Brain and Skeletal Muscle Monoamine Oxidase Activity in Schizophrenia

by Herbert Y. Meltzer, Herbert Jackman, and Ramesh C. Arora

Abstract

Monoamine oxidase (MAO) activity has been studied in postmortem brain specimens from chronic schizophrenics and comparison groups by various laboratories. There is no evidence for decreased MAO activity in the brains of the schizophrenic patients, but many possible sources of error in postmortem studies make the conclusions of these studies less than definitive. However, since almost complete inhibition of brain MAO activity appears necessary before it has any functional significance, reduced brain MAO activity is unlikely to have any significance for the pathogenesis of psychosis. Brain and platelet MAO activities in man have been found not to be significantly correlated with each other. There is some evidence that neuroleptic drugs may inhibit human brain MAO activity in vitro, but indirect evidence from spinal fluid and postmortem studies is not consistent with this.

Decreased MAO activity has been found in the skeletal muscle of various types of psychotic patients compared to normal controls. This suggests decreased MAO activity in peripheral tissues may be a non-specific marker for vulnerability to the development of psychopathology.

Monoamine oxidase (MAO) activity in schizophrenic patients has been studied in tissues other than blood platelets. Since the enzyme may be found in all mitochondrial-containing tissues, almost any tissue may be used to compare the activity of MAO in schizophrenic patients and normal controls or other comparison groups. We will review here studies on the MAO activity in brain and skeletal muscle of schizophrenics, other psychotic patients, and normal controls.

Postmortem Studies of Brain MAO Activity in Schizophrenic Patients

There have been eight published studies of MAO activity in postmortem brain specimens obtained from schizophrenics and normal controls (table 1). Birkhäuser (1941) reported a slight decrease in the MAO activity of the globus pallidus and putamen in schizophrenics under age 60 compared to age-matched normal controls, but the method used (oxygen consumption) was not especially reliable. Yutaka et al. (1968) also found low MAO activity, with serotonin (5HT) as a substrate, in the caudate nucleus and putamen of two of five chronic schizophrenics.

None of the other six publications cited in table 1 reported any significant difference in the brain MAO activity of various regions of the brain, using a wide range of substrates of MAO including 5HT, tryptamine, phenylethylamine (PEA), benzylamine (BA), tyramine (TYR), or dopamine (DA). In all, a total of 74 brains from schizophrenic patients and 56 control subjects have been studied. The study of Crow et al. (1979) may be the best of the group because the control subjects and schizophrenics were closely matched for age, sex, and conditions of storage of the bodies after death before the brain specimens were obtained. Crow et al. (1979) measured MAO activity in each of the 14 brain areas.
with four substrates, including BA, 5HT, TYR, and DA. No significant differences or trends toward differences were found.

Postmortem studies of schizophrenic brains must always be viewed cautiously for a variety of reasons. The diagnoses of the patients are frequently based on inadequate case records. The control material may also be of uncertain psychiatric and medical history. The effects on MAO activity of very prolonged use of psychotropic drugs or drugs used to treat the patient's terminal illness and of agonal changes are often unknown or only estimated from studies in small laboratory animals. Variations in the rate of freezing of the brain after death, storage conditions, and difficulties in dissection of the brain may make postmortem studies unreliable. The crucial period for determination of MAO activity may be during the early phase of the illness, but all postmortem studies have been carried out on older, chronic populations. It has been established that MAO activity increases with age (Robinson et al. 1971), but whether the age-related increase occurs at the same rate in schizophrenics and normal controls is not known. This point is not trivial in light of recent suggestions based on computerized tomographic studies that schizophrenics have prematurely aged brains (Weinberger et al. 1980).

Despite these considerations, one can reasonably conclude that there is no gross deficiency in the brain MAO activity of most schizophrenics. The significance of this finding should be considered in the context of the extensive evidence that MAO activity must be inhibited nearly completely before any functional significance is to be expected (Green et al. 1977). Based on the available data, we cannot exclude the possibility that there are small regions of the brain in some, if not all, schizophrenics, which have major deficiencies in MAO activity for some or all substrates. This seems unlikely, however, and one cannot advocate undertaking the large-scale studies that would be needed to investigate this possibility.

Effect of Neuroleptics on Brain MAO Activity

There is some evidence that neuroleptic drugs can produce very slight inhibition of rat brain MAO activity (Arora and Meltzer 1976). Roth et al. (1979) have recently reported that chlorpromazine (CPZ) and eight of its pharmacologically active metabolites produced significant inhibition of human brain frontal lobe MAO activity. A concentration of 20 nM of CPZ and its metabolites were tested for inhibition of MAO activity in vitro using a type A MAO substrate, 5HT, and a type B MAO substrate, PEA. Most of the metabolites inhibited type A MAO slightly more than type B MAO with the exception of 7,8-dioxo CPZ which inhibited 5HT metabolism 10-fold more potently than PEA metabolism. Roth et al. (1979) suggest that since the chronic administration of CPZ may produce 30-40 percent inhibition of MAO, it may be important to consider the functional significance of inhibition of MAO by neuroleptics.

