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Effects of amphetamine derivatives on brain dopamine and noradrenaline

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Summary

1. Intracisternally administered metaraminol, α-methyl-octopamine, α-methyl-*m*-tyramine, and α-methyl tyramine were found to lower brain noradrenaline without having an effect on brain dopamine.

2. Amphetamine, mephentermine, and norephedrine had no effect on brain catecholamines after intracisternal injection.

3. There was no reduction in brain dopamine content after intracisternal injection of α-methyl-*m*-tyramine, yet the resulting brain concentration of α-methyl-*m*-tyramine was several times higher than after intraperitoneal injection of α-methyl-*m*-tyrosine, which decreased brain dopamine.

4. The decreased synthesis of labelled catecholamines from ^{14}C-tyrosine after α-methyl-*m*-tyrosine suggested that this compound inhibits tyrosine hydroxylase in addition to its action of displacing brain amines.

Introduction

A number of studies have been reported in which sympathomimetic amines were injected into the cerebrospinal fluid to circumvent the blood-brain barrier and their behavioural effects noted (Leimdorfer, 1950 ; Feldberg & Sherwood, 1954 ; Gaddum & Vogt, 1956). Marley (1964) has extended such studies on behaviour, studying the structure-activity relationship of various phenylethylamine derivatives in immature fowl in which the blood-brain barrier is not fully effective. In spite of the many experiments in which amines have been injected into cerebrospinal fluid, however, little is known about the effects of these compounds on endogenous brain catecholamines.

The purpose of the following investigation was to study the effect on cerebral noradrenaline and dopamine of a series of amphetamine derivatives administered intracisternally. The effect of systemically administered α-methyl-*m*-tyrosine on central catecholamines was also examined and the amine products determined which accumulate in brain after its administration (Carlsson & Lindqvist, 1962 ; Shore, Busfield & Alpers, 1964).

Methods

General procedures

The α-methyl phenylethylamine (amphetamine) derivatives under investigation were injected intracisternally into Sprague-Dawley rats (180–200 g) as described pre-

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viously (Schanberg, Schildkraut, Breese & Kopin, 1968). Compounds were dissolved in Elliott's " B " solution (Baxter) which contained in each 100 ml 0·73 g NaCl, 0·03 g KCl, 0·02 g $CaCl_2 \cdot 2H_2O$, 0·03 g Mg $O_4 \cdot 7H_2O$, 0·02 g $Na_2HPO_4 \cdot 7H_2O$, 0·08 g hydrous dextrose and 0·19 g $NaHCO_3$; total volume injected was 20 μl. At various times after injection of the drugs, the animals were killed by cervical fracture and decapitated. Brains were removed, rinsed in cold water, homogenized in 10 ml of ice cold 0·4 N perchloric acid and kept frozen until analysed within 24–48 hours.

Determination of noradrenaline and dopamine

After thawing and centrifugation, the clear supernatant was adjusted to pH 8·6 with sodium hydroxide and the catecholamines absorbed on to alumina (Woelm, neutral) by a modification of the method of Anton & Sayre (1962). Endogenous noradrenaine in the 0·2 N acetic acid eluate was assayed using the fluorimetric method of Häggendal (1963) with the substitution of mercaptoethanol for BAL. Dopamine was assayed according to the method of Anton & Sayre (1964).

In some experiments, tyrosine-^{14}C and/or dopa-^{3}H was injected before or after the intracisternal administration of (−)-metaraminol (40 μg) or the intravenous injection of α-methyl-*m*-tyrosine (100 mg/kg). Labelled dopamine and noradrenaline formed from the radioactive dopa and tyrosine were separated on a Dowex-50 (Na^+) column (Sedvall, Weise & Kopin, 1968) and assayed for ^{14}C and/or ^{3}H by liquid scintillation spectrometry.

*Determination of metaraminol and α-methyl-*m*-tyramine*

After removal of catecholamines by absorption on alumina as described above, the effluent solution was brought to pH 6·0 and passed through a column of Dowex 50 Na^+ (5 × 0·8 cm). The column was washed with 10 ml water, 10 ml of 0·5 M phosphate buffer (pH 6·5) and 8 ml 1 N hydrochloric acid. Metaraminol was then eluted with 16 ml of 1 N HCl. After discarding 5 ml of 1 N HCl added to the column, α-methyl-*m*-tyramine was eluted with 16 ml of 3 N HCl. An aliquot was reacted with *o*-phthalaldehyde and the amines measured fluorimetrically (Shore & Alpers, 1964).

