A New Metabolic Pathway for *N,N*-Dimethyltryptamine

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N,N-*Dimethyltryptamine (DMT) undergoes a major structural alteration when added to whole human blood or its red blood cells in vitro. A new high-pressure liquid chromatography (HPLC) peak is present in extracts of these treated tissues. The compound responsible for this peak has been identified by ultraviolet spectrophotometry and by mass spectrometry as dimethylkynuramine (DMK). The enzyme responsible for this appears to be different from tryptophan 2,3-dioxygenase and also from indoleamine 2,3-dioxygenase.*

Introduction

Much of the work on the nature and metabolism of *N,N*-dimethyltryptamine (DMT) arose from the interest in the transmethylation hypothesis of schizophrenia. This conjecture is based on (1) the structural similarity between serotonin and its psychotomimetic analogs 5-OH-*N,N*-dimethyltryptamine (5-OH-DMT) and DMT, (2) the presence of tryptamine in human brain (Martin et al. 1972; Saavedra and Axelrod 1972a, 1972b), (3) the identification of enzymes capable of methylating serotonin (5-OH-TA) and tryptamine (TA) to 5-OH-DMT and DMT (Axelrod 1961, 1962), and (4) early reports suggesting that DMT is present in human body fluids. This hypothesis is supported with consistently reported observations that psychotic symptoms do become more intense in some schizophrenic patients treated with monoamine oxidase inhibitors and methionine. Presumably, these compounds increase the synthesis and decrease the breakdown of methylated indoleamines such as DMT (Pollin et al. 1961).

Tests of the transmethylation hypothesis have generally consisted of (1) a search in body fluids for 5-OH-DMT or DMT and (2) the identification of enzymes that could act on precursors to form 5-OH-DMT and DMT. The initial reports of DMT levels in the body fluids of schizophrenic patients and control subjects have not always been replicated (Walker et al. 1973; Wyatt et al. 1973a; Carpenter et al. 1975; Angrist et al. 1976; Oon et al. 1977; Corbett et al. 1978; Walker et al. 1979). One conclusion reached by all researchers, irrespective of whether they claimed to find DMT or felt that, if present, it was below their detectability level, was that no significant difference with respect to DMT

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concentrations could be found between schizophrenic and control populations. At the same time, *N*-methyltransferase enzymes have been reported in human lung, brain, and blood (Mandell and Morgan 1971; Mandel et al. 1972; Saavedra and Axelrod 1972b; Domino et al. 1973; Wyatt et al. 1973b, 1973c; Barchas et al. 1974; Wyatt et al. 1975; Rosengarten and Friedhoff 1976). Studies with these enzyme preparations showed that in addition to methylation of indoleamines, the formation of β-carbolines also occurred (Barchas et al. 1974). Searches of body fluids and tissues revealed that β-carboline and 1,2,3,4-tetra-hydro-β-carboline derivatives were present in brain and adrenal glands of rats and human platelets (Rommelspacher et al. 1980; Barker et al. 1981; Rommelspacher 1981; Rommelspacher et al. 1984).

Administration of DMT to humans resulted in a quick (2–3 min) onset of a psychotomimetic response that lasts about 1 hr (Szara 1956, 1961; Rosenberg et al. 1963). This paralleled DMT blood levels, which reached a maximum concentration 10 min after an intramuscular injection and almost disappeared 60 min later (Kaplan et al. 1974). Of the administered DMT, only 0.07% is recovered unaltered from urine (Kaplan et al. 1974) and only about 25% as the indoleacetic acid (IAA) (Szara 1956). Such low recovery suggests that there may be other unidentified, possibly psychotomimetic, metabolites of DMT. Incubation of DMT with rabbit liver microsomes produced additional metabolites, such as *N*-methyltryptamine (NMT), 6-hydroxy-DMT, DMT-*N*-oxide, and 6-hydroxy-DMT-*N*-oxide (Szara and Axelrod 1959). Metabolism of DMT by rat whole brain homogenate yielded IAA, DMT-*N*-oxide, NMT, TA, 2-methyl-1,2,3,4-tetrahydro-β-carboline (2-MTHBC), and 1,2,3,4,-tetrahydro-β-carboline (THBC) (Barker et al. 1980).

