The Role of Folate in Depression and Dementia

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Adequate levels of folate are crucial for proper brain and body functioning. Folate deficiencies may lead to an increased risk of depression and poorer antidepressant treatment outcomes, as well as an increased risk of cognitive impairment and dementia. In 1996, the U.S. Food and Drug Administration mandated fortification of grain products with folic acid, which has brought about vast reductions in folate deficiency. However, folate deficiencies may be caused by improper absorption and utilization, often due to genetic polymorphisms. Individuals, therefore, can have insufficient levels or lack needed forms of folate, despite adequate intake. Supplementation with the active form of folate, methyltetrahydrofolate, which is more readily absorbed, may be effective in the prevention and treatment of both depression and dementia. *(J Clin Psychiatry 2007;68[suppl 10]:28–33)*

Folate is a water-soluble B vitamin found in a variety of foods, including yeast, spinach, lentils, and orange juice. This vitamin, generally called folate or folic acid, also has a variety of technical names including pteroylpolyglutamate, pteroylglutamic acid, or vitamin B_9. In addition to having many names, folate also has many forms, such as folic acid, folinic acid or leucovorin, tetrahydrofolate, methylenetetrahydrofolate, and methyltetrahydrofolate (MTHF), which is also known as methylfolate. Methyltetrahydrofolate is the bioavailable form of folic acid, and unlike folic acid, MTHF is able to cross the blood-brain barrier into the cerebrospinal fluid.[1,2] Folate is consumed in the diet and, once in the body, is absorbed in the intestines. The liver then performs a number of metabolic transformations that produce several different forms of folate that all serve different functions in the body and exist in dynamic equilibrium with each other.

Folate deficiency has a number of causes. The most obvious reason for folate deficiency is inadequate dietary intake of B vitamins. A number of drugs such as oral contraceptives, anticonvulsants, alcohol, and tobacco can cause folate deficiency.[3,4] Folate may fail to be absorbed properly due to conditions such as jejunal diseases, atrophic gastritis, short-bowel syndrome, or conditions such as pregnancy, emotional stress, and oxidative stress. Also, certain diseases involving rapid cellular proliferation (such as leukemia) may deplete the body's folate supply. Some conditions lead to bacterial overgrowth, which results in competition by bacteria and the body for folate. Inborn errors of metabolism may prevent the body from breaking down folate that has been absorbed, or transport errors may render the body unable to transport the molecules across cell membranes and through the body. Finally, certain genetic polymorphisms such as the methylenetetrahydrofolate reductase (MTHFR) polymorphism affect the body's ability to metabolize folate, resulting in the body not having some of the functional forms of folate needed, such as MTHF.

When the body does not have adequate folate, a number of conditions may occur. Some of the potential consequences of folate deficiency are macrocytic or megaloblastic anemia, neural tube defects in newborn children, and an excess of the potentially neurotoxic amino acid homocysteine. Folate deficiency may also contribute to an individual's risk of developing cognitive deficits and depression. Folate is crucial to proper brain and body function, but despite adequate intake, individuals may have insufficient levels of needed forms of folate, and this deficiency may lead to or worsen depression and dementia. Supplementation with MTHF may therefore be effective in the prevention and treatment of both of these disorders.

FOLATE AND DEPRESSION

Low Folate May Lead to an Increased Risk of Depression

The apparent relationship between folate deficiency and depression was described in a 1962 study by Victor Herbert.[5] Using himself as the subject, Herbert consumed a diet lacking folate for 4.5 months and experienced insomnia, forgetfulness, and irritability, all of which became

