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Neurochemical Investigations of the Interaction of N,N-Dimethyltryptamine with the Dopaminergic System in Rat Brain

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Abstract. N,N-dimethyltryptamine (DMT) is a psychotomimetic indolealkylamine that has been suspected of being an endogenous causal factor in the aetiology of schizophrenia. Some aspects of its interaction with the dopaminergic system of the rat brain have been studied neurochemically, and comparisons have been made with the effects of *d*-amphetamine and apomorphine. In contrast to these two compounds, DMT has proved to be a potent, but short-acting MAO inhibitor with a rather selective effect on MAO A (serotonin-deaminating MAO).

Like classical MAO inhibitors, DMT also greatly increases the accumulation of ^{3}H-dopamine plus ^{3}H-3-methoxytyramine newly formed from ^{3}H-Dopa. Amphetamine and apomorphine have no comparable effect.

Striatal levels of 3,4-dihydroxyphenylacetic acid are more efficiently lowered by DMT than those of homovanillic acid. The reverse has been observed with apomorphine, whereas amphetamine increases the concentrations of homovanillic acid and decreases those of 3,4-dihydroxyphenylacetic acid.

Thus, in addition to its MAO inhibitory action, DMT probably also possesses dopamine-releasing effects. Both these properties could result in an indirect dopaminomimetic activity of DMT. It may be assumed, therefore, that the psychotomimetic activity of this compound is not only linked to its effects on cerebral serotonergic mechanisms, but to a combination of these with an indirect dopaminergic stimulant activity.

Key words: Dimethyltryptamine – Monoamine oxidase inhibition – Dopamine metabolism – Homovanillic acid – 3,4-Dihydroxyphenylacetic acid – Dopamine release.

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N,N-dimethylated indolealkylamines like dimethyltryptamine (DMT) or bufotenine have potent hallucinogenic properties (Szara, 1956; Fabing, 1955), qualitatively similar to those of LSD.

Endogenous production of these substances has been supposed to be a causative factor in the aetiology of schizophrenia (Gilka, 1975).

There have been reports of the presence in the brains and other organs of several species, including man, of enzymes that are able to N-methylate indoleamines using the cofactors S-adenosylmethionine (Axelrod, 1962; Saavedra and Axelrod, 1972) or 5-methyltetrahydrofolate (Banerjee and Snyder, 1973; Leysen and Laduron, 1974a). However, recent work suggests that formaldehyde is liberated during the incubation from both methyl donors leading to cyclized condensation products with indolealkylamines (Mandel et al., 1974; Leysen and Laduron, 1974b; Meller et al., 1974; Hsu and Mandell, 1975).

Thus, the transmethylation hypothesis, though still theoretically interesting, suffers from the lack of any data that would explain how the hallucinogenic products could be formed in sufficient quantities in vivo.

The mechanisms that mediate the hallucinogenic effects of DMT and bufotenin are also unknown. Owing to their structural similarity to serotonin and on the basis of pharmacological results (Andén et al., 1971; Bradley and Briggs, 1974), these compounds were thought to exert their psychotomimetic activity by interacting with central serotonergic receptors.

LSD, which for years has been assumed to act mainly in this fashion (Andén et al., 1968; Haigler and Aghajanian, 1974), has now recently been found to stimulate dopamine-sensitive adenylate cyclase (Da Prada et al., 1975; Kelly and Iversen, 1975; von Hungen et al., 1975). If stimulation of dopamine receptors does indeed play an important part in the psychotomimetic activity of the drug, then LSD psychosis and

amphetamine psychosis might be reduced to one and the same basic phenomenon.

DMT, structurally related to LSD, has been shown not to possess direct dopaminergic properties, as it did not stimulate dopamine-sensitive adenylate cyclase (von Hungen et al., 1975). However, up to now, possible indirect dopaminergic effects of DMT have not been investigated, and would, if demonstrated, underline the importance of dopamine in the genesis of psychotic states.

We have therefore undertaken experiments to characterize the neurochemical effects of DMT on the dopaminergic system of the rat brain.

