Plasma Concentrations of γ-Aminobutyric Acid (GABA) and Mood Disorders: A Blood Test for Manic Depressive Disease?

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γ-Aminobutyric acid (GABA), an inhibitory neurotransmitter that serves about one-third of brain neurons, is involved in the development of depression and in the treatment of depression and mania with pharmacological therapy. Brain activity of GABA may be conveniently measured in plasma, and changes in plasma concentrations of GABA reflect brain GABA activity. Plasma concentrations of GABA are significantly lower than control values in about one-third of patients with major depressive disorder; concentrations are also low in patients with mania and in bipolar patients who are depressed. These low concentrations of GABA appear to persist after recovery from depression and are not increased by treatments that improve depressive symptoms. Follow-up studies suggest that GABA concentrations remain relatively constant over at least 4 years. Additionally, preliminary data suggest that low plasma GABA is a familial marker of mood disorders in a subset of patients. Despite the difficulty of demonstrating that a particular biochemical measure is a true genetic trait marker for vulnerability for development of an illness, the accumulated data suggest that low plasma GABA may represent a biological marker of vulnerability for development of various mood disorders.

Indexing Terms: mood disorder/bipolar illness/brain/cerebrospinal fluid

Why Do Psychiatrists Want a Blood Test for Mental Illness?

Advances in laboratory medicine have paralleled our improved ability to understand the etiology of medical illness and, therefore, presumably, our ability to develop improved treatment and prophylaxis. In some respects, psychiatry has lagged behind other medical specialties. Partly, this reflects the predominately psychological (and, therefore, presumably nonbiological) orientation of most American psychiatrists in the 20th century. However, to some extent psychiatry is also limited by the fact that its organ of interest, namely the brain, is not routinely accessible to invasive laboratory procedures such as biopsy.

However, the idea of measuring a biochemical or physiological parameter in the periphery, which might provide some index of brain function, is not at all outlandish. Cardiovascular function, respiration, and in fact the peripheral sympathetic and parasympathetic nervous systems are to a large extent under central or brain control. Similarly, the major endocrine systems are also controlled at the level of the hypothalamus.

Therefore, since the ability to accurately diagnose mental illness has improved dramatically in the last 20 years, and since peripheral measures of mental function are conceivable, should a blood test for mental illness be pursued? There are several reasons—diagnostic, prognostic, genetic, and etiologic—why this might be a worthwhile exercise.

Ultimately, it is in the clinic that a blood test for mental illness must be validated. From the perspective of diagnosis, blood tests are already in widespread use in psychiatry to provide differential diagnosis in cases of hypothyroidism, Cushing disease, hypoglycemia, and so forth. Because most psychiatric diagnoses are ultimately clinical diagnoses and because most mental illness is reflected in maladaptive behavioral changes, it is conceivable that laboratory procedures will never play a truly key or central role in the formulation of an accurate psychiatric diagnosis for mental illness. However, there are often cases in clinical practice that do not neatly fit our preconceived symptom profiles, in which even a laboratory test with relatively poor reliability or predictability might be useful.

Diagnosis determines prognosis. This simple truism is as valid in psychiatry as in any other branch of medicine, and the increasing sophistication of psychiatric diagnosis along with follow-up studies continues to validate this concept. A laboratory test that could help in predicting outcome might be useful clinically, even if it were not a particularly useful clinical diagnostic instrument. For example, an electrocardiogram that demonstrates ventricular tachycardia is generally regarded as an indicator of poor prognosis, but tells us virtually nothing about the underlying cardiac diagnosis.

The evidence that psychiatric diseases are familial and probably also genetic is overwhelming. In fact, the evidence for a genetic component of mental illness is as strong as for any other specialty in medicine or surgery. Given that no serious medical illness has been conquered until it has first been prevented (e.g., bubonic plague and tuberculosis), it would be extremely useful to have a laboratory procedure that allowed determination of the genetic vulnerability for developing a specific mental illness. If this was clinically feasible, parents with children or adolescents who had exhibited behavioral disturbances might be offered early psychological or psychiatric intervention. Additionally, a well-informed patient is a good patient and, in a case where the early manifestations of an illness could be confirmed by a laboratory procedure, early intervention and early
treatment would probably be reflected in a more benign or favorable outcome.

