REVIEW ARTICLE

The Role of Folate and MTHFR Polymorphisms in the Treatment of Depression

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ABSTRACT

Major depressive disorder is most commonly treated with a combination of medication and psychotherapy. For those people that do not benefit from the standard therapy or prefer non-pharmacologic therapy, folate supplementation may be an option. Folate is normally acquired through the diet and folate deficiency is associated with depression. In the brain, folate is one nutrient among others involved in the production of the neurotransmitters that affect mood. Studies involving folate supplementation for the treatment of depression have had mixed results but have omitted to take into account the genetic polymorphisms, such as the ones in methyltetrahydrofolate reductase (MTHFR), that affect folate metabolism. Supplementation with L-methylfolate may overcome the folate metabolism problems seen in individuals with disadvantageous genetic polymorphisms. (*Altern Ther Health Med.* 2021;27(2):53-57).

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INTRODUCTION

Major depressive disorder is a common mental disorder. According to recent estimates, in the United States, 7.1% of all adults and 13.1% of adolescents aged 12 to 17 had at least one major depressive episode in 2017.[1] The most common therapy for the treatment of major depressive disorder is a combination of psychotherapy and pharmacotherapy with antidepressants as this combination currently provides the quickest and best-sustained response.[2] However, sixty percent of patients with depression are not treated effectively with psychotherapy and medication.[2] Therefore, additional evidence-based therapies are needed to be able to treat more patients successfully. Fortunately, there is emerging evidence on the effect of administration of nutraceuticals -such as folate supplementation-that can augment therapy for the treatment of depression.[3] This paper reviews the medical literature regarding the structure and function of folate, the risk of depression due to folate deficiency, genetic polymorphisms that affect folate metabolism and depression risk, and the use of folate as an adjunctive treatment in combination with pharmaceutical therapy or as a stand-alone treatment for depression.

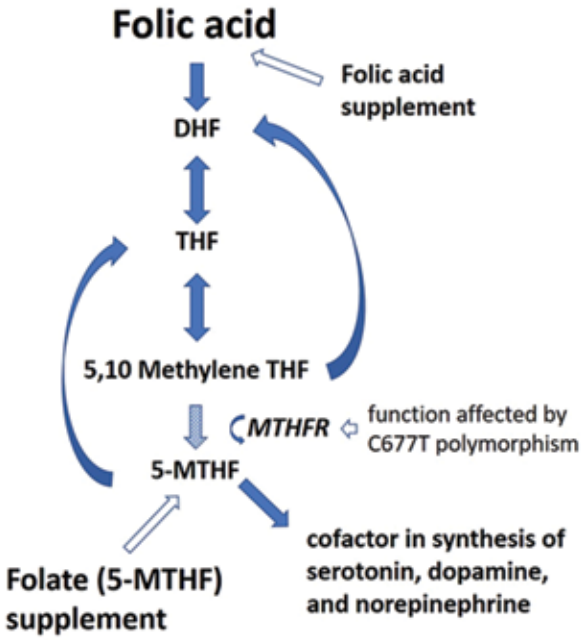
FOLATE OVERVIEW

Folate is a water-soluble member of the B vitamin group and is also referred to as vitamin B_9 or folacin.[4] The term folate refers to a family of compounds that includes both natural and synthetic folates.[5] There are several naturally occurring folates found in food and as metabolically active forms in the human body.[5] Folates are composed of an aromatic pteridine ring attached through a methylene group to p-aminobenzoic acid and a glutamate residue.[6] Humans are unable to synthesize folate and must acquire it from their diet.[5]

High folate food sources include spinach, liver, asparagus, and brussels sprouts. Other common foods that contain folates are dark green leafy vegetables, fruit and fruit juices, nuts, beans, peas, seafood, eggs, dairy products, meat, poultry, and grains.[7]

Folate is a coenzyme that has several functions, including the transfer of single carbon for the synthesis of nucleic acids and the metabolism of amino acids.[7] Another function of folate is the conversion of homocysteine to methionine in the synthesis of *S*-adenosylmethionine (SAM).[7] As will be discussed later, SAM is an important methyl donor and influencer of neurotransmitter formation. Folate is also involved in DNA methylation,[9] an essential process in epigenetics and regulation of gene expression. The metabolism of folate is very complex and involves a minimum of 30 different enzymes.[8] Folate's role in various "critical biochemical pathways" requires several other nutrient cofactors such as B_{12}, choline, vitamin B_6 (pyridoxine), and vitamin B_2 (riboflavin).[10]

Figure 1. Folic acid from diet is metabolized in various steps to generate 5-MTHF. This 5-MTHF crosses the blood-brain barrier and is a cofactor in the synthesis of the neurotransmitters serotonin, dopamine, and norepinephrine. The last step in the synthesis of 5-MTHF requires MTHFR. The function of MTHFR can be hampered by genetic polymorphisms such as C677T, resulting in a 5-MTHF deficiency and hence a neurotransmitter deficiency that can lead to depression. Folic acid or folate supplements can be administered in individuals with 5-MTHF deficiency. However, in individuals with deleterious MTHFR polymorphisms only folate supplements will lead to higher 5-MTHF bioavailability.



