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Review Article

The folate puzzle. Part IV: folate and depression

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Abstract

The World Health Organization (WHO) has predicted that depression will be the number two disabling condition worldwide by 2020. The increasing number of patients with recognized depressive disorders has caused a considerable rise in the prescription rate of antidepressant drugs, whereas at the same time it has become apparent that the remission rate for patients on monotherapy is lower then 40%. Therefore, augmentation strategies have been advocated for poorly responding or nonresponding patients. Many observational studies over the past two decades have shown elevated plasma homocysteine levels in patients with depression. The biochemical pathways of homocysteine indicate that plasma levels may be lowered by folic acid supplementation. Thus, it has been suggested that homocysteine may represent a modifiable risk factor for depression. Surprisingly, few studies on the effect of folic acid supplementation have been published. However, the limited available evidence from randomized, controlled interventional studies has confirmed that higher folate levels are associated with a lower incidence of depressive symptoms. It is therefore hypothesized that folate augmentation can be used to boost antidepressant efficacy, although further studies are necessary.

Introduction

Clinical depression is a common disabling condition and a major burden for both the individual and society. The World Health Organization (WHO) has predicted that depression will be the number two disabling condition worldwide by 2020, second only to cardiovascular disease. At present, depression affects about 120 million people worldwide. In Europe it has been estimated that depression comprises 6% of the burden of all diseases in terms of the sum of years lost due to early death due to disability. Within a 12-month period, 5.8% of males and 9.5% of females will develop a depressive episode (www.who.int), reflecting a striking gender difference (1). The lifetime risk for severe depression amounts to about 10% (2). In 28 European countries with a total population of 466 million, the number of people with depression is estimated to be at least 21 million.

Symptoms of depression may vary considerably among patients, as the condition may cause different experiences in different individuals. Major depression is characterized by impaired physical, social and professional functioning and may lead to drug misuse, alcohol abuse and suicide. The associated cost estimates correspond to about 1% of the economy of Europe (3). Epidemiological research suggests that clinical depression is related to life circumstances, such as poverty, unemployment and divorce (4). Depression in females is associated with life stresses such as single motherhood and lack of social support (5).

In the last decade of the 20th century, the prescription of antidepressant drugs increased by 4-10-fold in various age groups and countries (6), probably as a result of awareness campaigns directed at both the general public and prescribing physicians. The vast growth in the use of antidepressants has stimulated further investigation into the effectiveness of these drugs. Gedder *et al.* (7) concluded that there is no difference in clinical effectiveness between selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants. Furthermore, it appears that the rate of responders to antidepressant therapy is only 50-60%, which led investigators to look for ways to improve the efficacy of drug treatment for depressive disorders (8, 9).

Elevated plasma homocysteine levels have been found in patients with depression (10). One of the early firm observations that related homocysteine levels with depression was made by Bottiglieri *et al.* in 2000 (11), which was confirmed by Bjelland *et al.* in 2003 (12) and Tolmunen *et al.* in 2004 (13). An obvious suggestion from these findings is that hyperhomocysteinemia could cause depression, or at least the symptoms of depression.

Starting from this hypothesis, it has been suggested that folic acid supplementation leading to lowering of homocysteine levels could be useful for treating patients suffering from depressive disorders. Indeed, it has been recognized that low blood levels of folate contribute to the symptoms of depression (14). However, this does not mean that there is a universal consensus on this matter as various studies failed to support the relationship between folate deficiency and depressive disorders (15, 16).

This paper reviews the available knowledge on the role of folate in depressive disorders, including the results of interventional studies that investigated the effect of folic acid on depressive symptoms. This will be preceded by a short introduction to the biochemical pathways involved in homocysteine and folate metabolism, dwelling in particular on the role of these chemical processes in neurological function.

