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The effects of (+)-amphetamine, α-methyltyrosine, and α-methylphenylalanine on the concentrations of *m*-tyramine and α-methyl-*m*-tyramine in rat striatum

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1 The concentration in rat striatum of the *meta* and *para* isomers of tyramine and α-methyltyramine, after the administration of (+)-amphetamine, α-methyl-*p*-tyrosine (AMPT) and α-methylphenylalanine (AMPA) has been determined using chemical ionization gas chromatography mass spectrometry (c.i.g.c.m.s.).

2 Twenty hours after the last of 7 daily injections of (+)-amphetamine (5 mg kg^{-1} i.p.) the concentration of α-methyl-*p*-tyramine in striatal tissue increased twofold compared to the concentration 20 h after a single injection. In contrast the concentration of α-methyl-*m*-tyramine did not change.

3 α-Methyl-*m*-tyramine and α-methyldopamine were found in the striatum at concentrations of 42 ng g^{-1} and 13.5 ng g^{-1} respectively after treatment of rats 20 h before with AMPA (100 mg kg^{-1} i.p.). After treatment with AMPT (100 mg kg^{-1}, 20 h before decapitation) only the *para* isomer of α-methyltyramine could be detected (13.7 ng g^{-1}) although the striatal concentration of α-methyldopamine was 274 ng g^{-1}, a level 20 times greater than that observed after AMPA treatment. The combined administration of both AMPT and AMPA (100 mg kg^{-1} each, 20 h) resulted in a reduction of the striatal concentration of α-methyl-*m*-tyramine but not α-methyl-*p*-tyramine.

4 These data suggest that α-methyl-*m*-tyramine in rat striatum is formed by the enzyme tyrosine hydroxylase on substrate AMPA, rather than by ring dehydroxylation of α-methyldopa and α-methyldopamine. Significant reductions in the striatal concentrations of *m*-tyramine 2 h after the administration of AMPT, suggest that tyrosine hydroxylase is involved similarly in the production of *m*-tyramine.

Introduction

Para and *meta*-tyramine are endogenous biogenic amines found in the striatum of rats and mice (Boulton, 1979). Studies using 6-hydroxydopamine and reserpine suggest that both isomers of tyramine are stored in intraneuronal granules in aminergic nerve terminals (Boulton, Juorio, Phillips & Wu, 1977). The metabolic pathways involved in the synthesis of the isomers of tyramine are little understood but there is evidence for 3 possible pathways: the phenolic dehydroxylation of either DOPA or dopamine, the phenolic hydroxylation of phenethylamine and the decarboxylation of the precursor amino acids (Boulton, 1979).

Amphetamine has been shown to have paradoxical effects on the striatal concentrations of *para* and *meta*-tyramine depending on whether the drug was administered *in vivo* or *in vitro*. On the one hand, (+)-amphetamine causes the release from rat striatal slices in *in vitro*, of both isomers of tyramine (Dyck, Boulton & Jones, 1980). On the other hand in *in vivo* experiments, administration of (+)-amphetamine to rats for 30 min lowers the striatal content of *p*-tyramine but causes a marked increase in that of *m*-tyramine (Danielson, Wishart & Boulton, 1976). The particular pharmacological actions of (+)-amphetamine responsible for the paradoxical increase in the striatal concentration of the *meta* isomer of tyramine are not clear. Apart from the ability of (+)-amphetamine to release and inhibit the uptake of monoamines in aminergic nerve terminals, the

drug is also known to inhibit monoamine oxidase (Feltz & De Champlain, 1973) and, depending on the dose, it may stimulate or inhibit tyrosine hydroxylase (Kuczenski, 1977; 1980).

