The transmethylation and one-carbon cycle hypotheses of schizophrenia

The current literature contains a degree of confusion over the nature and origins of the transmethylation hypothesis of schizophrenia, partly occasioned by the fact that there are two quite different transmethylation hypotheses.

The first (TMH I) has been variously attributed to Osmond & Smythies (see e.g. Kety, 1959; Gillin et al. 1976), to Osmond, Harley-Mason & Smythies (see e.g. Smythies, 1967), and to Harley-Mason (see e.g. Smythies, 1960; Baldessarini et al. 1979). In the literature to date, 63 references for TMH I are given to Osmond & Smythies, 10 to Osmond, Harley-Mason & Smythies, and 6 to Harley-Mason. None of these is, however, correct. The facts of the matter are as follows. TMH I was the result of a single chain of observations and deductions carried out by four people, each of whose contribution was essential to the final formulation of the hypothesis as detailed in the following sequential time sequence:

1. The observation that the molecule of mescaline appeared to resemble some familiar compound (Smythies);
2. The identification of this compound with adrenaline (Redmill);
3. The observation that the clinical syndrome produced in some individuals by mescaline closely resembles the clinical syndrome seen in certain acute cases of schizophrenia (Osmond & Smythies);
4. The hypothesis that schizophrenia might result from some abnormality of adrenaline metabolism with the production of mescaline-like compounds in the brain (Osmond & Smythies);
5. The biochemical details of how such a metabolic error might occur (Harley-Mason).

Clearly, in such a process, it would be invidious to refer to any other than all those cooperatively responsible as "the author" of the TMH I. In order to make referencing as easy as possible, in view of the fact that the listed authors of this paper are Osmond & Smythies, I would suggest that the correct attribution and reference for TMH I should be: Osmond, H., Smythies, J., Harley-Mason, J. & Redmill, J. (1952). Schizophrenia: a new approach. Journal of Mental Science 98, 309-315.

The current relevance of TMH I does not lie in its 'correctness' for, of course, there is no evidence that schizophrenia is associated with the presence in the brain of mescaline-like compounds. Hallucinogens (methylated derivatives of tryptamine in the form of dimethyltryptamine (DMT), and O-methylbufotenin (OMB)) have been identified in human CSF and rat brain by definitive gas-chromatography/mass-spectrometry (GC/MS) methodology (Smythies et al. 1979), and in urine by GC methodology (Checkley et al. 1979), but the differences between schizophrenics and normal controls were only minor and much higher levels were seen in cases of liver disease without psychosis. Experiments by Harrison (1982) have shown that rat brain DMT and OMB levels are significantly increased by stress (pain, immobilization) and that this does not occur if the adrenals are removed, suggesting a physiological role related to stress rather than psychosis for these endogenous hallucinogens. Developmental studies by Beaton & Morris (1982) have shown that rat brain DMT and OMB levels increase rapidly from birth to around the 17th day and then decrease to low levels. Thus, DMT may have a significant role in the brain, but it does not appear to be directly related to the pathogenesis of schizophrenia.

The significance of TMH I arises (a) because of the impetus it gave to the use of hallucinogens in psychiatric research, and (b) because it presented the first formulation of the hypothesis that catecholamines might be O-methylated in the body, which adumbrated the later discovery of

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metanephrine and catechol-O-methyltransferase. It is noteworthy that the formula of the 4-methoxy-3-hydroxy isomer of metanephrine was printed for the first time in our 1952 paper.

The second transmethylation hypothesis (TMH II) (which should now be called the ‘one-carbon cycle’ hypothesis to avoid confusion) suggests that the biochemical fault in one of the schizophrenias might lie in the biochemical mechanism itself of transmethylation – namely the one-carbon cycle, in which methionine, S-adenosylmethionine (SAM) and folic acid are involved – rather than any abnormally methylated products. This hypothesis was first put forward in 1966 (Smythies, 1966), as follows: ‘The removal and addition of methyl groups is an operation of fundamental importance to the organism, and any fault in it might be expected to have a serious effect on the activity of neurons.’ The current evidence to support such a defective methylation system in schizophrenia is as follows:

1. Some 40% of chronic schizophrenics react by developing an acute psychotic reaction to 20 G/day of L-methionine. This reaction has been reported by ten groups with no reported failures to replicate, which makes it unique in the annals of schizophrenia research (see Cohen et al. 1974, for a review). In our study (Antun et al. 1971a), we found that in most cases the psychosis closely resembled clinically a schizophrenic reaction. In three out of the twelve cases, the patients were clearly delirious initially for some 48 hours, but they then reverted to a schizophreniform psychosis. Unfortunately, we do not know how manic-depressives would respond to methionine, and not enough careful studies have been carried out in normals. Furthermore, the experiment needs to be repeated in schizophrenics using modern methods of monitoring clinical status. However, the important point is that some 40% of schizophrenics respond dramatically to methionine and 60% do not. It would seem, therefore, worthwhile to find out by what mechanism methionine induces this effect and in what other ways methionine-sensitive schizophrenics differ from methionine-insensitive schizophrenics.