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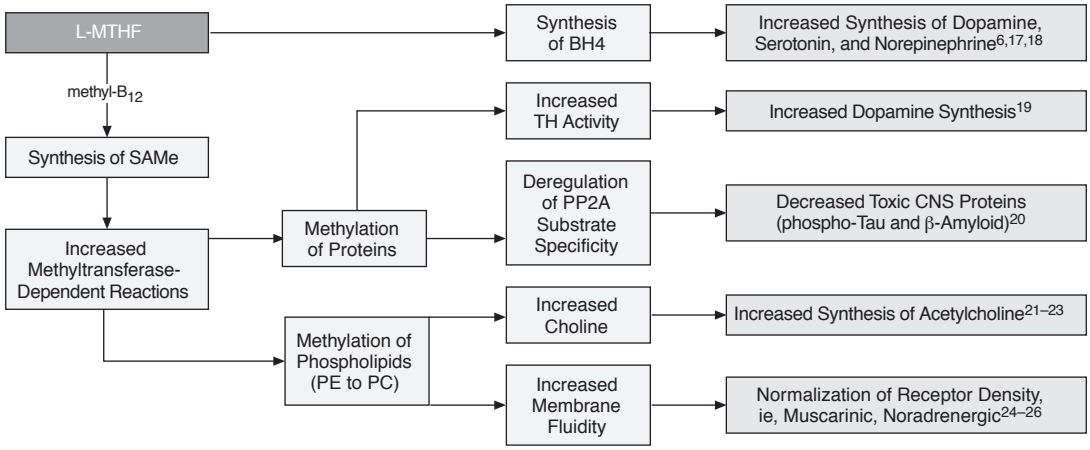
Figure 1. Proposed Mechanisms of Actions for MTHF, Methylation, and Neuronal Function[a]



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Abbreviations: BH4 = tetrahydrobiopterin, CNS = central nervous system, MTHF = methyltetrahydrofolate, PC = phosphatidylcholine, PE = phosphatidylethanolamine, PP2A = protein phosphatase 2A, SAMe = *S*-adenosyl-L-methionine, TH = tyrosine hydroxylase.

more progressive as his self-imposed folate deficiency continued. These conditions disappeared within 2 days of folate supplementation.[5] Thus, Herbert's self-imposed folate deficiency led him to develop a number of the cardinal symptoms of depression.

Since Herbert's initial work, studies[6–12] have continued to show an association between folate deficiency and depression, particularly with the endogenous[10,13] and melancholic[14] forms of depression. A study[15] of 2682 middle-aged men in the general population of Finland found that those with the lowest dietary folate intake had a 67% greater risk of depressive symptoms according to the Human Population Laboratory Depression Scale than those with the highest folate intake. Another community-based study[16] examined the relationship between low folate and the risk of lifetime depression among nearly 3000 American individuals aged 15 to 39 years. This study found that individuals who met criteria for a lifetime diagnosis of major depression had considerably lower serum and red blood cell (RBC) folate levels than individuals who had never been depressed.[16] The problem with epidemiologic studies is that correlation does not imply causation; folate deficiency could be a marker of depression or a risk factor for it.

One important function of folate is its role in the 1-carbon cycle. In this pathway, folate is converted by MTHFR into MTHF, which combines with the amino acid homocysteine to eventually produce, with the help of vitamin B_{12}, *S*-adenosyl-L-methionine (SAMe). SAMe is important because it functions as a methyl donor in a variety of biochemical reactions and has been suggested to be somehow involved in the synthesis of the 3 key neurotransmitters in the brain—dopamine, serotonin, and norepinephrine. Figure 1 illustrates the proposed mechanisms of action for MTHF, methylation, and neuronal function.[6,17–26] Thus, a folate deficiency could result in a deficiency of these neurotransmitters, so MTHF or SAMe supplements could act as antidepressants by directly or indirectly contributing to increased synthesis of dopamine, serotonin, and norepinephrine. There is also evidence that MTHF may modulate the release of monoamine neurotransmitters by binding to the presynaptic glutamate receptor.[27,28]

Homocysteine and B_{12} levels are also relevant to the potential mechanistic relationship between folate and depression due to their role in the 1-carbon cycle. Both folate and B_{12} are needed for homocysteine to be methylated into methionine, which is the immediate precursor of SAMe.[29] Thus, folate deficiency may lead to elevated total homocysteine,[8] and studies[6,30,31] have found increased total plasma homocysteine in patients with depression. Since vitamin B_{12} is also involved in the synthesis of neurotransmitters via the 1-carbon cycle, B_{12} deficiency may lead to an increased risk of depression. Studies[32,33] have found low B_{12} in mature community samples with depression.

