Methylenetetrahydrofolate reductase: a link between folate and riboflavin?1,2

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In this issue, McNulty et al (1) present data suggesting that the plasma homocysteine concentration in individuals with a mutation in methylenetetrahydrofolate reductase (MTHFR; EC 1.7.99.5) is influenced by riboflavin status. Hyperhomocysteinemia has received considerable attention as a possible risk factor for cardiovascular disease. It has also been observed in several other common conditions, including birth defects, pregnancy complications, and Alzheimer disease. Homocysteine concentrations can certainly be reduced with folate, vitamin B-6, and vitamin B-12 supplementation, but the benefit of riboflavin in hyperhomocysteinemia is a relatively new concept. Nonetheless, it is important to mention that the clinical benefit of homocysteine lowering has not yet been determined. The only common clinical group of conditions in which folate supplementation has clearly lowered disease risk is neural tube defects; whether the folate responsiveness of neural tube defects relates to homocysteine lowering is not clear. Results of homocysteine lowering in clinical trials of cardiovascular disease will not be available for a few years. Despite this caveat regarding clinical benefit, there is widespread opinion that maintaining plasma homocysteine at relatively low concentrations is advisable. Consequently, the factors that influence plasma homocysteine are under investigation.

In the past few years, a major genetic determinant of plasma homocysteine has emerged. A common variant in MTHFR, 677C→T, which results in a thermolabile enzyme, predisposes to hyperhomocysteinemia in persons who are homozygous for the polymorphism (2), ie, 10–15% of many North American and European populations (2, 3). The importance of folate status in these populations was shown in clinical and biochemical studies. Persons with the TT genotype with plasma folate concentrations at the lower end of the normal range are hyperhomocysteinemic, whereas those with a better folate status do not have elevated homocysteine concentrations (3). These persons are more responsive to folate supplementation (ie, their homocysteine concentrations decrease more) than are persons who are not homozygous (non-TT genotype) (4). Folate appears to protect the mutant enzyme from destabilization in studies of human lymphocyte extracts and of the purified bacterial and human enzymes (5, 6). The consistent protective effect of folate on mutant MTHFR indicates a higher folate requirement in persons with the TT genotype, although this issue has not been directly addressed.

Several reports that described the protective effects of folate also evaluated the influence of FAD, the cofactor for MTHFR (5, 6). These studies, which showed a similar stabilizing effect of FAD, provided some incentive for examining the effects of riboflavin, the vitamin precursor of FAD, on homocysteine concentrations in persons with the MTHFR variant. The study of an Irish population by McNulty et al was preceded by similar studies in Norwegian (7) and American (8) populations. All 3 studies concluded that riboflavin status may affect homocysteine concentrations in persons with the TT genotype.

An important difference between the 3 studies was in the influence of folate on this association. In the Norwegian study, Husted et al (7) found a riboflavin-homocysteine association in persons with the CT or TT genotype regardless of their folate status. However, Jacques et al (8) found that Americans with the TT genotype with low riboflavin intakes had high homocysteine concentrations only if their plasma folate concentrations were low. McNulty et al did not examine the combined influence of folate and riboflavin on homocysteine in persons with the TT genotype. In groups that are not well-nourished, low folate status may be observed together with low riboflavin concentrations, a factor that could contribute to the observed influence of both vitamins on homocysteine concentrations. The American study identified a modest but significant association between plasma folate and plasma riboflavin, whereas the Irish study reported a nonsignificant association between riboflavin status and red blood cell folate. Additional studies to determine the role of folate in the riboflavin-homocysteine association would be useful, particularly because the enrichment of grain products with folate in the United States has already been shown to alter homocysteine concentrations in Americans (9).

If riboflavin does indeed turn out to be an independent modifier of homocysteine concentrations in persons with the TT genotype, it is possible that such persons may benefit from additional riboflavin. As previously mentioned for folate, persons with the TT genotype might respond more rapidly to riboflavin supplementation, ie, reductions in homocysteine concentrations, than would persons without the TT genotype. These types of clinical investigations are important in determining the riboflavin requirements for this genotype group. Additional supporting data could be obtained through other types of biochemical analyses, such as measurements of the different folate forms (nonmethylated compared with methylated folates), of DNA methylation, or of DNA methylation intermediates. These types of processes are known to be disturbed in the presence of a mutation in MTHFR (10). Again, as previously mentioned for folate, fortification of food products

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with riboflavin in the United States in the 1940s may limit the extent of the problem of hyperhomocysteinemia in Americans with the TT genotype. A poor riboflavin status with elevated homocysteine may be more common in populations with poor nutrition or whose food supply is not fortified with folate.

The influence of genetic mutation on higher requirements for one or more vitamins has been recognized for many years. Persons with vitamin D–resistant rickets or with homocystinuria due to cystathionine β–synthase (EC 4.2.1.22) deficiency are routinely supplemented with vitamin D or vitamin B-6, respectively. These types of genetic disturbances are relatively rare and, consequently, have not influenced our perception of daily requirements for the general population. With the identification of polymorphisms, or common mutations, in vitamin metabolism, large percentages of the population may have higher requirements for specific vitamins. An additional complication with respect to vitamins involved in homocysteine metabolism is the uncertainty regarding the best markers of vitamin deficiencies. Although the range of folate concentrations indicating a normal folate status is designed to detect individuals at risk of folate deficiency with megaloblastic anemia, they clearly encompass folate concentrations that are associated with hyperhomocysteinemia. The values for “normal” riboflavin were certainly not generated with homocysteine in mind. One could even debate what range of homocysteine concentrations are considered normal.

It is likely that additional common genetic variants in vitamin metabolism will be identified, particularly because the sequence of the human genome is complete, and intensive searches for single-nucleotide polymorphisms are underway. As we face the onslaught of novel sequence variants, we need to ensure that studies examining the association of polymorphisms with various outcome measures are carried out in parallel with appropriate clinical and biological investigations. Nonetheless, our concept of vitamin requirements for populations will certainly shift toward more individualized recommendations on the basis of genetic variation.

REFERENCES