MATERIALS AND METHODS

Drugs

Dimethyltryptamine oxalate and deprenil were synthesized by Dr. A. Storni, clorgyline-HCl by Dr. E. Schmid, pargyline by Dr. W. Bencze and clonidine by Dr. E. Schweizer in our Chemistry Laboratories. *d*-Amphetamine sulphate and apomorphine-HCl were purchased from Siegfried AG (Zofingen, Switzerland), and tryptamine, N-methyltryptamine, and mescaline sulphate from Fluka AG (Buchs, Switzerland). FLA 63 was obtained from Labkemi AB (Göteborg, Sweden). Tranylcypromine sulphate was generously provided by Smith, Kline and French Laboratories (Philadelphia, U.S.A.), and LSD by Sandoz AG (Basle, Switzerland).

Methods

Determination of MAO Activity. The experiments were performed on female albino rats of a Sprague-Dawley strain, weighing 140 to 200 g. MAO activity in the whole brain or in the corpus striatum was determined by radioassay, essentially as described by Wurtman and Axelrod (1963).

[^{14}C]-Serotonin binoxalate (5-HT; 26.7 mCi/mmole, New England Nuclear, Boston, U.S.A.), [^{3}H]-dopamine (DA; 3.8 Ci/mmole, Radiochemical Centre, Amersham, England) and [^{14}C] phenethylamine HCl (PEA; 7 mCi/mmole, New England Nuclear) were used as substrates at a concentration of 6.25 nmoles (10 nCi with serotonin and phenethylamine, 20 nCi with dopamine) for a final incubation mixture of 0.3 ml. The reaction was carried out with 2.5 mg of brain tissue. The [^{14}C]- or [^{3}H]-labelled deaminated material formed after an incubation period of 20 min at 37° C was extracted into 6 ml of ethyl acetate. Aliquots of 4 ml were counted together with 1 ml ethanol and 10 ml scintillator. Groups of 4 rats were used in these experiments.

Accumulation of ^{3}H-Dopamine plus ^{3}H-3-Methoxytyramine from Dopa. At different times after treatment with the drugs to be investigated, male rats were injected with tracer doses of ^{3}H-L-Dopa (350 µCi/kg, i.v.: sp. act. 5.92 Ci/mmol, The Radiochemical Centre, Amersham, England). Brains were removed *in each case* 30 min after the injection of ^{3}H-Dopa and homogenized in 0.4 N perchloric acid. The labelled amines were then separated by a modification of the procedure of *Atack* and *Magnusson* (1970) into three fractions on Dowex 50 WX4 columns (0.5 × 3 cm), one fraction containing ^{3}H-Dopa, the second ^{3}H-noradrenaline (^{3}H-NA) and ^{3}H-normetanephrine (^{3}H-NMN), and the other ^{3}H-dopamine (^{3}H-DA) and ^{3}H-3-methoxytyramine (^{3}H-MT). Aliquots of 1 ml were counted with 10 ml of Instagel® (Packard Instruments Co., Inc., Warrenville, Ill., U.S.A.).

Methodological details have been described elsewhere (Waldmeier and Maître, 1976). In one experiment the fractions of the column eluate containing ^{3}H-DA + ^{3}H-MT were adsorbed on alumina at pH 8.6. The alumina was washed twice and ^{3}H-DA was eluted with 0.25 N HCl. The eluate as well as the supernatant from the adsorption (containing ^{3}H-MT) were counted.

Concentrations of Endogenous Homovanillic and 3,4-Dihydroxyphenylacetic Acids. Homovanillic acid (HVA) and 3,4-dihydroxyphenylacetic acid (DOPAC) were isolated from rat corpus striatum according to the technique used by Murphy et al. (1969). HVA was estimated fluorometrically by an automated procedure based on the method of Andén et al. (1963). DOPAC was determined fluorometrically as described by Sharman (1971). For these estimations four striata were pooled per sample, and four samples were used per time-point.

Accumulation of ^{3}H-HVA from ^{3}H-Dopa. Rats were also treated with *d*-amphetamine (10 mg/kg s.c.) before the intravenous injection of ^{3}H-Dopa (350 µCi/kg i.v.). Thirty minutes after ^{3}H-Dopa injection, the brains were removed and the striata isolated and homogenized in 0.1 M HCl. The samples were subsequently hydrolysed with β-glucuronidase/aryl sulphatase, and the deaminated metabolites were extracted into butyl acetate, chromatographed on thin-layer plates and subjected to electrophoretic separation. The procedure is described in detail elsewhere (Waldmeier and Maître, 1976).

