Observations on the Metabolism of the Psychotomimetic Indolealkylamines: Implications for Future Clinical Studies

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Although the psychotomimetic indolealkylamines N,N-*dimethyltryptamine, 5-methoxy-*N,N-*dimethyltryptamine, and 5-hydroxy-*N,N-*dimethyltryptamine have been unequivocally identified in human body fluids, evidence relating their concentration to the presence of psychotic illness in humans remains controversial. A series of studies on the metabolism of the compounds in the rat have highlighted the rapidity and with which these are metabolized and renally excreted. The implications of our observation for the interpretation of past clinical studies and the design of future ones is discussed.*

Introduction

The psychotomimetic indolealkylamines *N,N*-dimethyltryptamine (DMT), 5-methoxy-*N,N*-dimethyltryptamine (5-MeODMT), and 5-hydroxy-*N,N*-dimethyl-tryptamine (5-OHDMT) have now been unequivocally identified in human body fluids, including cerebrospinal fluid, blood and urine (Angrist et al. 1976; Oon et al. 1977; Raisenan et al. 1979; Smythies et al. 1979; Sitaram et al. 1983a). However, despite repeated claims that the concentrations of these compounds are elevated in the body fluids of subjects suffering from psychotic illnesses (Cottrell et al. 1977; Oon et al. 1977a,b; Vebelhack et al. 1983; Raisanen et al. 1984), to obtain unequivocal evidence to support these claims remains an elusive goal. A substantial body of evidence has indicated that the psychotomimetic indolealkylamines are subject to very rapid rates of metabolism both in animals and in humans (Kaplan et al. 1974; Agurell et al. 1969; Sanders-Bush et al. 1976; McLeod et al. 1985). The experimental strategies adopted in clinical studies conducted to date, however, have failed to reflect a recognition of this. As a consequence, clinical comparisons of the concentrations of these compounds in normal and psychotic states have almost exclusively been based on an analysis of the parent indolealkylamines alone.

In a series of recent studies (Sitaram et al. 1987a,b,c), we have examined the metabolism of DMT and 5-MeODMT in the rat and now attempt to address the issues raised by our findings. The objectives of our studies have been to develop analytical techniques suitable for the isolation, separation, and characterization of metabolites of the psycho-

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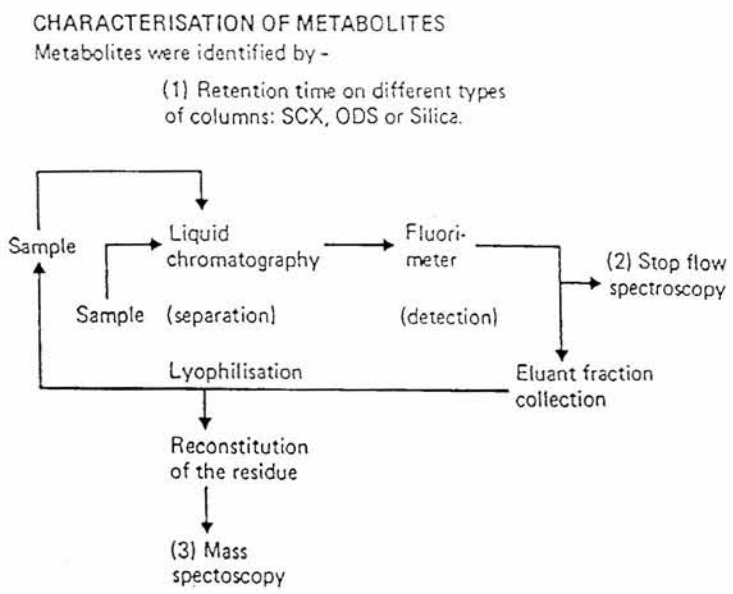

Figure 1. A summary of analytical strategies for the separation and characterization of the psychotomimetic indolealkylamines and their metabolites. Detailed descriptions of the component methodologies that form the basis for this strategy are presented in the following references. (Sitaram et al. 1981, 1983a,b, 1987a,b,c,d; McLeod et al. 1985).

tomimetic indolalkylamines generated in the presence of tissue extracts and in vivo, to delineate the potential routes of metabolism of these compounds, to identify quantitatively significant metabolites that retain structural characteristics uniquely identifiable with the parent compounds, and to determine the likely origins and distribution of such metabolites.

