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Some Effects of the Hallucinogenic Drug 2,5-Dimethoxy-4-Methyl Amphetamine on the Metabolism of Biogenic Amines in the Rat Brain

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Abstract. "Some effects of the hallucinogenic drug, 2,5-dimethoxy-4-methyl amphetamine on the metabolism of biogenic amines in the rat brain". B. E. Leonard, Pharmacology Section, Imperial Chemical Industries Limited, Pharmaceuticals Division, Alderly Park, Nr. Macclesfield, Cheshire.

In rats, 2,5-dimethoxy-4-methylamphetamine (DOM) caused piloerection, behavioural stimulation and pronounced "head twitching" in high doses (60 mg/kg). Lower doses had a less marked effect. DOM reduced the brain concentration of noradrenalin and elevated that of 5-hydroxytryptamine. Brain dopamine was initially elevated and then reduced by the drug. Tritiated tyrosine and tryptophan were used to study the effect of DOM on the rate of incorporation of these amino acids into the biogenic amines. It was found that DOM increased the rate of incorporation of tyrosine into noradrenaline but reduced the incorporation of tryptophan into 5-hydroxytryptamine. This effect on the "turnover" of noradrenalin and 5-hydroxytryptamine is shared by other hallucinogenic substances but not by the stimulant amphetamines.

Key words: 2,5-Dimethoxy-4-Methylamphetamine — Hallucinogens — Biogenic Amines.

Introduction

Studies have been made of the effects of a number of phenylethylamines on the metabolism of brain monoamines with the aim of differentiating neurochemically between the stimulant and the psychotomimetic drugs of this series (Leonard and Shallice, 1971a; 1971b; Leonard, 1971; Wallach and Gershon, 1971). From their effects on amine metabolism it was possbile to distinguish amphetamines which a have pronounced stimulant effect on the behaviour of rats (d-amphetamine, d-methamphetamine and p-nitromethamphetamine) from the non-stimulant drug, p-bromomethamphetamine.

In agreement with other investigators (Moore and Lariviere, 1963; Baird and Lewis, 1964; Carlsson, Lindquist, Dahlström, Fuxe, and Mosuoka, 1965; Iversen, Axelrod, and Glowinski, 1967) we found that the

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stimulant amphetamines decreased the concentration of brain noradrenaline by increasing its release from the central neurons whereas p-bromomethamphetamine did not act in this way (Leonard and Shallice, 1971a).

However, although p-bromomethamphetamine was found to have a similar profile to lysergic acid diethylamide in a number of behavioural tests in animals (Knoll, 1970) its effects on the metabolism of brain biogenic amines was quite different to that of several hallucinogenic drugs (Leonard and Tonge, 1969; Tonge and Leonard, 1969). Furthermore, preliminary evidence suggests that p-bromomethamphetamine is not hallucinogenic in man (Knoll, personal communication).

In an attempt to determine more precisely the relationship between the chemical structure and the pharmacological activity of some of the phenylethylamines a study has now been made of the hallucinogenic amphetamine 2,5-dimethoxy-4-methylamphetamine (DOM). The colloquial name for DOM is "STP", a drug which was widely used by some of the "hippie" communities in the United States (Snyder, Faillace, and Hollister, 1967).

A preliminary report of this investigation was first communicated to the Spring Meeting of the British Pharmacological Society in 1972 (Leonard, 1972).

Methods

Specific pathogen free rats (♂, 90—110 g) of the Alderley Park strain were used. DOM was administered intraperitoneally in a volume of 1 ml/kg body weight; the control groups were injected with an equivalent volume of distilled water. The rats were killed by decapitation at different times after injection. In all experiments, the drug treated and control groups were killed at approximately the same time (11.00—13.00 h) to avoid circadian changes in the neurochemical parameters. In a previous study, it was found that such a procedure enabled comparisons of the action of hallucinogens at different times of pretreatment to be made (Leonard and Shallice, 1972).

Effect on the Concentration of Amino Acids in Brain and Serum and on Biogenic Amine Concentrations in Brain

Groups of 5 rats were treated with DOM (doses, as the hydrochloride, given in Results) and killed at various times up to 96 h later. When serum tryptophan and tyrosine concentrations were determined, blood was collected from the severed jugular veins and carotid arteries, allowed to clot and then centrifuged at approximately 800 × g for 10 min. Portions of the sera were diluted 1:10 with a 1:1 (v/v) mixture of 10% (w/v) trichloracetic acid and 0.4 N perchloric acid and centrifuged at approximately 800 × g for 10 min. Portions of the supernatant were used for the determination of the tyrosine concentration by the fluorimetric method of Waalkes and Udenfriend (1957) as modified by Udenfriend (1962), and tryptophan by the fluorimetric method of Hess and Udenfriend (1959), as modified by Guroff, King, and Udenfriend (1961).