The folate cycle and homocysteine metabolism

Folate is a water-soluble B vitamin, often referred to as vitamin B_9 or vitamin B_{11}. It is found in a variety of plant foods, especially in green leafy vegetables and citrus fruits. Folate is a major determinant of one-carbon metabolism. Its metabolic pathways are closely related to the methylation cycle in which homocysteine is converted to *S*-adenosylmethionine (SAM). These reaction processes are extensively discussed in Part I of this series on folate (17). Briefly, referring to Figure 1, homocysteine is a sulfur-containing amino acid that is not available in the diet. The compound is synthesized intracellularly and serves as the precursor for the formation of methionine. SAM, which is the methyl donor for a large variety of biochemical reactions, is formed from the latter compound. SAM-dependent methylation reactions lead to the formation of *S*-adenosylhomocysteine (SAH). SAH hydrolase (adenosylhomocysteinase) catalyzes the conversion of SAH to homocysteine, which makes the process go around in circles. Thus, elevated homocysteine levels push the reaction process in favor of SAH formation. This is important, as SAH has been shown to inhibit SAM-dependent methylation reactions.

In brain tissue and also in other tissues, the biosynthesis of methionine from homocysteine requires the compound methyltetrahydrofolate (MTHF). The formation of MTHF from methylenetetrahydrofolate requires the enzyme methylenetetrahydrofolate reductase (MTHFR). By transferring its methyl group to homocysteine, MTHF is converted to tetrahydrofolate (THF). The latter compound is involved in the synthesis of the amino acids serine and glycine. (These amino acids participate in the biosynthesis of purines and pyrimidines and are important for DNA fidelity.) This process turns THF into methylenetetrahydrofolate, which closes the folate circle.

The mechanistic link between folate and depression

The action of MTHFR is associated with the formation of tetrahydrobiopterin (BH_4). This compound is an important enzyme cofactor for tryptophan hydroxylase (tryptophan 5-monooxygenase), the rate-limiting enzyme for the synthesis of 5-hydroxytryptamine (5-HT, or serotonin). Likewise, BH_4 is a cofactor for the rate-limiting enzyme tyrosine hydroxylase (tyrosine 3-monooxygenase) for the synthesis of dopamine and norepinephrine. The three monoamines dopamine, norepinephrine and serotonin are neurotransmitters. It is generally accepted that boosting the synthesis or availability of these compounds results in an antidepressant effect. Thus, MTHFR plays a crucial role in neurotransmitter biosynthesis and the concentration of monoamines in the synaptic cleft. Consistent with this mechanism is the finding by Kaufman (18), who showed that a reduced concentration of BH_4 and monoamine metabolites is present in patients with reduced MTHFR activity. Furthermore, *MTHFR* polymorphism resulting in a less functional variant appears to be associated with clinical depression (19).

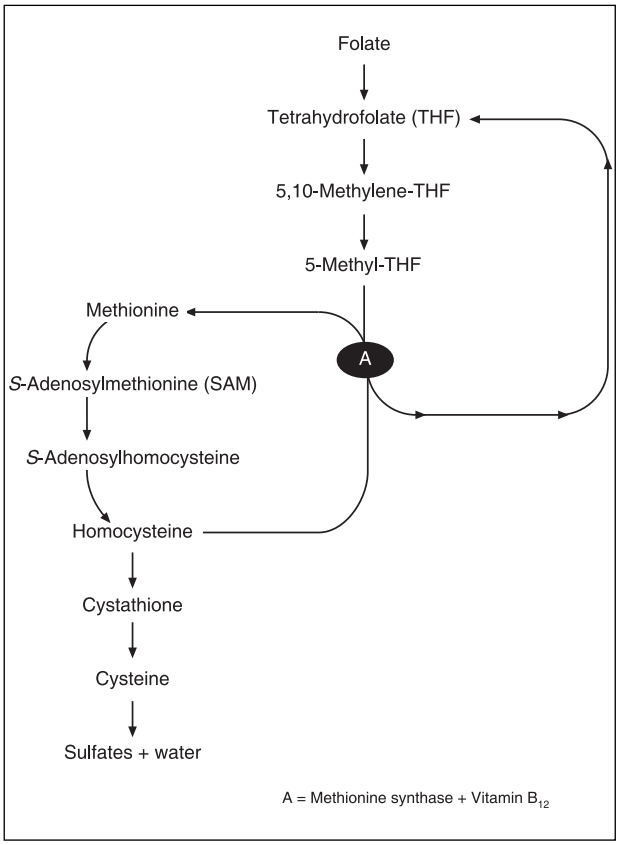

Fig. 1. Simplified representation of homocysteine metabolism in relation to the methionine cycle and the folate cycle.