Finally, the reason we do scientific research is that we are interested in why things work. Understanding the etiology of mental illness represents a multigenerational challenge. However, the examples of vitamin-deficit states, such as pellagra, which are frequently manifested by behavioral alterations, or the dementing illnesses accompanying thiamine deficiency, are excellent illustrations that mental, psychological, and behavioral symptoms may have a simple biochemical basis. Therefore, if a mental illness was demonstrated to be directly caused by a biochemical lesion, a more profound understanding of the neurochemistry of behavior might rapidly evolve.

Here I will present data suggesting that the determination of plasma concentrations of $\gamma$-aminobutyric acid (GABA) in patients with mood disorders, particularly depression, may have diagnostic, prognostic, genetic, and etiologic utility.

Can GABA Be Involved in Depression?

Current biochemical theories of mental illness date back to the early 1950s and have predominately involved presumed alterations in the function or activity of the biogenic amine neurotransmitters, specifically dopamine, norepinephrine, and serotonin. There is a rich historical literature supporting this. The idea that amino acid neurotransmitters such as GABA might be involved in mental function is relatively new. In large part, this is due to the fact that GABA was considered for ~20 years to be involved in brain energy metabolism via the "GABA shunt." Not until ~25 years ago was the neurotransmitter role of GABA initially formulated.

Most of the interest in GABA mechanisms of brain function has revolved around the central role of GABA in convulsive disorders. Specifically, most antiepileptic drugs seem to have direct or indirect action on the GABA system. Particular antiepileptics such as valproic acid lead directly to significant increases in brain GABA content without remarkably affecting biogenic amine neurotransmission. Pharmacological manipulations that decrease brain GABA invariably produce convulsive activity. Valproic acid was serendipitously developed as an anticonvulsant in the 1960s; however, early trials by psychiatrists with patients with severe mental illness suggested that the therapeutic spectrum of activity of valproic acid extended beyond the epilepsies (1).

Emrich et al. (2) published the first case series demonstrating a marked mood-stabilizing effect of valproic acid in a few patients with manic depressive disease (bipolar disorder). Of particular note was the observation that valproic acid appeared to decrease the intensity and frequency of both depressive and manic phases of the illness. From this, Emrich formulated the GABA hypothesis of affective disorders, in which manic depressive disease was conceptualized as a GABA deficit, and valproic acid was presumed to exert a therapeutic effect by correcting this deficit and returning the deficient brain levels of GABA to normal.

About this time, several studies of cerebrospinal fluid (CSF) documented a decreased concentration of GABA in CSF of patients with severe depressive disorder (3–7). In these studies, patients with mania had lower CSF concentrations of GABA than did healthy controls, although this failed to achieve statistical significance. Meanwhile, pharmaceutical development had proceeded to clinical testing of a GABA-agonist drug, progabide, which was soon found to be an effective antidepressant (8). Not surprisingly, progabide had been initially developed as an anticonvulsant.

Additional confirmation that GABA plays a key role in mood disorder has come from a few studies examining GABA directly in brain tissue. Some postmortem studies (9) have found that upregulation of GABA$_A$ receptors is compatible with a GABA deficit in prefrontal cortex. Most provocative was the study by Honig et al. (10), which directly measured GABA in brain tissue from patients undergoing cingulotomy for intractable depression. These patients had an inverse correlation between the cortical concentrations of GABA and the degree of depression determined by a psychological rating scale. That is, the patients with the most severe depression had the lowest amounts of GABA in brain cortex.

Independently and serendipitously, our laboratory found that the concentrations of GABA in plasma of patients with severe melancholic endogenous major depressive disorder were significantly lower than those of controls (11, 12).

Thus, the early research with GABA and mood disorders can be summarized as follows: Strong clinical evidence suggests that GABA agonists are effective therapeutic agents in the treatment of both depression and mania, and a GABA deficit is well documented to accompany depression.

