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EFFECTS OF DRUGS ON HUMAN BLOOD PLATELET AND PLASMA AMINE OXIDASE ACTIVITY *IN VITRO* AND *IN VIVO*

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Abstract—A method employing radioactive substrates has permitted sensitive assay of monoamine oxidase (MAO) activity in blood platelets and plasma. Kinetic studies indicate that while platelet and plasma MAO are distinct from that of liver mitochondria, the platelet and liver enzymes are quite similar, particularly in the characteristics of their response to inhibitors. Administration of six different MAO inhibitors including furazolidone to human subjects resulted in marked inhibition of platelet MAO, accompanied by expected changes in urinary tryptamine excretion. Effects of these drugs on plasma MAO were variable; an additional drug, isoniazid, in therapeutic dose was found to inhibit markedly plasma, but not platelet, MAO. Use of platelet MAO assay in the direct assessment of the MAO-inhibitory potency of drugs in man is suggested.

THE WIDESPREAD therapeutic use of inhibitors of monoamine oxidase (MAO) has made desirable a direct and rapid means of measuring the activity of this enzyme in man. With the exception of assays on jejunal biopsy specimens,[1] methods of detecting MAO inhibition in man have been of an indirect type, usually involving assays of urinary amines.[2, 3] Probably the simplest possible approach would be the use of blood as the enzyme source. Otsuka and Kobayashi[4, 5] attempted this with plasma monoamine oxidase. Their results were of a preliminary nature, however, and did not establish that enzyme activity measured in plasma was similar to that in other tissues.

In the present work, we have studied the substrate and inhibitor characteristics of MAO in plasma and in another component of blood, the platelets. In addition, comparison was made of the effects of several drugs in man on platelet and plasma MAO activity and on the urinary excretion of tryptamine; elevations of the latter afford a suitable indirect means of detecting overall MAO inhibition.[2]

MATERIALS AND METHODS

Studies in vitro

A. Materials. Tyramine-1-^{14}C hydrobromide (5·02 mc/m-mole), tryptamine-2-^{14}C bisuccinate (2·56 mc/m-mole), and 5-hydroxytryptamine-2-^{14}C hydrogen oxalate (2·09 mc/m-mole) were purchased from New England Nuclear Corp. Benzylamine-alpha-^{14}C hydrochloride (1·18 mc/m-mole) was purchased from Nuclear Research Chemicals, Inc.; β-phenylisopropylhydrazine (JB-516), tranylcypromine sulfate (Parnate), iproniazid phosphate (Marsilid), and isonicotinic acid hydrazide (isoniazid)

were obtained from Lakeside Laboratories, Smith, Kline & French Laboratories, Hoffman-LaRoche, Inc., and Calbiochem, respectively. Pargyline hydrochloride (MO-911, Eutonyl) was supplied by Abbott Laboratories and furazolidone (Furoxone) by Eaton Laboratories. Amberlite ion-exchange resin CG-50, 100–200 mesh, was purchased from Mallinckrodt Chemical Works.

B. Preparation of Amberlite columns. Amberlite CG-50 was prepared for use as described by Pisano.[6] The resin, which had been buffered at pH 6·5 before drying, was suspended in deionized water and columns of resin (0·5 × 2·5 cm) were prepared in Pasteur capillary pipettes which had been plugged with glass wool. The columns were washed with 3–5 vol. deionized water before use.

C. Platelet monoamine oxidase. Platelets were isolated from 500-ml units of fresh whole blood collected in EDTA anticoagulant, according to the method of Shulman *et al.*,[7] except that the ammonium oxalate wash step was omitted. Platelet suspensions in isotonic saline, prepared from several units of blood, were pooled and frozen until used for study *in vitro*.

