Fate and Metabolism of Some Hallucinogenic Indolealkylamines*

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Introduction

Many of the indole bases closely related to 5-HT have been studied as hallucinogenic agents. Among them are dimethyltryptamine (DMT), 5-hydroxydimethyltryptamine (5-OH-DMT, bufotenine) and 5-methoxydimethyltryptamine (5-MeO-DMT).

The first of these bases to receive pharmacologic attention was bufotenine (5-OH-DMT). Handovsky (1920) isolated this compound from toad venom and studied its effects on circulation. It was synthesized by Wieland *et al.* (1934). Bufotenine and DMT were later found to occur in a plant [*Piptadenia peregrina* (Leguminosae)] used for intoxicating purposes (Stromberg, 1954; Fish *et al.*, 1955). As a result of these studies synthetic dimethyltryptamine (DMT) has come to be used experimentally by psychiatrists in order to produce short-lasting states of illusion and hallucination (Szara, 1957; Szara and Rockland, 1962; Böszörményi and Brunecker, 1957).

The hallucinogenic properties of DMT are now well documented. The results with regard to bufotenine are more controversial. Hawkins and Fabing (1956) reported that intravenous injection in human volunteers resulted in primary visual disturbances, alteration of time and space perception, and paresthesias. However, neither Isbell (1957) nor Turner and Merlis (1959) in their carefully conducted studies could substantiate the claim that bufotenine injections had any effect on the central nervous system, whereas DMT under the same experimental conditions had a clear-cut psychotomimetic action.

5-MeO-DMT was found in plants for the first time by Pachter *et al.* (1959). It is the main component of certain intoxicating snuffs used by South American Indian tribes (Holmstedt *et al.*, 1964; Holmstedt, 1965). A full ethnopharmacologic description of the psychotomimetic effects of the drugs has been given by Holmstedt and Lindgren (1967). Recently the compound has been found together with bufotenine in the skin of a toad (Erspamer *et al.*, 1965).

* This investigation was supported by Grant MH 12007-02 from The National Institute of Mental Health, U.S. Public Health Service, Chevy Chase, Maryland and by Grant B 67-40X-671-02 from the Swedish Medical Research Council.

The animal experiments by Gessner and Page (1962) and Benington *et al.* (1965) have pointed to the strong action of synthetic 5-MeO-DMT on the central nervous system, and its important role in the elucidation of central nervous mechanisms.

It is generally believed that the tertiary tryptamines in mammals are metabolized by hydroxylation occurring at the six position. Szara and Hearst (1962) postulated that the behavioral effects of *N*,*N*-dimethyltryptamine in rats were due to a metabolite. They suggested on the basis of paper chromatography, that the 6-hydroxyl metabolite was the active form (Szara and Axelrod, 1959; Sai-Halász *et al.*, 1958). Their finding indicates that other indoles might also have their biological action altered by 6-hydroxylation. Such hydroxylation has been demonstrated to occur in tryptamine (Jepson *et al.*, 1962) and melatonin (Kopin *et al.*, 1961; Taborsky *et al.*, 1965). For other compounds no 6-hydroxylation has been found (Taborsky *et al.*, 1966).

Other possible pathways of metabolism are demethylation and deamination. Since either the original amine or metabolites can be made responsible for the psychotomimetic effect, it seemed warranted to study the metabolism of the compounds further and particularly that of the important new hallucinogen 5-MeO-DMT. A study of the possible formation of the urinary indolic acids was undertaken by means of gas chromatography and mass spectrometry and correlated to behavioral and motor activities of rat pretreated in different ways.

Material and Methods

Reference Compounds and Reagents

5-Methoxy-*N*,*N*-dimethyltryptamine was placed at our disposal by Dr. A. Hofmann, Sandoz A.G., Basle.

5-Methoxy-*N*,*N*-dimethyltryptamine-2′-^{14}C was synthesized by a method described by Kalberer *et al.* (1962) with the following modifications. 5-Methoxyindole was used as starting material and converted to 5-methoxygramine by treatment with dimethylamine in the presence of formaldehyde and acetic acid. 5-Methoxygramine was then converted to 5-methoxygraminemethosulfate according to Schöpf and Thesing (1951). The specific activity of the synthesized 5-MeO-DMT was found to be 0.93 mcuries/mmole, corresponding to 4.25 μcuries/mg base.

N,*N*-Dimethyltryptamine, indole-3-acetic acid (IAA), 5-hydroxyindole-3-acetic acid (5-OH-IAA), 5-methoxyindole-3-acetic acid (5-MeO-IAA) (Aldrich Chemical Co., Inc., Milwaukee, Wis.).

Bufotenine, a preparation from *Piptadenia peregrina*, prepared by E. C. Horning, Baylor University, College of Medicine, Texas Medical Center, Houston, Texas.

SKF 525 A (2-diethylaminoethyl-propyldiphenylacetate) was obtained from Smith Kline and French Co.

