Cellular Plasticity Cascades: Targets for the Development of Novel Therapeutics for Bipolar Disorder

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For a number of patients with bipolar disorder, current pharmacotherapy is generally insufficient. Despite adequate treatment, patients continue to have recurrent mood episodes, residual symptoms, functional impairment, psychosocial disability, and significant medical and psychiatric comorbidity. Drug development for bipolar disorder may occur through one of two approaches: the first is by understanding the therapeutically relevant biochemical targets of currently effective medications. Two promising direct targets of lithium and valproate are glycogen synthase kinase-3 and histone deacetylase. The second path results from our understanding that severe mood disorders, although not classical neurodegenerative disorders, are associated with regional impairments of structural plasticity and cellular resilience. This suggests that effective treatments will need to provide both trophic and neurochemical support, which serves to enhance and maintain normal synaptic connectivity, thereby allowing the chemical signal to reinstate the optimal functioning of critical circuits necessary for normal affective functioning. For many refractory patients, drugs mimicking “traditional” strategies, which directly or indirectly alter monoaminergic levels, may be of limited benefit. Newer “plasticity enhancing” strategies that may have utility in the treatment of mood disorders include inhibitors of glutamate release, N-methyl-D-aspartate antagonists, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid potentiators, cyclic adenosine monophosphate phosphodiesterase inhibitors, and glucocorticoid receptor antagonists.

Key Words: Antidepressant, bipolar disorder, depression, glutamate, plasticity, treatment

Bipolar disorder is one of the most severely debilitating of all medical illnesses and affects the lives and functioning of millions worldwide. Recent studies indicate that for a large percentage of patients, outcome is poor. Patients afflicted with bipolar disorder generally experience high rates of relapse, chronicity, lingering residual symptoms, cognitive and functional impairment, psychosocial disability, and diminished well-being (Fagiolini et al 2005; Revicki et al 2005; Tohen et al 2003). In addition many deleterious health-related effects are now being recognized. Bipolar disorder is increasingly being viewed as an illness not only with purely psychologic manifestations but as a systemic disease frequently associated with cardiovascular disease, diabetes mellitus, obesity, and thyroid disease (Kupfer 2005). Despite these facts, little is known about the precise neurobiological underpinnings of bipolar disorder, which is essential for the development of specific-targeted therapies that are more effective, work rapidly, and are better tolerated than existing therapies. In this perspective article, we discuss the prospect of developing new medications for bipolar disorder based on two approaches:

1. Understanding the presumed therapeutically relevant biochemical targets of medications currently in use and using that knowledge to design new drugs directed at these targets. This includes not only direct biochemical targets, but also downstream targets that are regulated by chronic drug administration (i.e., consistent with the clinical temporal profile).

2. Understanding the pathophysiology of the illness (admittedly in its infancy) and using that knowledge to design therapeutics to attenuate or prevent those pathologic processes.

Novel Therapeutic Targets Emerging from Our Understanding of the Mechanisms of Action of Existing Agents

The drugs that have revolutionized the treatment of bipolar disorder are lithium and, more recently, valproate. They are effective in the treatment of acute manic episodes, provide reasonable protection against recurrent mood episodes, and have modest antidepressant properties (Davis et al 2005; Keck and Manji 2002). Elucidation of the direct target(s) by which effective treatments stabilize an underlying dysregulation of limbic and limbic-associated function also offers the potential to delineate the underlying pathophysiology of bipolar disorder. Several direct targets of lithium and valproate have been identified (for a comprehensive review see Gould et al 2004). In this paper, we only discuss glycogen synthase kinase-3 (GSK-3, a direct target of lithium) and histone deacetylase (a direct target of valproic acid) because several inhibitors are likely soon to be available to clinically test. As of this writing, there are no clinically available modulators of the other direct targets of lithium or valproate. It should be noted that inositol monophosphatases (IMPases) may represent an important target for lithium’s actions; however, at this point, there are no selective central nervous system (CNS)-penetrant IMPases available for human use.

Glycogen Synthase Kinase-3

GSK-3 is a serine/threonine kinase that is believed to be, in general, constitutively active in cells, and is deactivated by signals originating from numerous signaling pathways [for example the Wnt pathway, PI3′-kinase (PI3K) pathway, protein kinase A (PKA), protein kinase C (PKC), among many others (Doble and Woodgett 2003; Figure 1). Thus, the activity of GSK-3 can be regulated by the action of a variety of other cellular signaling mechanisms,
which serve to fine-tune this critical enzyme’s activity. Initial interest in glycogen synthase kinase-3 (GSK-3) as a target for the treatment of mood disorders arose from the seminal observations that lithium directly inhibited the enzyme (Klein and Melton 1996). More recent preclinical evidence implicates the modulation of GSK-3 in either the direct or downstream mechanism of action of many other mood stabilizer and antidepressant medications currently in use (see Gould and Manji 2005 and references therein). Notably, these medications have been shown to regulate the GSK-3 signaling cascade in vivo, and in areas of the brain implicated in bipolar disorder. GSK-3 modulates apoptosis and synaptic plasticity and probably circadian cycle by modulating gene expression of proteins involved in these processes (reviewed in Gould and Manji 2005; Gould et al 2004).

Very recent data from a variety of leading laboratories has greatly strengthened the case for an important role for GSK-3 in the pathophysiology/treatment of bipolar disorder (see Gould and Manji 2005 and references therein):

1. GSK-3 is markedly regulated by serotonin, dopamine, psychostimulants, and antidepressants and is at the nexus of multiple neurotransmitter and signaling cascades putatively involved in bipolar disorder.

2. GSK-3 is a major regulator of apoptosis and cellular plasticity and resilience. Generally, increased activity of GSK-3 is pro-apoptotic, whereas inhibiting GSK-3 attenuates or prevents apoptosis (for review, see Gould and Manji 2002; Jope and Bijur 2002). Preclinical studies in animal models of Alzheimer’s disease have shown that GSK-3 inhibition has salutary effects on the two major pathways implicated in Alzheimer’s disease, namely, the β-amyloid and hyperphosphorylated tau cascades (Phiel et al 2003). As we discuss in more detail later, there is emerging knowledge that bipolar disorder is associated with cell loss and atrophy, and there is now considerable data demonstrating that lithium exerts neuroprotective effects. These effects are believed to be mediated in large part by inhibition of GSK-3 and upregulation of bcl-2 (Gould and Manji 2002; Jope and Bijur 2002).

3. GSK-3 has a major effect on regulating the circadian period in diverse species, an effect it shares with lithium (Gould et al 2004). Treatment strategies are being developed based on a chronobiological model of bipolar disorder.
4. Recent animal behavioral data (from pharmacologic and genetic models) have shown that manipulation of the GSK-3 signaling cascade produces both antimanic and antidepressant effects in models of depression or mania. To the best of our knowledge, other than lithium, this is the only manipulation that has been demonstrated to exert both antidepressant and antimanic effects.

