

Recent Advances in Depression Research: From Stress to Molecular Biology and Brain Imaging

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This article will heuristically overview some of the more recent conceptualizations of the pathogenesis and pathophysiology of major depression as well as the functional changes in the central nervous system accompanying its successful pharmacotherapy. The neuropharmacology of affective disorders is a rapidly advancing field of scientific interest with significant complexity and numerous apparently contradictory findings. Within the space limitations of this article, some of the relevant newer conceptualizations of the pathophysiology and treatment of affective disorders will be summarized. Major concepts to be presented include the following: (1) the pathogenesis of affective illness may be conceptualized as an interaction between early and current life stressors and genetic vulnerability; (2) affective illness has been increasingly conceptualized as a potentially chronic progressive illness rather than an intermittent illness with full recovery between episodes; (3) affective illness, including its various stages, may be readily documented and monitored through changes in functional brain imaging; and (4) due to advances in molecular biology technology, there has been increasing evidence documenting changes in genetic activity involved in the pathogenesis of affective disorders from environmental stressors and/or from inherited genetic alterations and of the reversal of these changes accompanying successful pharmacotherapy.

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A wealth of literature has documented an enormous variety and complexity of functional changes in the central nervous system accompanying affective illness. This brief overview will heuristically simplify some of the more recent findings in this area to provide a model for conceptualizing major depressive disorder.

Some of the more recent conceptual underpinnings of the pathogenesis, pathophysiology, and neuropharmacology of affective disorders have come from the rapidly developing areas of molecular biology and functional brain imaging. While findings in these areas are extraordinarily complex (sometimes internally contradictory, and rapidly advancing), nonetheless, some models integrating these developments have been conceptualized.

GENETICS, ENVIRONMENTAL STRESSORS, AND MOLECULAR BIOLOGY

With respect to recent findings in molecular biology, it has long been conceptualized that affective disorders may be inherited. The traditional support for the genetic inheritance model has come from numerous studies documenting increased prevalence rates of affective illness in families with a proband with affective illness including studies of monozygotic and dizygotic twins reared separately. While at the time of this writing no specific gene or genes for affective illness have yet been identified, several recent substantive reports have shown linkage of bipolar illness in some pedigrees to chromosome 18.² This chromosomal area is particularly intriguing since it may contain the genetic sequence encoding corticotropin releasing factor and guanosine triphosphate binding protein, both of which have been implicated in the pathophysiology of affective illness. Other investigators using "candidate gene" molecular biological techniques have shown associations of such complex behaviors as depression, suicide, and violence with alterations in the genetic activity of monoamine oxidase A³ and tryptophan hydroxylase⁴ in some pedigrees. However, these observations have neither been replicated in other pedigrees nor do they appear to generalize to large populations. Some of the difficulty in identifying genetic vulnerability in unipolar or nonbipolar major

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depressive disorder may result from the high prevalence of these disorders in the general population, many of which presumably are nongenetic in origin. An alternative, non-mutually exclusive model, of the pathogenesis of affective disorders extends from the voluminous literature that both early life stressors and current life stressors may precipitate affective illness even in individuals with no apparent genetic vulnerability. Thus, the difficulty in differentiating these two sometimes clinically identical but etiologically separate types of affective illness is manifest, and these two etiologic disparate pathogeneses could confound molecular biological genetic linkage studies. Numerous animal studies, including nonhuman primate studies, have suggested that "learned helplessness" and other types of environmental stressors may precipitate affective illness. For example, even brief separations of nonhuman primate infants from their mothers may result in apparently persistent central nervous system alterations in the monkeys when they reach adulthood.⁵ These neurochemical vulnerabilities include significant alterations in the serotonergic and noradrenergic responses to pharmacologic challenges in the adult animals.⁵ These animal studies are consistent with the numerous theoretical suggestions and clinical observations that severe, especially repetitive, life stressors during child and adolescent development can result in increased vulnerability to affective illness during adult life.⁶⁻⁸ In addition, increasing numbers of studies have also indicated that even single episode significant, severe life stressors during adolescent or adult life may precipitate affective illness.⁹ Thus, it is conceptualized that early or current life stressors may precipitate a cascade of neurochemical changes precipitating the syndrome of major depressive disorder even in the absence of genetic vulnerability. Recently, an elegant study by Kendler and colleagues¹⁰ has suggested an interaction between genetic vulnerability to depression and environmental stressors. These investigators examined the relationship between genetics and life events in monozygotic and dizygotic female twins in which the proband sister either did or did not have affective illness. Thus, four subgroups were identified: (1) monozygotic twins in which the proband sister suffered from an affective disorder; (2) monozygotic twins in which the proband sister did not have an existing affective illness; (3) dizygotic twins in which the proband sister suffered from an affective disorder; and (4) dizygotic twins in which the proband sister did not have an affective disorder. These twin pairs were then followed while the vulnerability of the nonproband sister to the development of affective illness and the relationship of the development of affective illness to both genetic vulnerability and severe life stressors (such as death of a close relative, assault, serious marital problems, and divorce/breakup) was studied. The study reports that sisters with a proband sister, either monozygotic or dizygotic, with an affective disorder were more likely to develop affective disorders themselves than

