low platelet monoamine oxidase activity and schizophrenia*

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Intrigued by the finding that blood platelet monoamine oxidase (MAO) activity is low in some schizophrenic patients, we and others in the field have been involved in a continuous effort to determine the potential significance of this low enzyme activity to schizophrenia. In this review, we examine this effort and assess the possible influence on our findings of the large number of artifacts that have plagued the investigation of biological factors related to psychiatric disorders.

MAO Assay in Blood Platelets

In our initial studies (Murphy and Wyatt 1972), venous blood was collected in heparin, or more recently, in Becton-Dickinson Co. Vacutainer tubes containing acid-citrate-dextrose (ACD), NIH formula A, and platelets separated and stored according to previously described methods (Wyatt, Saavedra, and Axelrod 1973). MAO activity was determined using 2-carbon 14-tryptamine hydrochloride (8 X 10^-5 moles (M), 8.9 microcuries (mCi) per millimoles (mM)) as substrate and was expressed as nanomoles (nM) of tryptamine converted per milligram (mg) of platelet protein. The product was indoleacetaldehyde, whose formation was linear with time and protein concentration.

During the last several years our samples were also obtained in the ACD solution, but the MAO activity was determined in platelet-rich plasma. The present assay (unpublished) uses carbon 14-benzylamine (2 X 10^-4 M, 2 mCi/mM) as substrate, and is expressed as nM of product per 10^-8 platelets per hour. Benzylamine is a good substrate for both platelet MAO and an entirely different enzyme occurring in the plasma. For this reason, platelet-rich plasma samples with and without the MAO inhibitor pargyline are assayed. Pargyline (2.4 X 10^-4 M) completely inhibits the platelet enzyme without affecting the plasma enzyme. The activity of the sample with the inhibitor is subtracted from the sample without—the difference being the platelet activity.

The advantage of the platelet-rich plasma assay over the previous one is that it is not necessary to determine platelet protein, which can easily be contaminated with red and white cells.

Stability of Enzyme

Because at times it is not immediately possible to obtain platelet-rich plasma from blood samples or assay enzymes, it is necessary to know the stability of the enzyme. Comparisons of blood samples processed immediately or kept on ice or at room temperature for 5 hours reveal no change in activity. Similarly, once the platelet-rich plasma is separated, MAO activity remains stable for at least 30 days when kept at -70°C.

Comparison of Assays

Pearson correlations were determined for platelet MAO activity for 48 normals and 20 chronic schizophrenics assayed by our former and present methods (figure 1). The correlation coefficient for the normals was .85, while that for the chronic schizophrenic patients was .76. For the combined group, the correlation was .83. For the purpose of this review, all platelet MAO activities are expressed in benzylamine values with a correction factor (derived from the normals) for values determined using the tryptamine assay.

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Figure 1. Correlation between assays in controls and chronic schizophrenic patients for tryptamine and benzylamine assays.

Reliability of Assay

Because the collection procedure and assay used have evolved with time and the data presented here have been collected over 4 years, the sources of methodological variances are many. Figure 2 presents the variances (both methodological and biological) for controls and acute and chronic schizophrenics. For all groups, followup assays cluster within 3 to 4 units of the original. When the three groups were examined (chi-square) at an interval of 3 months, there was no difference between the groups in frequency of samples deviating by more than 4 units.

Subjects

Blood was drawn from normal volunteers and hospital personnel at both the Clinical Center, National Institutes of Health, Bethesda, Md., and the William A. White Building at St. Elizabeths Hospital, Washington, D.C. Acute schizophrenics whose blood was studied largely came from a research ward at the Clinical Center, while chronic schizophrenic patients came from special research wards at the William A. White Building.

Age and Sex

Robinson et al. (1971) reported that females had 10
percent higher platelet MAO activity than males. In our sample, females have a slight but consistently higher MAO activity, although this difference is statistically significant only for the young adult group.

