

The Role of Abnormalities Related to the One Carbon Cycle in Depression and Schizophrenia*

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ABSTRACT

This paper reviews our present knowledge of the role of the one-carbon cycle in mood disorder and schizophrenia with particular attention to S-adenosyl methionine (SAM). After an historical introduction the clinical data is first reviewed of the anti-depressant action of SAM, in particular a survey of double blind placebo-controlled trials. Then follows an account of the biochemical parameters of the action of SAM, in particular the role of folic acid and 5-methyltetrahydrofolate (vitamin B9), polyamines, homocysteine, together with epigenetic studies. In schizophrenia the effect of oral l-methionine on worsening the symptoms of some chronic schizophrenics has been known since 1961. Recent epigenetic research covered has addressed the mechanism of this reaction. This includes the role of SAM in modulating DNA methyltransferase-1 mRNA activity, cytosine 5-methylation, spine numbers and the expression of mRNAs encoding for reelin and GAD67 in GABAergic neurons in the frontal cortex in schizophrenia. There is also evidence that marker D8S542 located within the methionine sulfoxide reductase (MSRA) gene may be involved in schizophrenia as well as 677C > T polymorphism in the methylenetetrahydrofolate reductase (MTHFR) gene. The possible roles of homocysteine and methionine S-adenosyl transferase kinetics are also discussed.

Keywords: One-Carbon Cycle; S-Adenosyl Methionine; l-Methionine; B Vitamins; Schizophrenia; Depression; Homocysteine; Reelin; Epigenetics

1. Introduction

The question of whether some abnormality in the one-carbon cycle might be related to psychiatric disease was first raised by Osmond and Smythies [1] in 1953. This paper put forward the first specific biochemical hypothesis of a possible biochemical lesion in this disease that proposed abnormal methylation of a catecholamine to produce a chemical relative of the psychotomimetic agent mescaline (3-methoxy-4,5-dimethyl dopamine). Although o-methylation turned out to be one of the normal routes of catecholamine metabolism no such further methylated products have been discovered in the body either in health or disease. However, the process of methylation has been linked to schizophrenia, depression and bipolar disorder in another way—in relation to the universal methyl group donor, S-adenosyl methionine (SAM).

SAM is synthesized from the essential amino acid l-methionine by the enzyme methionine adenosyltransferase (MAT). During the transmethylation SAM is converted to homocysteine in a two-enzyme step needing vitamin B6 (pyridoxyl phosphate). Homocysteine is then recycled

back to SAM in an enzymatic reaction that requires folic acid and vitamin B12 (cobalamin). Homocysteine is also converted to cystathionine in a reaction that needs vitamin B6 (pyridoxyl phosphate). S-adenosylmethionine is involved in numerous methylation reactions involving proteins, phospholipids, DNA, and neurotransmitter metabolism. Both folate and vitamin B12 deficiency may cause similar neurologic and psychiatric disturbances including depression, dementia, and demyelinating myelopathy [2].

2. Bipolar Disorder and Depression

2.1. Clinical Trials

There have been, over the last thirty years, a quantity of clinical studies of the anti-depressant effects of SAM. In the earlier period many of these studies were open studies of which the great majority had positive results. More recently several well controlled double-blind studies controlled against placebo (DBPC) or imipramine (DBIC) have been conducted.

Salmaggi *et al.* [3] conducted a DBPC 30-day trial of SAM (1,600 mg/day) in 80 postmenopausal women with a DSM-III-R diagnosis of major depression. They reported a significantly greater improvement in depressive symp-

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toms in the SAM group from day 10 of the study with only some mild and transient side effects. In a small DBIC study of 18 patients for 14 days, the result was that at the end of the second week 66% of the cases on SAM (i.m.i.) had significantly improved against 22% of cases on imipramine (oral) [4]. However, it must be noted that only “small” doses of imipramine were used. The same group [5] conducted a second DBIC 4-week trial of SAM against oral imipramine in 26 patients with a DSM-III-R diagnosis of major depression. At the end of the trial 62% of the SAM group, and 50% of the imipramine group, had significantly improved. Furthermore, in both treatment modes, all patients with a 50% decrease in HAM-D scores showed a significant increase in plasma SAM concentration.