The brains, minus cerebella, were quickly removed and dissected into two equal parts along the mid line. They were then weighed and kepton ice until homogenized in a "Silverson" homogenizer with 5 ml of the perchloric acid: trichloracetic acid mixture. The hemogenates were then centrifuged for 15 min at approximately 800 × g and portions of the supernatant were removed for the determination of tyrosine and tryptophan concentrations by the methods cited above. An additional portion of the supernatant was taken for the determination of γ-amino-n-butyric acid (γ-ABA) by the fluorimetric method of Uchida and O'Brien (1964).

5-Hydroxytryptamine (5-HT) was determined in half brains, prepared as described above, by the fluorimetric methods of Snyder, Axelrod and Zweig (1965) and Welch and Welch (1969) as modified by Leonard and Shallice (1971a).

In experiments in which catecholamine concentrations were determined, groups of 5 rats were injected intraperitoneally with 10 and 30 mg/kg DOM as HCl. Whole brains, minus the cerebella, were homogenized with 4 ml 0.01 N hydrochloric acid together with 0.2 ml 10% (w/v) ethylenediamine tetracetic acid (as the disodium salt), centrifuged and noradrenalin, dopamin and 5-hydroxy-indole acetic acid (5-HIAA) estimated on the supernatant fraction by the solvent extraction method of Welch and Welch (1969).

Effect of DOM on the Depletion of Brain Catecholamine by 4α-Dimethyl-m-Tyramine (H75/77)

Carlsson, Fuxe, Hamberger, and Malmfors (1969) reported that H77/77 displaces brain catecholamines, particularly noradrenaline, and utilizes a reserpine-resistant uptake mechanism to bring about this displacement. The effect of H77/77 together with DOM was therefore studied to see whether the latter drug may affect brain catecholamine concentrations by an action on the reserpine resistant uptake mechanism.

Groups of 5 rats were treated at 0 and 2 h with H77/77 alone or in combination with DOM; the latter drug was injected 30 min before H77/77 administration. The dose schedule for this experiment was:

Group 1 control group (distilled water)
Group 2 H77/77 alone (2 × 12.5 mg/kg i.p.)
Group 3 DOM alone (2 × 30 mg/kg i.p.)
Group 4 H77/77 + DOM.

Two h after the last injection of H77/77, the animals were decapitated and the catecholamines estimated on the whole brain (minus cerebellum) by the method of Welch and Welch (1969).

Effect of DOM on the Depletion of Brain 5-HT by 4-Methyl-α-Ethyl-m-tyramine (H77/12)

Carlsson, Corrodi, Fuxe, and Hökfelt (1969) have shown that H75/12 displaces brain 5-HT from its storage granules and possibly utilizes a reserpine resistant uptake mechanism to bring about this displacement. The effect of H75/12 together with DOM was therefore studied to see whether the drug affected brain 5-HT concentration by acting on reserpine resistant uptake mechanism.

H75/12 was injected at 0 and 2 h at a dose of 25 mg/kg and the animals killed by decapitation 2 h after the second dose. DOM was injected in a dose of 20 mg/kg 30 min before the administration of e each dose of H75/12. One group of rats was injected with distilled water (control group) and another with DOM alone

(2×20 mg/kg). 5-HT was estimated in the whole brain (minus cerebellum) using the method outlined above.

Effect of DOM on the Depletion of Brain 5-Hydroxytryptamine by p-Chlorophenylalanine (PCPA)

Koe and Weisman (1966) demonstrated that PCPA impairs the synthesis of 5-HT by inhibiting tryptophan hydroxylase activity. As this enzyme catalyses the rate limiting step in the synthesis of 5-HT it is possible to use PCPA to assess whether DOM affects the release of this amine.

Groups of rats were injected at 0 h with PCPA alone or simultaneously with DOM (10 mg/kg). The phenylethylamine was again injected 4.5 h later and the animals killed by decapitation 9 h after the first injection. One group of rats was also injected with DOM alone at 0 and 4,5 h; the control group was injected with the vehicle ("Dispersol"—I.C.I. Trade Mark) also at 0 and 4.5 h was 5-HT estimated in the whole brain fluorimetrically by the method already described.

