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Folate nutrition is related to neuropsychological functions in the elderly*

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Abstract

We investigated the nutritional state of B vitamins and the neuropsychological functions in 25 subjects, aged 63.1 ± 6.3 years, residing in rural areas of Korea. Nutritional states of thiamin, riboflavin, and pyridoxine were assessed enzymatically in the erythrocytes, and folate concentrations were measured microbiologically in the plasma and erythrocytes. A battery of composite neuropsychological test was administered to the subjects. Plasma folate was correlated with the total intelligence score (p=0.049). Folate levels in the erythrocytes were correlated with the performance intelligence scores such as block design (p=0.017) and picture arrangement (p=0.016). The red cell folate was correlated with memory scores such as general memory (p=0.009) and delayed recall (p=0.000). Although it did not reach statistical significance, verbal memory (p=0.053) was highly correlated with the red cell folate. The red cell folate was also correlated positively with the percent of conceptual level response number score (p=0.029), and negatively with the grooved pegboard test score for the non-dominant hand (p=0.010). Fine motor coordination was also influenced by folate nutrition, as finger tapping scores in both hands were significantly correlated with red cell folate (dominant hand; p=0.026, non-dominant hand; p=0.004). Other B vitamins such as thiamin, riboflavin, and vitamin B_6 were not as strongly correlated with neuropsychological function test scores as folate was. These results suggest that folate nutrition influences neuropsychological function test scores significantly in humans. Further studies are needed to explore the relationship between folate or other vitamin B nutrition and neuropsychological functions and the implications thereof.

Key Words: Folate, B vitamins, neuropsychological function, elderly

Introduction

B vitamins such as thiamin, riboflavin, vitamin B_6, and folate are known to be essential for the maintenance of normal metabolic functions in the brain. Thiamin and riboflavin coenzymes, thiamin pyrophosphate and flavin adenine dinucleotide and flavin mononucleotide namely, are involved in the mitochondrial energy metabolism in neurons (Baker & Tarnopolsky, 2003; Sheu *et al.*, 1998). Vitamin B_6 coenzyme, pyridoxal-5-phosphate is important for the metabolism of amino acids and proteins, neurotransmitters, and sphingolipids in the central nervous system (Dakshinamurti *et al.*, 1985). Folate is required in the synthesis of S-adenosylmethionine (SAMe), a methyl donor for many important brain biomolecules such as phospholipids, guanidoacetate, neurotransmitters, amino acids, and nucleic acids (Bottiglieri *et al.*, 2000; Hirata & Axelrod, 1980; Wagner, 1995).

Among other B vitamins, folate has received much attention recently as its low serum level is found to be closely associated with structural and functional abnormalities in the brain. Low serum folate levels have been related to atrophy of the cerebral cortex (Snowdon, 2000), dementia (Ramos *et al.*, 2005), cerebrovascular diseases (Maxwell *et al.*, 2002), and to specific domains of cognitive functioning such as episodic recall and recognition (Hassing *et al.*, 1999; Wahlin *et al.*, 1996). In addition to this, folate supplementation has shown a positive effect on cognitive functions (Durga *et al.*, 2007; Nilsson *et al.*, 2001) and memory deficits (Tettamanti *et al.*, 2006).

Nutritional inadequacy for B vitamins is a frequently observed phenomenon among the elderly in developing countries (Fakhrzadeh *et al.*, 2006) and also among those with low socioeconomic status in developed countries before a food folic acid fortification policy was mandated (Riggs *et al.*, 1996) or in countries where folic acid fortification is not mandated (Chen *et al.*, 2005; Joosten *et al.*, 1993; Lim & Heo, 2002). The objective of the present study was to investigate the relations between vitamin B status in the blood and neuropsychological functions in free-living elderly subjects residing in rural areas of Korea.

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Subjects and Methods

Subjects

Twenty-five elderly volunteers, 19 men and 6 women, residing on their own in rural areas of South Korea participated in the study. Participants with a history of medical, neurological or psychiatric illnesses, recent viral infection, use of antibiotics, or chronic metabolic diseases such as diabetes mellitus were excluded from the study. An informed consent form was obtained from each subject. The study was approved by the Human Investigation Review Committee of the Asan Medical Center.