RESULTS

Effects of Treatment with DMT, d-Amphetamine, and Apomorphine on MAO Activity in Rat Striatum and Whole Brain

DMT (50 mg/kg i.p.) decreased the deamination of 5-HT and DA in rat striatum concomitantly and to a marked extent. The onset of action was rapid, maximum MAO inhibition being noted 15 min after

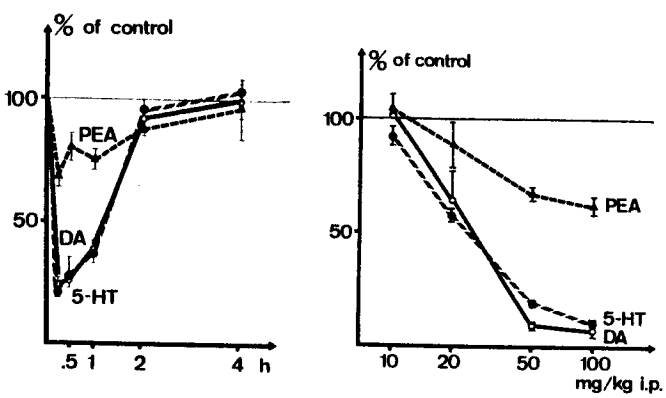


Fig. 1. Effect of DMT on MAO activity in rat striatum: Time-course (left) and dose-response curve (right). In the time-course experiment, a dose of 50 mg/kg i.p. was given. The points represent $X \pm$ S.E.M. in percent of controls ($n = 4$). In the dose-response experiments, DMT was given 30 min prior to the decapitation of the animals

Fig. 2
Effect of DMT on the accumulation of ^{3}H-NA + ^{3}H-NMN and ^{3}H-DA + ^{3}H-MT 30 min after ^{3}H-Dopa.
Left panel: DMT (30 mg/kg i.p.) was given at various times before the i.v. injection of ^{3}H-Dopa. The brains were removed 30 min thereafter. The points represent $\bar{X} \pm$ S.E.M. in percent of the control values. The absolute values of these were:
^{3}H-NA + ^{3}H-NMN 2814 ± 107 dpm/g
^{3}H-DA + ^{3}H-MT 2035 ± 80 dpm/g
(for controls and treated groups $n = 5$).
Right part: Graded doses of DMT were injected 30 min before ^{3}H-Dopa and the animals decapitated 30 min thereafter.
Absolute control values were:
^{3}H-NA + ^{3}H-NMN 2530 ± 266 dpm/g
^{3}H-DA + ^{3}H-MT 2647 ± 316 dpm/g
(controls: $n = 8$; treated groups: $n = 4$)

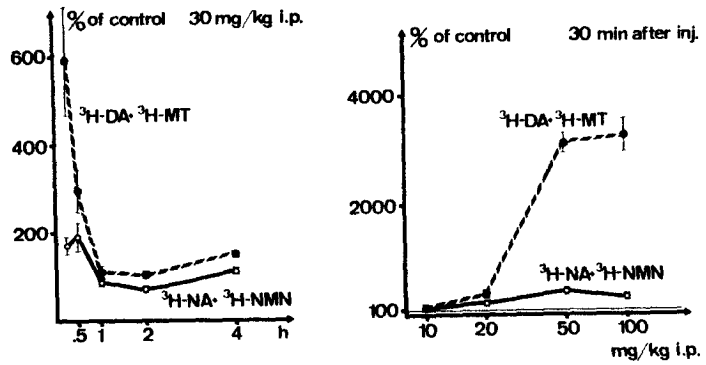
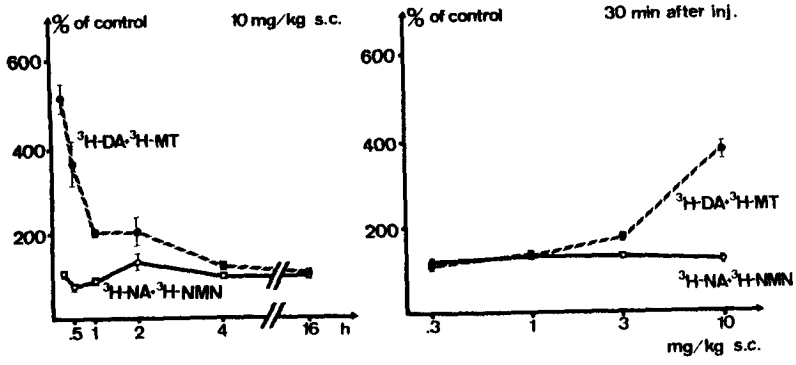


