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Determination and physiological disposition of dimethyltryptamine and diethyltryptamine in rat brain, liver and plasma

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DIMETHYLTRYPTAMINE (DMT) is the *N*-methylated analog of tryptamine. The compound occurs in various plants,[1] can be formed in rabbit lung and chicken brain,[2,3] and has been implicated in the pathogenesis of schizophrenia.[4,5] Diethyltryptamine (DET) does not seem to occur naturally. Both compounds are hallucinogenic in man and are occasionally abused for this reason.[6,7] In animals, they produce "abnormal" behavior and their effects on operant behavior have been carefully studied.[8–11]

Conclusions on the site and mode of action of DMT and DET and comparisons of the behavioral effects of these compounds with those produced by other psychoactive compounds have remained speculations so far, since they had to be based on doses injected. However, the injected dose is no indication of actual brain levels, since these levels are the result of a variety of factors including absorption, distribution, metabolism, excretion and penetration through the blood–brain barrier.[12] For this reason we developed a rapid assay procedure for the determination of injected DMT and DET in biological tissues and fluids, and we determined the concentrations of both compounds in rat brain, liver and plasma as a function of time and dose.

The assay procedure is based on the native fluorescence of DMT and DET after extraction of the compounds from biological tissues or fluids. The tissues (approximately 1–2 g) were homogenized in 3 ml of 1 N HCl. To the homogenates or plasma (1·0 ml plasma and 3 ml of 1 N HCl) 1·5 ml of 5 N NaOH and 30 ml toluene (ACS certified) were added. After shaking and centrifugating for 10 min, an aliquot of 25 ml toluene was removed and shaken with 1·5 ml of 0·1 N HCl for 10 min. After centrifugation for 10 min, 1 ml of 0·1 N HCl was combined with 1 ml of 0·1 M sodium borate buffer (pH 9·1), mixed, and then read in an Aminco-Bowman spectrofluorophotometer at 360 mμ (activation 280 mμ). Readings of extracts from plasma, brain and liver obtained from untreated animals were negligible. The sensitivity of the procedure is approximately 0·07 μg per ml or per g of sample and the recovery is approximately 80 per cent. The variability of the procedure showed a standard deviation of approximately 10 per cent of the mean.

To verify the assay procedure, tissue extracts from animals injected with DMT or DET were compared with the pure chemicals. A total spectral scan, the Brodie distribution test,[13] and thin-layer chromatography (chloroform–methanol–acetic acid, 75 : 30 : 5; ethanol–NH_3–H_2O, 8 : 2 : 1; and benzene–dioxane–NH_3, 50 : 45 : 5) showed that the assay procedure measured only DMT and DET.

DMT and DET were rapidly absorbed from the intraperitoneal cavity and quickly distributed through plasma, liver and brain (Table 1). Metabolism was also fast and most of the compounds had disappeared from brain, liver and plasma within 30 min, except DET in brain, which could still be detected at 60 min. The brain/plasma ratios of DMT and DET of 5·4 and 10·5 seem to indicate that the compounds cross the blood–brain barrier easily and are perhaps accumulated by an active transport mechanism.

TABLE 1. CONCENTRATION (μg/g OR ml) OF DMT OR DET IN RAT BRAIN, LIVER AND PLASMA AS A FUNCTION OF TIME*

Compound injected	Tissue or plasma	Minutes after injection (i.p.) 5	10	15	30	60
DMT (5 mg/kg)	Brain	0·9 ± 0·5	1·0 ± 0·2	1·8 ± 1·2	nd	nd
	Liver	6·8 ± 5·1	6·8 ± 3·4	4·0 ± 3·0	0·6 ± 0·4	0·09 ± 0·02
	Plasma	0·4 ± 0·2	0·3 ± 0·2	0·3 ± 0·2		nd
DET (5 mg/kg)	Brain	0·5 ± 0·4	3·4 ± 1·1	3·9 ± 1·2	2·6 ± 1·0	0·8 ± 0·4
	Liver	7·0 ± 3·7	4·0 ± 3·0	1·2 ± 0·3	0·2 ± 0·05	0·07 ± 0·04
	Plasma	0·3 ± 0·2	0·6 ± 0·1	0·4 ± 0·06	0·2 ± 0·08	0·08 ± 0·04

* Each value is the mean ± standard deviation from at least three animals; nd = not detectable.

