The Psychedelic Model of Schizophrenia: The Case of *N,N*-Dimethyltryptamine

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The authors review the research on N,N-*dimethyltryptamine (DMT) as a possible "schizotoxin." DMT produces psychedelic effects when administered to normal subjects, the means are present to synthesize it in man, it has occasionally been found in man, and tolerance to its behavioral effects is incomplete. However, DMT concentrations have not been proven to differ significantly in schizophrenics and normal controls. Also, in vivo synthesis of DMT has not been convincingly demonstrated, and the psychological changes it produces do not closely mimic the symptoms of schizophrenia. The authors conclude that more data are necessary before the validity of this theory can be determined.*

MANY THEORIES of schizophrenia are based on the assumption that the illness is caused by a chemical substance, a "schizotoxin," that would mimic the clinical symptomatology of schizophrenia if it were isolated and administered to normal individuals. An example of this research strategy is the transmethylation hypothesis, first proposed by Osmond and Smythies in 1952 (1). These researchers noted the similarity in chemical structure of mescaline and norepinephrine, an observation that spurred the search for psychedelic methylated metabolites of endogenous compounds in schizophrenic patients that might account for hallucinations, delusions, and other clinical symptoms.

Interest in the transmethylation hypothesis was further stimulated by the work of Pollin and associates (2), who reported in 1960 that methionine, a natural methyl donor, administered in combination with a monoamine oxidase (MAO) inhibitor, exacerbated clinical symptoms in 3 of 9 schizophrenic subjects. Since that time, methionine has been administered to schizophrenics in 10 studies reviewed by Cohen and associates (3). One-third of the patients in these studies exhibited increased clinical symptoms without evidence of organic brain dysfunction. These results suggest that methionine increases the synthesis of an abnormally methylated substance, as yet unidentified, that was responsible for the observed clinical exacerbation.

Several substances have been proposed as candidates for the schizotoxin, including 3,4-dimethoxyphenylethylamine (pink spot), bufotenine, 5-methoxy-*N,N*-dimethyltryptamine, and *N,N*-dimethyltryptamine (DMT) (see figure 1). The first two substances have not been shown to produce psychotic psychological changes when administered to normal individuals (4, 5); in the case of bufotenine, this may be because it does not cross the blood-brain barrier. Little is known about 5-methoxy-DMT, although it has been reported to produce psychedelic effects in normal individuals (6), and urinary concentrations of 5-methoxy-DMT have been noted to increase with clinical exacerbation in schizophrenic patients (7). Figure 1 presents the postulated routes of synthesis of DMT and 5-methoxy-DMT.

In this paper, we shall review current evidence on the role of DMT as a causative agent in schizophrenia. Fortunately there are criteria (modeled after Koch's postulation) with which to evaluate a hypothesized schizotoxin. The following criteria were initially proposed by Hollister (8) and have been slightly modified here:

1. The substance must mimic important clinical aspects of schizophrenia.
2. The substance must be found in man.
3. The precursor must be found in man.
4. The agent must be synthesized in man. (It remains a logical possibility that it is of dietary origin.)
5. The agent must be differentially synthesized or metabolized in schizophrenia.
6. Tolerance to the agent should not develop. (This assumes that schizophrenia is not caused by a substance that is present only briefly and sets irreversible changes in progress.)
7. Neuroleptic drugs must be capable of inhibiting the synthesis, increasing the metabolism, or antagonizing the behavioral effects of the agent.

The body of our paper will consist of an examination of each of these criteria as they apply to DMT.

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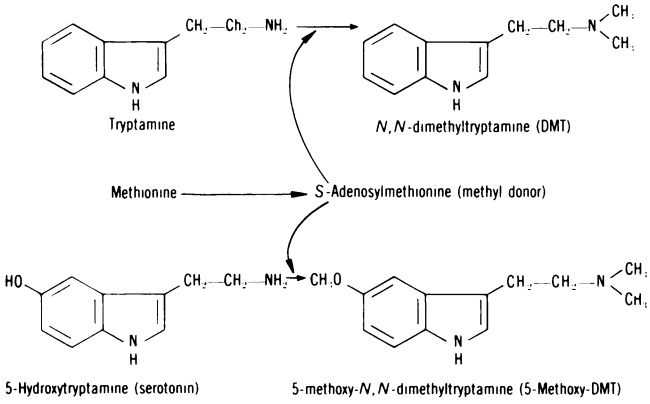
FIGURE 1
Postulated Routes of Synthesis of DMT and 5-Methoxy-DMT



DOES DMT PRODUCE SIGNIFICANT SCHIZOPHRENIC-LIKE SYMPTOMS?