Abbreviations: DHF, dihydrofolate; MTHFR, methyltetrahydrofolate reductase; THF, tetrahydrofolate; 5-MTHF, 5-methyl-tetrahydrofolate.

Folic acid is a human-made compound similar to folate that does not occur in nature, and that does not have the same molecular structure as folate.[11] Imbard et al. state: "In general, the term folic acid is applied to the more stable synthetic form while the term folate referred to the natural forms."[13] Nonetheless, folic acid is considered to be a type of folate. Folic acid is used in supplementation and food fortification due to its stability and low cost.[12] Research has shown that folic acid has high bioavailability but rapid renal excretion, and although high plasma levels can be achieved, tissue levels are often marginal.[11] Folic acid is not an active coenzyme and requires several metabolic steps for conversion into active tetrahydrofolate (THF).[5] However, people with specific genetic polymorphisms, such as *MTHFR* C677T have problems with folate metabolism and can have significantly lower serum folate levels.[9]

The absorption and metabolism of folic acid can be summarized as follows:[10] Folic acid is absorbed through the intestinal mucosa and quickly converted to reduced folates, with 5-methyl-tetrahydrofolate (5-methyl-THF or 5-MTHF) as the primary metabolite during first-pass liver metabolism (Figure 1). Depending on the dose, some folic acid can appear in the peripheral circulation. For folate to be retained by the tissues there must be a conversion to long-chain-length polyglutamate forms. The substrates folic acid and 5-methyl-THF are not easily converted into retainable polyglutamate. The incomplete conversion to polyglutamate by the intestinal mucosa and liver leads to the release of folate, primarily methylfolate, into plasma. Folic acid use differs from that of natural dietary folates in that it has to be reduced to THF by the enzyme dihydrofolate reductase (DHFR).[10] This first step of reduction is slow and influenced by individual DHFR activity variations.[10] Genetic polymorphisms affecting folate metabolism and depression will be reviewed more extensively below.

Overt folate deficiency is rare in the United States, but some people may have a minor folate deficiency.[7] Signs and symptoms of folate deficiency may include a sore tongue or pain with swallowing; swollen, beefy, red or shiny appearance of tongue; angular stomatitis; gastrointestinal symptoms including nausea, vomiting, abdominal pain, and diarrhea, which are more common after meals; anorexia; darkening of the skin and mucous membranes, especially the dorsal surfaces of the fingers, toes, and creases of palms of soles; modest temperature elevation (<102°F); as well as cognitive impairment, dementia, and depression.[14] The primary clinical sign of folate deficiency is megaloblastic anemia, which also occurs with B_{12} deficiency.[15] Symptoms of megaloblastic anemia include dyspnea, headache, fatigue, and the gastrointestinal symptoms mentioned above.[16] And lastly, folate deficiency may be a specific risk factor for neural tube defects[13,17] and associated with an increased risk of chronic diseases such as certain cancers, cardiovascular disease, and neurological conditions.[10]

Folate Deficiency and Depression

Several studies provided evidence that folate deficiency is associated with an increased risk for depression, more severe depressive symptoms, increased duration of episodes, and increased risk of depressive symptom relapse.[18] A 2017 meta-analysis of 43 studies examined the association of folate and depression.[18] The meta-analysis included studies that analyzed folate levels in people with depressive symptoms or depression compared to individuals without depression and that analyzed folate based on red blood cell folate, serum folate, or dietary folate intake.[18] The conclusion was that "individuals with depression have lower serum levels of folate and dietary folate intake than individuals without depression". Authors also stated that future research on folate supplementation in depression is warranted and that clinicians may wish to consider folate supplementation for patients with depression."[18] It should be noted that although red blood cell (RBC) folate is regarded as the most accurate method for measuring folate, the meta-analysis did not show a significant association of RBC folate with depression.[18]

The main cause of folate deficiency is a lack of dietary consumption.[4] However, additional causes can include chronic and excessive alcohol consumption which reduces absorption, smoking, pregnancy, cancer or inflammatory conditions, malabsorption associated with gastrointestinal illnesses such as inflammatory bowel disease and celiac disease, lactose intolerance, drug-induced deficiencies (e.g. phenytoin, methotrexate, sulfasalazine, triamterene, NSAIDs), and genetic variations that affect folate absorption, transport, or metabolism (*MTHFR* variations).[4,19,20]

