Betaine and Folate Status as Cooperative Determinants of Plasma Homocysteine in Humans

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Objective—Two published studies have demonstrated that betaine in the circulation is a determinant of plasma total homocysteine, but none had sufficient power to investigate the possible effect modification by folate status.

Methods and Results—We measured homocysteine, betaine, folate, vitamin B_6, and related compounds in serum/plasma from 500 healthy men and women aged 34 to 69 years before (fasting levels) and 6 hours after a standard methionine loading test. Choline, dimethylglycine, and folate were determinants of plasma betaine in a multiple regression model adjusting for age and sex. The increase in homocysteine after loading showed a strong inverse association with plasma betaine and a weaker inverse association with folate and vitamin B_6. Fasting homocysteine showed a strong inverse relation to folate, a weak relation to plasma betaine, and no relation to vitamin B_6. Notably, adjusted (for age and sex) dose-response curves for the postmethionine increase in homocysteine or fasting homocysteine versus betaine showed that the inverse associations were most pronounced at low serum folate, an observation that was confirmed by analyses of interaction.

Conclusions—Collectively, these results show that plasma betaine is a strong determinant of increase in homocysteine after methionine loading, particularly in subjects with low folate status. **(*Arterioscler Thromb Vasc Biol*. 2005;25:379-385.)**

Key Words: betaine ■ choline ■ homocysteine ■ folate ■ methionine

The concentration of total homocysteine (tHcy) in serum/plasma is associated with risk of occlusive cardiovascular vascular disease (CVD).[1] Most studies have investigated basal concentration of tHcy, often obtained after an overnight fasting (fasting tHcy). The high concentration of tHcy detected after a standard methionine loading dose (postmethionine load [PML] tHcy) seems to be a risk factor independent of fasting tHcy,[2] and fasting and PML tHcy identify overlapping but also different subjects with hyperhomocysteinemia and increased CVD risk.[2] The PML increase in tHcy (PML ΔtHcy) can be calculated as the difference between PML tHcy and fasting tHcy, but its separate role in CVD risk assessment is not settled.

Determinants of fasting tHcy include genetic and a variety of lifestyle factors and pathologies.[3] Strong predictors of fasting tHcy include renal function and cobalamin and folate status.[2] The methylenetetrahydrofolate reductase 677C→T polymorphism is the most influential common genetic factor.[4]

PML tHcy and ΔtHcy have some determinants in common with fasting tHcy, including folate status and the methylenetetrahydrofolate reductase 677C→T polymorphism, whereas renal function seems to have minor impact. Vitamin B_6 status has been reported to have a moderate effect on PML tHcy and a weaker or essentially no effect on fasting tHcy,[2] which is in agreement with the role of the vitamin B_6–dependent *trans*-sulfuration pathway in degrading superfluous homocysteine.[5] The effect of these B vitamins are explained by their role in homocysteine metabolism, as depicted in Figure 1.

Betaine (trimethylglycine) is obtained in small amounts from food[6] or is generated from choline.[5,6] It serves as a methyl donor in a reaction converting homocysteine to methionine, catalyzed by the enzyme betaine-homocysteine methyltransferase (BHMT; EC 2.1.1.5; Figure 1). This pathway is confined to liver and kidney and represents an alternative route of homocysteine remethylation, a reaction that is also performed by the ubiquitous folate-dependent methionine synthase.[5]

Treatment with high doses of betaine (≥6 g per day) has been used for years to reduce fasting (basal) tHcy in homocystinurics[6] but also has a marked effect (10% to 15% tHcy reduction) in healthy individuals.[7,8] PML tHcy seems to be even more responsive to betaine, and high doses of betaine markedly reduced PML tHcy in healthy subjects[9] and in renal patients treated with folic acid and vitamin B_6.[10] In comparison, folic acid supplementation reduces fasting tHcy more than betaine, but it has a marginal and nonsignificant effect