Perhaps the strongest evidence that GABA is involved in major depressive disorder comes from animal laboratory models of depression. Several of these models have been extensively studied in the last decade and are at present used to screen for potential new antidepressant compounds. Space does not permit an adequate review of this literature (13), but suffice it to say that in the three best-developed and most widely accepted animal models of depression—learned helplessness, olfactory bullectomy, and behavioral despair—GABA mechanisms are found to parallel those seen in human depression. That is, in the animal model, a GABA deficit state can be demonstrated to accompany the depressive analog, and drug treatments that improve depression do so in a manner compatible with remedying the deficit state (14).

How Can We Be Sure That GABA Does Not Measure an Epiphenomenon?

The problem with any biochemical or physiological measure of depression or mania involves the fact that major depressive disorder and the bipolar illness, manic
phase, are total body system diseases. People with severe depression do not maintain proper nutrition, exercise, or sleep patterns. Therefore, any biological marker of a mental illness must be demonstrated to be a reflection of the mental or psychological aspects of the illness and not a mere accompaniment of the changed physical status of the patient. A good example of this concept is the weight loss accompanying depression. If a research study demonstrated that patients with major depressive disorder weighed on the average less than a matched set of healthy controls, one might conclude that this was a biological marker of depression. However, if on recovery from the depressive state, patients promptly regained the lost weight and were again in the normal range, one could probably accurately conclude that the proposed biological marker, namely, weight loss, was a result of the decreased appetite that is a symptom of depression but was not a marker of the illness per se.

Stability of Plasma GABA as a Biological Marker

Behavioral manifestations are a cardinal feature of mental illness. In particular, disruption in activity is very often seen in patients with severe depression and in mania. These manifestations are usually referred to as psychomotor retardation or agitation; in severe depression, this usually results in a slowing of activity, whereas in severe mania, physical agitation and hyperactivity are common.

Changes in appetite are a hallmark of depression, with decreased appetite seen most commonly in cases of severe melancholia. Alternatively, some patients develop the so-called atypical or reverse vegetative symptoms and overeat on a compulsive basis. Change in appetite is not typically considered a cardinal feature of mania, but it is not uncommon for patients with mania to exhibit dramatic weight loss as a result of their hyperactivity and neglect of normal dietary intake. Change in activity or diet might also be important in determinations of peripheral GABA activity in light of some evidence that GABA neurons in the mesenteric plexus are under cholinergic control and involved in peristalsis (15). Similarly, the stage of the menstrual cycle might be important because GABA concentrations in the ovary and fallopian tubes, although much lower than the concentrations in brain, are still higher than in most peripheral organs. Moreover, clinical psychiatrists have long observed that some patients exhibit a seasonal pattern to their illness. Usually these patients develop symptoms of depression in the winter and become less depressed during the summer months. Similarly, patients with mania will typically develop symptoms in the spring and fall of the year, when the light cycle is changing rapidly.

Therefore, plasma GABA would be much more clinically useful as a biological marker of mood disorder if investigators could demonstrate that it is not dramatically altered by extraneous coincidental factors such as exercise, menstrual cycle, colonic status, season of the year, or time of day. Particularly, given preclinical laboratory evidence suggesting that GABA is critically involved in the circadian pacemaker in the suprachiasmatic nucleus, the demonstration of a circadian pattern in alterations of peripheral GABA activity might significantly interfere with practical application of a plasma GABA blood test.

My coworkers and I have accumulated evidence that suggests GABA levels are not significantly altered by these factors (Fig. 1). Review of these data suggests that there are no marked effects on plasma GABA concentrations due to gender, exercise, diet, season, time of day, or menstrual cycle (16).

Although it is not absolutely necessary that a laboratory measure be stable with time, especially if the pattern of instability is well understood, as with serum cortisol, it certainly facilitates research and clinical applications. Plasma GABA appears to demonstrate adequate stability for clinical and research purposes.