The Effect of DOM on the Noradrenalin, Normetanephrine, Dopamine and 5-HT Content of 3 Regions of the Rat Brain

Groups of rats were injected intraperitoneally with 30 mg/kg DOM and killed 3 h later. Following decapitation of the animals, the brains were removed and dissected on a cooled glass plate into two anatomical areas which were known to be relatively rich in catecholamines and 5-HT. The cerebral cortex was also taken; the cerebellum was discarded. The regions studied were the "middle" brain (consisting of the hippocampus, striatum, thalamus, hypothalamus and infundidulum), the "caudal" brain (consisting of the pons, medulla, tegmentum and colliculus) and the cerebral cortex which included the olfactory lobes. The brain regions were immediately frozen on solid carbon dioxide, weighed and homogenized in 9 ml of 0.01 N hydrochloric acid containing 0.2 ml 10% (w/v) ethylene diamine tetraacetic acid (as the disodium salt). The homogenate was centrifuged for 15 min at approximately 800×g and 4.3 ml of the supernatant fraction, plus the pellet, was extracted with salt saturated n-butanol. Noradrenalin, dopamine and 5-HT were determined by the methods already described. Normetanephrine was determined in 4.5 ml aliquots of the supernatant fraction by the method of Anton and Sayre (1966) as modified by Leonard and Tonge (1969).

Effect of DOM on the Conversion of Tritiated Tyrosine and Tryptophan Into Brain Noradrenalin, Dopamine and 5-HT

Groups of 6 rats (60—80 g) of either sex were treated for 2 h with DOM (20 mg/kg i.p.). Younger rats were used in this experiment because if was necessary to administer the highest possible activity of the amino acids yet at the same time ascertain that the animals were sufficiently mature to ensure that all the studies were comparable. This treatment time coincided with the period found in other studies when the drug caused a significant change in the concentration of most brain amines and amino acids. The control group was injected with distilled water (0.2 ml/rat). Exactly 30 min before the rats were killed by decapitation, they were injected with 2.86 Ci/kg of L-3H-tryptophan (G) (Specific activity 4.2 Ci/mmol[1]) and 2.86 mCi/kg of L-3H tyrosine (3,5-H^3) (Specific activity 52 Ci/mmol[1]) by the intraperitoneal

1 Obtained from the Radiochemical Centre, Amersham, Bucks.

route in a total volume of 0.2 ml. In this experiment 2 rats which had been otherwise untreated were killed, the brains removed and treated in the same way as the control and experimental groups. The extracts from the brains of these animals were used as "brain blanks" in the determination of the radioactivity. In a preliminary experiment, no difference was found in the specific activity of the amines and their precursors in rats which had been injected intraperitoneally from those which had been onjected intravenously.

After the rats had been killed, the brains were rapidly removed and the cerebellum discarded. They were then washed with physiological saline to remove the excess blood and the saline then removed by means of a filter paper. The brains were weighed, homogenized in 0.4 N perchloric acid and centrifuged. After centrifugation, the supernatants were then passed through Dowex 50×4 (200—400 mesh) columns. The amines and their amino acid precursors were selectively eluted and assayed spectrophotofluorimetrically by the method of Neff, Spano, Groppetti, Wang, and Costa (1971). The method of Neff *et al.* (1971) was also followed for the determination of the specific activities of the amines and these precursors. By using this methods the conversion rate of 3H-tyrosine and 3H-tryptophan into 3H-noradrenalin, 3H-dopamine and 3H-5HT was compared assuming that there exists in the brain 2 amine "compartments" which are in equilibrium. In this system the quantity of amine formed can be calculated from the ratio of the specific activity of the amine to that of its precursor amino acid. This ratio is essentially similar to the "conversion index" used by Costa, Groppetti, and Revuelta (1971) to obtain an approximate assessment of the rate of incorporation of the tritiated precursor amino acid into its amine. It is assumed that, even though this model fails to correct for the efflux of the amine from its stores, providing the measurements are taken shortly after injection of the amino acid it can be used for comparative studies of the incorporation rates of labelled amino acids into amines. In preliminary studies, it was found that the increase in labelled brain tyrosine and tryptophan were linearly related to the decrease in the serum concentrations of these amino acids for approximately 40 min following intraperitoneal injection. For this reason a 30 min period was allowed between the injection of the labelled amino acids and the decapitation of the rats.

In all the experiments described, the significance of the results was assessed using Student's *t*-test. Deviations are expressed as standard errors of the mean (s.e.m.).

Results

Behavioural Effects. Doses of DOM greater than 10 mg/kg caused pronounced "head shaking" which commenced approximately 15 min after injection and persisted for 45 min. Apart from slight piloerection, no other effects were apparent. High doses of the drug (50—60 mg/kg) caused head twitching and piloerection, the animals became difficult to handle and were generally more agitated. Hyperthermia did not occur even with the highest dose administered. A dose of 60 mg/kg caused convulsions in some animals but no deaths occurred. In experiments in which the animals were given more than one dose of DOM, qualitatively similar behavioural changes were seen after the second dose had been administered. The behavioural effects were most pronounced 30—90 min after injection of the drug and gradually decreased over the following 4 h period.

