New Understanding of Mechanisms of Action of Bipolar Medications

Gerard Sanacora, M.D., Ph.D.

The classical models of mood disorder pathophysiology and mechanism of antidepressant or mood stabilizing drug action focused on neurochemical deficits and the ability of medications to correct these deficits. Recent studies suggest alterations in neuroplasticity and cellular resiliency may be more closely related to the pathogenesis and pathophysiology of the disorders, as well as the mechanism of action related to effective treatments. Patients with mood disorders have been found to exhibit evidence of neuroplastic changes, such as reductions in hippocampal and cortical volume, glial and neuronal cell density, and levels of brain-derived neurotrophic factor; chronic stress, a major precipitator of depression, has been shown to cause many of the same neuroplastic changes to occur in animal models. Understanding the molecular mechanisms regulating neuroplasticity and their relationship to the pathophysiology of depression may provide insights into how current treatments work and point to novel targets for more efficacious treatments for patients with mood disorders.

For the Yale Depression Research Program, Department of Psychiatry, Yale University School of Medicine, New Haven, Conn. This article is derived from the planning teleconference series “Easing the Burden of Bipolar Disorder: From Urgent Situations to Remission,” which was held in February and March 2008 and supported by an educational grant from Eli Lilly and Company.

Dr. Sanacora is a consultant for AstraZeneca, Sepracor, Roche, and Ruxton; has received grant/research support from the National Institute of Mental Health, the National Alliance for Research on Schizophrenia and Depression, the Donahue Foundation, the Yale/Pfizer Imaging Alliance, the Stanley Foundation, AstraZeneca, Sepracor, and Ruxton; has received honoraria from Abbott, AstraZeneca, Bristol-Myers Squibb, Lundbeck, and Sepracor; has given expert testimony for Shook, Hardy & Bacon; and has received patents for U.S. patent application PCT/US06/108055.A1.

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The monoamine hypothesis of depression has been the primary focus in the understanding of the pathophysiology and treatment of mood disorders for more than 40 years.1 The classical model that depression is caused by a deficiency in synaptic levels of the monoamine neurotransmitters norepinephrine and/or serotonin led to the development of safe and effective treatments, including the monoamine oxidase inhibitors, tricyclic antidepressants, and selective serotonin reuptake inhibitors. Each new class of agents has sought to improve the safety, tolerability, and efficacy of antidepressants. However, the monoamine hypothesis does not fully explain why as many as 40% to 50% of patients with depression have an inadequate response to treatment with antidepressants.2,3 The monoamine theory also does not explain the delayed clinical effect seen in antidepressant treatment, so that while an antidepressant expresses its effect on intrasynaptic levels of serotonin within hours, it may take weeks for therapeutic action to occur. These and other observations have led to a new model of mood disorders, one which emphasizes neuroplasticity and the downstream effects of antidepressants and mood stabilizing medications on signaling pathways and gene expression4 rather than simple neurochemical deficits.

NEUROPLASTICITY MODEL OF MOOD DISORDERS

Neuroplasticity (Table 1) takes the form of many diverse structural, chemical, and energetic processes that occur in the brain in the form of generation of new neurons (neurogenesis), new glial cells (gliogenesis), new synapses (synaptogenesis), new blood vessels (angiogenesis), changes in intracellular signaling cascades and gene regulation, and structural changes to the axon or the dendrite down to the level of receptor trafficking. These processes result in phenomena such as long-term potentiation or long-term depression, which are changes in the efficiency of synaptic transmission as a result of repeated stimulation. Neuroplasticity allows the neurons and other cell types in the brain to adjust their activities in response to new situations or to changes in their environment, and provides the cellular mechanisms underlying the brain’s resiliency to injury and disease.

It is now believed that several disease processes, as well as stress, can have neurotoxic-like effects in the brain, leading to impaired neuroplasticity and, in some cases, neuroapoptosis. This mechanism is believed to contribute to the pathogenesis of several neurodegenerative disorders, possibly including the mood disorders.5–7 The regional specificity of the various disease processes and the effects of stress within the central nervous system may contribute to the varied clinical syndromes associated with the degenerative disorders. Conversely, several neurotrophic factors...
and antiapoptotic agents have been shown to provide a measure of neuroprotection and cellular resiliency to cope with changes that occur related to neurotoxicity and neurodegeneration. Increasing evidence suggests the clinical benefits of antidepressant and mood stabilizing treatments are mediated through their ability to alter the balance of the various factors regulating neuroplasticity and resiliency.