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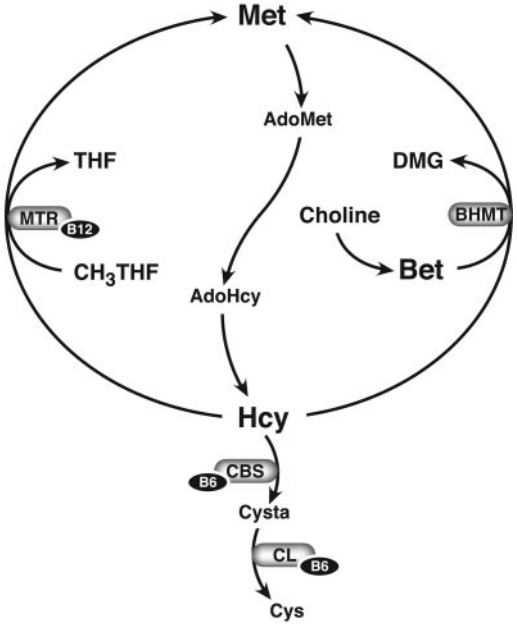

Figure 1. Homocysteine formation, remethylation, and degradation. AdoHcy, indicates S-adenosylhomocysteine; AdoMet, S-adenosylmethionine; Bet, betaine; BHMT, betaine-homocysteine methyltransferase; CBS, cystathionine β-synthase; CL, cystathionine lyase; CH3THF, methyltetrahydrofolate; Cys, cysteine; Cysta, cystathionine; Hcy, homocysteine; Met, methionine; MTR, methionine synthase; THF, tetrahydrofolate.

on PML tHcy.[9] Notably, low betaine doses in the range of dietary intake have been shown recently to reduce fasting and, in particular PML tHcy.[11]

There are few association studies on endogenous betaine in serum/plasma. An inverse association between tHcy and betaine was reported recently in 120 cardiovascular patients,[12] and plasma betaine has been shown to be a strong predictor of PML tHcy in 90 patients enrolled in a B vitamin intervention trial.[13]

We conducted a large study of 500 subjects undergoing methionine loading to investigate the relationship between plasma betaine and basal and PML tHcy and the possible effect modification by folate status.

Methods

Subjects and Protocol

Subjects were recruited through a general practice in The Hague, Holland. These subjects were healthy controls in a study on homocysteine and venous thrombosis. Details on recruitment, inclusion criteria, and data collection have been published previously.[14]

A 6-hour standard oral methionine loading test (0.1 g L-methionine per kg body weight in 200 mL orange juice) was performed as described.[14] The study was approved by the ethics committee of the Leyenburg Hospital, The Hague, Holland, and informed consent was obtained from all study participants.

Blood Collection and Biochemical Analyses

The EDTA plasma was stored at −20°C until analysis and serum kept at −70°C. Plasma tHcy,[15] serum creatinine, serum vitamin B_{12}, serum folate,[14] vitamin B_6 (sum of pyridoxal 5′-phosphate and pyridoxal),[16] betaine, choline, and dimethylglycine (DMG)[17] were determined with published methods.

Statistics

Data are presented as medians with 10th to 90th percentiles. Between-group comparisons of continuous variables were done by the Mann–Whitney *U* test. Spearman rank correlation and multiple regression analyses were used to evaluate associations between individual variables. Multiple linear regression analysis was used to assess the simultaneous relationship between various predictors of tHcy. Plasma tHcy was the dependent variable, whereas the independent variables were presented in the model as quartiles of betaine, folate, cobalamin, and creatinine. Thus, the regression coefficient was used to estimate the difference in mean tHcy between the reference and the other 3 quartiles. tHcy across quartiles was tested for homogeneity of means and for linear trend. Estimates were adjusted for age and sex, or B vitamin levels and creatinine, in addition to age and sex. We investigated the possible interaction between plasma betaine and folate and between betaine and vitamin B_6 by including a product term between the 2 variables in multiple linear regression models with tHcy as the dependent variable, retaining betaine and the B vitamin as independent variables. Because tHcy values (fasting and the increase after methionine loading) were not normally distributed, the multiple regression analyses, when appropriate, were also carried with log-transformed tHcy as outcome measures. The dose-response relationships between metabolites were also estimated with Gaussian generalized additive models (GAM),[18] as implemented in S-PLUS and R.[19] For other analyses, we used SPSS version 11.0 (SPSS).

