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Effect of Moclobemide, a New Reversible Monoamine Oxidase Inhibitor, on Absorption and Pressor Effect of Tyramine

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Summary: We determined in healthy subjects the pressor effect and the plasma level of free tyramine in response to intravenous and oral tyramine doses before and after therapeutic doses (3 × 100 mg/day) of moclobemide, a new reversible, preferential type A monoamine oxidase (MAO) inhibitor. In fasting subjects moclobemide increased the pressor effect of intravenously and orally administered tyramine; the tyramine dose–pressor curve was shifted to the left by factors of 2.4 and 4.1, respectively. No increase in systolic blood pressure occurred at free plasma tyramine concentrations lower than 70 ng/ml before, and 20 ng/ml after, moclobemide. Peak plasma tyramine concentrations increased dose-dependently after oral tyramine; after moclobemide similar peak plasma concentrations of tyramine were obtained with 2.6 times smaller doses of tyramine. Thus, the potentiation by moclobemide of the pressor effect of oral tyramine appears to be due to inhibition of tyramine first-pass metabolism, as well as to inhibition of tyramine catabolism by MAO within adrenergic nerve terminals. The peak concentrations of free tyramine in plasma and the concomitant increase of systolic blood pressure were significantly ($p < 0.01$) smaller when tyramine was administered with a meal (before or after moclobemide) than when given with tap water. We conclude that at doses of 3 × 100 mg/day moclobemide induces only a mild potentiation of the pressor effect of tyramine. This potentiation is virtually absent under natural conditions when tyramine is given with a meal. **Key Words:** Reversible MAO-A inhibitor—Moclobemide—Tyramine—Pressor effects.

The clinical use of irreversible monoamine oxidase inhibitor (MAOI) antidepressants has been limited mainly because of reports of the occurrence of acute hypertensive events leading, in very few cases, to fatal cerebral hemorrhage. This rare side-effect is also called the "cheese effect," because it was triggered by the intake of foodstuffs rich in tyramine, such as certain cheeses, particularly in combination with red wine (1).

The principle enzyme for monoamine catabolism, monoamine oxidase (MAO), is located in the outer mitochondrial membrane of many tissues, including the peripheral sympathetic noradrenergic nerves. After MAO inhibition, the levels of several monoamines are increased in the central nervous system (CNS), as is that of norepinephrine (NE) in peripheral noradrenergic neurons.

Tyramine, an indirectly acting sympathomimetic, is a good substrate of MAO. Hence, oral tyramine in not excessively high doses is almost completely desaminated presystemically. Tyramine reaching NE nerve endings is desaminated intraneuronally. For these reasons a pressor effect of tyramine is normally only seen at very high doses. When MAO is blocked, tyramine reaches systemic circulation because it is no longer metabolized presystemically; its intraneuronal deamination is also reduced. In addition, the displaced NE is not deaminated prior to release. These three factors contribute to a *potentiation of the tyramine pressor effect* (2).

In the past decade MAO has been shown to exist in two forms (isoenzymes), MAO type A (MAO-A) and MAO type B (MAO-B) (3). It was also found that the antidepressant effect of the MAOIs is

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mainly due to inhibition of the MAO-A in the CNS (4). Human intestinal tissues and peripheral noradrenergic neurons contain preferentially MAO-A activity. A marked inhibition of MAO-A activity in these tissues allows oral tyramine to reach the systemic circulation and to release active NE from the nerve terminals.

A new generation of short-acting, reversible preferential type-A MAOIs has recently been developed. The renewed interest in these compounds is due to the therapeutic need for MAOIs that lack the many side-effects of the first generation MAOIs, and most imipramine-like antidepressants, but that are still very effective in the treatment of depressive syndromes not responding to tricyclic antidepressants (5).