A DBIC trial on 293 patients with a diagnosis of major depressive episode compared the effects of 400 mg of SAM (i.m.i.) with oral imipramine (150 mg) [6]. Both treatments were equally effective and the SAM group had significantly fewer side effects. The same group [7] reported the results of another similar study using 281 patients with a diagnosis of major depressive episode. The 90% confidence interval of the estimated difference between treatments was $\times 4.39$ and $\times 1.84$ (statistically insignificant). The results were similar to that reported for their other study [6]. In a DBPC study of 40 patients with a diagnosis of moderate to severe depression it was shown that SAM (200 mg/day i.m.i.) speeded the onset of action of imipramine [8]. CSF levels of SAM these have been found to be significantly lower in severely depressed patients, as well as Alzheimer’s patients compared with a neurological control group [9].

Some trials have reported that SAM appears to trigger an episode of mania. Kagan *et al.* [10] conducted a DBPC study in 15 inpatients with severe depression. The results “suggested” that SAM is a safe and effective anti-depressant. They noted, however, that one patient, with no previous history of mania, developed this condition on SAM. Lipinski *et al.* [11] in a small open trial of SAM reported improvement in 7/9 cases. However, 2 cases on SAM had an apparent induction of mania.

In 2010 the APA Task Force, after a comprehensive study of a number of complementary and alternative medical (CAM) treatments including SAM contained in the literature from 1965 to 2010, came to the conclusion that the results of DBPC studies were “promising” and merited larger and more rigorous studies.

3. Biochemical Parameters in the Effects of SAM in Depression

3.1. Epigenetic Studies

Ye *et al.* [12] studied several single nucleotide polymorphisms in genes involved in folate uptake, retention and metabolism in 976 adults in relation to the presence of

depressive symptoms. They reported that individuals with the TT and TC genotypes were 49% less likely (odds ratio = 0.51, 95% confidence interval = 0.29 - 0.89) to report mild depressive symptoms (CES-D score ≥ 16 and ≤ 26) and 64% less likely (odds ratio = 0.36, 95% confidence interval = 0.18 - 0.69) to report moderate to severe depressive symptoms (CES-D score > 26), compared with those with the CC genotype. They concluded that FOLH1 1561 > T polymorphism may be associated with depressive symptoms.

3.2. Homocysteine and B Vitamins

Folic acid deficiency occurs in up to one third of cases of severe depression [13]. Sensitive measures of folate deficiency are total homocysteine and vitamin B 12 levels. There are also links between folic acid deficiency and impaired metabolism of serotonin, dopamine and noradrenalin. On this basis In a study has been conducted by this group of 46 inpatients with severe DSM-III depression and 28 controls, of the depressed patients 52% had raised total plasma homocysteine as well as significant lowering of serum, red cell, and CSF folate, CSF S-adenosylmethionine and all three CSF monoamine metabolites. Total plasma homocysteine was significantly negatively correlated with red cell folate in depressed patients, but not controls [13]. The authors propose that these patients represent a nosological subgroup of depressive illness identified with folate deficiency, impaired methylation, and monoamine neurotransmitter metabolism.

Abou-Saleh and Coppen [14] in a review article suggested that folate deficiency, with or without concomitant deficiencies of other nutritional factors such as monoamine precursors, vitamins B6, B12 and C, may predispose to or aggravate psychiatric disturbances, particularly depression. 5-methyltetrahydrofolate (MTHF) is involved in the synthesis of SAM. In a 4-week open trial of MTHF, 81% of 16 patients with a DSM-III-R diagnosis of depression showed a markedly significant clinical improvement in their symptoms with no adverse effects [15].

3.3. Miscellaneous

A possible link with the dopamine system has been provided by the observation that methamphetamine administration results in lowered hepatic and blood levels of SAM in mice that correlate with striatal dopamine levels [16]. The antidepressant action of SAM has also been linked to an effect on polyamine metabolism. SAM is essential for the synthesis of polyamines, which have a key role in protein synthesis, cell proliferation, and neuronal plasticity. In a validated rat model of depression (chronic unpredictable mild stress-induced anhedonia), there is a significant reduction of putrescine, spermidine and spermine in the hippocampus, and of only putrescine in the

nucleus accumbens septi. SAM, at a fully antidepressant dose (300 mg/kg i.m.i. daily for 7 days), completely restored the levels of putrescine in the nucleus accumbens, and restored in part the levels of both spermidine and spermine in the hippocampus [17]. The authors state that their results suggest 1) a role for brain polyamines in depression and in reward processes, and 2) that the antidepressant effect of SAM may be due, at least in part, to a normalization of putrescine levels in the nucleus accumbens septi.

