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N,N-Dimethyltryptamine — A Possible Relationship to Schizophrenia?

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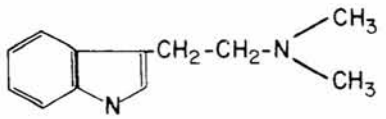
I. INTRODUCTION

Murphy and Wyatt (1972) recently demonstrated that platelet monoamine oxidase (MAO) activity is low in some schizophrenic patients compared with patients with affective disorders and normals. Subsequently Wyatt, Murphy, Belmaker, Cohen, Donnelly, and Pollin (1973*b*) found that platelet MAO activity was highly correlated in pairs of monozygotic twins discordant for schizophrenia, indicating that the enzyme activity was, at least in part, genetically determined. These data suggest that low platelet MAO activity is present in some individuals with a high susceptibility to schizophrenia.

Information is lacking as to whether abnormal MAO activity is present in parts of the schizophrenic's body other than platelets and whether it is causative or secondary to the schizophrenic illness. Nevertheless, some speculations can be made regarding biochemical defects which might be associated with low MAO activity. Our laboratory has been particularly interested in the possible role of N,N-dimethyltryptamine (DMT) in schizophrenia (Fig. 1). DMT is a known hallucinogen. An enzyme capable of forming DMT from tryptamine has recently been described in human blood (Wyatt, Saavedra, and Axelrod, 1973*c*), lung (Mandel, Ahn, VandenHeuvel, and Walker, 1972), and brain (Mandell and Morgan, 1971; Saavedra and Axelrod, 1972*b*). Since tryptamine is normally degraded by MAO, abnormally low levels of MAO could predispose to elevated levels of tryptamine, the immediate precursor of DMT.

Biochemical theories of schizophrenia often assume that the clinical symptoms of schizophrenia are caused by an offending chemical



DIMETHYLTRYPTAMINE
(DMT)

FIG. 1. Chemical structure of dimethyltryptamine (DMT).

substance. Furthermore, it is assumed that this substance could produce similar symptoms if it could be isolated or synthesized and administered to normal subjects. Based upon this reasoning, the following criteria (after Hollister, 1968) must be met before such an agent would be considered an endogenous hallucinogen causative of schizophrenia:

1. The agent must be capable of mimicking clinical aspects of schizophrenia.
2. The agent must be found in man.
3. The precursor of the agent should be found in man (see 4).
4. The agent should be synthesized in man (it remains a possibility that the agent could be of dietary origin).
5. The agent must be differentially synthesized or metabolized in schizophrenics.
6. Tolerance to the agent should not develop: Slow tolerance to the agent might be acceptable for acute schizophrenia but not for the chronic illness. (This assumes that the agent does not produce irreversible damage.)
7. Neuroleptic drugs must be capable of antagonizing the synthesis, increasing the metabolism, or antagonizing the effect of the agent.

II. CLINICAL EXPERIENCE WITH DMT

In this chapter we shall try to summarize how well DMT fits these criteria, where it fails, and where further research efforts are necessary.

In 1956, Dr. Stephen Szara (see also Sai-Halasz, Brunecker, and Szara, 1958) synthesized and gave DMT to a group of 20 normal volunteers. He noted that the effects of DM T (0.7 to 2 mg/kg) were similar to those produced by mescaline and LSD. Oral dosages were without effect. The minimally effective dosage was 0.2 mg/kg and the optimal, above which there was no increase in symptoms, was 0.7 to 1.0 mg/kg. The principal symptoms were visual illusions and hallucinations, distortion of spatial perception and of body image, disturbances of speech, and euphoria. He noted mydriasis and elevation of blood

