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Increased postprandial homocysteinemia in a group of depressed patients

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Summary. Elevated tissue and serum concentrations of homocysteine (HCY) are associated with neuropsychiatric disorders as well as with premature occlusive vascular disease, as seen in homocystinuria. In order to study dietary-related modifications in plasma HCY, total HCY was assayed in the fasted state and 2 hr after meals in 12 depressed female patients aged 54 to 81 yr and in 12 female controls aged 50 to 85 yr. Fasting HCY was also studied in 4 patients with dementia. Postprandial HCY varied only slightly in the controls compared with their fasting values, whereas a significant increase was noted in the depressives. To study the influence of normal and low protein diets on this abnormality, fasting and postprandial HCY were investigated in 4 of the depressives after one week of a normal diet, after a week on a diet without meat, fish or eggs, and then again after return to a normal diet for one week. Persistence of the abnormal increase in postprandial HCY in 2 of these 4 patients while on the low-protein diet may have been due to an inherited defect in HCY metabolism. Folate deficiency can also cause hyperhomocysteinemia, and as folate supplements constantly lower HCY concentrations, nutritional counseling and folate therapy might prove helpful in the treatment of depression.

Keywords: Amino acids – Homocysteine – Depression – Dementia

Introduction

Homocysteine (HCY), a sulfur-containing amino acid that is readily oxidized to homocystine, is an intermediary step in the synthesis of cystine from methionine by transsulfuration; it can also be re-methylated to methionine (Fig. 1).

A rare homozygous genetic disorder which is usually due to cystathionine b-synthase deficiency, homocystinuria is frequently associated with premature

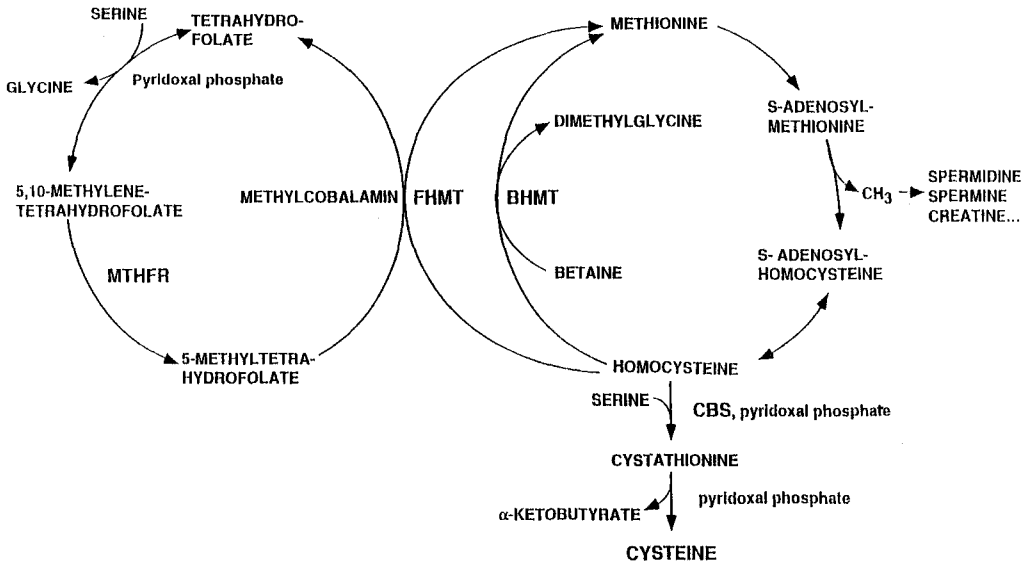

Fig. 1. Metabolic pathways of homocysteine. Homocysteine, formed from methionine, is catabolized via cystathionine to cysteine. Homocysteine may also be re-methylated to methionine. Pyridoxal phosphate (vitamin B6), cobalamin (vitamin B12), and folates are required co-factors. Homocystinuria is mainly caused by deficiencies in the activity of cystathionine b-synthase (*CBS*) and deficiencies in the activity of other enzymes: 5-methyltetrahydrofolate: homocysteine methyltransferase (*FHMT*), betaine: homocysteine methyltransferase (*BHMT*), and 5,10-methylenetetrahydrofolate reductase (*MTHFR*), which catalyzes the production of 5-methyltetrahydrofolate

occlusive vascular disease, neuropsychiatric disorders, and skeletal abnormalities (Mudd et al., 1989). The heterozygote carrier state, which is more common, occurs at an estimated frequency of 1:100 to 1:200 in the normal population (Mudd et al., 1989; Wilcken et al., 1992), and causes a milder form of hyperhomocysteinemia (Boers et al., 1985; Clarke et al., 1991). This biochemical abnormality can also be caused by inherited or acquired deficiencies in the coenzymes implicated in HCY metabolism: vitamins B6, B12 and folates (Fenton and Rosenberg, 1989; Brattstrom et al., 1988; Andersson et al., 1992).

