Abnormal *O*-methylated dopamine metabolites: the endogenous toxins of schizophrenia or parkinsonism?

In spite of much work that would suggest the involvement of 3,4-dimethoxyphenethylamine (DMPEA) and its derivatives in either schizophrenia (Takesada, Kakimoto & others, 1963; Takesada, Miyamoto & others, 1965; Creveling & Daly, 1967) or in parkinsonism (Barbeau, de Groot & others, 1963), the issue remains confused, particularly when other reports claim DMPEA to be present in normal controls (Rinne & Sonninen, 1967) and only in small amounts in parkinsonian patients (Boulton & Felton, 1966).

Although the original report of Friedhoff & Van Winkle (1962) that DMPEA is present in the pink spot of schizophrenic urine is now largely discredited, the transmethylation theory suggesting aberrant *O*-methylation still has wide support (Himwich, Narasimhachari & others, 1970). Indeed, both DMPEA and its *N*-acetyl derivative NADMPEA are known to produce behavioural changes in animals, the latter being the more potent (Bindler, Sanghvi & Gershon, 1968; Friedhoff & Schweitzer, 1968). Although these compounds possess the 4-methoxy group necessary for psychotomimetic activity, neither DMPEA nor NADMPEA produce the hallucigenic effects of the structurally similar mescaline when administered orally to man.

In addition, reports claiming that DMPEA is present in parkinsonian urine have been supported by Ernst (1965), Barbeau, Tetreault & others (1966) and Shulgin, Sargent & Naranjo (1969) who showed in animal studies, used as a model for parkinsonism, that DMPEA, 3-hydroxy-4-methoxyphenethylamine (3HMPEA) and mescaline produced the characteristic akinesia in rats.

A recent report by Barrass, Coult & Pinder (1972) showed that 3HMPEA but not the isomeric 4HMPEA nor DMPEA itself increased dopamine oxidation and inhibited 5-hydroxytryptamine (5-HT) oxidation *in vitro*. It was suggested, therefore, that 3HMPEA could be the endogenous toxin in parkinsonism producing akinesia and causing an imbalance in the dopamine: 5-HT ratio. Since DMPEA as well as 3HMPEA produces akinesia in lower animals, the position is clearly complicated. Also, in parkinsonism the substantia nigra, an area of the brain where the biochemical lesion could occur, is reported to be *depleted* of melanin deposit (Hornykiewicz, 1966) whereas increased dopamine oxidation would lead to *increased* melanin pigmentation.

We wish to draw attention, therefore, to the contentious role of *O*-methylated derivatives of dopamine in schizophrenia and parkinsonism. The possibility must now be considered that such abnormal metabolites are involved in both diseases. We consider it plausible that 3HMPEA and DMPEA may play a dual role for the following reasons:

(1) Both metabolites produce akinesia in animals and may conceivably thus produce the similar syndrome observed in parkinsonism.

(2) Both DMPEA and the more potent NADMPEA effect behavioural changes in animals although neither appear to have the hallucigenic activity of mescaline. Although no evidence is yet available it is possible that these compounds do not accumulate in the brain in sufficient amounts after oral administration. Should they be synthesized in the brain by abnormal methylation, then psychotomimetic activity may well be observed. Certainly NADMPEA can be produced *in vitro* by brain extracts (Friedhoff, Schweitzer & Miller, 1972) and by pineal homogenate (Hartley & Smith, 1973).

Such a dual role theory would need to explain why the hallucigenic and akinetic activities are not seen in both diseases simultaneously. In parkinsonism, the absence of psychotomimetic activity might well be due to low levels of 3HMPEA and DMPEA which is consistent with the low levels of dopamine associated with the condition.

Treatment with L-dopa is reported to produce psychotomimetic side-effects (Jenkins & Schweiger, 1971). In schizophrenia, the high dopamine levels in the extrapyramidal system could produce sufficiently high levels of DMPEA for hallucigenic activity and at the same time antagonize the akinetic effects as seen in animal studies (Ernst, 1965). This is supported by the fact that neuroleptic drugs used in the treatment of schizophrenia, effectively reduce dopamine levels by increasing its turnover rate and are well known to produce a parkinsonian syndrome as a side-effect (Ayd, 1961).

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Blood-brain barrier to carbidopa (MK-486) and Ro 4-4602, peripheral dopa decarboxylase inhibitors

L-α-Methyldopa hydrazine (α-methyl-α-hydrazino L-3,4-dihydroxyphenylpropionic acid, MK-486, carbidopa, Merck) and *N'*-(DL-seryl)-N^2-(2,3,4-trihydroxybenzyl) hydrazine Ro 4-4602 are powerful inhibitors of dopa decarboxylase *in vitro* and *in vivo*. Previous studies have indicated that these compounds do not cross the blood-brain barrier easily (Bartholini & Pletscher, 1969; Bartholini, Blum & Pletscher, 1969; Kuruma, Bartholini & others, 1972; Lotti & Porter, 1970). Porter, Watson & others (1962) found little or no radioactivity in the brains of rats given 5 mg kg^{-1} 1-[^{14}C]-DL-carbidopa intraperitoneally. For this reason they have been used to advantage in patients with Parkinson's disease receiving L-dopa, because they reduce peripheral loss of L-dopa and markedly reduce the doses of L-dopa needed for therapeutic effects.

We thought that it would be useful to directly measure their ability to cross the blood-brain barrier.

One approach to the problem of drug permeability is the oil-water partition coefficient method described by one of us (Dewhurst & Marley, 1965). It is based on the