In the present work the effects of (+)-amphetamine on striatal concentrations of *p*-tyramine and *m*-tyramine were investigated 2 and 20 h after acute administration and after chronic administration (7 daily doses). The effects of pretreatment with iprindole (a known inhibitor of the *para*-hydroxylation of amphetamine) on the concentrations of the *meta* isomers of tyramine and α-methyltyramine, in the striatum of rats injected with amphetamine, were examined. Further, the effects of AMPT and AMPA on the striatal levels of *m*-tyramine and *p*-tyramine are reported. Evidence is presented for the formation of the α-methyltyramine isomers and α-methyldopamine in rat striatum after acute administration of AMPA and AMPT.

The results of this study suggest that the striatal concentration of *m*-tyramine is changed by drugs which are known to affect the enzyme tyrosine hydroxylase.

Methods

Preparation of o-*tyramine and α-methyl-*m-*tyramine*

A 0.01 M solution of the amino acid (α-methyl-*m*-tyrosine or *o*-tyrosine) was incubated in acetate buffer (0.2 M, pH 5.5, 30 ml) with tyrosine decarboxylase (10 mg) and pyridoxal phosphate (5μg, Calbiochem, Behring Corp., La Jolla, Ca) for 6 h. The enzyme was precipitated with $HClO_4$ (4 M, 3 ml). The supernatant was prepared for assay by c.i.g.c.m.s. by the method described for the preparation of the rat brain extracts for the phenylamine assay (see below).

*Deuterium labelling of α-methyldopamine and α-methyl-*p*-tyramine.*

Platinum oxide (0.1 g; Johnson Matthey Chemical Ltd, Herts, was suspended in water and $NaBH_4$ (60 mg) added in 3 portions. The water was then decanted (care being taken that the catalyst was not allowed to dry). It was then washed with water (5 × 10 ml) and then deuterium oxide (2 × 5 ml). The catalyst was then transferred in deuterium oxide (1–2 ml) to a Pyrex glass tube containing either α-methyldopamine or α-methyl-*p*-tyramine (50 mg). The tube was frozen in dry ice/methanol, evacuated, sealed and heated at 110°C for 3 days. An aliquot was analysed by methane c.i.g.c.m.s. (as the pentafluoropropionate derivative). The final product was obtained as the hydrochloride by filtration and lyophilization, thus ensuring all the deuterium was bound to carbon.

α-Methyldopamine-$(PFP)_3$ (using the $[MH]^+$ ion at m/z 613) showed species ranging from $^2H_2$–$^2H_{10}$ (no $^2H_0$ species could be detected). Similarly α-methyl-*p*-tyramine (using the $[MH]^+$ species at m/z 453) has an isotopic distribution ranging from $^2H_5$–$^2H_{11}$ with no $^2H_0$ content detected.

Catecholamine and phenylamine assays

D, L-AMPA and D, L-AMPT were suspended in 2% Tragacanth gel prior to i.p. injection. α-Methyldopa, (+)-amphetamine and iprindole were injected i.p. in 0.9% saline. Dosages of AMPA, AMPT and α-methyldopa were 100 mg kg^{-1}, amphetamine was 5 mg kg^{-1} and iprindole was 10 mg kg^{-1}.

Rats (male, Fullinsdorf, 250–350 g) were killed by decapitation at either 2 or 20 h after one injection, or 20 h after the last of 7 daily injections. After rapid extraction the brains were dissected on ice. Pooled

Table 1 Chemical ionization gas chromatography mass spectrometry (c.i.g.c.m.s.) data for the separation and detection of the PFP derivatives of the isomers of tyramine, dopamine and their α-methylated and deuterated analogues

