B vitamins, homocysteine, and neurocognitive function in the elderly[1–4]

Jacob Selhub, Laura C Bagley, Joshua Miller, and Irwin H Rosenberg

ABSTRACT Evidence of the importance of the B vitamins folic acid, vitamin B-12, and vitamin B-6 for the well-being and normal function of the brain derives from data showing neurologic and psychologic dysfunction in vitamin deficiency states and in cases of congenital defects of one-carbon metabolism. The status of these vitamins is frequently inadequate in the elderly and recent studies have shown associations between loss of cognitive function or Alzheimer disease and inadequate B vitamin status. The question that arises is whether these B vitamin inadequacies contribute to such brain malfunctions or result from aging and disease. From a theoretical standpoint, these inadequacies could give rise to impairment of methylation reactions that are crucial to the health of brain tissue. In addition or perhaps instead, these inadequacies could result in hyperhomocysteinemia, a recently identified risk factor for occlusive vascular disease, stroke, and thrombosis, any of which may result in brain ischemia. Advances in the understanding of this putative relation between inadequate vitamin status and loss of cognitive function in the elderly are likely to be slow and may depend on the outcomes of both prospective studies and longitudinal studies in which nutritional intervention is provided before cognitive decline occurs. *Am J Clin Nutr* 2000;71(suppl):614S–20S.

KEY WORDS Alzheimer disease, cognitive function, cognitive decline, dementia, folate, folic acid, vitamin B-12, vitamin B-6, homocysteine, hyperhomocysteinemia, brain, B vitamins, elderly, aging

INTRODUCTION

No other organ system in the body has a greater minute-to-minute dependence on its nutrient supply than the central nervous system. In turn, that system has a profound effect on dietary intake. Current theories describe functions of brain receptors for cholecystokinins, opioid-like endorphins (1), and serotonin that appear to influence eating behavior and satiety. In animal studies, the number and function of such receptors have been found to decline with age. However, the importance of these observations with respect to declining appetite in the elderly is uncertain. In addition, there are well-documented declines in olfactory functions that may influence eating behavior and the taste threshold of the elderly (2).

The central nervous system requires a constant supply of glucose, and adequate brain function and maintenance depend on almost all the essential nutrients. For those B vitamins that participate in one-carbon metabolism (ie, folate, vitamin B-12, and vitamin B-6), deficiency of or congenital defects in the enzymes involved in these pathways is associated with severe impairment of brain function (**Table 1**).

Although severe vitamin deficiencies and congenital defects are rare, milder subclinical vitamin deficiencies are not uncommon in the elderly. Interest is increasing in learning the extent to which these mild, reversible deficiencies contribute to some decline in cognitive function in the later years of life. This article reviews currently available data that relate to aging, B vitamin status, and cognitive decline. Other reviews of these topics were published elsewhere (3–5). A review by Nourhashemi et al in this supplement addresses more directly the relation between B vitamin status and Alzheimer disease (6).

AGING AND DECLINE IN B VITAMIN STATUS

One of the most striking age-related changes in gastric histology and function is the increasing prevalence with aging of atrophic gastritis with hypochlorhydria or achlorhydria. Based on various studies of elderly people, the prevalence of atrophic gastritis ranges from 20% to 50% depending on how the diagnosis is made and which definitions are used. In the Framingham Heart Study, the prevalences of atrophic gastritis among 60–69-y-olds and those >80 y were found to be 24% and 37%, respectively; the criteria used were serum pepsinogen I and II concentrations as measured by radioimmunoassay (7).

The physiologic consequences of atrophic gastritis include changes in gastric emptying and decreased secretion of intrinsic

[1] From the Jean Mayer US Department of Agriculture Human Nutrition Research Center on Aging at Tufts University, Boston, and the University of California at Davis.