pressure as well as athetoid and compulsive movements. The most striking aspect of this "model psychosis" was its rapidity of onset (3 to 5 min) after injection and the brevity of duration (less than 1 hr). Arnold and Hofman (1957), administering DMT to psychologists who had previous LSD experience, found that DMT produced less intense hallucinations, with less movement and color, than were remembered for LSD. These results were confirmed in 1963 by Rosenberg, Isbell, and Miner in five human subjects (0.75 to 1 mg/kg). Turner and Merlis (1959) found intranasal (0.5 to 20 mg) and oral (up to 350 mg) DMT had no psychotomimetic effect in a group of schizophrenic subjects. Intravenous DMT injections of up to 25 mg were without effect except in one schizophrenic patient who saw nurses as paper dolls and walls as crumbling paper. Saline injections did not produce this effect. Turner and Merlis also gave 5 mg intramuscularly for 1 week without psychic changes. Intramuscular doses below 25 mg were without effect, but above 25 mg psychic changes were present. The patients became restless and withdrew from personal contact out of fear. The patients gave the appearance of hallucinating. There were periods of perplexity and of irrelevant or incoherent speech. Sai-Halasz (1962, 1963) gave DMT to 40 normal volunteers. Fifteen of these were then first given the 5-HT antagonist, 1-methyl-D-lysergic acid butanolamide, followed by DMT. The serotonin antagonist greatly potentiated the effect of DMT. Subsequently he found that pretreatment with a monoamine oxidase inhibitor (iproniazid) before DMT was given (0.65 to 0.83 mg/kg) produced an attenuated effect with illusions and hallucinations without color. After 14 to 20 min, nothing was of interest to the subjects even though the hallucinations had worn off unusually rapidly. The subjects were "emotionally bleak." Dosages of DMT below 0.65 mg/kg had no hallucinatory effect but produced the same bleakness.

Despite dramatic effects produced by DMT, we have been able to find no other published studies of this substance in man—most investigators having chosen to use longer acting but perhaps less physiological agents. Because of the potential importance of understanding how DMT works in man, we have initiated a study of the effects of DMT in a group of medically and psychologically healthy male volunteers, all of whom have had extensive previous experience with hallucinogens. To date five subjects have been studied. Each was administered an intramuscular dosage of DMT (0.7 mg/kg) and blood pressure, pulse rate, and pupillary diameter were measured at 5-min intervals. In addition, several behavioral and subjective tests were given.

In agreement with previous studies, we found that DMT is a short-acting, potent hallucinogenic drug with a rapid onset. DMT blood concentrations, autonomic and subjective measures demonstrate this and follow a very similar time course. Figure 2 shows that there is a

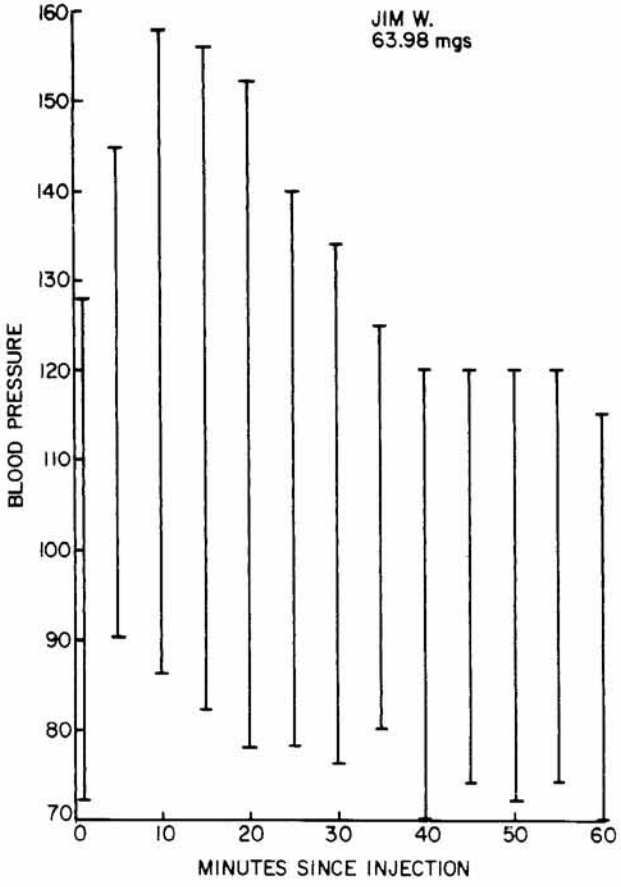


FIG. 2. Measurements of diastolic and systolic blood pressure in a normal subject receiving 64 mg of DMT.