There is some evidence that cere-

Table 1. Brain MAO activity of schizophrenia

<table>
<thead>
<tr>
<th>Studies</th>
<th>No. of patients</th>
<th>No. of controls</th>
<th>Substrate</th>
<th>No. of regions</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birkhäuser (1941)</td>
<td>8</td>
<td>6</td>
<td>—</td>
<td>5</td>
<td>Schiz. MAO activity 15% less in putamen and pallidum</td>
</tr>
<tr>
<td>Utena et al. (1968)</td>
<td>5</td>
<td>5</td>
<td>5HT</td>
<td>24</td>
<td>No significant differences</td>
</tr>
<tr>
<td>Vogel, Orfei, and Century (1969)</td>
<td>5</td>
<td>5</td>
<td>Tryptamine</td>
<td>12</td>
<td>No significant differences</td>
</tr>
<tr>
<td>Domino, Krause, and Bowers (1973)</td>
<td>11</td>
<td>6</td>
<td>Tryptamine</td>
<td>15</td>
<td>No significant differences</td>
</tr>
<tr>
<td>Wise, Baden, and Stein (1974)</td>
<td>18</td>
<td>12</td>
<td>Tryptamine</td>
<td>3</td>
<td>No significant differences</td>
</tr>
<tr>
<td>Schwartz, Aikens, and Wyatt (1974a)</td>
<td>9</td>
<td>9</td>
<td>Tryptamine</td>
<td>3</td>
<td>No significant differences</td>
</tr>
<tr>
<td>Schwartz et al. (1974b)</td>
<td>9</td>
<td>8</td>
<td>PEA, 5HT</td>
<td>14</td>
<td>No significant differences</td>
</tr>
<tr>
<td>Crow et al. (1979)</td>
<td>9</td>
<td>10</td>
<td>5HT, BA, TYR, DA</td>
<td>14</td>
<td>No significant differences</td>
</tr>
</tbody>
</table>

Note.—5HT = serotonin; PEA = phenylethylamine; BA = benzylamine; TYR = tyramine; DA = dopamine.
brosspinal fluid levels of 5-hydroxyindoleacetic acid (5HIAA), the major oxidative metabolite of 5HT, are decreased by 4 weeks' treatment with CPZ (Wode-Helgord et al. 1977). However, Bjerkens et al. (1977) found that neither melperon or thiothixene treatment for 4 weeks significantly affected CSF 5HIAA levels, while Rüther et al. (1976) reported increased CSF 5HIAA levels after 15 days' treatment with haloperidol.

Winblad et al. (1979a) found a trend toward decreased levels of 5HIAA in the cingulate and frontal cortex of deceased schizophrenics, all of whom were treated with neuroleptics, but the number of patients studied (two-four) was very small, and there was less difference in 5HIAA levels between patients and controls (n = 9-12) in the hypothalamus, caudate nucleus, or puta-

ten, where 5HIAA levels are much higher. Effects of diet and disease factors per se may have contributed to differences between the patients and controls, since there was also evidence for decreased brain 5HT levels in the patients. The concentra-

tion of homovanilliac acid (HVA), the major metabolite of dopamine, did not differ in any of the various brain areas (Winblad et al. 1979a).

Bacopoulos et al. (1979) recently reported a study of the levels of HVA in five brain regions from deceased neuroleptic-treated schizophrenics, nondrug-treated schizophrenics, and normal controls. There was a tendency for the neuroleptic-treated patients to have higher HVA levels in all brain regions. This was statistically significant only in the temporal cortex, cingulate cortex, and orbital frontal cortex. The neurolepticinduced increase in HVA probably reflects increased DA turnover due to blockade of postsynaptic DA recep-
tors. These data do not suggest neuroleptic treatment produces signif-

icant inhibition of the ability of brain MAO to metabolize DA, al-

though slight inhibition might have been masked by the increased turn-

over of DA. The lack of difference between HVA levels in the drug-free schizophrenics and normal controls does not suggest any abnormality of MAO activity in the brains of schizophrenics.

**Relationship Between Brain and Platelet MAO Activity**

Winblad et al. (1979b) studied platelet MAO activity in 19 hospitalized geriatric patients, using PEA as substrate. Subsequent to the patients' death from a variety of natural causes, MAO activity was determined in the hypothalamus, hippocampus, caudate nucleus, and cingulate cortex using 5-HT, PEA, and tryptamine as substrates. No correlation could be found between platelet and brain MAO activities for any of the substrates.

