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ROLE OF FOLATE AND HOMOCYSTEINE IN NEUROPATHOGENESIS OF DEPRESSION

Psychiatry

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ABSTRACT

Depression is a major cause of morbidity worldwide and despite a number of treatment options a vast proportion of patients are treatment resistant. Folate and homocysteine have been implicated in the neuropathophysiology of depression; however, its therapeutic implications are still largely unexplored. The need of the hour is to develop a greater understanding about their role in pathogenesis of depression, so that potential preventive and treatment options can be established. This review focuses on previous studies investigating the association between serum levels of folate, homocystiene and depression. The authors suggest that there is strong published evidence for the association between lower levels of serum folate, higher levels of homocysteine and depression; however more prospective studies are required to establish casuality and treatment implications.

KEYWORDS

Depression, folate, homocysteine

INTRODUCTION

Depression is one of the most common mental illnesses with lifetime risk of 7%–12% for men and 20%–25% for women.[1] It is associated with significant morbidity and deterioration in quality of life and productivity. Although neurobiological, genetic and environmental factors have been implicated in the etiology of depression, still there is dearth of understanding regarding its exact neuropathogenesis. Main etiology of depression has been linked with under-activity of several monoamine neurotransmitters: dopamine, norepinephrine, or serotonin, collectively referred to as the trimonoaminergic neurotransmitter system. The current pharmacological treatments are primarily aimed at increasing the availability of one or more of these monoamines at the synapse by reuptake inhibition. Folate and homocysteine play a critical role in the synthesis and metabolism of these neurotransmitters. Studies have shown a link between folate deficiency and neuropsychiatric disorders, most commonly depression. More recently, the total plasma homocysteine level has been shown to be a sensitive marker of folate and vitamin B12 deficiency, and higher concentrations of homocysteine have been observed in depressed patients.

Hence, the purpose of this review is to elucidate the pathogenesis of depression by analyzing the association between folate, homocysteine levels and depression.

Pathophysiology and role of Folate and Homocysteine in Depression

Folate is a vitamin B that occurs naturally in food, such as green leafy vegetables, legumes, beans, citrus fruits, yeast, egg yolk, liver and kidney, as dihydrofolate. Folic acid is the term for the synthetic molecule, which is highly absorbed (85-95%) compared to the dietary form (50%). Dihydrofolate and synthetic folic acid are metabolized in the body into their biologically active isomer l-5-methyltetrahydrofolate (l-5-MTHF), also known as L-methylfolate (LMF)—the only form of folate that can cross the blood-brain barrier.[2] A key regulatory enzyme known as methylene tetrahydrofolate reductase (MTHFR) is involved in this conversion. Apart from neurotransmitter synthesis, it is also involved – via its donation of a methyl group – in numerous other biochemical pathways, including DNA biosynthesis, regulation of gene expression, amino acid synthesis and metabolism, and myelin synthesis and repair.

LMF modulates the synthesis of all three monoamines in a multi-step process. Firstly, LMF assists in formation of tetrahydrobiopterin (BH4), which is a critical cofactor for synthesis of monoamines. Secondly BH4 results in activation of rate-limiting enzymes Tyrosine hydroxylase and Tryptophan hydroxylase, for synthesis of serotonin, nor-epinephrine and dopamine.[3]

Thus L-methylfolate is a triamonoamine modulator (TMM) and indirect regulator of trimonomamine neurotransmitter synthesis and monoamine concentrations. This folate cycle plays a central role in increasing the synaptic concentration of these transmitters. This is believed to be one of the mechanisms of action for many of the antidepressants. Rather than blocking catecholamine reuptake as occurs with the SSRI/SNRI class of compounds, folate works at the presynaptic level to support catecholamine production.[2] Thus, L-methylfolate represents a therapeutic option in the management of depression by enhancing BH4 to increase monoamine synthesis.

Patients known to be at risk for suboptimal CNS folate status and monoamine deficiency include older individuals, individuals with a history of poor nutrition (chronic dieting, anorexia, bulimia), malabsorption syndrome, individuals with a history of tobacco use or excess alcohol intake, women of childbearing age, and individuals who take medications that interfere with folate metabolism (lamotrigine, valproate, oral contraceptives, etc). In addition, functional folate deficiency has also been linked to genetic variation in folate metabolism (including genetic variants in the gene MHTFR: C677T and A1298C).[2,3]

Homocysteine is a sulphur-containing, nonessential amino acid, derived from the essential amino acid methionine through demethylation. Homocysteine is remethylated to methionine via the 5-methyltetrahydrofolate pathway and this reaction is mediated by methionine synthase and vitamin B12 acts as a cofactor in this reaction. The methyl group is donated by 5-methyltetrahydrofolate through 5-MTHFR enzyme. Homocysteine can be condensed with serine to form cystathionine in a reaction that uses vitamin B6. Methionine is subsequently metabolized into S-Adenosyl Methionine (SAM). This metabolite is involved in numerous methylation reactions, involving proteins, phospholipids, DNA, and neurotransmitter metabolism.