Tritium labelled (±)-metaraminol (10 μCi, 40 μg) administered to rats was determined by extracting the amine according to the method of Shore & Alpers (1964). Total radioactivity in brain was determined by assaying an aliquot of the homogenate supernatant for tritium. Internal standards of toluene-^{3}H and ^{14}C were used to correct for counting efficiency. In those experiments in which catecholamine was not assayed the use of alumina was omitted.

Drugs

The amines studied included (−)-metaraminol bitartrate (Merck Sharp and Dohme), α-methyl-octopamine HCl (Aldrich Chemical Co.), α-methyl-*m*-tyramine (Merck Sharp and Dohme), α-methyl-tyramine HCl (Smith Kline and French), (+)-amphetamine sulphate (Smith Kline and French), mephentermine sulphate (Wyeth Laboratories), norephedrine HCl (Aldrich) and α-methyl-*m*-tyrosine (Nutritional Biochemical). (±)-Metaraminol-7-^{3}H (28 mCi/mg) was purchased from New England Nuclear Corp. ; (−)-tyrosine-^{14}C (400 mCi/mmol) and dopa-^{3}H (34 mCi/mmol) were purchased from Searle. All drug doses refer to the free base.

Results

Effect of intracisternally administered amphetamine derivatives on dopamine and noradrenaline content of rat brain

Three hours after intracisternal injection of 40 μg, several amphetamine derivatives were found to have depleted brain noradrenaline (Table 1). Metaraminol was also given intracisternally after the systemic administration of ^{3}H-dopa to determine its effect on ^{3}H-noradrenaline formed from labelled dopa. ^{3}H-noradrenaline was found to be decreased significantly while ^{3}H-dopamine was unaltered (Table 2). A higher dose of metaraminol (100 μg) did alter dopamine levels, but not to the degree that noradrenaline levels were lowered (Tables 4 and 5).

Effect of systemically administered metaraminol on brain noradrenaline and dopamine

Because dopamine levels were not altered by intracisternally administered metaraminol (Table 1), the possibility existed that the route of administration could have contributed to this lack of effect on dopamine. However, 4 and 24 h after the systemic administration of metaraminol (10 mg/kg) levels of endogenous noradrenaline were reduced while no significant effect on dopamine levels was noted (Table 3).

TABLE 1. *Effect of intracisternally administered phenylethylamine derivatives on dopamine and noradrenaline content of rat brain*

	Dopamine		Noradrenaline	
Treatment	ng/Brain	% Control	ng/Brain	% Control
Control	841±28·5	—	552±24	—
Metaraminol	810±56·8	96±6·6	227±16·3	41·1±3·0
α-CH_3-octopamine	913±56·5	109±6·7	269±10·2*	48·7±1·9
α-CH_3-*m*-tyramine	797±45·5	95±5·4	278±31·5*	50·3±5·7
α-CH_3-tyramine	863±34	103±4·0	297±23·6*	53·8±5·4
Norephedrine	879±29·8	105±3·5	561±17·3	102±3·1
Mephentermine	890±25·1	106±3·0	553±11·6	100±2·1
Amphetamine	885±49·6	105±5·4	574±35·3	104±6·4
α-CH_3-*m*-tyrosine	236±16·7*	28±2·0	82·5±8·8*	15±1·6

Various phenylethylamines (40 μg) were injected intracisternally. α-Methyl-*m*-tyrosine (100 mg/kg) was administered intravenously. All animals were killed by cervical fracture 3 h after receiving the α-methylated compounds. Values represent the mean ± S.E.M. of six to twelve animals. *$P<0.001$.

TABLE 2. *Effect of metaraminol on dopamine and noradrenaline formed from ^{3}H-dopa*

Treatment	^{3}H-dopamine	^{3}H-noradrenaline
Control	764±50	578±29
Metaraminol	734±66	353±19*

Metaraminol (40 μg) was administered intracisternally 60 min after the intravenous injection of 200 μCi of ^{3}H-dopa. Animals were killed 2 h after the metaraminol. Values represent the mean c.p.m./brain ± S.E.M. of eight to ten determinations. *$P<0.01$.

TABLE 3. *Effect of systemically administered metaraminol on brain dopamine and noradrenaline*

Treatment	Dopamine	Noradrenaline
Saline	1,024±53	783±27
Metaraminol 4 h	1,104±45	328±35*
Metaraminol 24 h	956±59	527±26*

Metaraminol (10 mg/kg) was injected intraperitoneally and the animals killed either 4 or 24 h later. Each value represents the mean ± S.E.M. of eight to ten determinations. *$P<0.01$.