D. Liver monoamine oxidase. The enzyme activity of human liver (obtained at the time of autopsy, less than 6 hr after death) was studied in whole liver homogenates. The K_m and maximum velocity constants were determined by using preparations of rat liver mitochondria purified through step 3 as described by Nara *et al.*[8]

E. Enzyme assay. The assay devised for the studies *in vitro* is based on the fact that most substrates for amine oxidase are absorbed strongly by Amberlite CG-50, whereas the products (aldehyde or acid) are not bound by the resin. The enzyme was incubated in air at 37° with radioactive amine, usually 0·1 mM, in a total volume of 0·5 ml, which was 0·2 M with respect to Na_2HPO_4–KH_2PO_4 buffer, pH 7·5. Although pH optima differed in various tissues, pH 7·5 was used in most studies *in vitro* for comparative purposes. At the end of incubation, the reaction mixture was pipetted directly onto an Amberlite CG column, which was washed immediately with 2·0 ml deionized water. The effluent and the wash containing the radioactive product were collected in a counting vial. Ten ml of the scintillator solution of Bray[9] was added and the sample was counted in a Packard Tri-Carb liquid scintillation spectrometer. This assay was found to give a linear response to the amount of enzyme used and the time of incubation, with tyramine, tryptamine, serotonin, and benzylamine as substrates. The column assay procedure did not work well when crude plasma was used as the enzyme source owing to the relatively large amount of protein in the incubation mixture. Therefore, the plasma assays *in vitro* were performed as described under studies *in vivo*.

Studies in vivo

A. Subjects. Eleven normal male volunteers, three male and two female patients with scleroderma, and two male patients with mild essential hypertension, ranging in age from 18–58 yr, were the subjects of these studies while hospitalized in the Clinical Center. During periods of study, subjects were fed a constant diet of their own choosing, excluding cheese and amine-containing fruits. Various drugs were administered for 10–14 days in single or divided maximum daily oral doses as follows: pargyline hydrochloride, 100 mg (3 subjects); isocarboxazid (Marplan), 60 mg (3 subjects); phenelzine sulfate (Nardil), 45 mg (2 subjects); nialamide (Niamid), 100 mg (2 subjects); tranylcypromine, 20 mg (1 subject) and 30 mg (1 subject); furazolidone, 400 mg

(2 subjects); and isoniazid, 400 mg (4 subjects). In the case of pargyline and isocarboxazid, the dose listed was not achieved until several days after treatment was started. In general, the dosage selected was either the commonly recommended starting dose or the accepted therapeutic dose for each drug.

B. Sample preparation. Blood was obtained by venipuncture with a hemorepellent needle and 24-inch plastic tubing (Fenwal Laboratories). For preparation of a platelet suspension as cited above, 30 ml blood was added directly to a 50-ml polypropylene centrifuge tube containing 0·8 ml of 0·27 M (10%) disodium ethylenediamine tetraacetate (EDTA) adjusted to pH 7·4. The final platelet suspension in 0·15 M NaCl was adjusted to give a protein concentration of approximately 2 mg/ml, as determined by a modification of the phenol reagent assay.[10] The results of periodic counts of saline suspensions of platelets by the method of Brecher and Cronkite[11] correlated well with the protein concentration. Platelet suspensions were found to contain one leukocyte, usually a lymphocyte, per 1000–5000 platelets.

An additional 5 ml blood obtained at venipucture was added to a separate tube containing 0·2 ml of 40% sodium citrate solution. The blood was spun at top speed for 20 min in a refrigerated clinical centrifuge and the platelet-poor plasma was separated for assay. It was found that care must be taken in separating plasma from the buffy layer to avoid contamination with platelet MAO activity, which caused spurious elevations in plasma MAO values.

Twenty-four-hour urine specimens were collected in glass bottles containing 15 ml of 6 N HCl and stored at 4° until analyzed for tryptamine, as described previously.[12]

C. Enzyme assay. Benzylamine was selected as substrate for assay of platelets and plasma in the studies *in vivo*, since it was the substrate most actively deaminated by both platelets and plasma. The spectrophotometric assay of McEwen and Cohen[13] was modified for radioassay of MAO activity in platelets and plasma. Benzylamine alpha-^{14}C hydrochloride was diluted with nonisotopic benzylamine to give a substrate solution with an activity of 0·162 μc/μmole. One-tenth ml platelet suspension or 0·6 ml crude plasma was incubated with 1·2 μmole of benzylamine and 0·2 M phosphate buffer, pH 7·2, in a total volume of 1·5 ml in a Dubnoff metabolic shaking incubator at 37° in air for 1 hr. The reaction was stopped by addition of 0·15 ml of 60% perchloric acid. The reaction product, ^{14}C-labeled benzaldehyde, was extracted into 3 ml toluene. After centrifugation, 2 ml of the toluene supernatant was transferred to a counting vial, and 10 ml of a toluene scintillator solution (diphenyloxazole, 15 g and *bis*-2-5 phenyloxazolyl-benzene, 50 mg/l. toluene) was added. The samples were counted in a Packard model 3002 liquid scintillation spectrometer with an efficiency of 89 per cent as determined by using a standard of toluene-^{14}C. Quenching of individual samples, as determined by the channels ratio method from a standard quench curve for toluene-^{14}C with nitromethane as the quenching agent, was negligible (0–2 per cent). The assays for both platelets and plasma were found to be linear with respect to the amount of enzyme used and the time of incubation.