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[4] Address reprint requests to J Selhub, Jean Mayer US Department of Agriculture Human Nutrition Research Center on Aging, Tufts University, 711 Washington Street, Boston, MA 02111. E-mail: jselhub@hnrc.tufts.edu

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TABLE 1
Neurologic and behavioral dysfunctions associated with defects in one-carbon metabolism[1]

Vitamin deficiencies	
Folate deficiency	Depression
Vitamin B-12 deficiency	Subacute combined degeneration, peripheral neuropathy, dementia
Vitamin B-6 deficiency	Peripheral neuropathy, seizures
Congenital defects	
Cystathionine-γ-synthase	Mental retardation, psychiatric disturbances, seizure
MTHFR deficiency	Subacute combined degeneration, dementia, psychiatric disturbances, seizures
Methyl-B-12 (cblE, cblG)	Hypotonia, seizures

[1] MTHFR, methylenetetrahydrofolate reductase.

factor. However, the stomach appears to have a large reserve capacity for intrinsic factor secretion. Only in the most severe cases of gastric atrophy does intrinsic factor secretion become a rate-limiting factor for vitamin B-12 absorption. Nevertheless, atrophic gastritis has been reported to limit the bioavailability of vitamin B-12, although not because of impaired intrinsic factor secretion. Rather, the cause may be impaired release of vitamin B-12 from food proteins and peptides due to impaired acid secretion and reduced digestion by pepsin. Another potential effect of atrophic gastritis is bacterial overgrowth in the stomach and proximal small bowel, which in turn can reduce vitamin B-12 bioavailability because some types of bacteria take up vitamin B-12 for their own use.

Other consequences of atrophic gastritis include increased pH in the stomach and proximal small intestine. For example, mean (± SEM) pH measured at the ligament of Trietz was 7.1 ± 0.1 in subjects with atrophic gastritis compared with 6.6 ± 0.1 in a group of healthy elderly subjects (8). This increase in pH seems small but has been shown to significantly limit folic acid absorption; the optimum pH for active folate uptake is 6.3 (9).

In our studies of the original Framingham Heart Study cohort (subjects aged 67–93 y), we found a high prevalence of inadequate B vitamin status. The percentages of subjects with inadequate B vitamin status were ≈30% for folate, 20–25% for vitamin B-12, and ≈20% for vitamin B-6 (10). Homocysteine metabolism is closely associated with metabolism of folate, vitamin B-12, and vitamin B-6 (**Figure 1**); high plasma concentrations of this amino acid indicate disruption of its metabolism (10).

RELATION OF B VITAMINS TO COGNITIVE FUNCTIONS

As discussed above, the evidence supporting neurologic effects of folate, vitamin B-12, and vitamin B-6 is derived from studies of clinical vitamin deficiencies in both humans and laboratory animals, as well as the effects of homozygous mutations of genes that encode the enzymes of folate metabolism (Table 1). Epidemiologic evidence linking low vitamin status or intake with decline in neurocognitive function in the elderly was first described by Goodwin et al (11). These authors showed that healthy elderly subjects who had low blood concentrations or intakes of folate, vitamin B-12, vitamin C, and riboflavin scored poorly on tests of memory and nonverbal abstract thinking. Other studies (*see* **Table 2**) have, for the most part, reiterated these epidemiologic associations between vitamins and neuropsychologic functions, although the methods of assessment were different and correlations were not always statistically significant. The extent to which these and other manifestations of brain function impairment can be ascribed to diminished vitamin status in the elderly is unclear. Goodwin et al (11) pointed out that their study subjects ìwere not mentally impaired and none of them was diagnosed as having dementia at the previous three-year complete medical evaluation which included mental status testing.î Neurocognitive impairment in this study was defined on the basis of comparisons between normal and abnormal scores within the same population. It is also noteworthy that some studies have reported improvement in cognitive performance after supplementation with these vitamins (13, 28–31). Lindenbaum et al (13) found significant improvement in neuropsychiatric functions among cobalamin-deficient patients after vitamin B-12 supplementation and Martin et al (31) reported cognitive recovery after vitamin B-12 supplementation in patients with cobalamin deficiency states of short duration (<1 y). These results support the possibility that poor vitamin status is partially responsible for the cognitive decline seen in some elderly persons.