In attempting to do a DMT search in blood, a question arose as to whether DMT would be concentrated in plasma or associated with cells. Addition of radioactive DMT to whole blood revealed that over 50% of the added radioactivity was associated with cells. Addition of cold DMT to whole blood and the application of usual extraction procedures showed that the recovered DMT was significantly lower than expected for normal extraction losses. As DMT rapidly disappears from human blood in vivo and as there is an *N*-methyltransferase enzyme present in human erythrocytes, a possibility exists that there may be other erythrocytic enzymes that participate in the metabolism of methylated indoleamines. The objectives of this study were to determine if DMT can be metabolized and to identify the metabolites produced during the incubation of DMT with human erythrocytes in vitro.

Methods

Distribution of Radioactive DMT Between Plasma and Red Blood Cells

To a 10-ml sample of heparinized blood in a graduated conical test tube were added 10 μl (14 μg 556,000 dpm) of radioactively labeled DMT, containing ^{14}C in the α-position. The sample was mixed by inversion of the test tube 20 times. It was allowed to stand at room temperature for 15 min and then was centrifuged. The plasma was removed, and the cells were washed twice with 5-ml portions of isotonic saline. The saline washes were collected separately. The top 0.5 ml of the cells was removed and discarded in the process of removing the buffy layer. Acid protein-free filtrates of the plasma, the first and second saline washes, and the cells were prepared by treating 0.5 ml of each sample with the Folin-Wu (Hawk et al. 1954) tungstic acid solution (Hycel, Inc., Houston, TX). Alkaline protein-free filtrates were obtained by treating 0.5 ml of each sample with $Ba(OH)_2$ and

$ZnSO_4$ solutions (Friedman 1953) and with $ZnSO_4$ and NaOH solutions (Koch and Hanke 1953). One milliliter of each of the protein-free supernates was added to scintillation vials containing 10 ml of preblended liquid scintillation cocktail 3a70B (Research Products International Corporation, Mount Prospect, IL). A radioactivity count was accomplished on Beckman CPM-100 and LS-230 scintillation counters. Standard samples were also counted. The obtained counts were corrected for counting efficiency and dilutions.

High-Pressure Liquid Chromotography Analysis Showing DMT Disappearance from Red Blood Cells

Fifteen milliliters of human blood was centrifuged for 30 min at 2000 × *g*. The plasma and the buffy coat were removed. The red blood cells were washed with 15 ml of isotonic saline, centrifuged, and the saline wash was aspirated. To 2.5 ml of water, 2.5 ml of plasma, and 2.5 ml of red blood cells in separate tubes were added 15.4 μg (9.18×10^{-8} M) of DMT in 50 μl of isotonic saline and 23.1 μg of the internal standard desmethylimipramine (DMI) in 50 μl of isotonic saline. The samples were then mixed. The red blood cells were lysed by the addition of 5 ml of water. Two hundred microliters of 1.5 M NaOH was added to the water and the plasma samples; to the lysed cells, 1.0 ml of saturated NaOH solution was added. The approximate pH of the final solution was about 11.5 for H_20, 11.5 for plasmas, and 11.0 for RBCs. To each tube was added 10 ml of hexane, containing 1% isoamyl alcohol. The solutions were mixed on the vortex mixer for 2 min. After centrifugation, the organic layer was separated, and the aqueous layer was again extracted with the hexane–1% isoamyl alcohol solution. For each sample, the organic layers were combined and the DMT and DMI were back-extracted into 200 μl of 0.1 N H_2SO_4. One hundred microliters of the final solution was injected on the high-pressure liquid chromatography (HPLC) apparatus.

The analytical instrumentation consists of a Waters Associates (Milford, MA) solvent delivery system model 6000A, model U6K injector, and an Altex model 153 fixed wavelength UV detector. The separation was carried out on a C-18 reversed-phase column, 3.9 mm × 30 cm (μ-Bondapak, Waters Associates). The operating conditions were: flow rate, 1.5 ml/min; UV detector, 254 nm; sensitivity, 0.16 full scale. The mobile phase consisted of acetonitrile (40 ml) and 0.1 M phosphate buffer, pH 7.2 (60 ml), which was prepared from 0.05 mole Na_2HPO_4 and 0.05 mole NaH_2PO_4.

Additional Instrumentation

The UV spectra were obtained on a Beckman 25 spectrophotometer. The mass spectra were determined on a DuPont 21-491 double-focusing mass spectrometer (Dupont Instruments, Wilmington, DE) and an AEI M5-30 high-resolution instrument at Shrader Analytical and Consulting Laboratories, Inc. (Detroit, MI). Samples of interest eluting of the HPLC were collected and extracted into hexane. The hexane was concentrated to about 50 μl. Of the final solution, 10 μl was placed into a sample holder, which, after the evaporation of the solvent by a stream of N_2 gas, was mounted on the probe. The probe was inserted into the ionization chamber, and the sample was slowly heated. Automatic repetition of scanning by the mass spectrometer recorded the mass spectra of the evaporating compounds.

