Platelet Monoamine Oxidase Activity in Subgroups of Schizophrenic Disorders

by Joseph J. Schildkraut, Paul J. Orsulak, Alan F. Schatzberg, and James M. Herzog

Abstract

This article summarizes findings from a series of studies that examined platelet monoamine oxidase (MAO) activity in patients with nonaffective schizophrenic disorders and schizophrenia-related depressions. The findings indicate that mean platelet MAO activity was not different from control values in the subgroup of nonaffective schizophrenic disorders without auditory hallucinations (that is, the S-1 subgroup). However, mean platelet MAO activity was reduced in the subgroup of nonaffective schizophrenic disorders characterized by the presence of auditory hallucinations often occurring in conjunction with paranoid features (that is, the S-2 subgroup). Moreover, we found that mean platelet MAO activity was increased in schizophrenia-related depressions characterized by histories of chronic asocial, eccentric, or bizarre behavior.

Since the initial report of Murphy and Wyatt in 1972, a number of studies have now confirmed that some patients with schizophrenic disorders have lower platelet monoamine oxidase (MAO) activity than controls (Berrettini, Vogel, and Clouse 1977; Domino and Khanna 1976; Meltzer and Stahl 1974; Nies et al. 1974; Schildkraut et al. 1976; Sullivan, Stanfield, and Dackis 1977; Wyatt et al. 1973; Zeller et al. 1975), but this has not been observed in all studies (Belmaker et al. 1976; Brogdon et al. 1976; Friedman et al. 1974; Shaskan and Becker 1975; Takahashi, Yamane, and Tani 1975; White, McLeod, and Davidson 1976). In their early studies, the NIMH group reported that reduced platelet MAO activity occurred more commonly in chronic than in acute schizophrenic disorders (Carpenter, Murphy, and Wyatt 1975). However, other clinical characteristics that might be associated with reduced platelet MAO activity in schizophrenic patients had not been demonstrated at that time. Because of our interest in possible biochemical discriminators of subtypes of schizophrenic, as well as affective disorders, in 1973 we began a series of studies to explore this problem.

In our first pilot study of platelet MAO activity in schizophrenic patients hospitalized at the Massachusetts Mental Health Center or at the McLean Hospital in 1973, we observed that low platelet MAO activity occurred with some regularity in a subgroup of schizophrenic patients (most of whom were paranoid) with auditory hallucinations and delusions. However, this pilot study was performed at the time that we were first establishing the assay for platelet MAO activity in our laboratory and, although the findings of the pilot study were statistically significant, the assay variability at that time was quite large. Consequently, instead of reporting these findings, we undertook an independent replication of this study, once we had established adequate quality control of our assay for platelet MAO activity.

In this replication study, we examined platelet MAO activity in a subsequent series of patients who were hospitalized at the Mas-

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Aspects of the findings presented in this article have been reported elsewhere (Schildkraut et al. 1975, 1976, 1978a; Orsulak et al. 1978).

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Massachusetts Mental Health Center, during 1974, with a diagnosis of schizophrenia.

Patients with histories of alcoholism were excluded from this replication study, since we had observed (Schildkraut et al. 1976), as have other investigators (Brown 1977; Wiberg, Gottfries, and Oreland 1977; Major and Murphy 1978; Sullivan et al. 1978, 1979), that platelet MAO activity is reduced in patients with alcoholism. In this aspect of our research, we also excluded patients with prominent affective symptoms of depressions or manias since Murphy and Weiss (1972), as well as Nies et al. (1974), had reported alterations in platelet MAO activity in patients with depressive disorders. Patients were also excluded from the study if there was evidence of any major neurological or medical illness. To control for the possible effects of advancing age on platelet MAO activity (Robinson et al. 1972), patients over 45 years old were not studied. In this study, we also examined platelet MAO activity in an age- and sex-matched control group consisting of 28 staff members of the Massachusetts Mental Health Center.

As shown in table 1, mean platelet MAO activity was lower in a group of 32 nonaffective schizophrenic patients (that is, schizophrenic patients without prominent affective symptoms of depressions or manias) than in an age-matched control group. However, although the difference in mean platelet MAO activity was statistically significant, it was rather small in magnitude, and there was a considerable overlap of values in the two groups.

