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Nutrition and Alzheimer's Disease: The Role of Folate and Vitamin B

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Introduction

Folate and vitamin B12 are important nutrients we must obtain from our diets in order to perform a number of cellular processes related to methylation and DNA synthesis. Vitamin B12 deficiency (often caused by pernicious anemia) and folate deficiency (often caused by inadequate dietary intake) are associated with well known hematological consequences, and occasionally, neurological symptoms. Recent evidence has associated abnormal levels of these vitamins with Alzheimer's disease, although there is currently debate as to whether they represent a casual factor or simply a consequence of the disease process.

Folate and Vitamin B12 Biochemistry

Folic acid is a water-soluble vitamin that plays an essential role in methylation (1-carbon metabolism) of nucleic acids and proteins, and in the biosynthesis of the purines and the pyrimidine, thymine (1). Folic acid deficiency is probably the most common vitamin deficiency in the United States, particularly among pregnant women and alcoholics. Vitamin B12 is unique among all vitamins in that it is the largest and most complex, and because it contains a metal ion, cobalt. It is required for two essential enzymatic processes: the disposal of odd-numbered amino acids, and the synthesis of methionine in the methylation cycle (Figure 1). The main functions of these two vitamins are very interconnected, and it is difficult to distinguish a deficiency in one or the other.

In humans, the majority of active folate is in the form of methyltetrahydrofolic acid (5-methyl THFA). Tetrahydrofolate (THFA), however, is needed in a number of different forms in order to perform its duties as a coenzyme: 1) in the formation of thymidylate (the rate-limiting step in DNA synthesis), 2) in catabolism or interconversion of some amino acids, 3) in purine, and 4) in protein synthesis (2). In order to convert 5-methyl THFA to THFA, a B12-mediated reaction converts homocysteine to methionine, which, in turn, is converted to