Drugs

Although early studies of the effect of chlorpromazine on amine degradation in intact systems indicated that chlorpromazine had some inhibitory effects, this seemed to reflect poor amine accessibility to the enzyme because of alterations in the cell membrane (see Wyatt, Belmaker, and Murphy 1975 for references). Recently, Edwards and Burns (1974) found that the $I_{50}$ (50 percent inhibition of enzyme activity) for amitriptyline, a tricyclic antidepressant, was $2 \times 10^{-6}$ M for human platelet MAO in vitro when benzylamine was used as a substrate. The inhibition was competitive.

In studies on patients given neuroleptics, there does not appear to be a consistent difference in platelet MAO activity when patients are receiving or not receiving neuroleptics, or between patients receiving neuroleptics and their siblings not receiving drugs (table 1). In our laboratory, in vitro studies have indicated that platelet MAO is most sensitive to inhibition by irreversible MAO inhibiting agents such as tranylcypromine, pargyline, and deprenyl, all of which are used clinically (with $I_{50}$'s of 20, 4, and $2 \times 10^{-6}$ M, respectively). The tricyclic antidepressant drugs inhibit platelet MAO as noted above, although higher concentrations ($6 \times 10^{-5}$ M) are required. Chlorpromazine and d- and l-amphetamine require still higher concentrations (5 to $8 \times 10^{-5}$ M) to produce platelet MAO inhibition using tyramine ($10^{-3}$ M) as substrate (C. H. Donnelly and D. L. Murphy, unpublished data).

Hormones

One study of human platelet MAO activity measured at two times during the menstrual cycle found no alteration in activity (Gilmore et al. 1971). In another study that used samples collected three times a week, there were small (23 percent) peak-to-trough variations in activity in the majority of women (Belmaker et al. 1974). The peak MAO activity occurred during the pre-ovulatory interval and the nadir occurred 5-11 days...
Table 1. Effects of neuroleptics (dose per 24 hours) on mean platelet MAO activity.

<table>
<thead>
<tr>
<th>Patients</th>
<th>MAO activities on/off neuroleptics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eight chronic schizophrenics on more than 400 mg chlorpromazine (CPZ) for greater than 2 weeks, and off all drugs for 2 weeks to 6 months</td>
<td>8.58/8.54</td>
</tr>
<tr>
<td>Six chronic schizophrenics on more than 400 mg CPZ and other neuroleptics for greater than 2 weeks, and off all drugs for greater than 2 weeks</td>
<td>8.27/7.32</td>
</tr>
<tr>
<td>Nine chronic schizophrenics on non-CPZ neuroleptics for greater than 1 week, and off all drugs at least 2 weeks</td>
<td>11.09/6.94</td>
</tr>
<tr>
<td>Six depressed patients on thioridazine, 100-600 mg, for at least 2 weeks, and off all drugs for at least 2 weeks</td>
<td>13.37/13.87</td>
</tr>
<tr>
<td>Five neurologic patients on neuroleptics and their same-sex siblings not on any drug</td>
<td>11.97/7.59</td>
</tr>
<tr>
<td>Seven identical twins discordant for schizophrenia, with one twin taking neuroleptics and the other not on any drugs</td>
<td>12.01/14.10</td>
</tr>
</tbody>
</table>

1 This apparent effect was due to one patient whose MAO activity increased from 6.34 (no drug) to 42.99 (neuroleptic) on the two occasions it was measured.

Note.—No means were statistically different.

later. A small number of patients taking prednisone have been studied; they had MAO activities within normal limits (Murphy, Belmaker, and Wyatt 1974). Similarly, there does not appear to be any relationship between plasma thyroxin and triiodothyronine concentrations in psychiatric patients and platelet MAO activities.

Other Factors

The hematocrit, hemoglobin, and platelet counts, serum iron, and iron-binding capacity are not significantly different in patients with low and normal MAO activity. Other platelet enzyme activities including succinate dehydrogenase, lactate dehydrogenase, and cytochrome C reductase also do not differ in chronic schizophrenic patients with low MAO activity and in controls.

