Methylation: Fundamental to a Healthy Nervous System

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Introduction

Methylation, the addition of a methyl group to facilitate a biochemical reaction, is vital to a wide variety of biological processes. Among other things, methylation facilitates detoxification (especially in the liver), and is important for proper functioning of the hypothalamic-pituitary-adrenal (HPA) axis. It is critical for the synthesis of all monoamine neurotransmitters and histamine; for example, the enzyme that converts norepinephrine to epinephrine is dependent on methylation for activation.

A variety of extrinsic and intrinsic factors including stress, nutritional deficits, certain disease states, and genetics can contribute to insufficient methylation. This can result in a reduced ability to synthesize monoamine neurotransmitters and to remove toxins and metabolic waste, which in turn can lead to symptoms such as low mood, anxiousness, sleep issues, fatigue, and decreased cognition. Regaining appropriate neurotransmitter synthesis by supporting methylation pathways can lead to increased health and the reduction or prevention of symptoms.

Methylation and Neurotransmitters

Insufficient methylation can have a profound effect on neurotransmitter production, since the addition of methyl groups is critical to neurotransmitter synthesis (see Appendix, label 1). In addition, the folate and biopterin cycles (see Appendix, label 2) help ensure adequate monoamine neurotransmitter production. Consequently, certain cofactors and intermediates are often included in nutritional supplements to support methylation and associated pathways if there is a suspected deficiency. Some of the most commonly utilized supplements include S-adenosylmethionine (SAMe) and folic acid. These may be recommended for symptoms such as fatigue, anxiousness, pain, and others associated with a decrease in neurotransmission or reduced methylation.

Methylation Support

\(S\)-adenosyl methionine

SAMe has been used since the 1950s to support methylation pathways for optimal neurotransmitter levels (Bottiglieri, 2002; Wurtman, 1972). It is a naturally occurring molecule that has a wide variety of effects in the body, as it donates methyl groups necessary for the synthesis of DNA and RNA, phospholipids, dopamine, norepinephrine, epinephrine, serotonin, and melatonin. SAMe is also an important cofactor in the conversion of norepinephrine to epinephrine (see Appendix, label 3). In double-blind, randomized clinical studies, it has been shown to reduce low mood symptoms (Papakostas, 2010; Pancheri, 2002) and support cognitive function (Levkovits, 2011). Studies also suggest that patients who do not adequately respond to attempts to modulate serotonin function may benefit greatly from methylation support with SAMe (Papakostas, 2010; Levkovits, 2011).

In addition, SAMe plays an important role in liver health by acting as the main methylating agent and defending against the toxicity of free radicals generated by pathogens (Lieber, 2002). It is also a precursor to cysteine, an amino acid important for the production of glutathione and protection against oxidative stress.

Folic Acid

Folic acid (vitamin \(B_9\)) is necessary for a variety of functions including DNA repair and synthesis, methylation, and a number of other biological reactions. It is also particularly important during pregnancy as a deficiency may lead to negative effects on fetal development (Maloney, 2012; Morse, 2012). Folic acid is the unmethylated form of 5-methyltetrahydrofolate (5-MTHF) and is only biologically active after the addition of a methyl group by the enzyme methylenetetrahydrofolate reductase (MTHFR) (see Appendix, label 4) to form 5-MTHF. 5-MTHF is necessary for the methylation of homocysteine to create...
SAMe and is a primary methyl donor for the tetrahydrobiopterin (BH4) cycle. Evidence suggests that individuals with certain mutations in the MTHFR gene are deficient in the ability to convert folic acid into methylfolate (Deloughery, 1996). Thus, supplementation with 5-MTHF instead of folate can help to compensate for these mutations, as it does not require MTHFR for activation.

Other cofactors such as methionine, vitamin B₁₂ (Reynolds, 2006), and vitamin B₉ are also beneficial for ensuring complete methylation support. These cofactors are necessary at various stages in the formation of neurotransmitters (see Appendix, label 5) and are often included in nutritional supplements designed to support the methylation process.

Conclusion
Methyl groups are produced by the coordinated function of the methionine, folate, and biopterin cycles. These cycles are vital to a wide variety of biological processes including HPA axis function and the synthesis of monoamine neurotransmitters. It is important to recognize that deficiencies in the methylation cycle could be a potential cause of certain clinical presentations, particularly those tied to decreased neurotransmitter production.

A variety of internal and external factors including stress, nutritional deficits, certain disease states, and genetics can contribute to insufficient methylation. Methylation deficiencies and the subsequent decrease in neurotransmitter production can lead to a wide variety of clinical symptoms such as low mood, anxiousness, sleep issues, fatigue, and decreased cognition. Supporting healthy neurotransmitter synthesis with ingredients such as SAMe and folic acid can lead to increased overall health as well as the improvement or prevention of clinical symptoms associated with decreased methylation.

References