	[MH]⁺	*g.c. column*	*Temperature programme (°C)*	*Retention time (min)*
o-Tyramine-$(PFP)_2$	430	3% OV-17	130/12*	1.8
m-Tyramine-$(PFP)_2$	430			3.2
p-Tyramine-$(PFP)_2$	430			3.4
p-Tyramine-$[^2H_4]$-$(PFP)_2$	434			3.4
α-Methyl-*m*-tyramine-$(PFP)_2$	444			2.7
α-Methyl-*p*-tyramine-$(PFP)_2$	444			3.0
α-Methyl-*p*-tyramine-$[^2H_9]$-$(PFP)_2$	453			3.0
Dopamine-$(PFP)_3$	592	3% OV-101	155/12*	2.5
Dopamine-$[^2H_4]$-$(PFP)_3$	596			2.5
α-Methyldopamine-$(PFP)_3$	606			2.4
α-Methyldopamine-$[^2H_7]$-$(PFP)_3$	613			2.4

*Sample is injected at initial temperature and 1 min later the temperature is programmed to increase by 12°C min^{-1}.

striatal tissue (4 rats/sample) was weighed and homogenized in formic acid (5 M, 2 ml) containing appropriate internal standards (deuterated *p*-tyramine for *meta* and *para*-tyramine, deuterated α-methyl-*p*-tyramine for *meta* and *para* α-methyltyramine, deuterated dopamine for dopamine and deuterated α-methyldopamine for α-methyldopamine). The specific mass ions used in the assay are listed in Table 1.

A sample (0.2 ml) of the supernatant was used to assay dopamine and α-methyldopamine by methane c.i.g.c.m.s. (Duffield, Dougan, Wade & Duffield, 1982). The remaining supernatant, after drying (air and water bath at 50°C) and resuspension of the dried precipitate in $HClO_4$ (0.4 M, 3 ml) was assayed for tyramine and its *meta* analogue plus their α-methylated derivatives by c.i.g.c.m.s. (Duffield, Dougan, Wade & Duffield, 1981).

Instrumentation

A Finnigan chemical ionization g.c.m.s. system (Model 3200) was used for the assay in conjunction with the same manufacturer's Incos Data system (Model 2300). Methane c.i.m.s. were obtained using the conditions previously described (Duffield *et al.*, 1981).

Samples were derivatized with pentafluoropropionic anhydride (PFPA) in anhydrous ethyl acetate before c.i.g.c.m.s. analysis. Methane c.i.m.s. were obtained for all compounds and Table 1 lists the most abundant ions for each compound together with their retention times on the appropriate g.c. columns. The derivatized catecholamines were separated on glass g.c. columns (1.8 m, 2 mm i.d.) packed with 3% OV-101 on Gas Chrom Q (100–120 mesh). Similar columns (1.5 m) packed with 3% OV-17 on Gas Chrom Q (100–120 mesh) were used to separate the derivatized phenylamines. As can be seen in Table 1, *o*-tyramine was separated from both *meta* and *para*-tyramine. It was not assayed routinely.

Statistical analysis

Mean values are presented with their standard error of the mean. Statistical significance was determined by Student's *t* test (unpaired, two tailed) on log transformed data.

Materials

D, L-AMPA, D,L-AMPT, D,L-α-methyl-*m*-tyrosine, D,L-*o*-tyrosine and tyrosine decarboxylase were purchased from Sigma Chemical Company, St Louis, Mo, USA. α-Methyldopa was obtained from Merck, Sharp and Dohme (Australia) Pty, Ltd. *m*-Tyramine was a gift from Sterling-Winthrop Research Institute, Rensselaer, N.Y. Dex-amphetamine sulphate was provided by USV, Sydney, Australia and iprindole hydrochloride was purchased from John Wyeth and Brother Limited, Taplow, Maidenhead, Berks. Merck, Sharp and Dohme Research Lab., Rahway, NJ, supplied α-methyldopamine. *o*-Tyramine and α-methyl-*m*-tyramine were prepared using their precursor amino-acids and tyrosine decarboxylase.

Deuterated internal standards (*p*-tyramine-[1,1,2,2-$^2H_4$] HCl and dopamine-[1,1,2,2-$^2H_4$] HCl) were purchased from Merck, Sharp and Dohme, Canada. Deuterated internal standards (α-methyl-*p*-tyramine-[$^2H_9$] HCl and α-methyldopamine [$^2H_7$]HCl) were prepared as described below.

