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THE EFFECT OF MONOAMINE OXIDASE INHIBITORS ON 'FIRST-PASS' METABOLISM OF TYRAMINE IN DOG INTESTINE

KENNETH F. ILETT,* CHARLES F. GEORGE and DONALD S. DAVIES†

Department of Clinical Pharmacology, Royal Postgraduate Medical School, London W12 0HS, and Clinical Pharmacology, University of Southampton, Southampton, SO9 3TU, U.K.

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Abstract—The role of the intestine in metabolic inactivation of tyramine (TYR) has been studied in an isolated intestinal loop preparation in anaesthetized dogs. In control animals there was extensive metabolism of tyramine on passage through the intestinal wall and *p*-hydroxyphenylacetic acid (*p*-OHPA) was the only metabolite found in venous plasma from the loop (mean ratio *p*-OHPA/TYR = 5). Oral or intravenous pretreatment with the monoamine oxidase (MAO) inhibitors tranylcypromine or MD780515 significantly lowered the ratio of *p*-OHPA/TYR (range = 0.2–1.1) measured 3 hr after the last dose. Twenty-four hours after the last dose of MAO inhibitor *p*-OHPA/TYR ratios in dogs pretreated orally with MD780515 had returned to control levels while ratios in dogs pretreated orally with tranylcypromine remained low (mean = 1.6). *In vitro* rates of deamination of the substrates 5-hydroxytryptamine (selective for the A form of MAO) and β-phenylethylamine (selective for the B form of MAO) in homogenates of intestine paralleled the *in vivo* findings in most cases. Tranylcypromine produced a nonselective irreversible inhibition of both MAO-A and MAO-B whereas MD780515 was found to be a selective inhibitor of MAO-A and also appeared to be reversible.

Monoamine oxidase (MAO) inhibitors can provide an effective treatment for some groups of depressed patients [1] but extensive use of these drugs has been discouraged because they may cause a hypertensive crisis (cheese effect) when foods containing vasoactive amines such as tyramine (cheese), tryptamine (tomatoes) or phenylethylamine (chocolate) are ingested. It is generally assumed on the basis of indirect evidence [2] that such hypertensive crises occur largely as a result of inhibition of intestinal and hepatic monoamine oxidase which protect the body from the systemic effects of oral tyramine (TYR) and in part as a result of inhibition of neuronal MAO which normally degrades both noradrenaline and tyramine.

In the present investigation, the role of the intestine in metabolic inactivation of TYR has been studied using an isolated intestinal loop preparation in anaesthetized dogs. The effects of two MAO inhibitors, tranylcypromine and MD780515 [3-4-(3-cyanophenylmethoxy)phenyl-5-(methoxymethyl)-2-oxazolidinone] on TYR metabolism have also been measured in this preparation and the selectivity and reversibility of both inhibitors has been assessed by measurement of *in vitro* rates of metabolism of TYR and of 5-hydroxytryptamine (5HT, selective for the A form of MAO) and β-phenylethylamine (PEA, selective for the B form of MAO at low substrate concentrations) in intestine and brain.

For several drugs [3], large differences in metabolite pattern have been observed following administration by the oral and intravenous routes, suggesting that drug in the systemic circulation may not always have easy access to intestinal drug metabolizing enzymes. This hypothesis has been tested by assessing the effects of oral and intravenous MAO inhibitors on the intestinal metabolism of oral tyramine. Poor penetration of inhibitor to intestinal MAO following intravenous administration might be expected to decrease the magnitude of the 'cheese effect'.