those with proband sisters without affective disorders. The development of affective disorder was higher in the monozygotic sisters whose probands had affective disorders than in the dizygotic sisters whose probands had an affective disorder but was increased in both groups relative to the sisters of probands without affective disorders. These observations are consistent with a genetic inheritance model of affective illness. Most interestingly, twin sisters in all groups who experienced significant life stressors had an increased likelihood of developing affective illness independent of genetic vulnerability, consistent with an environmental stress model of affective illness. Finally, in the genetically vulnerable sisters, both monozygotic and dizygotic, there was an increased rate of depressive disorders in response to environmental stressors when compared with the nongenetically vulnerable sisters. This elegant study documents the associations of both genetic vulnerability to affective disorders and the influence of severe life stressors in both genetically and nongenetically vulnerable individuals. This model of the relationship between environmental stressors and vulnerability to affective illness is important with respect to patient education about depression. It appears that anyone with enough severe life stressors, even in the absence of genetic vulnerability, may develop affective illness. However, the model also suggests that patients who are genetically vulnerable to depression may be especially sensitive to environmental stressors and, thus, may need even more careful monitoring and attention to life styles and life stressors.

Molecular biological studies have also added significantly to our conceptualization of central neurochemical alterations accompanying affective illness. As reviewed in more detail elsewhere,¹¹ functional deficiencies in serotonergic transmission have been associated with depressive illness. These include, in both animal and human studies, absolute reductions in brain and spinal fluid serotonin content and associated alterations in presynaptic and postsynaptic serotonergic receptors and other serotonergic effector mechanisms.¹¹ One increasingly studied indice of serotonergic function in depression has been the serotonin transporter, which effects the reuptake of serotonin from the synapse back into the presynaptic nerve. A number of studies have indicated that in the brains of depressed humans there is a marked reduction in presynaptic serotonin reuptake transporters.^{12,13} Approximately 80% of serotonergic synaptic neurotransmitter activity is inactivated via reuptake of serotonin back into the presynaptic neuron. Functional deficiencies in serotonin transporters would presumably result in an impaired ability to inactivate serotonergic transmission. However, and potentially more importantly, the failure to transport serotonin back into the presynaptic neuron for reuse would allow synaptic degradation of serotonin and its ultimate depletion centrally. This could lead to a functional deficiency of presynaptic serotonin

pharmacology and the inability of the presynaptic neuron to secrete serotonin during subsequent repeated neurotransmitter events. Of additional interest in this regard is the accumulating large number of studies that has reported that serotonin transporters are depleted in platelets in patients suffering from major depression.¹⁴⁻¹⁶ Since platelets and neurons share common embryologic precursors, it is conceptualized that functional deficiencies of platelet serotonin transporters might potentially represent simultaneous changes occurring in central neurons.^{17,18} Thus, this reduction in platelet serotonin, as well as other observed changes in platelet serotonin pharmacology,¹⁹ might potentially represent a laboratory test for the diagnosis of depression. This is particularly promising given the relatively easy availability of accessing platelets through routine blood drawing. It is further believed that these deficiencies of serotonin transporters may be "state related" since it has been observed in some, but not all, studies that with clinical recovery from depression the platelet and neuronal serotonergic indices may normalize. Thus, these potential laboratory tests may be useful not only in diagnosis but also in the monitoring of treatment response. While antidepressant modalities have widespread effects on many neurotransmitter and neuromodulatory systems, a large literature has accumulated suggesting that virtually all antidepressant modalities result in a functional increase in CNS serotonergic responsivity.²⁰⁻²⁴ Functional deficiency in serotonin transporters presumably represents a functional inactivity of the presynaptic serotonin transporter gene. The restoration of presynaptic serotonin transporters accompanying pharmacotherapy and clinical response suggests that antidepressants may induce an activation of the serotonin transporter gene as part of their mechanistic effects. In this regard, it has been recently reported²⁵ that several antidepressant modalities, including a monoamine oxidase inhibitor and two tricyclic antidepressants, increased messenger RNA coding for serotonin transporter protein synthesis. This suggests that antidepressants may have a direct effect on gene expression via increasing messenger RNA and protein synthesis of the serotonin transporter even in the absence of direct binding of the medication to the serotonin transporter. Other molecular biological studies have reported effects of antidepressants and other psychotropic medications on genetic activity involved in the regulations of CNS transmitters and neuromodulators, including dopamine, norepinephrine, serotonin, and corticosteroid receptor gene expression.²⁶ The clinical relevance of these studies is that we have begun to understand at a DNA level the effects of antidepressant modalities, and thus, in this reviewer's opinion, the scientific and molecular biological understanding of the pathogenesis and treatment of depression parallels that of hypertension, diabetes, and other medical disorders.