MO 911 (pargyline = *N*-methyl-*N*-benzyl-2-propylamine hydrochloride) was obtained from Abbott Co.

Chlorpromazine and atropine sulfate were obtained commercially.

All other reagents used were of "reagent grade" from different manufacturers.

Material Used in Gas Chromatography–Mass Spectrometry

Gas Chrom P 100–120 mesh, Applied Science Lab., State College, Pa.

OV–17 phenylmethylsilicone, Applied Science Lab.

Dichlorodimethylsilane, Hopkin and Williams Ltd., Essex, England.

Extraction of Acids from Urine

Rat urine (24-hour collection) was adjusted to pH 7.0 and incubated with 100 mg of bacterial β-glucuronidase (Type 1, Sigma Chemical Co., St. Louis Mo.) in the presence of 3 ml phosphate buffer (pH 7.0) and 0.2 ml of chloroform at 37°C in a stoppered flask and subjected to shaking for 12 hours. The incubated sample was added to an equal volume of saturated sodium chloride solution and adjusted to pH 1.0 with 6 *N* hydrochloric acid. The solution was extracted with three 25-ml portions of ethyl acetate followed by extraction with three 25-ml portions of ether. The combined ethyl acetate and ether extracts were dried with sodium sulfate and filtered. The filtrate was taken to dryness under reduced pressure (Rotavapor). The residue containing extracted acids and neutral compounds was dissolved in 0.5 ml of methanol.

Preparation of Derivatives

The urinary acids in 0.5 ml methanol were converted to methyl esters with a solution of diazomethane in ether (prepared from Diazold, Aldrich Chemical Co.). The ether, excess diazomethane, and methanol were removed as quickly as possible with a stream of nitrogen. The residue was dissolved in 0.2 ml methanol.

Gas Chromatography

Gas chromatographic analysis was performed with an F & M Model 400 apparatus equipped with a hydrogen flame ionization detection system.

The column support, 100–120 mesh Gas Chrom P, was acid-washed and silanized according to the method described by Horning *et al.* (1963). The coating was applied by the filtration technique (Horning *et al.*, 1959, 1963). The column packing used was 5% OV-17. Separations were carried out with a 2.25 m × 3.2 mm inside diameter glass column. After 5 minutes delay at 160° the column was operated with temperature programming from 160° to 200°C at 1° per minute. The flash heater and detector cell were kept at 250°. The flow rate of the carrier gas, nitrogen, was 60 ml/min. Samples were

injected in methanol solution with a Hamilton syringe. The stream splitter system was used as described by Tham (1966).

Gas Chromatography–Mass Spectrometry

The principles of the technique have been described in detail by Ryhage (1964). The mass spectrometry work was carried out with LKB 9000 gas chromatograph–mass spectrometer including a fast scan system and the Ryhage "molecule separator." The ion source was at 250° and the ionizing potential and current were 70 eV and 60 μA, respectively. The separations were made on a system consisting of 5% OV-17 at 220°. The column consisted of a 2 m × 3.2 mm glass tube. Helium was used as the carrier gas. At the outlet of the column, the separated compounds were concentrated and continuously fed into the mass spectrometer. The mass spectrometer simultaneously serves as a gas chromatographic detector and for recording of mass spectra of the compounds as they emerge from the column. The reference compounds were run through the column, and the mass spectra of the compounds recorded. The urinary fractions prepared as described above were run under identical conditions, and mass spectra were recorded from the gas chromatographic peaks having the same retention times as those of the reference compounds.

Behavior

Male Sprague-Dawley rats of an approximate age of 200 days were used. The animals were allowed food and water *ad libitum*. The experiments were performed in ordinary Skinner boxes. The chambers were enclosed in ventilated and soundproof chests and all experimental contingencies were controlled by a system of relays and timers in an adjacent room. The behavior was recorded on counters and cumulative recorders.

A conditioned avoidance response schedule with external stimulus was used. On this schedule the animal is at rest during the first 30 seconds of the trial whereafter the conditioned stimulus (a buzzer) stays on for 15 seconds. If the animal fails to terminate the conditioned stimulus by pressing a bar, the unconditioned stimulus (electric shock of 2 mA) is presented for 3 seconds. By pressing the bar during the unconditioned stimulus period the animal terminates the shock (escape response). Each bar press or the end of the unconditioned stimulus starts the schedule from the beginning. Every test period contained 100 trials. The animals were extensively trained to almost complete avoidance response. All injections were made intraperitoneally.

Tremor Recording

Tremor was recorded according to a method described by Holmstedt and Lundgren (1966). The rat is placed on a plastic air cushion contained in an

isolation box. The pressure changes are transferred to electrical signals by means of a pressure transducer and filtered to exclude recording of normal activity and then amplified and converted to pulses. The output pulses are recorded on a printer in 1-minute intervals. Drugs were administered intraperitoneally.