Effect of DOM on the Amino Acid Concentrations in the Serum and Brain and on the Concentrations of Noradrenaline, Dopamine and 5-HT in the Brain

DOM (10 mg/kg) caused a biphasic change in the concentration of serum tryptophan, the initial decrease in the concentration of the amino acid being followed by a rise 2 h later (Fig. 1). Within 4 h of injection tryptophan returned to its resting concentration. The change in the concentration of brain tryptophan were small when a dose of 10 mg/kg of the drug was administered. However, when the dose was increased to 30 mg/kg there was a biphasic change in brain tryptophan concentration the initial rise being followed by a fall which persisted for up to 24 h following the injection; the concentration returned to the resting level at 48 h after DOM.

DOM (10 mg/kg) caused a marked decrease in the serum tyrosine concentration which lasted for approximately 4 h (Fig. 2). This was followed by an elevation in the concentration of the amino acid. These changes were not reflected in the brain tyrosine concentration. DOM did not cause any significant change at 10 mg/kg but a dose of 30 mg/kg

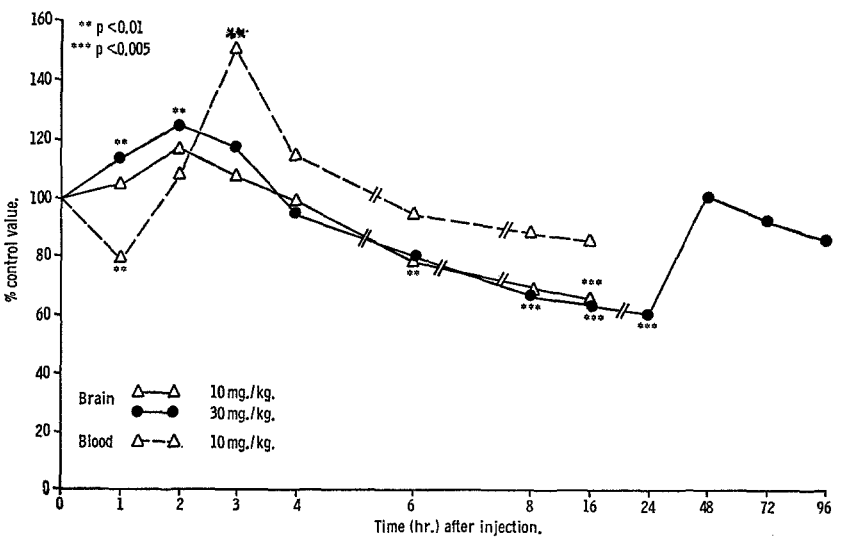

Fig. 1. Time courses of the effects of DOM on brain and serum tryptophan concentrations. Each point, expressed as a percentage of the control value, represents the mean of at least 5 animals. The significance of the difference from the control animals is shown by $^{**}P < 0.01$, $^{***}P < 0.005$. Control values for brain tryptophan were 2.59 ± 0.19 μg/g and for serum tryptophan 11.05 ± 0.66 μg/ml. These values represent the mean ± S.E.M.

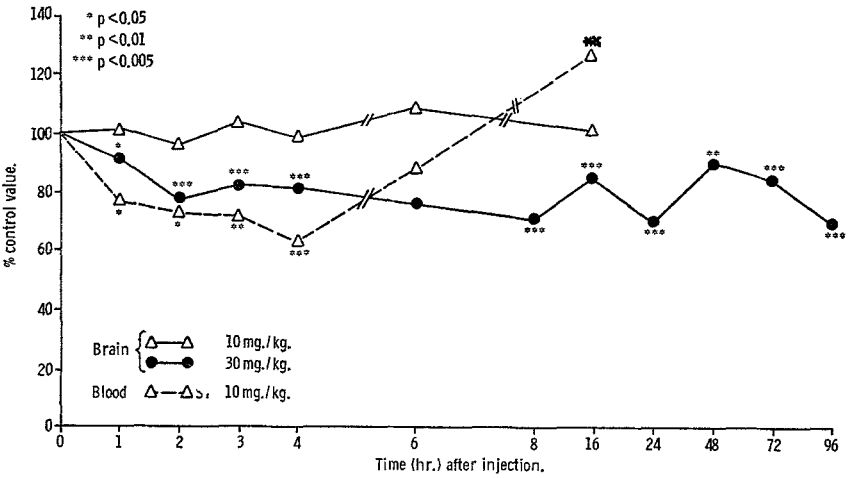

Fig. 2. Time courses of the effects of DOM on brain and serum tyrosinecon centrations. Each point, expressed as a percentage of the control value, represents the mean of at least 5 animals. The significance of the difference from the control animals is shown by $*P < 0.05$, $**P < 0.01$, $***P < 0.001$. Control values for brain tyrosine were 16.2 ± 0.57 μg/g and for serum tyrosine 11.2 ± 0.9 μg/ml. These values represent the mean ± S.E.M.

caused a marked decrease in brain tyrosine which lasted for up to 96 h after the injection.