Chronic Schizophrenics

To date we have studied platelet MAO activity in 62 male chronic schizophrenic patients (figure 3). Their mean plus or minus standard error MAO activity was 7.86 ± .56, while the value for 348 normal males (aged 18-50) was 11.04 ± .29. This difference, using a two-tailed t test, was significant at the .001 level. The mean for the 15 female chronic schizophrenics (figure 4) was 7.04 ± 1.06, while that for 332 normal females was 13.29 ± .29 (p < .001). To date we have not been able to find systematic differences related to length of illness or hospitalization (Murphy and Wyatt 1972, Murphy, Belmaker, and Wyatt 1974, Wyatt, Belmaker, and Murphy 1975, and Wyatt and Murphy 1975).

Acute versus Chronic Schizophrenics

To determine whether acute schizophrenics have a reduction in platelet MAO as did the chronic schizophrenics, the platelet MAO activity of 27 acute schizophrenics was studied. These patients were hospitalized on a special National Institute of Mental Health research ward in Bethesda, Md., supervised by Dr. William Carpenter (Carpenter, Murphy, and Wyatt 1975).
Figure 3. Distribution frequency of platelet MAO activity in normal, unipolar depressed, bipolar I depressed, chronic schizophrenic, and acute schizophrenic patients—male controls and patients.

- **CONTROLS (348)**
  \[ \bar{x} = 11.04 \]

- **CHRONIC SCHIZOPHRENIC**
  \[ \bar{x} = 7.86 \]

- **ACUTE SCHIZOPHRENIC**
  \[ \bar{x} = 10.68 \]

- **UNIPOLAR**
  \[ \bar{x} = 12.12 \]

- **BIPOLAR I**
  \[ \bar{x} = 7.47 \]

**BENZYLAMINE PLATELET MAO ACTIVITY (NM product/10⁶ platelets/hr)**

\( N \) = N

* p values for t-tests between patients and controls; chronic schizophrenic \( p < .001 \), acute schizophrenic not significant, unipolar not significant, bipolar I \( p < .001 \).
Figure 4. Distribution frequency of platelet MAO activity in normal, unipolar depressed, bipolar I depressed, chronic schizophrenic, and acute schizophrenic patients—female controls and patients.

- **CONTROLS** (332): $\bar{x} = 13.29$
- **CHRONIC SCHIZOPHRENIC** (15): $\bar{x} = 7.04$
- **ACUTE SCHIZOPHRENIC** (17): $\bar{x} = 13.85$
- **UNIPOLAR** (31): $\bar{x} = 13.00$
- **BIPOLAR I** (33): $\bar{x} = 11.01$

* p values for t-tests between patients and controls; chronic schizophrenic $p < .001$, acute schizophrenic not significant, unipolar not significant, bipolar I $p < .01$
male acute schizophrenics (aged 16-30) had a mean platelet MAO activity of 10.68 ± .78, which was not significantly different from that of normal males. The 17 female acute patients had a mean of 13.85 ± 1.12, which also was not significantly different from that of normal females.

Specificity with Regard to Other Illness

Since the various psychiatric diagnostic classifications are thought to represent different entities, a defect in one should not be seen in the other. The affective illnesses are the group we most diligently contrasted with the schizophrenias (Murphy and Weiss 1972).

Sixteen male and 13 female unipolar depressed patients were found to have platelet MAO activity that was no different from that of our controls, while 16 male and 33 female bipolar I depressed patients had significantly lower platelet MAO activity than controls \( (p < .001) \). The bipolar patients had a negative skew that was not so large as that of the chronic schizophrenics. Fewer than 10 percent of normal males and females were found to have platelet MAO activity less than 6 units and 8 units, respectively (table 2). Thirty-nine percent of male chronic schizophrenics and 60 percent of the female chronic schizophrenics had platelet MAO activities below these levels. The distributions were different in both sexes \( (p < .001) \). The bipolar patients also differed from normals \( (p < .001 \) for males; \( p < .02 \) for females). The male bipolar patients were not significantly different from the male chronic schizophrenic patients, but the percentage of female chronic schizophrenics with MAO activity below 8 units was significantly greater than that for the female bipolar I patients. Thus, using an arbitrary cutoff, bipolar I patients had a mean MAO that is low, but it is not yet clear whether they represent a separate group from the chronic schizophrenic patients.

