Platelet Monamine Oxidase in Chronic Schizophrenia

Some Enzyme Characteristics Relevant to Reduced Activity

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• To evaluate further the basis for the reduced activity of platelet monoamine oxidase (MAO) found in chronic schizophrenic patients, a number of characteristics of the enzyme were compared between patients and controls. Equivalent and statistically significant reductions in activity of the enzyme were found in the patients when tyramine and benzylamine were used as the substrates in comparison to previously reported reductions with tryptamine as the substrate. Michaelis constants for platelet MAO from chronic schizophrenic patients with reduced enzyme activity were not different from controls. Dialysis of the enzyme from patients and controls yielded no changes in activity. Studies of other platelet enzymes, including succinate dehydrogenase, cytochrome C reductase, and lactate dehydrogenase in patients, normal controls, and a subgroup of normal controls with reduced MAO activity, showed no parallel reductions in activity in patients or controls with low MAO activity. These findings suggest that the reduced MAO activity found in chronic schizophrenic patients is apparently not accounted for by nonspecific changes in platelets or platelet mitochondria.

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Reductions in platelet monomamine oxidase (MAO) activity have been reported in some[1-6] but no all[7-9] studies of schizophrenic patients. Alterations in MAO activity have also been reported in patients with affective disorders[4,10] and some other medical disorders.[11,12] Several of these reports have demonstrated that some clinical characteristics of schizophrenic patients, for example the chronic vs acute schizophrenia dichotomy, correlate with platelet MAO activity differences.[3,9,13] Other studies have evaluated evidence indicating menstrual cycle-related changes or other hormone effects, including those of testosterone, triiodothyronine, prednisone, and epinephrine, may contribute to individual differences in measured enzyme activities.[5,14-16] Treatment with psychoactive drugs other than the MAO-inhibiting antidepressants[10,17] and possibly lithium carbonate[18,19] does not appear to affect platelet MAO activity; comparisons of psychiatric patients treated or not treated with phenothiazines[1,20] and of individual patients prior to and during treatment with thioridazine[5] of chlorpromazine hydrochloride, imipramine hydrochloride, and thiothixene hydrochloride[8] showed no differences in MAO activity. Studies of the addition in vitro of several tricyclic antidepressants and chlorpromazine have demonstrated inhibition of human platelet and rabbit brain MAO activity[21,22] (Murphy and Donnelly, unpublished observations) and suggest the need for further investigation of their in vivo effects; however, 10-fold to 1,000-fold higher drug concentrations are required for in vitro inhibition than are obtained in plasma during clinical treatment with these drugs[21,22] (Murphy and Donnelly, unpublished observations).

In addition, there have been several reports of substrate-related differences in platelet MAO activity between patients and controls[3,4,6] and between subgroups of patients.[3] On the basis of some substrate-related differences, Zeller and co-workers[6] have suggested the existence of a specific, molecularly different form of platelet MAO in schizophrenic patients. However, other studies in schizophrenic patients[16] and normals[17] have found high correlations between platelet MAO activities measured with different substrates.

Recent studies of chronic schizophrenic patients with reduced MAO activity and of acute schizophrenic patients and controls with normal MAO activity have showed stable MAO activities in all three groups studied over time periods ranging from two weeks to two years, with no greater variability in the patient groups compared to normals and with a high correlation coefficient ($r = 0.86$, $P < .001$) for our largest group of normals (N = 42), which was studied after an interval of eight to ten weeks.[16,24] These data are in keeping with twin studies of schizophrenic patients, manic-depressive patients, and normals,[9] suggesting that the observed 20-fold range in human platelet MAO activities[23] is largely contributed to by genetic factors, although other factors (eg, the 20% peak-to-trough change in platelet MAO activity during the menstrual cycle[14]) may also contribute somewhat to between-individual differences and certainly to within-individual variability.