Fig. 3
Effect of *d*-amphetamine on the accumulation of ^{3}H-NA + ^{3}H-NMN and ^{3}H-DA + ^{3}H-MT 30 min after ^{3}H-Dopa.
Left panel: d-Amphetamine (10 mg/kg s.c.) was given at various times before the i.v. injection of ^{3}H-Dopa and the animals were decapitated 30 min thereafter. Absolute control values were:
^{3}H-NA + ^{3}H-NMN 2191 ± 100 dpm/g
^{3}H-DA + ^{3}H-MT 1798 ± 123 dpm/g
(control group: $n = 8$; treated groups: $n = 4$).
Right panel: Effect of graded doses of *d*-amphetamine given 30 min prior to ^{3}H-Dopa.
Absolute control values were:
^{3}H-NA + ^{3}H-NMN 3213 ± 186 dpm/g
^{3}H-DA + ^{3}H-NMN 2577 ± 196 dpm/g
(controls: $n = 10$; treated groups: $n = 5$)



treatment (the earliest determination): normalization occurred at 2 h. The effect of DMT on PEA deamination was far less pronounced, but followed a similar course (Fig. 1, left panel). The dose-response curve of the MAO inhibitory effect of DMT in striatum is given in Figure 1 (right panel). No difference between the deamination of 5-HT and DA could be observed, the ED_{50} for both being 25 mg/kg i.p. The oxidation of phenethylamine was less affected ($ED_{50} > 100$ mg/kg i.p.).

The data obtained from whole brain and striatum were practically identical, and therefore only those relating to the latter structure are presented in Figure 1.

Neither *d*-amphetamine (10 mg/kg s.c.) nor apomorphine (20 mg/kg i.p.) as estimated by the same technique with the substrates 5-HT, DA, and PEA, showed any sign of MAO inhibition up to 4 h after administration.

Effect of DMT and d-Amphetamine on the Accumulation of ^{3}H-DA + ^{3}H-MT and ^{3}H-NA + ^{3}H-NMN Formed from ^{3}H-Dopa in Rat Brain

Rats were treated i.p. with 30 mg/kg DMT at various times before the i.v. injection of ^{3}H-Dopa. Thirty minutes thereafter, the brains were removed and analysed for ^{3}H-DA + ^{3}H-MT as well as ^{3}H-NA + ^{3}H-NMN. As can be seen from Figure 2 (left panel), a large increase (600% of control) in the ^{3}H-DA + ^{3}H-MT fraction was obtained when the animals were pretreated with 30 mg/kg i.p. DMT 15 min before ^{3}H-Dopa. This effect declined rapidly as the interval between pretreatment with DMT and the injection of ^{3}H-Dopa was lengthened, reaching control levels after a lapse of 1 h. In contrast, DMT had very little effect on the ^{3}H-NA + ^{3}H-NMN fraction under these circumstances. The right panel of Figure 2 shows a dose-response curve of this effect of DMT on

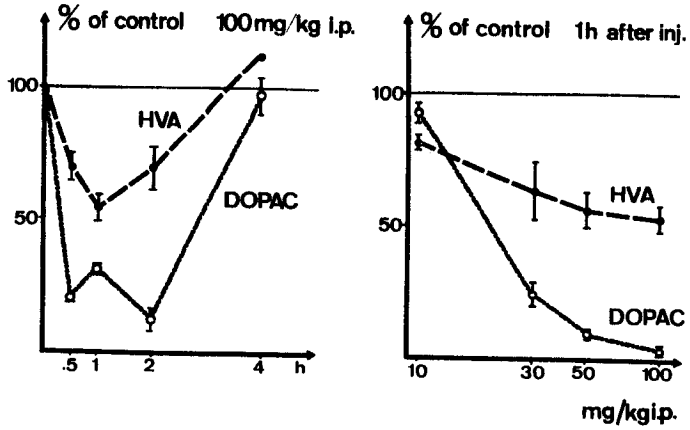


Fig. 4. Effect of DMT on striatal HVA and DOPAC: Time-course (*left*) and dose-response relationship (*right*). The points represent $\bar{X} \pm$ S.E.M. in percent of controls ($n = 4$ except for the control group of the dose-response curve, where $n = 12$). The absolute control values were: Time-course experiment: HVA 380 ± 75 ng/g, DOPAC 494 ± 33 ng/g. Dose-response curve: HVA 389 ± 15 ng/g, DOPAC 533 ± 33 ng/g