METHODS

Treatment of animals and experimental procedure. Mongrel dogs of either sex (13–28.2 kg) were used throughout the study and where appropriate were pretreated either orally or intravenously with 11.8 μmoles/kg tranylcypromine or 5.9 μmoles/kg MD780515 given once daily for 3 days. Both drugs were given orally in a gelatin capsule or intravenously as a slow infusion over 1.5 hr dissolved in 5–10 ml of normal saline (tranylcypromine) or propylene glycol (MD780515). Three or 24 hr after the last oral dose or commencement of the last i.v. infusion, isolated *in situ* jejunal loops were prepared in anaesthetized dogs as previously described [4]. [^{14}C]Tyramine (50 mg and 50 μCi/10 ml N saline) was introduced into the isolated loop and venous blood from the loop was collected for 10 × 3 min intervals (8–12 ml each). Arterial blood samples (5 ml) were also collected from the abdominal aorta at the same time intervals so that the effectiveness of the isolation

* Present address: Department of Pharmacology, University of Western Australia, Nedlands 6009, Western Australia.

† To whom all correspondence should be addressed.

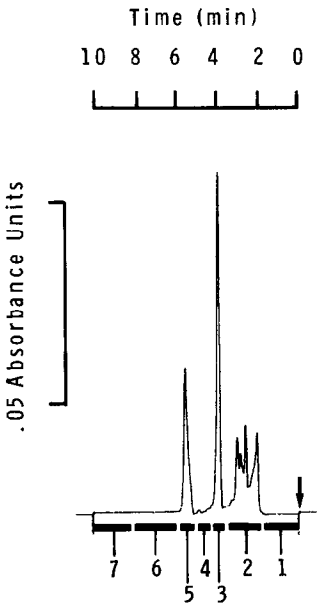

Fig. 1. High pressure liquid chromatogram showing the separation of tyramine and *p*-hydroxyphenylacetic acid in protein-free plasma supernatant fractions. Samples (20 μl) were injected as shown at the arrow and effluent from the column collected in seven fractions (fraction 3 = tyramine; fraction 5 = *p*-hydroxyphenylacetic acid) in which ^{14}C was quantified by liquid scintillation counting.

procedure could be assessed by comparison of radioactivity in arterial and venous plasma. At the conclusion of each experiment dogs were killed using intravenous KCl and samples of jejunum (5–10 g) immediately proximal to the isolated loop and brain cortex (1–3 g) were removed for *in vitro* determination of rates of deamination of TYR, 5-HT and PEA.

Measurement of total radioactivity, tyramine and p-hydroxyphenylacetic acid in plasma. Total radioactivity was determined in 0.1 ml aliquots of plasma using 10 ml Instagel in a Packard 2650 liquid scintillation counter.

Tyramine and *p*-hydroxyphenylacetic acid (*p*-OHPA) were separated in venous plasma samples using an Altex high pressure liquid chromatography system (model 100A pump; model 210 sample injection valve), a Waters Associates C_{18} μ-Bondapak column (30 cm × 4 mm i.d.) and a Hitachi 100-10 variable wavelength detector set at 275 nm. Plasma samples containing radiolabelled tyramine and its metabolites were diluted (2:1) with 20% w/v trichloracetic acid containing 0.8 mg/ml each of non radioactive TYR and *p*-OHPA, vortexed for 30 sec and centrifuged at 1200 *g* for 10 min. Aliquots (20 μl) of the resulting supernatant fraction were injected directly onto the column. The operating conditions were: mobile phase 4% acetonitrile in 0.05 M sodium phosphate (pH 4.5), flow rate 1.5 ml/min except between 4.3 and 6 min when it was increased to 3 ml/min, detector sensitivity 0.5 a.u.f.s. and chart speed 0.5 cm/min. Approximate retention times were 4 min for TYR and 5.5 min for *p*-OHPA. Recovery, as assessed by peak height measurements, was 100.7 ± 1.8 (mean ± S.D.; N = 10) and 98.9 ± 2.6 for non radiolabelled TYR and *p*-OHPA, respectively. The effluent was collected for 10 min in seven fractions as indicated in Fig. 1 and quantified by liquid scintillation counting as above. Fraction 1 was taken as background radioactivity and subtracted from fractions 2–7. Results are expressed as the ratio of radioactivity in the *p*-OHPA- and TYR-containing fractions.