In the present study, a number of properties of MAO in platelets from chronic schizophrenic patients with reduced MAO activity were compared to those from controls. Also, platelet preparations from both groups were studied after dialysis, and other platelet enzymes were measured to

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determine if reduced MAO activity might represent a generalized abnormality in platelets from the schizophrenic patients.

SUBJECTS AND METHODS

Twenty-two chronic schizophrenic patients, 17 male and five female, had received diagnoses of chronic undifferentiated schizophrenia or chronic paranoid schizophrenia, using DSM II categories. This was a new group of patients studied since our 1972 report.[1] The patients in this sample are representative of a larger sample of patients described in greater clinical detail elsewhere[2,4] whose mean age was 33 years and who had been hospitalized a mean of 11 years. Twelve of the patients were receiving neuroleptic drugs at the time of this study, including chlorpromazine, fluphenazine hydrochloride, haloperidol, as well as benztropine mesylate; none were receiving tricyclic antidepressants. In substudies described below in which not all patients were included, care was taken to insure that approximately one half (no less than 40%) of the patients studied had not received drugs for a minimum of three weeks prior to the study; as there were no suggestions of MAO activity differences in these or past study results[1,5] in the drug-treated patients, the results from both groups were combined.

The 48 male and 16 female controls included hospitalized normal volunteers, outpatient volunteers in other studies, and patients hospitalized on other hospital wards. Mean age of the controls was 26 years. Their mean values for platelet MAO activity measured with tryptamine as the substrate were 7% to 17% lower than those of 167 normal controls previously reported,[5] reflecting a combination of minor platelet preparation and MAO assay changes and possible population sample differences.

Blood Sampling and Tissue Preparation

Venous blood samples (18 ml) were collected in tubes containing 2 ml of ACD (acid-citrate-dextrose, NIH formula A). Platelet-rich plasma (PRP) was prepared by sequential ten-minute centrifugations at 175 and 300 g; the PRP was removed and pooled after each centrifugation. An aliquot of the pooled PRP was removed for platelet counting and MAO assay as described below. Platelet pellets for the MAO assay were obtained by centrifugation of the PRP at 1,800 g for 30 minutes; the pellets were washed once with saline before either immediate assay or, more routinely, storage at −70 C prior to assay. Less than a 5% ± 2% platelet MAO activity reduction has been observed after storage for eight weeks at −70 C (N = 10).

Platelet counts were determined using duplicate 20-μl samples of PRP diluted in 50 ml of a balanced electrolyte cell-counting solution, with each sample counted four times, using standard electronic particle counting procedures. As occasional platelet pellets containing less than 0.18 mg of protein per milliliter of PRP and PRP samples containing less than 10^8 platelets per milliliter tended to be associated with increased intraindividual variations in preliminary studies using repeated sampling in the same individual, those samples were routinely discarded.

Assays for Platelet MAO Activity With Tyramine, Benzylamine, and Tryptamine as Substrates

For the assay of platelelet MAO activity with tyramine or tryptamine, 50-μl aliquots of the platelet sonicates containing 0.2 to 0.5 mg of protein were incubated in 0.5 ml of 0.08M phosphate buffer with tyramine hydrochloride ^{14}C (9.2 mCi/mmole; final concentration, 10^{-3}M) or with tryptamine bisuccinate ^{14}C (47 mCi/mmole; final concentration, 8×10^{-5}M) for 20 minutes at 37 C.[23,25] Ascorbic acid (10^{-4}M) and edetic acid (10^{-4}M) were added to the buffer to prevent nonenzymatic substrate alterations in the

Table 1.—Mean (± SEM) Platelet Monoamine Oxidase (MAO) Activity With Different Substrates in Chronic Schizophrenic Patients and Controls

	Platelet MAO Activity, nmoles/mg of Protein/hr	
	Normal Controls	Chronic Schizophrenic Patients
Study 1	n = 34	n = 10
Tyramine	41.7 ± 4.1	18.7 ± 1.5*
Tryptamine	5.10 ± 0.36	2.43 ± 1.8*
Study 2	n = 48	n = 14
Benzylamine	60.1 ± 3.2	36.7 ± 2.9†
Tryptamine	5.64 ± 0.28	3.69 ± 0.41†

*P < .001, Student *t* test. †P < .01, Student *t* test.