Table 1
Effects of various drugs on the accumulation of ^{3}H-NA + ^{3}H-NMN and ^{3}H-DA + ^{3}H-MT formed from ^{3}H-Dopa in rat brain

Drug	Dose (mg/kg)		min before ^{3}H-Dopa	^{3}H-NA + ^{3}H-NMN % of controls	^{3}H-DA + ^{3}H-MT % of controls
DMT	100	i.p.	30	458 ± 50*	5768 ± 409*
N-methyltryptamine	100	i.p.	30	133 ± 8***	106 ± 9
Tryptamine	100	i.p.	30	202 ± 14*	174 ± 13*
Pargyline	50	s.c.	120	620 ± 179*	8589 ± 858*
Tranylcypromine	10	s.c.	120	400 ± 59*	6995 ± 559*
Clorgyline	10	s.c.	120	197 ± 27*	3101 ± 148*
Deprenil	10	s.c.	120	134 ± 12**	172 ± 10*
d-Amphetamine	10	s.c.	30	119 ± 12	374 ± 20*
Apomorphine	20	i.p.	15	312 ± 38**	279 ± 40**
Clonidine	1	p.o.	30	162 ± 17	177 ± 25***
FLA 63	25	i.p.	120	48 ± 4*	168 ± 17**
LSD	0.1	i.v.	30	153 ± 14**	123 ± 13
Mescaline	30	s.c.	30	125 ± 6**	109 ± 8

* $P < 0.001$, ** $P < 0.01$, *** $P < 0.05$, ($n = 5$; for controls 5–10)
The animals were decapitated 30 min after ^{3}H-Dopa. The results are given in percent of controls ± S.E.M. Statistical significances were calculated by means of Student's *t*-test. The values for DMT are given for comparison

^{3}H-DA + ^{3}H-MT at a fixed interval of 30 min between treatment with DMT and the ^{3}H-Dopa injection. The threshold dose is 20 mg/kg i.p. A 35-fold increase in ^{3}H-DA + ^{3}H-MT is obtained with 50 mg/kg i.p., which is not further augmented by 100 mg/kg i.p. Again, little effect on ^{3}H-NA + ^{3}H-NMN was noted.

d-Amphetamine (10 mg/kg s.c.) had a similar effect, which was, however, quantitatively less important. At 15 min pretreatment before ^{3}H-Dopa, a 500% increase in ^{3}H-DA + ^{3}H-MT was observed, but no effect on ^{3}H-NA + ^{3}H-NMN. After this initial increase, the concentration declined rapidly to reach control levels after 4 h, thus regaining normal values somewhat more slowly than with DMT (Fig. 3, left panel). The threshold dose for this effect was 3 mg/kg s.c. (Fig. 3, right panel). Higher doses of *d*-amphetamine were not used because of the occurrence of toxic effects.

A number of other compounds with different biochemical and pharmacological effects have been compared in this test system at a given dose and a given interval between their administration and the injection of ^{3}H-Dopa. The results are listed in Table 1.

The MAO inhibitors pargyline, clorgyline, and tranylcypromine, but not deprenil, induced large increases in ^{3}H-DA + ^{3}H-MT similar to those caused by DMT. Their effect on ^{3}H-NA + ^{3}H-NMN was also relatively small. Apomorphine and clonidine slightly increased both fractions. Mescaline and LSD were practically devoid of activity. The dopamine-β-hydroxylase inhibitor FLA 63 lowered ^{3}H-NA + ^{3}H-NMN and increased ^{3}H-DA + ^{3}H-MT. N-Methyltryptamine was practically inactive, and tryptamine itself led to a slight increase in both amine fractions.

In another experiment, ^{3}H-DA and ^{3}H-MT from the combined Dowex eluate were separated by adsorption of the former on alumina. In the controls, 46 ± 3% ($n = 10$) of the radioactivity in the ^{3}H-DA + ^{3}H-MT fraction was found to be ^{3}H-DA, and 54 ± 3% ^{3}H-MT. After 10 mg/kg s.c. *d*-amphetamine given 30 min before ^{3}H-Dopa, the proportions were: ^{3}H-DA 19 ± 1%, ^{3}H-MT 81 ± 1% ($n = 5$), and after 100 mg/kg i.p. DMT: ^{3}H-DA 3 ± 1%, ^{3}H-MT 97 ± 1% ($n = 4$). For comparison, this distribution was also measured with tranylcypromine (12 mg/kg s.c., 2 h before ^{3}H-Dopa): 3 ± 1% of the radioactivity was found to be ^{3}H-DA and the remainder ^{3}H-MT.