Preparation of tissue homogenates and mitochondria. For tissue homogenates, 3–5 g intestine and 1–2 g brain were homogenized with 9 vol. of 0.05 M phosphate buffer (Na_2HPO_4–KH_2PO_4 containing 10^{-4}M ascorbic acid and EDTA; pH 7.2) using a Polytron Model PT 10-35 homogenizer (Kinematica, Switzerland). The homogenates were centrifuged at 600 *g* for 10 min and the supernatant fraction retained. For mitochondria, 3–5 g intestine was homogenized as above in 4 vol. 0.25 M sucrose and following sedimentation of nuclei and cell debris by centrifugation at 600 *g* for 10 min; a mitochondrial pellet was obtained by centrifugation at 10,000 *g* for 20 min. All procedures were carried out at 4°. Mitochondria were resuspended in the phosphate buffer and protein concentration determined by the method of Hartree [5].

MAO activity studies. MAO activity was determined in duplicate by a modification of the method of Robinson *et al.* [6]. Aliquots of tissue homogenate (equivalent to 2–15 mg tissue wet wt) or mitochondria (0.2–0.4 mg protein) were diluted in 0.575 ml of the 0.05 M phosphate buffer and incubated with 25 μl [^{14}C]labelled substrate for 4–15 min at 37°. Final concentrations of substrates used were: TYR and 5HT (10^{-3}M) and PEA (10^{-5}M). Incubation blanks were established by inclusion of tranylcypromine (final concentration 5×10^{-4}M) in the incubation

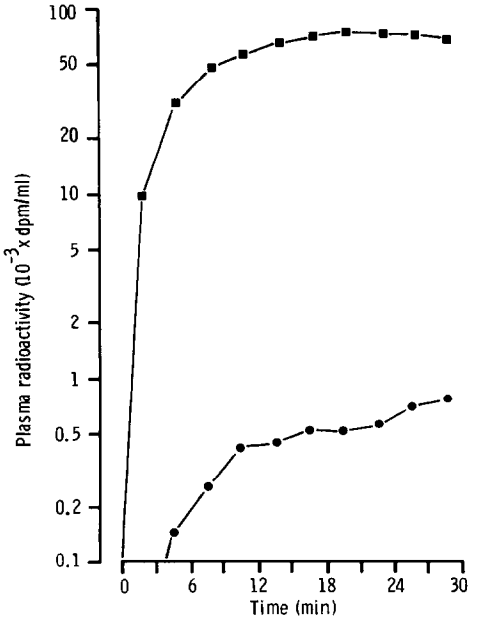

Fig. 2. Total ^{14}C in aortic arterial plasma (●—●) and venous plasma from an isolated dog intestinal loop (■—■) following intraluminal administration of 50 mg (50 μCi) ^{14}C-tyramine.

Table 1. Distribution of ^{14}C in fractions from h.p.l.c. analysis of venous plasma from isolated dog intestinal loop preparations*

Treatment group	Time after last dose (hr)	Route	N	^{14}C in h.p.l.c. area (%)					
				2	3	4	5	6	7
Control	—	—	4	1.6	14.9	1.3	80.6	1.4	0.4
Tranylcypromine	3	Oral	4	3.4	59.9	3.2	30.4	2.7	0.5
Tranylcypromine	3	Intravenous	3	2.8	78.1	2.2	13.8	1.8	1.2
Tranylcypromine	24	Oral	3	1.4	32.5	1.8	62.2	1.7	0.5
MD780515	3	Oral	4	3.2	56.1	1.2	35.2	3.2	1.3
MD780515	3	Intravenous	3	1.6	71.4	0.4	21.8	3.3	1.3
MD780515	24	Oral	3	2.1	10.2	1.9	81.5	2.8	1.7

* Mean results only shown for clarity.

mixture. After incubation, 0.5 ml aliquots of reaction mixtures were transferred to Pasteur pipettes containing 0.5 × 2.5 cm Amberlite resin (CG-50% 100–200 mesh, BDH Chemicals; prepared according to Tipton and Youdim [7]. The columns were washed twice with 1.25 ml distilled water and the entire eluate was collected into scintillation vials containing 11 ml Instagel and radioactivity quantified as above. MAO activity was determined under conditions which were linear with time and protein (mitochondria) or tissue (homogenate) concentration and such that not more than 10 per cent of the substrate was utilized.