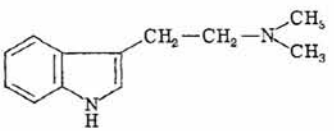
Urinary Excretion of Labeled Material

^{14}C-labeled 5-MeO-DMT was given intraperitoneally to four rats (Sprague-Dawley) at a dose of 10 mg/kg. The urine was sampled at different time intervals and the total content of labeled metabolites was calculated by scintillation counting in a Packard TriCarb 3375.

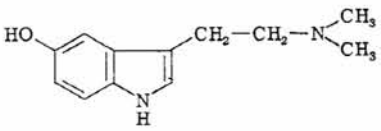
Results

Behavior and Tremor Experiments

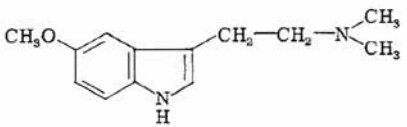
The general symptoms upon low doses of 5-MeO-DMT are a slight excitation, tremor, and some salivation. Higher doses (over 5 mg/kg) give rise to a pronounced tremor, and increasing the dose further may result in paralysis of the hindlegs, tapping with the forelegs, convulsions and respiratory arrest.



DMT



5-OH-DMT
(Bufotenine)



5-MeO-DMT

Fig. 1.

5-MeO-DMT given to rats at a dose of 1 mg/kg elicits a hyperactivity which gives rise to increased response rate in the conditioned avoidance response situation. The behavior is still adequate from the point of view that the animal avoids most of the shocks. When the same dose is given after

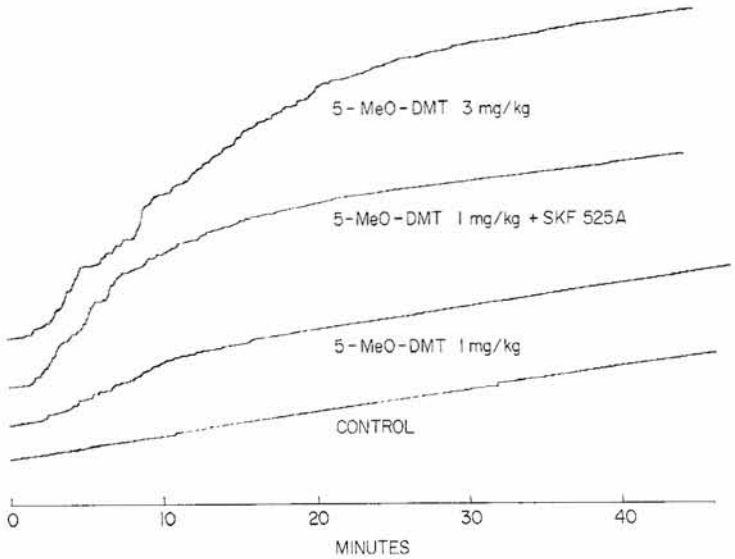


FIG. 2. Typical cumulative lever-pressing record for rat after treatment with 5-MeO-DMT and SKF 525 A. Note the increased response activity during the first 10–20 minutes after treatment. Brief deflections in the record indicate the delivery of a shock.

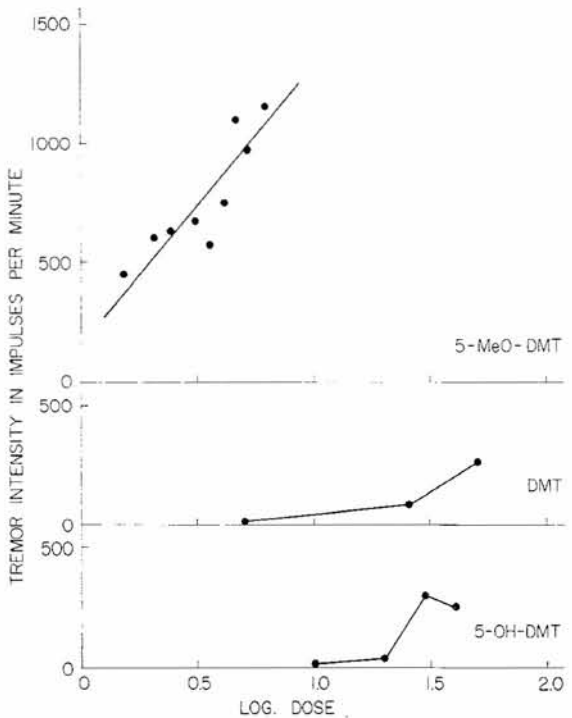


FIG. 3. Recording of tremor after various doses of 5-MeO-DMT, DMT, and 5-OH-DMT. Log dose given in mg/kg.

pretreatment with 25 mg/kg of SKF 525 A, the reaction to 5-MeO-DMT is intensified and prolonged but every shock is still avoided. Three milligrams per kilogram of 5-MeO-DMT given to animals that have not been pretreated elicits a reaction somewhat of the order of that after 1 mg/kg in the pretreated animals (Fig. 2).

