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Folate Nutrition and Blood-Brain Barrier Dysfunction

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Abstract

Mammals require essential nutrients from dietary sources to support normal metabolic, physiological and neuronal functions, to prevent diseases of nutritional deficiency as well as to prevent chronic disease. Disease and/or its treatment can modify fundamental biological processes including cellular nutrient accretion, stability and function in cells. These effects can be isolated to a specific diseased organ in the absence of whole-body alterations in nutrient status or biochemistry. Loss of blood-brain barrier function, which occurs in in-born errors of metabolism and in chronic disease, can cause brain-specific folate deficiency and contribute to disease co-morbidity. The role of brain folate deficiency in neuropsychiatric disorders is reviewed, as well as emerging diagnostic and nutritional strategies to identify and address brain folate deficiency in blood-brain barrier dysfunction.

Graphical Abstract

I. Introduction

Mammals require the provision of essential nutrients from dietary sources to maintain adequate nutritional status, which is needed to support normal metabolic, physiological and neuronal functions, to prevent diseases of nutritional deficiency as well as to prevent chronic disease (1). It has been recognized for decades that disease and/or its treatment can modify fundamental biological processes including cellular nutrient accretion, stability and/or

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function in cells, and that these effects can be isolated to a specific diseased tissue or organ in the absence of whole-body alterations in nutrient biochemistry (2). Disease-induced nutritional deficiencies often cannot be addressed by nutrient intakes derived from a whole food-based diet alone.

Numerous neurological and psychiatric diseases are associated with cerebral deficiency of folate, a water-soluble B-vitamin (3). Folate deficiency can be localized to the central nervous system in the absence of whole-body folate deficiency. Brain-specific nutrient deficiencies can contribute to disease initiation, its progression and/or related co-morbidities (3, 4), and clinical dietary management of brain folate deficiency can provide clinically meaningful therapeutic benefit (5, 6). However, the development of approaches to identify and manage tissue-specific nutrient deficiencies caused by disease is still in its infancy.

Nutrition and related genetic epidemiological studies and/or randomized controlled trials implicate impaired folate metabolism in several pathologies including neural tube defects (7), neurodegenerative and neuropsychiatric diseases (8, 9) and cancer (10–14). Tetrahydrofolates (THF) serve as cofactors that carry one-carbon units at three different oxidation states (Figure 2), and function in concert with other B-vitamins including vitamin B₁₂, vitamin B₆, riboflavin, and niacin in a metabolic network known as folate-mediated one-carbon metabolism (FOCM) (15, 16). FOCM occurs in the mitochondria, the cytosol, and the nucleus (17, 18). FOCM in the cytosol is necessary for the *de novo* synthesis of purines and for the remethylation of homocysteine to methionine. Methionine can be converted to S-adenosylmethionine, which is a one-carbon donor for numerous methylation reactions, including DNA methylation and neurotransmitter synthesis and degradation (17). The *de novo* thymidylate biosynthesis pathway functions in the nucleus and is essential for DNA synthesis and stability (19, 20). These THF-dependent critical biochemical functions are the basis of fundamental cellular processes that when disrupted by imbalanced nutrient supply may result in manifestation of disease. Folate- and vitamin B₁₂-associated pathologies are common and increase with age (21).

Biomarkers of folate and vitamin B₁₂ status and function include decreased plasma and/or red blood cell levels of the individual vitamins, as well as depressed S-adenosylmethionine levels and elevated plasma total homocysteine and S-adenosylhomocysteine (22, 23). Consequently, a resulting decrease in the ratio of S-adenosylmethionine to S-adenosylhomocysteine is associated with hypomethylated DNA which affects gene expression and DNA stability and alters synthesis of small molecules including neurotransmitters (24–27). Impaired one-carbon metabolism also depresses thymidylate synthesis (10), resulting in uracil misincorporation and accumulation into DNA leading to lower rates of cell division and cell death, which can compromise neurogenesis (Figure 2) (10, 28–30). Elevated homocysteine can also lead to homocysteinylolation of proteins, which may stimulate autoimmunity (31).