ONE-CARBON METABOLISM AND BRAIN FUNCTION

Possible biochemical interpretations of the putative effects of low vitamin status on cognitive decline can be made on the basis of the pathway shown in Figure 1. The pathway of one-carbon metabolism is characterized by the generation of one-carbon units, normally from serine, made active through association with tetrahydrofolate. The resulting 5,10-methylenetetrahydrofolate is subsequently used for the synthesis of thymidylate and purines (used for nucleic acid synthesis) and of methionine, which is used for protein synthesis and biological methylations. It is believed that methionine synthesis is the most crucial part of the pathway for the health of brain tissue. This synthesis is preceded by the irreversible reduction of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate in a reaction that is catalyzed by the flavin-containing methylenetetrahydrofolate reductase. Subsequently, 5-methyltetrahydrofolate serves a substrate to methylate homocysteine in a reaction that is catalyzed by a vitamin B-12-containing methyltransferase. Homocysteine is also methylated by betaine in a reaction not involving vitamin B-12; however, this reaction is confined mostly to the liver.

A considerable proportion of methionine is activated by ATP to form *S*-adenosylmethionine (SAM), which serves primarily as a universal methyl donor in a variety of reactions. In the brain, SAM-dependent methylations are extensive and the products of these reactions include neurotransmitters (catecholamines and indoleamines), phospholipids, and myelin (32–35). One hypothesis proposes that the loss of neurocognitive function in the elderly is due in part to impaired methylation

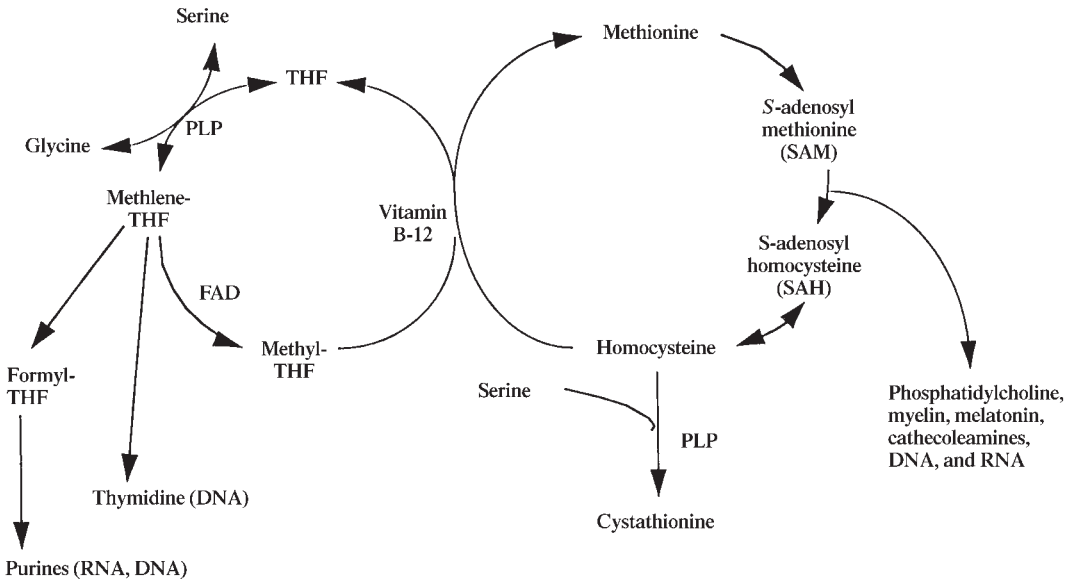

FIGURE 1. One-carbon metabolism in brain tissue. PLP, pyridoxal-5′-phosphate; FAD, flavin adenine dinucleotide; THF, tetrahydrofolate.

reactions in brain tissue. Because a considerable amount of SAM derives from methionine formed through the methylation reaction involving folate, vitamin B-12, and homocysteine, the hypothesis states that the observed association between loss of cognitive function and inadequate vitamin status is due to lower production of SAM (3, 36–40). Studies that have shown the efficacy of SAM as an antidepressant have provided some support for this hypothesis (41–46).