Disappearance of metaraminol from brain after intracisternal injection

After intracisternal injection, metaraminol was found to disappear from brain in a multiphasic fashion (Fig. 1). During the first hour, the " half-life " was approximately 12 min, thereafter progressively increasing. After 12 h the apparent " half-life " was approximately 24 h. Noradrenaline levels decreased during the first 6 h, but the beginning of recovery was apparent at 12 h. Forty-eight hours after metaraminol injection, noradrenaline levels were still significantly depressed and measurable amounts of metaraminol were found in the brain. At all times, metaraminol content was in excess of the noradrenaline lost.

*Effect of α-methyl-*m*-tyrosine and α-methyl-*m*-tyramine on levels of catecholamines, α-methyl-*m*-tyramine and metaraminol*

The depletion of brain noradrenaline following intracisternal administration of α-methyl-*m*-tyramine was related to dose (Fig. 2), but there was no significant effect on levels of dopamine, even at the highest dose given. When α-methyl-*m*-tyrosine was administered intravenously brain levels of metaraminol and noradrenaline were comparable with those seen after intracisternal injection of α-methyl-*m*-tyramine (Fig. 3). In spite of the fact that brain levels of α-methyl-*m*-tyramine were much higher after its intracisternal injection than after intravenous injection of the parent amino-acid, dopamine levels were significantly diminished only in animals receiving α-methyl-*m*-tyrosine (Fig. 3).

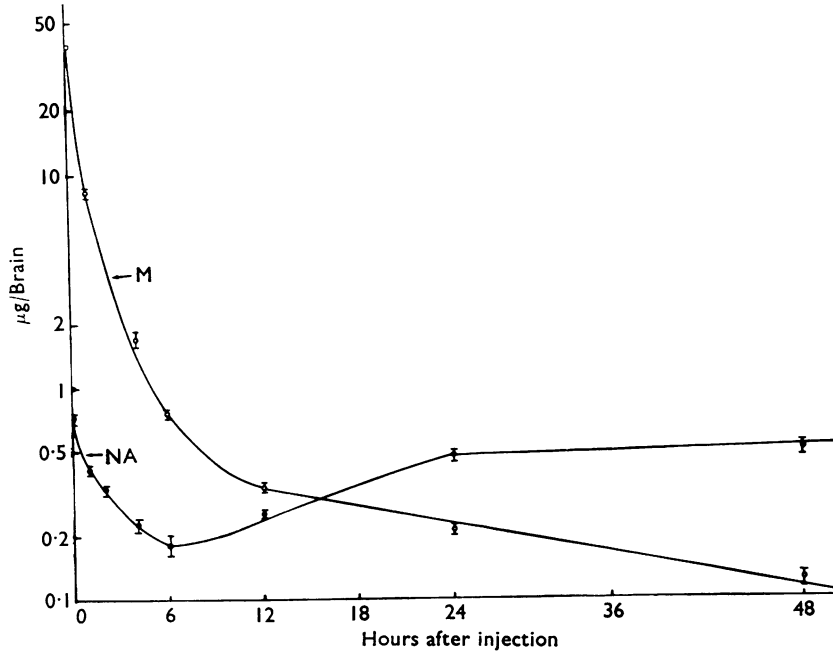

FIG. 1. Disappearance of metaraminol from brain and its relation to brain noradrenaline. (±)-Metaraminol (10 μCi, 40 μg) was administered intracisternally and the animals were killed at various times up to 48 h after injection. Values of both noradrenaline (NA) and metaraminol (M) are expressed as total amines (μg/brain). Each value represents the mean of six animals. Vertical bars indicate the standard error of the mean (S.E.M.).