RESULTS

A comparison of the monoamine oxidase activity of platelets and plasma with that of liver is presented in Table 1. For convenience of comparison the amount of enzyme activity present/g liver, platelets, and plasma has been calculated. It may be seen that, when expressed in this way, platelet MAO content approached that of liver, the richest

source of MAO, whereas platelet-poor plasma was a relatively poor source of MAO. Substrate characteristics of the enzyme from platelets, plasma, and liver are presented in Table 2. In these experiments, the values for V_{max} and K_m were calculated from double reciprocal plots for the platelet and liver enzymes, and as reported by McEwen[14] for plasma. Benzylamine was the substrate most actively deaminated by the enzyme

TABLE 1. MONOAMINE OXIDASE ACTIVITY OF HUMAN LIVER, PLATELETS AND PLASMA WITH BENZYLAMINE-^{14}C SUBSTRATE*

Enzyme source	Average enzyme activity	
	(mμmole/g tissue/hr)	(mμmole/ml whole blood/hr)
Liver	33,000	
Platelets	5,000	75
Plasma	30	15

* The results represent average values of assays of homogenates of liver, suspensions of platelets, and crude platelet-free plasma. The experiments for liver and platelets were done at pH 8·5 and for plasma at pH 7·2. For comparison of the amount of enzyme activity present in liver, platelets, and plasma, the average activity/g crude tissue has been calculated. The platelet activity/g was calculated assuming a platelet protein content of 15 per cent of wet weight.

TABLE 2. RELATIVE REACTION RATES AND SUBSTRATE AFFINITY CONSTANTS FOR MONOAMINE OXIDASES OF LIVER, PLATELETS AND PLASMA

Substrate	Liver*		Platelets		Plasma†	
	V_{max}‡	K_m	V_{max}‡	K_m	V_{max}‡	K_m
Benzylamine	100	$4{\cdot}5 \times 10^{-4}$ M	100	$1{\cdot}5 \times 10^{-4}$ M	100	$3{\cdot}3 \times 10^{-4}$ M
Tyramine	92	$6{\cdot}3 \times 10^{-5}$ M	45	5×10^{-5} M	12	
Tryptamine	62	$4{\cdot}5 \times 10^{-4}$ M	11	$1{\cdot}8 \times 10^{-5}$ M	10	
Serotonin	36	$4{\cdot}0 \times 10^{-5}$ M	10	2×10^{-3} M	<1	

* Enzyme source is mitochondrial fraction of rat liver as described by Nara *et al.*[8]

† Plasma values were calculated from the data of McEwen[14] on purified enzyme.

‡ The maximum reaction velocity rates were estimated from double reciprocal plots and are presented relative to benzylamine (100 per cent). The actual rates observed for benzylamine oxidation were 365, 40, and 2370 mμmole/mg protein/hr for liver, platelet, and plasma respectively. The liver and plasma values were derived from enzyme preparations of varying degrees of purification, and the platelet values from a saline suspension of pooled washed platelets as described in the text.

from each of the tissues. Marked differences in the relative rates of oxidative deamination were found; for example, it can be seen that the ratio of benzylamine to tryptamine oxidation for rat liver MAO was approximately 1·6, whereas for platelet MAO the ratio was approximately 10.

