L-Methylfolate: A Vitamin for Your Monoamines

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Issue: *Synthesis of the monoamine neurotransmitters serotonin, dopamine, and norepinephrine is regulated by L-methylfolate, a derivate of the vitamin folate.*

Folate (vitamin B_9) is well known as one of the 13 essential vitamins, but perhaps what is not as well known is that a derivative of folate—known as L-methylfolate—is actually the active form of the vitamin.[1-3] One of L-methylfolate's critical roles is to regulate the synthesis of the 3 monoamine neurotransmitters serotonin, dopamine, and norepinephrine.[1-6]

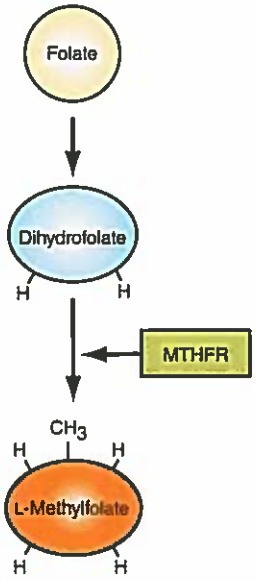
What Is L-Methylfolate?

Folic acid is the synthetic form of the vitamin folate and is present in artificially enriched foods such as bread and in over-the-counter multivitamins as well as in prescription vitamins.[3] Dihydrofolate is the dietary form of folate, derived from green vegetables, yeast, egg yolk, liver, and kidney.[3] A key regulatory enzyme known as methylene tetrahydrofolate reductase or MTHFR (Figure 1)[1-7] converts folic acid or dihydrofolate to a usable form in the body, L-methylfolate, that can then pass through the blood-brain barrier where it modulates the formation of the monoamines serotonin, norepinephrine, and dopamine.[1-7]

How Does L-Methylfolate Regulate the Synthesis of Monoamines?

L-Methylfolate acts to modulate the synthesis of monoamines in a 3-step process (Figure 2). First, L-methylfolate assists in the formation of a critical cofactor, known as tetrahydrobiopterin, or BH4 (Figure 2A), for the synthesis of monoamines.[4-6] Second, BH4 activates the rate-limiting enzymes tyrosine hydroxylase and tryptophan hydroxylase for the synthesis of monoamines.[4-6] Note that when these enzymes lack BH4 (shown as an empty "4" in the blue tyrosine hydroxylase and tryptophan hydroxylase enzymes

Figure 1. Synthesis of L-Methylfolate From Folate



Abbreviations: C = carbon, H = hydrogen, MTHFR = methylene tetrahydrofolate reductase.

