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INCREASED SYNTHESIS OF STRIATAL DOPAMINE BY N,N-DIMETHYLTRYPTAMINE

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Summary

The effect of acute doses of N,N-dimethyltryptamine (DMT) on the synthesis or degradation rates of rat diencephalon norepinephrine and striatal dopamine was estimated by administering 150 μCi L-tyrosine-3,5-^{3}H at various times before sacrifice. In all cases DMT, 20 mg/kg, was injected one-half hour before sacrifice. In both acute and chronically treated rats, an increase in endogenous levels of 3-methoxytyramine was observed, while no effect was observed in the diencephalon adrenergic system. The results suggest that DMT increases central dopamine turnover.

The effects of hallucinogens upon turnover rates of biogenic amines have been evaluated previously by nonisotopic techniques such as the employment of tyrosine hydroxylase inhibitors (1,2,3,4). Although most of the hallucinogens produced a net increase in the degradation of norepinephrine (NE), no similar effect was found for dopamine (DA).

Since hallucinogens of the indoleamine type such as LSD and psilosybin can give rise to stereotyped behavior - presumably due to activation of striatal dopamine systems (5,6,7) - the effect of N,N-dimethyltryptamine (DMT) on striatal DA and diencephalon NE synthesis was re-evaluated. As a further method for monitoring NE and DA neuronal activities, endogenous levels of their respective extraneuronal metabolites, normetanephrine and 3-methoxytyramine (8) were measured.

Materials and Methods

Radiotracer Procedures and Drug Schedules: Male Sprague-Dawley rats (190 - 220 g) were injected I.P. with 150 μCi L-tyrosine-3,5-^{3}H (200 μCi/μmole) at time zero and at various times thereafter were injected I.P. with DMT, 20 mg/kg. In all cases rats were sacrificed by decapitation thirty minutes after DMT injections. Control rats were given 0.4 ml saline corresponding in time to the DMT injections. The chronically treated rats received 5 mg/kg/day DMT for one month. Twenty-four hours after the last chronic injection of DMT, these rats received a single dose of DMT (20 mg/kg) before sacrifice as in the acute studies. Controls for the chronic study were injected with 0.1 ml saline per day for one month. Since, in a pilot study, no statistically significant difference was found between the acute and chronically treated controls, the control values given in the following tables are derived only from rats that

received a single injection of 0.4 ml saline one-half hour before sacrifice.

Isolation Procedures: Two rat brains were dissected in sequence and the tissue pooled. The striatum and diencephalon tissues were isolated as described previously (9). Each of the pooled striatae or diencephalons were then weighed, homogenized in 0.4 N perchloric acid, centrifuged at 15,000 g for 30 minutes, and the supernatant placed on an alumina-ion exchange system (submitted for publication) which separated into individual fractions, tyrosine, DA, NE, normetanephrine (NM), and 3-methoxytyramine (3-MT). An aliquot of each of these fractions was dissolved in 10 ml aquasol (New England Nuclear) and the radioactivity monitored on a Packard Tri-Carb scintillation counter model 3003. Aliquots of some fractions were used for fluorimetric determinations.

Spectrophotofluorimetric Procedures: The following compounds were assayed fluorimetrically: tyrosine (10); NE (11) except that the ascorbic acid was stabilized with ethylene diamine (12); NM (13); DA and 3-MT (12).

Statistics: Mean values ± (S.E.M.) are given and the significance of the difference between means was determined using the Student's test (14).

Materials: L-tyrosine-3,5-^{3}H was purchased from Schwarz-Mann; N-N-dimethyltryptamine, norepinephrine, dopamine, normetanephrine, and 3-methoxytyramine from Sigma.

Results

Spectrophotofluorimetric Studies: Both acute and chronic doses of DMT substantially elevated the endogenous levels of striatal 3-MT, while no real changes were observed in the steady state concentrations of the other amines analyzed (Table I).

TABLE I

Endogenous Levels of Amines in Brain Tissue (mg/g wet weight) 30 Minutes After I.P. Injections of 20 mg/kg DMT. Each value represents the mean (± S.E.M.) from 10-30 animals.

TISSUE ± S.E.M. µg/g WET WT.	DIENCEPHALON			STRIATUM		
	Control	Acute	Chronic	Control	Acute	Chronic
TYR	11.0 ±.6	11.5 ±.6	12.2 ±1.3	14.0 ±.5	14.7 ±.4	14.5 ±.4
NE	.82 ±.02	.81 ±.02	.83 ±.02	---- ----	---- ----	---- ----
DA	---- ----	---- ----	---- ----	8.9 ±.4	9.3 ±.3	10.7 ±.5
NM	.27 ±.03	.27 ±.03	.28 ±.01	---- ----	---- ----	---- ----
MT	---- ----	---- ----	---- ----	1.07 ±.05	1.76** ±.04	1.86* ±.13

Statistical difference from control: *P < .01, **P < .001

Radiotracer Studies: Only experiments employing acute dosages of DMT were used for the radiotracer analyses. DMT, in acute dosage, caused no significant change in the decline of specific activity of diencephalon tyrosine (Table II) or NE (Table III).