Results

Two hours after a single i.p. dose of (+)-amphetamine (5 mg kg^{-1}) the striatal concentration of *p*-tyramine was markedly reduced whereas the levels of *m*-tyramine were not significantly altered. In the same experiments α-methyl *meta* and *para*-tyramine-[$^2H_9$] HCl and α-methyldopamine [$^2H_7$]HCl) were prepared as described above.

Twenty hours after an acute dose of (+)-

Table 2 Effect of (+)-amphetamine (5 mg kg^{-1} i.p.) on the striatal concentrations of the tyramines

Treatment	m-*Tyramine* (ng g^{-1})	p-*Tyramine* (ng g^{-1})	α-*Methyl* m-*tyramine* (ng g^{-1})	α-*Methyl* p-*tyramine* (ng g^{-1})
Control	2.5 ± 0.2	11.1 ± 1.0	0	0
2 h	2.6 ± 0.2	2.8 ± 0.1 a	1.6 ± 0.1	32 ± 3
20 h	2.8 ± 0.2	9.7 ± 1.1	0.8 ± 0.1 b	20 ± 2 b
7 days (chronic)*	2.2 ± 0.2	11.1 ± 0.6	1.0 ± 0.1	40 ± 2 c

Results are in ng g^{-1} wet weight of tissue, and are the mean ± s.e. mean of at least 8 results.
[a] Change compared with control, $P<0.001$.
[b] Change compared with 2 h sample, $P<0.001$.
[c] Change compared with 20 h sample, $P<0.001$.
*20 h after the last of 7 daily injections.

Table 3 The effect of iprindole (10 mg kg^{-1}, i.p.) injected 10 min before (+)-amphetamine (5 mg kg^{-1} i.p., 2 h) on the concentration of striatal tyramines

Treatment	m-*Tyramine* (ng g^{-1})	p-*Tyramine* (ng g^{-1})	α-*Methyl* m-*tyramine* (ng g^{-1})	α-*Methyl* p-*tyramine* (ng g^{-1})
Control	2.6 ± 0.1	12.0 ± 0.6	0	0
Iprindole	2.3 ± 0.1	9.1 ± 1.6	0	0
(+)-Amphetamine	2.4 ± 0.6	3.0 ± 0.5 a	2.1 ± 0.5	34 ± 4
Iprindole + (+)-amphetamine	1.5 ± 0.1 a	1.8 ± 0.5	3.3 ± 0.3	3.1 ± 0.4 b

Results are in ng g^{-1} wet weight of tissue, and are expressed as the mean ± s.e.mean. of at least 4 results.
[a] Change compared with control, $P < 0.001$.
[b] Change compared with (+)-amphetamine alone, $P < 0.001$.

amphetamine (5 mg kg^{-1}) the striatal concentration of *p*-tyramine had returned to its control levels whereas the levels of both *para* and *meta* α-methyltyramine were approximately half of the 2 h levels. Twenty hours after the chronic administration of (+)-amphetamine (5 mg kg^{-1} daily for 7 days) the levels of *para* and *meta* tyramine remained unchanged while the striatal concentration of the α-methyl tyramines showed that α-methyl-*m*-tyramine did not accumulate in the striatum although the levels of α-methyl-*p*-tyramine increased two fold (Table 2).

The effects of iprindole (10 mg kg^{-1}) on the aromatic hydroxylation of a single dose of (+)-amphetamine (5 mg kg^{-1}) is shown in Table 3. Pretreatment with iprindole caused a ten fold reduction in the levels of α-methyl-*p*-tyramine in the striatum but had no effect on the levels of α-methyl-*m*-tyramine. (+)-Amphetamine alone lowered the level of striatal *p*-tyramine but had little effect on *m*-tyramine. Administration of (+)-amphetamine after pretreatment of rats with iprindole, however, produced a marked fall in *m*-tyramine levels.