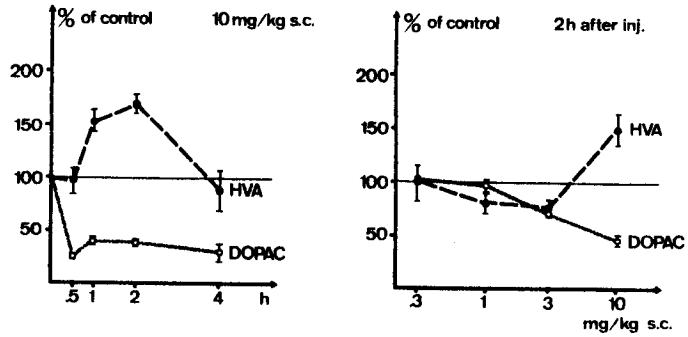


Fig. 5
Effect of *d*-amphetamine on striatal HVA and DOPAC: Time-course (*left*) and dose-response curve (*right*). The points represent $\bar{X} \pm$ S.E.M. in percent of controls ($n = 4$, control group of time course $n = 6$, control group of dose-response curve $n = 8$).
The absolute control values were:

Time-course experiment:	HVA	306 ± 15 ng/g
	DOPAC	894 ± 80 ng/g
Dose-response curve:	HVA	407 ± 22 ng/g
	DOPAC	865 ± 46 ng/g

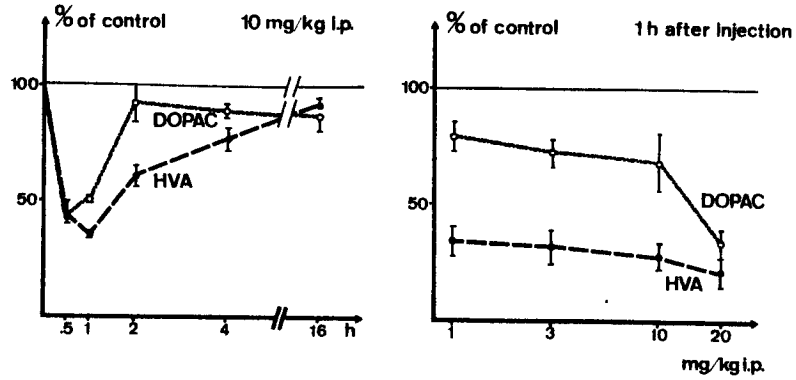


Fig. 6
Effect of apomorphine on striatal HVA and DOPAC: Time course (*left*) and dose-response relationship (*right*). Points represent $\bar{X} \pm$ S.E.M. in percent of controls ($n = 4$ except control group of time-course experiment where $n = 12$).
Absolute control values were:

Time-course experiment:	HVA	600 ± 25 ng/g
	DOPAC	702 ± 42 ng/g
Dose-response curve:	HVA	416 ± 32 ng/g,
	DOPAC	555 ± 27 ng/g

Comparison of the Effects of DMT, d-Amphetamine, and Apomorphine on Endogenous HVA and DOPAC Levels in the Rat Corpus Striatum

DMT (100 mg/kg i.p.) induced a short-lasting depletion of endogenous HVA and an even more pronounced depletion of DOPAC (Fig. 4, left panel). The onset of this effect was rapid, i.e., 30 min after administration the levels of the two metabolites were already lowered. The maximum effect was observed after 1 h, and normalization occurred after 4 h. A dose-response curve 1 h after DMT administration is shown in the right panel of Figure 4. The threshold dose for the depleting effect on both metabolites was about 10 mg/kg i.p. Maximum depletion of DOPAC levels was reached with 100 mg/kg. The dose-response curve for the levels of HVA was flatter, and only a reduction to about 50% of the control levels was reached with this dose.

A different pattern was observed with *d*-amphetamine. The time-course of the effect of 10 mg/kg s.c. is depicted in the left panel of Figure 5. Thirty minutes after injection, DOPAC levels were considerably lowered, whereas HVA was not yet altered. A marked increase of HVA concentrations was obtained 1 and 2 h after injection, which was normalized after 4 h. DOPAC levels remained low throughout the period investigated. The right panel of Figure 5 demonstrates that this amphetamine effect is only observed with the high dose of 10 mg/kg.