Other Platelet MAO Studies in Schizophrenia

Using tryptamine and octopamine as substrates in a study of 15 normal controls, 10 acute schizophrenics,

1 Bipolar I depressed patients were differentiated from unipolar depressed patients on the basis of the occurrence of mania severe enough to require hospitalization or specific treatment in the bipolar patients.

and 12 chronic schizophrenics, Meltzer and Stahl (1974) found low platelet MAO activity in the chronic schizophrenics only. Using metaidobenzylamine and tyramine as substrates, however, both the acute and chronic patients were found to have low platelet MAO activity. Our own studies using tyramine as a substrate in 10 chronic schizophrenic patients produced mean activities in pmoles per milligram of protein per hour of 17.8 ± 1.95. The activity for 16 acute schizophrenics was 36.2 ± 3.86, while that for 19 normal controls was 37.5 ± 4.95. The difference between the chronic schizophrenics and controls was highly significant \( (p < .01) \).

Nies et al. (1974) reported on 12 schizophrenic subjects who had at least two unequivocal episodes of schizophrenic illness resulting in hospitalization for no longer than 4 months in any year and had not been hospitalized for more than 1 year during the last 5 years. When not hospitalized, the patients generally were able to go about their normal activities. These subjects might be called relapsing schizophrenics, since at the time of the study they certainly had not demonstrated the signs of chronicity our patients had. When platelet MAO activity was examined for these patients, using both benzylamine and tryptamine, it was found to be decreased.

A fourth study by J. Schildkraut and his colleagues (personal communication), using tryptamine as substrate, found a subgroup of schizophrenic patients identified on the basis of the presence of auditory hallucinations who had significantly lower platelet MAO activity than a group of schizophrenics without this symptom. Platelet MAO was not correlated with number of previous hospitalizations or length of time since the first hospitalization.

<table>
<thead>
<tr>
<th>Group</th>
<th>Males &lt; 6.0 (No./total)</th>
<th>Males &gt; 6.0 (No./total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>36/348</td>
<td>36/332</td>
</tr>
<tr>
<td>Chronic schizophrenic</td>
<td>1 24/62</td>
<td>1 9/15</td>
</tr>
<tr>
<td>Acute schizophrenic</td>
<td>0/10</td>
<td>1/17</td>
</tr>
<tr>
<td>Unipolar depressed</td>
<td>2/16</td>
<td>1/31</td>
</tr>
<tr>
<td>Bipolar I depressed</td>
<td>1 6/16</td>
<td>2 8/33</td>
</tr>
</tbody>
</table>

\( p < .001, \) differences from normals using chi-square.

\( p < .02, \) differences from normals using chi-square; \( p < .01, \) difference from chronic schizophrenics.
There are two published studies that failed to find MAO differences between schizophrenics and controls. In a study by Friedman et al. (1974), 26 schizophrenics were compared to 23 normals and 12 psychiatric patients with other diagnoses. Using an analysis of variance across the three cells, the authors found no differences. They did find within-cell differences between males and females (females greater than males) in the normal group. Reanalyzing these data, we found that when a two-tailed t test was used, the difference between normals and schizophrenic females was nearly significant (.05 < p < .10) and when a one-way Kruskal-Wallis analysis of variance was used to compare all the normals with all the schizophrenics, the difference was significant (p < .05).

In the other negative study (Shaskan and Becker 1974), 24 schizophrenics were compared to 15 controls (8 alcoholics and 7 staff members). There was no difference in MAO activity between the groups. The schizophrenics did seem to fall into a high-low distribution and may represent the acute-chronic bimodal distribution we have observed. Further, combining alcoholics with normals may not represent a good control group unless it is demonstrated that alcoholics are not on the same continuum with schizophrenics.