Results and Discussion

The distribution of the radioactive DMT between plasma and cells is presented in Table 1. The acidic Folin-Wu protein precipitation technique resulted in the removal of a large portion of the radioactivity with the protein precipitate. Of the recovered radioactivity, the lesser portion is obtained from the plasma (42.7% for Folin-Wu supernate, 42.3% for the $Ba(OH)_2$–$ZnSO_4$ supernate, and 42.1% for $ZnSO_4$–NaOH supernate). These data indicate that a large amount of the indigenous DMT, if present, would be associated with the cellular fraction. The addition of 140 μg and 14 μg of DMT to two 10-ml whole blood samples resulted in the same percentage of distribution. The recovered radioactivity from plasma for the two respective samples was: Folin-Wu supernate 43.0% versus 46.0%; $Ba(OH)_2$–$ZnSO_4$ supernate 42.8% versus 42.1%; $ZnSO_4$–NAOH supernate 41.3% versus 41.5%.

The relatively high radioactivity of the first and second saline washes of the cells indicates that at least a portion of radioactive compound or compounds is weakly bonded to the cells and can easily be washed off the cells.

As it was observed that over 50% of the radioactivity was associated with the RBCs, cold DMT was added to whole blood and extracted. The amount of the recovered DMT was significantly lower than expected for normal extraction losses. This question was pursued by the addition of 15.4 μg DMT to 2.5 ml water, 2.5 ml plasma, and 2.5 ml RBCs in separate test tubes and by performing a chemical extraction. A separate extraction of cells to which no drugs had been added was also accomplished. The results of an HPLC analysis of these extracts is presented in Figure 1. The internal standard desmethylimipramine (DMI) came off the column at 19.7 min and DMT at 7.5 min. In the extract from cells, the amount of recovered DMT is reduced and a new peak at 5.52 min appears. Repetition of the cell extraction without the addition of the DMI resulted again in the reduction of DMT and the appearance of the new peak. We investigated blood samples from 30 individuals. In all cases, the DMT levels extracted from the cells were lower and the new peak was clearly observed.

Indoles are known to metabolize by one of three general routes. Two of these as applied to DMT have already been mentioned. They involve the changing of the functional groups on the indole moiety and the transformation of the indole structure to a three-ring compound, such as tetrahydro-β-carboline. A third alteration of indoles results from the oxidative opening of the five-member ring, as in the conversion of tryptophan to kyn-

Table 1. Distribution of Radioactivity from ^{14}C-DMT between Cells and Plasma (n = 7)

Source	Percent radioactivity recovered		
	Folin-Wu supernate	$Ba(OH)_2$ + $ZnSO_4$ supernate	$ZnSO_4$ + NaOH supernate
Plasma	20.0 ± 1.3	36.4 ± 3.3	37.9 ± 3.6
First saline wash of cells	5.1 ± 0.6	16.8 ± 1.3	16.7 ± 1.4
Second saline wash of cells	9.1 ± 0.4	12.2 ± 0.9	12.2 ± 1.0
Cells	12.6 ± 1.9	20.6 ± 2.8	23.2 ± 2.4
Total radioactivity recovered	46.8 ± 2.3	86.1 ± 6.4	90.0 ± 7.0

