-Second Messenger-

Abstract: Folate is an important dietary component needed for nervous tissue development, maintenance of neuronal communication, neurotransmitter production, and epigenetic modulation of gene expression. When folate metabolism goes awry, there are often serious consequences for neural development and susceptibility to psychiatric disorders. Methylenetetrahydrofolate reductase (MTHFR) is an enzyme involved in folate metabolism. Polymorphisms in this important enzyme have been associated with several different psychiatric disorders.

Psychiatric Disorders: A Messed Up MTHFR

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Issue

Polymorphisms in the gene for methylenetetrahydrofolate reductase (MTHFR) have been linked to several different psychiatric disorders.

Action

This article discusses how genetic polymorphisms in MTHFR can influence folate metabolism and ultimately lead to increased susceptibility to psychiatric disorders. Several pharmacological treatments to correct aberrant folate metabolism and its downstream consequences are currently under investigation.

Benefit

As personalized medicine becomes a reality, knowledge of the biochemical and molecular underpinnings of folate metabolism will be necessary for the optimal detection and treatment of psychiatric disorders associated with abnormal folate metabolism.

The Importance of Folate

Folate is an important and necessary vitamin B complex found in leafy greens such as spinach. It is required for several important biological processes, including normal cell growth and replication, nucleic acid synthesis, DNA repair, and modulation of the amino acid homocysteine. In fact, maternal folate deficiency has such a detrimental effect on embryonic neural tube development that several countries, including the United States, now require supplementation of many grain products with folic acid (a synthetic form of folate).[1] In addition to the more severe neural tube defects caused by extreme folate deficiency during development, folate deficiency has also been associated with several psychiatric diseases, including major depressive disorder (MDD), schizophrenia, and bipolar disorder (BP), indicating that folate deficiency may have more subtly damaging effects on brain development and maintenance throughout the lifetime of an individual.[1-3]

The Function of MTHFR

Methylenetetrahydrofolate reductase (MTHFR) is the enzyme responsible for synthesizing L-methylfolate from dietary folate sources. L-methylfolate has several very important roles.[2-6] First, L-methylfolate affects the synthesis of neurotransmitters by regulating levels of the cofactor biopterin. Biopterin is required by tyrosine hydroxylase and tryptophan hydroxylase in the synthesis of monoamines such as dopamine (DA) and norepinephrine (NE). Second, L-methylfolate is used in the conversion of the amino acid homocysteine to methionine and thus regulates homocysteine concentrations. Additionally, L-methylfolate is ultimately responsible for the regulation of gene expression. The methionine produced with the help of L-methylfolate is converted into s-adenosylmethionine (SAMe), the major methyl group (CH_3) donator for several enzymes, including DNA and histone methyltransferases. DNA and histone methyltransferases tag DNA and histones, respectively, with methyl groups, and in doing so, turn off the expression of genes (Figure 1).

Polymorphisms in MTHFR

Two significant polymorphisms have been discovered in the MTHFR gene, and both lead to consequences that are similar to those of reduced dietary folate intake.[1-6] The first MTHFR polymorphism, known as the "T allele," is a transition of cytosine to thymine at codon 677. The second common MTHFR polymorphism, known as the "C allele," involves a transversion of adenine to cytosine at codon 2398. Both of these polymorphisms result in the reduced activity of MTHFR, and the consequences of this reduced enzymatic activity include the diminished production of L-methylfolate, the reduced availability of methyl groups, and elevated homocysteine levels (i.e., hyperhomocysteinemia). The reduced production of L-methylfolate gives rise to a paucity of monoamine production, whereas the diminished availability of methyl groups is believed to have epigenetic effects on the expression of many genes.[2] Reduced methylation also results in the aberrant building of cell membranes and has detrimental effects on myelin structure, leading to impaired nerve conduction.[3] Hypercysteinemia has been shown to modulate the activity of N-methyl-D-aspartate receptors (NMDAR), which play an integral role in the long-term potentiation that underlies learning and memory. The actions of homocysteine on NMDAR therefore impair learning and memory and can even be excitotoxic, resulting in cell death.[7] Given the effects of MTHFR polymorphisms on decreased neurotransmitter production, aberrant gene expression, and synaptic transmission, it is not surprising that MTHFR polymorphisms have been linked to several psychiatric disorders, including MDD, schizophrenia, and BD. Inheritance of the MTHFR T or C allele increases the susceptibility of an individual to psychiatric disorders, but the determination of whether one develops a

psychiatric disorder is most likely also influenced by the inheritance of polymorphisms in other genes that affect folate metabolism as well as environmental influences on folate availability (e.g., smoking).[2]

Folate in the Treatment of Psychiatric Disorders

It seems clear that folate metabolism, which is influenced by MTHFR and other polymorphisms as well as environmental factors, has a major influence on neurobiological development and regulation. Abnormal folate metabolism may therefore greatly affect an individual's susceptibility to psychiatric disorders. It seems plausible that the modulation of folate levels may be useful as a potential treatment for many psychiatric disorders. Indeed, several studies have indicated the effectiveness of using folate and its metabolites or downstream effectors in the treatment of various psychiatric disorders.[3-4] For example, treatment with L-methylfolate has been shown to improve positive, negative, and cognitive symptoms in schizophrenia, and treatment with SAMe reduces depressive symptoms in Parkinson disease patients.