5. Gonadal steroids play a major role in regulating the GSK-3 signaling cascade.

6. Genetic variations in GSK-3 have been associated with age of onset and response to sleep deprivation in patients with bipolar disorder (discussed in Gould and Manji 2005). Although independent replication of these findings is clearly necessary, these preliminary reports are encouraging indeed.

In view of their therapeutic effects not only in bipolar disorder but also in Alzheimer’s disease and other neurodegenerative disorders, it is not surprising that numerous pharmaceutical companies are actively developing specific, brain penetrant GSK-3 inhibitors. Examples of classes of GSK inhibitors are summarized in Table 1. All but the thiadiazolidinones appear to exert their actions by being competitive with ATP (reviewed in Dorronsoro et al 2002; Martinez et al 2002).

In attempting to achieve selectivity for GSK-3 inhibition it is critical to avoid side effects that may occur with GSK-inhibition such as cardiac hypertrophy and the potential risk for cancer because of the concern that specific GSK-3 inhibitors may have carcinogenic properties (due to upregulation of the Wnt pathway, which is common in human cancers). However, epidemiological studies of lithium and preliminary rodent studies do not suggest a major cancer effect (reviewed in Gould et al 2003, 2004).

**Histone Deacetylases: A Therapeutically Relevant Target for Valproate?**

It has been appreciated for some time that many psychotropic agents may bring about their delayed therapeutic effects by regulating gene expression in critical neuronal circuits. In recent years, a novel mechanism has emerged by which valproate may regulate gene expression by acting as a histone deacetylase (HDAC) inhibitor. All of the human genome is packaged in the nucleus into chromatin, a dynamic macromolecular complex made up of repetitive units, the nucleosomes. A single nucleosomal core particle is composed of a fragment of DNA (146 bp) wrapped around a histone octamer formed by four histone partners, an H3-H4 tetramer and two H2A-H2B dimmers (Mornet et al 2005). Histones are small basic proteins that, by complexing with DNA, form the nucleosome core. Histones can be in one of two antagonist forms, acetylated or deacetylated, equilibrium regulated by the corresponding enzymes, histone acetylases (HATs), and histone deacetylases (HDACs). Acetylation of histones reduces their affinity for DNA and is a major epigenetic regulator of gene expression. Misregulation and aberrant activities of HATs and HDACs, due to overexpression, mutation, translocation, and

### Table 1. Examples of Candidate Drugs for the Treatment of Bipolar Disorder

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug/Compound</th>
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<tbody>
<tr>
<td>Direct targets of lithium and valproate</td>
<td>Zinc, indirubins, maleimides, hymenialdesine, paullones, thiadiazolidones, synthetic phosphorylated peptide,azole derivatives</td>
</tr>
<tr>
<td>GSK inhibitors</td>
<td>Small-molecular weight carboxylates (butyrate, valproic acid, sodium phenylbutyrate), hydroxamic acids (trichostatin A [TSA]), suberoylanilide (SAHA) and LAQ-824, benzamides (MS-275, CI-994), epoxiketones (2-Amino-8-oxo-9,10-epoxydecanoic acid [AOE] and trapoxin B, cyclic peptidic (depsipeptide, apicidin), hybrid molecules ([CHAP31, CHAP50])</td>
</tr>
<tr>
<td>HDAC inhibitors</td>
<td>Tamoxifen, LY33531, ruboxistaurin, rottlerin, indolocarbazoles, UCN-01, CGP41251, PKC412, bisindolylmaleimides, balanol, indolylindazolylmaleimides, aprinocarsen</td>
</tr>
<tr>
<td>Putative plasticity enhancers</td>
<td>Riluzole, Ketamine, memantine, feldzamine, zopiclone, benzylpiperdione (aniracetam), benzoylpyrrolidines (Ampakines), ary1propylsulfonamides (LY392098, LY451616), S18986</td>
</tr>
<tr>
<td>Inhibitors of glutamate release and AMPA potentiator</td>
<td>Group III mGlur agonists, Ketocozazol, aminoglutethimide, metyrapone, Milเฟpristone (RU-486), ORG 34517, ORG 34850, ORG 34116, AL082D06, cyproterone acetate</td>
</tr>
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| NMDA antagonists | Peptides (astressin, α-hel corticotropin releasing factor), small molecule non-peptides (CP-154526, antalarmin, DMP-695, DMP-696, CRA-1000, R-121919, SSR-125543, NBI 35965, NBI 27914)
| AMPA receptor potentiators | Pramipexole |
| Glutamatergic mGlur | |
amplification, have all been implicated in oncogenesis (Drummond et al 2005). For all these reasons, HDAC inhibition has been regarded as a promising anticancer drug target, and it is now well established that HDAC inhibitors display ability to affect several cellular processes that are dysregulated in neoplastic cells. Valproate, a mood stabilizer, is also an HDAC inhibitor and may cause spina bifida if taken during pregnancy. Gurvich and colleagues (2005) found that valproate and other HDAC inhibitors cause very similar and characteristic developmental defects in Xenopus and zebrafish, whereas valproate analogs with poor inhibitory activity in vivo have little teratogenic effect (Gurvich et al 2005). Indeed, valproate is already being investigated as a treatment for cervical cancer (Chavez-Blanco et al 2005).

Whereas dysregulation and aberrant activities of HATs and HDACs may lead to cancer in the CNS, the loss of HAT and HDAC regulation has been demonstrated to be involved in neuronal dysfunction and degeneration (Langley et al 2005). Consistent with this, a number of observations clearly establish that the HATs CBP and p300 (HAT family proteins) play vital roles in the development, function, and survival of neurons. CBP HAT activity has been identified also as a critical component of memory consolidation (Korzus et al 2004). Furthermore, Rouaux et al (2003), using an in vitro model of cell death (i.e., activity-deprived cerebellar granule neuron apoptosis) showed that the overexpression of either CBP or p300 is neuroprotective. One mechanism by which CBP and p300 are suggested to contribute to neuronal survival is through the transcription factor CREB (cyclic adenosine monophosphate [cAMP] response element binding protein). CREB binds to CREB-response elements (CREs) located in the promoters of number of genes largely implicated in neuroprotection, such as bcl-2 (Wilson et al 1996) and BDNF (Finkbeiner et al 1997; Tao et al 1998).

In recent years, there has been an increased interest in epigenetics, which is defined as the study of mitotically or meiotically heritable variations in gene function that cannot be explained by changes in DNA sequence (Kato et al 2005). Epigenetics purports to define the molecular mechanisms by which different cells from different tissues of the same organism, despite their DNA sequence identity, exhibit very different cellular phenotypes and perform very different functions. It is presumed that phenotypic and functional differences are the cumulative result of a large number of developmental, environmental, and stochastic events, some of which are mediated through the epigenetic modifications of DNA and chromatin histones. DNA methylation involves covalent binding of a methyl group to cytosines by enzymes called DNA methyltransferases; following promoter methylation, gene transcription is generally (but not always) suppressed. Methylation of DNA also interacts with a second, and perhaps more dynamic, level of epigenetic regulation, namely a large variety of posttranslational modifications to histones, such as acetylation, methylation, phosphorylation, and ubiquitination (for review, see Petronis 2004; Figure 2).