Chemicals. 3-4-(3-Cyanophenylmethoxy)phenyl-5-(methoxymethyl)-2-oxazolidinone (MD780515, Delalande, Paris), 5-hydroxytryptamine creatinine sulphate, β-phenylethylamine hydrochloride, tyramine hydrochloride and tranylcypromine hydrochloride (Sigma Chemical Co., St. Louis, MO, U.S.A.), [^{14}C]5-hydroxytryptamine creatinine sulphate, 58 mCi/mmole, and [^{14}C]tyramine hydrochloride, 50 mCi/mmole (The Radiochemical Centre, Amersham, U.K.) and [^{14}C]β-phenylethylamine hydrochloride, 48.25 mCi/mmole (New England Nuclear, Boston, MA., U.S.A.).

Data analysis. Results are expressed as mean ± S.E.M. unless otherwise stated. Differences in the ratio of *p*-OHPA/TYR in venous plasma from isolated gut loops in the various treatment groups were assessed by analysis of variance. All other group differences were evaluated by means of the Student *t*-test.

RESULTS

Results from a typical experiment on the absorption of [^{14}C]TYR from the isolated dog intestinal loop are shown in Fig. 2. Total ^{14}C in venous plasma from the loop increased with time to a steady maximum at around 15–20 min. In all experimental groups mean total ^{14}C in aortic plasma ranged from 1.6 to 4 per cent of that found in the venous effluent from the loop, indicating little spill-over of radioactivity into the systemic circulation.

Table 1 summarizes the mean results for the distribution of ^{14}C in the different fractions (see Fig. 1) obtained by h.p.l.c. analysis of venous plasma from the dog intestinal loops. Recovery of injected radioactivity was almost quantitative (97.8 ± 0.9, N = 8). In all groups, *p*-OHPA was the only major metabolite detected and, together with unchanged TYR, accounted for 91.2–95.5 per cent of the radioactivity recovered from h.p.l.c. Moreover, this recovery did not differ significantly between groups and in assessing the extent of metabolism after different treatments, results have therefore been

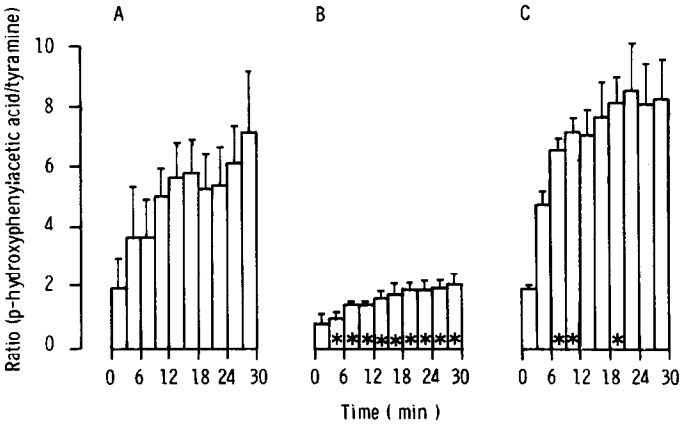

Fig. 3. Ratio of *p*-hydroxyphenylacetic acid/tyramine (mean results) in venous plasma from isolated dog intestinal loops in control dogs (A, N = 4) and 24 hr after the last oral dose of tranylcypromine (B, N = 3) or MD780515 (C, N = 3). Inset bars are S.E.M. *Indicates significantly different from corresponding control value, $P < 0.05$.