In 1956 Szara (9) found that the effects of DMT on 20 normal volunteer subjects were similar to those of LSD and mescaline: visual illusions and hallucinations, distortions of spatial perception and body image, speech disturbances, and euphoria. A striking finding was that the effects of DMT began within 5 minutes and ended within 1 hour after injection. Similar results have since been reported by Rosenberg and associates (10) and Turner and Merlis (5).

In order to reexamine the psychological effects of DMT and to correlate them with pharmacokinetic aspects, we administered .7 mg/kg of DMT intramuscularly to 15 male volunteers. Each subject was an experienced user of LSD, mescaline, or other psychedelic substances who expressed an intention to continue using these agents in the future. All subjects were interviewed by two psychiatrists and were given a complete medical history and examination prior to testing in order to ensure the absence of psychiatric and physical impairment.

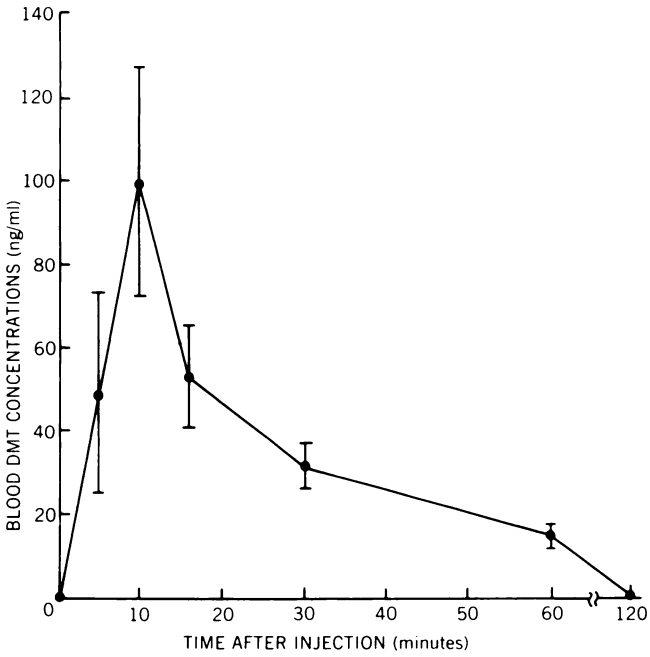
Like previous investigators, we found that DMT was a hallucinogen with rapid action and a short duration of effect. Psychological changes were evident within 5 minutes of injection, peaked at about 10 to 15 minutes, and ended within 45 to 120 minutes. The major psychological effects are shown in table 1. The subjects became so uncommunicative and withdrawn during the drug experience that we were forced to inquire about the subjective effects with simple "yes-no" questions. Although all subjects reported visual distortions and illusions, these were color or spatial distortions rather than formed visual hallucinations. Only 1 subject reported an auditory hallucination, a "buzzing bee" in his ear. We did not observe formal loosening of associations, although several subjects seemed to have thought blocking. Two subjects had paranoid symptoms that lasted less than an hour.

These psychological changes were accompanied by mydriasis, tachycardia, and increased blood pressure. Blood levels of DMT (see figure 2), assayed by a gas chromatographic-mass spectrometric (GC-MS) isotopic dilution technique, closely paralleled the psychological and autonomic changes (11). Peak concentrations of DMT, which averaged approximately 100 ng/ml,

TABLE 1
Subjective Effects of DMT Experienced by 15 Normal Volunteer Subjects, in Percents

Subjective Effect	Percent
Visual hallucinations	100
Hallucinations with eyes closed	100
Movement of surroundings	93
Difficulty talking	93
Difficulty describing feelings	93
Relaxation	93
Difficulty concentrating	93
Colors seem brighter	87
Excitation	87
Thinking faster	87
Dry mouth	87
Tenseness	80
People look different	75
Depersonalization	60
Nausea	60
People have orange-red hue	53
Hallucinating "real things"	27
Paranoia	20
Auditory hallucinations	7

FIGURE 2
Mean DMT Concentrations in Whole Blood Following Injection of DMT in 15 Normal Volunteers



were reached about 10 to 15 minutes after injection; the concentration then fell rapidly to baseline, undetectable levels within about 45 to 120 minutes after administration.

