Inadequate Homocysteine Metabolism: A Theory of Depression

ABSTRACT

Over the past 100 years, theories regarding the etiology of major depression have appeared as the proverbial blind man’s interpretation of the elephant. It is now possible to discuss depression in terms of neuroendocrine dysregulation, differences in neuroanatomy, inflammatory response, a gene-environment interaction, or in purely psychological terms—and without any contradiction in the evidence. Indeed, a disorder as complex and variable as depression is expected to have multiple risk factors and etiologic influences. Yet, all roads eventually lead to a functional shortage of monoamines, and the monoamine hypothesis remains the basis of treatment for millions of patients. Elevated homocysteine (HCY) has long been recognized as a risk factor for major depressive disorder (MDD), and many neurologic and psychiatric conditions; however, a full understanding of HCY metabolism and monoamine synthesis indicates that perhaps HCY elevation in the central nervous system is the driving force behind MDD. The HCY theory argues that a genetically based inability to optimally metabolize HCY leads to inadequate supplies of monoamines, particularly in the presence of psychosocial stress, and results in the clinical syndrome of MDD. [Psychiatr Ann. 2015;45(9):469-472.]
Twin and family studies consistently demonstrate the heritability of all affective disorders, but the exact genetic basis of depression has been elusive. The first report that a gene-environment interaction could be associated with polymorphisms of the genes coding for the serotonin transporter, 5-HTTLPR, spawned over a decade of focused research. Because the majority of antidepressants have their site of activity at this transporter, the explanation was particularly intriguing. Although many clinicians accept that the polymorphism associated with depression resides in the 5-HTTLPR region, it is now a subject of debate rather than a conclusion.

Two meta-analysis studies found that stressful life events did indeed predict depression, but that no association with the 5-HTTLPR genotype existed. Furthermore, the recent discovery of another monoamine transporter, the plasma membrane monoamine transporter (PMAT), is of great significance. Its activity, the transport of neurotransmitters back into neurons, is unaffected by antidepressants, unless overdose levels are reached. It is abundantly expressed, transports all monoamines, and although it is nonselective, it is a very high capacity transporter. Perhaps the reason remission rates are generally low in antidepressant trials, and with day-to-day clinical use of serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors, is that they are effective for blocking only a small percentage of monoamine reuptake.

As detailed in the guest editorial for this issue, we have accepted that depression is caused by a lack of adequate monoamines, and treated the illness by making better use of the short supply available. Yet, this does not address the root cause of depression, ie, exactly why some patients cannot produce an adequate amount of neurotransmitters, particularly in the presence of stress. The homocysteine (HCY) theory of depression explains the genetic reasons that certain people cannot synthesize adequate monoamines, and addressing the HCY theory clinically is synonymous with addressing the underlying genetic basis of depression.

**AN ELABORATION OF THE HOMOCYSTEINE THEORY OF DEPRESSION**

In summary, the HCY theory is that depression results from genetic polymorphisms, which result in suboptimal monoamine production—a genetic vulnerability that usually manifests by stressful life events. The step-by-step elaboration is as follows:

- **Lower than optimal levels of monoamines (serotonin and norepinephrine more so than dopamine) is not the cause of depression; it is a symptom of depression. This symptom results in various clinical manifestations of depression, but low monoamines are not the core etiology of illness.**
- **The cause of depression is the inability to produce adequate amounts of neurotransmitters at baseline (or in patients reporting past, acute, or chronic/ongoing stress).**
- **People who are unable to produce adequate amounts of monoamines could be lacking an adequate supply of coenzymes needed for their synthesis, or have less functional enzymes also critical in their synthesis (or some combination of these polymorphisms).**
- **In addition to the enzymatic steps that create monoamines (such as the two steps that convert l-tryptophan to serotonin), their synthesis is also reliant on methylation, which occurs via the HCY cycle.**
- **The HCY cycle is a series of reactions that metabolizes the toxic amino acid HCY and results in the methylation of monoamine (as well as DNA, RNA, phospholipids, myelin, and proteins); the production of glutathione as the principle antioxidant in the central nervous system (CNS); and the elimination of the toxic burden of HCY.**
- **Coenzymes associated with neurotransmitter production at various stages, and necessary for HCY, are reduced (or metabolized) B vitamins (and trace minerals such as zinc and magnesium are also critical for some enzymatic steps).**
- **B vitamins are pro-drugs that must be metabolized to their active coenzyme forms. This metabolism takes place predominately in the liver, but various stages could occur at other points from ingestion to final use in enzymatic reactions.**
- **The majority of people who are depressed have genetic variants (or polymorphisms) that code for less efficient vitamin-metabolizing enzymes, and thus, lower-than-optimal reduced B vitamins across the blood-brain barrier as a result.**
- **When reduced B vitamins are lower than optimal in the CNS, HCY is elevated and neurotransmitter (and antioxidant) production is suboptimal.**
- **Addressing depression with reduced B vitamins can circumvent all possible vitamin polymorphisms that have prevented adequate monoamine synthesis and monoamine methylation, and further, optimally metabolizing HCY will also allow for antioxidant production in the CNS, which will convey neuroprotective benefits.**
- **Providing the CNS with a plentiful supply of coenzymes will also compensate for the possibility of additional ineffective enzymes in the HCY cycle (such as defective methionine synthase).**
- **Addressing the HCY basis is a treatment aimed at the root cause of depression rather than simply providing symptomatic relief.**
EPIDEMIOLOGIC EVIDENCE FOR THE HOMOCYSTEINE THEORY

Epigenetics encompasses an array of molecular mechanisms by which psychologic and environmental influences interact with an individual’s genome (even in-utero) to alter or influence gene expression, or influence brain plasticity, and could result in pathology. The major mechanism at work is methylation of DNA, as this process “turns on or off” genes for expression. Because DNA and RNA methylation is accomplished via the HCY cycle’s creation of a supply of methyl donors, impaired HCY metabolism will result in impaired methylation of genetic material.