TABLE II

Comparison of Degradation rates of Diencephalon and Striatum Tyrosine in Control and Experimental Animals Injected I.P. with 0.4 ml Saline and 0.4 ml DMT (20 mg/kg), Respectively, ½ Hour Before Sacrifice. Each value represents the mean (± S.E.M.) for six to twelve animals.

Time (hr.) after inject. tyr. (150 µCi)	SPECIFIC ACTIVITY (dpm/µg tyrosine)			
	Diencephalon		Striatum	
	Control	Acute	Control	Acute
1.5	1580 ± 300	1630 ± 206	1400 ± 196	2070 ± 170
2.0	1120 ± 84	1082 ± 140	995 ± 150	1033 ± 216
3.0	830 ± 125	910 ± 165	820 ± 113	704 ± 104

TABLE III

Comparison of Degradation Rates of Diencephalon Norepinephrine in Control and Experimental Rats Injected I.P. with 0.4 ml saline and 0.4 ml DMT (20 mg/kg), Respectively, ½ Hour Before Sacrifice. Each value represents the mean (± S.E.M.) for six to twelve animals.

Time (hr.) after inject. tyr. (150 µCi)	SPECIFIC ACTIVITY (dpm/µg norepinephrine)	
	Control	Acute
1.5	900 ± 100	970 ± 100
2.0	741 ± 30	942 ± 102
3.0	666 ± 80	930 ± 91

However, striatal DA in the acute studies exhibited a substantial difference from controls at one-and-a-half hours after tyrosine injections (Table IV). These results indicate that DA reached its maximum specific activity at or before one-and-a-half hours in the acute studies, while the control DA specific activity is still climbing. Thus, DMT seems to increase the rate of synthesis of striatal DA.

TABLE IV

Comparison of Synthesis and Degradation Rates of Striatal Dopamine in Control and Experimental Animals Injected I.P. with 0.4 ml Saline and 0.4 ml DMT (20 mg/kg), Respectively, ½ Hour Before Sacrifice. Each value represents the mean (± S.E.M.) for six to twelve animals. Statistical difference from controls: *P < .01

Time (hr.) after inject. tyr. (150 µCi)	SPECIFIC ACTIVITY (dpm/µg dopamine)	
	Control	Acute
1.5	710 ± 54	1260 ± 87*
2.0	696 ± 110	947 ± 97
3.0	1000 ± 107	864 ± 44

Discussion

It has been reported elsewhere that DMT in large doses accelerates whole brain NE degradation to a slight but not statistically significant degree as evaluated by α-methyl tyrosine methyl ester, a tyrosine hydroxylase inhibitor (2). The results from the present investigation also show no statistically significant change in NE degradation. In fact there appears to be a tendency for NE turnover to be slowed after DMT treatment (Table III).

In contrast with previous reports using whole brain (1,2), DMT in acute dosage markedly accelerated striatal DA synthesis as reflected by the specific activity profile (Table IV). Since DMT had no effect on the steady state concentration of DA, it can be concluded that DA's degradation rate was enhanced proportionally. Furthermore, the route of increased degradation is probably extraneuronal, since DMT caused a substantial rise in 3-MT, DA's extraneuronal metabolite (8). In addition, the fact that pretreatment with chlorpromazine counteracts tremors produced by methoxylated indoleamines such as DMT and 5-MeO-DMT (15), further supports the possibility that enhanced dopaminergic activity is involved in the mechanism of DMT.

The chronic studies are of interest in that increased DA turnover due to DMT apparently was not attenuated after one month's treatment as judged by continued physiological signs (slight tremor, backward locomotion, and ablation of the hind limbs) and the consistent rise in striatal 3-MT. Thus, a tolerance to DMT does not appear to be developed, at least with the drug schedule used here. The inability for tolerance to develop to DMT has been documented in other animals recently such as cats and monkeys (16,17). In this respect, DMT is different from other hallucinogens such as psilocybin and LSD.

In the past, DMT has been implicated with schizophrenia (18,19). Also pertinent here is the hypothesis that schizophrenia symptoms are probably due to increased dopaminergic activity in the central nervous system (20). Although plasma levels of DMT from schizophrenics and controls have not been found to be

statistically different (21), the possibility still exists that, in some schizophrenics a localized increase in DMT occurs which is subsequently rapidly degraded before it can be detected in plasma. These localized perturbations in DMT levels could conceivably alter dopaminergic function.

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