Upon transfer of its methyl group, SAM is converted to *S*-adenosylhomocysteine (SAH), which is subsequently hydrolyzed to homocysteine and adenosine. This hydrolysis is a reversible reaction that favors SAH synthesis. Thus, in the state of folate or vitamin B-12 deficiency, inability to methylate homocysteine leads to SAH accumulation. SAH is a potent inhibitor of the various SAM-dependent methylations. Hence, the impaired methylations resulting from lower rates of SAM synthesis are augmented by the intracellular accumulation of SAH.

HOMOCYSTEINE AND NEUROCOGNITIVE DYSFUNCTION

Plasma homocysteine may be considered a functional indicator of B vitamin status, including that of folate and vitamin B-12 and, to a lesser extent, vitamin B-6. High plasma homocysteine concentrations can be largely attributed to inadequate status of these vitamins (47). Data from several laboratories indicate that plasma homocysteine increases with age independent of vitamin status, and that hyperhomocysteinemia is highly prevalent in the elderly (10).

Interest in the relation between neurocognitive dysfunction and plasma homocysteine concentrations arose from the growing epidemiologic evidence suggesting that mild elevations of this amino acid in the plasma are associated with increased risk of occlusive vascular disease, stroke, and thrombosis (48). The theory that elevated plasma homocysteine concentrations are related to cognitive dysfunction arose from results of several studies that showed associations between cognitive dysfunction and hyperhomocysteinemia (17, 48, 49). Riggs et al (24) investigated the relations between plasma concentrations of folate, vitamin B-12, vitamin B-6, and homocysteine and scores on a battery of cognitive tests in 70 men, aged 54–81 y, participating in the Normative Aging Study. Lower folate and vitamin B-12 concentrations were associated with poorer spatial copying skills ($P = 0.003$ and 0.04, respectively). In addition, plasma homocysteine concentration, which is inversely correlated with plasma folate and vitamin B-12 concentrations, was a stronger positive predictor ($P = 0.0009$) of spatial copying performance than either folate or vitamin B-12 concentrations.

A study by Bell et al (17) showed that elderly patients with depression who had lower cognitive screening test scores had significantly higher homocysteine concentrations than did either younger depression patients or elderly depression patients with normal cognitive screening test scores. Another study, by Joosten et al (26), showed that patients with Alzheimer disease had higher total plasma homocysteine concentrations than did age-matched healthy controls. However, these authors found no difference in total plasma homocysteine concentrations between the patients with Alzheimer disease and age-matched hospitalized patients. The significance of this observation is unclear. A case-control study of 164 patients with a clinical diagnosis of dementia of Alzheimer type, including 76 patients with histologically confirmed Alzheimer disease, showed that homocysteine concentrations were higher and serum folate and vitamin B-12 concentrations were lower in these patients than in matched control subjects ($n = 108$; 27).

CONCLUSIONS

Evidence of the importance of folate, vitamin B-12, and vitamin B-6 in neurocognitive and other neurologic functions derives from reported cases of severe vitamin deficiencies, particularly pernicious anemia, and homozygous defects in genes that encode for enzymes of one-carbon metabolism. The

TABLE 2
Cognitive dysfunction as related to low vitamin status and high homocysteine concentrations[1]