rapid and parallel increase in both diastolic and systolic blood pressure in a normal subject given DMT. This is also true for the pulse rate.

Subjects were asked to rate how high they were, on a scale of 0 to 10, with a rating of 10 as "high as you have ever been in your life." In this particular subject, who had taken LSD over 50 times, and in three of the four others, the DMT experience was rated as "more intense than any dose of LSD they had ever taken."

Figure 3 shows the subjective effects of DMT on subject J.B. It can be seen that DMT produces an intense experience, with the first rush perceived within 3 min of the injection. Almost immediately, the subjects became completely absorbed in a very complex experience which so far has defied their attempts to verbalize completely, and

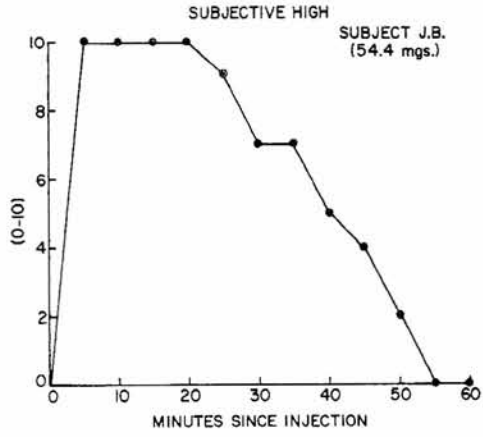


FIG. 3. Measurement of subjective "high" in a subject receiving 54 mg of DMT. The "high" is measured on a subjective 0 to 10 scale, with the rating of 10 as "high," that is, "as 'high' as you have ever been in your life."

which cannot be described at all while it is happening.

The DMT experience was described as being associated with an overload of thoughts and perceptions—so compelling that the subjects were forced to attend to them—neglecting interactions with the experimenters. They had problems with concentration. Their extreme difficulty with communication occasionally was associated with resentment. This necessitated the use of "yes" and "no" questionnaires, since open-ended questions led simply to perseveration and no answers.

The perceptions were largely visual, primarily with patterns and changing shapes. Colors seemed brighter and more beautiful than usual. There were sensations that the surroundings were moving. Some subjects reported that the experimenter looked different, became a yellow color, or broke into cubist abstracts. Only rarely were formed visual hallucinations noted.

There was a feeling among the subjects that they were generating thoughts faster than normal, and in two of the five sadness was reported. All subjects were at times euphoric. Four subjects reported feeling both calm and excited at the same time.

Three of the subjects had dysphoric reactions. One of these reported severe anxiety about losing control, one became very suspicious, and one frankly paranoid. Both of the latter felt, to different degrees, that the experimenters were controlling their minds. One demanded, "You started all this, now stop it." Inexplicably, as soon as the drug effect wore off (30 to 60 min), the subjects remembered the experience only as being pleasurable. This behavior, while at times somewhat similar to

that of schizophrenia, always took place with the realization that it was inappropriate. The subjects slid in and out of contact with reality.

Comment: DMT in normals was originally described as producing frank visual hallucinations. In our experience this has not been the case—DMT produced some illusions or distortions of overwhelming interest to subjects such that they ignored all outside communication. The subjects, however, did on rare occasions see objects that were not present. With effort, they could communicate, and when they did, it was relevant and clear. It is our experience that much of the schizophrenic communication, such as "Get away from me," or "No" is also relevant and clear. Nevertheless, schizophrenic thought disorder was not observed in our subjects. The presence of suspiciousness (frank paranoia in one subject), however, might have been indistinguishable from acute paranoid schizophrenia if it had been sustained. Of course, all our subjects were experienced with psychotomimetic drugs and, unlike schizophrenics, knew the source of the altered state of consciousness.