Moclobemide (Ro 11-1163), a benzamide derivative, is a new reversible MAOI that preferentially inhibits MAO-A (6). Short duration of action and reversibility of the MAO inhibition are characteristics of moclobemide (7) which a priori render severe interaction with tyramine unlikely. In rat experiments (8) and in studies with healthy subjects and depressed patients it was shown that, in contrast to previous irreversible MAOIs, moclobemide only slightly potentiated the effects of intravenous tyramine (9). Moreover, the ingestion of cheese-containing meals (70 mg tyramine/meal) was shown to have no pressor effect after inhibition of MAO by moclobemide (10).

In the present study volunteers were treated with moclobemide. The effect of tyramine administered i.v. and p.o. on systolic blood pressure, as well as on the concentration of free tyramine and NE in plasma, was measured.

MATERIALS AND METHODS

Subjects

Seven male subjects with a mean age of 26.2 ± 0.9 years and a mean body weight of 74.0 ± 2.3 kg, took part in the study. All volunteers selected were found to be healthy after thorough clinical examination and laboratory testing. The subjects took no medication for two weeks before the study began, nor throughout the complete study period. Alcohol was forbidden throughout, and the subjects were instructed to adhere to a tyramine-poor diet. Informed consent was obtained from all subjects. The experimental protocol was approved by the Ethics Committee of the I. Medical Clinic, University of Vienna, Austria.

Methods

Each subject was examined in a two-phase study: in phase I (no pretreatment), baseline cardiovascular sensitivity to i.v. and p.o. administered tyramine was established. In phase II (moclobemide treatment) the subjects were administered moclobemide (3 × 100 mg/day) on 14 consecutive days. Tyramine was always given 1 h after the first (morning) dose of moclobemide (100 mg).

Test schedule. To minimize variation due to unpredictably fluctuating gastric emptying, the subjects were tested in the morning after an overnight fast. Subjects were resting in supine position and fasted throughout the period of measurements unless otherwise stated.

A cannula was first inserted into an antecubital vein after a 30-min stabilization. Time-baseline measurements of systolic (SBP) and diastolic (DBP) blood pressure and heart rate (HR) were carried out, and blood samples for the analysis of free plasma catecholamines and tyramine were collected.

In the phase I study an i.v. tyramine pressure test was carried out according to Ghose (11) who demonstrated the reproducibility and safety of the method. The tests were single-blind, placebo-controlled, that is, 2 ml saline was occasionally injected between tyramine doses. Tyramine was injected over 30 s at increasing doses of 1, 2, 3, 4, and 6 mg in a volume of 2 ml saline. The next higher dose was injected after SBP had returned to baseline. The doses of tyramine were gradually increased until a SBP response of ⩾30 mm Hg occurred. This dose was considered to be the smallest "effective dose" or smallest "pressor dose."

The p.o. tyramine pressor test was performed as follows. After a 60-min rest period either placebo or a tyramine dose was given orally in form of capsules taken with 100 ml tap water. The doses of tyramine were gradually increased from 50, 100, 200, 400, and 600 mg. A 48-h interval between each tyramine dose was allowed, until a SBP increase of ⩾30 mm Hg (effective tyramine dose) was reached.

In the phase II study (moclobemide treatment) the i.v. tyramine pressor test was repeated by the procedure used in phase I. The p.o. test was also performed as in phase I except that the 400 and 600 mg tyramine doses were omitted.

After completion of the study (phase I and II), an additional 2-phase trial, identical to the one described above, was carried out in 3 of 7 subjects. In this study, only one oral dose of tyramine was administered, namely, the dose which was found effective (400–600 mg before, 100–200 mg after moclobemide treatment) for each individual subject. In this trial tyramine capsules were given with a tyramine-free meal consisting of white bread (2 bread rolls), some jam, and a weak herbal tea (100 ml) instead of tap water.

Assay procedures

Following each tyramine administration, HR was continuously recorded electrocardiographically (ECG) for 3 h. SBP was recorded by a manual sphygmomanometer every 5 min or every min when an increase in SBP occurred.