Evidence of Neuroplastic Changes in Patients With Mood Disorders

Studies have reported that structural and neuroplastic changes occur in the brains of patients with mood disorders. Drevets et al. found reduced metabolic activity and cortical volume in the subgenual prefrontal cortex of patients with bipolar or unipolar depression. These findings were confirmed and extended in a later histological study that showed a reduction in the number of glia in patients with major depressive disorder (MDD) and bipolar disorder. A meta-analysis by Videbech and Ravnkilde found strong evidence for reduced hippocampal volume in patients with unipolar depression, noting a correlation between the number of episodes of recurrent depression and the amount of reduction seen in hippocampal volume. Rajkowska and colleagues found reductions in neuronal and glial cell volume and density in the dorsolateral prefrontal cortex and decreased neuronal size and glial density in the caudal orbitofrontal cortex of patients with MDD, and reduced glial and neuronal density with glial hypertrophy in individuals with bipolar disorder. Cotter and colleagues also found that glial cell density and neuronal size were reduced in patients with MDD; they reported similar reductions in schizophrenia, but no difference in patients with bipolar disorder compared with controls. With regard to the relationship between mood disorders and neurotrophic factors, reduced levels of brain-derived neurotrophic factor (BDNF) have been consistently found in patients with depression in both postmortem studies of the brain (hippocampus and prefrontal cortex) and studies of serum in live patients. While fewer in number, other studies have also demonstrated significantly reduced levels of serum BDNF in type I and II bipolar disorder subjects.

The Effects of Stress on Neuroplasticity

Stressful life events are known triggers for major depressive and manic episodes. Animal models have been developed to study the effects of stress on the various cellular mechanisms and processes of the brain. Studies have found that repeated stress induces atrophy in the apical dendritic field of pyramidal cells in the medial prefrontal cortex in rats; Liu and Aghajanian reported that several stress-linked neuromodulators were found to selectively target these apical dendrites. Chronic psychosocial stress has been shown to decrease hippocampal volume and reduce both the size and number of glial cells in animal models. Furthermore, chronic stress has also been demonstrated to inhibit cell proliferation and survival, predominantly of glial and endothelial cells, in the area of the prefrontal cortex. These changes in hippocampal volume and the number and density of glial cells in the prefrontal cortex following chronic stress are similar to the changes found in the postmortem studies of subjects with mood disorders cited above. Further, a meta-analysis by Smith also confirmed the reduction of hippocampal volume in patients with posttraumatic stress disorder.

NEUROBIOLOGICAL MECHANISMS AFFECTED BY STRESS AND TARGETED BY MOOD DISORDER TREATMENT

Activation of receptors found on the cellular membrane—including ionotropic, metabotropic, steroid, and tyrosine kinase receptors—leads to stimulation of signal transduction cascades, the mechanism by which cells transcribe their effects from the synaptic membrane into the cytosol. These cascades lead to the phosphorylation of various kinases and enzymes that have multiple effects—structural, energetic, chemical, and epigenetic—on the brain. Activation of some signal transduction cascades can create kinases that promote apoptosis; activation of other cascades can activate kinases or enzymes that are antiapoptotic. A healthy brain maintains a delicate balance of apoptotic and antiapoptotic activity, and this balance of plasticity is constantly being changed throughout life by the activation of membrane receptors regulating these cellular processes. Stress and drugs acting on the different receptor subtypes can alter this balance, changing the signal transduction cascades and, ultimately, causing changes in gene expression and neuroplasticity (Figure 1). Understanding the processes involved in regulating neuroplasticity can further our understanding of the

