Folic acid, S-adenosylmethionine and affective disorder

Two independent lines of evidence suggest that methylation processes in the nervous system may play an important role in some forms of affective disorder. In the last 15 years there have been reports of a particular association between folic acid deficiency and depression. More recently, several studies have indicated that S-adenosyl methionine (SAM) may have antidepressant properties.

FOLATE DEFICIENCY AND DEPRESSION

Folic acid deficiency may cause a variety of neuropsychiatric disturbances, most commonly depression (Reynolds, 1976; Botez & Reynolds, 1979; Shorvon et al. 1980). In 34 consecutive patients with megaloblastic anaemia due to folate deficiency affective disorder occurred in 56%, more than twice the incidence in a parallel series of vitamin B12 deficient megaloblastic patients (Shorvon et al. 1980). Treatment of the megaloblastic anaemia with the appropriate vitamin was more often accompanied by improvement of the associated neuropsychiatric disorder in the folate deficient than the vitamin B12 deficient patients (M. W. P. Carney, personal communication).

Surveys of psychiatric in-patient populations indicate that between 10 and 30% may have low serum folate levels (Carney, 1967; Hällström, 1969; Källström & Nylöf, 1969; Reynolds et al. 1970; Reynolds, 1976; Thornton & Thornton, 1978). The deficiency may be associated with various diagnostic categories but it is most commonly associated with depression (Carney, 1967; Reynolds et al. 1970; Reynolds, 1976). In a study of 100 consecutive admissions with depression low folate levels were found in 24% (Reynolds et al. 1970). The deficient patients had significantly higher depression scores, lower Marke-Nyman validity (psychic energy) scores and responded less well to conventional antidepressant therapy. A recent study of 107 out-patients with affective disorder attending a lithium clinic again confirmed that those with lower serum folate had a higher affective morbidity, both at the time of the folate assay and during the previous two years (Coppen & Abou-Saleh, 1982).

As psychiatric disorders, including depression, may lead to loss of appetite it is reasonable to suppose that very often folate deficiency is a secondary phenomenon. In others, drugs, including alcohol, barbiturates and anticonvulsants, may be important (Carney & Sheffield, 1970; Reynolds, 1976). However, not all the deficiency states can be attributed to these factors (Carney & Sheffield, 1970; Reynolds et al. 1970; Thornton & Thornton, 1977), and it seems probable that folate deficiency may play a primary role in some. Even when secondary to psychological illness the possibility of a vicious circle effect has to be considered (Reynolds, 1968, 1976; Botez et al. 1979 a). Carney (1979) reported in a retrospective survey that psychiatric patients treated with folic acid spent less time in hospital and made significantly better social recoveries than those in whom the deficiency was untreated.

The earliest studies of the association of folate deficiency and mental illness were on anticonvulsant treated epileptic patients, in some of whom the most striking effect of vitamin therapy was on mood, drive, initiative and sociability (Reynolds et al. 1966; Reynolds, 1967). It appeared as if the vitamin were partially reversing the retarding effects of the drugs (Reynolds, 1967), and similar improvement in mental function has recently been reported by reducing polytherapy in epileptic patients (Shorvon & Reynolds, 1979). There have, however, been negative trials of folate therapy in epilepsy (Reynolds,
1976), and the relationship of drug-induced folate deficiency to the complex psychological disorders of epilepsy is discussed elsewhere (Reynolds, 1981a, b).

Botez et al. (1976, 1979a) have described a syndrome of longstanding functional gastro-intestinal disorder, abnormal diet, occult malabsorption and folate deficiency associated with depression, lassitude, and minor neurological signs. In 24 patients folic acid was significantly better than placebo in improving various neuropsychological measures. In an open treatment study of 50 patients improvement in mood was reported as very good or good in 86%. Other neurological studies have emphasized the association of folate deficiency with depression and dementia, especially in the elderly (Reynolds, 1976; Thornton & Thornton, 1977; Runcie, 1979). The importance of folate in nervous system metabolism at all ages is also emphasized by the association of inborn errors of folate metabolism with mental retardation (Niederwieser, 1979).