Table 2. Deamination of tyramine, 5-hydroxytryptamine and β-phenylethylamine in intestinal mitochondria*

Treatment group	Time after last dose (hr)	Route	N	Rate of deamination (nmoles/mg/min) Tyramine	5-Hydroxytryptamine	β-Phenylethylamine
Control	—	—	5	14.69 ± 1.65	22.29 ± 2.42	1.62 ± 0.19
Tranylcypromine	3	Oral	4	4.62 ± 1.09†	4.85 ± 1.68†	0.30 ± 0.10†
Tranylcypromine	3	Intravenous	3	3.87 ± 0.40†	4.71 ± 0.45†	0.27 ± 0.06†
Tranylcypromine	24	Oral	3	13.11 ± 0.47	18.84 ± 0.77	0.80 ± 0.06†

* Results are means ± S.E.M.
† Significantly different from controls, $P < 0.05$.

expressed as the ratio of radioactivity in the *p*-OHPA fraction to that in the TYR fraction. With both tranylcypromine and MD780515 at 3 hr, when there was significant inhibition of MAO activity, *p*-OHPA was still the only metabolite found and there was no significant change in other areas of the chromatogram.

In control dogs (Fig. 3) there was a tendency for the ratio of *p*-OHPA/TYR in venous plasma from the isolated gut loop to increase with time and attain a steady maximum of around 6 after about 20 min. Both tranylcypromine and MD780515 pretreatment resulted in a significant ($P < 0.05$) inhibition of MAO and decrease in the *p*-OHPA/TYR ration 3 hr after the last dose (Fig. 4) and although ratios tended to be lower after intravenous than after oral administration this difference was not significant because of the large variability in ratios in animals receiving the drugs orally. At 24 hr after the last oral dose of MAO inhibitor (Fig. 3) ratios for MD780515 treated dogs were similar to those in control animals whereas ratios for tranylcypromine-treated dogs were still significantly lower than in controls ($P < 0.05$).

In vitro studies with intestinal homogenates or mitochondria utilizing substrates selective for the A form (5-HT) or the B form (PEA) of MAO, and TYR (deaminated by both MAO-A and B), are summarized in Tables 2 and 3. At 3 hr after the last dose both tranylcypromine (Table 2) and MD780515 (Table 3) caused a significant ($P < 0.05$) decrease in rates of deamination of both TYR and 5-HT. There was no significant difference between the effects after intravenous or oral administration for both MAO inhibitors. At 3 hr, rates of deamination of PEA were lowered, but the change was only significant ($P < 0.05$) with tranylcypromine. With tranylcypromine, 24 hr after the last dose, *in vitro* rates of deamination of 5-HT and TYR were similar to those of controls whereas that for PEA still remained significantly depressed (Table 2). Deamination of TYR, 5-HT and PEA was also studied in whole homogenates of intestine 24 hr after the last dose of tranylcypromine. In contrast to findings in mitochondria, there was marked inhibition of the metabolism of all three substrates (Table 3). Rates of deamination of 5-HT, TYR and PEA were still slightly depressed 24 hr after the last dose of MD780515 but this was significant ($P < 0.05$) only for TYR.

In brain homogenates (Table 4) tranylcypromine treatment resulted in significant decreases ($P < 0.05$) in rates of deamination of TYR, 5-HT and PEA at 3 hr after the last dose. At 24 hr metabolism of all three substrates remained low, indicating a long-lived blockade of MAO. Treatment with MD780515 also decreased metabolism of TYR and 5-HT (Table 4) in brain at 3 hr but there was substantial recovery by 24 hr. On the other hand, PEA metabolism was unaffected by MD780515 at 3 hr and showed a small but significant ($P < 0.05$) depression at 24 hr when compared to control values but not when compared to the 3 hr rates of metabolism.