Results

Subject Characteristics

A total of 500 subjects (292 females and 208 males) with a mean age of 50 years (range 34 to 69) were investigated. Their blood indices before and after methionine loading and according to gender are given in Table 1. Fasting plasma tHcy, betaine, choline, DMG, methionine, creatinine and vitamin B_6, and PML betaine, choline, and DMG were all significantly higher in men than in women.

The distribution of plasma betaine in terms of median, 10th to 90th percentiles, and range were 30.3, 18.8 to 45.3, and 9.4 to 94.9 μmol/L. The corresponding values for serum folate were 12.7, 7.0 to 23.6, and 3.0 to 54.4 nmol/L, respectively. Median serum cobalamin was 217 pmol/L.

Loading caused a 20-fold increase in overall median plasma methionine and a 4-fold increase in tHcy. Loading was not associated with any change in median betaine, choline, or DMG (Table 1).

Bivariate Correlations

Spearman rank correlation coefficients are listed in supplemental Table I (available online at http://atvb.ahajournals.org). PML ΔtHcy was weakly and inversely related to the folate, cobalamin, and vitamin B_6 but showed a moderate inverse relation to fasting ($r=-0.27$) and PML betaine ($r=-0.32$; all $P<0.001$). Fasting tHcy showed a moderate positive relation to age ($r=0.30$) and creatinine ($r=0.37$), an inverse relation to folate ($r=-0.29$) and cobalamin ($r=0.27$; all $P<0.001$), and a weak but significant positive relation to choline and DMG.

Betaine (fasting and PML) was strongly and positively related to choline and DMG ($r=0.41$ to 0.50; $P<0.001$) and showed a weak but significant positive relation to folate and vitamin B_6 ($r=0.18$ to 0.22; $P<0.001$).

TABLE 1. Subject Characteristics and Blood Indices at Baseline According to Gender*

	Total n=500	Men n=208	Women n=292	P†
Age, years	50 (34–69)	50 (31–69)	50 (34–68)	0.7
tHcy, μmol/L	10.7 (6.7–15.5)	11.7 (7.2–16.7)	10.3 (6.4–15.0)	<0.001
PML tHcy, μmol/L	37.0 (25.5–57.2)	37.0 (26.2–51.6)	37.2 (25.1–61.5)	0.3
Betaine, μmol/L	30.3 (18.8–45.3)	34.7 (25.9–50.9)	26.8 (15.6–38.7)	<0.001
PML betaine, μmol/L	28.6 (18.6–42.6)	34.2 (24.8–48.2)	24.8 (16.3–37.7)	<0.001
Choline, μmol/L	7.8 (5.9–10.5)	8.2 (6.3–11.0)	7.6 (5.7–9.9)	<0.001
PML choline, μmol/L	7.2 (5.5–9.8)	7.7 (5.8–10.4)	6.9 (5.3–9.1)	<0.001
DMG, μmol/L	3.1 (2.0–4.9)	3.4 (2.4–5.2)	2.8 (1.9–4.6)	<0.001
PML DMG, μmol/L	3.6 (2.5–5.4)	3.8 (2.7–5.9)	3.4 (2.4–5.3)	<0.001
Methionine, μmol/L	23.6 (19.1–30.7)	25.1 (18.8–28.6)	23.0 (18.8–28.6)	<0.001
PML Methionine, μmol/L	469 (308–657)	478 (341–638)	458 (293–671)	0.4
Creatinine, μmol/L	74 (55–99)	87 (71–107)	66 (52–84)	<0.001
Folate, nmol/L	12.7 (7.0–23.6)	12.9 (7.3–22.7)	12.5 (6.9–24.9)	0.9
Cobalamin, pmol/L	217 (125–389)	216 (131–385)	219 (123–393)	0.5
Vitamin B6, nmol/L	27.7 (15.8–54.8)	32.7 (18.0–56.3))	25.3 (15.3–54.1)	<0.001

*Data are given as medians with 10th to 90th percentiles in parentheses.
†Mann–Whitney *U* test.
tHcy indicates total homocysteine; PML, postmethionine load; DMG, dimethylglycine.