Defects in HCY metabolism can be elicited by methionine loading (Boers et al., 1985), but such investigative procedures are laborious. Although food consumption is not known to increase plasma HCY concentrations (Ubbink et al., 1992; Fermo et al., 1993), we investigated the effect of a standard breakfast on homocysteinemia in search of an error in HCY metabolism. For this purpose, fasting and postprandial HCY values in 12 depressed patients not receiving any antidepressant drugs were compared with values in 12 healthy controls. Modifications in fasting and postprandial HCY concentrations were also studied in 4 of these depressives who exhibited increased postprandial HCY values in three situations: after 5 days of a 1,900 calorie "normal" diet, after 5 days of a 1,800 calorie low-protein diet (without meat,

eggs, or fish and thus low in methionine [a precursor of HCY] but reinforced in folate-rich fruits and vegetables), and then again after 5 days of the "normal" diet to determine whether a postprandial abnormality is due to intolerance of the methionine in the diet or is corrected by a balanced diet. Fasting HCY was also assayed in 4 patients with dementia, a psychiatric illness encountered in homocysteinemia (Abbott et al., 1987).

Material and methods

Twelve female patients aged 54 to 81 yr (mean 65.2 ± 5.6 yr) with major depression with melancholia (DMS-III-R criteria) were entered in the study; none had taken any antidepressant drugs for at least 3 weeks but some of them were given meprobamate. The 12 healthy female controls without any psychiatric, renal, gastrointestinal, or endocrine diseases were aged 50 to 85 yr (mean 64.7 ± 9.5 yr). HCY was also assayed in 4 patients (2 males, 2 females) with dementia of the Alzheimer type (DAT) aged 74 to 91 yr. Serum creatinine was <110 μmol/L in all subjects. Total plasma HCY corresponded to free and protein-bound HCY plus the disulfides homocystine and homocystine-cystine mixed disulfide.

Blood samples were drawn on tubes containing lithium heparinate between 7h00 and 8h00 am after an overnight fast and again in postprandial conditions at 2h00 pm, two hr after a balanced 1900 calorie lunch. In 4 of the depressed patients, fasting and postprandial HCY were studied in 3 consecutive situations: 1. after 5 days of a normal diet including milk, butter, meat, fish, or eggs (80 g), cheese, vegetables and fruit (3 servings of vegetables and 2 fruits a day); this 1900 calorie diet provided 65 g of protein containing 1.2–1.5 g of methionine, 70 g of fat, and 250 g of carbohydrates; 2. after 5 days of a 1800 calorie, low-protein diet with 400 g of vegetables and 2 fruits providing only 15 g of protein (no meat, fish, or eggs), 80 g of fat, and 265 g of carbohydrates; and 3. after 5 days of the same 1900 calorie normal diet described previously.

Total plasma HCY was assayed by ion exchange liquid chromatography with an LKB Alpha amino acid analyzer. For HCY assays, plasma samples were reduced according to Brattstrom et al. (1988); the intra-assay coefficient of variation was 7.5% (mean 16.4 μmol/L; 33 values). Results, which were normally distributed, were compared by Student's t-test.

Results

Fasting and postprandial HCY values: overall results

Results are summarized in Table 1. Mean fasting HCY in the depressives was only slightly higher than in the controls (9.19 μmol/L vs 8.12 μmol/L; not statistically significant). The main difference between the two depressives and the controls concerned postprandial values. Postprandial HCY concentrations in the controls were very close to their fasting values (mean 8.44 versus 8.12 μmol/L; not statistically significant). By contrast, the mean postprandial HCY level of the depressives was significantly higher than their fasting mean (12.22 versus 9.19 μmol/L; $p < 0.02$) and was also significantly higher than the postprandial mean of the controls (8.44 μmol/L; $p \approx 0.01$). There was no difference in the HCY response between subjects who were treated with meprobamate and those who were not.

Table 1. Homocysteine (μmol/L) in depressed patients (*P*) and in controls (*C*): Fasting and postprandial (*PP*) values

Depressed patients				Controls			
	Age (yr)	Fasting	PP		Age (yr)	Fasting	PP
P1	57	5.0	6.0	C1	53	6.0	7.0
P2	71	6.0	10.0	C2	70	10.0	10.0
P3	65	5.0	13.0	C3	58	10.0	12.0
P4	68	11.0	16.0	C4	70	9.7	8.1
P5	65	11.0	10.0	C5	60	14.7	11.8
P6	58	5.0	13.0	C6	60	7.0	7.4
P7	62	14.0	22.0	C7	56	8.5	8.5
P8	74	16.0	18.0	C8	80	8.0	7.0
P9	54	8.1	8.5	C9	50	7.0	6.0
P10	81	9.2	7.7	C10	85	7.0	8.0
P11	58	10.0	12.5	C11	55	8.5	8.5
P12	70	10.0	10.0	C12	80	8.0	7.0
Mean	65.6 ± 5.6	9.19 ± 3.35	12.22 ± 3.56		64.7 ± 9.5	8.7 ± 3.25	8.44 ± 1.78

Evolution of fasting and postprandial HCY levels in 4 depressed patients during dietary control (Table 2)

Normal HCY values in the literature vary from one study to another (Selhub et al., 1993); comparisons must thus be made with normal values determined for sex- and age-matched controls. Our normal values (5.0–16.0μmol/L in fasting conditions) are similar to those of Ueland and Refsum (1989) and Malinow (1990). At the beginning of our investigations, only patient P8 exhibited an increased fasting HCY value compared to the controls during the normal diet. Postprandial HCY values increased in all of the patients and were higher than in the controls. On the diet without protein, HCY values decreased after lunch, probably due to dietary supply of folates by the vegetables and fruit and especially due to the absence of any source of methionine. Following resumption of the normal diet, fasting HCY concentrations remained higher than at the beginning and did not increase in postprandial conditions for two patients (P3 and P7) whereas they increased in two others (P4 and P8).

