

Altered consciousness states and endogenous psychoses: a common molecular pathway?

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Abstract

Interest in the role of indolamines in the pathogenesis of psychoses has been renewed in recent years by the development of atypical antipsychotic drugs such as clozapine, olanzapine, and risperidone, which act on serotonin receptors. Discovery of the hallucinogenic compounds called methylated indolealkylamines (MIAs) (e.g. *N,N*-dimethylserotonin, or bufotenin, and *N,N*-dimethyltryptamine, or DMT) led proponents of the transmethylation hypothesis of schizophrenia to theorize that through some inborn error of metabolism, serotonin or tryptamine might undergo the addition of extra methyl radicals, thereby forming MIAs with hallucinogenic properties. Various studies have attempted to detect the excretion of MIAs, especially DMT, in the body fluids of psychotic patients and normal controls. Some of these studies have demonstrated elevated MIA concentrations in psychotic patients, including those with schizophrenia, compared with normal persons, and others have not. A number of variables may account for these contradictory findings. The mechanism whereby the beverage ayahuasca, which is used in certain cure and divination rituals in the Amazon Basin, exerts its hallucinogenic effects may serve as a model to explain the mechanism underlying hallucinogenic symptoms in schizophrenia and may lend support to the transmethylation hypothesis. Certain studies suggest that specific perceptual disturbances manifested by schizophrenic patients could contribute to progressive deterioration and negative symptomatology. All these findings point to the need for further study of the neurophysiology of MIAs and their pathogenetic role in endogenous psychoses. © 1997 Elsevier Science B.V.

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1. Introduction

The observation that endogenous psychoses such as schizophrenia and drug-induced hallucinogenic states have some similar features has been of interest for many years. A number of hallucino-

genic drugs are indolamine derivatives and exert strong effects on serotonergic neurotransmission (Fischman, 1983). However, because the mechanisms involved are complex and pose a challenge to investigators, little effort was made until recently to study the possible role of indolamines in the pathogenesis of psychoses. Interest in this field has been rekindled by the realization that atypical antipsychotic drugs (e.g. clozapine, risperidone,

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olanzapine) possess a different mechanism of action from traditional neuroleptics. These new drugs act on serotonin (5-HT) receptors, among others, a phenomenon that contributes to their unique pharmacologic and clinical profile (Jackson et al., 1993).

2. The transmethylation hypothesis

The transmethylation hypothesis was the first specific hypothesis of the biochemical etiology of schizophrenia. It was extensively explored by Osmond and Smythies (1952), Friedhoff and Van Winkle (1964), Stam et al. (1969), Fischer (1970), Fischer et al. (1971), Saavedra and Axelrod (1972), Smythies (1983), and Ciprian-Ollivier et al. (1988). This theory was based on the observation that hallucinogenic drugs like mescaline, psilocybin (Wolbach et al., 1962), and lysergic acid diethylamide (LSD) are chemically similar to certain neurotransmitters, such as the catechol and indole groups (Fischman, 1983). According to the theory, an inborn error of metabolism might cause some cases of schizophrenia by producing a hallucinogenic substance in the body similar to mescaline.

3. Methylated indolealkylamines

Several years later, discovery of a new group of hallucinogens permitted further refinement of the transmethylation hypothesis. These compounds were the methylated indolealkylamines (MIAs) *N,N*-dimethylserotonin (*N,N*-DMS), or bufotenin; 5-methoxy-*N,N*-dimethyltryptamine (5-MeO-DMT); and *N,N*-dimethyltryptamine (*N,N*-DMT), or DMT. Bufotenin derives from serotonin and DMT from tryptamine, by the action of the enzyme indolamine *N*-methyltransferase (Fig. 1). On pharmacologic testing, all these MIAs were found to have strong hallucinogenic properties (Keup, 1970; Kleinman et al., 1977). In fact, synthetic DMT is an abused drug in the United States. Recently, its psychogenic effects in human beings were carefully evaluated by Strassman (Strassman et al., 1994; Strassman and Qualls, 1994). Proponents of the transmethylation hypoth-

esis theorized that through some inborn error of metabolism, serotonin or tryptamine might undergo the addition of extra methyl (CH₃) radicals, thereby forming derivatives (MIAs) with hallucinogenic properties.