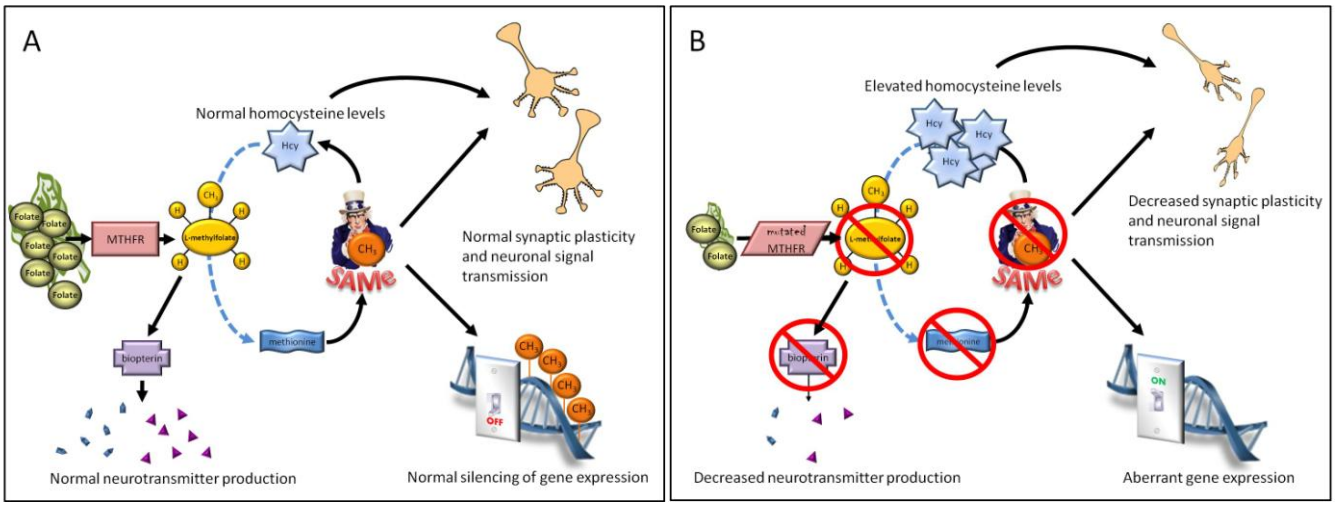

Figure 1. Folate Metabolism

A. In normal folate metabolism, the production of L-methylfolate from folate is mediated by the enzyme methylenetetrahydrofolate reductase (MTHFR). L-methylfolate regulates the production of biopterin, a cofactor required by tyrosine and tryptophan hydroxylases for the production of monoaminergic neurotransmitters, such as dopamine and norepinephrine. L-methylfolate also converts the amino acid homocysteine (Hcy) into methionine, reducing homocysteine levels and leading to the production of s-adenosylmethionine (SAMe), the major methyl (CH_3) donor in the brain. Along with modulated levels of homocysteine, the production of SAMe allows for normal nerve conductance, plasma membrane formation, and the synaptic transmission that underlies long-term potentiation. SAMe also provides methyl groups to the DNA and histone methyltransferase enzymes that mediate the epigenetic control of gene expression.

B. When folate metabolism is abnormal due to folate deficiency and/or genetic polymorphisms, such as the T and C polymorphisms in MTHFR, less L-methylfolate is produced. Ultimately, this may lead to reduced monoaminergic neurotransmitter production; the reduced conversion of homocysteine to methionine, leading to a buildup up homocysteine; and reduced SAMe concentration. The buildup of homocysteine and the decreased availability of methyl groups from SAMe bring about impairments in neural transmission and the aberrant expression of genes that should be silenced. Together, these changes in folate metabolism may increase an individual's risk for developing a psychiatric disorder.

The bottom line

Both dietary folate deficiency and genetic polymorphisms that affect folate metabolism, including the MTHFR T and C alleles, have wide-ranging consequences for the epigenetic regulation of gene expression, neurotransmitter production, and neural transmission. Combinations of genetic and environmental factors that affect folate metabolism likely underlie the susceptibility and development of various psychiatric disorders, including MDD, schizophrenia, and BD. It is possible that optimal treatment of these disorders may include addressing abnormal folate metabolism through the administration of folate or one of its metabolites or manipulating the epigenetic mechanisms of aberrant gene expression.

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