There are also studies demonstrating an association between elevated levels of homocysteine (hyperhomocysteinemia) and depression. Hyperhomocysteinemia is usually caused by folate deficiency and is treated with folate. Several genetic variations affecting the enzymes methionine synthase, methyltetrahydrofolate reductase (*MTHFR* C677T), cystathionine β-synthase, and cystathionine γ-lyase, as well as deficiency in the cofactors vitamin B_6, B_{12}, and folate, have been found to contribute to hyperhomocysteinemia. As a result of the excess homocysteine, there is a decrease of neurotransmitters: the SAM-dependent catecholamines (dopamine, norepinephrine, epinephrine) and the noncatecholamine serotonin. Also, hyperhomocysteinemia leads to elevated levels of the neurotoxic byproducts of homocysteic acid and cysteine sulfinic acid. An elevation of these two compounds acts as an *N*-methyl-D-aspartate receptor agonist, which has "neurotoxic effects on dopaminergic neurons."[21] The decrease of neurotransmitters and the neurotoxic effects on dopaminergic neurons are associated with depression. There are several physiological mechanisms (described above) that cause folate deficiency to be associated with depression, which include folate's activity in brain methylation reactions, neurotransmitter production, and the metabolism of homocysteine.[7] Nevertheless, low folate status is "linked to depression and poor response to antidepressants in some, but not all studies."[7]

Polymorphisms Affecting Folate Metabolism

There are several studies demonstrating that certain genetic polymorphisms affect folate metabolism. The most extensively studied polymorphisms are located in the methylenetetrahydrofolate reductase (*MTHFR*) gene, and they are C677T and A1298C.[22] The most studied polymorphism in regards to folate metabolism is the C677T variant. This variant involves a C to T transition at position 677 in the gene, resulting in the substitution of alanine with valine at position 222 in the MTHFR protein.[9] This variant reduces the activity of the enzyme MTHFR which converts folate to its active form, 5-methyltetrahydrofolate (5-MTHF).[22] In 1995 it was first reported that compared to individuals homozygous for the wild type allele (CC), heterozygotes (CT) had a mean in vitro MTHFR activity decrease of 35%, while individuals homozygous for the variant allele (TT) exhibited a 70% decrease activity.[23] In a more recent paper, it was also reported that for C677T the enzyme activity of individuals heterozygous and homozygous for the variation are respectively 67 and 25% of the wild type ones. Similarly, for A1298C, the enzyme activities of individuals heterozygous and homozygous for the variation are respectively 83 and 61% of the wild type subjects."[22]

The 667C>T variant results in a change in the MTHFR protein at the site responsible for flavin adenine dinucleotide (FAD) binding activity, which results in an enhanced loss of the FAD cofactor, the creation of a thermolabile protein, and decreased 5-MTHF concentrations and increased plasma total homocysteine concentrations.[9] As mentioned before, FAD is involved in folate's effect on several biochemical pathways.

There are also many other enzymes in which polymorphisms can affect folate metabolism. These include *CBS* 844ins68, GCPII H475Y, *MTR* 2756A>G, and *MTRR* 66A>G.[9] Liew and Gupta report 14 additional rare mutations identified with the MTHFR gene that are associated with severe enzymatic deficiency.[24]

A study of newborns from 16 areas around the world showed marked ethnic and geographical variation in the frequency of those who had the C677T variation.[25] The homozygous variation was common in northern China (20%), southern Italy (26%), and Mexico (32%).[25] A review has shown that in the population studied 11.7% are homozygous (TT) and 44.2% heterozygous (CT) for this polymorphism.[26]

MTHFR Polymorphisms and Depression

The two *MTHFR* polymorphisms most extensively studied in relation to psychiatric disease are C677T and A1298C.[22] *MTHFR* polymorphisms have been associated with the onset of various psychiatric diseases, including schizophrenia, bipolar disorder, autism, ADHD, and depression.[22] Wan et al. report that *MTHFR* polymorphisms "might be related to the episode and prognosis of depressive disorder, not the stage of the disease."[22]

A meta-analysis involving 26 published studies concerning *MTHFR* polymorphism demonstrated "an obvious association of MTHFR C677T polymorphism with increased risk of depression."[27] This association was strongest in Asian populations.[27] The results of this meta-analysis differed from earlier studies with smaller sample sizes.[28] However, another meta-analysis also found a moderate association of *MTHFR* C677T polymorphism and major depression.[29]

FOLATE THERAPY

Folate supplementation options for the adjuvant treatment or monotherapy of depression include folic acid, folinic acid, and 5-MTHF (L-methylfolate). Supplementation with 5-MTHF has advantages over synthetic folic acid.[5] For example, as opposed to folic and folinic acid, 5-MTHF is absorbed well even when there are changes in gastrointestinal pH (such as elevated gastric pH from proton pump inhibitors). Also, 5-MTHF overcomes metabolism defects due to *MTHFR* polymorphisms as there are several studies

demonstrating that 5-MTHF has higher bioavailability depending on the patient's genotype.[5,30,31]