In 1972, Saavedra and Axelrod demonstrated that tryptamine, the precursor of DMT, is present in the human brain (Saavedra and Axelrod, 1972). Subsequently, several papers were published that discussed the difficulties in detecting these compounds in urine and blood samples from schizophrenic patients and controls (Murray et al., 1979; Kärkäinen et al., 1988). Detection is difficult because of the rapid and complex metabolism of these compounds (Hryhorczuk et al., 1986; Sitaram and McLeod, 1990). However, some of the studies in which these MIAs, especially DMT, were isolated and identified with proper biochemical methods (Räsänen and Kärkäinen, 1979) demonstrated that MIAs were present in abnormally high concentrations in psychotic patients, compared with controls (Tanimukai et al., 1970; Rodnight et al., 1976; Murray et al., 1979; Checkley et al., 1980).

In a study of urinary excretion of DMT in 122 psychiatric patients and 20 normal subjects, Rodnight et al. (1976) detected DMT in 47% of those diagnosed as schizophrenic, 38% of those diagnosed with other non-affective psychoses, 13% of those diagnosed with affective psychoses, 19% of those diagnosed with neurotic and personality disorders, and 5% of the controls. These results appear to confirm a relationship between DMT excretion and schizophrenia, but a study of the psychopathology of the patients did not suggest that any specific schizophrenic symptoms were major determinants of DMT excretion. Instead, there seemed to be a general link between DMT detection and a range of psychotic syndromes.

Using a modified gas chromatography-mass spectrometry (GC-MS) isotope dilution assay, Angrist et al. (1976) checked for the presence of DMT in the venous blood of 19 schizophrenic patients, one alcoholic with endogenous depression, and 17 controls. Although the mean level of DMT was higher in the total patient group and acutely psychotic patients than in the controls, the differences were not statistically significant.

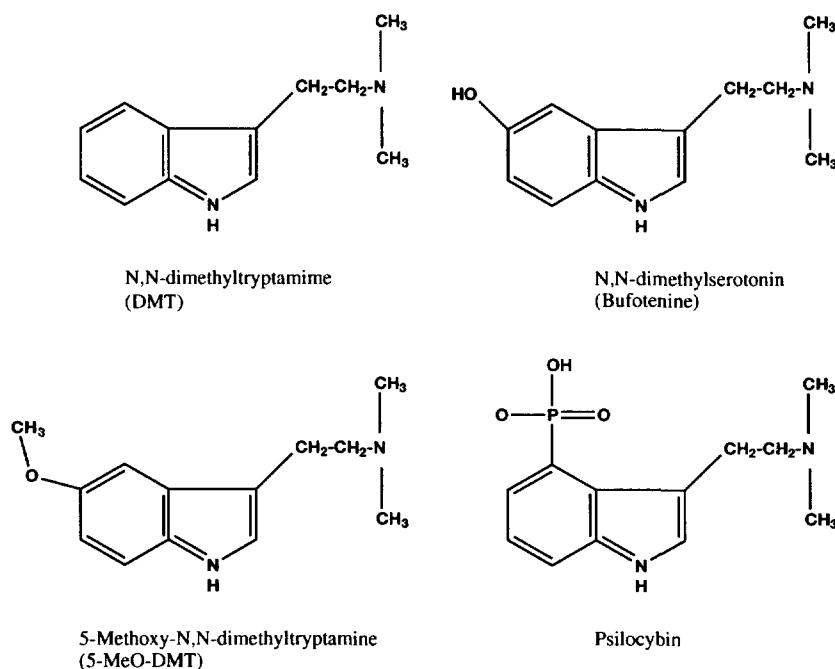


Fig. 1. Methylated indolealkylamines. The vegetal hallucinogen psilocybin is displayed in order to highlight molecular similarities.

However, the investigators suggested that testing cerebrospinal fluid (CSF) for DMT might be more informative than testing venous blood, because DMT metabolizes rapidly in human beings. The authors also pointed out that DMT might be produced episodically rather than continuously; if so, the wide variations in DMT concentrations noted in different studies would not be surprising.

Corbett et al. (1978), using a highly sensitive GC assay, tested the CSF of 50 schizophrenic patients and 41 non-psychiatric patients for the presence of DMT and 5-MeO-DMT. Although the concentrations of these MIAs were higher in the schizophrenic patients than in the controls, the differences were not statistically significant. However, DMT concentrations in six of the acute schizophrenic patients were higher than the highest control value, and a different group of six schizophrenic patients had higher 5-MeO-DMT values than controls, suggesting that meaningful subgroups of schizophrenic patients might exist.