5-MeO-DMT gives rise to tremor when administered intraperitoneally to rats. The tremor is dose-dependent in the range 1–10 mg/kg. DMT and bufotenine also give rise to tremor but at much higher doses, and the tremor

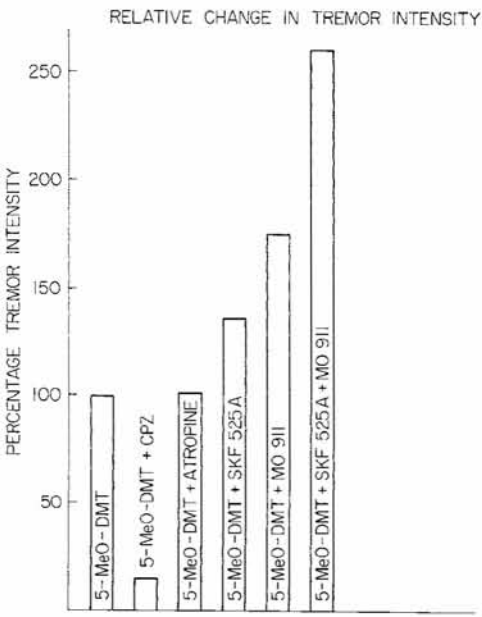


FIG. 4. Effect of pretreatment with various drugs on the tremor intensity expressed as percentage of the tremor elicited by a dose 5-MeO-DMT. Five milligrams per kilogram 5-MeO-DMT used except in experiments with SKF 525 A and MO 911, in which case 3 mg/kg was administered. Pretreatment with SKF 525 A 25 mg/kg, MO 911 5 mg/kg and atropine 100 mg/kg 30 minutes before administration of 5-MeO-DMT.

following the injections of these substances is not as well defined and can hardly be quantitated (Fig. 3).

The tremor produced by 5-MeO-DMT is not counteracted by atropine at a dose of 100 mg/kg (Fig. 4), but pretreatment with 5 mg/kg chlorpromazine gives a pronounced reduction of the tremor reaction (Figs. 4 and 5). Pretreatment with the enzyme inhibitor SKF 525-A (Fig. 4) or the MAO inhibitor MO 911 (Figs. 4 and 6) strongly enhances the tremor activity as does combined pretreatment with both compounds (Fig. 4).

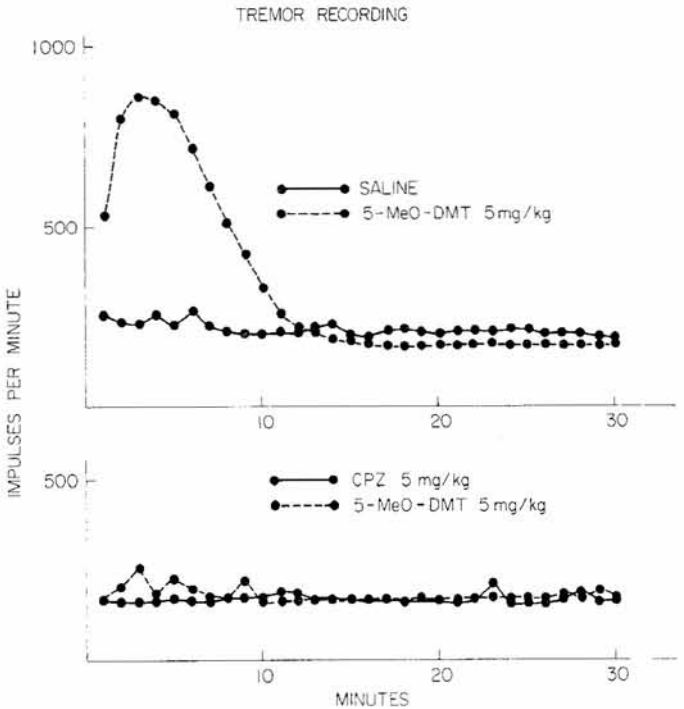


FIG. 5. Tremor curve in rat treated with 5-MeO-DMT alone (upper curve) and in combination with chlorpromazine (lower curve). Chlorpromazine given (5 mg/kg) 30 minutes prior to 5-MeO-DMT.

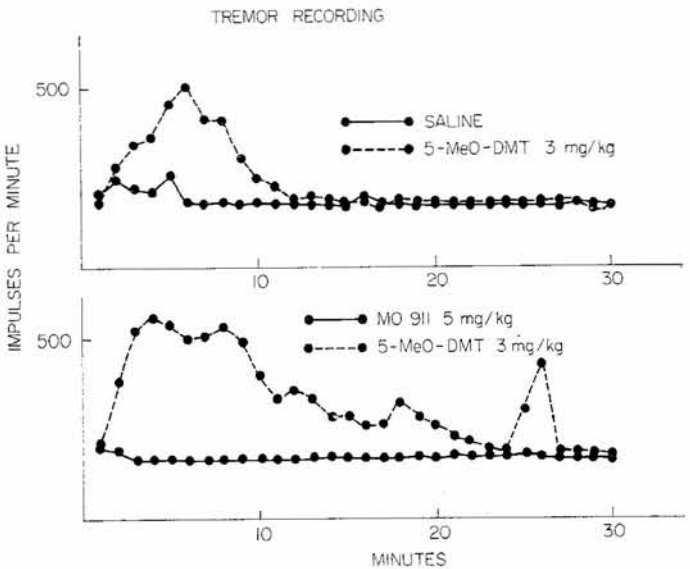


FIG. 6. Tremor curve in rat treated with 5-MeO-DMT alone (upper curve) and in combination with MO 911 (lower curve). MO 911 given 30 minutes prior to 5-MeO-DMT.