Epigenetic regulation is thus one of the molecular substrates for “cellular memory” that may help gain understanding of how environmental affect results in temporally dissociated altered behavioral responses. As discussed, valproate is known to be an HDAC inhibitor, raising the possibility that this direct target may play a role in some facets of its therapeutic effects or side effects (notably teratogenicity or impact on polycystic ovarian disease).

With respect to the potential role of HDAC inhibitors in psychiatric disorders, Weaver and colleagues (2004) have undertaken an elegant series of studies on epigenetic programming by maternal behavior. They reported that increased pup licking and grooming (LG) and arched-back nursing (ABN) by rat mothers altered the offspring epigenome at a glucocorticoid receptor gene promoter in the hippocampus. Offspring of mothers that showed high levels of these behaviors were found to have differences in DNA methylation compared with offspring of “low-LG-ABN” mothers. These differences were reversed with cross-fostering, persisted into adulthood, and were associated with altered histone acetylation. Central infusion of a HDAC inhibitor removed the group differences in histone deacetylation, DNA methylation, and hypothalamic–pituitary–adrenal (HPA) responses to stress. Thus, the authors showed that an epigenomic state of a gene can be established through behavioral programming, and it is potentially reversible. This line of research is interesting in that the sequelae of early life stressors often seen in patients with bipolar disorder (Leverich et al 2003) may be amenable to treatment with HDAC inhibitors. Recent

Figure 2. Histone deacetylase (HDAC) inhibitors and epigenetics: a putative role in cellular memory. Epigenetic changes represent a mechanism that can permanently alter gene expression, thus subsequently affecting behavior. Both decreased methylation of DNA (CH3) and increased acetylation (OCH2CH3) of histones modify the local chromatin structure, providing access to transcription factors that results in upregulation of the gene transcription. Such epigenetic changes are stable but potentially reversible over time. The figure depicts environmental stimuli increasing gene expression, but it is equally likely in some circumstances that gene expression is decreased. Notably, this raises the intriguing possibility that central nervous system–penetrant HDAC inhibitors may have the potential to reverse some of the deleterious epigenetic effects of early life events. Modified and reproduced with permission from Gurvich and Klein (2002). HATs, histone acetylases; VPA, valproate.
studies have also suggested that the downregulation of Reelin and GAD(67) expression in cortical interneurons in schizophreni
and bipolar disorder patients may be mediated by epigenetic hypermethylation of the respective promoters caused by the
selective increase of DNA-methyltransferase 1 in GABAergic neurons (Tremolizzo et al 2005). Tremolizzo and associates
(2005) investigated whether methionine-induced epigenetic reelin promoter hypermethylation and the associated behavioral alterations can be reduced by valproate in doses that inhibit HDACs. They found that not only did valproate prevent methionine-induced reelin promoter hypermethylation and reelin mRNA downregulation but also corrected deficits in prepulse inhibition and social interaction. Finally, the appreciation that transcriptional dysregulation may contribute to the molecular pathogenesis of Huntington’s disease has led to a trial of HDAC inhibitors in a Huntington’s disease mouse model (Ferrante et al 2003; Hockly et al 2003). Ferrante et al and Hockly et al observed dramatically improved motor impairment concomitant with in-
terestingly, neurotransmitter release, and long-term alterations in gene expression and plasticity. A considerable amount of biochemical data supports the potential involvement of PKC in the pathophysiology and treatment of bipolar disorder. Evidence supporting this are changes in PKC and its substrates in bipolar patients and changes in PKC signaling pathways after treatment with lithium or valproate (Manji and Lenox 1999; Young et al 1999). It is noteworthy that psychostimulants, which are capable of triggering manic episodes in susceptible individuals and induce manlike behaviors in rodents, are known to activate PKC. Thus, the evidence suggests that two structurally dissimilar antimanic agents, lithium and valproate, attenuate PKC function in a therapeutically relevant time frame, whereas promanic psychostimulants activate PKC (Figure 3). These data suggest that PKC modulation plays a critical role in the treatment of mania. Most recently, Birnbaum and associates (2004) have demonstrated that excessive activation of PKC dramatically impaired the cognitive functions of the prefrontal cortex, exposure to stress activated PKC and re-
sulted in prefrontal dysfunction, and inhibition of PKC (includ-
ing indirectly with mood stabilizers) protected cognitive function. Pharmacologic inhibition of PKC results in many behavioral changes similar to the ones induced by mood stabilizers. These include an attenuation of hyperactivity, risk-taking behavior, and hedonic drive (Einat and Manji, in press).

These findings led to a single-blind clinical trial investigat-
ing possible antimanic properties of the PKC inhibitor tamox-
ifen (Bebchuk et al 2000). Although best known for its antiestrogenic properties, tamoxifen is also a potent PKC inhibitor at high concentrations. Initial results are encourag-
ing, finding that tamoxifen treatment resulted in a significant decrease in manic symptoms (Bebchuk et al 2000). Larger double-blind placebo-controlled studies of tamoxifen are in progress.

PKC has multiple isoforms, and PKC-mediated cellular processes are tissue- and isoform-specific. This has allowed the modulation of function of individual isoymes. The possi-
ble development of isoyme-specific drugs for therapeutic use has led to advances in the treatment of certain conditions.
For example, selective PKC inhibitors are currently being tested to treat diabetic complications (for review, see Frank 2002 and Wheeler 2003) and examples are provided in Table 1. It remains unclear at this early stage of development which of these drugs cross the blood–brain barrier and whether the specific isoymes they inhibit are relevant to brain diseases. Compounds with properties similar to these may be used as potential medications for the treatment of bipolar disorder.

Understanding the Pathophysiology of the Illness to Design Therapeutics to Attenuate or Prevent the Pathological Process: Evidence for Impairments of Structural Plasticity and Cellular Resilience in Mood Disorders

Historically, the brain systems receiving the greatest attention in neurobiologic studies of mood disorders are the monoamin-
ergic neurotransmitter systems, which are extensively distributed throughout the network of limbic, striatal, and prefrontal cortical neuronal circuits. Such circuits are thought to support the behavioral and visceral manifestations of mood disorders (Drevets 2001; Nestler et al 2002). Although these neurotransmitter systems undoubtedly play an important role in mediating some of the signs/symptoms of bipolar and other mood disorders, the lack of significant advances in our ability to develop improved thera-
peutics for these devastating illnesses has led to the investigation of the putative roles of intracellular signaling cascades and synaptic plasticity. “Neuroplasticity” subsumes diverse processes of vital importance by which the brain perceives, adapts to, and responds to a variety of internal and external stimuli. The
manifestations of neuroplasticity in the adult CNS have been characterized as including alterations of dendritic function, synaptic remodeling, long-term potentiation (LTP), axonal sprouting, neurite extension, synaptogenesis, and even neurogenesis (for an excellent overview, see Mesulam 1999).