Use of inhibitors *in vitro* was also of value in characterizing monoamine oxidase of the various sources. It is now known that plasma MAO is a pyridoxal-containing protein, whereas the liver mitochondrial enzyme appears to be a flavoprotein.[15, 16] Since plasma MAO is a pyridoxal enzyme, it is inhibited by carbonyl reagents, as

was the case for both KCN and isoniazid (Table 3). The human and rat liver and platelet enzymes were not inhibited by these compounds. Other noncarbonyl but potent inhibitors of liver MAO, pargyline and tranylcypromine, inhibited the platelet enzyme at similar concentrations, whereas these two drugs had little effect on plasma MAO. The inhibitor characteristics *in vitro* of the platelet and liver enzymes were found to be similar for all six drugs tested.

TABLE 3. EFFECTS *IN VITRO* OF VARIOUS INHIBITORS ON MONOAMINE OXIDASE ACTIVITY OF LIVER, PLATELETS, AND PLASMA WITH BENZYLAMINE SUBSTRATE

Inhibitor	I_{50}*			
	Human liver†	Rat liver‡	Platelets	Plasma
Pargyline	1×10^{-7} M	2×10^{-8} M	2×10^{-8} M	$> 10^{-3}$ M
JB-516	1×10^{-5} M	3×10^{-6} M	2×10^{-7} M	5×10^{-6} M
Tranylcypromine	1×10^{-6} M	1×10^{-7} M	1×10^{-6} M	1×10^{-3} M
Iproniazid	5×10^{-5} M	1×10^{-6} M	2×10^{-6} M	1×10^{-3} M
Isoniazid	$> 10^{-3}$ M	$> 10^{-3}$ M	$> 10^{-3}$ M	1×10^{-3} M
KCN	$> 10^{-3}$ M	$> 10^{-3}$ M	$> 10^{-3}$ M	5×10^{-4} M

* Inhibitor concentrations resulting in 50 per cent enzyme inhibition are listed. Each value represents an average of several determinations.

† Enzyme source is human whole liver homogenate.

‡ Enzyme source is mitochondrial fraction of rat liver as described by Nara *et al.*[8]

The effects of various drugs *in vivo* at the maximal doses employed are summarized in Table 4. As shown by the results in subjects 1–12, platelet MAO activity was inhibited by all five of the MAO inhibitors which are currently in therapeutic use. Increases in urinary excretion of tryptamine, ranging from 2- to 6-fold, occurred during administration of these five drugs. The degree of platelet enzyme inhibition tended to parallel closely the urinary tryptamine changes. In the drug doses employed in this experiment, pargyline was noted to have the greatest inhibitory effect on platelet MAO and to produce one of the largest increases in tryptamine excretion. Tranylcypromine, the next most effective inhibitor of platelet MAO, also caused a 5- to 6-fold increase in urinary tryptamine. Both phenelzine and nialamide, in the doses employed in this experiment, were considerably less effective inhibitors as judged both by effects on platelet MAO activity and amine excretion. Isocarboxazid was found to be intermediate in effect, achieving greater than 90 per cent inhibition of the platelet enzyme in each of three subjects.

Plasma MAO inhibition by these therapeutically used MAO inhibitors was less striking and varied among individual subjects, ranging from 0 (subject 7, tranylcypromine) to 80 per cent inhibition (subject 9, phenelzine). The changes in plasma MAO activity correlated poorly with the changes in urinary tryptamine excretion. Isoniazid produced no significant changes in platelet MAO activity or urinary tryptamine excretion, but rapidly and nearly completely inhibited plasma MAO (subjects 13–16). Furthermore, in all of the subjects who received isoniazid the plasma MAO remained significantly inhibited for several weeks after discontinuance of the drug.

Of considerable interest is the MAO inhibition observed during furazolidone administration (subjects 17 and 18). Increased urinary tryptamine excretion and