Genetic polymorphisms, such as the C677T mutation in the MTHFR enzyme, may be responsible for impaired folate metabolism. This polymorphism renders the enzyme thermolabile, thus decreasing the activity of the enzyme and increasing homocysteine levels. A number of studies,[31,34–40] although inconclusive, suggest an association between the C677T polymorphism and depression. One study by Kelly et al.[36] found that 70% of their depressed population were positive for the C677T MTHFR polymorphism, with 14% of the individuals being homozygotes and 56% being heterozygotes. In the Hordaland Homocysteine Study,[31] Bjelland and colleagues examined almost 6000 individuals and found a significant relationship between depression and both hyperhomocysteinemia (95% CI = 1.11 to 3.25) and the T/T MTHFR genotype (95%

CI = 1.09 to 2.62). Other polymorphisms, such as the A1298C polymorphism for the MTHFR gene, as well as the A66G and A2746G polymorphisms for the methionine synthase gene, may also be associated with depression but have been less studied.

Low Folate May Affect Treatment for Depression

In addition to possibly increasing an individual's risk of depression, folate deficiency may lead to poor treatment outcomes in patients with depression by reducing treatment response, slowing clinical improvement, and increasing relapse. Fava and colleagues[14] found that among 189 patients receiving 8 weeks of fluoxetine treatment for depression, those with a folate deficiency were 2.2 times more likely to be nonresponders than those with normal folate levels. Papakostas and colleagues[41] found a 6.26 times greater rate of nonresponse among individuals whose serum folate levels were below normal. A further study by Papakostas et al.[42] examined the relationship between folate levels and treatment response among patients receiving next-step treatment after they failed to respond to 8 weeks of fluoxetine. These patients received either 40 to 60 mg/day of fluoxetine or a combination of 20 mg/day of fluoxetine augmented by either 25 to 50 mg/day of desipramine or 300 to 600 mg/day of lithium. A significant relationship ($p = .04$) was found between low folate and nonresponse among all treatment groups. Only 7.1% of patients with low folate responded to treatment compared with 44.7% of patients with normal folate levels. Thus, in addition to potentially contributing to an individual's risk of depression, low folate appears to diminish an individual's chance of responding to both initial antidepressant monotherapy and next-step augmentation strategies.

For those who do respond to treatment, those with low folate may experience slower clinical improvement. Another study by Papakostas et al.[43] found that patients with low folate levels who were receiving fluoxetine experienced, on average, a 1.5-week delay in the onset of clinical improvement compared with those who had folate levels in the normal range. A further study by Papakostas and colleagues[44] found a significant relationship ($p = .004$) between low folate and risk of relapse during the continuation phase of treatment with fluoxetine. None of these studies[14,42–44] found a significant relationship between B_{12} or homocysteine levels and response status, onset of clinical improvement, or risk of relapse. Adequate folate levels, therefore, may be critical to successful treatment outcomes for patients with depression.

Folate Supplementation for Depression

Because low folate levels may lead to an increased risk of depression and poor treatment outcomes, patients with depression may benefit from folate supplementation. Studies[45,46] have found that folate supplementation improves response rates to antidepressant treatment. The use of folate supplement augmentation for depression is discussed in detail in this supplement in the article by Maurizio Fava, M.D.[79] The mechanism of action of folate in depression is believed to stem from folate's role in the 1-carbon cycle and indirect regulation of trimonamine neurotransmitter synthesis through tetrahydrobiopterin (BH4; see Figure 1).[6,47,48] As mentioned, folate is necessary for the methylation of homocysteine into the essential amino acid methionine, which is then synthesized into SAMe, and thus, a folate deficiency may lead to elevated levels of homocysteine and reduced levels of SAMe. Reduced MTHF and/or SAMe may result in deficiencies of the key neurotransmitters serotonin, dopamine, and norepinephrine.[6,47–49] In addition, since low folate leads to elevated levels of homocysteine, homocysteine may be a better indicator of folate deficiency than blood folate levels, because measurements of blood vitamin levels often do not accurately reflect functional levels of folate.[50]