Recent evidence demonstrating that antidepressants and mood stabilizers exert major effects on signaling pathways that regulate cellular plasticity has reshaped views about the neurobiological underpinnings of these disorders (D’Sa and Duman 2002; Drevets 2001; Nestler et al 2002; Young 2002).

Thus, structural imaging studies report a decrease in the gray matter volume of multiple areas of the orbital, medial, and dorsolateral prefrontal cortex, with the most prominent reduction reported in the left (but not right) subgenual prefrontal cortex. An increase in ventricular size also has been consistently reported in patients with bipolar disorder (reviewed in Beyer et al 2004; Manji et al 2003).

Complementary postmortem neuropathologic studies have shown abnormal reductions in cortex volume, glial cell counts, or neuron size in the subgenual prefrontal cortex, orbital cortex, dorsal anterolateral prefrontal cortex, amygdala, and in basal ganglia and dorsal raphe nuclei (reviewed in Cotter et al 2001; Manji and Duman 2001; Rajkowska 2002). It is not known whether these deficits constitute developmental abnormalities that may confer vulnerability to abnormal mood episodes, compensatory changes to other pathogenic processes, or the sequelae of recurrent affective episodes per se. The marked reduction in glial cells in these regions may contribute to impairments of neuronal structural plasticity by reducing the neuron’s energy supply and reduced glial-mediated clearing of excessive synaptic glutamate (Coyle and Schwarcz 2000; Haydon 2001; Ongur et al 1998; Rajkowska 2000; Rajkowska et al 1999; Ullian et al 2001). Abnormalities of glial function could thus prove integral to the impairments of structural plasticity and overall pathophysiology of mood disorders.

Stress and Glucocorticoids Modulate Neural Plasticity: Implications for Mood Disorders

Although mood disorders undoubtedly have a strong genetic basis, considerable evidence has shown that severe stressors are associated with a substantial increase in risk for the onset of mood disorders in susceptible individuals (D’Sa and Duman 2002). Activation of the HPA axis seems to have a role in mediating these effects, as stress-induced neuronal atrophy is prevented by adrenalectomy and duplicated by exposure to high concentrations of glucocorticoids (Brown et al 1999; McEwen 1999; Sapolsky 2000). Cushing syndrome arises from adrenocorticotropic hormone- or corticotropin-releasing-hormone-secret ing tumors, resulting in hypercortisolism. The hypercortisolism of Cushing syndrome seems to be accompanied by reversible bilateral hippocampal atrophy. These observations are noteworthy with respect to the pathophysiology of major depressive disorders and bipolar disorder because a significant percentage of patients with mood disorders display some form of HPA axis activation. Indirect evidence suggests that hypercortisolism may be involved in the hippocampal volume reductions seen in patients with mood disorders (Sapolsky 2000; Watson et al 2004).

Furthermore, it has been suggested that the atrophy seen in patients with severe and recurrent mood episodes does not resolve over time; instead, it appears to be irreversible.

In addition to causing neuronal atrophy directly, stress and glucocorticoids also reduce cellular resilience, thereby making certain neurons more vulnerable to other insults, such as ischemia, hypoglycemia, and excitatory amino acid toxicity (Sapolsky 2000). The precise mechanisms of which glucocorticoids exert these deleterious effects on the hippocampus are unclear.
but likely involve the facilitation of glutamatergic signaling and inhibition of glucose transport (Sapolsky 2000). The reduction of resilience of hippocampal neurons might also reflect the propensity for various stressors to decrease the expression of brain-derived neurotrophic factor (BDNF) in this region (McEwen 1999; Sapolsky 2000). Together with other neurotrophic factors, BDNF is necessary for the survival and function of neurons, implying that a sustained reduction of these factors could affect neuronal viability. Neurotrophic factors are now known to promote cell survival largely by suppressing intrinsic, cellular apoptotic machinery. This process of cell survival occurs through binding of these factors to membrane receptors and regulation of intracellular signal transduction pathways that can control apoptosis, including regulation of Bcl-2 family members. Accumulating data suggest that not only is Bcl-2 neuroprotective, it also exerts neurotrophic effects and promotes neurite sprouting, neurite outgrowth, and axonal regeneration. Recent studies have demonstrated that severe stress exacerbates stroke outcome by suppressing Bcl-2 expression (Devries et al. 2001). In this study, demonstrated that severe stress exacerbates stroke outcome by suppressing Bcl-2 expression (Devries et al. 2001). In this study, the stressed mice expressed ~70% less Bcl-2 mRNA than un-stressed mice after ischemia. Furthermore, stress greatly exacerbated infarct in control mice but not in transgenic mice that constitutively expressed increased neuronal Bcl-2 (Devries et al. 2001). Finally, high corticosterone concentrations were significantly correlated with larger infarcts in wildtype mice but not in Bcl-2-overexpressing transgenic mice. Thus, enhanced Bcl-2 expression appears to be capable of offsetting the potentially deleterious consequences of stress-induced neuronal endangerment, which suggests that pharmacologically induced upregulation of Bcl-2 may have considerable utility in the treatment of various disorders.

Neurotrophic and Neuroprotective Effects of Lithium

Recent studies have shown that lithium robustly increases the levels of the cytoprotective protein Bcl-2 in various areas of rodent brain and in cells of human neuronal origin (Chen et al. 1999; Chen and Chuang 1999). Consistent with its effects on Bcl-2 and GSK-3β, lithium, at therapeutically relevant concentrations, exerts cytoprotective effects against the deleterious effects of a variety of insults, including glutamate. N-methyl-D-aspartate (NMDA)-receptor activation, serum/nerve growth-factor deprivation, radiation, striatal quinolinic acid infusion, and middle cerebral artery occlusion (Chen and Chuang 1999; Manji et al. 2000). Lithium also enhances hippocampal neurogenesis in the adult rodent (Chen et al. 2000). To determine whether lithium exerts neurotrophic effects in the human brain in vivo, recent studies have used proton magnetic resonance spectroscopy to quantify the levels of N-acetylaspartate (NAA) a putative marker of neuronal variability and function, Bates et al. 1996; Tsai and Coyle 1995. Four weeks of lithium treatment produced a significant increase in NAA levels, effects that were localized almost exclusively to gray matter (Moore et al. 2000). These findings provide intriguing indirect support for the contention that chronic lithium increases neuronal viability, and function in the human brain. Furthermore, an approximately .97 correlation between lithium-induced NAA increases and regional voxel gray matter content was observed, thereby providing evidence for co-localization with the regional specific bcl-2 increases observed (e.g., gray vs. white matter) in the rodent brain cortices. These results suggest that chronic lithium not only may exert robust neuroprotective effects (as has been demonstrated in a variety of preclinical paradigms) but also neurotrophic effects in humans. A follow-up volumetric magnetic resonance imaging (MRI) study demonstrated that 4 weeks of lithium treatment produced a significantly increased total gray matter content in the human brain (Moore et al. 2000), indicating an increase in the volume of the neuropil (the mosslike layer comprising axonal and dendritic fibers that occupies much of the cortex gray-matter volume). Taken together, these clinical studies support the hypothesis that some of the therapeutic actions of lithium may involve hitherto underappreciated neurotrophic and neuroprotective effects. To investigate the clinical significance of these findings, a longitudinal high-resolution volumetric MRI study in well-characterized depressed bipolar subjects has recently been undertaken (Moore et al., unpublished data). Total brain gray matter, prefrontal gray matter, and left subgenual prefrontal gray matter were determined using validated semiautomated segmentation and region of interest methodology in the patients at baseline (medication free) and after 4 weeks of blinded lithium treatment. Significant increases in total brain gray matter in bipolar subjects were observed following chronic lithium administration, and regional increases in the bipolar subjects revealed significant differences between responders (> 50% decrease on the Hamilton Depression Rating Scale) and nonresponders; only responders showed increases in gray matter in the prefrontal cortex and left subgenual prefrontal cortex. Together, these data suggest that pharmacologic strategies that enhance cellular plasticity and resilience may have utility not only for the long-term course of the illness but also for the treatment of the acute illness.