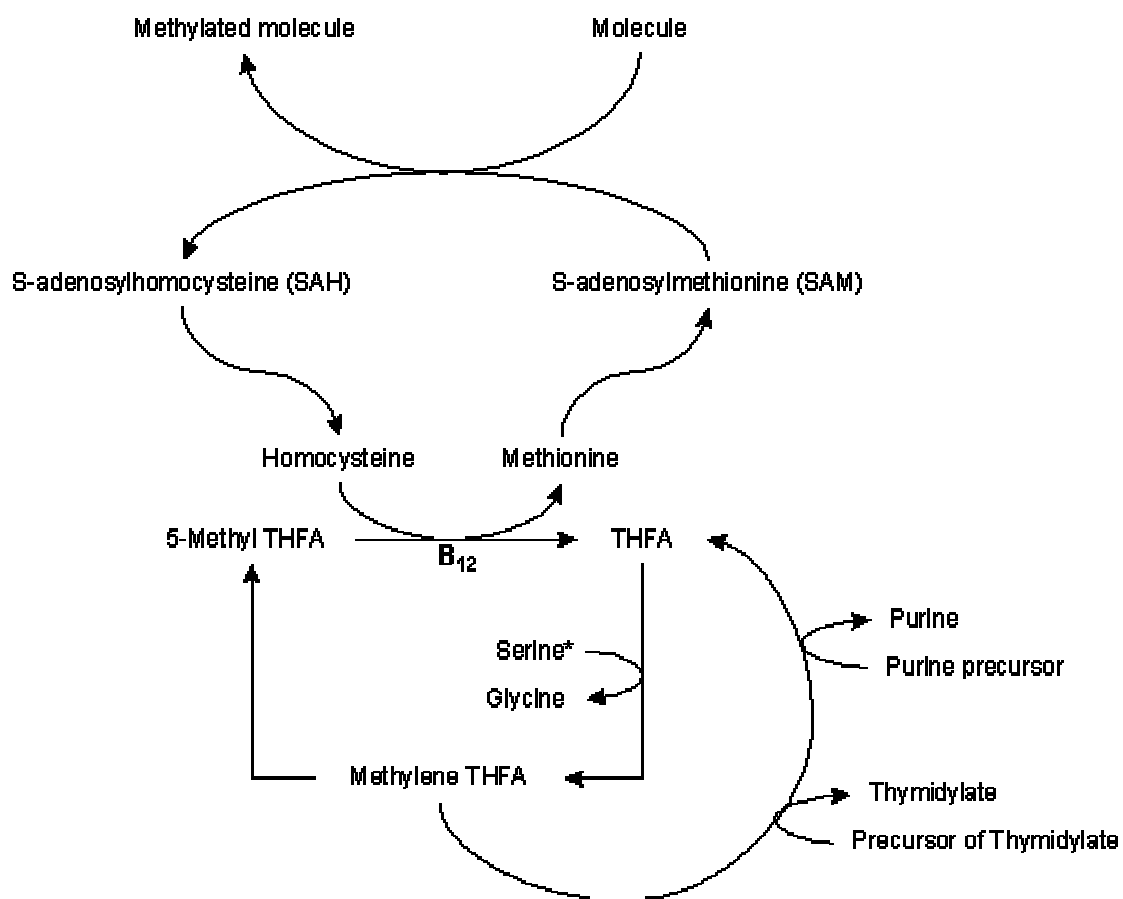


Figure 1. The role of folate and B12 in 1-carbon metabolism. *Serine is the source of most of the 1-carbon units involved in the methylation cycle. These methyl groups are used in the synthesis of thymidylate (a thymine precursor), purines, and methionine; THFA=tetrahydrofolate.

S-adenosylmethionine (SAM), the most common methyl-group donor in the body. In the absence of sufficient B12, folic acid accumulates in the 5-methyl THFA form and is unable to support synthesis of DNA, thus reducing cell proliferation. A similar situation arises in folic acid deficiency, where DNA synthesis is also reduced due to lack of THFA for thymidylate and purine synthesis. Those tissues most dependent on cell proliferation (including erythropoietic stem cells in bone marrow) are the first affected by a deficiency of THFA. The lack of DNA synthesis results in the formation of megaloblastic cells in the marrow (with sufficient cytoplasm but insufficient chromatin to divide), a condition known as megaloblastic anemia.

In addition to the haematological symptoms of B12/folate deficiency, there are a number of neurologic and psychiatric consequences, although they are much less understood (3). These vitamins are important in a number of metabolic pathways in the central nervous system, serving to generate methyl groups for the production of essential substances such as monoamine neurotransmitters and phospholipids. The most common CNS findings in severely vitamin B12 and folate deficient patients are peripheral neuropathy, demyelination, depression, and dementia. Current thinking proposes that these methylation reactions are central to the biochemical basis of these neuropsychiatric findings. The exact mechanisms, however, are unknown, but there are new theories related to pathogenesis of Alzheimer's disease that have emerged recently, and will be discussed subsequently.

Early Studies of B12 Deficiency in Alzheimer's Disease

While it has been known for decades that severely low B12 levels can cause dementia, the first report of vitamin B12 deficiency in Alzheimer's patients emerged in the mid-80s. In a landmark study, Cole et al. found serum B12 levels to be lower in Alzheimer patients than those with non-Alzheimer's type dementia (4). They conclude with some tentative hypotheses about the association of low B12 with AD, including damage to the Nucleus Basalis of Meynert (the source of many of the cholinergic projections that are destroyed in the disease), but are clearly left wondering about the causal nature of the relationship due to their small sample size. This study served to stimulate others working in the field to attempt clarification of this observed association between vitamin deficiency and one of the most common and costly diseases of the elderly.

More recently, a number of studies have looked at the association of mental impairment and vitamin B12 deficiency in the elderly. Some authors have reported low serum or cerebrospinal fluid (CSF) vitamin B12 levels in patients with Alzheimer's disease compared to a control group, and have suggested that patients with AD are particularly prone to vitamin B12 deficiency (5,6). Other investigators have found a low vitamin B12 level in cerebrospinal fluid but a normal serum vitamin B12 level in patients with AD (7). These results have not been reported by other studies, which fail to find any consistent correlation between B12 levels and Alzheimer's disease (8,9).

Although blood and serum CSF levels of vitamin B12 in Alzheimer's patients have been controversial, some researchers have remained convinced of a vitamin B12/folate abnormality associated with this disease. This has led investigators in the past few years to study the biochemistry of vitamin B12/folate metabolism more carefully in Alzheimer's patients, and assay some of the important metabolites involved in their biochemistry. An important study by Joosten et al. found levels of serum vitamin B12 and folate were very similar in Alzheimer patients and controls (10). However, differences were found with respect to serum methylmalonyl-CoA (MMA) and homocysteine (Hcy) levels (the assessment of MMA and Hcy levels more accurately reflects intracellular levels of vitamin B12 and folate), with those in the AD group demonstrating elevated levels. MMA accumulates in vitamin B12 deficiency because the conversion of methylmalonyl-CoA to succinyl-CoA requires this vitamin. Homocysteine, on the other hand, builds up in cases of folate deficiency due to a lack of methyl THFA. This finding led to the conclusion that interpretation of vitamin B12 and folate status in patients with AD depends on the methodology (serum vitamins versus metabolite levels), and that metabolic abnormalities (MMA and Hcy) can be masked by apparently normal levels of vitamin B12 and folate. Furthermore, examining the levels of MMA and Hcy are potentially more useful and specific because they assess the intracellular state of affairs rather than blood in general. Recent focus has confirmed the association of these metabolic abnormalities in Alzheimer's disease, and examined whether such abnormalities play a role in pathogenesis or are simply consequences of the disease process.