**MAO Activity of Skeletal Muscle Biopsy Specimens**

We have investigated the MAO activity of skeletal muscle from schizo-

phrenic patients, patients with affective psychoses, and normal controls. Skeletal muscle, like brain, is an ex-
citable tissue. Human skeletal muscle MAO has the same Michaelis con-

stant (Km) and maximal velocity (Vmax) and is the same isoenzyme (type B) as human platelet MAO (Arora and Meltzer 1976). Further, we have shown that rat skeletal muscle MAO activity is not affected by neuroleptic treatment in vivo or in vitro, although it is slightly inhibited by tricyclic antidepressants (Arora and Meltzer 1976). Skeletal muscle specimens can be obtained from living subjects by benign biopsy pro-
cedures, under local anesthesia, so that the problems of aged subjects, agonal changes, and postmortem diagnosis discussed above can be minimized or excluded. Skeletal muscle is also a relatively homo-
geneous tissue compared to brain. A final reason for an interest in skeletal muscle MAO activity is that our labo-

ratory has reported a variety of morphologic abnormalities of skeletal muscle fibers and subterminal motor nerves in psychotic patients (Meltzer 1976). The MAO inhibitor pargyline has been reported to induce muscle necrosis in female rats (Yu et al. 1974). Thus, the possibility that decreased muscle MAO activity might be a factor in the neuromuscular dys-

function of psychotic patients has to be considered.

The methods used to obtain peroneus brevis muscle specimens from psychotic patients and to de-

termine MAO activity using benzylamine as substrate have been re-

ported elsewhere (Arora and Meltzer 1979). The mean age of the patients was 25 and that of the controls, 23.

No significant difference in the muscle MAO activity of males and females was found, in contrast to the findings of such differences with blood platelets, so the muscle MAO activity data from both sexes can be combined. Skeletal muscle MAO ac-

tivity was found to be decreased in schizophrenic patients as well as in patients with affective psychoses (ta-

ble 2). Inspection of table 2 indicates that there was no significant differ-

ence in the MAO activity of acute and chronic schizophrenics or of
donic or depressed patients (all of whom were in psychotic phases of their illnesses at the time of the biopsy or shortly before).
Table 2. Skeletal muscle MAO activity in normal controls and patients with major psychoses

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Nanomoles/mg</th>
<th>Protein/30 minutes</th>
<th>Percent of control ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>25</td>
<td>14.05</td>
<td>4.48¹</td>
<td>100 ± 32</td>
</tr>
<tr>
<td>Schizophrenics</td>
<td>51</td>
<td>10.46</td>
<td>3.91</td>
<td>74 ± 28</td>
</tr>
<tr>
<td>Chronic</td>
<td>29</td>
<td>10.32</td>
<td>3.41</td>
<td>73 ± 24</td>
</tr>
<tr>
<td>Acute</td>
<td>22</td>
<td>10.64</td>
<td>4.08</td>
<td>76 ± 29</td>
</tr>
<tr>
<td>Affective psychoses</td>
<td>20</td>
<td>10.91</td>
<td>4.30</td>
<td>78 ± 31</td>
</tr>
<tr>
<td>Manic phase</td>
<td>9</td>
<td>10.70</td>
<td>3.82</td>
<td>76 ± 27</td>
</tr>
<tr>
<td>Psychotic depression</td>
<td>11</td>
<td>11.08</td>
<td>4.59</td>
<td>79 ± 33</td>
</tr>
</tbody>
</table>

Analysis of variance summary table

<table>
<thead>
<tr>
<th>Source</th>
<th>df</th>
<th>Mean square</th>
<th>F</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td>3</td>
<td>73.05</td>
<td>4.516</td>
<td>p &lt; .01</td>
</tr>
<tr>
<td>Sex</td>
<td>1</td>
<td>29.96</td>
<td>1.852</td>
<td>—</td>
</tr>
<tr>
<td>Diagnosis-sex</td>
<td>3</td>
<td>17.47</td>
<td>1.080</td>
<td>—</td>
</tr>
<tr>
<td>Error</td>
<td>99</td>
<td>16.18</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Tukey HSD post hoc comparison: chronic and acute schizophrenics significantly lower muscle MAO activity than controls (p < .05)

¹ Mean ± SD.

No significant differences in skeletal muscle MAO activity were found between paranoid and nonparanoid schizophrenics or between hallucinating and nonhallucinating schizophrenics (data not presented). Almost all the schizophrenic patients were receiving neuroleptic drugs at the time of the biopsy. We found no relationship between muscle MAO activity and the maximum neuroleptic dose expressed in chlorpromazine equivalents, duration of treatment with neuroleptics, or duration of illness. There was no significant correlation between the MAO activity in skeletal muscle of the patients and the presence of abnormalities of skeletal muscle fibers or subterminal motor nerves. There was a nonsignificant trend toward a correlation between skeletal muscle MAO activity and platelet MAO activity with BA as substrate (r = .29, n = 24, p < .10) for males but not females (r = -.15, n = 19, p = NS).

These results suggest that decreased MAO activity in skeletal muscle as well as the blood platelet may be a nonspecific marker of vulnerability to a variety of types of psychopathology. The finding of decreased skeletal muscle MAO activity adds some significance to the findings of decreased platelet MAO activity in schizophrenic patients. Since the decreases in both tissues are relatively small compared to the very large degree of inhibition that would be necessary before one might expect accumulation of the substrates of MAO, there may be no direct significance to the small differences found between patients and controls. However, it should be kept in mind that because of the very great muscle mass in the body, the decrease in muscle MAO activity may, in the aggregate, have some physiological significance.

References


References


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