We now turn to a discussion of several plasticity enhancing strategies currently under investigation in bipolar disorder.

Glutamatergic Strategies

One major neurotransmitter system regulated by glucocorticoids is the glutamatergic system. Regulated either via glucocorticoids or through alternative mechanisms, abnormal activity of the glutamatergic system represents a likely contributor to impairments in brain neuroplasticity and cellular resilience observed in patients with bipolar disorder. Glutamate is the major excitatory synaptic neurotransmitter in the brain and has several important roles including mediating neurotransmission across excitatory synapses and regulating numerous physiologic functions in the mammalian CNS such as synaptic plasticity, learning, and memory (Bannerman et al. 1995; Collingridge 1994; Collingridge and Bliss 1995; Watkins and Collingridge 1994). Several treatment strategies have been implemented to reduce glutamate-mediated excitotoxicity, which results in robust neuroprotective effects in a variety of preclinical paradigms; however, the evidence in humans with neurodegenerative disease is more equivocal. The same antiglutamatergic neuroprotective strategies used for these neurodegenerative disorders may have an important role in patients with mood disorders and are currently being tested in “proof-of-concept” studies in patients with mood disorders (for review, see Ketter and Wang 2003; Zarate et al. 2002; Figure 4B). Glutamate exerts its action at the presynaptic and postsynaptic level through the stimulation of specific receptors that can be classified by structural characteristics (Figure 2): the first group, ionotropic glutamate receptors, are ion channels that when stimulated open the channel pore allowing sodium, potassium, or calcium to flow freely into the cell. This opening of the pore changes the polarization of the neuronal surface and often activates intracellular signaling pathways. The second group, metabotropic receptors, are G-protein-coupled receptors that exert their actions through second messenger pathways. Therapeutics can target these receptors; it is additionally possible
to target the release of glutamate before it binds to either the ionotrophic or metabotropic receptors. Therapeutics directed at these targets may result in modulation of the glutamatergic system and ultimately to mood-enhancing effects. These agents include riluzole, memantine, ketamine, felbamate, and zinc. Testing different glutamate-modulating agents that affect different components of glutamatergic neurotransmission may help discern what aspects of this system are most relevant.

**Inhibition of Glutamate Release**

**Lamotrigine.** Clinical evidence that modulation of glutamate brain levels may be important in the treatment of mood disorders comes from the clinical use of the anticonvulsant lamotrigine (Calabrese et al 1999). Lamotrigine is approved by the U.S. Food and Drug Administration (FDA) as monotherapy and adjunctive therapy for epilepsy and for the maintenance treatment of adults with bipolar disorder. Although lamotrigine has multiple cellular effects, it is postulated that an inhibition of an excessive release of glutamate appears to be important to its mechanism of action (Calabresi et al 1996; Leach et al 1986; Wang et al 1996). Studying drugs that also inhibit release of glutamate would help discern whether this mechanism of action might be relevant to the therapeutic action of lamotrigine. There is now evidence that another drug that inhibits the release of glutamate (riluzole) also appears to have antidepressant properties.

**Riluzole.** Riluzole (2-amino-6-trifluoromethoxy benzothia-zole) is a neuroprotective agent with anticonvulsant properties that easily crosses the blood–brain barrier. Riluzole is the only drug currently approved by the FDA for the treatment of amyotrophic lateral sclerosis (ALS). It is neuroprotective in animal models of Parkinson’s disease, NMDA receptor hypofunction neurotoxicity, ischemia, and traumatic CNS injury (reviewed in Zarate et al 2002). Riluzole does not act directly on the NMDA receptor but rather inhibits release of glutamate through both the inhibition of voltage-dependent sodium channels in mammalian CNS neurons and P/Q-type calcium channels (reviewed in Zarate et al 2002). Other reported mechanisms of action of riluzole include its ability to increase clearance of glutamate from the synaptic space through enhancement of the reuptake process (Frizzo et al 2004) and its effect at α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid potentiators (AMPA) receptors (De Sarro et al 2000). Recent studies have shown that riluzole stimulates the synthesis of growth factors including BDNF in cultured mouse astrocytes (Mizuta et al 2001).

Supporting the viability of riluzole in treatment-resistant depression are two studies. The first study was a 6-week open-label study with riluzole in treatment-resistant DSM-IV major (unipolar) depression (Zarate et al 2004a). After a 1-week drug-free period, 19 subjects received riluzole at a mean daily dose of 169 mg. All patients had previously failed to respond to at least one antidepressant and more than half were considered Stage II of treatment-resistance. Significant improvement in depressive symptoms as measured by the Montgomery–Asberg Depression Rating Scale (MADRS) occurred on weeks 3 through 6 for all patients. In addition, significant improvements occurred in anxiety symptoms. The second study was an 8-week open-label study with riluzole in 14 patients with treatment-resistant DSM-IV bipolar depression. All patients had previously failed to respond to adequate trials of at least two antidepressants and at least 4 weeks of lithium or valproate. Patients received riluzole at a mean daily dose of 171 mg and significant improvement in MADRS occurred at weeks 5 through 8 for all patients. The response and remission rates at week 8 for the intent to treat sample was 50%. Four subjects (29%) had previously failed to respond to lamotrigine. Of these, one failed to respond to riluzole, 1 had a partial response to riluzole, and two achieved remission. Overall riluzole was well tolerated in these two trials. These preliminary results need to be confirmed in controlled studies.