Table 1. Glossary of Terms

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Neuroplasticity</td>
<td>The brain's ability to reorganize itself by forming new neural networks and connections throughout life</td>
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<tr>
<td>Resiliency</td>
<td>The brain's ability to withstand and/or recover from neurotoxic events or different types of cellular stressors</td>
</tr>
<tr>
<td>Neuroprotection</td>
<td>Mechanisms that protect neurons and glia from apoptosis or other forms of degeneration</td>
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<tr>
<td>Neurotoxicity</td>
<td>The tendency for some treatments or events to affect or damage the neurons and glia</td>
</tr>
<tr>
<td>Neuroapoptosis</td>
<td>The programmed cell death of brain cells thought to be involved in several neurodegenerative disorders</td>
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<tr>
<td>Epigenetics</td>
<td>Stable changes in gene expression that can be maintained between cell divisions, and sometimes generations, but do not involve changes in the underlying DNA sequence of the organism</td>
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<tr>
<td>Neurotrophic factors</td>
<td>Substances responsible for the growth and survival of neurons during development and for the maintenance of adult neurons</td>
</tr>
<tr>
<td>Receptor trafficking</td>
<td>The ability to insert or remove various receptors from the cell membrane</td>
</tr>
<tr>
<td>Apoptosis</td>
<td>A form of programmed cell death in multicellular organisms</td>
</tr>
<tr>
<td>Antiapoptotic</td>
<td>Agents that reverse or prevent the apoptosis from occurring</td>
</tr>
<tr>
<td>Epithelial growth factor (EGF)</td>
<td>A protein that stimulates the growth of epithelial cells</td>
</tr>
<tr>
<td>Neurotrophic factor</td>
<td>A factor (BDNF) that promotes the growth and survival of neurons</td>
</tr>
<tr>
<td>Neurotoxic event</td>
<td>An event that damages the neurons and glia</td>
</tr>
<tr>
<td>Neurodegeneration</td>
<td>The process of cell death that is not part of the normal cell turnover process</td>
</tr>
<tr>
<td>Neuroplastic event</td>
<td>A change in the balance of neuroplastic and antiapoptotic activity</td>
</tr>
<tr>
<td>Neuroprotective event</td>
<td>A change in the balance of neuroprotective and antiapoptotic activity</td>
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<tr>
<td>Neuroapoptotic event</td>
<td>A change in the balance of neuroapoptotic and antiapoptotic activity</td>
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Glutamatergic System

Glutamate is the most abundant excitatory neurotransmitter in the brain; it is necessary for most forms of learning and is involved in most aspects of human behavior. The glutamatergic system is a major factor in the regulation of brain plasticity and is also a principal target of the plasticity. The glutamatergic system is believed to contribute to the regulation of many forms of plasticity, both activating antiapoptotic/prosurvival pathways and neurotoxic/apoptotic pathways. Glutamate is released from the presynaptic neuron, crosses the synaptic cleft, and, upon reaching the postsynaptic neuron, has neurotransmitter effects on the N-methyl-D-aspartate (NMDA) receptors, metabotropic receptors, and the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. After the glutamate has its effect, it is rapidly cleared into the glial cells. In contrast to the monoamines, which are taken back up into the neurons, the glial cells play a critical role in clearing the large majority of glutamate out of the postsynaptic cleft and into the glial cell, where the glutamate is quickly converted to glutamine and cycled back for another round of neurotransmission. Glutamine is also used as the precursor for γ-aminobutyric acid (GABA), which is the major inhibitory neurotransmitter in the brain; therefore, in the case of the glutamate and GABA systems, the glial cells play a critical role in modulating metabolism and neurotransmission.

Stress has been shown to cause an increase in extracellular glutamate in the prefrontal cortex and hippocampus, which, in extremes, is believed to lead to neurotoxic-like events in both of these areas. Excessive glutamate stimulation, especially through the extrasynaptic NMDA receptors, leads to an increase in calcium influx that changes the calcium-dependent enzyme activity, ultimately leading to increased free radicals, cell damage and atrophy, and increased expression of proapoptotic factors. As mentioned above, stress has marked effects on glial cells. Since glial cells are the primary mechanism through which glutamate is cleared from the extracellular space, it is postulated that this will result in further increased levels of extracellular glutamate and increased levels of toxicity, as well as disrupted amino acid neurotransmitter metabolism. Additional studies also illustrate the potential role of other glutamate receptors including AMPA and the metabotropic receptors in the pathophysiology and treatment of mood disorders. Interestingly, there have been several recent studies demonstrating significantly abnormal concentrations of glutamate and the other amino acid neurotransmitters in the brains of mood disorder patients. A more complete understanding of the glutamatergic system may help to explain the mood stabilizing effects of medications such as lithium and lamotrigine that result in increased glutamate clearance and decreased release, and lead to several possible novel targets for the treatment of mood disorders (Figure 2).