The schizophrenics of Turner and Merlis (1959) given DMT had an increase of intensiveness of their schizophrenic symptomatology. Since a number of drugs, including methylphenidate (Janowsky, El-Yousef, Davis, and Sekerke, 1973), produce similar exacerbations of the illness, it is at the moment difficult to draw any conclusions from this data relevant to the involvement of DMT in schizophrenia.

III. DMT CONCENTRATIONS IN MAN

Several authors have reported the presence of DMT in human tissue (Franzen and Gross, 1965; Gross and Franzen, 1965; Tanimukai, Ginter, Spaide, Bueno, and Himwich, 1970; Rosengarten, Szemis, Piotrowski, Romaszewska, Matsumoto, Stencka, and Jus, 1970; Narasimhachari, Heller, Spaide, Haskovec, Meltzer, Strahilevitz, and Himwich, 1971). An important advance in this pursuit was the development of a gas chromatographic-mass spectrometric isotope dilution assay for DMT by Walker, Ahn, Mandel, and VandenHeuvel (1972). A year later Walker, Ahn, Albers-Schonberg, Mandel, and VandenHeuvel (1973) measured DMT in human plasma using this methodology and reported that DMT, when present, varied between 0.5 to 2.0 ng/ml. Analysis of plasma samples from patients who were chronic alcoholics, acute and chronic schizophrenics, and depressives showed no variation from these low levels (Wyatt, Mandel, Ahn, Walker, and VandenHeuvel, 1973*a*).

IV. SYNTHESIS OF DMT IN MAN

DMT is formed by the enzymatic addition of two methyl groups to the free amino group of tryptamine from S-adenosyl methionine (Fig. 4). Tryptamine itself is the product of decarboxylation of the essential amino acid tryptophan.

There has been a controversy over whether tryptamine is present in mammalian brain (Hess and Doepfner, 1961; Green and Sawyer, 1960; Eccleston, Ashcroft, Crawford, and Loose, 1966), but it now seems clear that it is normally present in human brain (Martin, Sloan, Christian, and Clements, 1972; Saavedra and Axelrod, 1972*a*,*b*). It also seems evident that under conditions of high tryptophan loading, with or without monoamine oxidase inhibitors, that tryptamine can be endogenously synthesized *in vivo* in rat brain (Saavedra and Axelrod, 1972*a*). The K_m, however, for L-amino acid decarboxylase toward tryptophan is 1.4×10^{-2} M (Ichiyama, Nakamura, Nishizuka, and Hayaishi, 1970), and does not favor the *in vivo* synthesis of tryptamine under normal circumstances. Nevertheless, inhibition of monoamine oxidase by parenteral administration of iproniazid does increase brain tryptamine, suggesting that tryptamine is normally synthesized in the body. (More direct studies, which are able to exclude the possibility of tryptamine being synthesized by bacteria in the gastrointestinal system, seem necessary.)

Whether tryptamine is exogenously or endogenously formed, it *is* present in human tissue (Saavedra and Axelrod, 1972*b*), including plasma (0.5 to 2 ng/ml) (Saavedra—personal communication), and its principal metabolite, indoleacetic acid, has been consistently found in human spinal fluid (Bertilsson and Palmer, 1972). Since tryptamine itself crosses the blood-brain barrier, it could be converted in the brain to DMT by the enzymes described by Mandell and Morgan (1971) and