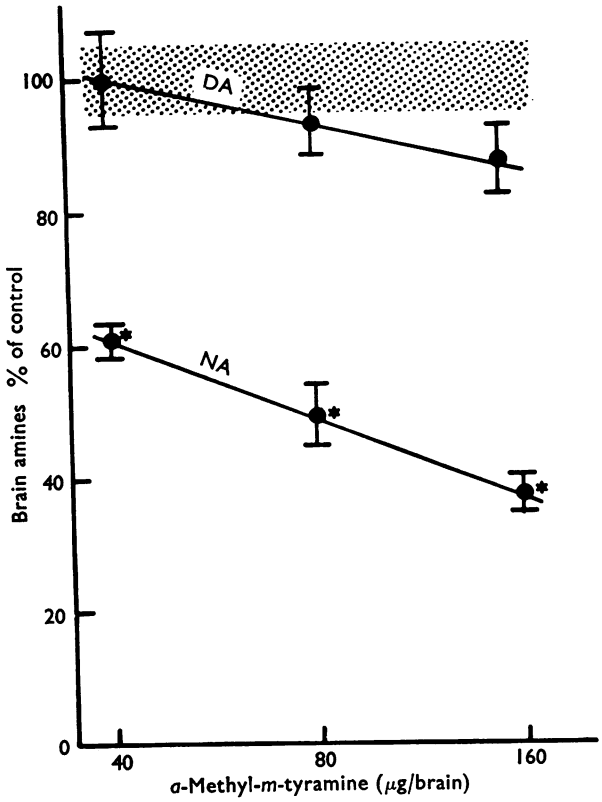

FIG. 2. Effect of various doses of α-methyl-*m*-tyramine on brain noradrenaline and dopamine. The compound was injected intracisternally and the animals killed 4 h later. Stippled area indicates control values ± S.E.M. Each value represents the mean ± S.E.M. of six or seven determinations. *$P<0.01$. NA, Noradrenaline; DA, dopamine.

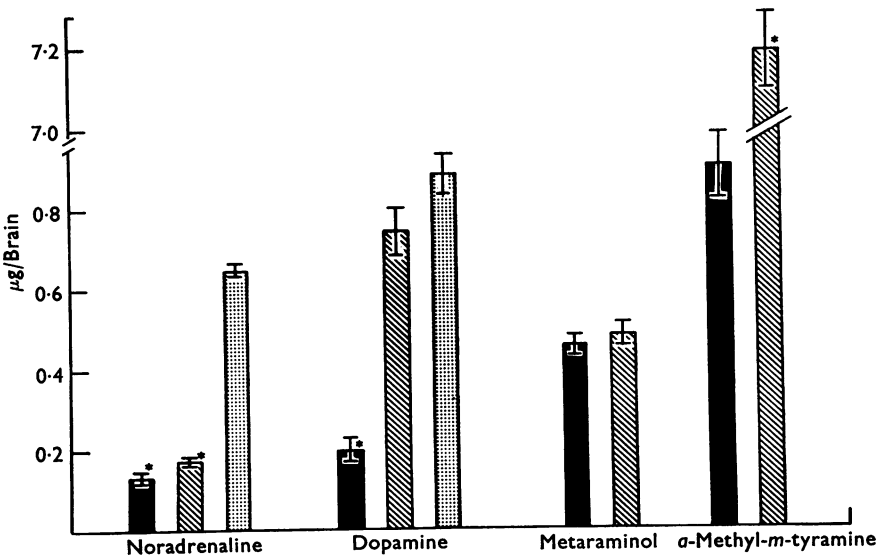

FIG. 3. Brain concentrations of noradrenaline, dopamine and α-methylated amines after α-methyl-*m*-tyrosine and α-methyl-*m*-tyramine. The α-methyl-*m*-tyramine (100 μg) was administered intracisternally and α-methyl-*m*-tyrosine (100 mg/kg) was administered intravenously. Animals were killed 4 h after drug administration. Vertical bars indicate S.E.M. *$P<0.01$. ■, After α-methyl-*m*-tyrosine; ≡, after α-methyl-*m*-tyramine; ⁘, controls.

Effect of metaraminol on brain catecholamine synthesis from dopa-^{3}H and tyrosine-^{14}C

Following simultaneous intravenous injection of tyrosine-^{14}C and dopa-^{3}H, labelled dopamine and noradrenaline are formed in brain (Sedvall *et al.*, 1968 ; Kopin, 1968). Two hours after intracisternal injection of 100 μg of metaraminol there is a striking decrease in noradrenaline formed from both tyrosine-^{14}C and dopa-^{3}H (Table 4). There is also a significant decrease in the ^{14}C/^{3}H ratio present in noradrenaline. Levels of noradrenaline are markedly reduced 2 h after metaraminol, but are even lower 7 h after administration of the amine (Table 4). At the later time noradrenaline formation from dopa-^{3}H is further diminished, but the amount of tyrosine-^{14}C converted to this catecholamine does not appear to be changed. Thus the ^{14}C/^{3}H ratio is not significantly different from that in control animals. A significant decrease in brain dopamine levels was also apparent 2 h or 7 h after this dose of metaraminol (Table 5). A highly significant decrease in formation of radioactive dopamine from both dopa-^{3}H and tyrosine-^{14}C was found 2 h after the amine was given, but there was only a slight decrease in labelled dopamine formation 7 h after the metaraminol.