Table 2.—Studies of Platelet Monamine Oxidase (MAO) in Schizophrenic Patients and Controls, Using Different Substrates

Source	Patients	N	MAO Activity for Different Substrates,* % of controls (*P*)		
			Tryptamine	Benzylamine†	Tyramine
Murphy & Wyatt, 1972[1]	Chronic schizophrenia	33	41 (< .001)	...	...
Wyatt et al, 1973[2]	Chronic & acute schizophrenia in discordant identical twins	13	61 (< .005)	...	...
Friedman et al, 1974[7]	Schizophrenia	26	83 (NS)	...	...
Nies et al, 1974[4]	Schizophrenia (2 episodes, but 1 yr in hospital in last 5 yr)	12	72 (< .01)	86 (NS)	...
Meltzer & Stahl, 1974[3]	Chronic schizophrenia	12	52 (< .025)	32 (< .001)	44 (< .001)
	Acute schizophrenia	10	60 (NS)	45 (< .001)	49 (< .001)
Carpenter et al, 1975[9]	Acute schizophrenia	44	97 (NS)	...	...
Zeller et al, 1975[6]	Chronic & some acute schizophrenia (males)	27	...	43 (< .001)	39 (< .001)
Domino & Khanna, 1976[20]	Chronic schizophrenia	13	47 (< .001)	...	...
Present report					
Study 1	Chronic schizophrenia	10	48 (< .001)	...	45 (< .001)
Study 2	Chronic schizophrenia	14	65 (< .01)	61 (< .001)	...

*Additional substrates reported in only one study comparing schizophrenic patients and controls include octopamine[3] and *p*-methoxybenzylamine[6]; the latter significantly differentiated patients and controls, while the former was different in chronic, but not acute schizophrenic patients.[3,6]

†The substituted compound, *m*-iodobenzylamine, was used by Meltzer and Stahl[3] and Zeller et al[6] in place of benzylamine.

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tyramine assay. Enzyme aliquots inactivated by heating at 100 C for ten minutes provided control values, which were subtracted from the experimental values. Following incubation, the samples were placed on ice and then transferred to Pasteur pipettes containing 0.5 × 2.5 cm of a carboxylic cation exchange resin. The columns were washed twice with 1 ml of distilled water and the entire 2.5 ml collected in glass vials containing 17.5 ml of a liquid scintillation cocktail. The radioactivity of the products was determined by liquid scintillation spectrometry.

For the patient comparison assays with benzylamine ^{14}C as substrate, previously described methods were used.[5,23,25] Protein was determined by the method of Miller.[26] With all of the substrates, MAO activity was found to be linear with respect to the previously described protein concentration and time of incubation.

Dialysis studies were carried out on sonified platelet pellets from a subgroup of 14 chronic schizophrenic patients previously identified as having reduced MAO activity and from 14 normal controls. The samples were placed in cellulose tubing and kept in a refrigerated, stirred bath for 12 hours. Aliquots were assayed both before and after dialysis for tryptamine ^{14}C deamination and protein content as described above.

The apparent Michaelis constants and maximum velocities were obtained from the Modellab interactive curve-fitting program,[27] using data from tryptamine deamination measurements over a substrate concentration range of 10^{-5}M to 8×10^{-3}M. Ten chronic schizophrenic patients previously identified as having reduced platelet MAO activity were studied together with ten normal controls. The same ten patients and ten controls were also included in the study of enzyme activity reductions produced by heat in which sonified pellets were incubated at 50 C for 0, 20, and 40 minutes prior to being assayed for tryptamine deamination.