Biochemical analysis

Overnight fasting venous blood samples were collected in heparinized tubes and centrifuged at 1,600×g. After removing the plasma and buffy coat by aspiration, the erythrocytes were washed three times with ice-cold saline (0.9%). The packed erythrocytes were dispensed into 0.5 ml aliquots and were stored frozen at -70℃ until biochemical analysis was performed. The B vitamin status of thiamin, riboflavin, and vitamin B_6 was assessed by conducting enzyme-coenzyme saturation kinetic assays on erythrocyte transketolase (TK; EC 2.2.1.1), glutathione reductase (GR; EC 1.6.4.2), and aspartate aminotransferase (AST; EC 2.6.1.1) (Bayoumi & Rosalki, 1976), respectively. Percent enzyme activations were calculated using the following equation.

(Enzyme activity with coenzymes-Enzyme activity without coenzymes)/ Enzyme activity without coenzymes×100

For blood folate status, folate concentrations in the plasma and red blood cells were determined microbiologically using *Lactobacillus casei* (ATCC 7469) (Buehring *et al.*, 1974).

Neuropsychological test

The participants underwent a battery of composite neuropsychological tests conducted by a neuropsychologist who was blinded to the subjects. Intelligence, memory, attention, problem solving abilities, and fine motor coordination were assessed using the following tests: the Korean standardized version (KWIS) of the revised version of the Wechsler Adult Intelligence Scale (WIS) for intelligence (Wechsler, 1981); the Wechsler Memory Scale, revised version (WMS-R) for memory (Wechsler, 1987); the Color Trail-making Test (CTT) for attention (Maj, 1993); the Wisconsin Card Sorting Test (WCST) for problem solving abilities (Heaton, 1981); and the Grooved Pegboard Test (GP) and Finger Tapping Test (FTT) for fine motor coordination (Ruff & Parker, 1993), respectively. We used an abbreviated version of the KWIS, using arithmetic and vocabulary sub-scale for the verbal intelligence, and block design and picture arrangement for performance intelligence. The neuropsychological test was performed on the same day as blood sample collection.

Statistical analysis

Test scores were found to be significantly influenced by age and years of education. The non-parametric Spearman's correlation analysis was performed between the neuropsychological test scores and blood B vitamin status with age and years of education as covariates. All statistical analyses were performed using a SPSS Statistical Analysis System Version 12.0 (Chicago, USA). Probability values less than 0.05 were considered statistically significant.

Results

The characteristics of the study population are summarized in Table 1. The mean age of the respondents was 63.1 years and the mean years of education were 5.3 years. The anthropometric characteristics such as height, body weight and BMIs of these participants were similar to those of average rural people in Korea of 60-69 years of age.

In Table 2 are the percent activation of TK, GR, and AST, and the blood folate concentrations of the study subjects. The mean percent activation of TK, GR, and AST enzymes were 36.5 ± 24.6%, 43.1 ± 20.2%, and 98.8 ± 37.4%, respectively, which were higher than the values considered nutritionally adequate, thus indicating a suboptimal functional B vitamin status on average in these subjects. Mean folate concentrations in the erythrocytes and plasma were 406.6 ± 162.3 nmol/L and 21.3 ± 12.8 nmol/L, respectively, which indicated that on average the folate status of these subjects was considered nutritionally adequate.

Table 1. Demographic and anthropometric characteristics of subjects[1)]

	Subjects (n=25)
Age (y)	63.1 ± 1.5
Gender (male:female)	16 : 9
Education (y)	5.3 ± 1.0
Height (cm)	157.2 ± 1.4
Weight (kg)	57.5 ± 2.2
BMI (kg/m^2)	23.3 ± 0.8

[1)] Values are the mean ± S.E.