A still different picture was obtained with apomorphine, which lowered the levels of both HVA and DOPAC. The former metabolite remained affected longer than the latter (Fig. 6). The onset of the effect of apomorphine (10 mg/kg i.p.) was rapid, and the levels of both metabolites had practically normalized after 4 h (Fig. 6, left panel).

The longer duration of action of apomorphine on HVA concentrations was also reflected in the dose-response curve (Fig. 6, right panel). The levels of the two metabolites were measured 1 h after administration, when DOPAC concentrations had already started to return to normal, whereas HVA was still maximally depressed (Fig. 6, left panel).

Effect of Amphetamine on ^{3}H-HVA Accumulated 30 min after ^{3}H-Dopa

The effect of *d*-amphetamine (10 mg/kg s.c.) given 15 min, 30 min, 1 h, and 2 h before the i.v. injection of ^{3}H-Dopa on the deaminated DA metabolites was investigated. The only labelled metabolite detected after electrophoretic and thin-layer chromatographic separation was ^{3}H-HVA, in the striata of the controls as well as of the amphetamine-treated animals, corresponding to what has already been observed in a similar experimental system with pargyline (Waldmeier and Maître, 1976). As in the case of endogenous striatal HVA, amphetamine led to an elevation of

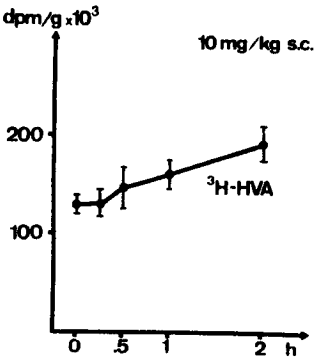


Fig. 7. Effect of *d*-amphetamine on the accumulation of ^{3}H-HVA formed from ^{3}H-Dopa in rat striatum. *d*-Amphetamine (10 mg/kg s.c.) was given at various times before ^{3}H-Dopa, and 30 min thereafter the animals were decapitated and the striata isolated. Points represent $\bar{X} \pm$ S.E.M. ($n = 6$ for controls and $n = 4$ for treated groups)

^{3}H-HVA, amounting to about 150% of the control values after 2 h (Fig. 7).

DISCUSSION

DMT exerted a short-lasting, dose-dependent inhibitory effect on rat striatal MAO. Very similar results were obtained in rat whole brain. The deamination of serotonin and DA was considerably more affected than that of phenethylamine, indicating that the substance interacted preferentially with MAO A. The good coincidence of the curves relating to the former two substrates is in agreement with recent results obtained in this laboratory and also by others, showing that DA is deaminated preferentially by an A-Type MAO in the rat brain in vivo (Braestrup et al., 1975; Waldmeier et al., 1976).

The fact that the MAO inhibitor iproniazid prolonged the half-life of DMT in rat brain (Lu et al., 1974) indicates that DMT is a substrate for MAO and that the inhibition of the enzyme found in our experiments is due to competition of the substance with the natural substrates.

Pretreatment with *d*-amphetamine and apomorphine, which were chosen for comparison with DMT because they possess indirect and direct dopaminergic activity respectively, did not affect rat brain monoamine oxidase activity, even in rather high dosages (10 mg/kg s.c. amphetamine and 20 mg/kg i.p. apomorphine). Both amphetamine (Glowinski et al., 1966) and apomorphine (Di Chiara et al., 1974) have been shown to inhibit MAO in vitro. In vivo results have only been reported in respect of amphetamine, which did not influence MAO activity under these circumstances, in agreement with our results (Jori and Bernardi, 1972).

DMT pretreatment also led to a large increase in the accumulation of ^{3}H-DA + ^{3}H-MT 30 min after i.v. injection of ^{3}H-Dopa, in contrast to only a minimal elevation of ^{3}H-NA + ^{3}H-NMN, an effect characteristic of MAO inhibitors (Table 1; detailed description of the effects of MAO-inhibitors: Maître et al., 1976). This effect of DMT was not observed with its analogues tryptamine and N-methyltryptamine.

d-Amphetamine showed activity similar to that of DMT, though quantitatively much less pronounced. In contrast to the MAO inhibitor pargyline, which decreased ^{3}H-HVA accumulated 30 min after ^{3}H-Dopa (Waldmeier and Maître, 1976), amphetamine led to a slight increase in the labelled deaminated metabolite. This suggests that the relatively small elevation of ^{3}H-DA + ^{3}H-MT might not be caused by MAO inhibition. In fact, such a pattern could be explained by the DA-releasing properties of amphetamine.