Two hours after the administration of AMPT the concentration of *m*-tyramine in the striatum was reduced to less than 50% of the control levels (Table 4). At 20 h 13.7 ng g^{-1} of α-methyl-*p*-tyramine was found in the striatum. AMPA administration, however, results in the production of the *meta* isomer of α-methyltyramine (42 ng g^{-1}). A combination of the two leads to a reduction (approximately 50%) in the concentration of the *meta* but no change was observed in the concentration of the *para* isomer.

Discussion

It has previously been reported that administration of (+)-amphetamine to rats 30 min before decapitation, produced a marked reduction in the striatal

Table 4 Striatal concentrations of *meta* and *para*-tyramine and their α-methylated analogues after administration (100 mg kg^{-1}) of α-methltyrosine (AMPT), α-methylphenylalanine (AMPA) and α-methyldopa

Treatment	m-*Tyramine* (ng g^{-1})	p-*Tyramine* (ng g^{-1})	α-*Methyl* m-*tyramine* (ng g^{-1})	α-*Methyl* p-*tyramine* (ng g^{-1})	α-*Methyl dopamine* (ng g^{-1})
Control	2.7 ± 0.2	11.7 ± 2.4	0	0	0
AMPT (2 h)	1.2 ± 0.2 a	32.0 ± 8.1 b	< 0.2	1.7 ± 0.2	ND
AMPT (20 h)	3.0 ± 0.2	20.6 ± 2.1 a	< 0.2	13.7 ± 2.8	274 ± 94
AMPA (20 h)	2.4 ± 0.2	11.4 ± 1.2	42 ± 3	< 0.5	13.5 ± 0.5 d
AMPA + AMPT (20 h)	ND	13.3 ± 1.0	22 ± 3 c	15.3 ± 1.5	ND
α-Methyldopa (20 h)	2.0 ± 0.1 e	12.5 ± 0.5	< 0.2	< 0.2	ND

Results are in ng g^{-1} wet weight of tissue, and are the mean ± s.e. mean for at least 4 results.
[a] Change compared with control, $P < 0.001$.
[b] Change compared with control, $P < 0.005$.
[c] Change compared with AMPA alone, $P < 0.005$.
[d] Change compared with AMPT, $P < 0.05$.
[e] Change compared with control, $P < 0.005$.
ND Not determined.

levels of *p*-tyramine and caused a significant increase in the *m*-tyramine levels (Danielson *et al.*, 1976). In the present experiments the reduction of *p*-tyramine levels in rat striatum 2 h after (+)-amphetamine was not accompanied by a concurrent change in the striatal concentration of *m*-tyramine (Table 2). The decrease in *p*-tyramine concentration but not the increase in *m*-tyramine concentration (Danielson *et al.*, 1976) is in accord with *in vitro* work on the release of *para* and *meta* tyramine by (+)-amphetamine from rat striatal slices. The different treatment time intervals for (+)-amphetamine (30 min and 2 h) may account for the discrepancy between the two studies, in the *m*-tyramine levels. Tissue concentrations of (+)-amphetamine 30 min after i.p. injection are 4 and 5 times greater than the concentrations at 2 h (Danielson & Boulton, 1976).

(+)-Amphetamine has a multiplicity of neurochemical effects. One effect which can account for the increased synthesis of *m*-tyramine is its ability to stimulate tyrosine hydroxylase activity in the striatum (Kuczenski, 1977). A recent report suggests that trace amounts of *m*-tyrosine are formed from phenylalanine by rat brain homogenates possibly by the enyzme tyrosine hydroxylase (Ishimitsu, Fujimoto & Ohara, 1980).