Folate deficiency leads to hyperhomocysteinemia. Increased plasma homocysteine levels enhance the risk for vascular disease, including stroke (20). There is clinical evidence that depression is associated with stroke (21, 22) and folate intervention reduces the risk for stroke (23), most likely by lowering homocysteine levels. In addition, there is a relationship between homocysteine and neurotransmitter deficiency. Patients with high plasma homocysteine levels were found to have lower plasma

neurotransmitter metabolite concentrations (24). Moreover, elevated homocysteine levels also cause the dysregulation of various gene-specific promoters by abnormal methylation. Recent advances in epigenetics (modifications in gene expression not accompanied by a change in DNA sequences) consider the study of DNA methylation a major factor in understanding the cause of depressive disorders (25). Thus, folate deficiency resulting in abnormal methyl group transfer is considered an important biochemical process affecting the central nervous system. It is likely that it plays a pivotal role in the pathophysiology of clinical depression (26) (see BOX).

Folate and clinical depressive disorders

Following the initial publications by Reynolds *et al*. (27, 28), various observational studies have demonstrated elevated homocysteine levels in patients suffering from depression. Tiemeier *et al*. (15) evaluated a group of 4,730 participants in the Rotterdam Study. In their final study group comprising 3,884 elderly subjects (7% prevalence of depressive symptoms), they found that homocysteine levels, but not folate levels, were significantly related to depression severity. Another study comprised 412 participants, 60-64 years of age, and found that low folate and high homocysteine levels, but not vitamin B_{12} levels, were related to depressive symptoms (29).

Despite these intriguing results, few studies have used this information to investigate the efficacy and effectiveness of folate in the treatment of depression. The scientifically correct way to evaluate a possible role for folate is via a randomized, double-blind, placebo-controlled trial. A systematic review and meta-analysis by Taylor *et al*. (30) identified only three randomized interventional trials comprising 247 participants. Two studies found a statistically significant improvement for adding folate to drug treatment of depressive disorders, whereas the third study did not show a significant difference when folate alone was compared with trazodone (a serotonin modulator). A recent study by Gariballa and Forster (31) investigated the effect of dietary supplements on depressive symptoms in acutely ill older people in a randomized, double-blind, placebo-controlled trial. This supplement contained, among other things, folic acid and vitamin B_{12}. These authors found a statistically significant benefit on depressive symptoms in a group of 116 subjects on a normal hospital diet plus supplements compared to a group of 119 subjects on a normal hospital diet plus placebo.

Some considerations

There is evidence to suggest that folic acid supplementation improves the antidepressant action of conven-

BOX:

Unraveling the risk factors for disease is an important issue for future medical research. The risk for various disorders has been associated with elevated plasma homocysteine levels. Parts I-IV of this series deal with this subject.

Homocysteine is a sulfur-containing amino acid generated in the body during demethylation of methionine. Its plasma concentration can be modified by folic acid or folate intake in the presence of adequate vitamin B_{12} status. Interested readers are referred to Part I of this series and the references therein. In short, the major form of folate in human serum is methyltetrahydrofolate, which is involved in key metabolic functions such as nucleotide synthesis, DNA methylation and the generation of methionine. *S*-Adenosylmethionine (SAM) is formed from the latter compound. SAM is known as the methyl donor in a large variety of biochemical reactions. Folate shortage (via dietary insufficiency, but also due to alcohol abuse or hereditary factors) leads to depletion of SAM and higher plasma homocysteine levels.

Periconceptional folic acid supplementation confers protection against neural tube defects (spina bifida) and led U.S. health officials to decide to fortify flour and cereal grain products with folic acid 10 years ago. Indeed, a significant reduction in neural tube defects of up to 50% has been reported in countries where this fortification has been implemented, such as Canada, the U.S. and Australia.