DISCUSSION

Ewins and Laidlaw [8] in 1910 identified *p*-OHPA as a major urinary metabolite of orally administered TYR in dogs. From the present study, it is evident that some 80 per cent of orally administered TYR is metabolized to *p*-OHPA while passing through the intestinal wall, thus identifying the intestine as the major site of metabolism for this compound. Administration of the MAO blocking drugs tranylcypromine and MD780515 resulted in substantial inhibition of tyramine metabolism during absorption from isolated dog intestinal loops (Table 1), providing direct *in vivo* evidence that inhibition of intestinal MAO activity is probably quantitatively more important in production of the 'cheese effect' than inhibition of hepatic MAO activity.

In rats, Tacker *et al.* [9] also identified *p*-OHPA as the major metabolite of TYR and additionally reported minor pathways producing tyramine -*O*-glucuronide, *N*-acetyltyramine and *N*-acetyltyramine conjugates with glucuronic and sulphuric acids. In the dog, inhibition of intestinal MAO markedly reduced production of *p*-OHPA but, interestingly, did not result in increased metabolism along alternative pathways (see Table 1), a surprising result because of the known activity of the dog intestine in conjugating drugs such as isoprenaline [4].

An indication of the relative abundance of forms A and B of MAO, respectively, in a given tissue may be obtained *in vitro* [10] using the selective substrates 5-HT and PEA provided that unduly high (> 125 μM) concentrations of PEA are avoided [11]. Our results in the dog indicate that the ratio of MAO-A : MAO-B is around 14 : 1 or 16 : 1 in intestinal homogenates and mitochondria, respectively, indicating in agreement with previous studies that the enzyme is mostly type A. In brain homogenates, absolute rates of deamination of both 5-HT and PEA were, respectively, 6- and 1.6-fold lower than in intestine with an MAO-A : MAO-B ratio of 4 : 1. This ratio differs from the ratio of 1 : 2 found in dog brain by Squires [12] who used different procedures. Murphy [13] in

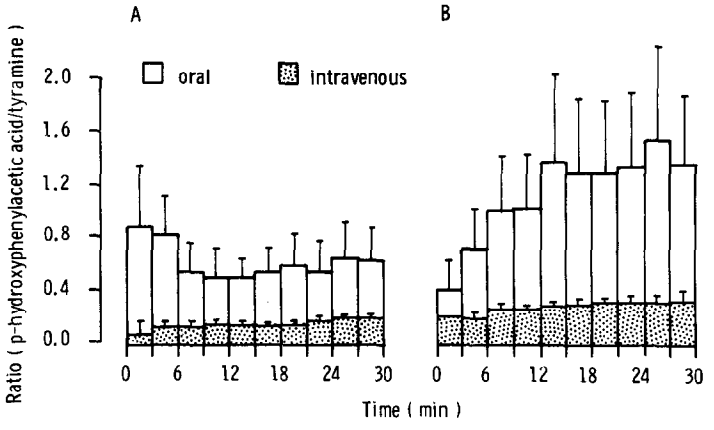

Fig. 4. Effect of tranylcypromine (A, oral N = 4, i.v. N = 3) and MD780515 (B, oral N = 4, i.v. N = 3) on the ratio of *p*-hydroxyphenylacetic acid/tyramine in venous plasma from isolated dog intestinal loops, 3 hr after the last dose. Open columns show mean results for the oral and stippled columns mean results for the intravenous routes of administration. Inset bars are S.E.M.

a recent commentary has pointed out that combined substrate–inhibitor studies are necessary for precise determination of A : B ratios.

In the dog intestine *in vitro* tranylcypromine inhibited both MAO-A and B activity but the activity of the B form was slower to recover, as evidenced by the 50 per cent depression of rates of deamination of PEA 24 hr after the last dose at a time when 5-HT deamination was only slightly lower than in control mitochondria. On the other hand, MD780515 was selective for MAO-A and in 10% homogenates only depressed the rate of deamination of 5-HT but not PEA. Reversibility of this effect of MD780515 was apparent 24 hr after the last dose. In brain homogenates, the nonselective and A-selective characteristics of tranylcypromine and MD780515 were again apparent. At 24 hr after the last dose, however, 5-HT metabolism was only 63 per cent of control rates with tranylcypromine, whereas with MD780515, 5-HT metabolism had returned to control levels. With tranylcypromine treatment, recovery of MAO-B activity was slower than for MAO-A activity. For tyramine, a mixed MAO-A and B substrate, a composite picture was found in both intestine and brain.