**Twins Discordant for Schizophrenia**

To exclude the possibility that the low platelet MAO activity seen in the chronic schizophrenics was caused by nongenetic factors as opposed to genetic ones, we studied monozygotic twins discordant for schizophrenia (Wyatt et al. 1973). If the low platelet MAO activity were due to some aspect of being schizophrenic, low platelet MAO should only be present in the schizophrenic twin. Thirteen schizophrenic index twins, all of whom had been hospitalized at least once for schizophrenia and had been extensively studied by Dr. William Pollin and his associates, were examined along with their nonschizophrenic co-twins (figure 5). At the time of the study, one patient was hospitalized, while five were in remission. Four of the patients had had acute forms of schizophrenia, and six patients were not receiving any antipsychotic medication. The nonschizophrenic co-twins had never been hospitalized for a behavioral disorder and were functioning well within their families and communities, except for one individual with borderline psychosocial adjustment.

Only two twin pairs were living in the same household, and nine of these co-twins were living in different cities. It was necessary, therefore, to obtain and prepare the blood samples at various facilities throughout the country. Because of this factor, normal control samples were obtained at the same time as those from the twins. They were coded and shipped to the laboratory. All samples were assayed together. (In all studies, samples are run in a manner ensuring that their origins remain unknown to investigators until the final calculations are made.)

The mean MAO activity of the 23 normal controls obtained at that time was the same as that for previous controls (16.02). The platelet MAO activities of schizophrenic twins (9.88, p < .005) and nonschizophrenic twins (12.08, p < .05) were significantly lower than that for the normals, but there was no difference between the twin groups. There was a significant Pearson correlation \(r = .67, p < .01\) between the MAO activities in the schizophrenic and nonschizophrenic twins.

Examination of figure 5 reveals that there were four pairs of twins whose MAO activities were especially low. The index twins of all four of these twin pairs were chronic schizophrenics, while the more acute patients had MAO activities closer to normal. The severity of impairment (based on number and duration of hospitalizations) was rated on a 5-point scale for the schizophrenic twins by an investigator with no knowledge of the platelet assay. A forced rank order was then made between the numerical ratings, with the highest number given to the most ill patient. Using this order, and comparing it to the MAO activities, a Spearman rank-order correlation of \(-.54 (p < .05)\) was found.

Platelet MAO activity was also examined in nine monozygotic and 10 dizygotic normal twins (Murphy, Belmaker, and Wyatt 1974). The intraclass correlation coefficient was .88 for the monozygotic and .45 for the dizygotic twins. The correlations were significantly different from one another (Mann-Whitney \(U\), \(p < .001\)). Same-sex siblings matched for age and sex were about the same as the dizygotic twins, while unrelated pairs were not significantly correlated with each other. These results are similar to those reported by Nies et al. (1973) for normal monozygotic and dizygotic twins using benzylamine instead of tryptamine as a substrate.

Taken together, these data indicate that platelet MAO activity is in a large part determined by genetic factors.
Figure 5. MAO activity in 23 normal and 13 pairs of monozygotic twins discordant for schizophrenia. Correlation is between discordant twins ($p < .01$).

\[ r = 0.67 \]
and that the low platelet MAO activity seen in the chronic schizophrenic is not simply secondary to being ill, but is, at least in part, genetically related to vulnerability to being schizophrenic.

**Family Studies**

In order to study further the relationship of low platelet MAO to schizophrenia, the enzyme activity of first-degree nonschizophrenic relatives of index schizophrenics (N = 16) was studied (table 3). Dividing schizophrenic indexes at their median, we found that the low indexes had a mean of 4.64 and the high indexes had a mean of 10.81. The mean MAO activity for the low-index, first-degree relatives was 8.56. The mean activity for high-index, first-degree relatives was 11.84. The difference between the means for the low versus high first-degree relatives was significant (p<.02; Mann-Whitney U). No attempt was made in this small sample to account for sex differences. These differences between nonschizophrenic first-degree relatives of high and low schizophrenics are another indication of the genetic nature of platelet MAO activity.