2. Ismail et al. (1978) showed that the C14 labelled methyl group of methionine converts abnormally slowly to C14O2 in schizophrenic cells, suggesting a possible defect in the one-carbon cycle. One might naively suppose that, since methionine is the ultimate source of all the methyl groups used in transmethylation reactions, these clinical effects of methionine might be due to an overpromotion of transmethylation reactions. However, methionine (a) did not increase urine levels of methylated metabolites of catecholamines in humans in our study (Antun et al. 1971b), and (b) did not increase SAM levels in human blood, had no effect on methylation of tritiated levadopa in rodent tissues, and actually decreased the production of DMT by rabbit lung, possibly due to end-product inhibition by homocysteine, a potent inhibitor of transmethylation reactions (Stramentinoli & Baldessarini, 1978; Schatz et al. 1981; Baudry et al. 1973). Hence, it may well be that the ‘methionine effect’ in chronic schizophrenics might be due to a further inhibition of an already defective transmethylation system. This hypothesis can be tested by measuring both (a) Vmax levels of MAT and SHMT (see below), and (b) conversion rates of the C13 labelled methyl group of methionine to C13O2 using GC/MS methodology in methionine-sensitive and methionine-insensitive schizophrenics.

3. Kinetic analyses over a period of five years by our group (Carl et al. 1978; Kelsoe et al. 1982) have shown that the Vmax of methionine adenosyltransferase (MAT) and serine hydroxymethyltransferase (SHMT) are significantly underactive in schizophrenics, whereas four other enzymes of the one-carbon cycle showed no changes. Moreover, the patients (except one) low in MAT activity were not those with low SHMT activity, indicating two possible subgroups. Preliminary results indicate that a low Vmax activity for SAM is also seen in patients with major affective (depressed) patients, whereas manics show high values, suggesting a state rather than a trait change (Tolbert et al. 1983). An earlier observation by Sprince et al. (1965) is of interest. They showed that excess methionine intake in rats decreased urinary output of methylnicotinic acid and increased urinary indoleacetic acid excretion, due possibly to a block of methylation of nicotinic acid on the kynurenine pathway of tryptophan metabolism and a resultant augmentation of the rival pathway to tryptamine and indoleacetic acid.

It is also possible that endogenous O-methylated derivatives of catecholamines may have some physiological properties, as was first suggested by Smythies (1969) (rather than being inert excretory
products, as is commonly supposed). Furgeson et al. (1976) have presented evidence that the dyskinesia, but not the stereotyped behaviour, induced by dopamine may actually be due to methoxy derivatives as it is abolished by inhibitors of catechol-O-methyltransferase. A link between the transmethylation and dopamine hypotheses is suggested by the report of Le Fur et al. (1981). They found that low doses of dopamine stimulate phospholipid methylation. They further state that incubation of mouse B-lymphocytes with l-methionine unmasks cryptic dopamine receptors—a response depending on phospholipid methylation.

Transmethylation reactions are now recognized to represent a widespread biochemical mechanism. Transmethylation of the carboxyl groups of proteins by carboxymethylases has been shown to affect neurotransmitter release and the chemotactic behaviour of Escherichia coli. In this organism a carboxymethylase has been shown to be a key factor in the development of habituation to chemical stimuli (Springer et al. 1979; Smythies, 1980). Chemical attractants increase methylation and decrease demethylation, whereas chemical repellants have the reverse effect (Toews et al. 1979; Kleene et al. 1979). Transmethylation of lipids has been shown to be an essential step in many membrane reactions, including coupling of adrenergic and other receptors to adenylyl cyclase, histamine release by immunoglobulin E antigens, nerve growth factor responses and others (Strittmatter et al. 1979). Transmethylation of histones, DNA and RNA play an important role in gene expression, DNA repair, mutation, DNA replication and recombination (Doerfler, 1981; Cato & Burdon, 1979). Thus, a defect in methylation even at the kinetic level might have widespread effects on brain and behaviour.

REFERENCES


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