Platelet Monoamine Oxidase in Affective Illness and Alcoholism

by Robert H. Belmaker, Haim S. Bracha, and Richard P. Ebstein

Abstract

The authors review the literature on the relationship of platelet monoamine oxidase (MAO) to affective disorders and alcoholism. Although some studies have reported an association between low platelet MAO and bipolar illness, others have failed to replicate this finding. Alcoholism has been related to affective disorders, and it is of note that three studies have found low MAO in alcoholics. Given the physiological consequences of alcoholism, however, the interpretation of these findings is unclear. The authors conclude that non-specificity of low platelet MAO as a possible correlate of bipolar affective disorder, as well as schizophrenia, increases the burden of proof necessary before findings of low platelet MAO can be accepted as primary.

The conflicting reports on platelet monoamine oxidase (MAO) in schizophrenia have been reviewed previously (Wyatt, Potkin, and Murphy 1979). However, the number of reports on platelet MAO in affective disorder has only recently become large enough to necessitate review. This is true despite the fact that the first report of low platelet MAO in manic-depressive illness (Murphy and Weiss 1972) was published in the same year as the first report of low platelet MAO in schizophrenia (Murphy and Wyatt 1972). Reasons for the relative paucity of platelet MAO studies in manic-depressive illness may include the greater difficulty of finding large patient populations for study in manic-depressive illness, and also the less impressive reduction in MAO activity in the original report on manic-depressive patients compared with the original report on schizophrenic patients. Some investigators have even suggested that the small reduction of platelet MAO activity in bipolar manic-depressives may be an artifact of contamination of the patient sample with schizophrenic patients, as diagnostic criteria for bipolar illness have widened considerably at the expense of schizophrenia in recent years.

Eight reports are available on platelet MAO in affective disorder as of this review (Belmaker et al. 1976; Edwards et al. 1978; Fieve et al., in press; Landowski, Lysiak, and Angielski 1975; Leckman et al. 1977; Murphy and Weiss 1972; Nies et al. 1974; and Sullivan et al. 1977). Three studies can be said to have at least partially replicated the original findings of reduced platelet MAO activity in bipolar patients (Landowski, Lysiak, and Angielski 1975; Leckman et al. 1977; Sullivan et al. 1977); three studies have not achieved replication, including one which found significantly increased platelet MAO activity in bipolars (Belmaker et al. 1976; Edwards et al. 1978; Nies et al. 1974); and one study found a reduction in bipolar females only compared with controls and a much more marked reduction in unipolar males (Fieve et al., in press). Most studies (Murphy and Weiss 1972; Nies et al. 1974) have not found any platelet MAO reduction in unipolar patients. The problem, as with the issue of platelet MAO in schizophrenia, is how to make sense of these conflicting data without discussing how many angels can dance on the head of a pin, but also without prema-

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Table 1. Platelet MAO in affective disorder

<table>
<thead>
<tr>
<th>Studies</th>
<th>Clinical state</th>
<th>Substrate</th>
<th>No. of patients</th>
<th>No. of controls</th>
<th>Drugs</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Murphy and Weiss (1972)</td>
<td>Depressed inpatients</td>
<td>Tryptamine</td>
<td>Unipolar=34, bipolar=23</td>
<td>52</td>
<td>Drug-free</td>
<td>Bipolars=65% controls; Unipolars=controls</td>
<td></td>
</tr>
<tr>
<td>Nies et al. (1974)</td>
<td>Depressed inpatients</td>
<td>Benzyamine</td>
<td>Unipolar=176, bipolar=26</td>
<td>162</td>
<td>Drug-free</td>
<td>Affective disorders &gt; controls</td>
<td>Bipolars=unipolars</td>
</tr>
<tr>
<td></td>
<td>and outpatients</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Landowski et al. (1975)</td>
<td>Depressed inpatients</td>
<td>Benzyamine</td>
<td>Unipolar=35, bipolar=13</td>
<td>30</td>
<td>Drug-free</td>
<td>Bipolars=59% controls; Unipolars=controls</td>
<td>MAO up with remission</td>
</tr>
<tr>
<td>Belmaker et al. (1976)</td>
<td>Euthymic</td>
<td>Benzyl, trypt</td>
<td>Bipolar=27</td>
<td>19</td>
<td>All on lithium</td>
<td>Bipolars &gt; controls</td>
<td></td>
</tr>
<tr>
<td>Leckman et al. (1977)</td>
<td>Euthymic</td>
<td>Benzyamine</td>
<td>Bipolar=75</td>
<td>680</td>
<td>All on lithium</td>
<td>Bipolars=70-80% controls</td>
<td>Relatives low</td>
</tr>
<tr>
<td>Sullivan et al. (1977)</td>
<td>Manic inpatients</td>
<td>Tryptamine</td>
<td>Bipolar=24</td>
<td>27</td>
<td>Drug-free</td>
<td>Bipolars=73% controls</td>
<td>Controls=medical inpatients</td>
</tr>
<tr>
<td>Edwards et al. (1978)</td>
<td>Depressed inpatients</td>
<td>Tryptamine</td>
<td>Unipolar=42, bipolar=19</td>
<td>32</td>
<td>Drug-free</td>
<td>Bipolars=unipolars=controls</td>
<td>Increased variance in bipolars</td>
</tr>
<tr>
<td>Fieve et al. (in press)</td>
<td>Euthymic outpatients</td>
<td>Tryptamine</td>
<td>Unipolar=20, bipolar=86</td>
<td>34</td>
<td>All on lithium</td>
<td>Bipolar females = 75% controls; unipolar males = 72% controls</td>
<td>Controls = relatives and spouses</td>
</tr>
</tbody>
</table>