The results of several other early studies failed to support the theory that MIA concentrations are higher in the body fluids of psychotic patients than

in those of normal persons. In a carefully controlled trial, Carpenter et al. (1975) measured the concentration of bufotenine and DMT in the urine of 26 acutely psychotic schizophrenic patients and 10 controls but did not find MIAs present more often in the schizophrenic patient group. Gillin et al. (1976) reviewed the current evidence on the role of DMT as a 'schizotoxin'. They concluded that although the transmethylation model of schizophrenia is appealing, most of the evidence is indirect and the model fails to meet Hollister's criteria as modified by Wyatt and Gillin (1976). Luchins et al. (1978), in a review of the studies done to date on the presence of DMT and other MIAs in human body fluids, concluded that although N-methylated indolamines can be produced in vivo and have significant psychomimetic effects, there is little evidence of a generalized increase in transmethylation in schizophrenia or of a more specific increase in the methylation of indolamines.

In a review of the transmethylation hypothesis and of studies on the association between schizophrenia and DMT excretion, Smythies (1979)

explained that his version of the hypothesis centers on the transmethylation process itself rather than the production of MIAs. Smythies noted that in some types of schizophrenia, transmethylation processes may be underactive rather than overactive, leading to defective protein synthesis in the brain and schizophrenic symptoms.

Using GC–MS methodology, Smythies studied DMT concentrations in the CSF of 11 subjects with different psychiatric or medical disorders. The highest DMT concentration was in a patient with diffuse liver disease, and the next highest in a patient with chronic schizophrenia. Another patient with schizophrenia (acute) also had an elevated DMT concentration, but an acute catatonic schizophrenic patient enrolled in the study had a very low concentration, even lower than those of the medical patients. Smythies speculated that DMT may have a normal function as a neuroregulator in control of some pain, stress, or emotional reaction and that disturbances in these reactions might be somehow related to schizophrenia.

Murray et al. (1979) studied primary DMT excretion in 74 psychiatric patients and 19 normal controls. Although excretion tended to be greatest in patients with schizophrenia, mania, and ‘other psychosis’ and to decline with improvement in patients’ clinical state, the differences in excretion were significant only for those patients with ‘other psychosis’. These differences were quantitative rather than qualitative and not absolute; that is, normal persons also excreted DMT but in smaller amounts than many acutely psychotic patients. Syndromes suggesting elation, perceptual abnormalities, and difficulty in thinking and communicating had the highest correlation with elevated urinary DMT excretion. The investigators concluded that it seems unlikely from the evidence to date that DMT is causally related to psychosis. Rather, increased DMT might be the consequence of some psychoses, an intermediary factor produced by some ill persons, or a chemical marker for increased transmethylation and increased circulation of some psychotoxin not yet detected. Checkley et al. (1980) reported very similar findings to Murray et al. in a small study of urinary DMT excretion in psychotic patients.

As pointed out by various investigators, inter-

pretation of the contradictory findings just reviewed is complicated by a number of variables. Among them is the sensitivity of the detection method used, the body fluid selected for testing (urine, blood, or CSF), and the method used to diagnose and classify schizophrenia and other psychoses in study subjects. In addition, study results may be affected by how DMT and other MIAs are synthesized and metabolized in the body and whether their production is intermittent or continuous.

In contrast to the paucity of research undertaken to explain these contradictory findings, the dopamine theory of schizophrenia has been extensively investigated (Carlsson, 1995). Yet a review of early versions of that theory reveals data as controversial as those associated with the transmethylation hypothesis. For example, various research groups reported finding widely different concentrations of homovanillic acid in schizophrenic patients (Kahn and Davis, 1995). However, modern research has demonstrated that serotonin influences dopamine pathways by showing that 5-HT receptors reduce extrapyramidal side effects induced by dopamine blockers (see the review by Kahn and Davis, 1995).

4. Possible mechanisms of MIA excretion

Two different mechanisms were postulated to explain urinary excretion of MIAs. The first mechanism, hyperactivity of *N*-methyltransferase, was tested in the 1960s by Buscaino’s group in Italy (Buscaino et al., 1966, 1969). The second mechanism, which is related to reports of decreased activity of monoamine oxidase inhibitors (MAOs) in schizophrenic patients (Paik et al., 1988; Zureick and Meltzer, 1988), takes into account that all MIAs are preferential substrates of MAOs. A third—and to us the most probable—possibility is that a combination of both enzymatic disorders causes the excretion.

We studied urinary excretion of MIAs in psychotic and non-psychotic patients for several years, finding that abnormal levels of *N,N*-DMS, 5-MeO-DMT, and DMT strongly correlated with psychotic features. Our first study, the results of which were presented at the 3rd World Congress of Biological Psychiatry (Ciprian-Ollivier et al.,

1988), demonstrated that schizophrenic patients had significantly higher urinary concentrations of *N,N*-DMS and DMT than normal controls, as measured by Spatz's GC method (Spatz, 1967), later double-checked by GC–MS.