Authors	Subjects	Age	Tests	Low folate	Low B-12	Low B-6	High homocysteine	Comments
Goodwin et al (11), 1983	260 healthy noninstitutionalized Compared top 10% with bottom 5%[a] and 10%[b,2]	>60 y	Halstead-Reitan Categories Test (test of abstract thinking) (A) Wechsler Memory Test (B)	Blood concentrations: A, $P < 0.01$[a] B, NS	Blood concentrations: A, $P < 0.05$[a] B, $P < 0.05$[b]			Also found small positive correlations for riboflavin and vitamin C with verbal memory. No correlations were found for protein, thiamine, and pyridoxine
Karnaze and Carmel (12), 1987	Primary degenerative dementia patients ($n = 17$) (A) Secondary dementia patients ($n = 11$) (B)	Mean = A, 70.5 y B, 70.9 y	Mental status of neurology patients	A not significantly different from B	B much greater than A ($P = 0.001$)	NS	NS	No disease was responsible for the low B-12 status
Lindenbaum et al (13), 1988	40 neuropsychiatric patients with cobalamin deficiency but no anemia or macrocytosis	>17 y	Neurologic examination				3 SDs above normal in 36 of 37 patients	MMA concentrations were 3 SDs above normal in 36 of 37 patients before treatments but fell in all but 2 after treatment with cobalamin
Renvall et al (14), 1989	AD patients ($n = 22$) and cognitively normal individuals ($n = 41$) (A) Dementia patients ($n = 154$) and cognitively norma l patients ($n = 49$) (B)	>60 y	MMSE DSM-III	A, RBC: $P < 0.06$ B, RBC: $P < 0.03$	A, Serum: $P < 0.047$ (multivitamin supplement users: $P < 0.003$) B, Serum: $P < 0.004$			Also measured riboflavin and thiamine; RBC folate and B-12 concentrations were lower in those with low MMSE scores. In the most severe patients, however, mean values were higher
Tucker et al (15), 1990	28 volunteers	>60 y	Cognitive performance and electroencephalographic indexes	Weak				Positive correlation for plasma carotene ($P < 0.10$); no correlation with albumin; negative correlation with riboflavin
Nijst et al (16), 1990	293 neurologic patients	>11 y		Serum compared with CSF concentrations $P < 0.01$	Serum concentrations for AD ($P = 0.016$)			For a given individual, CSF B-12 varied for a given serum B-12 Vitamin B-12 in CSF was lower in DAT patients ($P < 0.024$) and in the MS groups ($P < 0.014$) than in control subjects
Bell et al (17), 1992	Elderly individuals ($n = 13$ with and 14 without VD) Young adults ($n = 15$)	Mean = 73 and 74 y Mean = 31 y	DSM-III-R, Montgomery-Asberg Depression Rating Scale, and MMSE	Negative correlation with homocysteine in elderly with no VD, $P = 0.06$	Negative correlation with homocysteine in elderly with VD, $P < 0.05$		Positive correlation for depressed elderly only; $P = 0.03$	
Levitt et al (18), 1992	Forty AD patients: 31 with other dementia 26 cognitively impaired but with no dementia	Mean = 68.4, 72.1, and 71.0 y, respectively	MMSE DSM-III	MMSE: $P < 0.08$	Attention and calculation ($P < 0.006$), 3-stage command ($P < 0.008$), design copying ($P < 0.005$)			Duration of illness, vitamin B-12 status, and education level together contributed 67% of the variance in MMSE scores
Kristensen et al (19), 1993	AD patients ($n = 26$) (A) Patients with other dementia ($n = 24$) (B) Patients with mental disorders ($n = 25$) (C) Control subjects ($n = 20$) (D)	Mean = 73.2, 68.9, 77.9, and 73.4 y, respectively	A, B, C: DSM III criteria D, Senile cataracts	A, RBC: $P < 0.05$	A, $P < 0.05$			Higher MMA concentrations in AD patients than in any other group; positive correlation between RBC folate and B-12 concentration ($r = 0.57$; $P < 0.0001$)

(Continued)

