Platelet Monoamine Oxidase in Families of Chronic Schizophrenics

by Wade H. Berrettini, Thomas C. Benfield, Anna O. Schmidt, Robin K. Ladman, and Wolfgang H. Vogel

Abstract

Many reports have described low platelet monoamine oxidase (MAO) activity in chronic schizophrenia. In an effort to determine whether this low activity is genetically controlled, the authors studied platelet MAO activity in the first-degree relatives of 12 chronic schizophrenics (who themselves had low platelet MAO activity). The 29 relatives had significantly lower mean $V_{\text{max}}$ and $K_m$ values than a control group. The authors postulate that the low platelet MAO activity among chronic schizophrenics may be a genetic marker for vulnerability to chronic schizophrenia.

Seven years ago, Murphy and Wyatt (1972) first described decreased platelet monoamine oxidase (MAO) activity among chronic schizophrenics. Since that time, numerous investigations have confirmed their report (Berger et al. 1978; Berrettini, Prozialeck, and Vogel 1978; Nies et al. 1974; Schildkraut et al. 1976; Sullivan et al. 1978; Zeller et al. 1975), but several have failed to replicate it (Friedman et al. 1974; Groshong et al. 1978; Owen et al. 1976). It has been suggested that this reduced activity of platelet MAO may be a genetic marker for a predisposition to develop chronic schizophrenia (Wyatt et al. 1973). There is good evidence that MAO activity is genetically determined (Leckman et al. 1977; Nies et al. 1973; Pandey et al. 1979; Wyatt et al. 1973). If low platelet MAO activity is a genetic marker for vulnerability to chronic schizophrenia, then the first-degree relatives of chronic schizophrenics (with low MAO activity) should have a lower mean MAO value than a similar group of controls without the positive family history. This hypothesis is based on the well-described fact that first-degree relatives of chronic schizophrenics have a 10-fold increased risk (compared to the general population) of developing the disorder. To test this hypothesis, we studied first-degree relatives of 12 chronic schizophrenics, all of whom had low platelet MAO activity, as previously defined (Berrettini and Vogel 1978).

Methods

The clinical characteristics of the 12 patients have been previously described (Berrettini, Prozialeck, and Vogel 1978). In addition, these patients satisfied Research Diagnostic Criteria for chronic schizophrenia (Spitzer, Endicott, and Robins 1975) and all had low platelet MAO activity. Both patients and all participating family members gave informed consent. All first-degree relatives were free of current major illness and had no history of iron-deficient anemia or platelet pathology. In only three families were all first-degree relatives available.

Of the 29 relatives studied, only one had been hospitalized for schizophrenia. One relative was identified as addicted to alcohol, and had multiple convictions for robbery and possession of drugs. All participating relatives underwent brief psychiatric examinations, which revealed only one additional relative as having a nonpsychotic psychiatric illness.

The details of the enzyme preparation and assay have been described previously (Berrettini and Vogel 1978). Maximal velocity ($V_{\text{max}}$) and
the Michaelis constant ($K_m$) were estimated by plotting $V$ against $V/S$, where $V$ is enzyme velocity and $S$ is substrate concentration. The best line through the resulting points of this plot was determined by the least squares method of linear regression.

**Results**

The results are given in table 1. Seven relatives (24 percent) from four different families had $V_{\text{max}}$ and $K_m$ values less than 2 standard deviations below the mean control values.

**Discussion**

It is to be expected that the patients' mean $V_{\text{max}}$ and mean $K_m$ values are lower than those of the controls, for these patients were selected using low MAO values as one of the criteria. It is interesting that the patients’ mean $K_m$ is very similar to that of the relatives, but the patients' mean $V_{\text{max}}$ is significantly lower than the mean $V_{\text{max}}$ of the relatives. This significant difference between the relatives and the patients probably reflects the fact that these patients were chosen for their very low $V_{\text{max}}$ values. However, we cannot rule out an environmental or treatment artifact as the cause for this $V_{\text{max}}$ difference.

It is noteworthy that the relatives’ mean $K_m$ and mean $V_{\text{max}}$ are significantly lower than the means for the controls. The same is true for the patients' values, which supports the concept of genetic control of platelet MAO activity.

These data support the conclusions of several investigators who have conducted similar studies. Wyatt et al. (1973) found a high intratwin pair correlation of platelet MAO activity among 13 sets of twins discordant for schizophrenia. In studying normal twins, Nies et al. (1974) found that dizygotic twins showed more intratwin pair variance than did monozygotic twins. In a recent study of 112 normal families, Pandey et al. (1979) concluded that the parent–offspring correlations and the sibling-sibling correlations indicated that genetic factors control platelet MAO activity to a substantial extent. Leckman et al. (1977) studied the first-degree relatives of patients with manic-depressive illness; they concluded that the most striking finding was the generalized reduction of MAO activity among those families whose ill member(s) also showed reduced activity. Wyatt et al. (1978) studied platelet MAO activity in the first-degree relatives of 16 chronic schizophrenics; the patients were separated into a high MAO group ($n = 8$) and a low MAO group ($n = 8$). The relatives of the low MAO group had significantly reduced activity when compared to the relatives of the high MAO group.

Thus there seems to be substantial evidence to suggest that the kinetically different MAO found in chronic schizophrenics may be on a genetic basis. The current study is the only one, to our knowledge, to establish this apparently genetic difference, in kinetic terms, for chronic schizophrenia. The mechanism through which this kinetic alteration occurs remains unknown. The platelet enzyme is not altered electrophoretically (Belmaker et al. 1976). It has been suggested that an endogenous inhibitor may be responsible for the kinetic difference (Berrettini and Vogel 1978), but this is highly controversial (Wise et al. 1979).

**Table 1. Platelet MAO activity in first-degree relatives of chronic schizophrenics who have low MAO values**

<table>
<thead>
<tr>
<th>Subjects</th>
<th>$n$</th>
<th>$V_{\text{max}}^{1} \pm \text{SD}$</th>
<th>$K_m \times 10^{2} \pm \text{SD}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>12</td>
<td>6.9±1.5</td>
<td>3.0±1.2</td>
</tr>
<tr>
<td>Relatives</td>
<td>29</td>
<td>12±6.2</td>
<td>3.0±1.6</td>
</tr>
<tr>
<td>Controls</td>
<td>13</td>
<td>16±3.8</td>
<td>4.4±1.5</td>
</tr>
</tbody>
</table>

Note.—Patients’ $V_{\text{max}}$ ($p < .001$) and $K_m$ ($p < .02$) were lower than those of controls; patients’ $V_{\text{max}}$ ($p < .01$) was lower than that of relatives; relatives’ $V_{\text{max}}$ ($p < .03$) and $K_m$ ($p < .05$) were lower than those of controls. Two-tailed $t$ tests were used in all comparisons.

$1$ $V_{\text{max}}$ in nanomoles dopamine/mg protein/hr.

**References**


Friedman, E.; Shopsin, B.; Sathananthan, G.; and Gershon, S. Blood platelet monoamine oxidase activity in psychiatric patients. *American

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