Folate, Choline, and DMG as Determinants of Betaine

We investigated the relationship between betaine and indices showing a simple correlation with betaine, such as folate, choline, DMG, creatinine, vitamin B_6, and age, using a Gaussian generalized additive regression (GAM), which produces dose-response curves adjusted for age, sex, and other parameters (Figure 2). Serum folate, choline, and DMG showed a positive relation to betaine, but the curve for choline leveled off at 14 μmol/L (99.5 percentile) and that for DMG at 4 μmol/L (80 percentile; Figure 2). Betaine showed no relation to vitamin B_6 and was inversely related to creatinine in this regression model. The associations obtained by GAM were essentially in agreement with those obtained by multiple linear regression (Figure 2, legend).

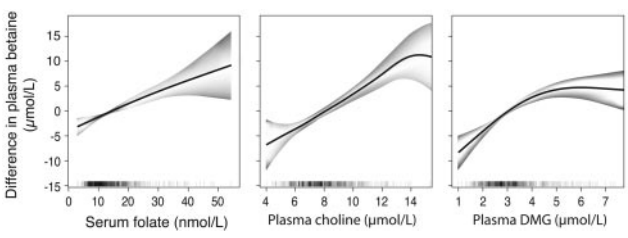

Figure 2. Dose-response relationship between plasma betaine and folate, choline, and DMG in serum/plasma. The curves were obtained by additive Gaussian generalized regression model (GAM). The model includes folate, choline, DMG, creatinine, vitamin B_6, sex, and age. All blood indices are fasting. The solid lines indicate the estimate dose-response curves, and the shaded areas 95% CI. A corresponding multiple linear regression analysis yielded the following regression coefficients: folate (β=0.2; P<0.001), choline (β=0.33; P<0.001), DMG (β=0.18; P<0.001), creatinine (β=−0.12; P=0.005), vitamin B_6 (β=−0.002; P=0.9), age (β=0.04; P=0.2), and sex (β=−0.42; P<0.001).

Estimated Change in PML ΔtHcy and Fasting tHcy by Betaine and Other Determinants

Determinants of ΔtHcy were estimated by multiple regression analysis (Table 2). For all variables, we estimated the difference in mean ΔtHcy between each quartile and the reference quartile. The mean tHcy difference across the extreme quartiles adjusted for age and sex was highest (8.3 μmol/L) for betaine, intermediate (5.7 μmol/L; data not shown) for creatinine, and moderate (4.3 to 4.9 μmol/L) for folate, cobalamin, and vitamin B_6; all P values were <0.001. The betaine–tHcy relationship remained strong (P<0.001) after additional adjustment for all blood indices (including folate and vitamin B_6), whereas multiple adjustments weakened the associations of tHcy with folate, cobalamin, vitamin B_6, and creatinine (P=0.006 to 0.03; Table 2). Betaine (P<0.001), creatinine (P=0.02), folate (P=0.1), cobalamin (P=0.02), and vitamin B_6 (P=0.005) showed nearly identical associations after log transformation of ΔtHcy (in a model containing age, sex, and all blood indices), and inclusion of the product term of betaine and vitamin B_6 in this regression model demonstrated no interaction between betaine and vitamin B_6 (P for interaction=0.8).

We performed the same calculation of the differences in mean fasting tHcy between quartiles of betaine, folate, cobalamin, vitamin B_6, and creatinine (Table 2). The tHcy difference across the extreme quartiles adjusted for age and sex was moderate (2.2 μmol/L) for betaine, weak (0.6 μmol/L) for vitamin B_6, intermediate (2.6 μmol/L) for cobalamin, and highest (3.7 to 3.9 μmol/L) for folate and creatinine; all P values were <0.001. Additional adjustment for all blood indices reduced the tHcy difference across the extreme betaine quartiles to 0.9 μmol/L, which now became of borderline significance (P=0.07). This adjustment had essentially no effect on the tHcy change across the quartiles

TABLE 2. Estimated Change in PML Increase in tHcy and Fasting tHcy According to Quartiles of Betaine and B-Vitamins