BRAIN IMAGING

To this reviewer, one of the most dramatic and exciting developments in psychiatric research has been the significant technological advancements in functional brain imaging. This is an area that previously has been plagued by relatively primitive technology and inconsistencies among studies. However, technological advances have rapidly progressed in this area and there are now a number of studies that have shown some consistency in defining the neuroanatomical circuitry of affective illness. George and colleagues²⁷ have recently reviewed both the technology and the literature of structural and functional brain imaging of the affective disorders, and the reader is referred to this excellent article for a more comprehensive synopsis of this area. The majority of recent functional brain imaging studies have demonstrated a reduction in neuronal activity most pronounced in the left prefrontal cortical and limbic areas, particularly in recurrent or chronic depressive disorders.²⁸ This reduction in neuronal activity is evidenced by decreased blood flow and glucose utilization in these neuroanatomical areas.

These observations have been made with positron emission computed tomography (PET), single photon emission computed tomography (SPECT), and most recently with functional magnetic resonance imaging (fMRI), which is potentially more available and cost effective. The development of these technologies offers the promise of direct imaging diagnostic technology in the field of psychiatry.

In a creative approach to brain imaging, George and colleagues²⁹ have used functional brain imaging to study normal individuals experiencing transient alterations of normal affective states such as sadness and happiness. In contrast to the deficiencies in frontal and limbic blood flow observed in chronically depressed individuals, an activation of seemingly these same circuits occurs during self-induced sadness. Specifically, they observed increased cingulate and limbic activation during PET scanning of normal individuals asked to recollect very sad events in their life. As noted above, these findings contrast with those observed in chronically depressed patients who evidenced decreased neuronal activity in these circuits. A possible bridge to these separate observations has been imaging studies of Drevets and colleagues³⁰ in "familial pure" depressive disorder subjects. PET images of these pure depressions (those involving subjects with no comorbid psychiatric or medical disorders) are remarkably similar to those of George and colleagues²⁹ in normal sadness. Although alternative explanations exist, one heuristic model may be that stressors resulting in dysphoria in normal individuals activate this specific anatomical circuitry which, when persistent, results in depression and with further persistence and/or recurrence may eventually produce burnout or inactivation of this same circuitry. These collective observations may be integrated into a model that

brain activity, as reflected in functional brain imaging, may change during the course of affective illness, presumably modeling the development of chronic illness. Some investigators have even preliminarily hypothesized that these different stages of affective illness, observed in functional brain imaging studies, may be differentially responsive to pharmacologic and other treatment interventions, with the earlier overactive stages being more treatment responsive than the later underactive stages.³¹

Finally, in serial brain imaging studies it has been observed that the reductions in brain metabolic activity may be reversible with pharmacologic treatment response allowing the potential utility of these functional brain imaging methods in not only the diagnosis but in the monitoring of treatment response.

CONCLUSION

This brief overview of some of the more recent research findings in the neurobiology of depression suggests that changes in DNA occur during depression, and vulnerability may either be inherited or occur via environmental stress effects. In addition, these two indices, genetics and environmental stressors, appear to interact synergistically. These changes at the DNA level initiate a cascade of events that result in widespread synaptic neurotransmitter and neuroreceptor alterations and ultimately decreased neuronal activity, evidenced by reductions in blood flow and glucose utilization in specific neuroanatomical circuits of the brain. Antidepressant treatment may reverse these functional neuronal alterations restoring normal central nervous system pharmacology.

Finally, depression may potentially represent a spectrum of illness with stages of development beginning with normal mood alterations that, when recurrent, may result in depression and chronicity of neurobiological dysfunction. Preliminary evidence suggests that treatment response may be more favorable at these earlier rather than later stages of illness underlining the potential importance or early diagnosis and treatment.

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