Plasma GABA Is Low in Major Depressive Disorder and Does Not Improve with Clinical Recovery

The data presented in Fig. 2 are representative of our consistent and replicated finding in patients with major depression (17). Close examination of these data reveals the following: First, for ~60% of patients with major depressive disorder, plasma GABA concentrations are within the normal range and appear to have a distribu-

![Diagram of GABA levels](attachment:diagram.png)

Fig. 1. Effects of sex, mild exercise, colonic status, menstrual cycle, and time on concentrations of plasma GABA in nine women and eight men.

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tion similar to that of healthy, normal, nondepressed controls. Second, the 100 nmol/L concentration provides a natural cutoff value, with only ~6% of healthy normal controls having plasma GABA concentrations less than that. Third, ~40% of patients with major depressive disorder have plasma GABA <100 nmol/L, or outside ~95% of the normal healthy control range.

Several conclusions are obvious. First, low plasma GABA is by no means a diagnostic procedure. Its selectivity is quite low. However, there does appear to be a subset of patients with major depression whose plasma concentrations of GABA are below the control range. Second, the validity and utility of plasma GABA in mood disorders revolve around the question of its stability with time in patients with major depressive disorder. As noted above, plasma concentrations of GABA appear to be remarkably stable in healthy controls (18). In patients with major depressive disorder, follow-up and outcome studies are under way to better establish issues of stability of patients' concentrations of plasma GABA. Preliminary data, derived from a cohort of 27 patients who had repeat plasma GABA determinations 6 to 12 months after the initial measurement, suggest that plasma GABA is a stable biological marker in patients with major depressive disorder (Fig. 3B). Although the mean values for plasma GABA did not significantly change over this follow-up period, the Hamilton Rating Scale for Depression scores dropped on follow-up (Fig. 3A), suggesting that most of the patients had clinically improved over this time. In other words, the depression got better, but the plasma GABA stayed the same. Preliminary results of a more extended follow-up outcome study are presented in Fig. 4; this follow-up study showed a high correlation between plasma GABA concentrations at entry into the study and at follow-up, as long as 48 months later. These data suggest that plasma GABA has one characteristic of a biological trait marker for major depressive disorder, namely, a continuation of the abnormality into the well state, after resolution of clinical symptoms.

Specificity of Low Plasma GABA as a Biological Marker for Depression

Demonstration that a particular biochemical or physiological marker is abnormal in patients with mental illness needs to be considered judiciously. All patients with psychiatric conditions share a number of features, including visits to a clinic or hospital; ingestion of psychotropic medication; participation in psychological modalities of treatment such as group or individual psychotherapy; disability; decreased ability to function in the community, resulting in unemployment or underemployment; and, often, difficulties with interpersonal relationships. Therefore, a physiological or biochemical abnormality in one specific or particular psychiatric diagnosis should be considered in the context of its specificity. In this regard, a conclusive answer is obviously difficult to obtain because, according to our classification of psychiatric illnesses, a host of conditions would need to be studied to conclusively demonstrate that the putative biological marker was specific to a given mental illness. This is particularly true if the mental illness in question is depression, given that secondary depression is frequently seen in the context of a primary diagnosis of schizophrenia, alcoholism, drug abuse, eating disorders, anxiety disorders, obsessive-compulsive disorder, and so forth. In fact, it is difficult to consider any mental
illness in which depression is not a frequently observed clinical feature.

However, there has been some progress in analyzing this situation, as demonstrated by Table 1. The conditions in which preliminary studies have shown plasma GABA to be low in a subset of patients include bipolar (manic depressive) illness and alcoholism. The conditions that have not, to date, demonstrated any remarkable alterations in plasma GABA include schizophrenia, anxiety disorders, and eating disorders.

A relationship between alcoholism and depression has long been observed in the clinic and in the psychiatric research literature (19). The nature of this relationship is still open to debate, because chronic ingestion of large amounts of alcohol over a protracted period induces a toxic reaction that is, in many cases, accompanied by sleep disturbance, poor appetite, social isolation, and feelings of low self-esteem and inadequacy. Therefore, one might speculate that the depressed alcoholic is suffering a toxic reaction. Some evidence supports this view: In many cases, the symptoms of depression clear rapidly after the patient achieves and maintains sobriety for a few weeks.