We also studied 24-h urinary excretion of four MIAs (*N,N*-DMS, 5-MeO-DMT, DMT, and dimethoxy-phenylethylamine, or DMPE) in a large psychiatric population (Ciprian-Ollivier et al., 1986) and compared the results with those for a control group of normal healthy persons. Both qualitative (existence or absence) and quantitative characteristics for each methylated compound were determined, except for bufotenin, which was quantified only. As shown in Table 1, the patients who had schizophrenia excreted more of each MIA than did the controls. The mean difference was statistically significant for each compound except bufotenin. Abnormally high concentrations of MIAs were present in many but not all untreated schizophrenic patients. A gradient or continuum was evident between increased urinary excretion of the MIAs and the severity of psychotic symptoms, especially disorientation. Perceptual disturbances were evaluated by means of the

Hoffer–Osmond Diagnostic Test, which possesses a special item for the detection of subtle perceptual symptoms, not just true hallucinations (Kelm, 1970).

Searching for the cluster of symptoms correlated with abnormal MIA concentrations, we focused on those symptoms studied mostly in experimental psychoses and less so in schizophrenia-perceptual disturbances. In a sample of bipolar patients (Ciprian-Ollivier, 1991), manic patients displayed greater perceptual alterations than the other patients, as measured with the Hoffer–Osmond Diagnostic Test. This finding was clearly correlated with urinary excretion levels of MIAs. In summary, the greater the perceptual disturbance, the higher the MIA concentration. These results are similar to those reported by Murray et al. (1979) in England.

5. Ayahuasca: a vegetal model of experimental psychosis

We recently found a vegetal model of experimental psychosis that may help explain the pathogene-

Table 1
Twenty-four-hour urinary excretion of MIAs in schizophrenic patients and normal controls

	Number of patients	Geometric mean	s.d.	Vs. A	Vs. B	Percentage of patients ^a	Vs. A	Vs. B
<i>N,N</i> -dimethylserotonin								
Controls (A)	33	3.54	0.28189	—	—	0.0	—	—
Schizophrenics (B)	59	3.61		NS	—	13.6	*	—
5-MeO-DMT								
Controls (A)	33	0.2345	0.1462	—	—	0.0	—	—
Schizophrenics (B)	52	0.5551		**	—	34.6	**	—
<i>N,N</i> -DMT								
Controls (A)	33	0.3685	0.3406	—	—	6.1	—	—
Schizophrenics (B)	54	2.5036		**	—	64.8	**	—
DMPE								
Controls (A)	33	0.2598	0.0696	—	—	0.0	—	—
Schizophrenics (B)	48	0.4373		*	—	37.5	**	—

s.d., root square of the mean square of the error of the ANOVA (in logarithms).^aRefers to percentage of patients who excreted the MIA, except for *N,N*-dimethylserotonin, which had pathologic values above 8.9 µg% of excretion.

* $p < 0.05$.

** $p < 0.01$.

Variable criteria: in the case of 5-MeO-DMT, *N,N*-DMT and DMPE, due to method sensitivity, in order to allow the statistic analysis, when the compound was not detected a random value between 0 and 0.5 was assigned. When the compound was detected in too small amounts to be measured, a random value between 0.6 and 1 was assigned.

sis of endogenous psychoses. This model centers on a dense, dark green hallucinogenic beverage called ayahuasca. It is made by boiling together, for several hours, the bark of *Banisteriopsis caapi*, a vine rich in β -carboline derivatives (e.g. harmine and harmaline)—potent natural MAO inhibitors—and the leaves of *Psychotria viridis*, a bush rich in DMT (McKenna et al., 1984). Used by shamans in the Amazon Basin in their cure and divination ceremonies (Pinkley, 1969), the tea is brewed in a weekly ritual by members of a cult called União do Vegetal. The cult, whose members are well known in the community, even has a medical department that oversees the use of the tea for medical and experimental purposes.

How ancient shamans of the Amazon ever discovered that boiling the two plants together preserves the hallucinogenic power of the *P. viridis* leaves is a mystery. Today, we know that MAO inhibition by the β -carbolines prevents hepatic destruction of DMT in the bush, allowing it to cross the blood–brain barrier and exert its hallucinogenic effects on the central nervous system (Kärkäinen and Räisänen, 1992). This action could explain why DMT is difficult to detect in serum samples. The same effect could occur in schizophrenic patients. Decreased MAO activity in schizophrenic patients was reported in the 1970s. Zureick and Meltzer (1988) and Paik et al. (1988) correlated this decreased MAO activity with delusions and hallucinations. Decreased MAO activity because of a genetic disturbance prevents proper destruction of MIAs that once accumulated at proper levels. These MIAs are able to alter the functioning of neural circuits in charge of normal perceptual processing.