TABLE 2 *(Continued)*

Authors	Subjects	Age	Tests	Low folate	Low B-12	Low B-6	High homocysteine	Comments
Crystal et al (20), 1994	410 volunteers	>75 y	Blessed Test of Information, Memory, and Concentration and Fuld Object Memory Evaluation		NS			No conclusions can be drawn owing to lack of significant results and limited *n*
Nilsson et al (21), 1996	Neuropsychiatric dementia patients (*n* = 295) (A) Neuropsychiatric patients with no dementia (*n* = 215) (B) Control patients (*n* = 163) (C)	Mean = 78, 78, and 75 y, respectively	Psychiatric, neurological, somatic and laboratory investigations	A lower than B and C $P < 0.001$	NS		A and B higher than C $P < 0.001$	
Ortega et al (22), 1996	Elderly Spanish persons (*n* = 177)	>65 y	Katz' Scale of ADL, instrumental ADL, mental status questionnaire, MMSE, and Geriatric Depression Scale	Subjects with adequate folate status performed better on cognitive testing ($P < 0.05$)				Compared RBC and serum folate concentrations
Dror et al (23), 1996	Volunteers (*n* = 21)	>65 y	Functional Independence Measure, MMSE, Tinetti Balance Evaluation, and Geriatric Depression Scale			B-6 status correlated with Tinetti Balance scores ($P < 0.05$)		Also made recommendations for riboflavin and ascorbic acid
Riggs et al (24), 1996	Male volunteers (*n* = 70)	>54 y	Spatial copying (A) Two memory tests (B)	A, $P = 0.003$ B, NS	A, $P = 0.04$ B, NS	A, NS B, $P = 0.03$ $P = 0.05$	A, $P = 0.0009$ B, NS	No correlations of folate, B-12, or homocysteine with memory or language
La Rue et al (25), 1997	Elderly community residents (*n* = 137)	>66 y	Abstraction scale, logical memory and visual reproduction, Rey-Osterrieth Complex Figure Test	RBC: $P < 0.01$; plasma: $P < 0.05$; dietary intake: $P < 0.05$	Plasma: $P < 0.10$; dietary intake: $P < 0.10$	Dietary intake: $P < 0.05$		Positive correlations of abstraction performance with thiamine, riboflavin, and niacin; visiospatial performance with ascorbate; dietary protein with memory; and serum albumin or transferrin with memory, visiospatial performance, or abstraction
Joosten et al (26), 1997	AD patients (*n* = 52) (A) Hospitalized control subjects (*n* = 50) (B) Healthy elderly (*n* = 49) (C)	>70 y	DSM-III, NINCDS-ADRDA (AD diagnostic test), MMSE, Hachinski	$P < 0.04$ for A compared with C	NS		$P = 0.003$ for A compared with C $P = 0.003$ for A compared with B	MMA for A compared with B, $P = 0.028$
Clarke et al (27), 1998	Patients with DAT (*n* = 164, including 76 with histologically confirmed AD) and 108 control subjects	>55 y	CAMCOG MMSE Minimum medial temporal thickness	Lower serum folate ($P < 0.001$) in DAT patients and confirmed AD subgroup	$P < 0.05$ for DAT; $P < 0.001$ for confirmed AD subgroup		$P < 0.05$ for DAT; $P < 0.001$ for confirmed AD subgroup	

[1] Subject group and test abbreviations (ie, A, B) denote results within the same row. MMSE, Folstein's Mini-Mental State Exam; DSM-III, Diagnostic and Statistical Manual of Mental Disorders, 3rd ed; MMA, methyl malonic acid; AD, Alzheimer disease; RBC, red blood cell; MS, multiple sclerosis; VD, vascular disease; CSF, cerebrospinal fluid; ADL, activities of daily living; DAT, dementia of Alzheimer type; CAMCOG, cognitive section of the Cambridge Examination for Mental Disorders.

[2] Superscript letters link *P* levels with comparisons in same row.

neurologic dysfunctions seen in these cases allow for biochemical interpretations of the roles of vitamins in neurophysiology. The extent to which these interpretations are applicable to the observed epidemiologic relations between inadequate vitamin status (or inadequate vitamin intake) and neuropsychologic dysfunctions remains unclear. Advances in the understanding of this complex area are likely to be slow and may depend on the outcomes of both prospective studies and early nutritional interventions provided before signs of neurocognitive decline occur.

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