Free catecholamine and free tyramine concentrations in plasma were measured only in the trial in which tyramine was administered orally. For this purpose, venous blood samples were collected using as anticoagulant 1 IU heparin/ ml blood, immediately before and every 10 min during 1 h following tyramine ingestion and then every 30 min for additional 2 h. Additional blood sampling was carried out when pronounced SBP changes occurred. Plasma was obtained by centrifugation (20 min at 5,000 *g*).

Free catecholamines were determined in plasma by a radioenzymatic assay (12). The coefficient of variation for NE was 4.2%, epinephrine 8.7%, and dopamine 9.0%.

Free tyramine was determined by high pressure liquid

chromatography (HPLC) with fluorometric detection (Zürcher, Wüthrich, and Da Prada, in preparation). Using this method the limit of sensitivity for tyramine detection was 2 ng/ml and the recovery 80%. The coefficient of variation was 2.4%. Endogenous monoamines and moclobemide did not interfere with the assay procedure.

Calculations and statistical methods

Results are expressed as mean ± SEM.

The increase in tyramine sensitivity (TS) after moclobemide was calculated as follows: TS = tyramine dose (mg) required to increase SBP by ≧30 mm Hg above baseline before moclobemide/tyramine dose (mg) required to increase SBP by ≧30 mm Hg above baseline after moclobemide.

The area under the curve (*AUC* mm Hg × min^{-1}) for the time-dependent changes in SBP and plasma tyramine concentrations was calculated by the trapezoidal rule (13). The two-way analysis of variance followed by the Duncan's test and the Mann-Whitney *U*-test (parallel line design) (14) were used.

RESULTS

Effects of moclobemide on basal cardiovascular parameters and plasma catecholamines

As shown in Table 1, no significant effects were observed on basal mean values for SBP, HR, or plasma NE after 14 days of moclobemide administration (3 × 100 mg/day). The basal mean values for DBP, plasma epinephrine, and dopamine were also unaffected (unpublished observations).

Pressor test after intravenous injections of tyramine

The results of the i.v. tyramine pressor test are shown in Fig. 1a. The mean tyramine dose required to increase the SBP by 30 mm Hg was 4.1 ± 0.4 mg before and 1.8 ± 0.1 mg after repeated treatment with moclobemide (300 mg/day for 14 days). The treatment with moclobemide thus produced a 2.4 ± 0.3-fold increase in tyramine sensitivity as calculated from the left shift of the dose–pressor curve ($p < 0.001$).

Pressor test after oral tyramine

The effect of tyramine p.o. on SBP is shown in Fig. 1b. Before moclobemide treatment, doses of tyramine ≤200 mg had a very slight effect (mean change in SBP <10 mm Hg). However, after moclobemide treatment, the only tyramine dose tested which did not provoke a SBP increase was 50 mg.

There was great interindividual variation in the SBP responses to p.o. tyramine. For this reason only 4 subjects received the highest tyramine dose (600 mg) before moclobemide treatment, and following moclobemide treatment only 4 subjects received the highest tyramine dose (200 mg).

Peak SBP values correlated with the tyramine dose administered. The coefficient of correlation before moclobemide was $r = 0.729$ ($p < 0.001$, n = 25) and after moclobemide $r = 0.691$ ($p < 0.01$, n = 14).

The sensitivity to p.o. tyramine after moclobemide treatment was increased 4.2 times ($p < 0.001$) compared to baseline.

All pressor responses to tyramine were preceded and accompanied by decreases in HR (unpublished observations).

As for changes in DBP, slight but not significant increases after pressor doses of tyramine (5–30 mm Hg before and 5–25 mm Hg after moclobemide) were observed.

Free plasma tyramine concentrations after tyramine p.o.

The free tyramine concentrations in plasma before and after moclobemide treatment are shown in Fig. 1c.