Table 2. Nutritional state of thiamin, riboflavin, vitamin B_6 and folate in subjects[1)]

Nutritional state of B vitamins	Mean ± S.E.	Normal range[2)]
Thiamin Percent activation of enzymes	36.5 ± 4.8	≤15
Riboflavin Percent activation of enzymes	43.1 ± 3.9	≤20
Vitamin B_6 Percent activation of enzymes	98.8 ± 7.3	≤80
Erythrocyte folate (nmol/L)	406.6 ± 31.9	≥362
Plasma folate (nmol/L)	21.3 ± 2.5	≥15.9

[1)] Values are the mean ± S.E.
[2)] See references (Herbert, 1987; Leklem, 1990; Sauberlich *et al*., 1972; Tanphaichitr *et al*., 1970) for normal ranges of thiamin, riboflavin, vitamin B_6 and folate status, respectively.

Table 3. Spearman's correlation between vitamin B levels and intelligence scores

Intelligence scores	Correlation coefficients	P value
Arithmetic		
Nutritional state		
Thiamin	0.054	0.807
Riboflavin	0.110	0.618
Vitamin B_6	-0.122	0.578
RBC folate	-0.181	0.409
Plasma folate	0.240	0.270
Vocabulary		
Nutritional state		
Thiamin	0.113	0.608
Riboflavin	-0.076	0.730
Vitamin B_6	0.011	0.960
RBC folate	-0.157	0.475
Plasma folate	0.327	0.128
Block design		
Nutritional state		
Thiamin	-0.100	0.648
Riboflavin	-0.310	0.150
Vitamin B_6	-0.326	0.129
RBC folate	0.491	0.017*[1)]
Plasma folate	0.217	0.319
Picture arrangement		
Nutritional state		
Thiamin	-0.149	0.498
Riboflavin	-0.365	0.087
Vitamin B_6	-0.218	0.319
RBC folate	0.496	0.016*
Plasma folate	0.163	0.459
Total intelligence quotient		
Nutritional state		
Thiamin	0.036	0.869
Riboflavin	-0.346	0.106
Vitamin B_6	-0.112	0.612
RBC folate	0.194	0.374
Plasma folate	0.414	0.049*

[1)] Significant correlation was observed (*p<0.05).

Table 4. Spearman's correlation between vitamin B levels and memory scores

Memory scores	Correlation coefficients	P value
General memory		
Nutritional state		
Thiamin	-0.133	0.513
Riboflavin	-0.085	0.679
Vitamin B_6	0.140	0.496
RBC folate	0.505	0.009**[1)]
Plasma folate	0.296	0.142
Verbal memory		
Nutritional state		
Thiamin	0.089	0.667
Riboflavin	0.039	0.849
Vitamin B_6	-0.083	0.687
RBC folate	0.384	0.053
Plasma folate	0.157	0.443
Visual memory		
Nutritional state		
Thiamin	-0.087	0.671
Riboflavin	-0.033	0.875
Vitamin B_6	0.040	0.847
RBC folate	0.337	0.093
Plasma folate	0.232	0.255
Attention & concentration		
Nutritional state		
Thiamin	-0.001	0.997
Riboflavin	0.024	0.908
Vitamin B_6	0.024	0.906
RBC folate	0.204	0.317
Plasma folate	-0.016	0.940
Delayed recall		
Nutritional state		
Thiamin	-0.068	0.741
Riboflavin	-0.198	0.332
Vitamin B_6	0.084	0.684
RBC folate	0.675	0.000***
Plasma folate	0.119	0.564

[1)] Significant correlation was observed (**p<0.01, ***p<0.001).

The adjusted correlation coefficients between blood B vitamin concentrations and cognitive test scores showed that red cell folate concentration was significantly correlated with the visuo-spatial abilities as shown in the positive correlation between red cell folate and the scores for block design (p=0.017) and picture arrangement (p=0.016). Plasma folate was significantly correlated with the total intelligence quotient scores (p=0.049) (Table 3). With regard to the correlation between blood B vitamin concentrations and memory scores, red cell folate was positively correlated with general memory (p=0.009) and delayed recall (p=0.000) scores. Although it did not reach statistical significance, verbal memory (p=0.053) was also highly correlated with the red cell folate (Table 4).