Methyltetrahydrofolate reductase (MTHFR) status is an established source of impaired methylation, and it has also been well established that carriers of the CT or TT genotype for MTHFR are at greater risk for depression; in fact, those positive for the TT genotype have a 70% higher risk of depression than those with the normal CC type. A groundbreaking 2013 study examined the relationship of childhood trauma, MTHFR polymorphism, and depression. Victims of childhood trauma were indeed more prone to depression if they possessed the MTHFR CT or TT genotype and, over a period of 5.5-years, were at an ongoing, greater risk of a relapse. The authors noted the link between MTHFR and DNA methylation, as well as the link between MTHFR and management of oxidative stress in the CNS.

Posttraumatic stress disorder (PTSD) is also a subject of intense epigenetic research, as trauma so severe as to create such pathology, and persistent memory-based symptoms, clearly indicate some genomic changes as a result of trauma exposure. In one study, PTSD patients demonstrated elevated serum HCY levels on average, and the duration of PTSD was found to actually predict serum HCY levels. The authors noted that elevated levels of HCY in the PTSD sample could be related to pathophysiologic aspects associated with the chronicity of this disorder. Thus, impaired methylation could put one at risk for PTSD, and the ongoing stress of illness may further elevate HCY levels.

Finally, we are just beginning to uncover the role of inflammation as it relates to the cause and course of depression, and the link is, at least in part, related to methylation. A recent study of patients with chronic disease was able to link inflammation with global “hypermethylation” and even with increased mortality in these patients.

CLINICAL EVIDENCE

Many studies indicate that MDD patients are more likely than controls to demonstrate higher HCY levels, and low folate and B12 levels in the periphery. In a study of patients with elevated HCY levels who suffered with severe depression, low folate levels were noted both in red blood cells and in the cerebrospinal fluid (CSF), and, as expected, s-adenosyl-methionine levels were also low in the CNS. Decreased levels of monoamine metabolites were also noted in the CSF. It has been established that approximately one-third people with depression have low folate levels. It has also been noted that patients with lower than optimal folate levels simply have a poorer outcome when treated with antidepressants and significantly more antidepressant responders than nonresponders will show a rise in red blood cell folate during antidepressant treatment.

Reduced folate, or L-methylfolate, is critical for monoamine synthesis, and not only in HCY metabolism. L-methylfolate is necessary for the creation of BH4, a cofactor needed for the conversion of tryptophan to serotonin, and for the conversion of phenylalanine to tyrosine. Also, L-methylfolate can even “stand-in” for BH4 as a cofactor.

Inadequate folate or folate metabolism will result in a lower production of monoamines. A summary of the clinical results indicate that low folate levels
are associated with depression; patients are prone to more severe episodes; patients are more resistant to treatment; and patients have a poorer response to medications, as well as electroconvulsive therapy. Data from these studies have led to folate usage as an adjunctive therapy for MDD, and this topic is covered in detail in the other article that I authored in this issue.

**VITAMIN AND OTHER ENZYME POLYMORPHISMS**

Although MTHFR polymorphisms are the most commonly studied polymorphisms associated with depression, as well as developmental and neuro-psychiatric disorders, new evidence indicates that they rarely exist as a sole defect. In fact, other B vitamin polymorphisms can coexist with or without MTHFR, and lead to inadequate monoamine synthesis. For example, adequate reduced B12 is not only needed as a coenzyme for HCY metabolism, but also for intracellular formation of the l-methylfolate as needed, so it is possible to have impaired B12 metabolism that results in a functional folate deficiency, despite adequate intake and fully functional folate-related enzymes.

The reduced vitamins are ultimately coenzymes, yet the actual enzymes that they assist in HCY metabolism can also be affected by polymorphisms that result in reduced activity. Methionine synthase, and cystathionine beta-synthase are two common enzymes also vulnerable to polymorphic variances—and as outlined in the other article that I authored in this issue, their activity can still be restored through coenzyme or reduced vitamin therapy.

Finally, enzymes that are not involved in vitamin reduction or monoamine methylation, but rather directly in the conversion of l-tryptophan to serotonin or l-tyrosine to norepinephrine and dopamine could be expressed in variant forms that result in pathology or even enhanced activity. These polymorphisms are also areas of ongoing research.

**SUMMARY**

The HCY theory explains the genetic basis of depressive disorders. Because of less functional enzymes involved in HCY reduction and/or coenzyme (reduced B vitamin) synthesis, patients are simply unable to produce adequate serotonin, norepinephrine, and dopamine.

**MTHFR polymorphism often coexists with other polymorphisms in patients who are depressed.**

Although the most common, MTHFR polymorphism often coexists with other polymorphisms in patients who are depressed, and clinicians must address all possible defects in HCY metabolism to ensure therapeutic benefit.

Epigenetic evidence of the HCY theory is most clear when examining the polymorphisms and clinical courses of victims of childhood trauma, and patients with PTSD. Indeed, PTSD duration may even predict HCY levels. Epidemiologic studies leave no doubt that polymorphisms that effect HCY metabolism not only result in a risk of depression but multiple neuropsychiatric and vascular morbidities. Clinically, attempts to address the HCY theory have had mixed results, as the success of addressing only MTHFR variants relies on the patient only having a single HCY-related polymorphism, which would be a minority of patients with psychiatric and neurologic disorders.

With these insights, we can explore treatment options for depression that account for all possible enzymatic defects in the HCY cycle that result in monoamine deficits.

**REFERENCES**