A basic element that has continually dogged research into the psychotomimetic indolalkylamines and their involvement in the psychotic illnesses has been the failure to apply techniques with adequate specificity and sensitivity. The minute quantities of these substances detectable in mammalian tissue and body fluids has greatly compounded the problems encountered. A major priority in our own studies has therefore been to establish a highly integrated analytical strategy (Figure 1) in which the identification of the indolealkylamines and their metabolites is supported by a number of different analytical procedures (Sitaram et al. 1981, 1983,a,b). The use of multidimensional liquid chromatographic separation using techniques as diverse as cation-exchange, reverse-phase, and normal phase chromatography have greatly enhanced the ability to separate and characterize a wide range of structurally related indolealkylamines. The use of on-line stop–flow spectroscopic analysis has provided valuable confirmation of assigned identities. The employment of appropriate mobile phase conditions has also permitted the recovery of select metabolites from the column eluent and their unequivocal characterization by gas-chromotography–mass-spectrometry (Sitaram et al. 1987d). These developments form a basis for accurate quantitation and unequivocal identification.

Studies on the elimination of both DMT and 5-MeODMT (Figures 2 and 3) following drug administration to rats (Sitaram et al. 1987b) attest to an extraordinarily rapid clearance of these compounds from the tissues. Despite this rapid clearance from the tissues and their concomitant appearance in the urine, a detailed examination of metabolic profiles

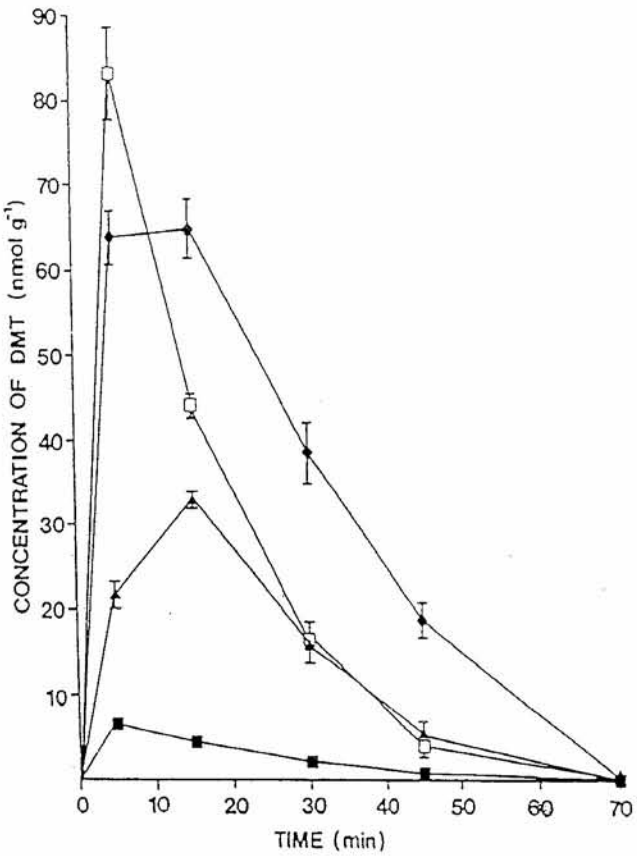

Figure 2. Concentration of DMT in tissues following its ip administration (10 mg/kg). Rats were killed at specified intervals, and the levels of DMT were determined in brain (▲), liver (□), kidney (◆), and blood (■), as described (Sitaram et al. 1987b). Results are expressed as mean ± SEM for 4 determinations.

in urine has indicated that less than 1.5% of an administered dose of DMT and less than 0.1% of 5-MeODMT appears in the urine unmetabolized (Sitaram et al. 1987c). These observations point to the very major role of metabolism in the elimination of these compounds from mammalian tissues.