5-MTHF is the only form of folate that can cross the blood-brain barrier.[32] In the brain, 5-MTHF is a cofactor involved in the synthesis of the neurotransmitters serotonin, dopamine, and norepinephrine that are essential for mood regulation.[32] The 5-MTHF plays a role in the formation of tetrahydrobiopterin (BH_4), which activates the rate-limiting enzymes tryptophan hydroxylase and tyrosine hydroxylase that are necessary for the synthesis of the neurotransmitters.[33]

In one trial, patients with major depressive disorder were supplemented with 7.5 mg or 15 mg 5-MTHF (Deplin).[32] Participants rated their experiences before and after three months of supplementation with a phone questionnaire. The trial involved 502 patients supplemented with 5-MTHF in addition to their antidepressant, while 52 patients were supplemented with 5-MTHF alone. The satisfaction of taking antidepressant medication supplemented with 5-MTHF was significantly higher than before supplementation. Overall, 67.9% of patients responded to therapy with significant improvements in depressive symptoms and function, and 47.5% achieved remission over 12 weeks.[32] Also, those taking 5-MTHF as monotherapy had similar response rates compared to those patients taking it as adjuvant therapy.[32]

Another study of patients with major depressive disorder who had a partial response, or no response, to selective serotonin reuptake inhibitors (SSRIs) found 5-MTHF at a dose of 15 mg per day to be "an effective, safe, and relatively well-tolerated augmentation strategy…"[33]

Studies involving the use of folic acid as an adjunct with antidepressants have had mixed results in terms of efficacy. For example, a study of 127 patients with major depression was randomly assigned to either 500 mg of folic acid or a placebo in addition to 20 mg fluoxetine daily.[37] Overall there was a significantly greater improvement in the folic acid plus fluoxetine group compared to fluoxetine plus placebo.[37] Another smaller study found participants randomly given folic acid (10 mg/day) and fluoxetine (20 mg) had significantly improved Hamilton Depression Rating Scale scores compared to those given fluoxetine and placebo.[38] However, a 12-week, double-blind, placebo-controlled, randomized trial involving 475 adult patients with moderate to severe depression who were not folate deficient were given 5 mg of folic acid in addition to their antidepressant medication.[39] The researchers found no evidence that folic acid supplementation was clinically effective in augmenting the effects of antidepressant mediations.[39] The authors of a recent systematic review and meta-analysis of adjunctive nutraceuticals for depression state that "folic acid cannot be firmly recommended; however, the "active" forms of methylfolate and folinic acid can be tentatively recommended."[3]

Surprisingly, there appears to be little research done to investigate the effects of folic acid or 5-MTHF supplementation in individuals with depression who have specific *MTHFR* polymorphisms. Such research might be more relevant as the polymorphisms strongly affect folate metabolism.

There are also adverse effects of high dose 5-MTHF supplementation. These may include sleep pattern changes, concentration difficulties, irritability, overactivity, excitement, confusion, impaired judgment, anorexia, nausea, abdominal distention, flatulence, and bitter or bad taste.[40]

Nutrition oriented doctors often recommend starting with lower doses of 5-MTHF such as 400 mcg daily and slowly increasing the dose or supplementing intermittently depending on symptoms.[41] The concurrent use of other nutrient cofactors involved in folate metabolism are recommended as mentioned earlier and include B_{12} (methylcobalamin), choline, vitamin B-6 (pyridoxine), and vitamin B_2 (riboflavin) individually or in the form of a B complex is recommended.

CONCLUSION

Folate is an essential nutrient that carries out single carbon transfer for a variety of metabolic functions, including the synthesis of neurotransmitters. Folic acid is a synthetic folate that requires several metabolic steps to be converted into active tetrahydrofolate. There are several studies that demonstrate folate deficiency or lower levels of serum folate is associated with an increased risk of depression. Those with specific genetic polymorphisms, especially *MTHFR* C667T, have problems with their folate metabolism and are at a higher risk of low serum folate. Research has also demonstrated an association between *MTHFR* polymorphisms and depression. Folate supplementation is effective in some but not all studies as an adjuvant to antidepressant therapy or monotherapy for the treatment of depression. There is research suggesting that 5-MTHF (L-methylfolate) has advantages over folic acid in overcoming metabolism problems due to *MTHFR* polymorphisms. However, more research is required to confirm that 5-MTHFR or folic acid is effective in individuals with depression who have *MTHFR* polymorphisms compared to those with wild type *MTHFR*.

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