Observational studies have related high homocysteine levels with neuropsychiatric disorders such as dementia and clinical depression. Numerous studies have shown that elevated homocysteine concentrations and folate deficiency correlate positively with higher depression scores and the severity of cognitive impairment. As discussed in the present article, the few interventional studies that have been reported show an improved antidepressant response when conventional pharmacotherapy is augmented with folic acid. As for cognitive function, there is firm evidence that folic acid supplementation prevents age-related deterioration.

With regard to cardiovascular disease, there is ample preclinical evidence that folate protects endothelial function and maintains vascular tone, playing a fundamental role in antithrombogenic, antiproliferative and antiinflammatory processes. There is epidemiological evidence from observational studies that elevated homocysteine levels are associated with an increased risk for cardiovascular disease. However, in randomized studies folic acid supplementation has failed to show a significant effect on the risk of cardiovascular disease, with the exception of the risk for stroke.

Its role in DNA synthesis and DNA methylation has led researchers to investigate the protective effect of folic acid supplementation in carcinogenesis. Animal models have demonstrated intestinal carcinogenesis under conditions of folate deficiency. Epidemiological studies in humans indicated that the intake of folic acid is associated with a lower risk for colorectal carcinoma. However, preclinical studies have also demonstrated that both hypo- and hypermethylation of DNA can cause genetic instability. Hypomethylation in essential genetic coding regions may result in dysfunctional tumor suppressor genes and DNA repair mechanisms. Aberrant hypermethylation may promote malignant proliferation. Thus, both folate deficiency and overuse of folic acid supplementation may increase the risk of cancer, and further research on the net effect of folic acid intake on carcinogenesis is needed.

tional pharmacotherapy. Coppen and Bailey (32) indicated already in 2000 that folic acid 'is a simple method of greatly improving the antidepressant action of fluoxetine and probably other antidepressants'. In their editorial, Abou-Saleh and Coppen (33) suggested that a well-tolerated dose of 2 mg of folic acid would sufficiently lower plasma homocysteine levels to confer a clinical effect. However, apparently no clinical trials have been conducted to prove the efficacy of this dose. Also, a tumor-promoting effect cannot be excluded with long-term use of this dose (34) (see BOX). Therefore, the question about the dosage has not yet been answered and a dose-finding trial followed by a long-term randomized, placebo-controlled study with sufficient power would be necessary to demonstrate the ability of folate to potentiate the action of standard antidepressants.

Much of the evidence that low folate status is associated with depression comes from observational studies and not from treatment studies. Observational studies cannot definitively determine whether folate supplementation has a positive effect on depressive disorders. However, a recent systematic review using only high-quality studies provided further encouraging evidence (35): a meta-analysis from 11 relevant studies comprising a total of 15,315 participants showed a significant relationship between folate status and depression even after correction for confounding factors (odds ratio [OR] = 1.42; 95% confidence interval [CI]: 1.10-1.83). This heartening result lays the foundation for future interventional studies, such as the randomized, controlled FoLATED trial to be carried out in 730 patients who will receive folate augmentation as new or continuing treatment (36).

Which patients are likely to benefit from folic acid augmentation? To answer this question it should be taken into consideration that the remission rate for patients on monotherapy suffering from nonpsychotic major depression is often below 40% (37). Patients who require more treatment steps often have higher relapse rates than those who reach remission at the first step of treatment. Therefore, augmentation strategies have been advocated for those who do not respond adequately to antidepressant monotherapy. Fava (38) illustrates the way a clinical psychiatrist envisions the role of folate: 'Folate augmentation can be used to enhance antidepressant efficacy from the start of treatment or [.....] can be used to boost antidepressant efficacy in an attempt to convert partial responders or nonresponders into responders or remitters'. Clearly, to provide solid ground for this thesis, appropriate trials are needed. It is worth the effort, as a positive outcome would represent a real step forward in the treatment of depression.

Disclosure

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