Studies Implicating Correlation but not Causation

Kristensen et. al confirmed the high levels of methylmalonyl-CoA in Alzheimer patients compared to patients with other types of dementia and controls, but found no association between these high levels and the severity of dementia (11). This finding motivated a conclusion that elevated MMA levels are an associated finding with Alzheimer's disease, but are not related to etiology or pathogenesis. They hypothesize that AD patients have a predisposition to develop B12 deficiency which may add to cognitive

burden of the disease process by leading to demyelinating lesions in the brain, and should thus be corrected with supplements.

A study by Levitt et. al examined the relationship between folate, vitamin B12, other metabolites, and the severity of cognitive impairment in patients with Alzheimer's disease (12). Low folate/B12 and high metabolite (MMA and homocysteine) levels were associated with dementia in some, but not all cases. They cite the lack of a relationship between these metabolic abnormalities and dementia, combined with failure of replacement therapy to have any positive effect on cognition, as evidence that these biochemical findings in Alzheimer's disease represent consequences of the disease process rather than etiological factors. They propose that the underlying disease process may lead to decreased absorption or storage of B12, or increased rates of utilization or excretion. Thus, while metabolic indicators of low folate/B12 may correlate highly with AD, these authors suggest such findings are consequences of the disease process.

Studies Implicating Causation

Trolin et al. have looked at the biochemistry of vitamin B12 methylation pathways, and provide good evidence that disorders of such physiology may be involved in the pathogenesis of Alzheimer-type dementia (13). They found that methionine S-adenosyltransferase, the enzyme that converts methionine to the major methyl donor molecule in the body (S-adenosylmethionine), has reduced activity in erythrocytes of AD patients, and correlates with low vitamin B12 levels and elevated homocysteine values. Although deficiencies in transmethylation in the CNS have been hypothesized to represent a pathogenic mechanism in the general development of dementia, this study directly links such deficiencies to the erythrocytes of Alzheimer patients. Due to the low metabolic activity of the erythrocytes, the functional role of SAM is relatively limited, while in brain, it is involved in the synthesis of amino acids, neurotransmitters, membrane phospholipids, proteins, and in DNA methylation. These findings support the notion that abnormalities in the transmethylation systems may be involved in the pathogenesis of Alzheimer-type dementia.

The most exciting study in this area emerged last November, and also implicates nutritional deficiency in the pathogenesis of Alzheimer's disease (14). Clarke et al demonstrated significantly elevated serum homocysteine levels in patients with histologically confirmed AD (which is more specific diagnosis than can be made on clinical grounds alone); an association that was independent of age, sex, apoE e 4, and social class. They propose a number of consequences to elevated levels of homocysteine in the pathogenesis of dementia. Homocysteine has been shown to activate the NMDA receptor, and thus, high Hcy levels in these patients may lead to excitotoxic cell death of neurons. Homocysteine may also be converted to homocysteic acid, which also has excitotoxic effects on neurons. In addition, elevated Hcy levels are strongly associated with cerebrovascular disease, which many are beginning to regard as common in AD. They suggest that microvascular disease may play a role in the cause of "pure" AD. For instance, small vessel disease (arising as a consequence of high Hcy levels), may result in the deposition of β -amyloid plaques and neurofibrillary tangles that are the pathological hallmarks of Alzheimer-type dementia. Further evidence for high Hcy levels being a cause and not a consequence of the disease include the stability of homocysteine levels in patients in varying stages of the disease and lack of relationship with duration of symptoms.

Conclusion

Although it has proven difficult to establish a global deficiency of vitamin B12 and folate in patients with Alzheimer's disease, more careful examination of the biochemistry of these nutrients has uncovered more consistent metabolic abnormalities. The study of homocysteine, in particular, has suggested that abnormally high levels may contribute to the pathogenesis of AD. However, despite the plausible mechanisms, further work is required to establish whether the observed associations are causal or consequential as they relate to the disease process. If an etiological role for elevated homocysteine is established, the potential for supplementation of folate as a preventive measure represents an exciting possibility. If the maintenance of normal folate levels throughout life turns out to be protective for Alzheimer's disease, wider efforts than are currently being made to supplement diets with folate should be undertaken.

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