In all measurements performed before the administration of tyramine, the concentration of the tyramine in plasma was below the detection limits of the assay (2 ng/ml). In the subjects not treated with moclobemide, the maximum concentration of free tyramine was 11.1 ng/ml (n = 3) after 50 mg tyramine and 9.8 ± 1.7 ng/ml (means ± SEM, n = 7) after 100 mg tyramine. After 200 mg tyramine, the maximum concentration of free tyramine was 29.1 ± 5.5 (n = 7). With tyramine doses of 50, 100, and 200 mg there was no concomitant increase in SBP. As shown in Fig. 1c tyramine doses >200 mg produced a very steep increase of the free tyramine concentration in plasma.

After moclobemide administration, the peak con-

TABLE 1. *Baseline values of SBP, HR, and NE before and after treatment with moclobemide*

	SBP (mm Hg)	HR (beats/min)	NE (pg/ml)
Phase 1			
Baseline	103.22 ± 1.16 (45)	55.64 ± 0.60 (45)	231.03 ± 6.24 (39)
60 min after placebo	103.56 ± 1.14 (45)	54.31 ± 0.55 (45)	248.67 ± 13.05 (39)
Phase 2			
Baseline	102.38 ± 1.23 (21)	56.14 ± 1.12 (21)	221.37 ± 13.32 (19)
60 min after moclobemide (100 mg)	104.05 ± 1.18 (21)	55.43 ± 1.22 (21)	210.09 ± 17.44 (19)

Values are mean ± SEM. Values in parentheses represent number of experiments.

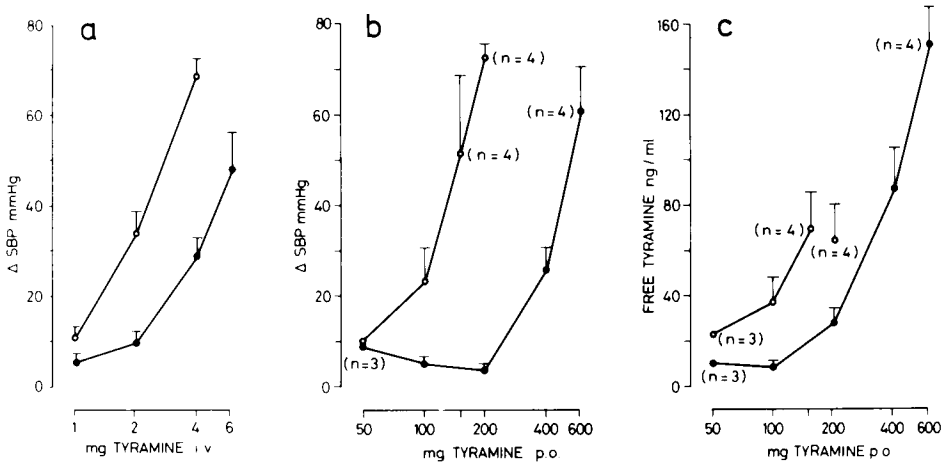

FIG. 1. Peak SBP changes (ΔSBP mm Hg) after i.v. tyramine **(a)**, and oral tyramine **(b)**, as well as free tyramine concentrations in plasma (ng/ml) following oral tyramine **(c)**, before (●—●) and after (○—○) moclobemide treatment. Tyramine i.v. or p.o. was administered 60 min after placebo (phase 1) or 60 min after 100 mg p.o. moclobemide (phase 2). Values are means ± SEM, n = 7 (unless otherwise stated).

centration of plasma tyramine was increased to 24.7 ng/ml after the lowest dose of tyramine (50 mg).

Statistical analysis (parallel line design) showed that following moclobemide the plasma tyramine concentration was on the average increased 2.6-fold.

In trials without moclobemide, a good correlation was obtained between the tyramine dose administered and the peak concentration of tyramine in the plasma ($r = 0.849$, $p < 0.001$, n = 25). In contrast, after moclobemide treatment no such correlation was observed ($r = 0.375$, NS, n = 14) due to the great individual variability of the concentration of tyramine in plasma.