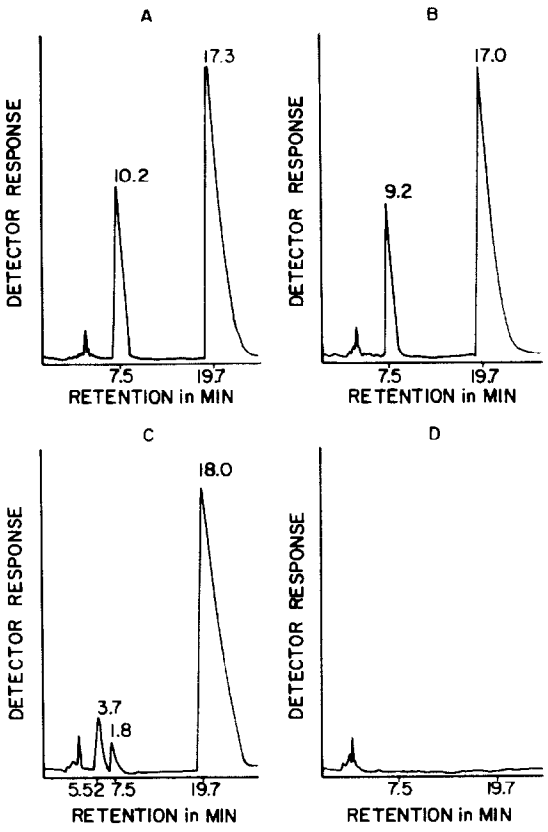

Figure 1. Results of HPLC analysis of extracts of the following: (A) 2.5 ml of H_2O containing 15.4 μg DMT and 23.1 μg DMI; (B) 2.5 ml of plasma containing 15.4 μg DMT and 23.1 μg DMI; (C) 2.5 ml of red blood cells containing 15.4 μg DMT and 23.1 μg DMI; (D) 2.5 ml RBCs with no added drugs.

urenine. It is this third mechanism that is needed to explain the formation of the new peak observed in the HPLC.

A tentative identification of the unknown peak was accomplished by the collecting the HPLC eluent at approximately 5.5 min and subjecting it to ultraviolet, fluorometric, and mass spectrometric analysis. The ultraviolet spectrum of the unknown (Figure 2) was compared to that of a number of substituted indoles, including IAA, 5-OH-DMT, and TA, and also to β-carboline, 1,2,3,4-tetrahydro-β-carboline, and kynuramine. The ultraviolet spectrum of the unknown most closely resembled that of kynuramine. A comparison of the UV spectra of the unknown, kynuramine, and kynurenine at different pH is presented in Table 2. The fluoresence spectra of kynuramine was most similar to that of the unknown (excitation 370 nm, fluoresence 490 nm). These data strongly suggest that the unknown has a structure similar to kynuramine-type compounds.

From the comparison of the mass spectrum of the unknown (Figure 3) with that of available kynuramine, it was concluded that the unknown may be *N,N*-dimethylkynuramine (DMK). The molecular ion of the unknown at m/e 192 is 28 mass units higher than the molecular ion of kynuramine at m/e 164. In terms of mass, this difference corresponds to a loss of two hydrogens from kynuramine and a replacement of them with two CH_3 groups. This was supported by a peak at m/e 58 in the unknown, which is absent in mass spectrum of kynuramine and which can be attributed to the species $CH_2{=}N(CH_3)_2{}^+$. Other major peaks of the two compounds are in good agreement. The

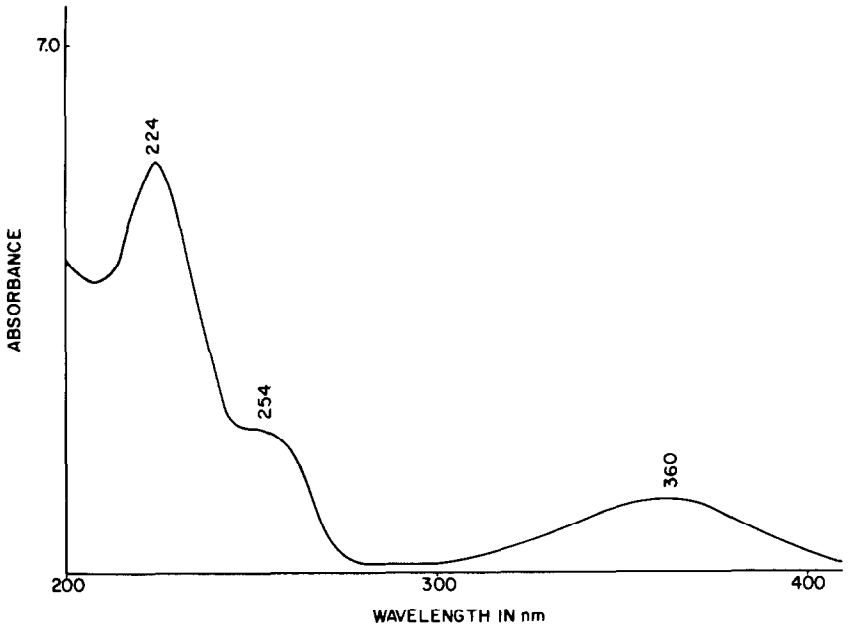

Figure 2. The ultraviolet spectrum of the unknown at pH 3.

chemical composition of the mass spectral peaks was established by high-resolution mass spectrometry. It was consistent with the proposed DMK structure. The mass spectra (Figure 4) of an authentic DMK sample (Adams Chemical Co., Round Lake, IL) confirms the identification of the unknown as *N,N*-dimethylkynuramine.