The intracisternal injection of saline had no effect on the formation of dopamine, but this procedure, which included anaesthesia with ether and surgical manipulation, apparently resulted in an acceleration of conversion of tyrosine-^{14}C to labelled noradrenaline ($P<0.025$) (Table 4).

*Effect of α-methyl-*m*-tyrosine on catecholamine synthesis from dopa-^{3}H and tyrosine-^{14}C*

Five hours after intraperitoneal injection of α-methyl-*m*-tyrosine there were striking decreases in brain content of noradrenaline and dopamine (Tables 4 and 5).

TABLE 4. *Effect of metaraminol and α-methyl-*m*-tyrosine on noradrenaline synthesis in brain*

Treatment	NA (ng)	^{3}H-NA (c.p.m.)	^{14}C-NA (c.p.m.)	^{14}C/^{3}H
Metaraminol 1 h	248±20*	129±10*	181±16*	1·44±0·14**
Metaraminol 6 h	103±8*	74±18*	207±11*	3·21±0·47
Control (i.c. saline)	768±97	218±20	741±66	3·61±0·56
α-methyl-*m*-tyrosine	137±29*	147±11*	180±25*	1·42±0·21***
Control (i.p. saline)	656±56	237±8	486±24	2·05±0·06

All values are the mean ± S.E.M. of six animals and refer to amounts per whole brain; NA, noradrenaline.
*$P<0.001$; **$P<0.005$; ***$P<0.05$ when compared with corresponding control.
Metaraminol (100 μg) was administered intracisternally 1 or 6 h and α-methyl-*m*-tyrosine (100 mg/kg) intraperitoneally 4 h before the intravenous injection of ^{3}H-dopa (30 μCi) and ^{14}C-tyrosine (30 μCi). i.c. saline refers to the intracisternal administration of Elliott's "B" solution; i.p. saline refers to the intraperitoneal administration of vehicle (saline solution adjusted to pH 9). Animals were killed 1 h after receiving the labelled compounds.

TABLE 5. *Effect of metaraminol and α-methyl-*m*-tyrosine on dopamine synthesis in brain*

Treatment	Brain DA	^{3}H-DA	^{14}C-DA	^{14}C/^{3}H
Metaraminol 1 h	795±35**	103±13**	1,009±43*	11·38±1·11
Metaraminol 6 h	835±36***	126±20	1,171±95***	8·28±1·9
Control (i.c. saline)	1,035±44	142±15	1,470±57	10·97±1·3
α-methyl-*m*-tyrosine	279±21*	140±12	491±26*	3·48±0·58*
Control (i.p. saline)	989±40	114±12	1,254±66	11·39±0·88

All values are the mean ± S.E.M. of six animals and refer to amounts per whole brain: dopamine (DA) expressed as ng/brain and labelled compounds as c.p.m./brain.
*$P<0.001$; **$P<0.01$; ***$P<0.05$ when compared with corresponding control.
See Table 4 for procedure.

The amount of noradrenaline-^{14}C and noradrenaline-^{3}H formed from tyrosine-^{14}C and dopa-^{3}H were both decreased 5 h after the α-methyl amino-acid was given, with a significantly greater decrease in formation of noradrenaline-^{14}C than noradrenaline-^{3}H as indicated by the decrease in ^{14}C/^{3}H ratio. There was also a decreased formation of dopamine-^{14}C from tyrosine ^{14}C, while the amount of dopamine-^{3}H formed from dopa-^{3}H was not decreased (Table 5).

Discussion

The studies presented here demonstrate that various amphetamine derivatives when injected intracisternally cause depletion of brain noradrenaline without having an effect on brain dopamine (Table 1). Similarly, metaraminol released labelled noradrenaline formed from dopa-^{3}H without affecting concentrations of dopamine-^{3}H formed from labelled dopa (Table 2). Systemic administration of metaraminol also lowered brain noradrenaline without decreasing brain dopamine (Table 3). Amphetamine, mephentermine and norephedrine had no effect on brain noradrenaline at the dose given. It would appear, therefore, that one structural requirement for noradrenaline depletion in brain by phenylethylamines is a phenolic group. However, the depletion of brain noradrenaline by α-methyl-tyramine and α-methyl-*m*-tyramine may be dependent on their conversion to their corresponding β-hydroxy derivative. This view was suggested earlier from data obtained on heart (Shore, Alpers & Busfield, 1966). In support of this concept, measurable amounts of metaraminol were found after the administration of α-methyl-*m*-tyramine (Fig. 3). Depletion of heart noradrenaline by α-methyl-tyramine and α-methyl-*m*-tyramine has previously been reported to be prevented by an inhibitor of dopamine, β-hydroxylase (Shore *et al.*, 1966).