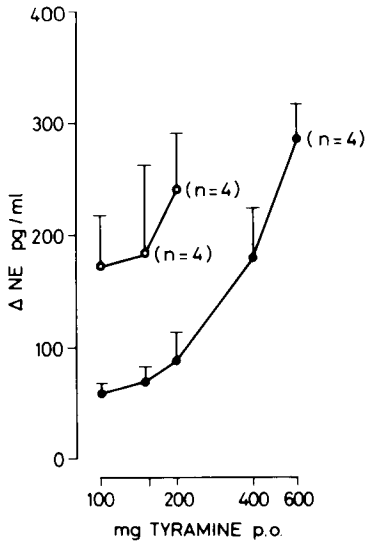

FIG. 2. Peak NE concentrations in plasma (pg/ml) following oral tyramine before (●—●) and after (○—○) moclobemide treatment. Oral tyramine was administered 60 min after placebo (phase 1) or 60 min after 100 mg moclobemide (phase 2). Values are means ± SEM, n = 7 (unless otherwise stated).

Plasma norepinephrine concentrations after oral tyramine

In both phases I and II of this study, increasing tyramine doses induced dose-dependently an increase of the NE concentration in plasma (Fig. 2). Before moclobemide, 200 mg tyramine produced an increase in NE of 87.3 ± 26.7 pg/ml which was not accompanied by increases in SBP. The NE values obtained after 50 mg tyramine are not given because only a small number of samples have been measured. A good correlation was found between the dose of tyramine administered and the peak concentration of NE in plasma before the administration of moclobemide ($r = 0.65$, $p < 0.001$, n = 25). No correlation was found after moclobemide ($r = 0.261$, NS, n = 14).

Relationship between the concentrations of tyramine and norepinephrine in plasma and the systolic blood pressure

The relationship between the concentration of tyramine in plasma and the pressor effect is shown in Fig. 3.

No changes in SBP or plasma NE levels were observed when the concentration of tyramine in plasma was <22 ng/ml. Even after moclobemide administration, there were no changes in SBP after 50 mg tyramine p.o. At this dose the maximum concentration of tyramine attained in the plasma was 24.7 ng/ml (see Fig. 1c). With tyramine doses ≧100 mg, the increase in SBP as well as the increase in the concentration of NE in plasma were greater with moclobemide than without moclobemide (2.5-fold, $p < 0.001$ and 2.1-fold, $p < 0.001$, respectively).

The values of the pressor effect responses showed a high correlation with the peak concentration of the free tyramine in plasma both before and after moclobemide administration ($r = 0.812$, $p < 0.001$, n = 25 and $r = 0.781$, $p < 0.001$, n = 14, respectively). An excellent correlation was also found between the maximum concentrations of free tyramine and NE in plasma before and after admin-

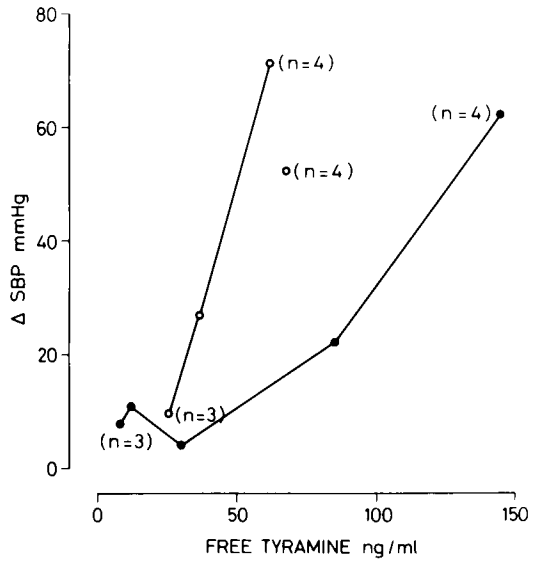

FIG. 3. Peak plasma tyramine concentrations vs. peak ΔSBP, following oral tyramine, before (●—●) (50, 100, 200, 400, and 600 mg) and after (○—○) (50, 100, 150, and 200 mg) moclobemide treatment. Values are means ± SEM, n = 7 (unless otherwise stated).

istration of moclobemide ($r = 0.849$, $p < 0.001$, n = 25 and $r = 0.839$, $p < 0.001$, n = 14, respectively).