**Ionotropic Glutamate Receptors**

Three subgroups of glutamatergic ion channels have been identified using their pharmacologic ability to bind different synthetic ligands, each composed of a different set of subunits: NMDA receptors, α-amino-3-AMPA receptors, and kai-

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**Figure 4.** (A) Cellular mechanisms underlying the deleterious effects of stress and episodes of depression and mania. This figure depicts the multiple mechanisms by which stress (and perhaps depressive episodes) may attenuate cellular resiliency, thereby resulting in atrophy, death, and endangerment of hippocampal neurons. NMDA, N-methyl-D-aspartate glutamate receptor; GR, glucocorticoid receptor; BDNF, brain derived neurotrophic factor. Modified and reproduced, with permission from Manji et al (2003). (B) Modulation of glutamatergic throughput: therapeutic effects. This figure depicts the hyperglutamatergic state associated with regional atrophic changes and disruption of critical neuronal circuitry. Modulators of glutamatergic throughput may serve to reverse illness-related atrophy, thereby reinstating the critical circuitry modulating affective, cognitive, motoric and neurovegetative functioning. Modified and reproduced, with permission from Nestler et al (2002).
nate (KA) receptors. The latter two groups are often referred to together as the non-NMDA receptors.

**NMDA Receptor.** A growing body of preclinical and clinical research suggests that the NMDA receptor complex may be involved in the pathophysiology of mood disorders and the mechanism of action of antidepressants and possibly mood stabilizers (reviewed in Zarate et al 2002). The NMDA receptor antagonists such as MK-801 and AP-7 and an AMPA receptor potentiator have been shown to have antidepressant properties in animal models of depression, including the forced swim test, the application of inescapable stressors, and tail suspension immobility tests, in animals exposed to chronic mild stress, as well as in the learned helplessness models of depression; effects that are comparable to the tricyclic antidepressants (reviewed in Zarate et al 2002). MK-801 increases neurogenesis in the brains of rats (Cameron et al 1995). There is evidence that the high-affinity NMDA receptor antagonist ketamine has efficacy in the treatment of a single dose of the NMDA receptor antagonist ketamine resulted in rapid antidepressant effects in seven patients with depression.

**Memantine.** Memantine is an anticonvulsant and neuroprotective property and has been shown in double-blind placebo controlled studies to be effective in reducing clinical deterioration in Alzheimer’s, vascular, and mixed dementia of all severities (Areosa and Sherriff 2003; Onggozoo et al 2002; Reisberg et al 2003). Chemically, memantine is a 1-amino-3,5-dimethyladamantan-5-one of the amantadine class, a compound that can easily cross the blood–brain barrier. Memantine is neuroprotective in animal models of Alzheimer’s disease, ischemia, and CNS trauma. Memantine is a noncompetitive voltage-dependent NMDA antagonist with a receptor effect comparable to MK-801 (Bormann 1989). Memantine appears to block the NMDA-receptor-associated ion channel only when it is open for long periods, thus promoting the view that it may be specific for blockade of pathologic glutamate release. Because of this mechanism of action, the untoward effects of pathologic concentrations of glutamate are prevented to a greater extent than the effects of physiologic concentrations, which are relatively spared with memantine (Chen and Lipton 1997; Chen et al 1998). Memantine is an ideal candidate drug to examine whether a low- to moderate-affinity NMDA antagonist has antidepressant effects because it is fairly selective to the NMDA receptor at doses of 5–20 mg/day. At these doses, memantine has low to negligible affinity for GABA, benzodiazepine, dopamine, adrenergic, histamine, and glycine receptors and for voltage-dependent Ca 2+, Na +, or K+ channels.

In preclinical studies, Moryl and colleagues (1993) described a dose-dependent decrease in the immobility time in the forced swim test in rats following administration of memantine. A synergistic effect was seen when imipramine and fluoxetine were given jointly with memantine to rats in a forced swim test study (Rogoz et al 2002).

We recently completed a double-blind, placebo-controlled trial of memantine in patients with major depression (Zarate et al, in press). In this study, 32 patients (mean age = 47 years) were randomized to memantine 5–20 mg/day (n = 16) or placebo (n = 16). The linear mixed models for total MADRS showed no treatment effect. Similarly, no anxiolytic effect was found. Although no significant antidepressant effects were found with the low- to moderate-affinity NMDA antagonist memantine, this finding does not exclude the possibility that antidepressant or mood-stabilizing effects might occur using much higher doses of memantine or if used synergistically in combination with other agents (e.g., antidepressants, lamotrigine). At higher doses of memantine, however, it becomes nonselective for the NMDA receptor and binds to other receptors (discussed earlier) some of which have been implicated in the mechanism of action of currently available antidepressants. Finally, it is possible that higher-affinity NMDA antagonists such as ketamine may have antidepressant properties.

Studies in progress are examining the possible therapeutic value of other NMDA receptor antagonists including ketamine, felbamate, and zinc.

**AMPA Receptors.** The AMPA receptors are a subfamily of ionotropic glutamate receptors that mediate the fast component of excitatory neurotransmission, which, like NMDA receptors, are involved in learning and memory. Several classes of compounds can allosterically modulate AMPA receptors. These compounds (so-called AMPA receptor positive modulators or AMPA receptor potentiators [ARPs]) do not activate AMPA receptors themselves but slow the rate of receptor desensitization or deactivation in the presence of an agonist (e.g., glutamate and AMPA; for review, see Bleakman and Lodge 1998; Borges and Dingledine 1998). AMPAkines, a subclass of ARPs, are small benzamide compounds that allosterically produce positive modulation of AMPA receptors are being studied in cognition, anxiety, stroke, Parkinson’s disease, and depression (reviewed in Black 2005). Table 1 summarizes AMPA potentiators that penetrate the blood–brain barrier (for review, see also Black 2005). Aniracetam was found to have antidepressant properties in the forced swim test (Black 2005). Studies have shown that the biarylpropylsulfonamide ARPs (LY392098 and LY451616) have antidepressant effects in animal models of depression (including the application of inescapable stressors, forced swim test, and tail-suspension-induced immobility tests), in learned-helplessness models of depression, and in animals exposed to chronic mild stress procedure (Li et al 2001). In one of these preclinical studies, the AMPAkine Ampalex was reported to have a more rapid effect (during the first week of treatment) than fluoxetine (after 2 weeks; Knapp et al 2002). In contrast to traditional antidepressants, this group of compounds does not appear to affect the extracellular concentration of monoamines (Skolnick et al 2001). They can, however, enhance the neurotrophic actions of BDNF mRNA and protein in primary neuronal cultures (Lauterborn et al 2000, 2003). Modulation of neurotrophic factor expression and altering the rate of neurogenesis may be critical factors in understanding the therapeutic effects of antidepressants and mood stabilizers in mood disorders. In support, chronic treatment with the AMPA receptor potentiator LY451616 increased progenitor cell proliferation in the dentate gyrus in a dose-dependent manner. The antidepressant-like activity of ARPs in animals may be attributed, at least in part, to the regulation of cell proliferation in the hippocampus (Bai et al 2003). Another ARP that is being investigated in depression is S18986, which has also been reported to increase BDNF expression (Lauterborn et al 2000, 2003).