II. The Blood-Brain Barrier in Health and Disease

The blood-brain barrier (BBB) is critical for meeting the nutritional needs of the brain that cannot be met by the vasculature, as certain nutrients are concentrated several-fold across

the BBB into the cerebral spinal fluid (CSF). The BBB is a monolayer of epithelial cells that isolate the brain from the blood/vasculature and selectively transport small molecules to the brain (32). The CSF has been described as the “nourishing liquor” for the brain, as recently reviewed (33). In healthy individuals, the BBB regulates the exchange of nutrients and other constituents between the blood and the CSF, creating a microenvironment that supports neurological functions (34, 35). Many nutrients and metabolites are transported and concentrated up to several-fold higher in CSF than plasma concentrations by specific transport systems through the BBB or choroid plexus (36). The ratio of CSF/serum for such nutrients can be used as a measure of brain nutrient status, and report on physiological processes such as nutrient transport and degradation and also report on the adequate functioning of the BBB (37). Folate is concentrated 1.5 to 3-fold across the BBB, and thus transport across this concentration gradient requires ATP (38).

The critical role of the BBB in maintaining adequate brain folate status has been demonstrated in pediatric patients with in-born errors of metabolism. Low CSF folate can result from genetic loss-of-function mutations that affect folate utilization, energy metabolism, or folate transport across the BBB, and the resultant cerebral folate deficiency is associated with neurological and neuropsychiatric symptoms (Table 1). Rare genetic mutations in genes encoding proteins involved in folate transport, including the folate receptor alpha (FR α) (39) and the proton-coupled folate transporter (PCFT) (40), result in cerebral folate deficiency, as do mitochondrial DNA depletion syndromes associated with defective oxidative phosphorylation(41), and the Kearns-Sayre syndrome (41). In addition to mutations in genes that are involved in brain folate transport and accretion, mutations in folate-metabolism genes including methylenetetrahydrofolate reductase (MTHFR) (41), dihydrofolate reductase (41) and mutations in genes that result in brain serine depletion also affect brain folate levels. Serine is a major source of one-carbon groups for folate-mediated one-carbon metabolism. Deficiencies in these enzymes likely increase rates of folate catabolism and turnover because unstable forms of folate accumulate when enzyme activity is impaired. Alternatively, brain folate deficiency can result from lack of ATP (energy) required to maintain the energy gradient across the BBB (42).

Adults can also be at risk for brain nutrient deficiencies, including folate deficiency because of diminished BBB function (43). Adult-onset BBB dysfunction can be caused by, mitochondria depletion, as well as chronic conditions and diseases including inflammation, hypoxia, diabetes mellitus, hypertension, cerebrovascular ischemia, acute kidney injury, viral infection, parasitic infection, and Alzheimer’s Disease (34, 44–47). Chronic disease can accelerate age-associated deterioration of BBB functions including nutrient transport (47), which can lead to nutritional deficiencies that are isolated to the central nervous system. When the barrier deteriorates, it becomes permeable and can compromise the supply of nutrients and small molecules, such as folate, that are maintained at higher levels in the CSF than the serum. Folate status in the central nervous system can be negatively affected by certain pharmaceuticals, environmental insults, autoimmunity or other factors that affect folate transport into the CSF, and/or increased rates of leakage across the BBB, and/or increased rates of folate catabolism. Importantly, nutrient supplementation can repair a damaged BBB. Patients with mild cognitive impairment who were supplemented with a

high-dose supplement containing vitamin B₁₂, vitamin B₆ and folate for 270 days demonstrated improved blood-brain barrier function (48).

Autoimmunity is an emerging risk factor for late-onset cerebral folate deficiency. Autoantibodies against the folate receptor alpha (FR α) that block folate transport across the blood-brain barrier have been correlated with low CSF folate (49–52). The presence of autoantibodies against FR α and cerebral folate deficiency are seen in some autism spectrum disorders, depression, schizophrenia and seizures (51). Patients with depression or schizophrenia are more likely to have autoimmunity to folate receptors. In a study of 18 patients diagnosed with schizophrenia, 15 (83.3%) had positive serum FR α autoantibodies compared to only 1 in 30 controls (3.3%) (53).

Common genetic variants can also contribute to low CSF folate in disease. The best-characterized gene variant is the 677C→T MTHFR polymorphism. The MTHFR variant has dual effects on FOCM that include both its effect on folate status and its impacts on MTHFR catalysis, including its role in providing (6S) 5-methyltetrahydrofolate for the homocysteine remethylation pathway and cellular methylation. The MTHFR variant contributes to risk for neural tube defects by decreasing folate status in tissues, as opposed to its effects on homocysteine remethylation and cellular and methylation capacity (54). Patients with depression or schizophrenia are more likely to have common genetic variants that contribute to folate deficiency, and many of these polymorphisms are also associated with neuropsychiatric disease. The C677T MTHFR variant has been associated with an increased risk of and schizophrenia; up to 70% percent of patients with either depression or schizophrenia have been shown to carry MTHFR variants (55–57).