DMK is a thermally unstable compound, which, on heating, decomposes to a compound of molecular weight 147, which may be either 4-oxo-1,2,3-trihydroquinoline (1,2,3-trihydro-4-quinalone) or 2′-anilinyl-2-propen-1-one (2-anilinyl-vinylketone). This new decomposition product has prominent mass spectral fragments at m/e 147, 146, 120, 92, and 65 and minor peaks at m/e 130, 118, 104, and 77. The heating of DMK on the probe not only evaporates the sample, but also causes some decomposition and evaporation of the decomposition products. The resulting mass spectra consist of the fragmentation pattern of the parent compound overlapped by the fragments of the decomposition product. This resulted in some intensity differences between the unknown sample, which was heated by 200°C, and the synthetic DMK sample, which was heated at 150°C.

Table 2. The UV Spectra (nm) of the Unknown, Kynuramine, and Kynurenine at Different pH

	Unknown	Kynuramine	Kynurenine
pH 1	239	241	242
	282	278	282
pH 3	224	224	225
	254	254	255
	360	357	360
pH 12	210	207	208
	254	255	254
	355	355	356

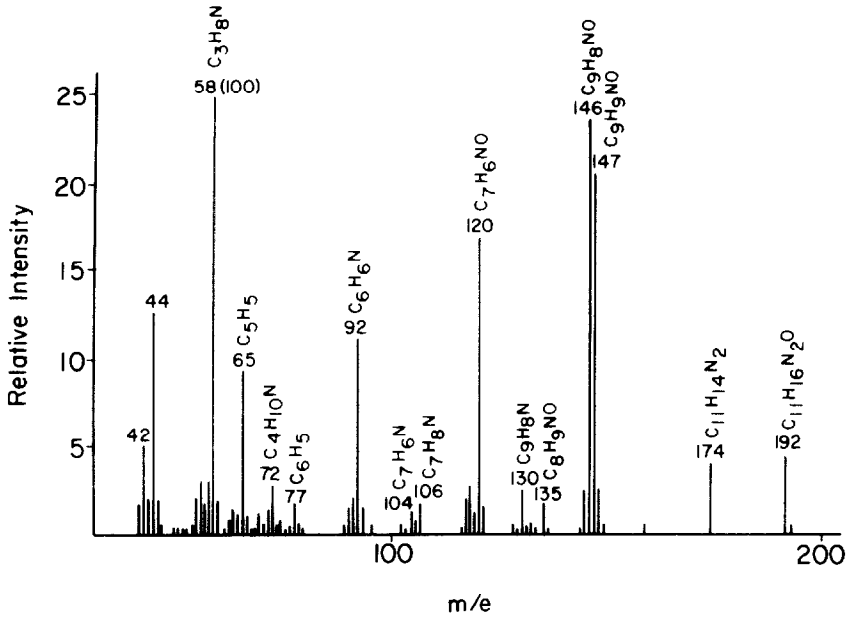

Figure 3. The mass spectrum of the unknown at 200°C. The chemical composition of the fragment ions was determined by high-resolution mass spectrometry.

The conversion of L-tryptophan to L-formylkynurenine and then to L-kynurenine has been established as a major metabolic pathway of tryptophan (West and Todd 1964). The active enzyme in this reaction, tryptophan 2,3-dioxygenase, has been well characterized (Tanaka and Knox 1958). It is found in liver and acts on L-tryptophan by utilizing molecular oxygen. Hayaishi (1976) reported another enzyme identified as indoleamine 2,3-dioxygenase. It acts not only on L- and D-tryptophan and L- and D-hydroxytryptophan, but also on tryptamine, serotonin, and melatonin. Its activity on DMT was characterized as "much slower." This enzyme has been identified in various mammalian tissues, including the brain. High activity was reported in lung, colon, and the lower part of the intestine. In human bodies, it has been found in choriodal plexius, pia mater, aorta, heart, and other organs that belong to the circulatory system (Okuma et al. 1976). Instead of oxygen, it was shown that superoxide anion (O_2^-) was the active agent in these reactions. Sephadex column chromatography and ultracentrifugation indicate an apparent molecular weight of about 105,000.

