of nutritional supplements. It seems reasonably well established for example that low folate signals MCI, but this does not necessarily mean that MCI or AD can be prevented or postponed by ingestion of folate. The most important question is therefore, whether these manipulations actually halt or decelerate cognitive decline or even enhance cognitive functions. Moreover, it is difficult to compose a diet in which all putatively cognition enhancing nutrients are properly taken into account. A proper dietary composition is only the ratio of carbohydrates to proteins as well as the inclusion of sufficient micronutrients seems to be favourable to the maintenance of cognitive function under stress and putatively at older age. In general, there appears to be a limited amount of controlled studies in the area of nutrients and cognitive function in human subjects, particularly in the elderly.

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