6. Ayahuasca study

With the official approval of the Medical Department of União do Vegetal, we studied the effects of ayahuasca on a small sample of healthy volunteers in Argentina (Pomilio et al., 1997). Relatives were informed of the possible reactions to the procedure and gave their written consent to proceed. Blood and urine samples were taken before and during the study, to assess concen-

trations of serotonin, prolactin, and cortisol in serum and DMT in urine. The Hoffer–Osmond test designed to detect perceptual alterations was administered before and during the study. A battery of neuropsychologic tests was also given, to evaluate the effects of ayahuasca on neurocognitive performance.

The study results demonstrated that ayahuasca produces a strong, rapid hallucinogenic effect that lasts, on average, for 45 min. Neuropsychologic test results showed that the liquid causes perceptual impairment. DMT was clearly detected by GC–MS in urine samples taken after the study (Vitale et al., 1994). The same method was used to identify harmine derivatives in a sample of the tea and to confirm the presence of DMT. Furthermore, the same method applied to one urine sample from a non-medicated schizophrenic patient revealed the presence of DMT and confirmed that it was chemically identical with the substance in the tea and in the urine samples obtained from the study subjects. These study findings confirm that the experimental psychosis induced by drinking ayahuasca is similar to certain clinical manifestations of schizophrenia. In addition, the mechanism whereby ayahuasca produces its hallucinogenic effects lends support to the transmethylation hypothesis of schizophrenia.

7. Perceptual disturbances and psychosis

Two aspects of the theory of pathologic transmethylation merit further discussion. The first aspect—the relevance of perceptual disturbances in the pathophysiology of psychosis—is often neglected. A distorted perception of reality not only causes positive symptoms (Kay, 1991) but also may contribute to the progressive deterioration of the patient and negative symptoms. Misunderstanding is the first step to not understanding at all, allowing the emergence of such symptoms as social withdrawal, cognitive impairment, flattened affect, and illogical thinking and speech. We have observed the presence in psychotic patients of subtle, hard-to-detect perceptual disturbances, such as dyschronognosia (disordered perception of time), dysbarognosia (abnormal

perception of weight), and dysestereognosia (disordered perception of distance).

In a study of 13 male schizophrenic patients and 13 normal controls, O'Donnell et al. found specific types of visuospatial deficits in the patients with schizophrenia. Results of the study suggested that the schizophrenic patients showed both slowing and impaired accuracy on tests of visual perception and immediate visual recognition. In addition, these patients demonstrated a differential deficit in accuracy of location and trajectory processing, in contrast to spatial frequency and pattern processing, which were relatively unimpaired. When the patients' trajectory and pattern performance were matched against comparison group accuracy, the patients showed more severe impairment in immediate recognition performance than in perceptual discrimination (O'Donnell et al., 1996).

Perceptual alterations, always present during the onset of schizophrenia, could play a major role in the progressive deterioration of cognitive processes by altering the process of synaptic selection, thereby inducing excessive synaptic pruning by stimulation overload and, in turn, causing secondary functional deterioration.

The second aspect of the theory has biologic and pharmacologic implications. Recently, considerable interest has been shown in atypical antipsychotics, not only because they act on both positive and negative symptoms but also because they have potent effects on serotonergic receptors. Studies of drugs such as clozapine, olanzapine, and risperidone (Jackson et al., 1993; Beasley et al., 1996) have clearly demonstrated that, as postulated by the transmethylation hypothesis of schizophrenia, indole derivatives could play an important role in the pathophysiology of schizophrenia. This theory is supported by the well-established fact that most hallucinogenic drugs act via serotonergic receptors (Heym and Jacobs, 1987; Glennon and Dukatz, 1995). So far, serotonin has received more attention than MIAs or other derivatives. Also, investigators have shown little interest in fully exploring the meaning and pathophysiological basis of perceptual alterations in schizophrenia, with the exception of those at the Bonn School, where the recognition of perceptual

disturbances plays a major role in the early detection of schizophrenia (Huber and Gross, 1989).

8. Conclusions

It is possible that through an extracerebral genetic metabolic error, abnormal peripheral production of endogenous hallucinogens occurs. These compounds can then act secondarily on the central nervous system. The ability of some of these substances to cross the blood-brain barrier is well known (Wyatt and Gillin, 1976). For this reason, we believe that further study of the neurophysiology of MIAs is warranted. The goal of this research would be to elucidate the pathophysiological basis of schizophrenia and stimulate the development of new pharmacologic strategies for treating this complex disorder.

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