IS DMT FOUND IN MAN?

Several investigators have reported the presence of DMT in blood and urine of psychiatric patients (see table 2). Positive reports were more common with the earlier, less specific methods of analysis than with the later GC-MS techniques. Although DMT has occasionally been identified by GC-MS techniques in some subjects, the concentration has been extremely low. Also, the presence of DMT has not been reported more frequently in patients with particular diagnoses or in psychiatric patients in general compared with normal controls. The origin and significance of the identified DMT is unknown. Although it might reflect endogenous synthesis, it could also result from diet, bacterial products, laboratory error, or other sources.

TABLE 2
Recent Research on DMT in the Blood and Urine of Schizophrenics

Authors (in chronological order)	Method*	Sample	Subjects	Number Tested	Number Positive
Heller and associates (12)	TLC, GLC	Whole blood	Acute unmedicated schizophrenics	5	5
		Urine		2	2
		Whole blood	Chronic schizophrenics	9	0
			Psychotic depressives	1	0
			Normal subjects	2	0
Rosengarten and associates (13)	TLC	Urine	Schizophrenics	15	3
Narasimhachari and associates (14)	TLC, GLC	Serum	Acute schizophrenics	22	13
			Neurotics	5	1
			Chronic schizophrenics	4	0
			Normal subjects	10	2**
			Mother of manic-depressive	1	1
Narasimhachari and associates (15)	TLC, GLC	Urine	Chronic unmedicated schizophrenics	216***	9
			Normal subjects	56	0
Kanabus and associates (16)	PC	Urine	Nonschizophrenics	16	1
			Schizophrenics	26	4
Wyatt and associates (17)	GC-MS	Plasma	Acute schizophrenics	10	0
			Chronic schizophrenics	9	0
			Psychotic depressives	10	1**
			Normal subjects	11	1**
Narasimhachari and associates (18, 19)	TLC, GLC, GC-MS	Urine	Chronic schizophrenics	6	3
			Normal subjects	4	0
Axelsson and Nordgren (20)	Gel C TEC	Plasma	Acute and chronic schizophrenics	9	0
			Neurotics	4	0
Bidder and associates (21)	GC-MS	Whole blood or plasma	Psychiatric patients	37	2
		Urine		39	7
Lipinski and associates (22)	GC-MS	Whole blood or plasma	Chronic schizophrenics	6	0
			Schizophreniform psychotics	11	2
			Patients with hepatic coma	11	0
			Normal subjects	11	0
Mandel (23)	GC-MS	Whole blood, plasma, serum	Acute schizophrenics	35	6
			Chronic schizophrenics	46	4
			Nonschizophrenics	66	3
			Normal subjects	84	4
Oon and associates (24)	TLC, MS	Urine	Schizophrenics	42	20
			Affective psychotics	30	4
			Other psychotics	18	7
			Neurotics	32	6
			Normal subjects	20	1
Carpenter and associates (25)	GC-MS	Urine	Acute schizophrenics	12	4
			Normal controls	9	4

* TLC=thin layer chromatography, PC=paper chromatography, GLC=gas-liquid chromatography, GC-MS=gas chromatography-mass spectrometry, Gel C=gel chromatography.
** Doubtful.
*** Number of samples for 6 patients.

IS THE PRECURSOR OF DMT PRESENT IN MAN? CAN DMT BE SYNTHESIZED IN MAN?