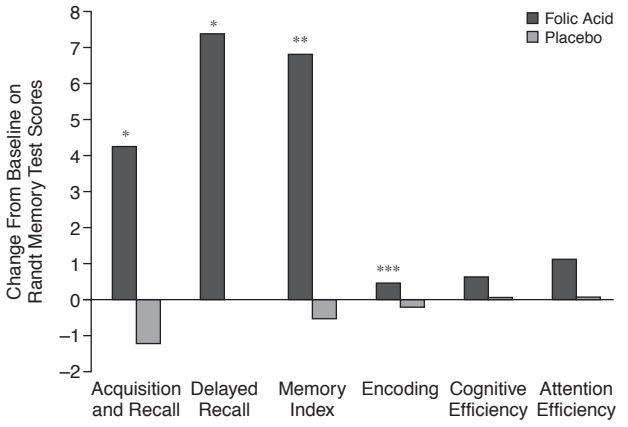
FOLATE AND DEMENTIA

Low Folate May Lead to an Increased Risk of Dementia

Dementia is a serious neurodegenerative disorder that becomes more prevalent with age. Dementia affects about 5% to 8% of individuals over age 65 years, 15% to 20% of those over 75 years, and 25% to 50% of those over 85 years.[51] Alzheimer's disease is the most common form of dementia, followed by vascular dementia.[51] The current standard for the treatment of dementia involves trying to slow the progression of the disease rather than cure it; this is done by increasing acetylcholine and blocking the glutamate stimulation of the *N*-methyl-D-aspartate (NMDA) receptor. The possibility of preventing the development of dementia through lifestyle modifications and risk factor reduction is also being studied. Untreated depression may be a risk factor for dementia because patients with depression have a decrease in hippocampal cell proliferation and neurogenesis.[52] Neurogenesis is helped by not only long-term antidepressant treatment[52] but also exercise.[53,54] Diet and health changes, such as controlling weight,[55] cholesterol,[56] and blood pressure,[57] and adding folate, as discussed below may also help prevent dementia.

Folate supplementation may be effective for the prevention and treatment of cognitive decline and dementia.[58–60] The Baltimore Longitudinal Study of Aging[58] found a significantly decreased risk of Alzheimer's disease (95% CI = 0.21 to 0.97) among individuals whose daily folate intake was at or above recommended levels. This study found that only 35.1% of participants had daily folate intake at or above the recommended dietary allowance, and these individuals' risk of developing Alzheimer's disease was reduced by nearly 60%. A study[61] conducted as part of the MacArthur Studies of Successful Aging found that those with low serum folate levels had worse baseline cognitive functioning than those with normal folate levels and a sig-

Figure 2. Effects of Folate on Memory in Patients With Cognitive Deficits[a]



[a]Data from Fioravanti et al.[59]
*p < .007, **p < .002, ***p < .005.

nificantly greater risk of cognitive decline (95% CI = 1.01 to 2.31). The Sacramento Area Latino Study on Aging[62] found an inverse relationship between folate status and dementia. Participants in the study were screened for RBC folate levels and given tests to assess global cognitive function. The study found that as RBC folate concentration increased, the individual's relative risk of cognitive impairment and dementia decreased. The results of these studies indicate that low folate may lead to cognitive impairment and an increased risk of dementia.

Folate Supplementation for Dementia

Since deficiencies in folate may lead to cognitive impairment, folate supplementation may be an effective treatment for cognitive deficits and dementia. Fioravanti and colleagues[59] conducted a double-blind, placebo-controlled study of elderly patients with memory complaints. The active treatment group received 15 mg/day of folic acid. After 60 days of treatment, the patients receiving folic acid showed improvements in memory, including significant improvements in acquisition and recall, delayed recall, memory index, and encoding (Figure 2). Additional studies[60,63,64] have also found evidence that folate supplementation, either alone or in conjunction with other B vitamins, may improve memory loss.

In the same way that inadequate folate levels may lead to depression by impairing 1-carbon metabolism, folate deficiency may lead to cognitive impairment and dementia via this pathway (see Figure 1). The elevated homocysteine levels that result from low folate are particularly relevant to the development and treatment of dementia. Elevated homocysteine levels have been found in individuals experiencing cognitive decline and dementia.[65–69] As part of the Framingham Study,[70] total plasma homocysteine levels were taken for 1092 elderly individuals at baseline and then 8 years later. This study found that an individual's risk of dementia increased incrementally as total plasma homocysteine levels increased; the individuals with the highest homocysteine levels had a doubled risk of dementia.

