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DO MEGADOSES OF VITAMIN C COMPROMISE FOLIC ACID'S ROLE IN THE METABOLISM OF PLASMA HOMOCYSTEINE?

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ABSTRACT

This article is a brief review of current literature. Hyperhomocysteinemia has been implicated as a risk factor for coronary artery disease. Folic acid supplements in the range of 1 to 2 mg per day have been recommended to normalize high homocysteine levels, since Folic acid plays an active role in the conversion of homocysteine to methionine. Vitamin B-12 is a coenzyme in this conversion, which participates in a transmethylation reaction by transferring a methyl group from methyltetrahydrofolate (MTHF) to homocysteine, yielding tetrahydrofolate (THF) and methionine. It is known that megadoses of Vitamin C (500 mg – 1000 mg) are able to inactivate Vitamin B-12, especially in the presence of iron, thereby precipitating a Vitamin B-12 deficiency. Without Vitamin B-12 to participate in the transmethylation reaction, the dependent conversion of homocysteine to methionine will likewise be compromised, causing the hyperhomocysteinemia to continue. The bottom line for the consumer who wishes to lower his/her plasma levels of homocysteine is that a dose of Vitamin C in the range of 500 mg per day or greater may interfere with Folic acid's ability to accomplish this.

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KEYWORDS: Homocysteine, Hyperhomocysteinemia, Folic acid, Vitamin B-12, Folate-trap, Hypervitaminosis C

INTRODUCTION: Homocysteine levels and vascular disease

Homocysteine is a sulfur-containing amino acid that is an intermediary product in the metabolism of the essential amino acid methionine [1]. Recently an association has been demonstrated between elevated levels of homocysteine in the blood plasma (hyperhomocysteinemia) and cardiovascular disease [2]. An association between plasma homocysteine and cerebrovascular disease has also been demonstrated [3]. In retrospective and cross-sectional studies, several investigators have shown that fasting plasma homocysteine levels in patients with vascular disease are, on average, 31% higher than in normal subjects, and that an increase of 12% above normal homocysteine levels is associated with a 3.4 fold increase in the risk of myocardial infarction [4]. In the Framingham Heart Study, the longest observed longitudinal study on vascular disease,

homocysteine plasma levels were strong predictors of carotid artery narrowing, which, in turn, was predictive of both stroke and heart disease [3, 5]. In addition, the Framingham Study also demonstrated that Folic acid, Vitamin B-12 and Vitamin B-6 are determinants of, and inversely related to, plasma homocysteine levels with Folic acid showing the strongest association [5]. Ubbink, et.al. found that the homocysteine-lowering effect of a multivitamin combination containing Folate, Vitamin B-6 and Vitamin B-12 was mainly due to its Folic acid content [6]. Numerous other studies have demonstrated that homocysteine levels are responsive to Folic acid intervention, with or without Vitamins B-12 and B-6.

Homocysteine metabolism

As mentioned earlier, homocysteine is a sulfur-containing amino acid that is an intermediary product in the metabolism of the essential amino acid methionine. The transfer of the methyl group (CH₃) from methionine is an important step in the metabolism of nucleic acids, fats, and high-energy bonds. When methionine donates its methyl group, homocysteine is formed. In normal metabolism the majority of homocysteine is recycled into methionine by a transmethylation reaction requiring methyltetrahydrofolate and Vitamin B-12 as a coenzyme [7]. Another pathway, the condensation of serine to homocysteine, forms cystathionine in the first reaction of the transsulfuration pathway, which requires Vitamin B-6 (FIG.1).

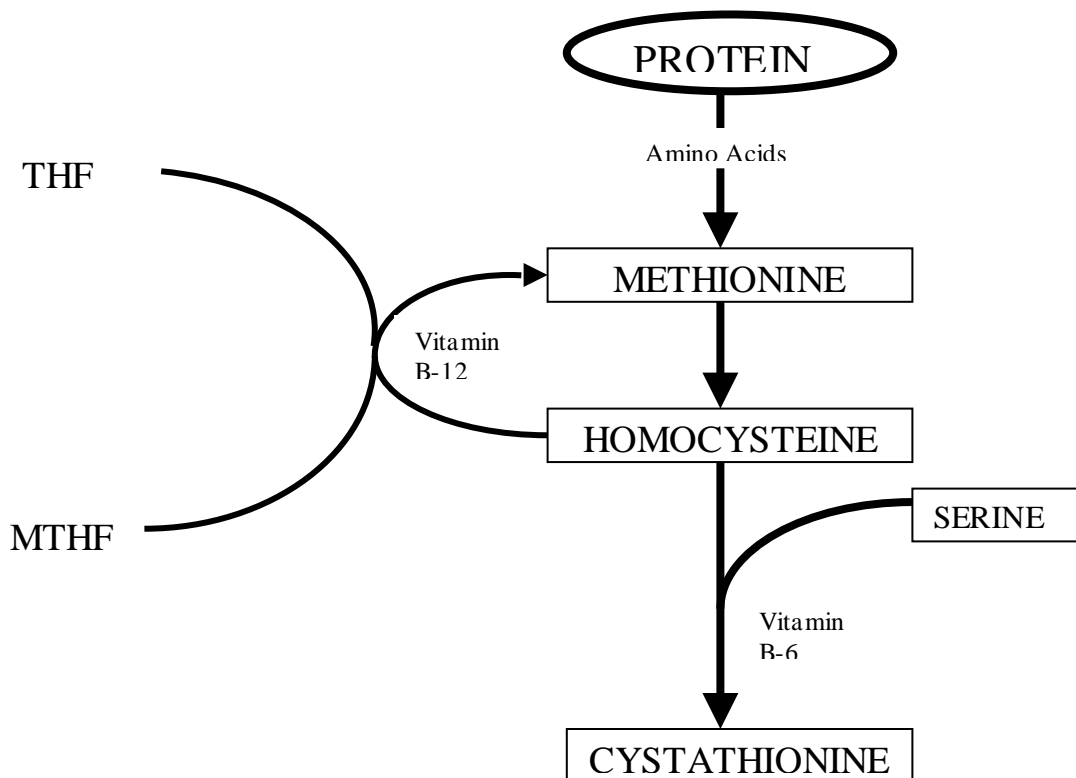


FIG.1. The metabolism of methionine and homocysteine showing the roles of Folic acid (as methyltetrahydrofolate), Vitamin B-12, and Vitamin B-6