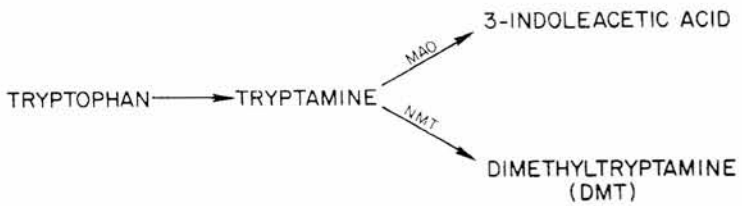


FIG. 4. Metabolism of tryptamine. MAO = monoamine oxidase, NMT = N-methyltransferase.

by Saavedra and Axelrod (1973). Tryptamine urinary excretion may be high in some schizophrenics (Brune and Himwich, 1962). High tryptamine concentrations favor its conversion to DMT.

DMT, however, does not have to be formed in the brain to be active there. Mandel et al. (1972) described very active enzymatic conversion of tryptamine to N-monomethyl tryptamine and of N-monomethyl tryptamine to DMT in the human lung. The lung also appears to accumulate high concentrations of tryptamine (Saavedra and Axelrod, 1973). Since the lung is the last filtering organ of blood on its way to the brain, DMT formed in the lung would be shunted directly to the brain. An enzyme capable of forming DMT has also been described in human plasma (Wyatt et al., 1973*b*), serum (Narasimhachari, Plant, and Himwich, 1972), platelets (Wyatt et al., 1973*c*), and red blood cells (Wyatt et al., 1973*c*; Rosengarten, Meller, and Friedhoff, 1973).

Comments: To date there has been no demonstration of *in vivo* DMT synthesis in man. Saavedra and Axelrod (1972*b*), however, using ^{14}C-tryptamine injected intracisternally, were able to demonstrate its conversion to N-methyltryptamine and DMT in rat brain. Similar experiments are possible in man.

V. DMT METABOLISM

The implication of the rapid disappearance of DMT's psychological effects is that the drug is rapidly metabolized in the body (Szara, 1956). Erspamer (1955), studying rats, noted that DMT appeared to be broken down in the urine to 3-indoleacetic acid (3-IAA). Szara (1956) identified 8.6% of an original DMT dosage as free 3-IAA in the urine of normals. Alkalinization of the urine brought the recovered product up to 25% of the administered DMT. DMT itself could not be found in the urine. In 1959, Szara and Axelrod identified 6-hydroxy DMT-N-oxide as an *in vivo* metabolite of rats.

Szara (1961) and Szara and Hearst (1962) proposed that the behavioral effects of DMT are due to a metabolite because they isolated a high-potency substance (not DMT) in the urine of rats administered DMT. Using chromatographic techniques, this compound was identified as 6-hydroxy-DMT. Subsequently, however, Kalir and Szara (1963) found that 6-fluoro-N,N-diethyltryptamine (N,N-diethyltryptamine is a longer acting hallucinogen than DMT) produced no hallucinogenic effects in man. In addition, Rosenberg et al. (1963) administered 6-hydroxy-DMT, DMT, and placebo in a single-blind study in equal dosages to five volunteers. The 6-hydroxy compound failed to produce signs or symptoms that might be considered peripherally (changes in blood pressure, kneejerk threshold, and pupil size) or centrally (the presence of hallucinations and perceptual distortions) associated with the hallucinogen DMT.

Using a fluorescent technique, Cohen and Vogel (1972) studied the disposition of DMT in rat tissues. After injecting DMT intraperitoneally, it was found to peak within 5 min, remain at a plateau for another 5 min, and have a sharp decrease thereafter. No DMT was detectable after 30 min. The highest concentrations of DMT were achieved in the liver, with the brain and plasma having one-sixth and one-seventeenth the liver concentration, respectively. There was a high brain-to-plasma ratio (5.4:1), suggesting that DMT penetrates the brain with ease.

In studies in our laboratories using gas-liquid chromatography and mass spectrometry, mice given 15 mg/kg of DMT intraperitoneally (Fig. 5) had peak DMT concentrations at 10 min, which fell within 30 min. The peak concentration of 4500 ng/g tissue was in the liver, with the brain and lung having about two-thirds that concentration.