In assessing the possible route-dependent effect of MAO inhibitors on TYR metabolism in the intestinal loop preparation we first studied tranylcypromine. No significant difference between the i.v. and oral routes was found and similar decreases *in vitro* deamination of tyramine were also measured. Route-dependency of MD780515 was therefore studied but again no difference in TYR metabolism was evident either *in vivo* or *in vitro*. Hence it appears that intravenously administered MAO inhibitors have good access to the intestinal MAO despite its probable location on the epithelial cells of the microvilli [14] and a decreased 'cheese effect' cannot be anticipated for this route of administration.

Correlation between *in vitro* rates of deamination for TYR in intestinal mitochondria or homogenates and the extent of its metabolism in the intestinal loop (ratio *p*-OHPA/TYR) was generally good but some discrepancies were observed. For example, *p*-OHPA/TYR ratios for MD780515 24 hr after the last dose were similar to those of controls whereas *in vitro* deamination of tyramine still showed significant (36 per cent) inhibition (Table 3). Metabolism of TYR in intestinal mitochondria 24 hr after the last dose of tranylcypromine was not significantly different from controls, whereas the ratio of *p*-OHPA/TYR in the intestinal loop showed a significant inhibition of TYR metabolism. In this latter case *in vitro* metabolism of TYR in whole hom-

Table 3. Deamination of tyramine, 5-hydroxytryptamine and β-phenylethylamine in intestinal homogenates*

Treatment group	Time after last dose (hr)	Route	N	Rate of deamination (pmoles/mg/min) Tyramine	5-Hydroxytryptamine	β-Phenylethylamine
Control	—	—	7	766 ± 75	836 ± 107	52 ± 9
MD780515	3	Oral	4	199 ± 85†	197 ± 82†	25 ± 11
MD780515	3	Intravenous	3	174 ± 3†	101 ± 7†	37 ± 6
MD780515	24	Oral	3	485 ± 82†	584 ± 69	33 ± 8
Tranylcypromine	24	Oral	3	151 ± 23†	186 ± 22†	6 ± 4†

* Results are means ± S.E.M.
† Significantly different from control, $P < 0.05$.

Table 4. Deamination of tyramine, 5-hydroxytryptamine and β-phenylethylamine in brain homogenates*

Treatment group	Time after dose (hr)	Route	N	Rate of deamination (pmoles/mg/min)		
				Tyramine	5-Hydroxytryptamine	β-Phenylethylamine
Control	—	—	4	150 ± 10	123 ± 8	31 ± 2
Tranylcypromine†	3	Oral	2	47	37	5
Tranylcypromine	3	Intravenous	3	33 ± 5‡	14 ± 1‡	0.6 ± 0.2‡
Tranylcypromine	24	Oral	3	48 ± 6‡	77 ± 3‡	1.1 ± 0.6‡
MD780515	3	Oral	4	80 ± 20‡	56 ± 11‡	21 ± 7
MD780515	3	Intravenous	3	77 ± 16‡	27 ± 7‡	30 ± 4
MD780515	24	Oral	3	137 ± 5	129 ± 5	21 ± 2‡

* Results are means ± S.E.M.
† Means of two determinations only.
‡ Significantly different from control, $P < 0.05$.

ogenates was inhibited by some 80 per cent, which is in agreement with the intestinal loop findings. Tranylcypromine has been described as a partially reversible MAO inhibitor [15] and drug may have been lost in the preparation of mitochondria.

In conclusion, these data demonstrate for the first time the quantitative importance of intestinal MAO in the deamination of oral tyramine and illustrate the influence of MAO inhibition on this protective mechanism.

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