As figure 1 indicates, DMT is thought to be synthesized from tryptamine in a reaction catalyzed by an *N*-methyltransferase (NMT). Tryptamine is reportedly present in human lung and elsewhere (26). NMT activity has been reported in human brain (27, 28) and blood (29), but its highest activity and specificity is in human lung (30). Mandel and associates (30), using GC-MS techniques, demonstrated in vitro conversion of *N*-methyltryptamine to DMT in human lung. Wyatt and associates (31) and Murphy and Wyatt (32) have found that MAO activity in platelets is low in some schizophrenics compared with control subjects, and that this defect may be genetically determined. Low MAO activity may lead to elevated concentrations of tryptamine, which would favor the synthesis of DMT.

In vivo human synthesis of DMT has not been convincingly demonstrated to date. We studed 1 male chronic schizophrenic patient before and during administration of 45–60 mg/day of the MAO inhibitor phenelzine. Although the patient was more hallucinatory and autistic on phenelzine than he had been during the placebo period, DMT concentrations in venous blood did not change from their very low placebo values (approximately .07 ng/ml). We also studied another male schizophrenic patient before and during treatment with 20 g/day of L-tryptophan, the biosynthetic precursor of tryptamine. Again, there was no change in blood DMT concentration. The patient's clinical condition was not altered by L-tryptophan.

IS DMT SYNTHESIZED OR METABOLIZED DIFFERENTLY IN SCHIZOPHRENICS THAN IN CONTROLS?

Synthesis of DMT in man has yet to be conclusively demonstrated, and little knowledge currently exists on the metabolism of DMT in schizophrenics compared with normal control subjects. Szara (9) suggested two major routes of metabolism of DMT: 1) dealkylation and oxidative deamination, leading to indole-3-acetic acid and 2) 6-hydroxylation followed either by glucuronide formation of 6-hydroxy-DMT or by dealkylation and oxidative deamination leading to 6-hydroxyindoleacetic acid (33). To our knowledge, there have been no studies comparing the concentrations of these metabolites in schizophrenics and controls.

Our recent study of the effects of DMT on volunteer subjects (11) suggested that the drug is rapidly metabolized. Assuming that DMT is distributed equally throughout the blood, we could account for only about 2% of the administered dose at the time of the peak blood concentration. Moreover, less than .01% of the administered dose was found in urine within 24 hours, and most of that amount was excreted within the first 6 hours.

Thus the failure of various investigators to find elevated concentrations of DMT in venous blood or urine of schizophrenics may be explained by the rapid metabolism of this compound. If DMT is actually formed by lung NMT, then schizophrenia is a lung disease, and DMT may be transported directly from lung to brain via the arterial system. Once DMT is exposed to liver, kidney, or muscle, it may be so rapidly metabolized that measurable concentrations cannot be detected in venous blood.

DOES TOLERANCE TO DMT DEVELOP?

Since schizophrenia is a clinical syndrome that lasts for weeks to months in its acute forms and for years to decades in its chronic forms, a biochemical theory must be able to explain long-term symptoms. The issue of tolerance has been a major problem in the schizotoxin theory of schizophrenia. Tolerance to LSD, mescaline, and psilocybin develops rapidly in man and animals, for some if not all behavioral effects.

In our initial efforts, we found that tolerance did not develop to unconditioned behavioral and EEG effects of DMT in cats administered DMT twice daily for 15 days or every 2 hours for 24 hours (34). Also, lack of behavioral tolerance has been reported in squirrel monkeys given DMT once daily for 38 days (35).

More recently, we studied the issue of tolerance in 4 normal male volunteers who received 0.7 mg/kg of DMT intramuscularly twice daily for 5 days. Repeated administration did not consistently alter the peak blood concentration of DMT; autonomic changes in pupil size, pulse, or heart rate; the number of psychological items changed in a psychological scale; or the frequency of errors in a test requiring the subject to cross out a specific number in a list of random numbers. Three of the 4 subjects reported diminished subjective "highs" on a scale of 0 to 10 after two to four injections of DMT, but their subjective responses were variable from trial to trial and did not indicate a general loss of responsiveness to DMT. Rather, these subjects exhibited a variable or aperiodic partial tolerance to DMT. This pattern is reminiscent of Koella and associates' report of a cyclic change in ambulation produced by LSD in goats (36). Further studies, including longer or more frequent trials with DMT, are necessary to fully evaluate this phenomenon.

