Platelet Enzyme Abnormalities in Neuropsychiatric Disease

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ABSTRACT

Blood platelets accumulate, store and release a variety of biogenic amines including norepinephrine, serotonin and dopamine (DA) which are known to act as neurotransmitter substances. Platelet monoamine oxidase (MAO) shares many biochemical properties with the mitochondrial MAO present in brain tissue. For these reasons it has been suggested that platelets might serve as a diagnostic and research model for nerve cells in a variety of neuropsychiatric diseases. In some patients with schizophrenia and manic depressive psychoses, platelet MAO activity is significantly decreased. Central nervous system inhibition of MAO could lead to excess accumulation of monoamines in the brain; this would be consistent with the DA hypothesis of schizophrenia. Disturbances of monoamines and enzyme kinetics in the hereditary ataxias and in Huntington disease have been described, but these findings are unproven and controversial. If platelet models for human neuropsychiatric disease can be established, they will be immensely important in preclinical diagnosis, therapy and genetic counseling.

The Biology of Schizophrenia

There is a growing body of evidence that schizophrenia and other disabling psychiatric diseases have a biochemical basis. In particular, the "dopamine hypothesis" of schizophrenia proposes that the psychotic symptoms are related to the overactivity of dopamine (DA) in the mesolimbic forebrain. This hypothesis was suggested by two facts of clinical pharmacology. First, monoamine oxidase (MAO) inhibitor drugs cause an exacerbation of psychotic symptoms in schizophrenic patients and, secondly, drugs which block DA receptors in the brain (the phenothiazines) are effective in the treatment of schizophrenia.

Support for the DA theory was lent by the finding of increased DA concentration in the nucleus accumbens in post-mortem studies of schizophrenic brains. Simple DA excess may not be the only mechanism for the production of psychotic symptoms. A deficiency of endogenous inhibitory neurotransmitters, which normally act to oppose DA, might result in relative DA overactivity. One inhibitory substance is gamma-aminobutyric acid (GABA), a neurotransmitter normally
present in large amounts in the mesolimbic brain. Both GABA and its synthetic enzyme, glutamic acid decarboxylase, may be reduced in schizophrenic brain tissue according to some authors.5

A failure to convert DA to inert metabolites would certainly be another and more direct mechanism to account for the elevated brain DA levels in schizophrenia. DA and a variety of other biogenic amines are catabolized by MAO. This enzyme is present in many body tissues in several molecular forms.20 Early and unconfirmed reports suggested diminished MAO activity in the hypothalamus, tegmentum and other areas of post-mortem schizophrenic brains.36

Neurochemical analyses on post-mortem human brain tissue are difficult to perform because of conceptual and technical problems.24,30 Enzymes and neurotransmitters are unstable after death, and their breakdown is usually non-linear with time. The problems of assessing psychiatric diagnosis retrospectively and of establishing controls sometimes seem insurmountable. Fresh human brain tissue from schizophrenics is obviously not available, and there is no satisfactory animal model for human psychiatric disease. These limitations have encouraged investigators to search for a more accessible tissue which might serve as a model for the chemistry of brain function.

Blood Platelets as a Neurochemical Model

Several authors have suggested that blood platelets might serve in this capacity.12,25,31 This proposal is based on the fact that platelets accumulate, store and release several neurotransmitter amines such as serotonin, noradrenalin and DA. The appropriateness of platelets as a model for monoamine containing neurons has been reviewed recently.27 This model is especially attractive in that platelets can be collected from living patients without trauma and can be concentrated and sepa-

rated from other cellular components. Platelets have been used with mixed success to study neurologic disorders including Down's Syndrome,6 infantile autism10 and phenylktonuria.23

Platelet MAO in Schizophrenia and Effective Psychoses

During the 1970's, a series of studies was performed under the auspices of the National Institutes of Mental Health (NIMH) to investigate MAO activity in the platelets of schizophrenics. The rationale behind these studies is as follows:

(1) Theoretically, excess DA activity in the brains of schizophrenics might be due to reduced brain MAO activity. (2) Human platelets contain a mitochondrial MAO which is closely related to the iso-enzyme found in brain tissue (B form). (3) MAO inhibitor drugs can produce an exacerbation of symptoms when administered to psychotic patients.