The use of a combination of in vitro and in vivo techniques has led to the elucidation of a number of routes of metabolism and has resulted in the identification of several metabolites within tissues and body fluids of animals administered DMT or 5-MeODMT (Sitaram et al. 1987a,b,c). The routes of metabolism of DMT and 5-MeODMT so far identified in our studies on the rat include monoamine oxidase catalyzed oxidative deamination, *N*-demethylation, *O*-demethylation, and *N*-oxidation. Of these, only oxidation deamination and *N*-oxidation appear to be of major quantitative significance. Oxidative deamination of DMT and 5-MeODMT to their indoleacids was shown to be a major route of metabolism in brain, liver, and kidney. In contrast, although both in vitro studies (Sitaram et al. 1987a) and analyses of the levels of metabolites in vivo (Sitaram et al. 1987b) indicated that *N*-oxidation constituted a major route of metabolism in peripheral tissues, such as kidney and liver, it was of very minor significance in brain. *N*-Demeth-

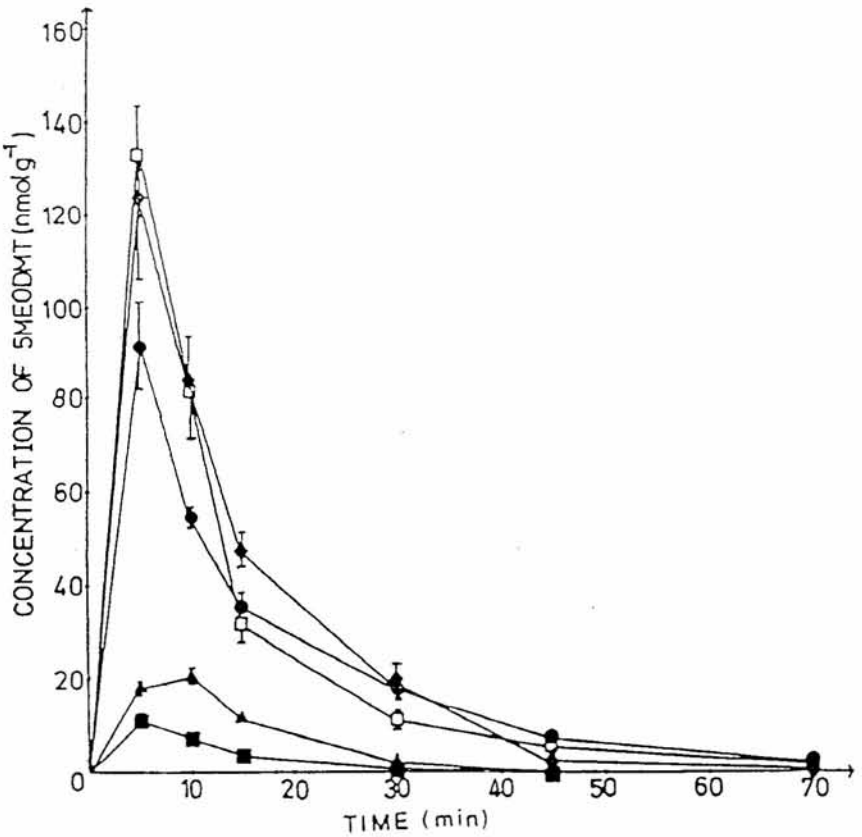

Figure 3. Concentration of 5-MeODMT in tissues following its ip (10 mg/kg) administration. Rats were killed at specified intervals, and the levels of 5-MeODMT were determined in brain (▲), liver (□), kidney (♦), adrenals (●), and blood (■) as described (Sitaram et al. 1987b). Results are expressed as means ± SEM for 4 determinations.

ylation and *O*-demethylation were extremely minor routes of metabolism in all tissues examined (Sitaram et al. 1987a,b). Such observations provide valuable insights into the likely origin and ultimate distribution of key metabolites.

A study of the rate of elimination of the characteristic metabolites of DMT and 5-MeODMT from rat tissues (Figures 4 and 5) indicated that not only the parent compounds, but also their metabolites (Sitaram et al. 1987b), were subject to rapid clearance. Furthermore, a study of the renal excretion of these compounds confirmed that their appearance in urine was concomittant with their disappearance from the tissues (Sitaram et al. 1987c).