Assays for Cytochrome C Reductase, Succinate Dehydrogenase, and Lactate Dehydrogenase

The assay for reduced nicotinamide adenine dinucleotide (NADH) cytochrome C reductase was similar to the method described by Sottocasa et al.[28] The incubation medium contained 2.65 ml of 50mM potassium phosphate buffer, pH 7.5; 0.1 ml of potassium cyanide, 0.15M; and 0.1 ml of nadide solution (2.5 mg/ml of 1.0% $NaHCO_3$) plus 50μl of enzyme protein solution. The reaction was started by the injection of 0.1 ml of cytochrome C solution (equine heart, salt-free), 3mM, and read at 550 nm on a spectrophotometer. The assay for succinate dehydrogenase was performed as described by Pennington.[29] The reaction was started by the injection of 2-(*p*-iodophenyl)-3-(*p*-nitrophenyl)-5-phenyltetrazolium chloride, and the product, formazan, was read at 490 nm. The assay for lactate dehydrogenase was similar to that described by Wroblewski and LaDue.[30] Included in the incubation medium were 2.8 ml of 0.1M potassium phosphate buffer, pH 7.4, 0.1 ml of sodium pyruvate solution (2.5 mg/ml), and 10μl to 20μl of protein solution. The reaction was started by the injection of 0.1 ml of nadide solution (2.5 mg/ml of 1.0% $NaHCO_3$) and was read at 340 nm.

RESULTS

Platelet MAO activity was significantly reduced in the chronic schizophrenic patients compared to the controls in the replicated studies using tryptamine, tyramine, and benzylamine as substrates ($P < .01$, Table 1). Comparisons of results with tryptamine vs the other substrates showed reductions in activity that were of similar magnitude (Tables 1 and 2); for reference, comparative substrate data from other studies of schizophrenic patients are reviewed in Table 2. Pearson correlations between MAO activities measured with benzylamine and tyramine compared to tryptamine were highly significant ($P < .001$, Table 3).

Comparisons of kinetic constants calculated from enzyme activity measurements with tryptamine as the substrate in samples from indivudal chronic schizophrenic patients and normal controls yielded essentially identical results for both groups (Table 4). Heat inactivation studies also showed similar small reductions in activity over time, with no significant difference between patients and controls (Table 4).

Table 3.—Correlations Between Platelet Monoamine Oxidase Activity Measured With Three Different Substrates in Chronic Schizophrenic Patients and Controls

Substrates	*r*	*P*
Tyramine/tryptamine (N = 44)	0.70	< .001
Benzylamine/tryptamine (N = 62)	0.75	< .001

Table 4.—Michaelis Constants, Maximum Velocities, and Heat Inactivation Results for Platelet Monoamine Oxidase (MAO) Activity*

	Normal Controls (N = 9)	Chronic Schizophrenic Patients (N = 10)
Michaelis constant, μM	13.3 ± 1.2 (range, 6.6-18.1)	12.0 ± 1.3 (range, 2.6-15.6)
Maximum velocity, nmoles/mg of protein/hr	17.4 ± 3.2 (range, 11.2-42.3)	9.1 ± 0.9† (range, 5.6-16.2)
Platelet MAO activity, % of control, after 50 C incubation for 20 min	92 ± 6	101 ± 7
40 min	87 ± 6	92 ± 5

*Mean ± SEM. Tryptamine used as substrate.
†$P < .05$, Student *t* test.

Determinations of the activities of a cytoplasmic enzyme (lactate dehydrogenase) in platelets and of two other enzymes located, like MAO, in platelet mitochondria (succinate dehydrogenase and NADH cytochrome C reductase) indicated no significant reductions in activity in a group of chronic schizophrenic patients with reduced MAO activity (as determined with both tryptamine and benzylamine as substrates [Table 5]) in comparison with normal controls. A comparison group of selected controls who had reduced MAO activity also did not manifest comparable reductions in these other platelet enzymes (Table 5). Correlation coefficients used to compare platelet MAO activity with the activity of lactate dehydrogenase ($r = .23$), succinate dehydrogenase ($r = .01$) and NADH cytochrome C reductase ($r = .12$) across the three study groups were not statistically significant. Platelet counts and platelet protein concentrations were also similar in all three groups (Table 5).