The medical records of these schizophrenic patients were then reviewed in detail by a psychiatrist blind to the biochemical data, and the patients were categorized according to whether they had a well-documented record of both auditory hallucinations and delusions. The subgroup of schizophrenic patients with both well-documented auditory hallucinations and delusions was designated S-2, whereas the remaining subgroup of schizophrenic patients was designated S-1. Most of the patients in the S-2 subgroup had delusions or auditory hallucinations that were of a persecutory or accusatory nature and thus were also classified as paranoid.

As shown in table 2, patients with a diagnosis of schizophrenia, but without documented auditory hallucinations and delusions (the S-1 subgroup), had platelet MAO activity that was very similar to that of the control group. In contrast, schizophrenic patients with both auditory hallucinations and delusions (that is, the S-2 subgroup) had significantly lower platelet MAO activity.

The S-1 and S-2 schizophrenic subgroups, as well as the control group, were well matched with respect to age (table 2). To rule out the possibility that sex differences might be contributing to these differences in platelet MAO activity, the data on male and female patients were examined separately. As reported elsewhere (Orsulak et al. 1978), in both the male and the female patients, platelet MAO activity was significantly lower in the S-2 sub-

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**Table 1. Platelet MAO activity in nonaffective schizophrenic patients**

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Age</th>
<th>MAO activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>28</td>
<td>27 ± 1</td>
<td>5.72 ± .38</td>
</tr>
<tr>
<td>Schizophrenic</td>
<td>32</td>
<td>27 ± 1</td>
<td>4.70 ± .31</td>
</tr>
</tbody>
</table>

Platelets were isolated from blood by a modification of the procedure of Murphy et al. (1969). MAO activity was determined by measuring the deamination of C'N-trypamine bisucinate (Murphy and Weiss 1972) and is expressed as means ± SEM in nanomoles of tryptamine deaminated per hour per milligram of platelet protein. When this method was used in a series of 26 subjects on whom three or more consecutive daily samples were examined, the intrasubject coefficient of variation was 10 percent ± 1.5 percent (means ± SEM). Similarly, the average coefficient of variation for samples of pooled platelets analyzed repeatedly over a period of 4 months was approximately 10 percent. Age is expressed as means ± SEM in years.

1 p < .05 for difference from control values.

**Table 2. Platelet MAO activity in subgroups of nonaffective schizophrenic disorders**

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Age</th>
<th>MAO activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>28</td>
<td>27 ± 1</td>
<td>5.72 ± .38</td>
</tr>
<tr>
<td>S-1</td>
<td>16</td>
<td>26 ± 1</td>
<td>5.95 ± .35</td>
</tr>
<tr>
<td>S-2</td>
<td>16</td>
<td>29 ± 2</td>
<td>3.45 ± .27</td>
</tr>
</tbody>
</table>

See note to table 1 for methodological details.

1 p < .001 for difference from controls or S-1 subgroup.
group than in the S-1 subgroup or the controls.

Since it had been suggested that reduced platelet MAO activity may occur principally in chronic schizophrenic patients, we examined several measures that might reflect chronicity. As shown in table 3, there were no meaningful differences in the number of hospitalizations in patients in the S-1 and S-2 subgroups. Moreover, there was no meaningful correlation between MAO activity and the number of hospitalizations. Similarly, the number of years since first hospital admission was slightly larger in the S-2 subgroup than in the S-1 subgroup, but the difference was not statistically significant. Moreover, there was no meaningful correlation between platelet MAO activity and years since first admission (table 3). These findings thus suggest that the reduced platelet MAO activity in the S-2 subgroup was not merely related to chronicity of the illness.

It was not feasible to conduct this aspect of our research on schizophrenic patients under drug-free conditions, but the comparison between the S-1 and S-2 subgroups provides some control for possible effects of antipsychotic drugs, since many of the patients in both subgroups were treated with these drugs. Although the antipsychotic drug dosage (expressed in chlorpromazine equivalents) was slightly higher in the S-2 subgroup than in the S-1 subgroup, there was no meaningful correlation between platelet MAO activity and antipsychotic drug dosage ($r = -0.09$).

As described previously, in this aspect of our research we excluded those schizophrenic patients with prominent affective symptomatology. However, in another aspect of our work, we have examined platelet MAO activity in a series of depressed patients with diagnoses of schizophrenia-related depressions characterized by the presence of chronic asocial, eccentric, or bizarre behavior (Schildkraut et al. 1978a, 1978b).