The concentration of brain γ-ABA was slightly reduced by 10 mg/kg DOM (Fig. 3). This effect was more marked when the dose was raised to 30 mg/kg; at this dose of the amphetamine, the fall in γ-ABA was followed 24 h after injection by a marked rise which persisted for up to 96 h following the injection.

DOM (10 mg/kg) caused a slight increase in the brain 5-HT 2 h after injection which rapidly returned to the resting concentration (Fig. 4). However a dose of 30 mg/kg produced a biphasic change in the concentration of this amine, the initial rise being followed by a marked fall approximately 8 h after the drug had been injected. This reduction in the brain 5-HT persisted for approximetaly 8 h. Higher doses of DOM (60 mg/kg) caused a marked rise in the brain 5-HT concentration which lasted for at least 4 h (Fig. 5). This change was associated with a significant decrease in the deaminated metabolite, 5-hydroxyindole acetic acid (5-HIAA).

The changes in brain noradrenalin and dopamine produced by 30 mg/kg DOM were similar (Fig. 4), the drug producing a decrease in the concentration of these amines which lasted for approximately 8 h after injection. This effect was followed by a rise in the concentrations of

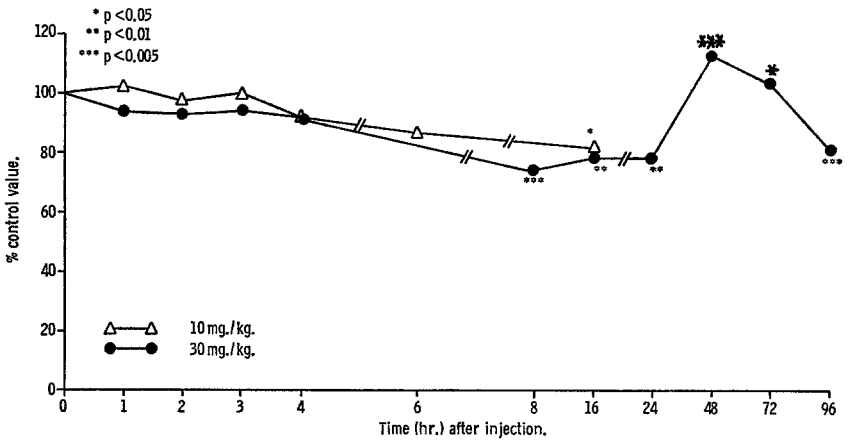

Fig. 3. Time course of the effect of DOM on brain γ-aminobutyric acid concentration. Each point, expressed as a percentage of the control value, represents the mean of at least 5 aminals. The significance of the difference from the control animals is shown by $*P < 0.05$, $**P < 0.01$, $***P < 0.005$. Control value for brain γ-ABA were 480 ± 39.8 µg/g. This value represents the mean $\pm$ S.E.M.

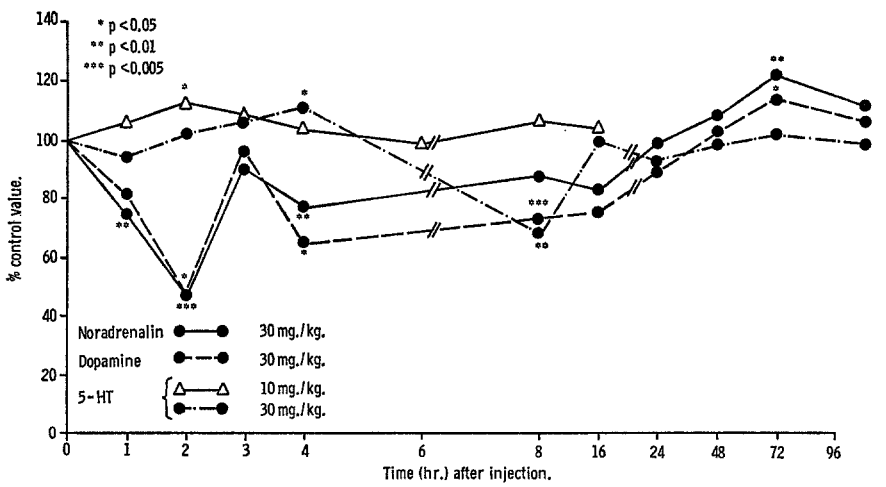

Fig. 4. Time courses of effects of DOM on brain amine concentrations. Each point, expressed as the percentage of the control value, represents the mean of at least 5 animals. The significance of the difference from the control animals is shown by $*P < 0.05$, $**P < 0.01$, $***P < 0.005$. Controls values for noradrenalin were 0.51 ± 0.024 µg/g for dopamine 0.89 ± 0.078 µg/g and for 5-hydroxytryptamine 0.43 ± 0.006 µg/g. These values represent the mean $\pm$ S.E.M.