An increase in dose from 2·5 to 25 mg/kg caused a rise in all tissue concentrations with no apparent saturation (Table 2).

The high standard deviations point to a biological variation in the handling of the compounds by individual animals, since the variability of the method showed only standard deviations of approximately 10 per cent of the mean.

Data obtained in this study can now be used to gain information on the site and mode of action of DMT and DET, and to compare these two compounds with similar tryptamine analogs. The minimal doses of DMT and DET necessary to disrupt operant behavior are somewhat less than 5 mg/kg i.p. for both compounds, indicating almost equal potency.[8] However, brain levels of DMT and DET present during such periods of "abnormal" behavior in these studies can now be estimated to be approximately 1·3 and 2·4 μg/g of brain respectively. These results seem to indicate that DMT is twice as potent as DET. The presence of both compounds in the rat central nervous system correlates well with periods of "abnormal" behavior, suggesting a central site of action and implicating both compounds, and not a metabolite, as the active principle. The first conclusion is in agreement with Winter,[14,*] who suggested a central site of action of DMT and DET, since the effects of both compounds were not antagonized by xylamidine tosylate. The second conclusion is in agreement with Rosenberg *et al.*[15] but in disagreement with Szara and Hearst,[16] who suggested a metabolite of DET as the active principle.

A comparison of the minimal doses necessary to produce "abnormal" behavior of DMT and DET and various other tryptamine analogs revealed the following relationship: bufotenin[17] (15 mg/kg)

TABLE 2. CONCENTRATIONS (μg/g OR ml) OF DMT AND DET IN RAT BRAIN, LIVER AND PLASMA AS A FUNCTION OF DOSE INJECTED*

Compound injected	Tissue or plasma	Dose (mg/kg) 2·5	5·0	10	25
DMT	Brain	0·9 ± 0·3	1·8 ± 1·2	8·5 ± 3·8	19·4 ± 2·6
	Liver	2·0 ± 0·7	4·1 ± 3·0	12·2 ± 3·0	44·6 ± 3·4
	Plasma	nd	0·3 ± 0·2	1·6 ± 0·8	4·6 ± 0·5
DET	Brain	1·3 ± 0·08	3·9 ± 1·2	8·9 ± 3·4	21·4 ± 9·07
	Liver	1·0 ± 0·8	1·2 ± 0·3	20·0 ± 4·0	60·5 ± 20·0
	Plasma	0·2 ± 0·02	0·4 ± 0·06	1·8 ± 0·8	4·6 ± 1·2

* Each value is the mean ± standard deviation from at least three animals. Rats were killed 15 min after i.p. administration of DMT or DET; nd = not detectable.

* J. C. Winter, personal communication.

< 5-methoxytryptamine[18] (6) < tryptamine[19] = DMT = DET[8] (5) < serotonin[17] (4) < 5-methoxy-DMT[8] (1·5). Based on actual brain levels, a new structure–activity relationship can be established: DET (2·4 μg/g) < DMT (1·3) < bufotenin[20] (0·9) < 5-methoxy-DMT[20] = serotonin[21] (0·5) < tryptamine[22] (0·2) < 5-methoxytryptamine[18] (0·05).

It is known that neither tryptamine[22] nor serotonin[21] crosses the blood–brain barrier easily. As shown in this paper, methylation or ethylation of the amino group of tryptamine (DMT, DET) promotes penetration into the central nervous system. Methylation of the hydroxyl group (5-methoxy-tryptamine) of serotonin does not help penetration,[18] whereas methylation of the hydroxyl and amino group (5-methoxy-DMT) of serotonin promotes penetration through this barrier.[20] Thus, both the free hydroxyl and amino group of indolealkyls seem to impair penetration into the brain. This is different from the catecholamines where only a free hydroxyl but not a free amino group impairs penetration into the brain; dopamine does not cross the blood–brain barrier, whereas methylation of the hydroxyl groups (3,4-dimethoxyphenylethylamine) promotes penetration, in spite of the free amino group.[23]

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