Preliminary investigation of the enzyme responsible for converting DMT to DMK indicates that this enzyme affects diethyltryptamine in the same way as DMT. It is present in rat blood. This enzyme was inactivated by boiling lysed cells diluted with water for 15 min. Treatment of the incubation mixture with catalese (EC 1.11.1.6) or with superoxide dismutase (EC 1.15.1.1) had no effect on DMK formation. Saturation of the reaction mixture with carbon monoxide and nitrogen gas significantly reduced the production of DMK. Reintroduction of oxygen after saturation with carbon monoxide reversed the CO effect. A separation of cell membranes from cytoplasm demonstrated that the activity is in cytoplasm. Filtration of the red blood cell lysate through a 50,000 molecular weight filter did not reduce the enzyme activity.

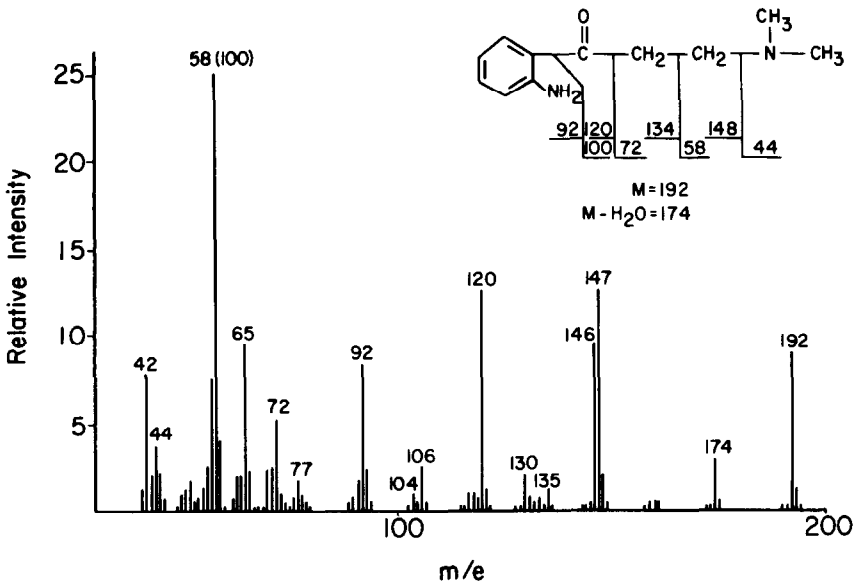

Figure 4. The mass spectrum of synthetic DMT heated at 150°C.

Kynuramine and its derivatives have been shown to possess important biological activity. Studying contractions of helically cut strips of cerebral arteries, Fu and Toda (1979) observed that kynuramine, 5-hydroxykynuramine, 2′-amino-3-dimethylamino-3′-hydroxypropiophenone (3-hydroxy-DMK), and 2′-amino-3-dimethylamino-5′-hydroxypropiophenone (5-hydroxy-DMK) caused dose-related contractions. These compounds antagonized the contractile response to serotonin with the following potency: 5-HO-K > 5-HO-DMK > K > 3-HO-DMK. Serotonin induces human platelet aggregation. This induction is inhibited by kynuramine and its derivatives (Okuma et al. 1976). The inhibitory degree of the various compounds studied was: 5-HO-K, 89%; 5-MeO-K, 81%; K, 69%; 5-HO-DMK, 64%; 3-HO-DMK 27%; and *N*-acetyl-5-methoxykynuramine, 0%. With respect to inhibition of diazepam binding by tryptophan derivatives, *N*-acetyl-5-methoxykynuramine was one of the most potent inhibitors, whereas serotonin was one of the weakest inhibitors (Marangos et al. 1981). Johnson and Clarke (1981) studied the inhibitory action of kynuramine on norepinephrine, phenylephrine, and clonidine and concluded that kynuramine had an inhibitory action on α-adrenoceptors at both presynaptic and postsynaptic sites. These reports, showing biological activity of kynuramine and its derivatives, indicate that DMK may also possess some significant biochemical activity.

The in vitro addition of dimethyltryptamine to red blood cells results in the disappearance of DMT and an appearance of a new compound that has been identified as dimethylkynuramine. The association of the major portion of added DMT with the cellular fraction suggests that blood may not be the tissue of choice for the conduction of a DMT search. A study of the formation of the new metabolite suggests a new metabolic pathway for indoleamines and a new enzyme system controlling the pathway. Preliminary data indicate that this enzyme is different from the indoleamine 2,3-dioxygenase reported by Hayaishi (1976). To our knowledge, this is the first report of a presence of an enzyme in red blood cells capable of an oxidative opening of the pyrrole moiety in DMT. Literature suggests that the proposed product, DMK, may have biological activity.

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