This type of variable tolerance has also been reported recently by Kovacic and Domino (37), who studied the suppressive effects of DMT on the operant behavior of appetitively conditioned rats who were given DMT every 2 hours for periods of up to 21 days.

Böszörményi and Szara (38) reported that schizophrenics are less sensitive to the effects of DMT than controls. If schizophrenics do show diminished responsiveness to DMT, this may result from increased metabolism or variable tolerance resulting from long-term endogenous synthesis of DMT.

DO NEUROLEPTICS INHIBIT THE SYNTHESIS, INCREASE THE METABOLISM, OR ANTAGONIZE THE EFFECTS OF DMT?

Although the evidence is currently incomplete, there are data suggesting that antipsychotic medications may inhibit the activity of NMT. Axelrod (39) has suggested that chlorpromazine might have this effect. Moreover, a dialyzable inhibitor of NMT has been reported in bovine pineal gland (40), which is an interesting finding because Bigelow (41) obtained favorable clinical results in some schizophrenic patients with an aqueous extract of bovine pineal gland. Some dimethylated metabolites of chlorpromazine have also been reported to be competitive inhibitors of NMT (42). Thus it is conceivable but unproven that antipsychotic drugs inhibit the synthesis of a methylated schizotoxin. Little is known, however, about the influence of antipsychotic medications on the metabolism or behavioral effects of DMT.

DISCUSSION

Although the DMT model of schizophrenia remains attractive, most of the positive evidence is indirect, supporting the plausibility rather than the reality of the model. DMT does produce striking psychological changes in normal subjects, the enzymes and precursors are present to synthesize it in vitro in human tissue, it has been found occasionally in man, and tolerance to its behavioral effects is incomplete. Moreover, effective antipsychotic treatments may conceivably interfere with the synthesis of DMT.

On the other hand, significant differences in DMT concentrations in schizophrenics versus controls have not been proven, in vivo synthesis of DMT in man has not been demonstrated, and the psychological changes induced in man by DMT do not closely mimic the clinical symptoms of schizophrenia. When psychological changes have been produced in normal subjects, this has been with DMT blood concentrations 50 to 100 times greater than those in the few schizophrenic patients in whom DMT has been identified.

Arguments can undoubtedly be produced to refute each of these objections. The psychological effect of DMT in normal individuals probably should not be expected to mimic schizophrenia. After all, the volunteer knows what is happening to him when the experimenter administers DMT, but DMT is (hypothetically) synthesized endogenously in schizophrenic patients. The data on DMT in blood and urine may be of dubious relevance in view of its rapid clearance from blood and its failure to appear in appreciable amounts in urine.

Like any good scientific theory, the DMT model of schizophrenia will ultimately live or die by the data that it heuristically generates. We hope that, within the foreseeable future, forthcoming data will give this theory either a new lease on life or a decent burial.

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Recent Developments in the Drug Treatment of Schizophrenia

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The author reviews six topics relevant to the drug treatment of schizophrenia. The quantitative effectiveness of promazine is of interest with respect to the structural models of the phenothiazines and the dopamine theory of schizophrenia. The quantitative effectiveness of antipsychotic drugs is also important in evaluating new agents and therefore relevant to a discussion of two newly released neuroleptics, molindone and loxapine. The author's discussion of high-dose treatment for typical acute schizophrenics or treatment-resistant patients reviews the available data and calls attention to the fact that these areas of pharmacologic research have not received sufficient attention.

SOME RECENT DEVELOPMENTS in the drug treatment of schizophrenia are relevant to six problems of practical importance: 1) the effectiveness of the antipsychotic agents as compared with placebo in the treatment of schizophrenia; 2) indications for use of antipsychotic drugs; 3) the usefulness of massive doses in improving clinical response in typical acute schizophrenia; 4) drug treatment of the phenothiazine-resistant patient; 5) phenothiazine effectiveness and molecular models; and 6) the effectiveness of two new neuroleptic agents, molindone and loxapine. Since the use of the intramuscular depot drugs such as fluphenazine decanoate (a useful strategy for schizophrenic patients who tend to forget to take their pills and an important addition to clinical therapeutics) has already been reviewed recently in the *American Journal of Psychiatry* (1), I will limit the content of this paper to avoid redundancy.

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