Dialysis of platelet homogenates from 14 chronic schizophrenic patients with a mean MAO activity of less than one half that of 14 controls showed no overall change in activity after dialysis in either the patient or the control samples (Table 6). Only three samples from both the patient and control groups manifested a 10% or greater increase in activity after dialysis.

COMMENT

Monoamine oxidase activity in human platelets is located in mitochondria and shares a number of properties with other tissue MAOs; it appears to have distinctly different

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Table 5.—Platelet Enzyme Studies in Normals and Chronic Schizophrenic Patients (Mean ± SEM)

	Normal Controls (N = 6)	Normal Controls With Reduced MAO* Activity (N = 6)	Chronic Schizophrenic Patients With Reduced MAO Activity (N = 6)
MAO (tryptamine), nmoles/mg of protein/hr	4.95 ± 0.40	2.80 ± 0.53†	2.74 ± 0.60†
MAO (benzylamine), nmoles/10^8 platelets/hr	12.8 ± 1.0	8.4 ± 1.1†	7.2 ± 1.0†
NADH‡ cytochrome C reductase, μmoles/mg of protein/min	8.3 ± 0.8	10.0 ± 2.3	9.4 ± 0.7
Succinate dehydrogenase, nmoles/mg of protein/min	8.9 ± 1.0	10.9 ± 1.8	9.9 ± 1.0
Lactate dehydrogenase, μmoles/mg of protein/ min	50 ± 8	52 ± 6	44 ± 3
Platelets, 10^9/liter	218 ± 62	195 ± 13	208 ± 29
Protein, mg	0.24 ± 0.05	0.24 ± 0.02	0.23 ± 0.03

*Monamine oxidase. †$P < .05$. ‡Nicotinamide adenine dinucleotide.

properties from the soluble amine oxidase found in human plasma.[31] It is different from most other tissue MAOs in exhibiting characteristics of the MAO type B form only; brain, liver, and other tissues in most species contain varied proportions of MAO type A and MAO type B forms identified on the basis of substrate preferences and inhibitor responses.[32,33]

Platelet MAO activity is readily inhibited by clinically used MAO-inhibiting antidepressants in vitro as well as during chronic administration of these drugs in man.[10,17] Under standard conditions, human platelet MAO exhibits the highest specific activities for benzylamine, dopamine, tyramine, and phenylethylamine as substrates, a lower specific activity for tryptamine, and the enzyme is least active towards norepinephrine and serotonin.[17,31,34]

The close agreement between the MAO activities measured with tyramine, benzylamine, and tryptamine as substrates in both patients and controls in the present study does not support the suggestion made by Zeller and coworkers[6] that schizophrenic patients possess a qualitatively different MAO with an altered molecular structure. In their study, Zeller et al[6] investigated tyramine and two substituted benzylamines, *m*-iodobenzylamine and *p*-methoxybenzylamine, using spectrophotometric and spectrophotofluorometric assays, and found similar per cent reductions in MAO activity with tyramine and *m*-iodobenzylamine (39% and 43%), but a significantly smaller reduction with *p*-methoxybenzylamine (61%) in 27 male schizophrenic patients compared to controls.[6] It remains a possibility that their choice of substrates having different side-chain lengths and different positions for the ring substitutions is more sensitive to some characteristics of the MAO active site than the physiologic substrates we have studied to date, and this question should certainly be studied further. Meltzer and Stahl[9] also observed substrate-related differences in reporting significantly reduced platelet MAO activity in chronic and acute schizophrenic patients compared to controls, although these differences between substrates were not statistically significant. Their report of a hierarchial relationship in the inhibition sequence of *m*-iodobenzylamine and tyramine results is in agreement with the report of Zeller et al[6]; likewise, their observations of approximately equal values

Table 6.—Effects of Dialysis on Platelet Monoamine Oxidase (MAO) Activity in Chronic Schizophrenic Patients Compared to Normal Controls (Mean ± SEM)