A given increase in plasma NE was accompanied by virtually the same increase of SBP regardless of whether or not moclobemide had been administered. Following tyramine alone at the dose of 400 mg the concentration of NE increased to 180.4 ± 46.2 pg/ml (n = 7). This increase was accompanied by an increment of the SBP (ΔSBP of 25.0 ± 5.6 mm Hg, n = 7). Very similar increases of NE and SBP were also observed after administration of moclobemide and 100 mg tyramine p.o. (NE: 170.8 ± 47.6 pg/ml, n = 7; ΔSBP: 23.6 ± 8.3 mm Hg, n = 7).

No significant changes in plasma dopamine levels could be related either to the moclobemide or to the tyramine administration. As for plasma epinephrine it was observed that occasionally, and always in concomitance with a rapid increase of the SBP, the concentration of epinephrine increased from basal values of 20–40 pg/ml to ≦90 pg/ml, regardless of whether or not moclobemide has been administered.

Time course of the changes of the plasma concentration of free tyramine and of systolic blood pressure

In the absence of moclobemide the plasma level of tyramine increased rapidly in the plasma following each dose reaching a maximum within 20 min and returning to baseline levels within 1 h. However, in 5 of 7 subjects administered moclobemide, the increase of the concentration of tyramine in plasma was delayed and peak levels were attained only 90 min after oral tyramine. The maximum of the plasma tyramine concentration as attained at 90 min was preceded in some subjects by a smaller increase at 20 min. A typical curve is shown in Fig. 4. In all cases the increase of the free tyramine in plasma was accompanied by changes in SBP.

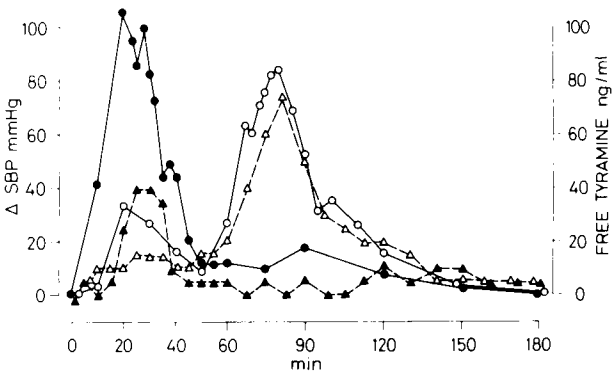

FIG. 4. Typical time course profile (one subject) of free tyramine concentration in plasma and ΔSBP after an effective tyramine dose (400 mg before and 150 mg after moclobemide treatment). Free tyramine concentrations before (●—●) and after (○—○) moclobemide treatment; ΔSBP before (▲– –▲) and after (△– –△) moclobemide treatment.

Administration of tyramine capsules during a meal

When tyramine capsules were given together with a light tyramine-free meal, the smallest effective doses of tyramine (which were 400–600 mg before and 100–150 mg during moclobemide treatment) induced only minor changes in the plasma tyramine concentration (not exceeding 15 ng/ml). Interestingly enough, in fasted subjects the same doses of tyramine induced an increase of the tyramine concentration in plasma which was 4 times higher than observed in nonfasting conditions. Tyramine given with a meal, produced virtually no increase in tyramine plasma concentration and blood pressure in the absence as well as in the presence of moclobemide ($p < 0.01$) (Table 2; Fig. 5, lower panel). In subjects not treated with moclobemide, the lowest effective dose of tyramine administered (400–600 mg) generated *AUC* values (5,442 ng/ml/min) much higher in fasting conditions than when tyramine was administered with a meal (1,808 ng/ml/min). In subjects treated with moclobemide the lowest effective dose of tyramine administered (100–150 mg) produced also higher *AUC* values in fasting conditions (3,930 ng/ml/min) than when tyramine was administered with a meal (1,693 ng/ml/min).