Blood Indices	Adjusted for Age and Sex	Adjusted for all Parameters*
	Change in PML Increase in tHcy, μmol/L (Mean [95% CI])	
Betaine (μmol/L)	*P*<0.001†	*P*<0.001
vs >37.0, n=125		
30.4–37.0 (n=125)	3.2 (0.2–6.2)	2.6 (−0.3–5.6)
24.8–30.3 (n=126)	6.4 (3.3–9.4)	6.0 (2.9–9.0)
<24.8 (n=123)	8.3 (5.0–11.6)	7.2 (3.9–10.6)
Folate (nmol/L)	*P*=0.001	*P*=0.03
vs >18.1, n=125		
12.8–18.1 (n=127)	2.1 (−0.9–5.1)	1.0 (−1.8–4.0)
9.4–12.7 (n=127)	3.9 (0.9–6.9)	1.8 (−1.2–4.7)
<9.4 (n=120)	4.9 (1.8–7.9)	3.2 (0.2–6.2)
Cobalamin (pmol/L)	*P*=0.004	*P*=0.02
vs >291, n=125		
218–291 (n=124)	3.6 (0.6–6.6)	2.9 (0.0–5.9)
168–217 (n=126)	4.5 (1.5–7.5)	3.7 (0.8–6.6)
<168 (n=124)	4.3 (1.3–7.3)	3.2 (0.3–6.1)
Vitamin B6 (nmol/L)	*P*<0.001	*P*=0.006
vs >37.4, n=125		
27.7–37.4 (n=125)	1.3 (−1.6–4.3)	0.7 (−2.2–3.6)
20.8–27.7 (n=125)	4.5 (1.5–7.6)	3.2 (0.2–6.2)
<20.8 (n=125)	4.9 (1.9–8.0)	3.7 (0.7–6.8)
	Change in Fasting tHcy, μmol/L (Mean [95% CI])	
Betaine (μmol/L)	*P*<0.001	*P*=0.07
vs >37, n=125		
30.4–37.0 (n=125)	1.6 (0.6–2.7)	1.0 (0.0–2.0)
24.8–30.3 (n=126)	2.0 (0.9–3.1)	1.3 (0.3–2.4)
<24.8 (n=123)	2.2 (1.0–3.3)	0.9 (−0.2–2.1)
Folate (nmol/L)	*P*<0.001	*P*<0.001
vs >18.1, n=125		
12.8–18.1 (n=127)	1.2 (0.2–2.2)	0.8 (−0.1–1.8)
9.4–12.7 (n=127)	2.3 (1.3–3.3)	1.8 (0.8–2.7)
<9.4 (n=120)	3.7 (2.7–4.8)	3.4 (2.4–4.4)
Cobalamin (pmol/L)	*P*<0.001	*P*<0.001
vs >291, n=125		
218–291 (n=124)	0.8 (−0.2–1.9)	0.6 (−0.3–1.6)
168–217 (n=126)	1.7 (0.6–2.7)	1.4 (0.4–2.3)
<168 (n=124)	2.6 (1.5–3.6)	2.3 (1.4–3.3)
Vitamin B6 (nmol/L)	*P*=0.1	*P*=0.9
vs>37.4, n=125		
27.7–37.4 (n=125)	0.0 (−1.1–1.0)	−0.4 (−1.4–0.6)
20.8–27.7 (n=125)	0.9 (−0.2–1.9)	0.0 (−1.0–1.0)
<20.8 (n=125)	0.6 (−0.5–1.7)	−0.2 (−1.2–0.9)

*All parameters (betaine, folate, cobalamin, vitamin B6, creatinine, age, and sex) are included in the model.
†*P* for trend.
PML indicates postmethionine load.

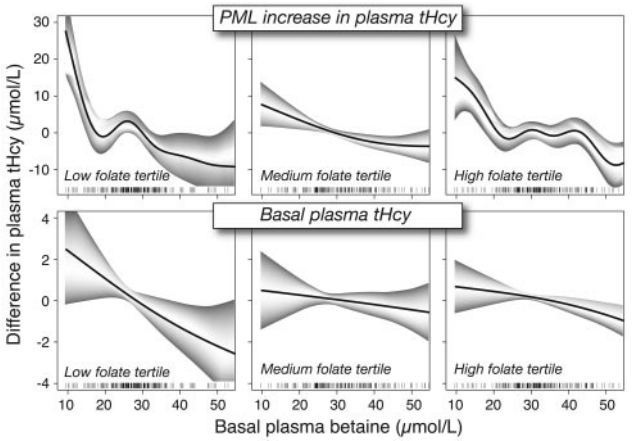

Figure 3. Dose-response relationship between plasma betaine and the increase in tHcy after methionine loading (top panels) or fasting tHcy (bottom panels) according to tertiles of serum folate. The curves are obtained by additive Gaussian regression analysis and are adjusted for cobalamin, vitamin B_6, creatinine, sex, and age. The solid lines indicate the estimate dose-response curves and the shaded areas 95% CI.