Alteration in the level of homocysteine, either because of genetic abnormalities or due to the acquired/ environmental influences like low intake of vitamins involved in the metabolism, would theoretically correlate with the neurochemical abnormalities seen in the various neuropsychiatric disorders.

Folate and other B vitamins (B12 and B6) are closely connected with homocysteine metabolism such that total plasma homocysteine level is considered to be a sensitive marker of the functional deficiency of these vitamins. Also, homocysteine causes oxidative stress resulting in neurological and vascular damage and an interruption of the optimal biosynthesis of neurotransmitters.[3,4] As the folate cycle and homocysteine metabolism are intricately linked with the synthesis of neurotransmitter, their role in depression and related therapeutic

implications are of much interest.

Folate, Homocysteine levels and likelihood of Depression: A review of previous studies

The studies date back to 1967 when Carney et al estimated serum folate levels in 423 psychiatric patients and 22.5% had low folate levels (<2ng/ml).[5] Another study by the same author in 1978 examined serum folate and vitamin B12 status in 272 psychiatric in-patients and reported that low folate had greater association with depressed patients, while patients with low B12 levels had a greater association with psychosis.[6] In another study by Shorvon et al, it was reported that no less than 56% of patients with affective disorders had folate deficiency.[7]

Ghadirian et al (1980) studied 48 in-patients (depressed patients, psychiatrically ill but nondepressed patients, and medically ill patients).[8] They reported that depressed patients had significantly lower serum folate levels than did the patients in the other two groups, and patients with low serum folate levels obtained higher ratings on certain items of the Hamilton rating scale for depression (HAM-D). Similar studies by Abou- Saleh and Coppen (1986) found significantly lower serum and RBC folate in patients with major depressive disorder compared to healthy controls.[9] Leavitt and Joffe (1989) reported a significant correlation between serum folate and the severity and duration of depression in 44 unmedicated patients with depression.[10]

It needs to be noted that most of these earlier studies were cross sectional, had small sample size and comprised of heterogenous sample. Nonetheless, they found that a low folate status was associated with depression though a causal relationship could not be established.

An Australian study conducted in 2005 on 412 people aged 60-64 found low serum folate and high plasma homocysteine being associated with increased risk of depression.[11] The authors reported that being in the lowest quartile of homocysteine was associated with fewer depressive symptoms, after adjusting for sex, physical health, smoking, creatinine, folate and B12 levels. On the other hand, being in the lowest quartile of serum folate levels was associated with increased depressive symptoms, after adjusting for confounding factors.

In another cross sectional study done by Ng (2009) on 669 Chinese aged 55 or older, levels of folate and homocysteine were examined for their independent relationship with depressive symptoms.[12] Respondents with depression (n=178) had lower mean serum folate concentrations (21.5 nmol/L) than those without (n=491, 24.0 nmol/L, p=0.04). There was a linear relationship between descending quartiles of folate concentrations and increasing odds of association with depressive symptoms which was independent of other risk factors (demographic, psychosocial, alcohol and smoking, chronic morbidity, functional status, nutritional risk, albumin, anemia, depression-inducing medications, use of antidepressants and vitamin supplements). The odds ratio (OR) of association between low folate (lowest quartile:<14.6 nmol/L) and depressive symptoms independent of other risk factors, including homocysteine and B12, was 1.72. This study concluded that decreasing and low levels of serum folate were associated with greater risk of depressive symptoms in older Chinese adults.

Another U.S. based study done on 2524 adults aged 20-85 years found elevated depressive symptoms (PHQ score of ≥10) to be inversely associated with folate status, particularly among women, but not significantly related to total homocysteine.[13]

A Japanese study aimed to investigate the cross-sectional and prospective associations between serum folate concentrations and depressive symptoms.[14] In the cross-sectional analysis, serum folate concentration, analyzed in 545 subjects, were significantly associated with a decreased prevalence of depressive symptoms. A prospective analysis, done among 272 subjects without depressive symptoms at baseline showed serum folate concentrations at baseline to be significantly inversely associated with depressive symptoms after 3 years. These findings suggest that a higher serum folate may be associated with decreased risk of depressive symptoms.