Excretion Experiments

When upon administration of labeled 5-MeO-DMT the total amount of radioactivity in urine was measured against time, it was found that most of the material had been excreted within 12 hours. A slow excretion proceeds during the following days, reaching approximately 60% of the administered labeled compound (Fig. 7). When urine was extracted at pH 1, 90% of the radioactivity was recovered in the organic solvent. This fraction was taken for further analysis by means of gas chromatography–mass spectrometry.

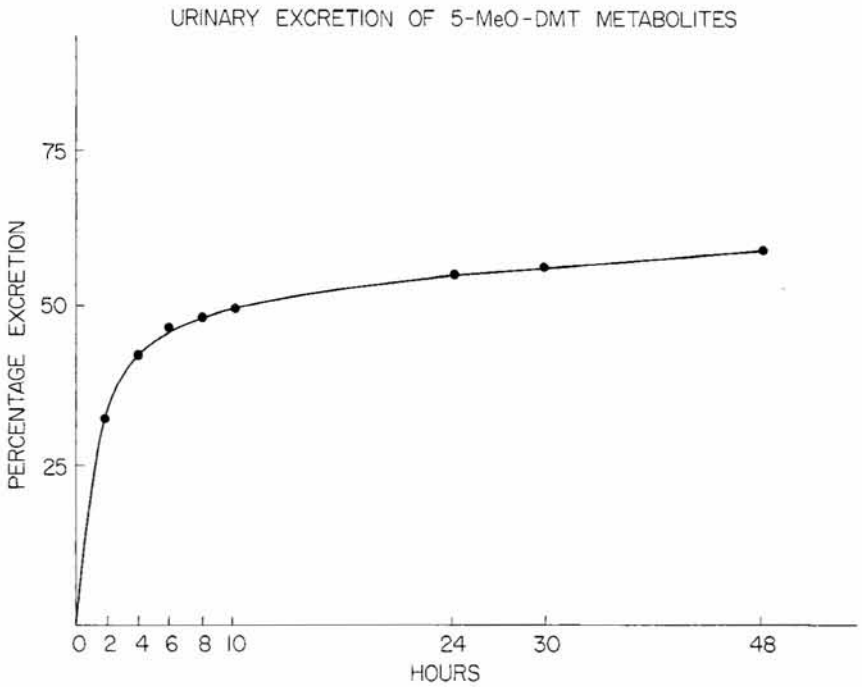


Fig. 7. Excretion of radioactive material in the urine of rats treated with ^{14}C-labeled 5-MeO-DMT (10 mg/kg).

The gas chromatograms from urine of rats treated with the three amines are presented in Fig. 8. In all three cases the corresponding indolic acids were found in fractions of the urine extracted at pH 1. The acids could be unequivocally identified by their mass spectra as compared to mass spectra of synthetic compounds run under identical conditions (Figs. 9, 10, and 11).

The gas chromatogram of the excretion products after treatment with labeled 5-MeO-DMT (lower panel) was trapped at intervals through the stream splitter system of the instrument and the eluate subjected to analysis

for radioactivity. The radioactivity was limited exclusively to the peak representing 5-methoxyindoleacetic acid methylester.