	Platelet MAO Activity (cpm*/mg of Protein)		Dialyzed: Undialyzed Activity Ratio
	Undialyzed	Dialyzed	
Normal controls (N = 14)	96.61 ± 14.27	95.78 ± 13.33	1.04 ± 0.02
Chronic schizophrenic patients (N = 14)	39.45 ± 2.96	39.36 ± 2.42	1.02 ± 0.03

*Radioactivity (cpm) of deaminated product.

with tyramine and tryptamine are in agreement with the results of the present study. Unfortunately, the other substrates in question have not yet been studied by more than one laboratory, and these possible substrate-related MAO differences in patients compared to controls have not yet been confirmed. The possibility that substrate-related differences might also contribute to the greater reductions in platelet MAO activity in chronic compared to acute schizophrenic patients (Table 2) requires more comprehensive comparisons of the clinical populations identified as "acute" or "chronic."

The lack of difference in the Michaelis constants for schizophrenic patients compared to controls provides some further evidence that the considerable reduction in MAO activity in the patients may not be the result of a change in the active site of the enzyme—at least as it is reflected in the enzyme's affinity for tryptamine. Again, it would be of interest to obtain data on Michaelis constant comparisons with other substrates, such as those studied by Zeller et al[6] in schizophrenic patients and controls.

Endogenous inhibitors, including high concentrations of substrates in some tissue preparations, may result in apparent reductions in enzyme activity. Preliminary studies had not suggested the presence of endogenous inhibitors,[1] but because relatively high concentrations of serotonin and other amines may be found in platelets, a more comprehensive experiment employing dialysis was carried out. The lack of any selective increase in MAO activity in the schizophrenic patients, nor any change in

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the controls, would seem to exclude both the presence of endogenous substrate concentrations sufficient to produce a measurable reduction in enzyme activity, as well as the presence of an endogenous, reversible inhibitor of the enzyme responsible for the enzyme activity differences in patients.

The absence of a reduction of the platelet numbers, platelet protein or lactate dehydrogenase, NADH cytochrome C reductase, or succinate dehydrogenase activities in platelets from individuals with low platelet MAO activity compared to controls argues strongly against the observed reductions in MAO activity being attributable to generalized alterations in platelets from chronic schizophrenic patients. We and others have speculated that one basis for reduced MAO activity might be altered populations of platelets of different ages, since there are some data that younger, larger platelets may possess higher glycolytic cycle enzyme activities[35]; MAO activity has not yet been compared in such different platelet populations. The present data render this possibility less likely, as no hint of other enzyme differences was observed. In addition, it seems unlikely that a generalized deficiency in the cofactor for MAO, flavin adenine dinucleotide,[36] is responsible for the reduction in platelet MAO activity in the patients, as one of the other enzymes studied, NADH cytochrome C reductase, is also a flavoprotein enzyme. No reductions in the activity of this enzyme were observed in the low MAO groups, nor were the activities of this enzyme and MAO significantly correlated.

In conclusion, the studies reported here provide further evidence against the likelihood that the platelet MAO activity reductions observed in chronic schizophrenic patients result from some nonspecific, platelet-related changes. The substrate and Michaelis constant studies tend to argue against an alteration in the active site of the enzyme, although this question remains open, as is evidenced by other data from patient group-substrate interactions reported previously by Zeller et al[6] and Meltzer and Stahl.[3] While the dialysis studies rule out the presence of a reversible inhibitor of the enzyme, there exist a number of drugs that act as irreversible, nondialyzable MAO inhibitors that are not very dissimilar to some naturally formed compounds; an agent of this sort could account for the reduced MAO activities in chronic schizophrenic patients. Alternatively, changes in the synthesis or degradation rates of the enzyme could also account for enzyme activity differences in some psychiatric patient groups.[5]

Nonproprietary Names and Trademarks of Drugs

Thioridazine—*Mellaril.*
Nadide—*Enzopride.*

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