4. Schizophrenia

The connection between l-methionine and schizophrenia was discovered serendipitously by Pollin, Cardon and Kety [18] in 1961. They were interested in possible relations between brain amines and schizophrenia, so they administered a number of amino acids to patients together with isoniazid. The latter was included because they wished to prevent the amino acids from being metabolized by monoamine oxidase. The only amino acid that had any effect was l-methionine. This induced an exacerbation of psychotic symptoms in a proportion of cases.

4.1. Epigenetic Studies

There is evidence that marker D8S542 located within the methionine sulfoxide reductase (MSRA) gene is involved in schizophrenia [19]. By sequencing the *MSRA* gene in individuals carrying this haplotype, this group identified a novel 4-base pair deletion 1792 bases upstream of the *MSRA* transcription start site. This deletion was significantly under-transmitted to schizophrenia patients in the CVCR sample ($P = 0.0292$) using FBAT, and this was replicated in a large independent sample of 321 schizophrenia families from the Hispanic population ($P = 0.0367$). The authors suggested that these findings suggest a protective effect of the deletion against schizophrenia. A meta-analysis showed 677C > T polymorphism in the methylenetetrahydrofolate reductase (MTHFR) gene that resulted in reduced enzyme activity and, subsequently, in elevated homocysteine [20]. In addition, a meta-analysis of 10 studies (2265 cases and 2721 control subjects) on the homozygous (TT) genotype of the MTHFR 677C > T polymorphism was carried out to assess if this association is causal. The authors reported that a 5 μ mol/l higher homocysteine level was associated with a 70% (95% confidence interval, CI: 27-129) higher risk of schizophrenia. The TT genotype was associated with a 36% (95% CI: 7-72) higher risk of schizophrenia compared to the CC genotype [20].

Recently the important role of SAM in epigenetics has become evident since the essential reaction in epigenetics is the methylation of nucleotides in DNA. A recent review stresses that increasing evidence links genomic and

epigenomic instability, including multiple fragile sites regions to neuropsychiatric diseases including schizophrenia and autism [21]. The authors state, "The results of studies on genetic, epigenetic and environmental components of schizophrenia and autism point to the importance of the folate-methionine-transsulfuration metabolic hub."

Costa's group in Chicago [22] reported that the level of SAM is significantly increased in the prefrontal cortex in schizophrenia and bipolar disorder patients, but not in unipolar depressed patients. This is associated with an over-expression of DNA methyltransferase-1 mRNA. This may promote cytosine 5-methylation and down regulation of the expression of mRNAs encoding for reelin and GAD67 in cortical GABAergic neurons in these illnesses. Costa's group [23] also traced a link between the exacerbation of schizophrenic symptoms produced by l-methionine and the loss of dendritic spines in the frontal cortex that is characteristic of schizophrenia. This group showed that the decrease induced by l-methionine of reelin and GAD67 transcription in mice is prevented by valproate. L-methionine also decreases dendritic spine numbers and this too is prevented by valproate. These authors conclude that, "... down regulation of spine density in L-methionine-treated mice may be because of the decreased expression of reelin and that valproate may prevent spine down regulation by inhibiting the methylation induced decrease in reelin." (Note: These authors state that valproate inhibits histone deacetylases, and thus increases acetylated histone 3 and lysine 9,14 brain levels, remodels chromatin, and thereby 1) induces promoter demethylation 2) facilitates GABAergic gene transcription, and 3) prevents spine down regulation in L-methionine-treated mice).

In a review Krebs *et al.* [24] concluded that altered DNA methylation, abnormal glutamatergic transmission, folate deficiency and high maternal homocysteine levels (that all involve one-carbon metabolism) might be involved in the etiology of schizophrenia.