Platelet MAO in alcoholism

<table>
<thead>
<tr>
<th>Studies</th>
<th>Clinical state</th>
<th>Substrate</th>
<th>No. of patients</th>
<th>No. of controls</th>
<th>Drugs</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brown (1977)</td>
<td>Abstinent</td>
<td>Benzyamine</td>
<td>14</td>
<td>14</td>
<td>Drug-free</td>
<td>Alcoholics low</td>
<td></td>
</tr>
<tr>
<td>Major and Murphy (1978)</td>
<td>Withdrawal</td>
<td>Benzyamine</td>
<td>99</td>
<td>84</td>
<td>Drug-free</td>
<td>Alcoholics reduced 13%</td>
<td></td>
</tr>
<tr>
<td>Sullivan et al. (1978)</td>
<td>Acute and followup</td>
<td>Tryptamine</td>
<td>27</td>
<td>20</td>
<td>Drug-free</td>
<td>Alcoholics reduced 20-30%</td>
<td></td>
</tr>
</tbody>
</table>
turally giving up on one of the few possible etiologic leads we have for research in the major psychoses.

Table 1 shows that there is both one clearly positive (Leckman et al. 1977) and one clearly negative study (Belmaker et al. 1976) in which all the patients are taking lithium. Similarly, there is a clearly positive (Murphy and Weiss 1972) and a clearly negative (Edwards et al. 1978) study in which all the patients are drug free. (This issue is of importance because of the single report by Bockar, Roth, and Heninger, 1974, that lithium therapy can increase platelet MAO. Another study by Berrettini, Vogel, and Ladman, 1979, found no effect of lithium on platelet MAO.) There are clearly positive reports and clearly negative reports using both benzylamine and tryptamine as substrate. Finally, there are clearly positive and clearly negative reports with inpatients and outpatients. Thus, the explanations for the conflicting data are not obvious. As with platelet MAO in schizophrenia, further research may depend on sophisticated biochemistry and analysis of the platelet MAO enzyme itself, in an attempt to find molecular abnormalities. Further replication attempts using simple MAO activity will probably not be useful for resolution of the conflicting data.

Leckman et al. (1977) found in a family study that family members of bipolar patients also have reduced platelet MAO, but the reduction is unrelated to the presence or absence of affective illness in the family members. This genetic study suggested that low platelet MAO is not genetically correlated with affective illness. Pandey et al. (1979) have found, however, that low platelet MAO activity is a marker of affective disorder in the relatives of bipolar patients; moreover, low platelet MAO activity and high red blood cell lithium ratio behaved as additive predictors in an exciting multivariate genetic approach. Schildkraut et al. (1978) have reported increased platelet MAO activity in schizophrenia-related depressive disorders. It would seem impossible to fit such a finding into any possible theoretical connection between such disorders and schizophrenia on the one hand or bipolar illness on the other hand.

Alcoholism has been genetically related to affective illness, and it is logical that three recent reports (Brown 1977; Major and Murphy 1978; Sullivan et al. 1978) have studied platelet MAO in alcoholism. All three publications so far are in agreement on a reduction in platelet MAO in alcoholism, and all the groups were careful to study the alcoholics when physically recovered as well as when ill. However, alcoholism is a clearly recurrent illness with known severe physiological consequences. It is doubtful that reports of low platelet MAO in alcoholism would carry much weight a priori if it were not for the findings in schizophrenia and manic-depressive illness. The meaning of low platelet MAO activity will have to be unraveled in the psychoses before the alcoholism finding can be intelligently interpreted. What is clear is that low platelet MAO does not respect the schizophrenic spectrum as defined in genetic studies (Rosenthal et al. 1971), since this spectrum has quite clearly excluded bipolar illness (and also usually alcoholism).

The concept of a genetic spectrum correlated with low platelet MAO activity has been expanded by Buchsbaum, Coursey, and Murphy (1976) to include vulnerability to psychiatric disorder in a random sample of college student volunteers. However, one must always remember that correlation does not imply causation. Data presented by Wyatt (this conference) suggest strong correlations between height and platelet MAO. Could it be that fat college students have protein-laden platelets with low platelet MAO per protein, and also have a predisposition to psychiatric disorder? If so, low platelet MAO would be an effect and not a cause of vulnerability to psychiatric disorder. Such a possibility would not be excluded by evidence of genetic control of platelet MAO activity, since such genetic control might be mediated via genetic influences on dietary habits and body build. Considerable research has been invested in the relationship between serum cholesterol and personality. Genetic factors influence serum cholesterol, and serum cholesterol correlates with numerous psychologic variables. However, no one would claim that serum cholesterol is a cause rather than an effect of personality. The fact that MAO is an enzyme and enzymes are built on DNA templates should not seduce us into believing that platelet MAO activity per mg protein or per platelet (young or old) must be a primary cause or marker and not an effect. The nonspecificity of low platelet MAO as a possible correlate of bipolar affective disorder as well as of schizophrenia increases the burden of proof necessary before we can accept low platelet MAO as primary.

References


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