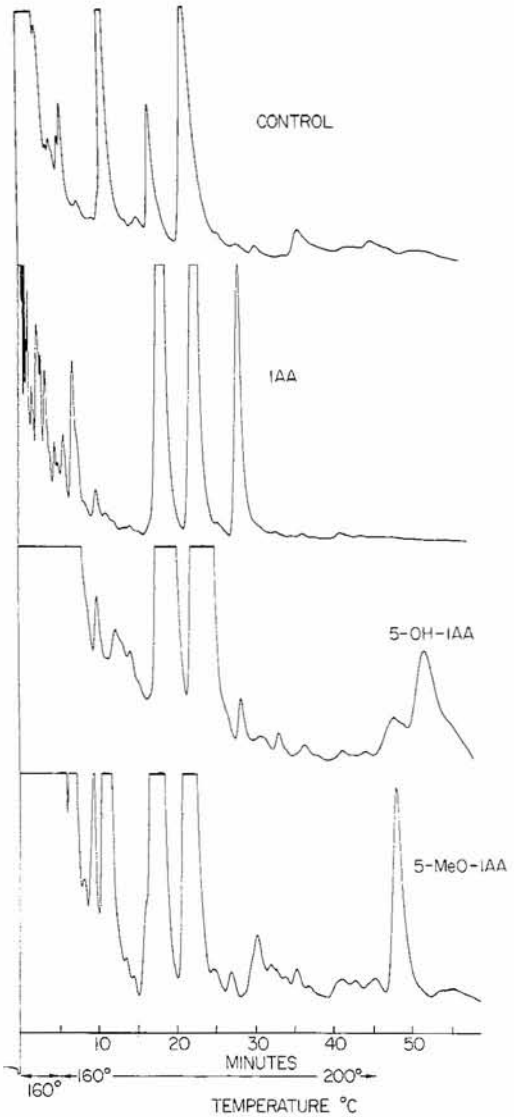


FIG. 8. Gas chromatographic analysis of urinary aromatic acids as methyl esters. Gas-liquid chromatography conditions as described in text. Temperature programming. Upper panel: Urine from untreated rat. Second panel: Urine from rat after injection of DMT (5 mg/kg). Third panel: Urine from rat after injection of 5-OH-DMT (5 mg/kg). Lower panel: Urine from rat after injection of 5-MeO-DMT (5 mg/kg).

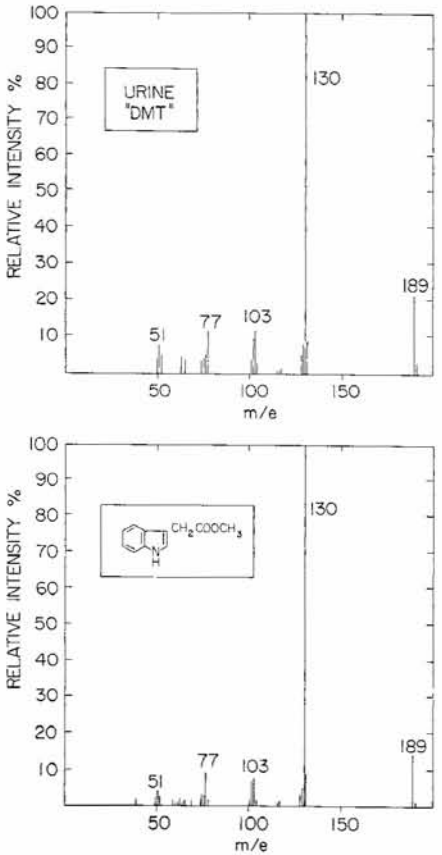


FIG. 9. Upper panel: Mass spectrum of gas chromatographic peak in urine extract from rat treated with 5 mg/kg DMT. Peak at same retention time as that of synthetic IAA (methyl ester). Lower panel: Mass spectrum of methyl ester of synthetic IAA.

Discussion

Unsubstituted and 5-substituted indoles command special interest with regard to their toxicological effects in two instances. First, there are reports of cases of a disease in Australian sheep called "staggers." The sheep are pastured largely on a perennial grass *Phalaris tuberosa L.* (Gallagher *et al.*, 1964). Investigation of this and related species of *Phalaris* has led to the isolation of DMT, 5-MeO-DMT, and 5-OH-DMT (Wilkinson, 1958; Culvenor *et al.*, 1964). Second, as mentioned in the introduction, the same tryptamines are present in drugs used in South America for intoxicating purposes (Holmstedt and Lindgren, 1967). Both the somatic and the psychic effects of the substances are thus documented.

The most active of the compounds mentioned above is 5-MeO-DMT (Gessner and Page, 1962). Benington *et al.* (1965) report that the effect of 5-MeO-DMT on cat behavior is dramatic. An intense sham rage response is induced within a few minutes. Of all drugs examined that induce sham rage

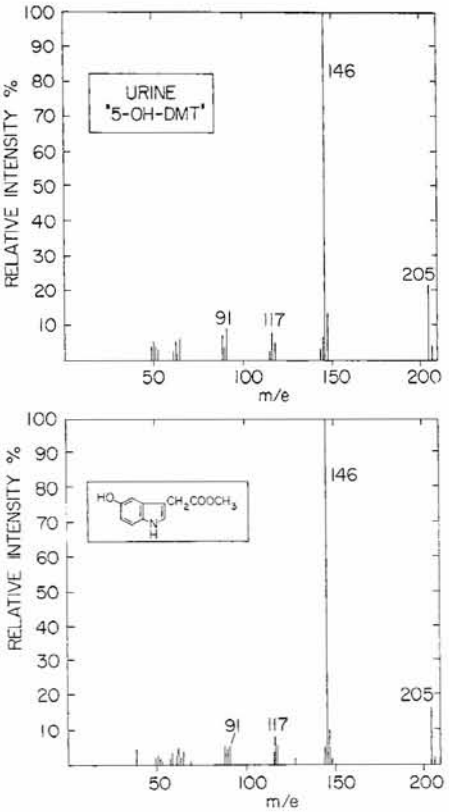


FIG. 10. Upper panel: Mass spectrum of gas chromatographic peak in urine extract from rat treated with 5 mg/kg 5-OH-DMT. Peak at same retention time as that of synthetic 5-OH-DMT (methyl ester). Lower panel: Mass spectrum of the methyl ester of synthetic 5-OH-IAA.

in the cat, 5-MeO-DMT is one of the most potent, and its potency is very close to that of lysergic acid diethylamide (LSD-25). From the rapid onset of the rage response induced by 5-MeO-DMT by different routes of administration, it is evident that the drug reaches the sites of action rapidly. The nature of the response suggests a central effect of a relatively short duration.