4.2. Homocysteine

Normal homocysteine (Hcy) serum level is maintained by remethylation of Hcy to methionine by enzymes that require folic acid and vitamin B12 and by catabolism to cysteine by a vitamin B6-dependent enzyme. Elevated homocysteine is often explained by folate dependency due to mutations in the gene for methylenetetrahydrofolate reductase (MTHFR). In a case-controlled study, Regland [25] found that a majority of schizophrenic patients had elevated methionine, and a smaller subgroup had elevated homocysteine in cerebrospinal fluid. The same group [26] reported a single case study of a 27-year old female schizophrenic patient, who had an increase serum level of homocysteine. She responded to injections of cobalamin (vitamin B12), and relapsed in between injections. In cultures fibroblasts MTHFR activity was severely reduced

which indicates a deficiency of folate with a consequent reduction of the conversion of homocysteine to methionine. Kale *et al.* [27] studied 31 medication-naïve first-episode psychotic (FEP) patients and 48 matched normal controls (HC). They reported significantly lower levels of folate and vitamin B(12) in plasma and folate in red blood cells in FEP compared to HC. These reductions paralleled the significant increase in plasma homocysteine and cortisol levels. Significantly reduced levels of membrane docosahexaenoic acid were also observed in FEP compared to HC.

In another single-case study Freeman *et al.* [28] reported homocysteinuria and homocysteinemia in an adolescent girl with folate-responsive schizophrenic symptoms. Enzymes in homocysteine-methionine metabolism were normal, but a defect in the ability to reduce N-5-10-methylenetetrahydrofolate to 5-methylenetetrahydrofolate was demonstrated to a level of 18% of control values. This would result in a deficiency of methionine and excess of homocysteine. In a preliminary study, Miodonik *et al.* [29] administered high doses of vitamin B6 (pyridoxyl phosphate: 1200 mg/day) to 11 patients with schizophrenia or schizoaffective disorder for 12 weeks. This resulted in a significant decrease of homocysteine levels in men but not in women.

Because SAM increases catecholamine inactivation by catecholamine-O-methyl transferase, Strous *et al.* [30] suggested that SAM should decrease aggressive behavior in certain patients. They tested this hypothesis in a DBPC trial of 18 schizophrenics with low activity COMT polymorphism with positive results

Smythies *et al.* [31] reported the effects on erythrocyte methionine adenosyltransferase (MAT) kinetics (V_{max}) of a 2-week treatment in a population of patients housed on a psychiatric research ward. On admission the drug-free schizophrenic patients and depressives had low V_{max} values, and the drug-free manic patients had high V_{max} values. After 2 weeks of appropriate treatment, the values for all three patient samples showed significant normalization (*i.e.*, the levels rose in schizophrenics and depressives and fell in manics). Reynolds *et al.*, [32]. argued that, as SAM has antidepressant properties and as the commonest neuropsychiatric complication of severe folate deficiency is depression, then methylation in the nervous system may underlie the expression of mood and related processes and may be implicated in some affective disorders.

5. Miscellaneous Studies

During a DBPC study of SAM in 20 depressed subjects over 14 days a highly significant fall in blood prolactin levels was reported [33]. Erythrocyte methionine adenosyltransferase (MAT) activity (V_{max}) and phosphatidylcholine levels (PC) are increased in drug free manic pa-

tients and decreased in drug free depressed and schizophrenic patients. Specific medication tends to normalize these levels [34]. In normal volunteers one week's DB administration of 400 mg p.o. of SAM reduced standing heart rate and plasma NE levels. Similar effects were produced by administration of MAOIs over the same period of time. However, unlike MAOIs, SAM did not induce any changes in plasma levels of the NE metabolite MHPG [35]. Low CSF SAM levels have been found in neurological disorders such as Alzheimer's disease, subacute combined degeneration of the spinal cord and HIV-related dementias [36]. A significant depression of methionine recycling with homocysteine occurs in blood when choline or creatine are infused [37]. SAM has been reported to have effects on the microviscosity of cell membranes that may be related to stimulation of phospholipid synthesis [38]. Vitamin B12 deficiency leads to a decrease of liver, but not brain, levels of SAM in the rat, and a decrease in the activity of methionine adenosyl transferase [39].

6. Conclusions

There is now a good case that patients diagnosed as suffering from depression should have their serum levels of folic acid, vitamin B 12 and homocysteine measured, and the appropriate measures taken if these are abnormal. A number of leading groups have presented evidence that SAM, particularly if given parenterally, is as good an antidepressant as imipramine. Further double blind controlled studies are needed to evaluate to what extent giving SAM together with a standard anti-depressant improves the clinical response above that achieved with the standard antidepressant alone.

In schizophrenia the transmethylating hypothesis in its new guise presents a promising avenue for further research [40].

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