Vitamin B-12 and the “folate-trap”

As mentioned above, most homocysteine is recycled into methionine by a transmethylation reaction requiring methyltetrahydrofolate (MTHF) and Vitamin B-12. This transmethylation reaction is catalyzed by the enzyme “methionine synthetase” which transfers a methyl group from MTHF to Vitamin B-12 (cobalamin). The addition of the methyl group to cobalamin generates methylcobalamin, which serves as the methyl donor for converting homocysteine to methionine (Fig. 2). Without Vitamin B-12, the methyl group can not be removed from MTHF which becomes “trapped”. This situation is known as the “Folate methyl trap hypothesis” and demonstrates the synergistic relationship between Folic acid and Vitamin B-12. Thus, a Vitamin B-12 deficiency results in Folate being trapped as MTHF, blocking the conversion of homocysteine to methionine. The hypothesis also explains the fact that hematological damage of Vitamin B-12 deficiency is indistinguishable from that of folate deficiency.

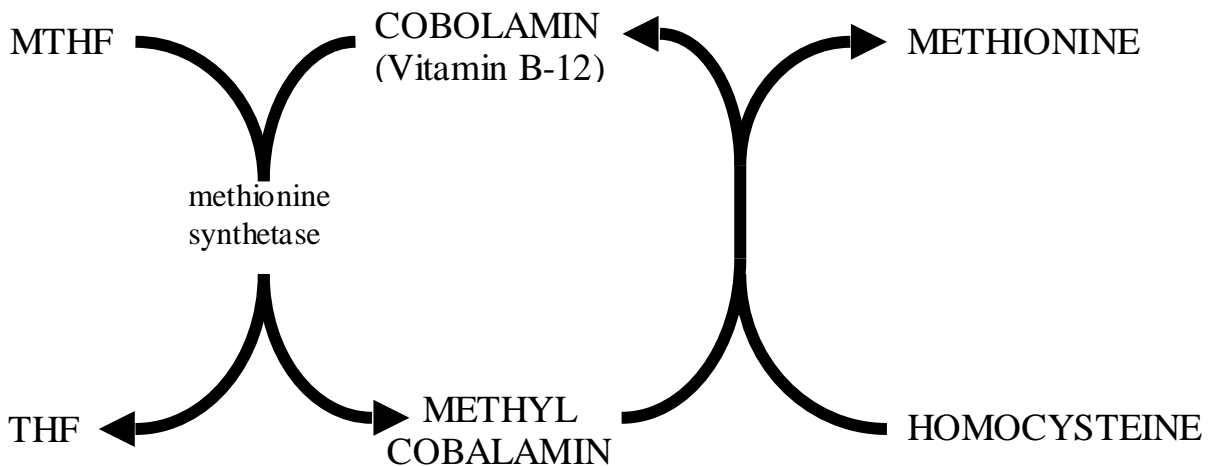


FIG.2. A series of methyl transfer reactions from MTHF to Vitamin B-12 to homocysteine yields the essential amino acid methionine.

Effects of megadoses of Vitamin C on Vitamin B-12

Megadoses (500 mg) of Vitamin C may adversely affect the availability of Vitamin B-12 from food, and persons taking even greater doses of Vitamin C (1 g or more) may develop Vitamin B-12 deficiency disease [8-14]. A Vitamin B-12 deficiency that occurs as a result of megadoses of Vitamin C may not respond to Vitamin B-12 supplementation. Herbert, et.al. found that 10 – 30% of the Vitamin B-12 in multivitamin preparations was converted to analogues worthless to humans, some with anti-B-12 action, by the redox action of Vitamin C, iron, and other antioxidant nutrients in those preparations. At pharmacological doses, in the presence of iron, Vitamin C is

one of the most potent oxidants known, driving iron-catalyzed generation of billions of free radicals, which can not only damage Vitamin B-12 but destroy intrinsic factor as well [12,14].

CONCLUSIONS

Plasma homocysteine levels are associated with an increased cardiovascular and cerebrovascular risk. Folic acid, in the range of 1 to 2 mg per day, has been shown to lower plasma homocysteine levels as a result of its role in the metabolic conversion of homocysteine to methionine. Vitamin B-12 acts as a coenzyme and participates with Folic acid in this conversion. Megadoses (500 – 1000 mg per day) of Vitamin C have been shown to decrease the bioavailability of Vitamin B-12. A deficiency in Vitamin B-12 would, therefore, compromise the dependent conversion by Folic acid of homocysteine to methionine, and the plasma homocysteine levels would not be lowered. Persons taking megadoses of Vitamin C should have their blood checked regularly for evidence of Vitamin B-12 deficiency or, preferably, stop taking megadoses of Vitamin C, because even taking additional Vitamin B-12 might not protect against Vitamin B-12 deficiency when megadoses of Vitamin C are taken [13]. Clinical trials are needed to further explore the impact that large doses of Vitamin C might have on the metabolism of homocysteine by Folic acid.

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