DISCUSSION

Moclobemide is a reversible, preferential type A MAOI of short duration of action. Therefore, it was expected that potentiation of the pressor effects of tyramine would be less marked after moclobemide than after the classical MAOIs, such as after tran-

TABLE 2. *Effect of a meal on peak plasma tyramine concentration (C ng/ml) and peak SBP changes following oral pressure tyramine doses before and after moclobemide treatment*

	Phase 1					Phase 2				
		A		B			A		B	
Subjects	Oral pressure tyramine dose (mg)	C (ng/ml)	Δ (mm Hg)	C (ng/ml)	Δ (mm Hg)	Oral pressure tyramine dose (mg)	C (ng/ml)	Δ (mm Hg)	C (ng/ml)	Δ (mm Hg)
1	600	108.1	65	48.1	15	100	94.9	65	19.9	20
2	400	109.1	50	13.4	15	150	84.1	75	35.1	25
3	400	182.8	50	17.9	5	150	108.0	70	16.7	10

Phase 1, before; Phase 2, after moclobemide; A, tyramine given with tap water; B, tyramine given with a meal.

ylcypromine, an irreversible, nonselective MAOI which potentiates tyramine effects up to 50-fold. Oral tyramine doses of only 10–15 mg are required after tranylcypromine to provoke the same pressor effect as 400–600 mg tyramine before treatment (15, unpublished observations). However, it could not be excluded that treatment with moclobemide in therapeutic doses over a period of two weeks or longer would produce a certain enhancement of the pressor effect of tyramine. Recent results have shown the new reversible MAOIs cimoxatone (16) and brofaremine (15) to potentiate oral tyramine up to seven- to eightfold.

To study this question of tyramine potentiation, we administered tyramine in different ways (i.v. in fasting, p.o. in fasting and nonfasting subjects) after 14 days of moclobemide administration. The dose of moclobemide was within the clinically effective dose range, that is, 300 mg/day. Tyramine was given one hour after the moclobemide dose, that is, at the time when peak MAO inhibition is known to occur (6,8).

The dose–effect curve for the pressor effect of i.v. tyramine was shifted toward the left by a factor of 2.4. This potentiation is likely to reflect MAO inhibition in noradrenergic nerve endings, which would protect tyramine taken up into nerve endings and, to some extent, also NE displaced by tyramine from storage sites. An additional left-hand shift of 1.7 is seen in the dose–pressor curve to oral tyramine; this additional potentiation is likely to represent inhibition of presystemic inactivation of tyramine. As it is known that during MAO type A inhibition potentiation of tyramine effects are