Figure 2. Regulation of Monoamine Synthesis by L-Methylfolate

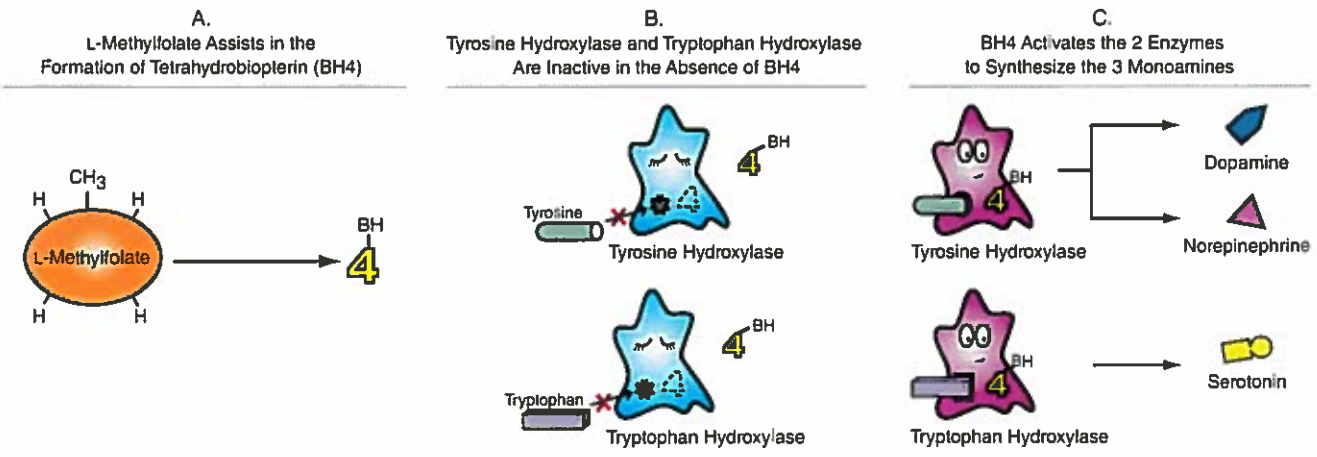


Table 1. Characteristics of Patients With Depression Who Might Be the Best Candidates for L-Methylfolate Treatment

Documented low levels of folate and its active metabolites such as L-methylfolate
Inadequate responses to a standard antidepressant
High risk for low folate levels resulting from
• Alcoholism
• Eating disorders
• Pregnancy
• Gastrointestinal disorders
• Documented low levels of MTHFR (methylene tetrahydrofolate reductase) or being from a group (Hispanic and Mediterranean populations) at high risk for decreased levels of this enzyme
• Documented high homocysteine levels, which tend to rise when folate falls
• Drugs that can interfere with folate conversion to L-methylfolate such as lamotrigine and valproate
Preference for a natural product approach with few or no side effects

Take-Home Points

- L-Methylfolate is the centrally active derivate of the vitamin folate and is utilized not only for neurotransmitter synthesis, but also for many vital methylation reactions in all cells.
- L-Methylfolate regulates the availability of the critical enzyme cofactor BH4 (tetrahydrobiopterin), required by tryptophan hydroxylase for serotonin synthesis and by tyrosine hydroxylase for dopamine and norepinephrine synthesis.
- Low levels of folate and L-methylfolate are linked to some forms of depression and to some patients who fail to respond to antidepressants, suggesting that augmentation of antidepressants with L-methylfolate may be a useful treatment option in these cases.

in Figure 2B), they are inactive and cannot bind to their amino acid substrates, tyrosine and tryptophan, which are the precursors for the monoamines. Third and finally, when L-methylfolate forms the critical amount of BH4, BH4 can activate these enzymes (Figure 2C), and tyrosine hydroxylase and tryptophan hydroxylase can now form the trimonoamines serotonin, norepinephrine, and dopamine.[4-6] Specifically, tyrosine can now bind with tyrosine hydroxylase and ultimately be converted into both dopamine and norepinephrine, and tryptophan can now bind with tryptophan hydroxylase and ultimately be converted into serotonin.

Therapeutic Implications?

One practical application of the central action of L-methylfolate may be for depressed patients who have inadequate monoamine neurotransmitter synthesis, especially if caused by an actual or functional deficiency in brain L-methylfolate (Table 1).[1-8] In such cases, administration of L-methylfolate could theoretically boost monoamine synthesis to the necessary levels and either treat depression or boost the therapeutic action of antidepressants dependent upon adequate levels of monoamines.

So, who might be the best candidates to receive L-methylfolate? Research is still trying to answer this question, but the current evidence suggests that the best candidates for L-methylfolate treatment might be depressed patients who have documented low levels of folate and its active metabolites, including L-methylfolate, and who fail to respond to treatment with a standard antidepressant.[1-8] Investigators are also determining whether those at risk for low L-methylfolate levels, such as those who have certain concomitant illnesses, have certain genetic risk factors for low L-methylfolate levels due to inheritance of low MTHFR enzyme activity, or are taking certain drugs that interfere with L-methylfolate formation (Table 1), might also be responsive to antidepressant augmentation with L-methylfolate.[1-8]

Summary

L-Methylfolate modulates the synthesis of the monoamines serotonin, norepinephrine, and dopamine. Some depressed patients may have their disorder or their lack of response to an antidepressant linked to low levels of folate and L-methylfolate. Research is currently working to establish which patients with depression would be the best candidates for L-methylfolate treatment. ◆

References

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