TABLE 4. EFFECT OF VARIOUS DRUGS ON PLATELET AND PLASMA MONOAMINE OXIDASE AND URINARY TRYPTAMINE EXCRETION

Subject no.	Age	Sex	Drug	Drug dose (mg/24 hr)	Platelet MAO activity* (mμmole/mg protein/hr)			Plasma MAO activity* (mμmole/ml plasma/hr)			Urinary tryptamine (μg/24 hr)	
					Control	Drug	%Change	Control	Drug	%Change	Control	Drug
1	20	M	Pargyline	100	32·7	0·0	−100	22·9	11·7	−49	156	1000
2	20	M	Pargyline	100	32·7	0·1	−99	14·1	8·7	−38	90	459
3	18	M	Pargyline	100	17·7	0·5	−97	20·5	10·7	−48	264	1600
4	58	M	Isocarboxazid	60	37·1	2·8	−93	25·7	17·0	−34	106	585
5	20	M	Isocarboxazid	60	38·0	3·9	−90	16·9	15·5	−8	34	122
6	20	M	Isocarboxazid	60	29·3	1·7	−94	15·5	6·0	−61	158	940
7	52	F	Tranylcypromine	30	57·3	1·8	−97	20·3	21·1	+ 4	33	184
8	58	M	Tranylcypromine	20	39·4	2·5	−94	31·4	20·6	−31	185	1141
9	20	M	Phenelzine	45	33·3	7·5	−78	16·2	3·3	−80	181	545
10	20	M	Phenelzine	45	34·0	10·5	−69	17·7	3·9	−78	95	174
11	20	M	Nialamide	100	30·0	9·8	−66	15·6	13·7	−12	177	856
12	18	M	Nialamide	100	23·7	12·5	−47	16·3	13·1	−20	293	944
13	21	M	Isoniazid	400	33·2	30·4	− 8	17·6	1·0	−94	70	70
14	50	F	Isoniazid	400	41·9	49·4	+18	23·0	0·7	−97	71	60
15	43	M	Isoniazid	400	31·7	32·3	+ 2	17·3	0·1	−99	71	54
16	63	M	Isoniazid	400	41·7	52·0	+25	18·3	0·5	−97	66	79
17	44	M	Furazolidone	400	26·8	2·6	−90	16·0	2·7	−83	24	135
18	47	M	Furazolidone	400	22·6	1·3	−94	30·6	5·1	−83	19	88

* Each value represents the average of 3 determinations.

platelet MAO inhibition were apparent within the first few days of drug therapy. After a week of therapy, the urinary tryptamine excretion had increased more than 4-fold over control value, and the platelet MAO was at least 90 per cent inhibited. Plasma MAO was also significantly inhibited in both subjects. An effect of furazolidone *in vitro* could not be demonstrated at a concentration of 10^{-5} M on either platelet or plasma MAO, and only minimal inhibition of the platelet enzyme was noted at 10^{-4} M.

Typical changes observed with isocarboxazid, pargyline and isoniazid in individual subjects are shown in Figs. 1, 2 and 3. In a subject treated for 14 days with isocarboxazid, a 400 per cent increase in urinary tryptamine occurred in association with a 90 per cent inhibition of platelet MAO activity (Fig. 1). These effects developed and

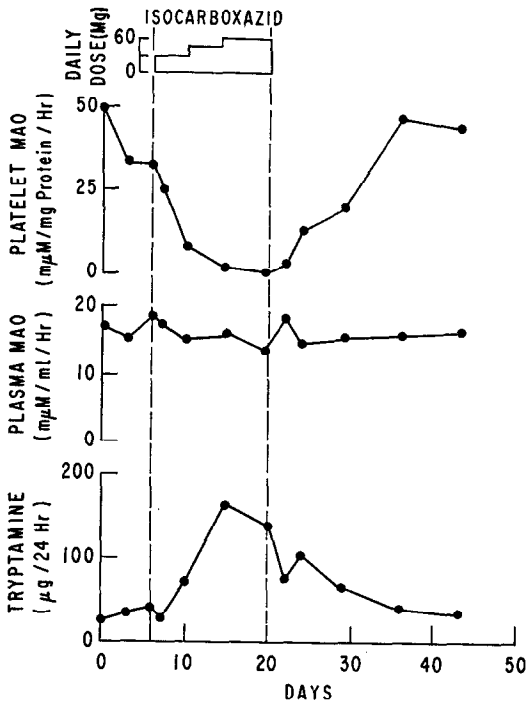

FIG. 1. Platelet and plasma MAO and urinary tryptamine in a subject (No. 5) given isocarboxazid.