of folate, cobalamin, and creatinine but attenuated the tHcy–vitamin B_6 relationship (Table 2). Again, essentially the same associations with betaine ($P=0.03$), folate ($P>0.001$), cobalamin ($P>0.001$), vitamin B_6 ($P=0.8$), and creatinine ($P>0.001$) were obtained after log transformation of tHcy (data not shown).

Additional adjustment for smoking, alcohol, and body weight did not materially change the estimates (data not shown).

Effect Modification of the PML ΔtHcy: Betaine Relationship by Folate Status

We used GAM to estimate the dose-response relationship between ΔtHcy and betaine, adjusted for cobalamin, vitamin B_6, creatinine, sex, and age. The estimation was done separately in each tertile of plasma folate. In the lowest folate tertile, there was a strong negative relationship between ΔtHcy and betaine. In the top 2 folate tertiles, there was a weaker negative association (Figure 3). Accordingly, we observed an interaction between betaine and folate of borderline significance ($P=0.05$) by multiple regression (adjusting for cobalamin, vitamin B_6, creatinine, sex, and age), with log-transformed ΔtHcy as the outcome parameter.

Adjusted dose-response curves for fasting tHcy versus betaine for each tertile of serum folate were generated by the same procedure. In the lower tertile, there was an inverse association between tHcy and betaine, whereas in the top 2 tertiles, essentially no such association was observed (Figure 3). A significant interaction between betaine and folate ($P=0.01$) was observed by multiple regression with log-transformed fasting tHcy as the outcome parameter.

Discussion

We investigated the role of circulating plasma betaine as a determinant of fasting and PML tHcy in 500 healthy subjects undergoing methionine loading. Plasma betaine was a stronger predictor of the increase in PML Hcy (ΔtHcy) than other parameters investigated, including folate, vitamin B_6 and cobalamin, and the inverse association was particularly pronounced in subjects with low serum folate. We also observed that plasma betaine was a predictor of fasting tHcy, but only at low folate status.

Study Design

The strength of this study is the number of subjects included, which is high considering the resources and logistics required to perform methionine loading. The logistics are even more complicated for methionine testing, with a sampling interval of 6 hours used in the present study compared with short 2- or 4-hour tests. However, the 6-hour test has been recommended because the homocysteine response has lower within-subject variability than for the short tests.[20] This has been attributed to variable rate of methionine absorption.

Plasma Levels and Determinants of Betaine, Choline, and DMG

The median concentrations of betaine (30.3 μmol/L), choline (7.8 μmol/L), and DMG (3.1 μmol/L) determined for this study population of healthy adult men and women were similar to the concentration of betaine,[12,17,21] choline,[17,22,23] and DMG[17,21,24] reported previously by us and others.

The size of the study population investigated here allowed detailed assessment of predictors of betaine in regression model, including sex, age, and all blood indices (Figure 2). Choline showed a linear relation to betaine and was the strongest metabolic predictor of betaine, which could be explained by choline being the immediate precursor. Folate also showed a linear relation to betaine, suggesting common dietary sources[25] or a mutual sparing effect. Finally, the initial linear relationship between DMG and betaine at low DMG may reflect DMG production from betaine, whereas the plateau phase could be attributable to product inhibition of BHMT by DMG.[26]

Betaine as Determinant of PML and Fasting tHcy

This study demonstrated that betaine is a strong determinant of PML ΔtHcy. This effect was only slightly reduced after multiple adjustments (including folate and vitamin B_6; Table 2). The observation that betaine is a strong determinant of PML ΔtHcy confirms similar results from a recent small study[13] and is in agreement with consistent reports that oral intake of betaine markedly reduces PML tHcy.[9,11]