In a group of normal volunteers given 0.7 mg/kg of DMT, we have found a large range in peak blood concentrations. Figure 6 demonstrates one subject at the extreme high end of the range. The time course, however, of the peaks and troughs is very similar, no matter

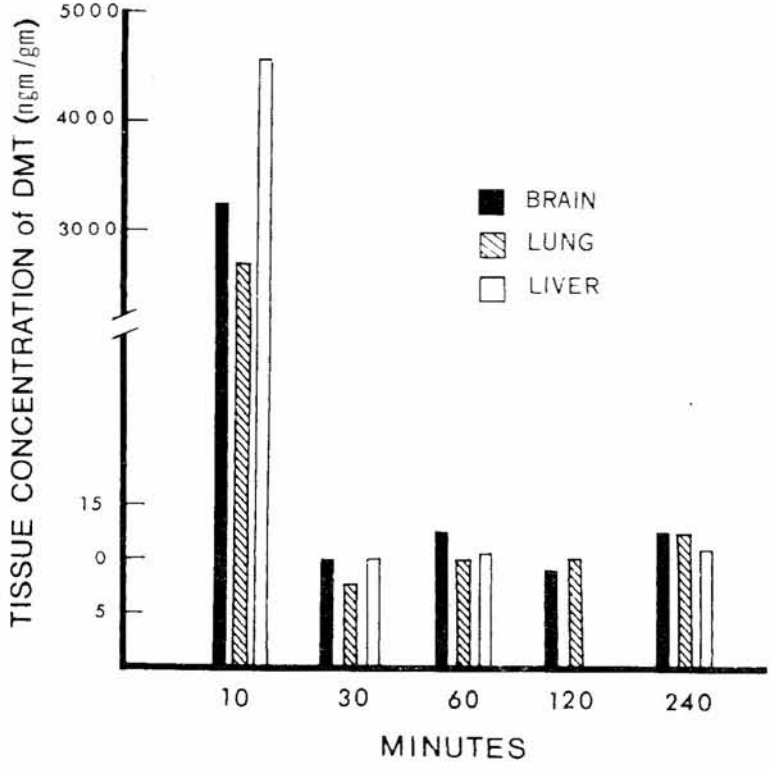


FIG. 5. Tissue concentration of DMT in mice, given 15 mg/kg, over time. Two animals used for each point.

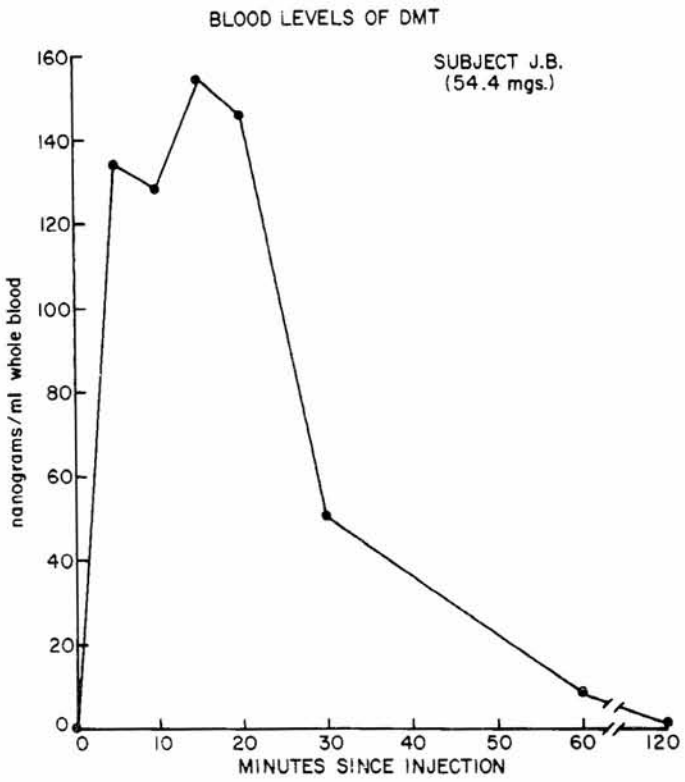


FIG. 6. Concentrations of DMT in whole blood over time after intramuscular injection of 54 mg in one normal subject. Subject had highest blood concentration of anyone studied.