Finally, it should be noted that, as with other metabolic stresses to the nervous system, only a proportion of folate deficient subjects develop neuropsychiatric disorders. As many as one third of those with a deficiency severe enough to produce megaloblastic anaemia did not have any nervous system complications (Shorvon et al. 1980). In milder deficiency states this figure is likely to be very much higher. Clearly, other factors are important in determining whether or not neuropsychiatric complications ensue (Reynolds, 1976). Further, although depression is the commonest manifestation, other less common features include organic mental states and peripheral neuropathy (Reynolds, 1976; Botez & Reynolds, 1979; Shorvon et al. 1980).

S-ADENOSYLMETHIONINE (SAM) AND DEPRESSION

In the last 5 years several trials have suggested that SAM has antidepressant properties. This observation arose inadvertently from the use of SAM, the normal methyl donor in brain, to study the transmethylation hypothesis of schizophrenia (Fazio et al. 1973, 1974). The antidepressant effects of SAM were confirmed in double-blind placebo controlled trials (Agnoli et al. 1976; Muscettola et al. 1982); SAM has also been reported to be as effective as chlorimipramine or amitriptyline in single-blind (Mantero et al. 1975; Del Vecchio et al. 1978) or double-blind (Miccoli et al. 1978; Kufferle & Grunberger, 1982) trials for 3–4 weeks. SAM was administered parentally in doses up to 200 mg daily and was reported to be remarkably free of side-effects, although occasional increases in anxiety or manic rebound have been described. Interestingly, the latter has also been noted rarely with folic acid administration (Reynolds, 1981b). SAM influences specific ‘core’ depressive symptoms, e.g. depressed mood, guilt, suicidal tendencies psychomotor retardation, work and interests, and is reported to have a more rapid action than conventional antidepressants, many patients showing significant improvement after 4–7 days. Preliminary experience in the UK (Carney et al. 1983) is in keeping with the Italian reports and further controlled trials are being undertaken in the UK and in the USA.

FOLATE AND SAM IN NERVOUS SYSTEM METABOLISM

Common interest in the observations on folate deficiency and depression, and on the antidepressant effect of SAM, is stimulated by knowledge of the intimate relationship between these two metabolites within and outside the nervous system (see Fig. 1).

The first step in the biosynthesis of SAM in the nervous system is the reduction of methylene tetrahydrofolate to 5-methyltetrahydrofolate (5-MTHF). This reaction is catalysed by methylene tetrahydrofolate reductase, which is the rate-limiting and key regulatory enzyme in this pathway to SAM which inhibits the enzyme (Kutzbach & Stockstad, 1971; Ordonez & Wurtman, 1973; Burton & Sallach, 1975). The next step involves the transfer of a methyl group from 5-MTHF to homocysteine to form methionine. The enzyme for this reaction is 5-MTHF-homocysteine methyltransferase and requires vitamin B$_{12}$ and SAM in catalytic amount (Spector et al. 1980). Finally, methionine is converted to SAM by the enzyme methionine adenosyl transferase (MAE).
A major function of folate-SAM interrelations is the synthesis of methyl groups in the folate cycle which are subsequently utilized by SAM as the methyl donor in many methylation reactions.

The relation between folate and SAM metabolism in brain has been demonstrated by in vivo experiments in which rats treated with a commercial folate-deficient diet had significantly lower cerebral levels of SAM than those on a standard diet (Ordonez & Wurtman, 1974). The administration of $L$-dopa, a methyl acceptor, lowered brain SAM to a greater extent in the folate-deficient than control rats. This suggests the existence of a homeostatic mechanism in brain capable of regenerating SAM by the re-methylation of homocysteine when demand for methyl groups is increased by the presence of methyl acceptors such as $L$-dopa.