**Metabotropic Glutamate Receptors.** Three groups comprising eight G-protein-coupled metabotropic glutamate receptors (mGluRs) mediate slower modulatory actions of glutamate on neurotransmitter release and cell excitability. Activation of mGluR leads to a variety of cellular responses, including the inhibition of calcium and potassium currents, presynaptic modulation of synaptic transmission, and postsynaptic interaction with ionotrophic glutamate receptors (Anwyl 1999; Baskys et al 1990; Ikeda et al 1995). The mGluRs are involved in the early phase of memory formation and the mechanism of long-term depression (Riedel et al 2003; Salinska and Stafiej 2003; Tan et al 2003).
and emotional response in the light-dark test compared with were found to improve measures of physical state, weight gain, mice, both antalarmin (10 mg/kg) and fluoxetine (10 mg/kg) behaviors (Habib et al 2000). Using the chronic stress model in reversed stress-induced inhibition of exploratory and sexual oral doses of 20 mg/kg in primates, significantly diminished the Holmes et al 2003; Saunders and Williams 2003). Preclinical identified (examples are provided in Table 1; for review, see Quiroz 2004). Some of these drugs have been investigated for proof of concept, and it is expected that modified and improved medications would lack some of the limiting side effects observed with these compounds.

**Glucocorticoid Synthesis Inhibitors.** Treatment with glucocorticoid synthesis inhibitors (e.g., ketoconazole) has been observed to ameliorate depression rapidly in treatment-resistant depression (reviewed in Quiroz et al 2004; examples are provided in Table 1. Most recently, in a double-blind, randomized, placebo-controlled study 63 inpatients with major depression were randomized to receive either placebo or metyrapone (1 g/d) for the first 3 weeks of a 5-week trial with nefazodone or fluvoxamine. A higher proportion of patients receiving metyrapone showed a positive treatment response at day 21 and at day 35 compared with placebo patients. The clinical course of patients treated with metyrapone showed an earlier onset of action beginning in the first week. The plasma concentrations of corticotropin and deoxycortisol were significantly higher during metyrapone treatment, whereas cortisol remained largely unchanged (Jahn et al 2004).

**Corticotropin-Releasing Factor (CRF) 1 Receptor Antagonists.** A number of small molecule CRF 1R antagonists have been evaluated using in vivo paradigms in animal models keto attenuate CRF-induced corticotropin release (Saunders and Williams 2003). Several classes of CRF 1R inhibitors have been identified (examples are provided in Table 1; for review, see Holmes et al 2003; Saunders and Williams 2003). Preclinical studies have shown that CRF 1 antagonists reduce CRF-induced corticotropin release and CRF-induced cAMP production (for review, see Saunders and Williams 2003).

Antalarin, a novel pyrrolopyrimidine compound, given in oral doses of 20 mg/kg in primates, significantly diminished the CRF-stimulated corticotropin release and the pituitary-adrenal, sympathetic, and adrenal medullary responses to stress. It also reversed stress-induced inhibition of exploratory and sexual behaviors (Habib et al 2000). Using the chronic stress model in mice, both antalarmin (10 mg/kg) and fluoxetine (10 mg/kg) were found to improve measures of physical state, weight gain, and emotional response in the light-dark test compared with untreated stressed animals (Ducottet et al 2003).

Developed by Pfizer, CP-154,526 has been evaluated in animal paradigms for anxiety. It has similar high penetrability as antalarmin and decreases synthesis of CRF in the paraventricular nucleus (Seymour et al 2003). Mansbach et al (1997) showed it efficacy in the learned helplessness model of depression in rats. SSR125543A is a 2-aminothiazole derivative that displays high affinities for human CRF R1 receptors; it has shown efficacy in the forced swim test model and in chronic mild stress model in rats in a study comparing it to antalarmin and fluoxetine (Griebel et al 2002). In other studies, CRA 1000, a nonpeptide pyrimidine CRF 1 antagonist being developed by Taisho Pharmaceuticals (Okuyama et al 1999), reduced immobility in the learned helplessness paradigm in male Wistar rats when given by intraperitoneal injection (Harro et al 2001). Developed by Dupont, DMP696 is a selective, potent, and highly bioavailable nonpeptide CRF 1R antagonist. It has been tested in behavioral models of anxiety and is being tested in behavioral paradigms for depression (Li et al 2003).

In an open-label trial, R-121919 reduced anxiety and depressive symptoms in patients with major depression (Zobel et al 2000). The clinical development of the compound was discontinued, probably because of elevated liver function tests (Kunzel et al 2003).

**Dehydroepiandrosterone.** Dehydroepiandrosterone (DHEA) serves as a precursor for both androgenic and estrogenic steroids; together with its sulphated form (DHEA-S), it is secreted by the adrenal gland and also produced in the CNS. Thus, DHEA and DHEA-S are neuroactive steroids that have a number of effects that can be described as functional antagonism of the actions of glucocorticoids (DHEA does not directly interact with the glucocorticoid receptor, and there is no known receptor for DHEA in any tissue). It has been reported to have antidepressant efficacy in dysthymic and depressed patients (reviewed in Quiroz et al 2004).

In a recent double-blind, randomized placebo-controlled crossover study involving 23 men and 23 women with midlife-onset major or minor depression given DHEA (90–450 mg/day) for 6 weeks was found to be superior to placebo in reducing depressive symptoms (Schmidt et al 2005).

**GR Antagonist.** Mifepristone (RU-486) is a nonselective antagonist of the GR receptor that has been reported to have antidepressant and antipsychotic properties in patients with psychotic depression (Belanoff et al 2002; reviewed in Quiroz et al 2004). In a recent double-blind, placebo-controlled crossover study, Young and colleagues (2004) compared mifepristone (600 mg) to placebo in 20 subjects with bipolar depression. They found not only improvements in depressive symptoms with mifepristone but also benefits for cognitive functioning, specifically in spatial memory. This is especially noteworthy because the same investigators failed to find cognitive benefits with mifepristone in patients with schizophrenia (Gallagher et al 2005), suggesting that the cognitive enhancing properties of this drug might be limited only to patients with mood disorders. Ongoing controlled trials of mifepristone are underway in psychotic depression. Such studies will help clarify the extent of its antidepressant and antipsychotic effects in patients with psychotic depression and bipolar disorder. Examples of other GR antagonists being developed are provided in Table 1.