In the NIMH study, blood was collected from patients with schizophrenia, unipolar depression and manic-depressive psychoses (bipolar depression) as well as age and sex matched controls.19 Platelets were isolated by centrifugation, washed and sonicated. Technical details of platelet MAO assay are given by Wurtman and Axelrod and reviewed in individual papers referenced in this article. Using tryptamine-2-14 C as a substrate, indolacetaldehyde-14 C formation is linear with MAO concentration and time.38 MAO activity is expressed as a fraction of platelet protein in milligrams.

The results of these analyses show that platelet MAO activity is significantly lower in schizophrenic patients than in normal controls.17 There are no significant differences in enzyme activity among the different diagnostic subgroups of schizophrenia, nor are the values related to the severity or chronicity of schizophrenic symptoms.
Studies in patients with affective psychoses indicate reduced MAO activity in platelets of manic depressive patients but normal activity in unipolar depressed patient15 (see table I). No change in MAO activity was noted as the bipolar patients cycled through the different phases of mania and depression. The investigators analyzed several non-specific factors of possible relevance to the measurement of abnormally low MAO activity in these psychiatric patients. No relationship was found to the effect of drug therapy, diet, sleep and activity patterns, length or type of hospitalization or day to day changes within individuals.19

Genetic Studies

These data raise the question of the precise relationship of platelet MAO activity to the biology of schizophrenia. Is the reduced enzyme activity a reflection of the symptomatology of the disease state (state variable) or the manifestation of a genetic predisposition to disease (trait variable)? In an effort to answer this question, the NIMH group measured MAO activity in monozygotic twins discordant for schizophrenia, i.e. one of the twin pair was schizophrenic and the co-twin was asymptomatic. Their data, illustrated in table II, indicate that both schizophrenic and nonschizophrenic twins had platelet MAO values significantly lower than normal controls.39 This evidence strongly suggests that the reduced MAO in the schizophrenic patients does not represent the effect of the disease itself or its treatment, but seem to be related to a genetic predisposition or vulnerability to the disorder which is modified by environmental, psychological and perhaps other biological factors.19

Significance

The relationship between the finding of reduced platelet MAO activity and the symptomatology of schizophrenic and manic-depressive psychoses is not known. While there is no evidence for a marked, generalized inhibition of MAO activity in all tissues in schizophrenics, diminished platelet activity may be associated with diminished activity in schizophrenic brain with which it shares some biochemical characteristics.2 Reduced MAO activity in schizophrenic brain has been reported,36 but other studies have contradicted these findings.26 Nevertheless, brain MAO inhibition in schizophrenia is consistent with several firmly established biochemical mechanisms. Some speculation as to the possible role of MAO inhibition is in order.

(1) Reduced MAO could lead to the accumulation of excess DA in mesolimbic brain structures. This is the simplest and most direct possibility and is consistent with the dopamine hypothesis of schizophrenia.

### TABLE I

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<th>Nanomoles/mg of Protein/hr</th>
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<tr>
<td>Controls</td>
<td>6.21 ± 0.36</td>
</tr>
<tr>
<td>Unipolar depressed</td>
<td>6.92 ± 0.48</td>
</tr>
<tr>
<td>Manic-depressive</td>
<td>3.65 ± 0.46</td>
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### TABLE II

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<tr>
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<th>Nanomoles/mg of Protein/hr</th>
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<tr>
<td>Controls</td>
<td>6.4 ± 2.7</td>
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<tr>
<td>Schizophrenic twin</td>
<td>3.9 ± 2.3</td>
</tr>
<tr>
<td>Non-schizophrenic twin</td>
<td>4.7 ± 2.9</td>
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(2) MAO inhibition may lead to an accumulation of a variety of monoamine neurotransmitters, e.g., DA, norepinephrine, serotonin, but not necessarily all in the same amount. This could lead to an imbalance in the various amines which have synaptic function.