Hypothalamic-Pituitary-Adrenal Axis

Stress also affects the hypothalamic-pituitary-adrenal axis, one of the central stress-response systems. Activation of the cortisol glucocorticoid receptor has direct effects on gene expression leading to many proapoptotic pathways, including decreases in some of the modulators of energy metabolism, such as decreased expression of the glucose transporters. Several drugs are thought to act by modulating these effects. First, glucocorticoid antagonists such as mifepristone are thought to directly antagonize the effects of glucocorticoid at various sites both inside and outside the brain. Second, other agents such as metyrapone are thought to affect the synthesis of glucocorticoids and may have some effects on mood. Third, corticotrophin-releasing factor antagonists seem to block the effect of corticotrophin-releasing hormone within the brain, while regulating some of the release of...
3) Group I metabotropic glutamate receptor (mGluR) modulation

6) Facilitation of glutamate clearance by excitatory amino acid transporters (EAATs)—Evidence suggests facilitation of glutamate clearance can protect against neurotoxicity.60 Chronic lithium, now recognized to have potent neuroprotective properties,37 has been demonstrated to increase glutamate clearance.38 Recent studies suggest that this effect may also be associated with antidepressant-like effects, as seen with the beta-lactam ceftriaxone60 and possibly the effectiveness of riluzole.44 Exploratory clinical trials are now underway to further explore the utility of this approach to treating treatment resistant mood disorders.

Figure 2. Potential Glutamatergic Targets for Drug Development*

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1) α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor modulation—Several animal models suggest that changes in AMPA receptor function are tied to the pathophysiology of mood disorders and that AMPA modulating drugs have antidepressant and mood-stabilizing properties.31,32 Current studies are underway to determine the effectiveness of these medications in several neuropsychiatric disorders.

2) N-methyl-D-aspartate (NMDA) receptor modulation—Acute administration of NMDA receptor antagonists such as ketamine rapidly produce antidepressant-like responses in both clinical and preclinical studies.37-40 The potential development of selective agents targeting the various NR2 (NMDA receptor) subunits may provide a differential ability to modulate extrasynaptic (2a) and synaptic (2b) NMDA receptors.

3) Group I metabotropic glutamate receptor (mGluR) modulation—mGluR1/5 antagonists such as 2-methyl-6-(phenylethynyl) pyridine (MPEP), 3-[(2-methyl-1,3-thiazol-4-yl) ethynyl]pyridine (METP), and several others have been shown to have antiexcitatory and antidepressant-like activity in preclinical animal models.41,42

4) Voltage-dependent Na+ channels—Inhibition of stimulated glutamate release via actions on the voltage-dependent sodium channel is believed to be the primary mechanism related to the mood stabilizing action of lamotrigine.43 It may also be related to the antidepressant and antianxietyotic effectiveness of riluzole that has been reported in several open-label studies.44

5) Group II metabotropic receptor modulation—mGluR2/3 receptor agonists have been shown to have anxiolytic properties while mGluR2/3 receptor antagonists have demonstrated antidepressant activity.41,42 Early phase clinical trials have recently been initiated, demonstrating the effectiveness of mGluR2/3 receptor agonists in the treatment of schizophrenia,43 and examining the effectiveness and safety of this class of drugs for the treatment of neuropsychiatric disorders.

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the hormone in the adrenal gland through activation of the pituitary.

**Monoaminergic Pathways and Signal Transduction Cascades**

Another system affected by stress and shown to have significant effects on the regulation of neuroplasticity are the monoaminergic pathways,44 which have long been considered a component of the pathophysiology and treatment of mood disorders. The regulation of monoamine transmission can be targeted by the classic monoaminergic agents, such as selective serotonin reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors, and atypical antipsychotics. Through actions at serotonin, noradrenaline, and dopamine receptors on the cell surface membrane, these drugs elicit variable effects on signal transduction cascades that lead to downstream changes in metabolism, energetics, and gene expression. It is also possible to more directly target the downstream signal transduction cascades associated with these neurotransmitter systems through alteration of the adenosine triphosphate to cyclic adenosine monophosphate (cAMP) ratio using a phosphodiesterase inhibitor like rolipram.55 Rolipram blocks the degradation of cAMP, enhancing the activity of some signal transduction pathways involved in the regulation of neuroplasticity.