Our own experiments demonstrate, in addition, that 5-MeO-DMT has the

ability to produce tremor in rat similar to that produced by well-known tremor-producing agents. The tremor can be quantitated and this parameter has been utilized.

Tremor produced by oxotremorine or arecoline has been shown to bear a certain relationship to the acetylcholine concentration in brain and may be

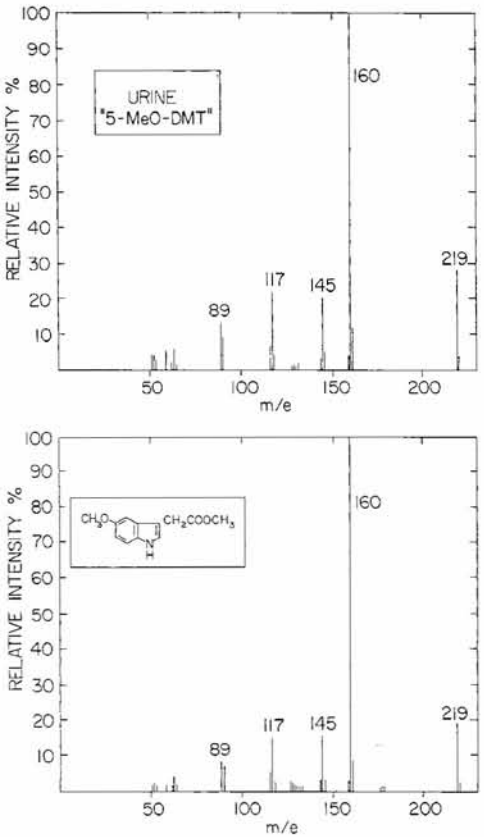


FIG. 11. Upper panel: Mass spectrum of gas chromatographic peak in urine extract from rat treated with 5 mg/kg 5-MeO-DMT. Peak at same retention time as that of synthetic 5-MeO-IAA (methyl ester). Lower panel: Mass spectrum of methyl ester of synthetic 5-MeO-IAA.

counteracted by atropine (Holmstedt and Lundgren, 1966). This is not the case with the tremor produced by 5-MeO-DMT and it indicates a different origin. The tremor produced by the indole can, however, be counteracted by chlorpromazine and is strongly enhanced by pretreatment with MAO inhibitors. The combined pretreatment with SKF 525 A and an MAO

inhibitor gives an even more increased tremor response. The tremor-producing target area for 5-MeO-DMT in the central nervous system is unknown at the moment but could possibly be related to serotoninergic fibres in the brain that have recently been shown to be involved in extrapyramidal functions (Sourkes and Poirier, 1966).

5-MeO-DMT is not an MAO inhibitor (Ahlborg, to be published). The fact that its action on the tremor can be potentiated by inhibitors of that enzyme can perhaps best be explained by interference with its breakdown through oxidative deamination (see below). A synergism with accumulated monoamines cannot, however, be excluded at the moment.

Gessner and Page (1962) made a quantitative comparison of the behavioral effects of several substituted tryptamines and showed that 5-MeO-DMT was the most active one followed in order by DMT, DET, and 5-OH-DMT. The dose range used for 5-MeO-DMT was very high as compared to our experiments, in fact so high that a pronounced tremor ought to have been an outstanding symptom. It might be suspected that this somatic effect may have influenced the recorded behavior. If with a similar technique lower doses are used, behavior is still affected but the result is a temporary increase in response activity, adequate avoidance behavior being maintained.

According to Szara (1961), DMT undergoes hydroxylation to produce *N*,*N*-dimethyl-6-hydroxytryptamine as a principal urinary metabolite. Szara also observed that schizophrenic patients who have a more intense psychological reaction to the related *N*,*N*-diethyltryptamine also have a correspondingly high urinary output of *N*,*N*-diethyl-6-hydroxytryptamine. As a result of this work, Szara and Rockland (1962) suggested a possible role of 6-hydroxylation in the production of endogenous psychotoxic metabolites.

It is of interest in this connection to recapitulate what is known with certainty about the metabolism of related compounds, especially with regard to ring hydroxylation and oxidative deamination.

Liver microsomes *in vitro* hydroxylate tryptamine, indoleacetic acid, and related indoles to the corresponding 6-hydroxy derivatives. The microsomal system does not form 5- or 7-hydroxyindoles and is, therefore, not a mechanism for 5-HT biosynthesis (Jepson *et al.*, 1962).