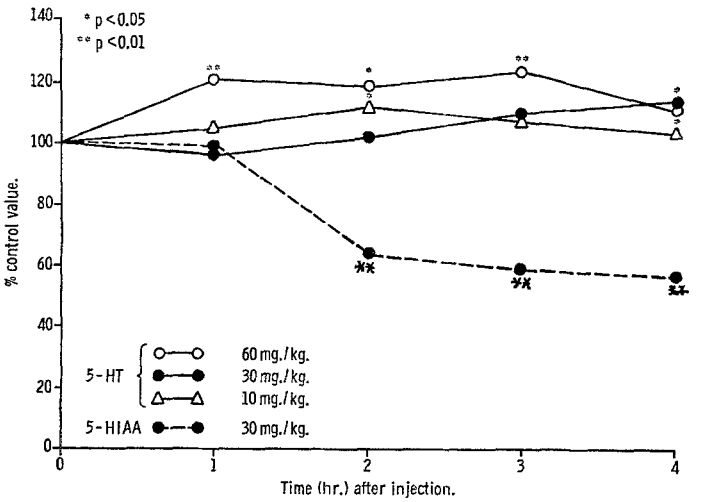

Fig. 5. Time course of the effect of DOM on brain 5-hydroxytryptamine and 5-hydroxyindoleacetic acid concentrations. Each point, expressed as a percentage of the control value, represents the mean of at least 5 animals. The significance of the difference from the control animals is shown by $*P < 0.05$, $**P < 0.01$, $***P < 0.005$. Control values for 5-hydroxytryptamine were 0.56 ± 0.04 μg/g and for 5-hydroxyindoleacetic acid 0.38 ± 0.06 μg/g. These values represent the mean $\pm$ S.E.M.

these amines after 72 h which returned to the resting levels within 96 h of injection.

Effect of DOM on the Depletion of Catecholamines by H77/77

DOM (2×20 mg/kg) did not significantly affect the depletion of brain noradrenalin caused by H77/77 (Table 1). It did, however, potentiate the effects of the catecholamine depleting agent on the concentration of brain dopamine. The concentration of noradrenalin in the brains of rats treated with DOM is somewhat higher than would have been expected from other experiments reported here. One possible explanation could be the effect of the two dose regimen. The reason for the somewhat lower noradrenalin concentrations in the control group, approximately 60% of the value usually obtained for this strain of rats, is not apparent. However, this is unlikely to have affected the qualitative changes due to the interaction between DOM and H77/77.

Effect of DOM on the Depletion of Brain 5-HT by H75/12

DOM (2×20 mg/kg) did not significantly affect the depletion of brain 5-HT caused by H75/12. The concentration of this amine was increased from 0.60 ± 0.03 μg/g to 0.71 ± 0.02 μg/g by DOM. H75/12 reduced the

Table 1. Effect of DOM on the depletion of brain catecholamines caused by H77/77

Treatment	Dose (mg/kg)	Noradrenalin (μg/g)	Significance from control	Significance from H77/77	Dopamine (μg/g)	Significance from control	Significance from H77/77
Control	—	0.29 ± 0.018	—	—	0.82 ± 0.04	—	—
H77/77 alone	2×12.5	0.17 ± 0.004	< 0.0005	—	0.65 ± 0.02	< 0.0005	—
DOM alone	2×20	0.28 ± 0.005	n.s.	—	0.89 ± 0.04	n.s.	—
H77/77 + DOM	$2 \times 20 + 12.5$	0.17 ± 0.003	< 0.0005	n.s.	0.51 ± 0.02	< 0.0005	< 0.05

Results expressed as mean $\pm$ s.e.m. for 5 animals per group.

concentration of 5-HT by 20% relative to the control group. In combination with DOM, H75/12 reduced the concentration by 18%.

Effect of DOM on the Depletion of 5-HT by PCPA

DOM (2×10 mg/kg) slightly reduced the depletion of brain 5-HT by PCPA (Table 2).

Effect of DOM on the Concentration of Noradrenalin, Normetanephrine, Dopamine and 5-HT in 3 Regions of the Rat Brain

The results (Table 3) show that DOM increases the dopamine concentration of the cortex and middle brain and slightly reduce the nor-

Table 2. Effect of DOM on the depletion of 5-HT caused by PCPA

Treatment	Dose (mg/kg)	5-HT concentration
Control	—	0.56 ± 0.040
PCPA alone	400	0.34 ± 0.035*
DOM alone	2×10	0.61 ± 0.042
PCPA ± DOM	400 + (2×10)	0.44 ± 0.030**

* Difference from control significant at $P < 0.01$.