Detailed studies of urinary excretion (Sitaram et al. 1987c) revealed that despite the identification of several structurally characteristic metabolites of DMT and 5-MeODMT, such as *N*-methyltryptamine (NMT) *N*,*N*-dimethyl-tryptamine-*N*-oxide (DMT-NO), 5-methoxy-*N*-methytryptamine (5-MeONMT), 5-methoxy-*N*, *N*-dimethyltryptamine-*N*-oxide (5-MeODMT-NO), and 5-hydroxy-*N*, *N*-dimethyltryptamine (5-OHDMT), only about 8% of an administered dose of DMT or 5-MeODMT (10 mg/kg) could ultimately be accounted for in the form of these metabolites.

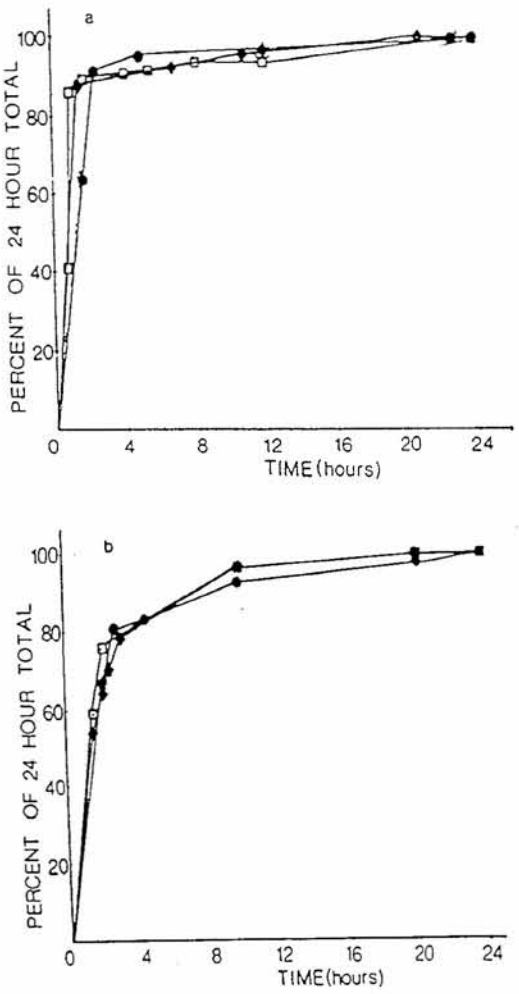

Figure 4. Amount of 5-MeODMT appearing in the urine during the 24 h following 5-MeODMT administration (10 mg/kg) to (a) control animals (100% = 18.9 ± 3.6 nmol/24 h) and (b) animals pretreated with iproniazid (100% = 470 ± 57 nmol/24 h). Analyses were performed as described by Sitaram et al. (1987c).

An examination of the pathways of metabolism so far identified indicates that metabolism proceeds to both derivatives, which retain structural characteristics uniquely identifiable with the parent compounds (e.g., the *N*-oxides) and to noncharacteristic metabolites such as indoleacetic acid and 5-methoxyindoleacetic acid, which are major products of the catabolism of other endogenous indoleamines.

In view of the major quantitative significance of oxidative deamination as a route of metabolism for both DMT and 5-MeODMT and the fact that this route resulted in the formation of noncharacteristic metabolites of very limited value as potential indicators of the presence of the psychotomimetic indolealkylamines in human body fluids, the possibility of redirecting metabolism toward structurally characteristic metabolites has been explored. The prior treatment of animals with the monoamine oxidase inhibitors iproniazid and pargyline was shown in our studies to successfully redirect metabolism, resulting in marked increases in the levels of characteristic metabolites (in particular the *N*-oxides of DMT and 5-MeODMT) detected in peripheral tissues, such as kidneys and liver, and in urine. In animals pretreated with monoamine oxidase inhibitors, the per-