**Physical-Chemical Studies**

To date we have found no physical differences between the low and normal platelet MAO. The K_m's (the Michaelis constant—numerically equal to the substrate concentration that gives half-maximal velocity) from six schizophrenic patients using tryptamine as substrate (all below 8.37 units benzylamine) and from eight normals were nearly identical (4.1 X 10^{-5} and 4.3 X 10^{-5} M). The heat inactivation curves for both groups showed reductions in activity at 50°C that were not different for the two groups. The platelet MAO is not easily solubilized, a problem that has, to date, prevented reliable electrophoretic studies. Dialysis of platelet sonicates from 10 schizophrenic patients and 7 controls did not reveal any postdialysis differences in activity between schizophrenic patients and controls (Murphy and Wyatt 1972).

**Function**

To determine whether the low platelet MAO activity might have a functional significance, platelet-rich plasma was obtained from 20 normal controls (mean age, plus or minus the standard error = 29.6 ± 1.1) and 16 chronic schizophrenic patients (mean age = 27 ± 1.4) (Garelis et al. 1975). Since plasma serotonin is almost entirely contained in the platelet, the values were expressed in platelet units (nanograms per 108 platelets). The platelet counts for the normals and schizophrenics were the same. When 12 of the patients had been off phenothiazines for 30 days or longer, the serotonin concentration was higher (p<.01) in the schizophrenics (127 ± 12) than in the normals (80 ± 4); when the 12 patients were taking phenothiazines, platelet serotonin concentration was normal (90 ± 9). The reason for the discrepancy between values for patients when they were taking and when they were not taking phenothiazines may be due to the ability of these drugs to block serotonin uptake into platelets. Since serotonin is not a good substrate for platelet MAO (K_m > 10^{-3}), other substrates might be much more affected.

**Relationship of Platelet MAO to Brain MAO**

The number of types of MAO’s present in the brain is an unresolved question. Original studies (Sandler and Youdim 1972) indicated that there might be as many as four isoenzymes of MAO within the brain. Recently, Houslay and Tipton (1973) suggested that the multiple enzymes found using polyacrylamide-gel electrophoresis might be artifacts produced in a preparatory step. They propose that these multiple MAO forms may represent a
single protein with varying amounts of phospholipid attached; the amount of phospholipid may in turn determine the enzyme mobility during electrophoresis.

Another approach to this problem has come from the finding that selective inhibition of MAO can be used to identify multiple forms of MAO. Clorgyline was the first MAO inhibitor employed in this manner (Johnston 1968). It was found that tissue homogenates pretreated with increasing concentrations of clorgyline produced stepwise inhibition to the substrate tyramine, suggesting the presence of an enzyme sensitive to the inhibitor and one relatively resistant to it. Considerably more work has been done to identify these enzymes, and for convenience they are called type A and type B (Yang and Neff 1973).

The preferred substrates for the type A MAO are norepinephrine, serotonin, and normetanephrine, while for the type B MAO, they are benzylamine and \( \beta \)-phenylethylamine. Dopamine, tyramine, and tryptamine are common substrates. Clorgyline, Lilly 51641, and harmaline are specific inhibitors of type A, while deprenyl and pargyline inhibit type B. Most of the other MAO inhibitors used in clinical medicine, however, are nonspecific. Platelet MAO, forming one band on electrophoresis, appears to be a single enzyme with type B characteristics. That is, the platelet enzyme demonstrates only a single sigmoid curve for inhibition using deprenyl, pargyline, or clorgyline (Murphy and Donnelly 1974). Furthermore, the platelet enzyme is 200-fold more sensitive to inhibition to deprenyl than clorgyline. The conclusion that the platelet enzyme is a simple type B MAO is also supported by the high activity of the platelet enzyme with the relatively specific MAO-B substrates, benzylamine and \( \beta \)-phenylethylamine, in contrast to its lesser activity with serotonin, an A substrate (Murphy and Donnelly 1974 and Robinson et al. 1968).