In a 2014 study done in South India, 40 patients each with schizophrenia and depression and 40 healthy controls were recruited from the psychiatry department of a referral centre.[15] The mean total plasma homocysteine level was significantly higher in the depressed versus controls in males (p=0.04) but not in females (p=0.313). The plasma homocysteine levels increased significantly with the HAM-D score in a linear fashion ($p<0.001$) and also with the duration of the depression ($R=0.7$; $p<0.001$).

A pivotal meta-analysis from 11 studies with 15315 participants (1769 patients with depression and 13546 control subjects) was conducted by Gilbody et al (2007), which found strong association between low folate levels and depression (OR=1.55, 95% confidence interval 1.26 to 1.91). This association was present even after adjusting for confounding variables like age, gender, alcohol and tobacco intake, education, socio-economic status and medical condition.[16]

Apart from these studies which showed positive correlation between low serum folate and raised homocysteine levels and depression, a few other studies did not show a very strong correlation.

A case control study from Hong Kong (1998) found that patients with major depression (n=117) had a significantly lower mean serum folate level (24.6±10.2 vs. 30.3±11.4 nmol/l, $p<0.001$) but a higher mean erythrocyte folate level (801.8±284.6 nmol/l vs. 699.5±248.7 nmol/l, $p<0.01$) than control subjects. In this area, the traditional Chinese diet contains a high proportion of green vegetables and is hence rich in folate. Nevertheless, the study also showed that patients who responded well to lithium maintenance treatment had higher serum folate concentrations than those with unsatisfactory response ($p<0.05$).[17]

Another study by Penninx et al in 2000 did not show any significant correlation between serum homocysteine levels, folate levels and depression in 700 disabled, nondemented women aged 65 years and over.[18]

In a major study conducted as a part of the Rotterdam study, folate, vitamin B12, and homocysteine blood levels were compared in 278 persons with depressive symptoms (including 112 with depressive disorders) and 416 randomly selected reference subjects, all aged 55 years and over.[19] Adjustments were made for age, gender, cardiovascular disease, and functional disability. Hyperhomocysteinemia, vitamin B12 deficiency, and to a lesser extent, folate deficiency were all related to depressive disorders (but not with depressive symptoms). For folate deficiency and hyperhomocysteinemia, the association with depressive disorders was substantially reduced after adjustment for functional disability and cardiovascular disease, but for vitamin B12 this appeared independent. This population-based study showed a significant relationship of hyperhomocysteinemia and a nonsignificant relationship of folate deficiency to depression that were due to physical co-morbidity and cardiovascular risk factors in subjects with depression. Overall, it concluded that the relation of depression with folate was due to physical co-morbidity and cardiovascular factors.

Association between folate levels and treatment response, and use of Folate in treatment of Depression

In parallel to relation between folate levels and depression, the association between low folate levels and response or outcome of treatment has also been studied. Several studies show that lower folate levels are associated with poorer antidepressant response.[20-26] Further evidence suggests that baseline levels of folate within the normal range tend to predict antidepressant response. These findings raise the possibility of folate being used to augment antidepressants. A 2003 Cochrane review meta-analysis,[27] based on three intervention trials that compared folic acid or 5'-methyltetrahydrofolic acid to alternative treatments included 247 patients and concluded that folate may have a potential role as a supplement to other treatment modalities for depression, although it was not clear if this was the case both for patients with normal and low folate levels. In another recent meta-analysis of RCTs of folate which included 11 RCTs, it was found that the short-term use of vitamins (days to a few weeks) did not contribute to improvement in depressive symptoms in adults with major depression treated with antidepressants (5 studies, standardized mean difference= −0.12), but more prolonged consumption (several weeks to years) may decrease the risk of relapse (1 study, OR=0.33) and the onset of clinically significant symptoms in people at risk (2 studies, risk ratio=0.65).[28] The results of these meta-analysis suggested that treatment with folate and vitamin B12 does not decrease the severity of depressive symptoms over a short period of time, but may be helpful in the long-term management of special populations.

Conclusion

To sum up, the results from epidemiological studies have established a link between serum folate and homocysteine levels, and depression. However, most of these studies are cross sectional and largely from elderly or heterogenous populations. Also, a strong casual relationship has been difficult to establish because of confounding factors and reverse casuality. Additionally very few studies have longitudinally assessed these parameters and their association with treatment response. Folate is an essential nutrient involved – via its donation of a methyl group – in numerous biochemical pathways. Homocysteine is not only a sensitive marker of folate and/or B12 deficiency, but is also responsible for causing oxidative stress resulting in neurological and vascular damage and an interruption of the optimal biosynthesis of neurotransmitters. This review further suggests that dysregulation of pathway of one-carbon metabolism is an important implicating factor in the etiopathogenesis of depression and can be a potential target for treatment. More long term studies are required to explore the potential therapeutic implications of folate in depression.

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