As shown in table 4, patients with schizophrenia-related depressions had significantly higher platelet MAO activity than did a group of age-matched control subjects. It is worth noting that the patients with schizophrenia-related depressions did not differ significantly in the number of hospitalizations, the time since first hospitalization, and the age of first hospital admission from patients with nonaffective schizophrenic disorders— that is the S-1 and S-2 subgroups.

In considering this finding of elevated platelet MAO activity in the schizophrenia-related depressions that are characterized by chronic asocial behavior, it is of some interest that Murphy et al. (1977), Schooler et al. (1978), and Coursey, Buchsbaum, and Murphy (1979) have found that volunteer human subjects with low platelet MAO activity were socially more active and scored higher on the Zuckerman Sensation Seeking Scale (Zuckerman 1974) than did subjects with high platelet MAO activity. Moreover, in rhesus monkeys, Redmond, Murphy, and Baulu (1979) have found that behavioral indices reflecting social activity and social contact were inversely correlated with platelet MAO activity, while time spent alone was positively correlated—that is time spent alone was associated with high platelet MAO activity. Thus, it may be that social isolation is indeed a behavioral variable that correlates with elevated platelet MAO activity; and in another article in this issue Adler et al. (1980)

### Table 3. Number of hospitalizations and years since first hospital admission in subgroups of nonaffective schizophrenic disorders

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Number of hospitalizations</th>
<th>Years since first admission</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-1</td>
<td>2.43 ± .33</td>
<td>3.18 ± .46</td>
</tr>
<tr>
<td>S-2</td>
<td>3.12 ± .44</td>
<td>5.93 ± 1.42</td>
</tr>
</tbody>
</table>

Correlation with MAO activity: $r = -0.12$ $r = -0.11$

See note to table 1.

### Table 4. Platelet MAO activity in schizophrenia-related depressions

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Age</th>
<th>MAO activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>28</td>
<td>27 ± 1</td>
<td>5.72 ± 0.38</td>
</tr>
<tr>
<td>Schizophrenia-related depressions</td>
<td>8</td>
<td>27 ± 4</td>
<td>8.16 ± 0.53$^1$</td>
</tr>
</tbody>
</table>

See note to table 1.

$^1 p < 0.025$ for difference from controls.
presents new data supporting this possibility.

Our findings thus indicate that reduced platelet MAO activity is not found in all schizophrenic patients, but that it tends to occur in a clinically identifiable subgroup. The original blind selection of the S-2 subgroup was made on the basis of a history of both auditory hallucinations and delusions. However, further examination of our data showed that the primary discriminating symptom may have been the presence of auditory hallucinations, since none of the patients in the S-1 subgroup had auditory hallucinations, although many had delusions. These findings suggested that in schizophrenic patients without prominent affective symptomatology, the presence of auditory hallucinations might be a criterion for identifying a subgroup of schizophrenic patients with reduced platelet MAO activity. Recent data from a number of groups of investigators including Demisch et al. (1977), Becker and Shaskan (1977), as well as Meltzer and associates (Meltzer 1979), support this association between low platelet MAO activity and hallucinations in schizophrenic patients, although this association has not been observed in all studies (Groshong et al. 1978; Mann and Thomas 1979). Moreover, the association of low platelet MAO activity with auditory hallucinations in psychiatric patients has also been confirmed in our laboratory in a prospective study reported by Adler et al. (1980; this issue).

Thus, to summarize our data on platelet MAO activity in schizophrenic disorders, as shown in figure 1, we observed that mean platelet MAO activity was not different from control values in the subgroup of nonaffective schizophrenic disorders without auditory hallucinations (that is, the S-1 subgroup). However, mean platelet MAO activity was reduced in the S-2 subgroup of nonaffective schizophrenic disorders characterized by the presence of auditory hallucinations often occurring in conjunction with paranoid features. Moreover, we found that mean platelet MAO activity was increased in schizophrenia-related depressions characterized by histories of chronic asocial, eccentric, or bizarre behavior. These findings of differences in platelet MAO activity in a clinically defined subgroup of nonaffective schizophrenic disorders and in the schizophrenia-related depressions may help to account for some of the discrepancies in the results of various studies of platelet MAO activity in schizophrenic disorders.

References


Becker, R.E., and Shaskan, E.G. Platelet monoamine oxidase activity

Figure 1. Platelet MAO activity in subgroups of nonaffective schizophrenic disorders and in schizophrenia-related depressions

![Figure 1. Platelet MAO activity in subgroups of nonaffective schizophrenic disorders and in schizophrenia-related depressions](image)


Acknowledgments

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