**MAO in the Brain and Liver of Schizophrenic Patients**

Birkhäuser (1941), studying the putamen and globus pallidus of eight schizophrenics and six normals, found a 15-percent reduction in MAO activity. In 1955, Takahashi found a 40-percent increase in MAO activity in biopsied liver tissue in 25 schizophrenic patients compared to 14 non-schizophrenic patients. Utena et al. (1968), comparing 5 chronic schizophrenics and 15 patients without mental illness, found no difference in brain MAO activity in any of 24 regions studied; when the areas were organized into functional units including hypothalamus, tegmentum, and striatum, however, the schizophrenics had lower MAO activity in these regions. Finally, three recent studies (Domino, Krause, and Bowers 1973, Vogel, Orfei, and Century 1969, and Wise, Baden, and Stein 1974) have failed to find differences in brain MAO activity using methods very similar to those used for our platelet assay.

In order to examine further the apparent contradiction described above, we studied 15 regions of autopsied brain from nine chronic schizophrenics and nine persons without history of psychiatric illness (Schwartz, Aikens, and Wyatt 1974). Using tryptamine as a substrate, there was no difference in mean MAO activity in any region examined. The brains were subsequently examined using serotonin and clorgyline to test for MAO-A, and \( \beta \)-phenylethylamine and deprenyl for MAO-B. Again, there were no differences in mean MAO activity between the schizophrenics and controls (Schwartz et al. 1974).

**Discussion**

Platelet MAO activity has now been reported from four laboratories to be low in some schizophrenics. Two other laboratories did not find this difference. Aside from a number of methodological problems such as reliability of the assay, a more serious question arises: What do we mean when we diagnose someone as schizophrenic? As part of that question, how are we defining acute, chronic, as well as the intermediate phases of the illness. This seems to be a particularly important question because both Meltzer's (Meltzer and Stahl 1974) and our laboratories find the MAO abnormality in chronic patients while we do not find it in acute patients. Meltzer and Stahl (1974) found a difference in MAO activity between acute schizophrenics and controls but only with certain substrates.

This review is not the proper vehicle for an effort to define the differences between the acute and chronic forms of the syndrome. If others are to be able to replicate our findings, however, it is important to try to be as clear as possible as to who the patients are that we find have low platelet MAO activity. The chronic schizophrenics (about 40 percent of whom have low platelet MAO) that we are studying are generally patients who have been continuously hospitalized for 2 or more years, are either undifferentiated or paranoid (in the latter
case, they may not always have a formal thought disorder), and are only minimally responsive to neuroleptic drugs. Historically, they seem to have had considerable life disruption prior to their first hospitalization. We are currently attempting more precise definitions and also to understand who the controls are who also have low platelet MAO activity.

What does it mean to have low platelet MAO activity in view of seemingly normal brain MAO activity? The argument that postmortem measurement of brain MAO activity does not reflect its true activity because of autolysis has little support since brain MAO seems to be a very stable enzyme. It remains a possibility, of course, that we have either not measured brain MAO activity in the right region or with correct methods—an argument that is not easily dealt with.

Enzyme activity must now be measured in other regions of the body, such as the muscle, lung, liver, and kidney. If these areas turn out to have normal MAO activity while the platelet is low, intriguing explanations will be needed.

Part of the attractiveness of the concept of low MAO activity is that it is congruent with the two most generative biological hypotheses of schizophrenia. The first of these suggests that there is a functional excess of dopamine. A defect of MAO, an enzyme involved in dopamine metabolism, might be able to produce "dopamine excess." The second hypothesis suggests the formation of a hallucinogenic methylated indoleamine (transmethylation). Since the indoleamines, as well as their methylated congeners, are metabolized by MAO, this theory is also consistent with a finding of low MAO activity. One of many questions that must be answered before low MAO activity can be considered causative is, Why don't the vast majority of people given drugs that inhibit MAO become psychotic?

If the deficit in platelet MAO activity is real, we cannot describe it beyond an in vitro inability to metabolize certain substrates. Preliminary physical chemical studies have not yielded any consistent difference between the low and normal platelet MAO. Clearly, further studies along these lines are necessary.

References


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