III. Administration of High-Dose Folate Addresses Brain Folate Deficiency

The recommended dietary allowance (RDA) for folate dietary equivalents is 0.4 mg/day for healthy adults (58), but this recommended level of intake may not be sufficient for some individuals with chronic CNS disorders. The World Health Organization (WHO) report from 2008 on folate and vitamin B₁₂ deficiencies states “that low serum or red blood cell folate concentrations are associated with either a higher prevalence or a longer duration of depression” (59). In its current practice guideline for the overall therapy of major depressive disorders, the American Psychiatric Association recognizes folate as adjunctive therapy to antidepressant medication (60). Blood folate levels are poor indicators of CSF folate levels, but elevated intake of folate can correct low CSF folate levels in patients with in-born errors of metabolism. Parenteral folinic acid (5 mg, twice weekly) or oral folinic acid (0.5–20 mg/kg/day) is used, tolerated and normalizes CSF folate levels with improvements in neurological outcomes and white matter morphology (Table 1) (3, 41, 61). Exposure to high levels of reduced forms of folate (such as folinic acid) can overcome transport defects that may arise and restore CSF folate levels, physiological function and improve clinical outcomes. The level of folate intake required to address brain folate deficiency cannot be met by natural foods alone. Elevated doses of reduced folate are necessary to overcome both the energetic and structural barriers to deliver this essential nutrient to the brain at the required concentrations.

Few studies have assessed the role of high-dose reduced folate administration in ameliorating low CSF folate in adult chronic disease, although folate administration has been shown to improve neuropsychiatric symptoms related to brain nutritional deficiency. Several trials indicated that a dose 7.5 mg (6S) 5-methyltetrahydrofolate/day resulted in clinically meaningful reductions in the patient-reported and/or clinician-rated severity of depressive symptomology (5, 6). The clinical response and/or mean reduction in depressive symptoms were significantly greater in patients with gene variants in the B-vitamin biochemical pathway including: the folate-associated enzymes methionine synthase (MTR), methionine synthase reductase (MTRR), and the reduced folate carrier (RFC); the methylation-associated enzymes catechol-O-methyltransferase (COMT) and DNA methyltransferase 3B (DNMT3B); as well as GTP cyclohydrolase 1 (GCH1), calcium voltage-gated channel subunit alpha1 C (CACNA1C), and dopamine receptor 2 (DRD2) variants (5). In addition, patients with schizophrenia who were unresponsive to conventional drug treatments and positive for FR α autoantibodies exhibited improved clinical outcomes when high doses of folinic acid (between 0.3 and 1.0 mg/kg/day) were administered (50). In one case report, a patient presented with low CSF folate levels (29 nmol/L; reference, 40–120 nmol/L) but with normal serum folate levels. The patient's serum contained high levels of FR α autoantibodies. The clinical symptoms resolved following 6 months of reduced folate administration (25 mg/d)(52).

Not all forms of dietary folate are equally efficacious in addressing low CSF folate levels. Folic acid, the synthetic, biologically inactive form of folate used in food fortification and dietary supplements, at high doses is not deemed beneficial and is not recommended in many cases of cerebral folate deficiency. Folic acid is a non-natural provitamin that must be first converted to a reduced folate form before it can serve a biological function in the cell, and this bioconversion rate is very slow. Furthermore, experimental studies have shown that folic acid can inhibit the transport of 5-methyltetrahydrofolate across the BBB (62). Folic acid also exhibits toxicity when administered at high dose (63). Patients with kidney disease receiving a B-vitamin supplement containing folic acid (2.5 mg/day), vitamin B₆ (25 mg/day) and vitamin B₁₂ (1 mg/day) exhibited a decline in glomerular filtration rate (the primary outcome of the study) relative to the control group and exhibited an increase in vascular events (64). High-dose folic acid administration in mice is lethal and causes acute renal damage (65). Mouse models of folic acid-induced nephrotoxicity have been developed and used to mimic nonimmune related acute tubular necrosis for the study of organ protection and tissue regeneration (65–67). Reduced, biologically-active forms of folate that are found in cells, including folinic acid and (6S) 5-methyltetrahydrofolate, have demonstrated efficacy in elevating CSF folate without toxicity at elevated levels of intake.

IV. Conclusions and Future Directions

It is estimated that approximately 50% of the United States population suffers from chronic disease, and the prevalence of age-related chronic disease is expected to increase in the coming years (68). Addressing the nutritional needs of this growing segment of the population will require: increased understanding of the role of disease processes in essential nutrient transport, utilization and turnover; developing prognostic biomarkers that report on

the linkage between tissue-specific nutrient needs and their relationship to the disease process; and improved nutrient delivery mechanisms that target the diseased tissue.