Folate is present in brain in high concentrations, especially in the synaptic region (McClain et al. 1975), where it may be involved in neurotransmission (Hommes et al. 1979; Brennan et al. 1981). Methyl folate is the form which is actively transported into the nervous system (Spector & Lorenzo, 1975), where it has been shown in man to be concentrated in the cerebrospinal fluid (CSF) (Reynolds, 1979). CSF folate levels decline in the presence of folate deficiency (Reynolds et al. 1972). Folate derivatives, in particular the active co-enzyme forms, are potent excitatory compounds, especially if the efficient blood–brain barrier mechanism for the vitamin is circumvented (Hommes et al. 1979). The mechanisms of these excitatory effects are unknown.

Little is known about the transport or neurophysiology of SAM. However, a 2-week course of SAM in depressed patients led to a rise in CSF SAM levels, demonstrating the entry of this compound into the nervous system (Carney et al. 1983). Unlike folates, SAM is not convulsant but may indeed reverse the convulsant properties of the former in experimental models (O. R. Hommes, personal communication).
METHYLATION AND AFFECTIVE DISORDERS

How might the methylating function of folate and SAM in brain influence the expression of mood? There are several possible areas to be considered. There has been longstanding interest in transmethylation in relation to schizophrenia since Osmond & Smythies (1952) postulated the production in the brain of schizophrenics of abnormal methylated toxins. However, after 25 years of research such compounds have not been demonstrated (Smythies, 1977) and interest in the biochemistry of schizophrenia has switched to dopamine and other neurotransmitter hypotheses (Snyder, 1982). It seems to us unlikely that the psychotropic effects of SAM in depression could be related to the formation of abnormal psychoactive compounds. Indeed, as SAM is used in so many important methylation pathways in brain, involving amines, proteins, nucleoproteins, neurotransmitters and membrane phospholipids, it is unnecessary to postulate some aberrant metabolism which might underlie its mode of action.

There is already evidence of an effect of SAM and folate on brain monoamines which suggests to us a link between methylation and amine hypotheses of depression (van Praag, 1982). The administration of SAM increased the turnover of serotonin (5-HT) and noradrenaline in rat brain (Curcio et al. 1978; Algeri et al. 1979). Similarly, SAM increased CSF 5-hydroxyindoleacetic acid (5-HIAA) in depressed patients (Agnoli et al. 1977; Bottiglieri et al. 1983). Both folate deficiency or excess decreased brain 5-HT turnover in the rat and altered CSF amine metabolites in man (Botez et al. 1979). The mechanisms of these effects of SAM and folate on monoamine metabolism are uncertain. Another interesting possibility arises from the discovery by Axelrod and his colleagues (Crews et al. 1980) of two methyltransferase enzymes in brain and other tissues which methylate membrane phospholipids, using SAM as a methyl donor. Hirata & Axelrod (1980) suggest that phospholipid methylation is an initial common pathway for the transduction of many receptor-mediated biological signals through membranes. It is thus possible that changes in neurotransmitter function, receptor sensitivity (e.g. noradrenaline) or endocrine function in depression may be mediated by disturbances in membrane function and may be modified by the administration of SAM. Cimino et al. (1983) have shown that 3 months treatment with SAM in senescent rats restored membrane fluidity to control values and significantly increased beta receptor activity in brain striatum. Furthermore, the combination of a beta adrenergic stimulant and SAM was more potent than a beta stimulant alone in the treatment of depression (Manna et al. 1982).

SAM is also required for the methylation of proteins and nucleoproteins. There are no data linking this specifically to mood or depression, but it is interesting that in bacteria it has been shown that carboxyl-methylation of proteins is essential for behavioural control mechanisms and signal transduction (Springer et al. 1979).

It may simply be that the ubiquitous influence of methylation in so many different essential metabolic reactions in the nervous system is more important than any single postulated mechanism in influencing mood and related functions.

CONCLUSION

It is remarkable that (1) deficiency of folic acid, a vitamin with excitatory properties, should most commonly lead to depression; and that (2) a closely related metabolite, SAM, should have antidepressant properties with few side-effects. These separate and independent observations suggest that methylation processes in the nervous system may underlie the expression of mood and may be implicated in some affective disorders. Clearly, further controlled studies are required, especially of the effects of treatment with folic acid and SAM in depression. If substantiated, the observations that we have reviewed have important research and therapeutic implications in psychiatry (Reynolds et al. 1983).
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