Table 5 shows the data on the relationship between B vitamin status and fine motor coordination scores. Red cell folate was negatively correlated with Grooved Pegboard Test scores of the non-dominant hand (p=0.010). Fine motor coordination was associated with folate status as finger tapping scores of both hands were significantly correlated (dominant hand; p=0.026, non-dominant hand; p=0.004) with red cell folate. In the Wisconsin Card Sorting Test, red cell folate was positively correlated with the percent of the conceptual level response number scores (p=0.029).

Discussion

In our study, among other B vitamins, folate status as assessed by folate concentrations in the plasma and red blood cells was significantly correlated with test scores for several domains of

Table 5. Spearman's correlation between vitamin B levels and fine motor coordination scores

Fine motor coordination scores	Correlation coefficients	P value
Grooved pegboard test scores, dominant hand		
Nutritional state		
Thiamin	0.258	0.234
Riboflavin	0.340	0.112
Vitamin B_6	-0.312	0.147
RBC folate	-0.341	0.111
Plasma folate	-0.061	0.783
Grooved pegboard test scores, non-dominant hand		
Nutritional state		
Thiamin	0.203	0.353
Riboflavin	0.134	0.541
Vitamin B_6	-0.245	0.029*[1)]
RBC folate	-0.525	0.010*
Plasma folate	0.101	0.646
Finger tapping scores, dominant hand		
Nutritional state		
Thiamin	-0.264	0.224
Riboflavin	-0.054	0.808
Vitamin B_6	0.128	0.562
RBC folate	0.463	0.026*
Plasma folate	-0.135	0.540
Finger tapping scores, non-dominant hand		
Nutritional state		
Thiamin	-0.155	0.480
Riboflavin	0.035	0.874
Vitamin B_6	0.008	0.971
RBC folate	0.571	0.004**
Plasma folate	0.090	0.685

[1)] Significant correlation was observed (*p<0.05, **p<0.01).

Table 6. Correlation of vitamin B levels and Wisconsin Card Sorting Test scores

Wisconsin Card Sorting Test scores	Correlation coefficients	P value
Percent response number scores		
Nutritional state		
Thiamin	-0.139	0.527
Riboflavin	-0.059	0.788
Vitamin B_6	-0.069	0.755
RBC folate	-0.102	0.644
Plasma folate	0.115	0.601
Percent of the conceptual level response number scores		
Nutritional state		
Thiamin	0.337	0.115
Riboflavin	-0.175	0.426
Vitamin B_6	0.075	0.733
RBC folate	0.455	0.029*[1)]
Plasma folate	0.191	0.383

[1)] Significant correlation was observed (*p<0.05).

cognitive function. Plasma folate was significantly correlated with total intelligence quotient scores, while red cell folate was correlated with the scores for memory, fine motor coordination, and problem solving ability.

Folate, along with vitamin B_{12}, is known to be important for cognitive function. In elderly subjects, folate has been positively correlated with the auditory verbal learning test, digit symbol test, block design test, delayed recall, percentage of forgetting, and categorical verbal fluency test (Duthie *et al.*, 2002; Feng *et al.*, 2006). Elderly subjects with low serum folate have impaired spatial copying skills (Riggs *et al.*, 1996) and abstraction performance (LaRue *et al.*, 1997), and score lower on tests of nonverbal abstract thinking when compared with age-matched individuals with high serum folate concentrations (Goodwin *et al.*, 1983).