(3) MAO inhibition could lead to the accumulation of false neurotransmitters such as tryptamine, tyramine and octopamine. These bioamines normally have reduced effector activities when compared to other neurotransmitters. However, in increased concentrations they could have multiple effects at neuronal synapses.16

(4) Tryptamine accumulates in the brain and periphery following MAO inhibition. This amine is the precursor of dimethyltryptamine (DMT), a naturally occurring psychotomimetic agent. There is a distinct possibility that endogenous DMT might play a role in the symptomatology of schizophrenia.13

(5) The compound 6 hydroxydopamine (6-HD) produces destruction of caholamine nerve endings in experimental animals, and its toxic effect is potentiated by MAO inhibition. The possibility that psychotic symptoms might be caused by endogenous production of 6-HD has been raised by some authors.37

Platelet Enzymes in Hereditary Ataxias

Friedreich’s disease is an inherited, degenerative, neurologic disorder characterized by progressive ataxia, sensory abnormalities and cardiomyopathy. Some patients develop abnormally elevated pyruvate blood levels following a glucose load.3 This relative pyruvate intolerance prompted an investigation of a possible enzymatic disturbance of carbohydrate metabolism is Friedreich’s ataxia.

A group of investigators found abnormalities of the pyruvate dehydrogenase complex in muscle slices, fibroblasts and blood platelets from ataxic patients. Specifically, partial deficiencies of activity and kinetic abnormalities of lipoamide dehydrogenase (LAD) in platelets in some patients was reported by Kark, Blass and associates.7,12 Their kinetic data suggest that genetic carriers of the inherited ataxias (i.e., heterozygotes) and asymptomatic family members might also be identified by biochemical methods. These reports offered enormous potential for genetic counseling and preclinical diagnosis in this disease.55 Subsequent publications, however, have reduced this initial enthusiasm. Other laboratories have failed to substantiate the earlier work and have found normal platelet LAD activity.11,33,34 Methodologic differences probably account for these discrepancies, and the significance of the original work is now in doubt.

Disturbed Platelet Function in Other Neurologic Diseases

A variety of disturbances in monoamine neurotransmitter systems has been described in the brains of patients with Huntington’s chorea. Aminoff et al reported elevated uptake of DA and serotonin by platelets from choreic patients.1 If substantiated, these observations could be of value in providing a test for preclinical Huntington disease in family members at risk. Citing certain methodologic problems, more recent reports have contradicted Aminoff’s data.14,21 Nevertheless, continued efforts may confirm a bioamine abnormality in platelets in Huntington disease. Meanwhile current investigations suggest abnormalities in DA and serotonin kinetics in platelets in a wide range of neuropsychiatric diseases including Down’s Syndrome,8 infantile autism,10 phenylketonuria,23 affective disorders,35 muscular dystrophy,18 Parkinson’s disease,2 multiple sclerosis9 and migraine.29
Summary and Conclusions

Blood platelets accumulate, store and release a variety of biogenic amines, including norepinephrine, serotonin and DA, which are known to act as neurotransmitter substances. Platelet MAO shares many biochemical properties with the mitochondrial MAO present in brain tissue. For these reasons, it has been suggested that platelets might serve as a diagnostic and research model for nerve cells in a variety of neuropsychiatric diseases. In some patients with schizophrenia and manic depressive psychoses, platelet MAO activity is significantly decreased. Central nervous system inhibition of MAO could lead to excess accumulation of monoamines in the brain; this would be consistent with the DA hypothesis of schizophrenia. Disturbances of monoamine and enzyme kinetics in the hereditary ataxias and in Huntington disease have been described, but these findings are unproven and controversial. If platelet models for human neuropsychiatric disease can be established, they will be immensely important in therapy, preclinical diagnosis and genetic counseling.

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References