However, another possibility relates to the concept of depression spectrum disease (20). Careful family studies have suggested the existence of a familial illness in which alcoholism is manifested in the male members of a family, depression in the females. Therefore, finding that plasma concentrations of GABA are low in a subset of alcoholics is not surprising, nor does it particularly decrease the validity of low plasma GABA as a biological marker for depression, at least from a research perspective.

The idea that patients with bipolar illness also have low plasma GABA might seem on the surface to be counterintuitive, because mania and depression are commonly considered to be opposite poles of a psychological process. This conventional wisdom is derived from the observation that patients with mania are frequently overactive and appear to have an elevated mood with increased energy and enhanced self-esteem, whereas patients with depression are slowed down, self-deprecatory, and generally anything but manic. However, from a theoretical perspective the observation that “manic depressive insanity” is one illness with various clinical presentations depending on time and circumstance is still valid. Finding a low concentration of plasma GABA in bipolar patients, whether manic or depressed (Fig. 5), is proof positive that low plasma GABA is not a marker for states of depression. Additional research with families in which both bipolar and nonbipolar major depression are found is required to resolve questions on the meaning of this finding.

![Fig. 4. Correlations of plasma concentrations of GABA (nmol/L) at time of entry (EGABA) and at various follow-up periods (6 to 48 months; M6, M12, M24, M36, and M48). Correlations range between r = 0.43 (M24) and r = 0.88 (M6).](image)

![Fig. 5. Percentages of three study groups with low plasma GABA (<100 nmol/L).](image)

From left to right healthy controls (3/50), bipolar manic (7/24), bipolar depressed (14/33), unipolar depressed (31/77), and sober alcoholic (32/84).
In summary, low plasma GABA has some selectivity for depression and related conditions, but low sensitivity as a test for depression. Thus, determination of low plasma GABA might become a useful clinical laboratory procedure if it could be developed as a familial trait marker, to predict vulnerability in persons who have never been mentally ill but have a strong history of mood disorders.

Preliminary data (Fig. 6) suggest that plasma GABA may be familial: We found a statistically significant correlation between plasma concentrations of GABA in probands with major depressive disorder and the concentrations in their first-degree relatives. A detailed pedigree analysis is in progress to further elucidate the nature of this familial relationship. However, so far the results indicate a possibility that low plasma GABA might evolve into a "vulnerability marker" for patients at risk for developing depression.

Future Directions and Possible Clinical Applications

Naturally, this question comes to mind: If indeed a GABA deficit accompanies depression and perhaps other mood disorders, why not treat patients with GABA agonists and use plasma GABA as a predictor of treatment response? A few of our preliminary studies suggest that, in some cases, plasma GABA concentrations determined before treatment do predict treatment response. The work to date has involved treatment of major depression with electroconvulsive therapy, treatment of mania with valproic acid, and treatment of schizophrenia with adjunctive alprazolam added to haloperidol. So far, in these three investigations, plasma GABA may predict treatment response. However, large-scale clinical treatment studies will be required to establish with certainty whether the prognostic ability of plasma GABA will become clinically useful.

Finally, the physiological and biochemical mechanisms involved in the regulation of GABA in plasma deserves some comment (Fig. 7). Careful consideration reveals that plasma concentrations of GABA may be directly influenced by liver function. Therefore, additional research should examine the mechanism of clearance of GABA from plasma to determine the precise extent to which plasma GABA concentrations are under the control of synthetic mechanisms vs catabolic, metabolic, or clearance mechanisms. These experiments are relatively tedious but fairly straightforward. We should always keep in mind that, regardless of how exciting the potential results, plasma GABA may just be a more technically difficult and expensive test of liver function!

The GABA receptor in brain has been cloned and is known to consist of several subunits. The enzymes responsible for GABA synthesis and metabolism are also well characterized and have been cloned. Therefore, if the GABA concentration in plasma is successfully demonstrated to be a familial trait marker of mood disorder, molecular genetic studies may be considered.

In conclusion, plasma GABA may have the potential to develop into a useful research tool for studies on the etiology of mood disorders. Whether it will become a standard laboratory measure depends in large part on whether it can be shown to predict treatment response to specific antidepressant therapies.

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