We also observed a significant relationship between betaine and fasting tHcy, which became of borderline significance after multiple adjustments, including folate (Table 2). The weak overall association between betaine and fasting tHcy is consistent with such association in 120 cardiovascular patients[12] and the observation of moderate reduction in fasting tHcy by betaine supplementation.[8,9,11]

Vitamin B_6

We measured vitamin B_6 in this study because of the prevailing view that vitamin B_6 status is an important determinant of PML tHcy. This idea is based mainly on experiments with vitamin B_6–deficient rats[27] and studies of subjects with low vitamin B_6 status.[28] However, in most studies of

humans without overt deficiency, vitamin B_6 is not related to PML tHcy[24,29–32] or is a weaker determinant than folate.[33,34] In a previous study on cardiovascular patients,[13] we observed no association between vitamin B_6 and tHcy (fasting and increase after loading). The present study demonstrates that in healthy subjects, vitamin B_6 is not a predictor of fasting tHcy and is a weaker determinant of the PML increase in tHcy than betaine (Table 2).

Effect Modification by Folate Status

We observed that betaine was a strong predictor of PML ΔtHcy in subjects with low serum folate and a weaker predictor at high folate (Figure 3). The effect modification by folate status is the most notable finding in the present study. It elaborates the preliminary observation demonstrating attenuation of the betaine–PML ΔtHcy relationship in subjects supplemented with combinations of B vitamins (cobalamin, folate, and vitamin B_6).[13]

We also observed that the weak overall association between betaine and fasting tHcy (Table 2) was attributable to such association in subjects with serum folate in the lower tertile (Figure 3). We are pursuing latter observation in a large ongoing study of the betaine as a determinant of tHcy in folate-deficient subjects.

Mechanisms

The strong association between betaine and PML ΔtHcy at low folate suggests increased catalytic activity of the BHMT at low 5-methyltetrahydrofolate, which is supported by measurement of rat liver enzyme activity[35] and by a mathematical model, based on known enzyme kinetics.[36] The increased catalytic activity is accomplished by increasing homocysteine availability and by lowering S-adenosylmethionine, which relieves S-adenosylmethionine–mediated BHMT inhibition.[36]

An important message from this and a previous work,[13] as well as from studies of betaine supplementation,[8,9,11,12] is that betaine reduces tHcy under conditions of high methionine. This seems to be in conflict with the prevailing view based on rat and chick experiments,[5] suggesting that BHMT conserves homocysteine under conditions of methionine deficiency.[5] However, in pigs, BHMT activity in liver increases in response to methionine.[37] Thus, in some species at least, including humans, homocysteine accumulating during folate deficiency may be directed into the BHMT pathway, even in the presence of superfluous methionine.

Betaine is more strongly associated with PML ΔtHcy than with fasting tHcy. This may indicate a role for betaine in regulating postprandial homocysteine status. However, the PML tHcy probably reflects a massive first-pass homocysteine export from the liver after uptake of excess methionine. One may speculate whether high betaine directs the first-pass homocysteine metabolism after loading into betaine-dependent remethylation, thereby reducing homocysteine export and the resulting increase in plasma tHcy. In fasting subjects, betaine may influence homocysteine status in the liver to a larger extent than is reflected by fasting tHcy, which is mainly determined by the activity of ubiquitous methionine synthase, and therefore by overall folate status.[38]

Implications and Conclusion

Folate, in addition to choline and DMG, is a major predictor of plasma betaine, which, in turn, is the strongest determinant of PML increase in tHcy hitherto recognized. Notably, the betaine–tHcy relationship is particularly pronounced at low folate status. The plasma betaine varies substantially (ie, 10-fold [from 9.4 to 94.9 μmol/L] between individuals), but a recent study demonstrates that the intraindividual variability is small, with an individual set point that remains stable for years.[39] This suggests that plasma betaine is under strict metabolic control and justifies the concept of betaine status as a component of an individual's biochemical make-up with ramifications to one carbon metabolism. Betaine status should be investigated in pathologies related to altered metabolism of homocysteine and folate, including cardiovascular disease and cancer.

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