Considerable evidence has accumulated suggesting involvement of catecholamines in the behavioural effects of amphetamine (Sanan & Vogt, 1962 ; Van Rossum, 1964 ; Weissman, Koe & Tenen, 1966 ; Hanson, 1967). When injected in relatively high doses systemically, amphetamine has consistently decreased endogenous content of brain noradrenaline (Sanan & Vogt, 1962 ; Baird & Lewis, 1964 ; Glowinski, Axelrod & Iversen, 1966). Recent studies suggest that amphetamine depletion of adrenaline may be due to its conversion to *p*-hydroxy-norephedrine (α-methyl octopamine) (Thoenen, Huerlimann, Gey & Haefely, 1966 ; Groppetti & Costa, 1969 ; Gessa, Cho, Clay, Tagliamonte & Brodie, 1969). In the present study, amphetamine had no discernible effect on noradrenaline levels, suggesting that either it leaves brain rapidly or that conversion to α-methyl octopamine is minimal after intracisternal injection. Perhaps *p*-hydroxylation in the liver must precede β-hydroxylation in brain. Norephedrine, β-hydroxylated amphetamine, was also ineffective as a depletor of brain noradrenaline, while α-methyl octopamine lowered brain adrenaline significantly (Table 1), supporting the view that both ring and β-hydroxy substitution are necessary for depletion by amphetamine and that *p*-hydroxylation in brain is a slow reaction if it occurs at all.

There are numerous reports which show that α-methyl-*m*-tyrosine causes a marked reduction in brain noradrenaline with only a transient effect on brain dopamine (Hess, Connamacher, Ozaki & Udenfriend, 1961 ; Sourkes, Murphy, Chavez & Zielinska, 1961 ; Carlsson & Lindqvist, 1962). When Carlsson & Lindqvist (1962) found that α-methyl-*m*-tyrosine was decarboxylated and subsequently β-hydroxylated to metaraminol, a concept of " false transmitters " displaced

an earlier explanation that tissue reduction of noradrenaline by α-methylated amino-acids was due to decarboxylase inhibition. Subsequent to this study, Anden (1964) found that α-methyl-*m*-tyramine did produce a depletion of dopamine corresponding to that seen after α-methyl-*m*-tyrosine. Results in the present report show that concentrations of α-methyl-*m*-tyramine in brain were lower after α-methyl-*m*-tyrosine, which lowered dopamine, than after the intracisternal administration of α-methyl-*m*-tyramine, which had no significant effect on brain dopamine (Fig. 3). Furthermore, the ratio of $^{14}C/^{3}H$ in dopamine was depressed after the administration of ^{14}C-tyrosine and ^{3}H-dopa, indicating that the conversion of ^{14}C-tyrosine to ^{14}C-dopamine was decreased. The diminished conversion of tyrosine-^{14}C to dopa provides direct evidence for the suggestion that α-methyl-*m*-tyrosine inhibited catecholamine synthesis, thereby resulting in a greater depletion of endogenous amines than could be accounted for by replacement of these catecholamines with its decarboxylated products (Anden, 1964).

The inability of α-methyl-*m*-tyramine (Figs. 2 and 3) as well as of several other compounds (Table 1) to deplete dopamine may be the result of differences in dopaminergic and noradrenergic neurones. It appears that "false transmitter" phenylethylamine derivatives will either not displace dopamine or that dopaminergic neurones are unable to concentrate phenylethylamine compounds other than dopamine itself. As previously indicated, however, such compounds as α-CH_3-*m*-tyrosine may lower this catecholamine by inhibition of synthesis. Dopamine concentration can be significantly reduced by phenylethylamine compounds when very high doses are administered (Table 5). In accordance with this latter observation, prolonged depletion of dopamine and noradrenaline has been found to occur after intracisternal injection of 6-hydroxydopamine (2,4,5-trihydroxyphenylethylamine) to animals pretreated with pargyline (Breese, unpublished observations).

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