The results presented in this paper support this alternative suggestion that an increase in the production of *m*-tyrosine (the immediate precursor of *m*-tyramine) from phenylalanine by the enzyme tyrosine hydroxylase is responsible for the ability of (+)-amphetamine to increase striatal *m*-tyramine levels. Thus in rats treated with the tyrosine hydroxylase inhibitor AMPT, 2 h before they were killed, the striatal concentration of *m*-tyramine was reduced to less than 50% of the control value (Table 4). A similar decrease has been reported in mouse striatum (Juorio, 1979a). Further, the production of α-methyl-*m*-tyramine 20 h after the administration of AMPA is halved if AMPT is given in conjunction with the AMPA (Table 4).

Evidence for a second possible source of *m*-tyramine via the dehydroxylation of dopamine or DOPA, is not supported by the data from experiments with α-methyl compounds (Table 4). Twenty hours after α-methyldopa administration there were no α-methyl analogues of tyramine detected in the striatum. After the administration of AMPT, α-methyl-*m*-tyramine was not detected in the striatum although the concentration of α-methyldopamine was high (274 ng g^{-1}). In contrast, the concentration of α-methyl-*m*-tyramine is high (42 ng g^{-1}) and α-methyldopamine is low (13.5 ng g^{-1}) after administration of AMPA. This suggests that the production of α-methyl-*m*-tyramine is not linked to α-methyldopa or α-methyldopamine.

There appear to be two possible mechanisms involved in the marked reduction in the striatal concentration of *m*-tyramine observed after the administration of (+)-amphetamine, to iprindole-treated rats (Table 3). Although *in vivo* experiments have shown that (+)-amphetamine releases both *meta* and *para* tyramine from rat striatal slices (Dyck *et al.*, 1980), the most probable explanation is that the elevated concentrations of (+)-amphetamine in the brain in this experiment, have inhibited tyrosine hydroxylase (Kuczenski, 1977). Iprindole markedly enhances the action of (+)-amphetamine, and prolongs the half-life from 45 to 190 min (Freeman & Sulser, 1972).

The reduction in striatal *p*-tyramine levels 2 h after (+)-amphetamine administration, in the present experiments (Table 2), is consistent with the release of this amine from amphetamine-sensitive storage sites in the striatum. The increase in α-methyl-*p*-tyramine concentration 20 h after the last of 7 daily doses of (+)-amphetamine, as compared with 20 h after a single dose, suggests a storage site for this amine also (Table 2).

The increase in α-methyl-*p*-tyramine concentrations in striatal tissues is unlikely to be responsible for the reduction in *p*-tyramine levels as the accumulation of α-methyl-*p*-tyramine after chronic administration of (+)-amphetamine for 7 days, had no effect on striatal concentrations of *p*-tyramine (Table 2). Further, the marked reduction in striatal α-methyl-*p*-tyramine levels caused by iprindole pretreatment in rats administered (+)-amphetamine compared to rats dosed with (+)-amphetamine alone was not accompanied by a corresponding increase in the levels of *p*-tyramine (Table 3). This indicates that α-methyl-*p*-tyramine does not displace *p*-tyramine from storage sites in aminergic nerve terminals.

The hypothesis that the acute administration of (+)-amphetamine produces an increase in *m*-tyrosine, and its decarboxylation product *m*-tyramine, by stimulating the enzyme tyrosine hydroxylase, is compatible with the observation that the combination of amphetamine with a neuroleptic drug further increases striatal concentrations of *m*-tyramine (Juorio, 1977; Juorio & Danielson, 1978). Further, the ability of stress and L-DOPA administration to increase striatal concentrations of *m*-tyramine is also compatible with the known effects of these treatments on the activity of tyrosine hydroxylase (Juorio, 1979b). Again, the hypothesis that drug-induced changes in the activity of the enzyme tyrosine hydroxylase modulate striatal *m*-tyramine concentrations, can account for the complex alterations in striatal *m*-tyramine levels caused by the neuroleptic, molindone (Juorio, 1980).

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