**Neurotrophic Factors**

Stress and mood disorder treatments appear to have opposing effects on the expression of neurotrophic factors, especially BDNF. Activation of BDNF promotes antiapoptosis and cell proliferation that is involved in cell maintenance and survival;46 stress has been shown to decrease the expression of BDNF.57 Decreases in BDNF cause further decreases in the antiapoptotic cascades, and decreases in the antiapoptotic enzymes and kinases, so that the balance may be shifted more toward cell death or cell atrophy. Increases in BDNF expression in the hippocampus have been shown in animals with the chronic administration of almost all classes of antidepressant agents and with electroconvulsive therapy (ECT).58,59 In addition, ECT and chronic administration of antidepressants enhance induction and prolonged expression of BDNF. Antidepressant treatment has also been shown to increase serum BDNF levels.60,61 The 2 major mood stabilizers, lithium and valproic acid, also enhance the expression of BDNF;62,63 while the effects of antipsychotic and atypical antipsychotic agents on neurotrophic factor expression remain less well defined.64 Other agents without antidepressant or mood stabilizer properties, such as morphine and cocaine, appear to have little or no effect on BDNF expression. Exercise has also been shown to enhance the expression of BDNF in the rat hippocampus.59 Pittenger and Duman44 have suggested that multiple neurotrophins may be involved in antidepressant action. For example,
vascular endothelial growth factor increases hippocampal long-term potentiation, increases neurogenesis, and seems to be necessary to the actions of antidepressants.

**Regulators of Cellular Resilience and Death**

Much recent attention has turned to the effects of stress and mood stabilizing medications on the regulation of apoptotic and antiapoptotic kinases or enzymes. The apoptotic glycogen synthase kinase (GSK-3β) and the antiapoptotic protein Bel-2 have gained prominence in the study of mood disorders. Both lithium and valproic acid inhibit GSK-3β activity, and increase Bel-2 levels, which is the protective factor, in the frontal cortex. Modulation of these apoptotic and antiapoptotic enzymes is believed to influence rates of programmed cell death and survival and provide a novel target for future drug development.

**Chromatin Remodeling**

While all of the targeted mechanisms described can affect the regulation of transcription factors, gene expression can also be affected in the long term by change within the nucleus. Chromatin remodeling within the nucleus can chronically alter gene expression through histone acetylation and methylation, changing the structure of the DNA and determining which genes are expressed and which are silenced. Recent studies illustrate that environmental factors or events that occur throughout life can have long-lasting consequences. Tsankova and colleagues have shown that chronic social defeat stress administered to mice induced decreased BDNF expression and increases in repressive histone acetylation. A study by Weaver and colleagues found that DNA methylation patterns at a glucocorticoid receptor in the hippocampus were influenced by external stimuli (quality of maternal care) and that these patterns persisted into adulthood. In both of these studies, these changes were reversible by the administration of a histone deacetylase (HDAC) inhibitor. Valproic acid and ECT are known to have effects on histone acetylation and may, therefore, target this mechanism. A study by Leng and colleagues demonstrated the efficacy of the combined use of an HDAC inhibitor with a GSK-3β inhibitor in blocking the glutamate excitotoxicity.

**Perceived Stress**

Finally, a target of treatment for mood disorders is the stress itself. The direct effects of stress or perceived stress may be modulated with psychotherapies such as cognitive-behavioral therapy, interpersonal therapy, and social rhythm therapy. Furthermore, physical exercise also has many effects consistent with promoting neuroresiliency, including stimulation of neurogenesis and increasing BDNF and other neurotrophic factor expression, which may provide mood-stabilizing and antidepressant effects.

**CONCLUSION**

Neuroplastic changes in the brain are believed to play a major role in the pathogenesis and pathophysiology of mood disorders. The conceptualization of the role of neuroplastic mechanisms in mood disorders represents a break from the classical psychiatric model of neurochemical deficits and provides an alternative model to view the mechanism of antidepressant and mood stabilizing drug actions. Using the neuroplasticity model of mood disorders, specific neurobiological mechanisms can be targeted for novel treatments.

**Drug names:** ceftriaxone (Rocephin and others), ketamine (Ketalar and others), lamotrigine (Lamictal and others), lithium (Eskalith, Lithobid, and others), metyrapone (Metopirone), mifepristone (Mifeprex), morphine (Kadian, Avinza, and others), riluzole (Rilutek and others), valproic acid (Depakene and others).

**Disclosure of off-label usage:** The author has determined that, to the best of his knowledge, ceftriaxone, ketamine, metyrapone, mifepristone, riluzole, and rolipram are not approved by the U.S. Food and Drug Administration for the treatment of mood disorders.

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