The status of vitamin B_6, vitamin B_{12} and folate is frequently inadequate in the elderly and several studies have shown associations between loss of cognitive function (Ramos *et al.*, 2005; Smith, 2002; Tettamanti *et al.*, 2006) or Alzheimer's disease (Snowdon *et al.*, 2000) and inadequate B vitamin status. It is interesting, though, that in our study the proportion of subjects who were folate deficient was much lower when assessed by plasma (9.4%) and erythrocyte (19.8%) folate, respectively, than those (50-70%) for other B vitamins, and yet folate was the only vitamin which was related with cognitive function. An earlier study (Lindeman *et al.*, 2000) found that cognitive function was significantly associated with serum folate concentrations, but not with vitamin B_{12}, vitamin C and other vitamin concentrations in the serum of elderly subjects. In their study, the most significant associations observed were those between serum folate and various measures of cognitive function, even after adjusting for the presence of depression. Even in healthy older adults in developed countries with normal blood levels of B vitamins, test scores for delayed recall, abstract reasoning, and selective attention were shown to be positively associated with B vitamin levels in the serum (Bell *et al.*, 1990).

Folate is found in high concentrations in the central nervous system. Some studies have found an association between folate deficiency and a variety of neurological and psychiatric disturbances such as impaired cognitive function, dementia and depression (Hassing *et al.*, 1999; Ramos *et al.*, 2005; Snowdon, 2000). Folate is important in one-carbon metabolism, contributing carbon atoms to purines, thymidine, and amino acids. Folate deficiency, by hindering the synthesis of DNA and protein synthesis for neuronal and glial growth and proliferation during critical points, can detrimentally influence neurotransmission and memory functions (Albright *et al.*, 1999). Folate is also involved in maintaining adequate methionine pools for the synthesis of S-adenosylmethionine (SAMe) (Balaghi *et al.*, 1993). SAMe is required in numerous transmethylation reactions involving nucleic acids, proteins, phospholipids, amines and other neurotransmitters (Bottiglieri *et al.*, 1994). Folate deficiency can reduce SAMe concentrations in the central nervous system, thus increasing uracil misincorporation (Blount *et al.*, 1997) and negatively affecting methylation of cellular DNA (Scott *et al.*, 1994), proteins, and neurotransmitters, thus impeding neural function. Folate deficient mice also display behavioral abnormalities (Gospe *et al.*, 1995). In the SENECA study, education and high plasma levels of folate and beta-carotene appear to be associated with a lower risk of developing dementia (Haller *et al.*, 1996). Low concentrations of folate were associated with neocortical atrophy at autopsy in subjects with Alzheimer's disease (Snowdon *et al.*, 2000).

In our study, folate concentrations in red cells had stronger associations with cognitive function than those in plasma, confirming the observation by Durga *et al.* (2007), who reported that low concentrations of erythrocyte folate but not serum folate were associated with poor cognitive performance. Since folate concentration in tissue reflects long-term body folate status better than that in serum (Varela-Moreiras & Selhub, 1992), we may have observed in our subjects a stronger association between cognitive function and red cell folate. In our subjects, the positive correlation of plasma folate was limited to total intelligence quotient scores whereas that of erythrocyte folate was with other domains of cognitive function such as memory, fine motor coordination and Wisconsin Card Sorting Test scores. If we had a larger number of subjects in the study, we might have been able to see positive associations between more domains of cognitive function with plasma folate.

Although the number of participants was small, our study results clearly indicate that folate nutrition is related with cognitive function test scores for intelligence, memory attention, visuo-spatial abilities, and fine motor coordination in our elderly subjects. It may be difficult to apply what we found in our study directly to general pubic, however, there is growing evidence supporting the view that good nutritional status of folate and other B vitamins is an important determinant for cognitive function. It may be possible that some of the decline in cognitive function associated with aging is preventable or reversible with improved folate nutrition as suggested by Rosenberg *et al.* (1992). It is interesting to note, however, that study results on the effects of folic acid supplementation on cognitive function, dementia and Alzheimer's disease have not been consistent, some showing it to be beneficial (Bryan *et al.*, 2002; Luchsinger *et al.*, 2007; Nilsson *et al.*, 2001), others showing a negligible effect (Baker *et al.*, 1999; Wahlin *et al.*, 2008) and still others showing it to be even detrimental (Sommer *et al.*, 2003). Further studies should explore the relationship of the state of blood B vitamins to neuropsychological function and also the possibility of improving cognition with the dietary manipulation of natural sources of food folate.

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