what the peak blood concentration. In subject J.B., blood peak concentrations occurred at 15 min, about 5 min after the peak behavioral and autonomic change. The subsequent decay corresponds with the subjective effects. The peak blood concentration, calculated for total body blood, represents about 2% of the injected dosage.

Urinary excretion over 24 hr in the same individual was 36 μg, representing 0.067% of the injected dosage with 97% of that being excreted in the first 5.5 hr of collection: DMT, a nonpolar substance, quickly reaches tissues with high lipid concentrations such as the brain, and is found in low concentrations in urine, which is a highly polar solvent. In fact, after an injection of 0.7 mg/kg, only about 7/10,000 of the total dosage was found in a 24-hr urine. In addition, it is clear from the animal studies that DMT is not sequestered in the liver and brain, but is metabolized very quickly. While there is some evidence that metabolism occurs through hydroxylation and oxidation, which of

these represents the principal metabolic route is not known. DMT is reported to be a poor substrate for monoamine oxidase, and may even inhibit this enzyme.

Comments: What is clear is that the normal person has excellent mechanisms for dealing with this highly toxic substance. It is also clear that looking for abnormal concentrations of DMT in the blood and urine of schizophrenic patients may be unrewarding due to DMT's rapid metabolism. Urine seems to be a very poor place to look for DMT, with blood only a little better. If DMT is produced and released in spurts rather than constantly, frequent blood sampling from the same person might be more rewarding than occasional samples. Demonstrating an increased quantity of DMT in schizophrenic patients (if present) will require attempts at determination of turnover rates or finding a specific stable metabolite if one exists. Prior to resorting to these measures, it will be necessary to determine if exogenous DMT is cleared from the blood in schizophrenics as rapidly as it is in controls.

VI. FAILURE OF DMT TO PRODUCE TOLERANCE

One of the chief arguments against a DMT-like compound being involved in a psychosis is the well-known development of tolerance to LSD and mescaline. Normal humans as well as schizophrenic patients and animals have the expected reaction to these drugs when they are first given them, but when dosages are given over consecutive days the effects usually disappear by the third day. Bridger, Stoff, and Mandel (1973), using a shuttle-avoidance test, have recently found that while tolerance develops to the inhibitory effects of mescaline, the excitatory effects produced by mescaline do not decrease with time.

Cole and Pieper (1973) trained five squirrel monkeys for food reinforcement on fixed-ratio schedules. A DMT dosage (up to 2 mg/kg) which was found to disrupt the operant behavior was administered once daily for 36 to 38 consecutive days. No tolerance developed using this measure.

Kovacie and Domino (personal communication) demonstrated that rats given DMT, 10 mg/kg, once a day for 14 days do not become tolerant in fixed-ratio 4 schedule; however, when the same dosage of DMT was given every 2 hr for 14 days, there at first appeared a hypersensitivity, but subsequently three of nine rats became tolerant to the drug.