Kruman and colleagues[71] examined the role of homocysteine and 1-carbon metabolism in hippocampal neurogenesis. This study found that low folate dramatically increased blood homocysteine levels, resulting in impaired 1-carbon metabolism and reduced neurogenesis, possibly because impaired 1-carbon metabolism may lead to a suppression of neuroprogenitor cell proliferation. Contrary to previous belief, neurogenesis is now known to occur in the hippocampus throughout the lifespan, and this brain region is the first area affected by Alzheimer's disease.[71] By impairing 1-carbon metabolism and suppressing neurogenesis, folate deficiency and elevated homocysteine may contribute to the neurodegeneration that leads to cognitive decline and dementia.

Elevated homocysteine may also lead to an increased risk of dementia by acting as a DNA-damaging neurotoxin. A study[72] of homocysteine in rat hippocampal neurons found that exposure of neuronal cells to homocysteine led to DNA damage. When the DNA cells were damaged, the repair enzyme poly-ADP-ribose polymerase (PARP) was activated, and homocysteine induced a rapid two-fold increase in PARP activity that depleted the energy in the cell, resulting in an influx of calcium-causing oxidative stress and apoptosis of the cell. Thus, neuronal cells exposed to homocysteine had impaired ability to repair damaged DNA, and this made the cell more vulnerable to oxidative stress and excitotoxicity, both of which led to cell death. Homocysteine also acts as a neurotoxin by overstimulating the NMDA receptors, leading to excess calcium influx and a considerable decrease in neuronal cell viability.[73] Accumulation of β-amyloid is characteristic of Alzheimer's disease, and homocysteine has been found to increase the neurotoxicity of β-amyloid, thus leading to increased neurodegeneration.[74]

In addition to improving memory loss, folate supplementation has been found to lower blood homocysteine levels,[75] which may reduce neuronal cell loss and thus slow the progression of dementia. Due to the genetic polymorphisms that may render an individual unable to metabolize certain forms of folate into needed forms, supplementation with the active form MTHF, which is more readily absorbed in the body,[50] may be more effective than supplementation with folic acid. Pharmacologic doses of folic acid can lead to large quantities of unmetabolized folic acid in the plasma, which has been shown to impair the passage of MTHF into the central nervous system.[76,77]

CONCLUSION

The U.S. Food and Drug Administration mandated that all grain products be fortified with folic acid in 1996; this

process was completed by 1998 and has been highly successful in reducing the prevalence of low folate. A study[78] measured plasma folate and homocysteine before and after mandated fortification among participants in the Framingham Offspring Study who did not use vitamin supplements and found that the prevalence of low folate dropped from 22.0% to 1.7%, which was a 92% decrease. The prevalence of high homocysteine dropped from 18.7% to 9.8%, which was a 48% decrease.

Although the vast reductions in folate deficiency brought about by mandated fortification appear to make folate supplementation unnecessary, folate deficiencies in some people are now understood to be caused by improper absorption and utilization, often due to genetic polymorphisms, disease states, or drugs, rather than to inadequate intake. The fact that the reduction in homocysteine was not as great as the reduction in low serum folate in the Framingham Offspring Study[78] underscores this point. Serum and RBC folate levels may not accurately reflect available folate levels due to genetic polymorphisms that prevent the body from transforming folic acid into the active agent, MTHF. Because functional folate deficiencies lead to raised homocysteine, plasma homocysteine measurement may be a better indicator of folate deficiency.[60] Furthermore, since genetic polymorphisms may render the body unable to convert folic acid into needed forms, supplementation with the more easily absorbed MTHF may result in greater reductions of homocysteine than folic acid supplementation.

In short, adequate levels of folate are crucial for proper brain and body functioning, and deficiencies may lead to an increased risk of depression and poorer antidepressant treatment outcomes, as well as an increased risk of cognitive impairment and dementia. Low levels of folate may lead to increased levels of homocysteine, and high homocysteine is also a risk factor for depression and dementia. Unlike some other risk factors for these disorders, folate and homocysteine levels are modifiable. Folate supplementation may lower an individual's risk of developing depression and dementia, as well as improve treatment outcomes and cognitive function.

Drug names: desipramine (Norpramin and others), fluoxetine (Prozac and others), lithium (Eskalith, Lithobid, and others), methylfolate (Deplin, Cerefolin NAC).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, folate, folic acid, folinic acid, and l-methylfolate are not approved by the U.S. Food and Drug Administration for the treatment of depression and dementia.

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