Apomorphine produced a small increase in ^{3}H-DA + ^{3}H-MT as well as in ^{3}H-NA + ^{3}H-NMN. Compared with the effects of MAO inhibitors (Table 1) and DMT, its effect on ^{3}H-DA + ^{3}H-MT accumulation was almost negligible.

The increase in the accumulation of ^{3}H-DA + ^{3}H-MT 30 min after ^{3}H-Dopa given i.v. produced by DMT and classical MAO inhibitors can be regarded as an effect of these drugs on a form of cerebral MAO. Certainly, there is a fairly intensive decarboxylase activity in rat brain capillaries (Langelier et al., 1972), and it might be inferred that Dopa is decarboxylated to DA and subsequently deaminated in the latter. It has been shown, however, that a similar increase in ^{3}H-DA + ^{3}H-MT occurs after pargyline pretreatment, if ^{3}H-Dopa is injected intracisternally (Waldmeier and Maître, 1976), which suggests that the phenomenon after i.v. injection of ^{3}H-Dopa occurred in the brain.

As one would expect from the fact that DMT inhibited striatal MAO, the endogenous levels of HVA and DOPAC in rat striatum were considerably lowered by the drug. Interestingly enough, however, DOPAC concentrations were depressed appreciably more than those of HVA. With classical MAO inhibitors, both metabolites are approximately lowered to the same extent (Maître et al., 1976; Waldmeier and Maître, 1976). A tentative explanation might be given after comparison of these DMT effects with those of amphetamine and apomorphine under similar conditions. Amphetamine, which is known as a releaser of DA, increased HVA (in agreement with data reported by Laverty and Sharman, 1965; Jori and Bernardi, 1972; Fuentes and Del Rio, 1972; Jori et al., 1973), but lowered DOPAC contents in rat striatum. Assuming that HVA is predominantly an extraneuronal and DOPAC an intraneuronal metab-

olite of DA (Roffler-Tarlov et al., 1971), this might be interpreted as a direct consequence of the releasing properties of amphetamine.

Conversely, the direct dopamine agonist apomorphine lowered HVA contents more efficiently than those of DOPAC. This might arise from the simultaneous occurrence of inhibition of DA synthesis as a consequence of postsynaptic receptor stimulation by apomorphine (Andén et al., 1967) and inhibition of DA release by stimulation of presynaptic autoreceptors (Carlsson, 1975).

According to this line of argumentation, the differential effect of DMT on striatal HVA and DOPAC could be interpreted as a superimposition of its MAO inhibitory properties and a DA-releasing action. The assumption that DMT releases DA from presynaptic stores can also be inferred from the results of Smith (1975), who found that the substance given either acutely (20 mg/kg i.p.) or chronically (5 mg/kg i.p.) increased the levels of ^{3}H-3-methoxytyramine after a pulse injection of ^{3}H-tyrosine. This effect especially of the chronic dose cannot be explained by MAO inhibition (Fig. 1, right panel).

LSD and DMT seem to have similar effects on serotonergic receptors (see Introduction). Their interference with dopaminergic systems seems to differ mechanistically, because the former stimulates DA-sensitive adenylate cyclase in contrast to the latter, which, on the other hand, possesses MAO-inhibitory and probably DA-releasing properties not shared by LSD.

However, the properties of both psychotomimetics are likely to cause increased dopaminergic transmission either by direct (LSD) or indirect (DMT) stimulation of dopaminergic receptors. It seems possible, therefore, that the psychotropic effects of DMT are not only due to its interaction with central serotonergic receptors, but rather to the combined interference with cerebral serotonergic and dopaminergic mechanisms, as has been suggested for LSD (von Hungen et al., 1975). This view is corroborated by the fact that the EEG activation induced by DMT in rabbits could be antagonized by neuroleptics, i.e., dopamine receptor-blocking compounds (Moore et al., 1975).

The theory that not only amphetamine psychosis, but also those induced by LSD and DMT, might be at least partially the consequence of interference with the dopaminergic system is of considerable interest. It underlines the importance of the dopaminergic systems in the generation of psychoses.

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