** Difference from PCPA treated group significant at $P < 0.05$. Each result shown as the mean ± s.e.m. for 5 rats per group.

Table 3. Effect of DOM on the concentration of brain noradrenalin, dopamine, normetanephrine and 5-HT in 3 regions of the rat brain

Treatment	Concentration of			
	Normetanephrine	Noradrenaline	Dopamine	5-HT
	Cortex			
Control	0.034 ± 0.021	0.51 ± 0.024	1.20 ± 0.117	0.72 ± 0.03
DOM	0.038 ± 0.034	0.65 ± 0.15	1.61 ± 0.193*	0.73 ± 0.19
	Middle brain			
Control	0.032 ± 0.021	1.13 ± 0.21	1.43 ± 0.08	0.70 ± 0.04
DOM	0.040 ± 0.034	0.97 ± 0.09	2.00 ± 0.16*	0.92 ± 0.07*
	Caudal brain			
Control	0.045 ± 0.029	1.02 ± 0.029	1.00 ± 0.132	1.52 ± 0.09
DOM	0.041 ± 0.030	0.92 ± 0.06	1.02 ± 0.162	1.54 ± 0.10

All values given in μg/g wet weight brain. Results expressed as mean ± s.e.m. for 5 animals per group. Significance of difference between the untreated and treated groups shown by $*P < 0.05$. Treated groups given DOM (30 mg/kg) and killed 3 h later.

Table 4. Effect of DOM on the incorporation of H^3-tyrosine and N^3-tryptophan into noradrenalin, dopamine and 5-hydroxytryptamine in the rat brain

Treatment	Tyrosine	Tryptophan	Noradrenalin	Dopamine	5-Hydroxytryptamine
	Concentration[a]				
Control (saline)	229.5 ± 14.0	20.1 ± 1.21	2.063 ± 0.113	3.772 ± 0.593	2.818 ± 0.443
DOM (20 mg/kg)	157.2 ± 9.9***	24.62 ± 0.96**	1.892 ± 0.042	4.95 ± 0.515	6.604 ± 0.902**
	Specific activity[b]				
Control	93.7 ± 5.8	609.6 ± 58.6	36.43 ± 8.18	26.5 ± 2.17	30.25 ± 5.71
DOM	139.5 ± 13.7**	1041.5 ± 104.8***	110.08 ± 10.43***	38.64 ± 3.13**	22.67 ± 2.53
	Conversion index[c]				
Control			0.416 ± 0.105	0.301 ± 0.029	0.040 ± 0.009
DOM			0.682 ± 0.063	0.281 ± 0.026	0.020 ± 0.003

[a] Expressed as nmole/g brain.

[b] Expressed as d.p.m./n/mole/g brain.

[c] Expressed as ratio of specific of amine to its amino-acid precursor.

Results expressed as mean ± s.e.m. for at least 6 rats per group. Significance of results relative to the saline treated group, using Students "t"-test, indicated by * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$. DOM was injected 120 min before the animals were killed.

adrenalin concentration of the middle and caudal brain. The concentration of 5-HT was significantly increased only in the middle brain region. There was no significant change in the concentration of normetanephrine in any of the brain regions.

Effect of DOM on the Conversion of Tritiated Tyrosine and Tryptophan to Brain Noradrenalin, Dopamine and 5-HT

DOM (20 mg/kg) increased the concentration of tryptophan and 5-HT and reduced that of tyrosine (Table 4). At this dose it did not significantly affect the concentration of noradrenalin or dopamine. However, the specific activity of tyrosine, tryptophan, noradrenalin and dopamine were significantly increased whereas that of 5-HT was unaffected. The results also showed that DOM affected the conversion of tyrosine and tryptophan to noradrenalin and 5-HT; the conversion to noradrenaline was increased whereas that to 5-HT was reduced. If it is assumed that the conversion index is an approximate measure of the "turnover" rate of the amines then it can be concluded that the drug increases the "turnover" of noradrenalin but reduces that of 5-HT.

Discussion

The effect of DOM on the behaviour of the rats suggest that it is not an amphetamine of the "stimulant" type. Although convulsions did occur in some rats after a dose of 60 mg/kg had been administered, no such effect was seen after the highest dose which was used in the biochemical studies (30 mg/kg) had been administered. Although such a dose seems high in terms of the human equivalent, and in terms of the dose needed to produce EEG changes in the cat (Wallach, Friedman, and Gershon, 1972), it is unlikely that the changes observed are due to non-specific toxic effects as there is evidence for a direct relationship between the dose of DOM and its effect on the neurochemical parameters.

