Four decades ago, Victor Herbert [1] treated successfully his self-induced folate deficiency syndrome (insomnia, irritability, impaired memory and fatigue) by folate supplementation. However, our understanding of the role of folate in mental disorders is still insufficient to make practical recommendations. Most studies on folate and depression are cross-sectional and compare folate status in depressed patients with the status in patients with other mental disorders or in healthy subjects. These studies suggest that low folate status is associated with depression, especially with more severe forms, prolonged episodes and weak treatment response [2]. The limitations of these studies are related to a lack of longitudinal design, small sample size, highly selected patients and a lack of adequate control groups. Notably, two population-based studies [3, 4] controlling for possible confounders demonstrated no association between folate status and depression.

The population-based study by Morris et al. [5] published in this issue of *Psychotherapy and Psychosomatics* demonstrates an association between folate status and lifetime depression. However, the association was significant only in the group who had recovered from depression during the previous year, and not for the group of currently depressed subjects. They observed no association between low folate status and loss of appetite, weight loss or underweight, but rather a positive relation to overweight and weight gain. However, one certainly can question the diet quality in obese subjects.

Indications that folate deficiency increases the risk for depression have been obtained from biochemical and in vitro studies (fig. 1). Folate metabolism is linked to biotin-dependent neurotransmitter synthesis [6] and methylation of biogenic amines and phospholipids in the central nervous system (CNS) [7]. Homocysteine, or its metabolites, may have a direct excitotoxic effect on the N-methyl-D-aspartate glutamate receptors in the CNS, or may inhibit via S-adenosylhomocysteine the S-adenosylmethionine; THF = tetrahydrofolate.

---

**Fig. 1.** Components of one-carbon metabolism and CNS functions. Hcy = Homocysteine; Met = methionine; MS = methionine synthase; 5mTHF = 5-methyltetrahydrofolate; 5,10mTHF = 5,10-methylene-tetrahydrofolate; SAH = S-adenosylhomocysteine; SAM = S-adenosylmethionine; THF = tetrahydrofolate.
methionine (SAM)-dependent methylation of biogenic amines and phospholipids in the CNS [7]. Some smaller clinical trials suggest that SAM is superior to placebo in the treatment of depression [8].

In the study by Morris et al. [5], there was no association between serum total homocysteine and depression. Only one study [9] has shown such an association, while other studies have not [3, 10]. Cobalamin, or vitamin B₁₂, is a cofactor in the methylation of homocysteine to methionine, which in turn affects the levels of both homocysteine and SAM. Low serum levels of cobalamin have not been reported in depression [4, 10, 11], but there is a population-based study demonstrating elevated levels of the cobalamin marker, methylmalonic acid, among depressed physically disabled older women [3].

The C677T polymorphism of the methylenetetrahydrofolate reductase (MTHFR) gene, affects MTHFR activity and thereby folate distribution and homocysteine remethylation [12]. Inconsistent data on the relation between depression and the C677T MTHFR polymorphism have been obtained [13, 14]. In case such a relation can be confirmed, it provides strong evidence that altered folate status may precede the onset of depression.

Despite our incomplete understanding of the relation between methylation and mood, a number of clinical trials examining the effect of folate on antidepressant treatment have been conducted. Assuming no publication bias, the results are promising, though the samples are small, and in only four of the studies, patients were randomised to folate or control treatment [15–18]. The largest (n = 127) and better designed study [16] showed a significant beneficial effect only in women, but the lack of significance in males could be due to the small sample size or an insufficient dosage. Still, we do not know which patients should be supplemented with folate, the duration of treatment, the dosage required [2] and the safety of high-dosage folate supplementation [19].

In conclusion, there is some evidence that one-carbon metabolism is involved in depression, but more studies with a prospective design are required. Future work should include adequately sized double-blind randomised trials, and should address additional components of biological methylation (fig. 1), and dose-response relationship between B vitamins, metabolic markers and depression. Unfortunately, such studies of the US population may be of less value after the folic acid fortification program [20].

References