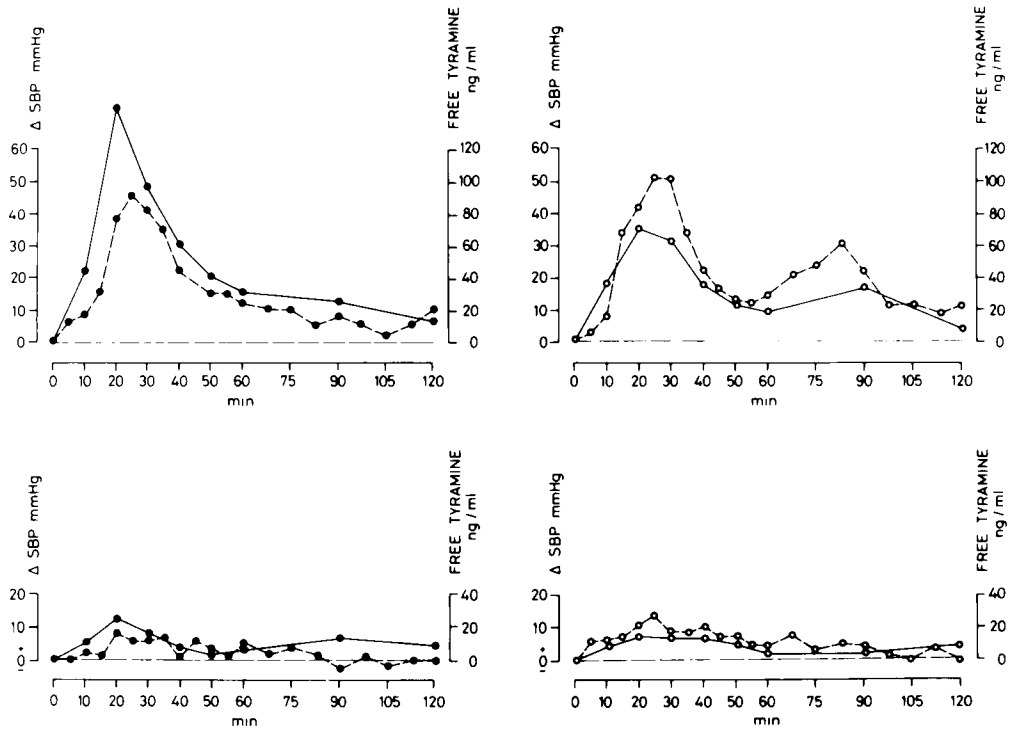

FIG. 5. Concentration of the free tyramine in plasma before (●—●) and after (○—○) moclobemide treatment and ΔSBP before (●– –●) and after (○– –○) moclobemide treatment following individual effective doses of tyramine. **Upper panel,** tyramine given with tap water; **lower panel,** tyramine given with a meal. Values are means ± SEM, n = 3.

dependent on the increased first-pass tyramine metabolism in the gut and liver and on the inhibition of neuronal MAO-A (16,17), we may conclude that increases in tyramine sensitivity by moclobemide are due to both decreased first-pass tyramine metabolism and increased response at the sympathetic nerve terminal to even parts.

High correlation between SBP and NE increments also confirmed that tyramine pressor effects are due to increased release of NE from noradrenergic nerve endings. The poor correlation between tyramine dose and tyramine plasma concentration after MAO inhibition suggests that any variation in the pressor response to tyramine will be due rather to variable tyramine absorption than to variable response to given tyramine concentrations at the adrenergic nerve terminal. Moclobemide treatment did not affect basal plasma NE levels and pressor responses to NE confirming previous findings that moclobemide is a specific MAO inhibitor and does not alter NE release, NE reuptake, or α-adrenergic receptors (18).

Increments of peripheral venous NE up to a concentration of 100 pg/ml after tyramine administration were not accompanied by pressor responses. These data are in accordance with recent findings (19). The increments in plasma epinephrine may be interpreted as due to psychic stress during pronounced increases of SBP, as tyramine has no known effect on epinephrine release (19).

The reason for the delayed absorption of tyramine after moclobemide treatment is unclear. We did not find any indication in the literature on an enterohepatic recirculation of tyramine. However, such a recirculation cannot be excluded, although the shape of the curves with a smaller or missing first peak does not favor this possibility. Another explanation could be that intestinal MAO inhibition by moclobemide induces changes in splanchnic blood flow due to local NE release (20).

Since there is a pronounced difference between the interaction of MAOI with tyramine alone, and MAOI with tyramine and food, it is suggested that future studies should be carried out not only using i.v. and oral tyramine in the fasting state but in the form of tyramine-rich food (e.g., cheese) since this would provide an experimental situation with more validity than the use of tyramine capsules.

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