disappeared in consonance. On the other hand, plasma MAO activity did not change significantly during isocarboxazid administration in this subject. It was noted in all three subjects receiving isocarboxazid that the drug had a gradual onset of effect, but an average inhibition of platelet MAO of at least 90 per cent was achieved by the tenth day of therapy. When isocarboxazid was stopped, the inhibitory effect persisted for more than 2 weeks, being second only to pargyline in duration of effect. With both pargyline (Fig. 2) and tranylcypromine, a rapid onset of action was noted, as evidenced by the fact that the platelet enzyme was at least 95 per cent inhibited in all subjects within 24 hr after either drug was started. The degree of inhibition reached 100 per cent by the fourteenth day of pargyline administration, and only gradually returned to

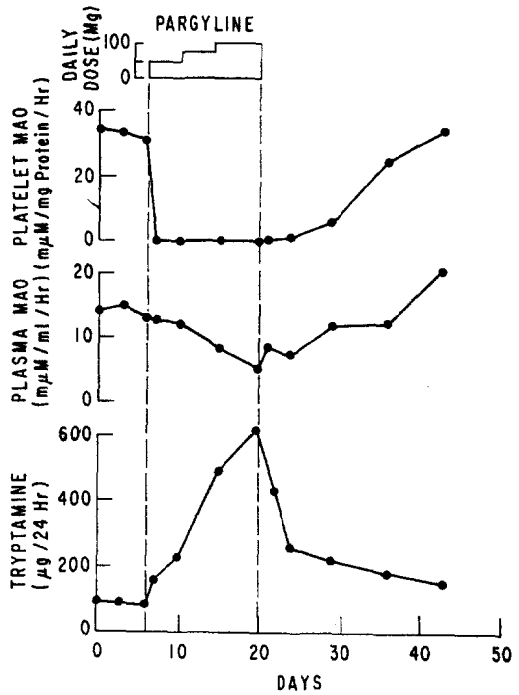

FIG. 2. Platelet and plasma MAO and urinary tryptamine in a subject (No. 2) given pargyline.

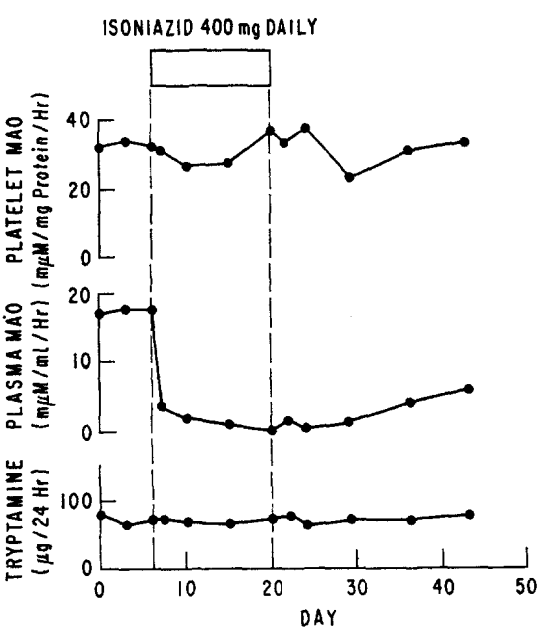

FIG. 3. Platelet and plasma MAO and urinary tryptamine in a subject (No. 13) given isoniazid.

control levels over a period of 3 weeks after discontinuance, the longest time for the drugs studied. Plasma MAO activity was less inhibited by pargyline and the effect developed more gradually than with the platelet enzyme (Fig. 2). The plasma MAO also showed a gradual return to control levels after the drug was stopped. Both nialamide and phenelzine had a gradual onset of effect on platelet MAO and urinary tryptamine excretion. With both drugs an average of only 75 per cent inhibition of the platelet enzyme was achieved by the last day of drug therapy, and the effect was dissipated within 7 days after the drugs were stopped. In the case of furazolidone, also, the MAO inhibition disappeared rather rapidly, within 10 days after it was discontinued.

In a subject who received isoniazid (Fig. 3), it can be seen that the plasma MAO was rapidly and almost completely inhibited within a few days after the drug was started. No effect on either platelet MAO or urinary tryptamine excretion was noted. The plasma MAO remained significantly inhibited for several weeks after the discontinuance of the drug in all of the subjects.