The development of new, minimally-invasive diagnostics and associated biomarkers to identify those at risk for brain nutritional deficiencies and those likely to respond favorably to a nutritional intervention are needed. Currently, blood biomarkers used to assess whole-body nutritional deficiencies are insufficient to identify individuals at risk for, or with existing, CNS-specific nutritional deficiencies. Loss of BBB integrity is diagnosed by the presence of brain-specific proteins and small molecules that leak into blood from the CSF including S100 β , an early marker that precedes neuronal damage, and glial fibrillary acidic protein (GFAP) (69). Likewise, detection of blood proteins in the CSF, including albumin, plasminogen and/or fibrinogen (70) and decreased amyloid beta clearance into serum (71) also indicate loss of BBB integrity. The relationship of these markers to brain nutritional status is unclear. Validated markers of BBB dysfunction and CNS inflammation that predict the onset of brain nutritional deficiencies and associated clinical disease are needed. Finally, the ongoing development of nanoscale drug delivery systems that are designed to deliver pharmaceuticals to the CNS (72) could be applied to nutrition to permit more targeted delivery of nutrients to the CNS to address disease-induced brain nutritional deficiencies.

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Highlights

- Tissue-specific nutrient deficiencies occur without whole-body deficiencies in disease.
- The brain concentrates folate across the blood-brain barrier.
- Blood-brain barrier dysfunction in chronic disease results in brain nutrient deficiencies.
- Brain folate deficiency contributes to neuropsychiatric disease.
- Diagnostic advancements are needed to identify brain-specific nutritional deficiencies.

Figure 2. Folate- and vitamin B₁₂-mediated one-carbon metabolism

One-carbon metabolism is required for the synthesis of purines, thymidylate and methionine. The hydroxymethyl group of serine is a major source of one-carbon units, which are generated in the mitochondria in the form of formate via SHMT2, or in the cytoplasm through the activity of SHMT1 or SHMT2a. Mitochondrial-derived formate can enter the cytoplasm and function as a one-carbon unit for folate metabolism. The synthesis of thymidylate occurs in the nucleus and mitochondria. At S phase, the enzymes of the thymidylate synthesis pathway undergo SUMO-dependent translocation to the nucleus. The remethylation of homocysteine to methionine by MTR requires vitamin B₁₂. The one carbon is labeled in “bold”. The “inset” shows the thymidylate synthesis cycle which involves the enzymes, SHMT1, SHMT2a, TYMS and DHFR. THF, tetrahydrofolate; DHF, dihydrofolate, MTHFR, methylenetetrahydrofolate reductase; MTR, methionine synthase; SHMT, serine hydroxymethyltransferase; DHFR, dihydrofolate reductase; TYMS, thymidylate synthase; MTHFD1, methyleneTHF dehydrogenase; AdoMet, *S*-adenosylmethionine; AdoHcy, *S*-adenosylhomocysteine.

Cerebral folate deficiency in inborn errors and response to high dose reduced folate administration

Table 1

Citation	# Patients	Disease Etiology	Cerebrospinal Fluid Folate (Normal Range: 43–159 nmol/L)	Intervention	Cerebrospinal Fluid Folate After Intervention	Clinical Improvement
(73)	3	Folate Receptor Mutations	<5.0 nmol/L	3.5–5.0 mg folinic acid/Kg/day	41–53 nmol/L	Improved cerebrospinal fluid folate MRS brain metabolites improved or normalized
(74)	1	Folate Transport Mutation	undetectable	50 mg folinic acid/day IM	33 nmol/L	Improved cerebrospinal fluid folate levels
(75)	1	Folate Receptor Mutation	2 nmol/L	30 folinic acid mg/day		Seizures reduced
(76)	2	Folate Receptor Mutations	“very Low”	High dose folinic acid		Seizures reduced
(61)	1	Mitochondrial DNA Depletion	8 nmol/L	1.0–2.5 folinic acid mg/Kg/day	48 nmol/L	White matter lesions normalized
(77)	1	Mitochondrial DNA Depletion	38.5 nmol/L	1.2 mg/Kg folinic acid/day + riboflavin		Recovered hypo-myelination; seizures reduced
(41)	8	Mitochondrial DNA Depletion	1.0–24 nmol/L	1.0–3.0 folinic acid mg/Kg/day	48 – 82 nmol/L	Neurological and radiological improvement in one patient; authors conclude early intervention is key
(78)	1	Folate Transport Mutation	undetectable	15 folinic acid mg/day; 180 mg/day	20 nmol/L	Seizures disappeared