L-Methylfolate

L-Methylfolate (5-methyltetrahydrofolate), an altered or activated form of the B vitamin Folate or Folic Acid, is essential, amongst several other metabolic functions, for the synthesis of THB the rate limiting cofactor for Tyrosine/Tryptophane Hydroxylase (TH), the rate limiting enzyme in the production of the central catecholamines Dopamine, Norepinephrine, and Serotonin. Lack of these essential catecholamine substances is thought to be an important causal mechanism in Depression and Anxiety. Lack of Dopamine activity is the cause of Parkinson’s disease and is involved in Attention Deficit Disorder. Low levels of Norepinephrine may be a factor in reduced control or modulation of pain.

There are some relatively common mutations or single nucleotide polymorphisms (SNPs) in the genes coding for MTHFR, one of the enzymes involved in the four step conversion of Folate to Methylfolate. These result in reduced enzyme activity and therefore reduced levels of Methylfolate, and thence of THB, of TH activity, and of the essential Catecholamines. Providing supplemental Methylfolate to those unable to synthesize full amounts of this substance has been shown to improve depression in unipolar depression and bipolar mood disorders. It has also been reported to improve the treatment of schizophrenia. Sometimes the improvement in depression is literally life altering.

The MTHFR polymorphisms are also associated with Migraine, with elevations in Homocysteine (which is a risk factor for occlusive vascular disease), with risk for Venous Thrombosis, with risk for Alzheimer’s and vascular dementia, with risk for Parkinson’s Disease, and with the risk for several malignancies, including endometrial, breast, ovarian, and prostate cancers. These are also associated with increased risk in pregnancy of Pre-eclampsia, Placental Abruption, and Neural Tube Defects. There are also reports of the defects being associated with fibromyalgia and Irritable Bowel Syndrome, which often co-occur with migraine headaches. Replacing missing methylfolate with supplements helps control or prevent migraine and reduce homocysteine levels. Whether it reduces the associated risk for cancers or venous thrombosis are matters which have been less studied to date.

Insomnia, irritability, forgetfulness, organic psychosis, peripheral neuropathy, myelopathy and restless leg syndrome are all also mentioned in the literature as potentially being influenced by this enzyme deficiency.

We have for some time sent simple tests for the MTHFR genes to determine which patients have the SNP altered genes which lead to 30%, 50%, or 60% reductions in enzyme activity and then, in turn, to the mechanisms and clinical situations discussed above.

Often the genetic pattern of some members of a family or kinship lead to finding others, “uncovering” other opportunities to beneficially impact the various disorders noted above with economical L-methylfolate supplements.

5-MTHF was shown in a study from Harvard University to increase production of serotonin, dopamine, and norepinephrine. Fava M, Mischouluon D. Folate in depression: efficacy, safety, differences in formulations, and clinical issues. J Clin Psychiatry. 2009;70 Suppl 5:12-7.


It does this by increasing production of bioptrialin, thereby enhancing the effect of SSRI drugs. Miller AL. The methylation, neurotransmitter, and antioxidant connections between folate and depression. Altern Med Rev. 2008 Sep;13(3):216-26.