DISCUSSION

Three types of amine oxidase that are known to be present in blood are: diamine oxidase, plasma monoamine oxidase, and platelet monoamine oxidase. Each of these enzymes appears to be a distinct protein and may have clinical relevance. Diamine oxidase is characteristically elevated in the plasma of pregnant women,[17] whereas plasma monoamine oxidase has been reported to be elevated in congestive heart failure.[18] The platelet monoamine oxidase studied here appears to be very similar to the enzyme present in liver mitochondria, a major reservoir of MAO in the body. Solatunturi and Paasonen[19] indeed found the platelet amine oxidase activity to be associated with the mitochondria of these cells.

The experiments *in vitro* revealed substantial similarity between the platelet and liver MAO, and confirmed significant differences between the liver and plasma enzymes as reported by others.[8, 15] The platelet amine oxidase was found to have slightly different substrate specificity from the rat liver enzyme. However, differences in substrate specificities of monoamine oxidases have been reported previously,[20] and it is likely that several molecular species of MAO exist in mammalian tissue.

The similarity of the platelet enzyme to liver MAO, particularly with regard to the inhibitor characteristics, presents a unique opportunity for assessment of MAO inhibition *in vivo*. The excellent correlation between amine excretion and platelet enzyme inhibition observed in this study suggests that this MAO activity reflects the body's overall ability to metabolize some of the physiologically active amines. The use of platelets for monitoring MAO activity in man has several advantages over existing methods. The amine excretion studies are perhaps the most widely used, but these provide only indirect information and require careful regulation of diet to eliminate variability due to the ingestion of amines and precursor amino acids. The jejunal biopsy technique, although it is a direct method of assay, presents more difficulties in obtaining the tissue for assay than in the case of platelets. In general, assay of platelet MAO appears to provide an easy and reproducible means of measuring the effects of drugs on monoamine oxidase in man.

Both pargyline and tranylcypromine were found to be rapidly acting, potent inhibitors of platelet MAO *in vivo*. One would judge that nialamide and phenelzine,

in the doses employed in this study, are less effective than pargyline and tranylcypromine as MAO inhibitors. This could account for the differences in effectiveness of these drugs noted clinically. Therapeutic results with MAO inhibitors might be improved if this convenient test were used to monitor the chemical effect of the drug in a given patient.

The contrast between the effects of isoniazid and the other inhibitors on plasma and platelet MAO and amine excretion clearly demonstrates a difference in the two enzymes. This provides additional evidence for the uniqueness of the plasma enzyme. Because of the dissimilarity between plasma MAO and that of other tissues, it would appear that the platelet MAO assay is superior to the plasma assay as a convenient and accurate index of the effects of drugs on overall MAO activity.

This study provides further confirmation that furazolidone causes MAO inhibition which has clinical importance in the usual dosage in man. The slight inhibition by furazolidone *in vitro* noted in the present work is in agreement with the recent report of Stern *et al.*,[21] who found a furazolidone metabolite, hydroxyethylhydrazine, to be a potent MAO inhibitor, whereas the parent drug produced only minimal inhibition *in vitro* at 10^{-4} M concentration. As is the case with other MAO inhibitors, it would appear desirable to avoid amine-containing foods during and immediately after furazolidone administration.

The authors recently became aware of an interesting reaction occurring in a medical colleague during self-medication with isoniazid, 400 mg daily. After 2 months of therapy he experienced several acute episodes of severe generalized flushing, feelings of warmth, nasal stuffiness, mild tachycardia and systolic hypertension (140–150 mm Hg), each occurring within 30 min after ingestion of various cheeses and lasting up to 45 min. The episodes were severe enough that medical consultation was sought, but failed to reveal any etiology. When the patient was seen by us, it was found that his urinary amine excretion was normal but that plasma MAO activity was markedly inhibited. The attacks ceased after discontinuance of isoniazid, despite rechallenge with cheese, and the plasma MAO activity also became normal. It is interesting to speculate that amine sensitivity exacerbated by isoniazid inhibition of the plasma enzyme and possibly other pyridoxal-amine oxidases (e.g. diamine oxidase) might be responsible for the symptoms in this individual. A survey of the large population of patients receiving isoniazid should be done to establish the incidence and clinical importance of such reactions.

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