Gillin, Cannon, Magyar, Schwartz, and Wyatt (1973) gave DMT (3 mg/kg), LSD (150 to 200 μg/kg) and saline in a double-blind fashion to five cats implanted with cortical EEG, electrooculogram, electromyogram, and lateral geniculate body electrodes. Drug injections were both given twice daily for from 7 to 15 consecutive days and every 2 hr for

24 hr. Neurological and autonomic effects of LSD were mild compared to those of DMT, and became attenuated with repeated administration. High-voltage slow waves produced by both drugs did not occur beyond the fourth or fifth day with LSD. DMT, on the other hand, produced sustained neurologic, autonomic, and EEG effects for as long as it was given. Even when DMT was given every 2 hr for 24 hr, no tolerance was seen. The typical DMT response began within 5 to 15 min of the injection and lasted 1 to 2 hr. Spontaneous movements decreased, pupils dilated, were unresponsive to light, and abnormalities of posture were evident. There was a wide-based stance, particularly of the hindlimbs. The cats assumed unusual fixed postures, such as hanging for long periods by the forelimbs when placed on the edge of a table. Pontine-geniculate-occipital ("PGO spikes") monophasic waves, said to be present during waking with LSD administration (Stern, Morgan, and Bronzin, 1972), were not present with DMT administration. In this experiment it was our impression that the DMT effect became greater with time.

In still another species (male albino mice), we attempted to determine whether tolerance developed to a DMT-produced impairment in a conditioned avoidance to an electric shock. Five groups of animals were trained to avoid an electric shock by running from a start box with an electrified grid. Each group of mice was given four injections at 90-min intervals ranging from all saline (group 1), DMT (15 mg/kg, i.p.), and three saline injections to four DMT injections (group V). DMT significantly interfered with established avoidance in all mice receiving DMT, no matter how many DMT injections had preceded it (no tolerance developed).

Chronic administration of DMT, 15 mg/kg, twice a day continued to disrupt avoidance for a 10-day period, also indicating a failure to develop tolerance to DMT. In the experiment with mice there was no evidence of increased sensitivity to repeated DMT administration.

Comment: Failure to develop tolerance to DMT has been found in four species of mammals. Even repeated dosage over very short time periods does not produce tolerance. An initial hint of reverse tolerance or hypersensitivity in our cat experiments was not seen in similar studies in mice, but was in Kovacie and Domino's rat experiments. Almost continuous DMT administration to their rats produced tolerance in three of nine animals.

Ultimately, tests will have to be made to determine whether tolerance to DMT develops in normal and schizophrenic individuals.

VII. EFFECTS OF ANTIPSYCHOTIC DRUGS ON DMT

While there are a fairly large number of studies demonstrating the

ability of antipsychotic drugs to block the effects of other hallucinogens, data for DMT are sparse. Teixeira, Bueno, and Do Lago (1968) gave chlorpromazine (1.5 mg/kg) intramuscularly for 27 days and found that *in vitro* red blood cell uptake of DMT was diminished 11%. In our laboratory we have demonstrated that pretreating mice for 3 days with 2.5 mg/kg of chlorpromazine partially blocks a DMT-produced depression of motoric activity.

VIII. DISCUSSION

DMT is one of a number of substances which have been from time to time considered as a cause of schizophrenia. Our laboratory is interested in DMT because an increase in DMT synthesis is consistent with a deficiency of monoamine oxidase. While a deficiency of monoamine oxidase has been found in some patients with schizophrenia, to date only blood platelets have been found deficient, and whether the deficiency is more generalized remains unknown. Nevertheless, an examination of whether DMT could fit a number of required criteria for serious consideration as a schizophrenogen seems warranted.

DMT does appear to fit at least several of the criteria. In single dosages it is capable of producing at least some schizophrenic-like symptomatology. It and its precursor can be found in human tissue, and the enzymes for DMT synthesis are present in man. In several species tolerance to repeated administration has not been found to develop. The most significant piece of negative evidence is the failure to find elevated DMT plasma concentrations in schizophrenic individuals, but in retrospect the extremely short *in vivo* life of DMT suggests that it might be metabolized too quickly to be able to use blood concentrations to differentiate schizophrenics and normals. Urine appears to provide an even poorer measurement. Even those criteria that are met at this point are met only in a small number of experiments. It would seem that DMT remains a candidate for the causative agent for at least some schizophrenias.

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