The results of this investigation show that DOM produces changes in brain biogenic amines and their amino acid precursors which are qualitatively similar to those produced by other hallucinogenic drugs (Giarman and Freedman, 1965; Andén, Corrodi, Fuxe, Hökfelt, 1968; Leonard and Tonge, 1969; Tonge and Leonard, 1969, 1970). Thus DOM, like most other hallucinogens, decreases the concentration of γ-ABA and, for most of the duration of the drug effect, brain tryptophan. The concentration of brain noradrenalin is aslo reduced. DOM causes a biphasic change in the concentration of brain dopamine; 3 h after the drug had been administered there was a slight rise in the concentration of this amine which appeared to be restricted to the cortical and subcortical regions of the brain, the concentration of dopamine in the caudal brain being unaffected. This rise in brain dopamine was preceded and succeeded by a fall in the concentration of the amine. The concentration

of the principle o-methylated metabolite of noradrenalin, normetanephrine, was unaffected by DOM which suggests that the reduction in the concentration of brain noradrenalin caused by this drug is associated with an increased intraneuronal metabolism. Another possible explanation of the reduction in brain noradrenaline is that DOM decreases the availability of tyrosine to the brain. It has been estimated that only 1—2% of available brain tyrosine is converted to noradrenalin (Schubert, Nyback, and Sedvall, 1970) which suggests that the change in the concentration of his amino acid may not be of decisive importance in determining the changes in the concentration of brain catecholamines. Nevertheless, such an indirect effect on catecholamine synthesis still remains a possibility which cannot be entirely excluded.

DOM has a pronounced effect on the metabolism of brain 5-HT. It increased the concentration of this amine and this effect appears to be related to the dose of drug administered—the higher the dose, the more prolonged the increase in the concentration of brain 5-HT. The rise in brain 5-HT is closely associated with a marked decrease in 5-HIAA which suggests either that the release or the intraneuronal metabolism of 5-HT is reduced by DOM. The increase in 5-HT seems to be restricted to the subcortical regions of the brain.

As the subcortical region of the brain is thought to be involved in the control of emotions it is speculated that the effects produced by DOM in man, which have been described in detail by other investigators (Snyder, Faillace, and Hallister, 1967; Faillace, Snyder, and Weingartner, 1970), may be associated with changes in amine metabolism in this region.

DOM also partially antagonized the depletion of brain 5-HT by p-chlorophenylalanine, a drug which has been shown to deplete 5-HT by inhibiting tryptophan hydroxylase which is rate limiting in the synthesis of this amine (Koe and Weisman, 1966). This suggests that DOM increases the intraneuronal concentration of 5-HT by decreasing its release, an effect which is shared by other hallucinogenic drugs (Tonge and Leonard, 1969). Such an effect could also account for the decreased 5-HIAA concentration found after the administration of this amphetamine.

DOM increases the conversion of tyrosine into noradrenalin and reduces that from tryptophan to 5-HT. It seems reasonable to assume that these effects are a reflection of the drug increasing or decreasing respectively the "turnover" of these amines in the brain. Such an assumption would seem justified as the other findings reported here indicate that DOM increases the intraneuronal metabolism of noradrenalin and reduces that of 5-HT. The final effect of the action of DOM on brain amines could therefore be to reduce that efflux of 5-HT onto its receptor site and possibly also affect the efflux of noradrenalin.

Precisely how DOM causes the changes in brain amines is uncertain. Denber and Teller (1968) suggested that mescaline can stabilize the neuronal membrane and thereby reduce its permeability to the efflux of such transmitters as noradrenalin and 5-HT. If this effect on neuronal membranes is a property which is common to all hallucinogenic drugs then DOM, which has a qualitatively similar effect on brain amines as mescaline, may affect the release of 5-HT and noradrenalin by a specific action on the neuronal and/or storage granule membrane.

It is clear from this study that DOM differs considerably in its effect on brain amine metabolism from the other amphetamines which have been investigated (see refrs. in "Introduction"). Thus the stimulant amphetamine (d-amphetamine, d-methamphetamine, p-nitromethamphetamine) increase the release of both noradrenalin and 5-HT from central neurons. However, p-bromomethamphetamine, which is only slightly stimulant even at high doses, reduces the release of noradrenalin but increases that of 5-HT. The differences in the effects produced by these amphetamines which have been studied are presumably related to their structural differences. Substitution of the methoxy-group in the meta- and ortho-positions increases the hallucinogenic properties and reduces the stimulant effects of the drug. It could be that these structural differences are related to the differences in action of the amphetamines on the neuronal membrane.

Since the completion of this investigation, Wallach, Friedman, and Gershon (1972) have reported that DOM increases the concentrations of both noradrenalin and 5-HT in different regions of the cat brain. They conclude that the effect on the 5-HT concentration may be a consequence of the drug acting on postsynaptic serotonergic receptors. Discrepancies in their neurochemical findings and those reported here may be due to species variation.

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