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Review article

Homocysteine and folate metabolism in depression

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Abstract

Homocysteine is a sensitive marker of folate and vitamin B12 deficiency. Numerous studies have confirmed the association between folate deficiency and depression. It is not completely understood whether homocysteine is solely a marker for folate deficiency or if it may play a more direct role in the expression of mood disorders. This review describes the biochemical, neurochemical and clinical correlations of folate deficiency and hyperhomocysteinemia in relation to depression.

Keywords: Depression; Folate; Homocysteine; Methylation; Vitamin B6; Vitamin B12

Contents

1. Introduction

Since the discovery of folate in 1945, and vitamin B12 in 1948 numerous reports have described the neuropsychiatric complications associated with deficiencies in these vitamins. There are similarities and differences in the clinical presentation observed in folate and vitamin B12 deficiency, which stem largely in part to their intimate metabolic relationship. The one central biochemical reaction that unifies folate and vitamin B12 metabolism involves the methylation of homocysteine (Hcy) to methionine, which is catalyzed by methionine synthetase (MS). Diminish activity of MS and the ensuing increase in Hcy can lead to severe

Abbreviations: BH4, tetrahydrobiopterin; BHMT, betaine-homocysteine methyltransferase; CBS, cystathionine-beta-synthetase; CNS, central nervous system; COMT, catechol methyl-transferease; DHFR, dihydrofolate reductase; HAM-D, Hamilton depression scale; Hcy, homocysteine; HVA, homovanillic; MHPG, 3-methoxy-4-hydroxyphenylglycol; MS, methionine synthetase; MTHF, methyltetrahydrofolate; MTHFR, methyltetrahydrofolate reducase; NMDA, *N*-methyl-D-aspartate; PNMT, phenylethanolamine *N*-methyltransferase; SAH, *S*-adenosylhomocysteine; SAM, *S*-adenosylmethionine; 5HT, serotonin.

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metabolic consequences. High concentrations of Hcy are toxic not only to vascular endothelial cells (Austin et al., 2004; Weiss et al., 2002) but also to neuronal cells (Mattson and Shea, 2003; Parnetti et al., 1997). Elevated blood levels of Hcy have been associated with several psychiatric and neurodegenerative disorders including depression, schizophrenia, Alzheimer's disease, and Parkinson's disease. Although research in this field has intensified over the last decade there is a lack of a complete mechanistic understanding of homocysteine toxicity in vascular and central nervous system disorders (CNS). Several potential mechanisms have been proposed, supported by extensive experimental studies, which may aid in defining the development of effective prevention and treatment approaches. This review will focus on the biochemical and neurochemical aspects of methylation and altered homocysteine metabolism with particular reference to depression.

2. Homocysteine metabolism and the folate-methylation cycle

Homocysteine is a sulfur containing amino acid that cannot be obtained from any dietary source. It is solely the product of the methylation cycle, which is critical not only for its formation but also its removal. All methylation reactions that utilize *S*-adenosylmethionine (SAM) as the methyl-donor generate *S*-adenosylhomocysteine (SAH) (Fig. 1). Inside cells SAH is rapidly converted to Hcy by SAH-hydrolase. Although this reaction is reversible, the metabolic flow under normal physiological conditions proceeds in the hydrolytic direction, when Hcy is rapidly removed and concentrations remain low. However, when intracellular Hcy concentrations increase the SAH-hydrolase reaction proceeds in favor of SAH formation. This is of particular biochemical relevance since SAH has been shown to be a potent inhibitor of SAM dependent methylation reactions (Cantoni, 1985). Experimental studies that have manipulated Hcy levels in cell cultures or animal models have shown that when Hcy levels are increased there is a corresponding elevation of intracellular SAH. The ensuing altered SAM/SAH ratio can potentially inhibit methyltransferase reactions involving DNA (Sibani et al., 2002; Yi et al., 2000), proteins (Hackett and Campochiaro, 1988), phospholipids (Innis et al., 2003) and catecholamine neurotransmitters (Waldmeier and Feldtrauer, 1987; Bottiglieri et al., 2000). It has been calculated that when SAH is present at a ratio of 1:4 with respect to SAMe, a variety of methyltransferases will decrease their activities by 10% to 60% (Cantoni, 1985).

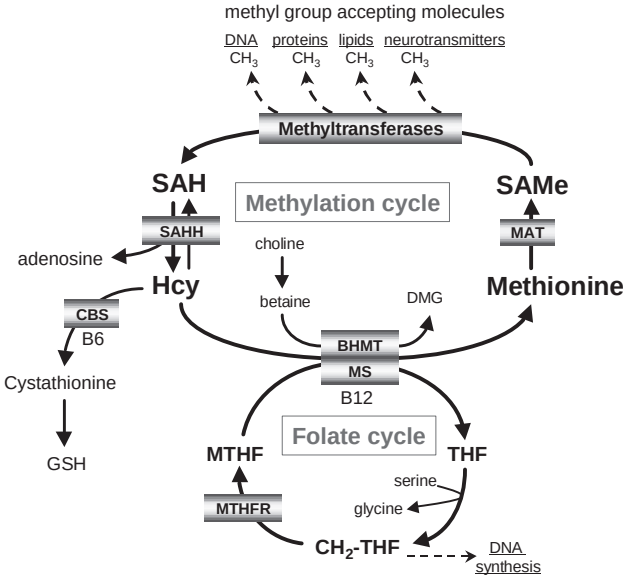

Fig. 1. The metabolic relationship between the folate and the methylation cycle.

There are three metabolic reactions that function to maintain low intracellular concentrations of Hcy. The first involves the methylation of Hcy, which is catalyzed by methionine synthetase (Fig. 1). In this reaction the methyl group from 5-methyltetrahydrofolate (MTHF) is transferred to Hcy to form methionine and tetrahydrofolate. This de novo synthesis of methionine requires vitamin B12, which is directly involved in the transfer of the methyl group to Hcy. An alternative route for the synthesis of methionine is via the betaine:homocysteine methyltransferase (BHMT) reaction. This reaction does not require vitamin B12 or MTHF since labile methyl groups supplied in the diet as choline are converted to betaine and then transferred to homocysteine. There is an essential and important difference between peripheral and central nervous (CNS) tissue in that the enzyme BHMT is absent in the latter (Sunden et al., 1997). Therefore, MTHF is the only methyl donor involved in the methylation of Hcy to methionine in CNS tissue. All of the folate-dependent enzymes are present both in peripheral and CNS tissue. These are important for the recycling of one-carbon (C-1) units, supplied to the cycle from serine, which are transferred to 5,10-methylenetetrahydrofolate and other folate forms. In addition to their role in methionine formation, the folate coenzymes play an important role in the synthesis of deoxythymidine (dTNP), required in the synthesis of DNA (Fig. 1). The third route of metabolism of Hcy involves condensation with serine to form cystathionine by the enzyme cystathionine-β-synthetase (CBS). In this reaction homocysteine is committed to the transulfuration pathway as it is converted to cystathionine, leading to the formation of glutathione, a major cellular antioxidant (Fig. 1). Vitamin B6 (pyridoxal phosphate) is required as a cofactor for CBS activity.

3. Hyperhomocysteinemia

Hyperhomocysteinemia may be defined as a sustained elevation above normal of Hcy in plasma or serum. The