Table 2. Homocysteine (μmol/L) during controlled protein diets

Diet	Patient P3		Patient P4		Patient P7		Patient P8	
	F	PP	F	PP	F	PP	F	PP
Normal diet 1	5	13	11	16	14	22	16	18
Low-protein diet	8	7	15	12	18	16	23	15
Normal diet 2	10	9	14	20	16	15	23	30

F fasting HCY; *PP* postprandial HCY; *Normal diet* 1 after 5 days of a normal diet (results during normal diet 1 are listed in Table 1); *Low-protein diet* after 5 days on a diet without meat, fish, or eggs; *Normal diet* 2 after resumption of the normal diet for another 5 days.

Fasting HCY in 4 patients with dementia

Fasting HCY values were respectively 8.3 and 13.9 μmol/l for the two male patients, both aged 74 yr. For the two females aged 91 and 75 yr, HCY values were respectively 9 μmol/L and 24.8 μmol/L; this latter value is higher than the concentrations observed for the controls and the depressed patients.

Discussion

Possibility of heterozygote homocystinuria

In the literature, analysis of variations in homocysteinemia have failed to detect any circadian rhythm for HCY concentrations in healthy subjects; in particular, no elevation has been noted in HCY concentrations after meals (Fermo et al., 1993), and even food consumption can significantly lower HCY values (Ubbink et al., 1992). This was also true in our controls, some of whom exhibited a decrease in their mean HCY concentration two hr after lunch; the maximum increase observed in the controls was 2 μmol/L (control C3). By contrast, some of our patients exhibited increased postprandial HCY levels. Six patients (P3, P4, P6, P7, P8, P11) had higher postprandial HCY values than the controls: 5 of them (P2, P3, P4, P6, P7) exhibited a postprandial rise in HCY of over 4 μmol/L while an increase of 2.5 μmol/L was seen in patient P11.

Hyperhomocysteinemia has several possible causes: a genetic enzymatic deficiency in HCY metabolism (transsulfuration, remethylation, vitamin B12 pathway) or an acquired deficiency in the coenzymes implicated in HCY metabolism (vitamines B6, B12, and folates). A link has been described between homocysteinemia and neuropsychiatric disorders, and folate deficiency has been reported in patients with affective disorders (Reynolds and Stramentinoli, 1983; Carney et al., 1990). Moreover, both folate and vitamin B12 deficiencies have been observed in neuropsychiatric patients (Botez, 1987). Folate administration has led to clinical improvement in elderly patients, who are often deficient in folates and vitamin B12, and replacement therapy has improved demented and depressive patients (Brocker, 1990) as an inverse relation has been described between homocysteine and folates-vitamin B12, and HCY assays have been proposed as a means of screening for folate deficiencies (Stampfer and Willett, 1993).

Analysis of HCY evolution over three 5-day periods of dietary control, with particular attention paid to protein and vitamin intake, revealed normalization of postprandial HCY values in patient P3 at the end of the study. Fasting values for patient P7 remained high but did not increase in postprandial conditions. By contrast, patients P4 and P8 had decreased postprandial HCY values when dietary methionine intake was severely restricted whereas normal intake of animal proteins elicited an abnormal response in HCY metabolism. Their postprandial homocysteinemia values increased respectively 6 and 7 μmol/L compared to their fasting values.

Certain patients with dementia appear to present hyperhomocysteinemia, and homocystinuria, which causes severe hyperhomocysteinemia, has been

described in cases of dementia (Bracken and Coll, 1985). HCY may play multiple roles in neuropsychiatric disorders owing to its atherogenic and excitotoxic properties, and it may thus be directly involved in the depression pathway. A correlation has been shown between increased HCY values and cognitive impairment in elderly depressives (Bell et al., 1992) while 51% of a cohort of 63 homocystinurics presented psychiatric disorders (depression, behavior disorders, personality disorders, obsessive-compulsive disorders) (Abbott et al., 1987).

While the increased postprandial HCY values observed in this study could have been due to folate deficiency, the abnormalities persisted even during dietary control in some patients. Like vitamin deficiency, heterozygosity for an inborn error in HCY metabolism (transsulfuration or re-methylation) is another possible cause. The preliminary results observed in dementia require further study. The observations that supplementation with folates, vitamins B12 and B6 (Brattström et al., 1988; Nilsson et al., 1994) lowers HCY levels and that a folate-rich diet corrected the homocysteinemia abnormality in two patients may be of practical importance for the establishment of nutritional guidelines and therapy applicable to individuals with depression.

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