Labeled 5-HT is excreted to 35–83% as 5-HIAA. It is also acetylated (McIsaac and Page, 1959) and occurs in the form of six other metabolites (Iskrić and Keglević, 1964). These compounds appear in much smaller amounts than 5-HIAA.

The related compound, melatonin, according to Kopin *et al.* (1960, 1961) is metabolized to 79–80% as the sulfate conjugate of 6-hydroxymelatonin, whereas the glucuronic acid conjugate of this compound represents only 5% of the administered radioactivity. Free 6-hydroxymelatonin also occurs (Taborsky *et al.*, 1965). Less than 0.5% of administered melatonin is con-

verted to 5-methoxyindoleacetic acid. Efforts to detect melatonin and 6-hydroxymelatonin in human urine have been unsuccessful (Greer and Williams, 1967). Melatonin thus seems to be extraordinary in the series in that it is metabolized mainly through 6-hydroxylation.

Szara and Hearst (1962) have reported in several papers that the presumed metabolite of diethyltryptamine, 6-hydroxydiethyltryptamine, was more active in disturbing animal behavior than the parent compound. The elicited behavior changes were qualitatively similar, but the reaction to 6-hydroxydiethyltryptamine was more stable. In human experiments Rosenberg *et al.* (1963) have found the 6-hydroxylated derivative of DMT to be inactive.

Taborsky *et al.* (1966) have shown that 6-hydroxy-5-methoxy-*N*,*N*-dimethyltryptamine is less potent in disturbing behavior than its non-hydroxylated form. In their metabolic study, however, they postulated the possible occurrence of another hydroxylated metabolite.

There is good evidence that SKF 525 A inhibits demethylation and deamination as well as hydroxylation of ring structures (Brodie, 1956; Netter, 1962). The treatment with SKF 525 A would, therefore, be suspected to decrease the effects of 5-MeO-DMT if the compound has to be metabolized to the hydroxylated form in order to be active. To test this hypothesis, the effect of 5-MeO-DMT was studied before and after pretreatment with SKF 525 A on both conditioned avoidance response and tremor-producing activity. Our results show that the pretreatment with SKF 525 A enhances both the behavioral effect and the tremor after 5-MeO-DMT, which indicates that the substance is active in its unmetabolized form.

With regard to other compounds, it may be mentioned that Erspamer (1955) upon administration of bufotenine to rats could detect 5-HIAA in the urine but also unchanged bufotenine and two unknown compounds. Gessner *et al.* (1960) could only identify about 7% of administered bufotenine as 5-HIAA as compared to 22% unchanged bufotenine. Administration of 5-methoxytryptamine is followed by the appearance in urine of great amounts of 5-methoxyindoleacetic acid, that of tryptamine and *N*-methyltryptamines by the appearance of varying amounts of indoleacetic acid, both free and conjugated (Erspamer, 1955).

Taborsky and McIsaac (1964) found 90% of injected 5-methoxy-*N*-methyltryptamine excreted in urine within 24 hours. 5-Methoxyindoleacetic acid accounted for 95% of the excretion products. There was evidence that a minor metabolite was a glucuronide, presumably a 6-hydroxy derivative.

There is thus generally good evidence that the indoleacetic acids can be found in urine following administration of the corresponding indolealkylamines. Our own evidence corroborates this. Substantial amounts of the corresponding acids occur in urine of rats after administration of DMT, 5-OH-DMT, and 5-MeO-DMT. In the latter case it could be demonstrated

with modern techniques that a major part is excreted as 5-MeO-IAA. This quantitatively leaves very little for supposed metabolites with higher psychoactivity. The investigation of Taborsky *et al.* (1966) has also made this highly unlikely.

Summary

The behavioral action and the tremor-producing activity and metabolism of 5-methoxy-dimethyltryptamine, dimethyltryptamine, and bufotenine has been studied.

5-Methoxydimethyltryptamine in low doses elicits hyperactivity in a conditioned avoidance response situation. This effect is enhanced by pretreatment with SKF 525 A.

5-Methoxydimethyltryptamine and, to a lesser degree, dimethyltryptamine and bufotenine give rise to tremor. The tremor is antagonized by pretreatment with chlorpromazine and enhanced by pretreatment with SKF 525 A and an MAO inhibitor. Atropine does not counteract the tremor.

After administration of radioactive 5-methoxy-dimethyltryptamine 60% of the radioactivity was excreted within 12 hours.

The metabolic fate of the three substances has been studied in rats, and metabolites in urine identified by gas chromatography and mass spectrometry. The main metabolite of administered 5-methoxy-dimethyltryptamine is 5-methoxyindoleacetic acid which represents a major part of the urinary excretion. Of the other compounds, the corresponding acids seem to represent main excretion products.

The metabolism of the indolealkylamines and the theory of 6-hydroxylation are discussed.

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