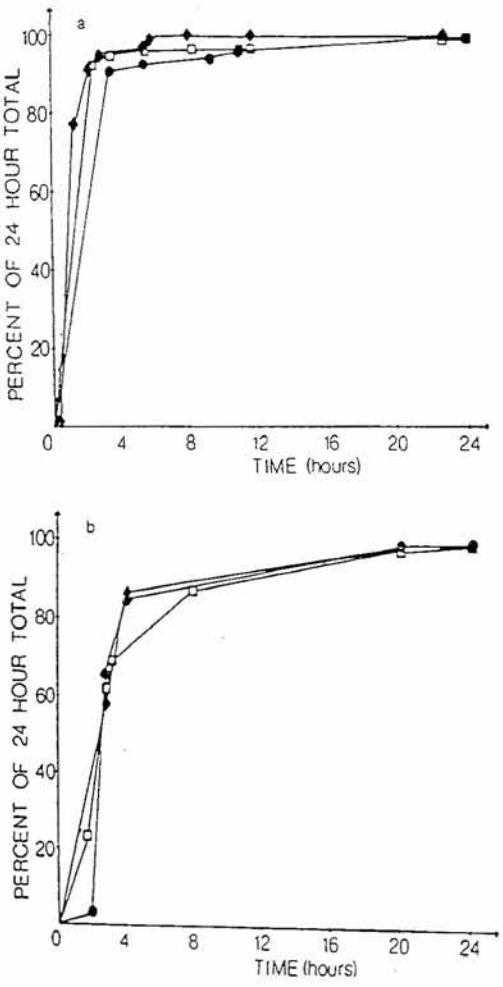

Figure 5. Amount of DMT appearing in the urine during the 24 h following DMT administration (10 mg/kg) to (a) control animals (100% = 191.3 ± 33.7 nmol/24 h) and (b) animals pretreated with iproniazid (100% = 360 ± 82 nmol/24 hr). Analyses were performed as described by Sitaram et al. (1987c).

centage of the administered dose of DMT and 5-MeODMT appearing as the parent compound or as structurally characteristic metabolites was increased from 8% to 25% and 52%, respectively.

Conclusions

Although numerous studies in the last 10 years have identified DMT, 5-MeODMT, and 5-OHDMT in human body fluids and many have suggested a relationship between their concentrations and the presence of psychoses, not a single report, with the exception of those emanating from the laboratories of Richard Rodnight (Oon et al. 1977b), has involved an analysis of any structurally characteristic metabolites of these compounds. It is interesting to note that the only metabolite studied by Rodnight et al. (Oon et al. 1977b) was NMT, which our studies on the rat indicate is an extremely minor metabolite.

Given the observations just described, it is clear that the identification of suitable structurally characteristic metabolites and the development of strategies to increase the

probability of recovering them from body fluids is an absolute prerequisite to the development of clinical studies that have the capacity to provide unequivocal evidence that the psychotomimetic indolealkylamines are involved in the processes of psychotic illness.

Our studies have identified a number of potentially suitable metabolites and emphasize the need to consider the effect of renal clearance on their ultimate disposition. The potential use of monoamine oxidase inhibitor pretreatment to maximize the probability of detecting the psychotomimetic indolealkylamines and their characteristic metabolites has been demonstrated.

Although our studies to date on the rat have provided valuable insights into the potential routes of biotransformation in mammalian tissues, complete metabolic profiles for DMT, 5-MeODMT, and 5-OHDMT remain to be established. In view of possible species differences, it is desirable that similar studies be ultimately performed in humans. Although ethical considerations will undoubtedly limit the nature of such experimentation, studies using extracts from human postmortem or biopsy tissues may provide valuable confirmatory evidence for the existence and relative significance of individual routes of metabolism. In addition, detailed analyses of metabolic profiles in human body fluids, such as cerebrospinal fluid, plasma, and urine, following administration of the psychotomimetic indolealkylamines to humans should be given serious consideration.

We believe that the development of suitable analytical strategies, such as those outlined in Fig. 1, and the accumulation of comprehensive data on the metabolism, tissue distribution, and clearance of the psychotomimetic indolealkylamines in animals will maximize the opportunity for credible interpretation of data generated by the limited experimental approaches available in human studies.

In summary, it is hoped that a convincing case has been made for the need to systematically elucidate the biotransformation of these compounds prior to attempting further clinical studies on the psychotomimetic indolealkylamines.

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