**Strategies to Enhance Neurotrophic Factor Signaling**

Seminal work from the Duman laboratory has shown that antidepressants regulate neurotrophic signaling cascades (D’Sa and Duman 2002; Duman et al 1997). Different classes of long-term www.sobp.org/journal
antidepressant treatments, including norepinephrine (NE) reuptake inhibitors, selective serotonin reuptake inhibitors (SSRIs), and electroconvulsive seizure, upregulate CREB and BDNF expression, which indicates that CREB and BDNF are common postreceptor targets of these therapeutic agents; furthermore, the increase was only seen with chronic use, which corresponds to the onset of action of these medications. More evidence that links upregulation of these pathways and antidepressant activity comes from behavioral models (D’Sa and Duman 2002; Nestler et al 2002). Chronic, but not acute, antidepressant treatment also increases neurogenesis of dentate gyrus granule cells. At this point, it is unclear what role the regulation of hippocampal neurogenesis plays in the pathophysiology and treatment of depression (for a critique, see Sapolsky 2004). Nevertheless, the accumulating evidence strongly supports the contention that neurotrophic effects play an important role in the actions of antidepressants and mood stabilizers. The trophic effects are postulated to reverse illness-related atrophic changes, thereby reinstating the neurochemical throughput in critical circuitry regulating affective, cognitive, motoric, and neurovegetative functions.

One approach to enhance the activity of CREB is to use an inhibitor of phosphodiesterase (PDE), the enzymes responsible for the breakdown of cAMP. In this context, Takahashi et al (1999) demonstrated that chronic antidepressant administration increases the expression of cAMP-specific PDE 4A and 4B isoforms; these effects likely represent a compensatory “counter-regulatory” response to the chronic antidepressants (Nibuya et al 1996). This study suggests that PDE4A and PDE4B may be relevant targets for development of agents that possess antidepressant effects either as monotherapy, or in combination with agents that increase intrasynaptic monoamine levels because of the possible synergism of effects on the cAMP cascade. Indeed, the idea that PDE inhibitors may have potential antidepressant activity is not new and was initially proposed by Wachtel in the 1980s (Wachtel and Schneider 1986). In the 1980s and early 1990s, a number of open and controlled clinical trials demonstrated that rolipram, a specific inhibitor of the high-affinity cAMP PDE4, may have antidepressant efficacy in depressed patients (reviewed in Manji et al 2003). In addition, there is some evidence that rolipram may have a faster onset of response compared with standard antidepressants. Although the overall literature on the use of rolipram is suggestive that PDE inhibitors may have antidepressant efficacy and may have a faster onset of action, the potential use of rolipram for depression was limited because of side effects such as nausea and emesis.

Recent studies demonstrating that PDE4 is expressed in inflammatory cells such as eosinophils and that inhibition of PDE4 downregulates the inflammatory response has generated renewed excitement about the possible utility of this class of agents in the treatment of diseases such as asthma, chronic obstructive pulmonary disease (COPD), rheumatoid arthritis, Crohn’s disease, and multiple sclerosis (Dyke and Montana 2002; Huang et al 2001). Second-generation compounds with markedly improved tolerability are rapidly being developed (Dyke and Montana 2002; Huang et al 2001), and it is anticipated that the availability of CNS-penetrant PDE4 inhibitors may lead to the development of a novel class of antidepressants.

Human phase I and II trials of recombinant methionyl human BDNF have already been undertaken wherein BDNF was administered by intrathecal infusion to patients with amyotrophic lateral sclerosis (Ochs et al 2000). Unfortunately, treatment-limiting side effects were encountered at higher doses, precluding further study. The recent report of dysregulation of several fibroblast growth factor (FGF) system transcripts in frontal cortical regions of brains from human subjects with major depressive disorder suggests that this growth factor family may also represent an important target for the development of novel therapeutics (Evans et al 2004).

An increasing number of strategies are being investigated to develop small molecule switches for protein–protein interactions, which have the potential to regulate the activity of growth factors, mitogen-activated protein (MAP) kinase cascades, and interactions between homo- and heterodimers of the Bcl-2 family of proteins (Figure 5). Bcl-2 has traditionally been viewed as a “long-term neuroprotective protein”; however, it is a key regulator of mitochondrial function, and there is a growing appreciation of the diverse functions that mitochondria play in regulating integrated CNS function. Thus, increasing evidence suggests that mitochondrial Ca2+ sequestration has a key role in modulating the tone of synaptic plasticity in a variety of neuronal circuits and that regulation of mitochondrial function is likely to play important roles in regulating synaptic strength of neuronal circuitry mediating complex behaviors. Indeed, it is possible that lithium’s ability to upregulate Bcl-2 robustly may play a role in its antidepressant potentiating effects. It is also noteworthy that pramipexole also upregulates Bcl-2 in several brain areas (Takata et al 2000) and has been shown to exert antidepressant effects in double-blind, placebo-controlled trial in patients with bipolar II depression (Zarate et al 2004b). Although the dopamine agonistic effects of pramipexole clearly may also contribute to its purported antidepressant effects, its robust neurotrophic effects suggest that it may have broader utility as an antidepressant potentiator. In this context, ongoing longitudinal studies at the National Institute of Mental Health are investigating pramipexole’s antidepressant and neurotrophic effects with the use of serial magnetic resonance spectroscopy (MRS) measurements of N-acetyl-aspartate (NAA), and volumetric MRIs.

Conclusions

In conclusion, emerging results from a variety of clinical and preclinical experimental studies suggest that a reconceptualization about the pathophysiology, course, and optimal long-term treatment of recurrent mood disorders may be warranted. Understanding the biochemical targets of the most effective medications used in bipolar disorder as well as understanding the presumed pathophysiology of the illness will provide us with the greatest opportunity to develop next generation therapies. Drugs that inhibit the direct targets of lithium and valproate (e.g., GSK-3 and HDAC) and drugs that act on the shared downstream biochemical targets of lithium and valproate (e.g., PKC) offer considerable promise in drug development for bipolar disorder. Less evidence exists to support the other direct targets of lithium and valproate for the development of novel therapeutics for bipolar disorder. In terms of the presumed pathophysiology of bipolar disorder and other severe recurring mood disorders, increasing evidence supports the idea that regional reductions in brain volume are most likely a consequence of impairments of structure plasticity and resilience. Thus, optimal acute and long-term treatment for these severe illnesses will require both neurochemical and neurotrophic support. As reviewed, there are a number of pharmacologic “plasticity-enhancing” strategies that may be of considerable utility in the treatment of mood disorders (see Table 1 and Figure 5). Among the most immediate candidates are glutamate-release-reducing agents, NMDA antagonists,
Figure 5. Plasticity regulators as targets for the development of novel agents for the treatment of mood disorders. This figure depicts the multiple targets by which neuroplasticity and cellular resilience can be increased in mood disorders. Genetic and neurodevelopmental factors, repeated affective episodes (and likely elevations of glucocorticoids), and illness progression may all contribute to the impairments of cellular resilience, volumetric reductions, and cell death and atrophy observed in mood disorders. Bcl-2 attenuates apoptosis by sequestering proforms of death-driving cysteine proteases (called caspasps) preventing the release of mitochondrial apoptogenic factors such as calcium, cytochrome c, and apoptosis-inducing factor (AIF) into the cytoplasm and by enhancing mitochondrial calcium uptake. Antidepressants regulate the expression of brain-derived neurotrophic factor (BDNF) and its receptor TrkB. Both Trk A and TrkB utilize the PI-3-kiase/Akt and ERK MAP kinase pathways to bring about their neurotrophic effects. The ERK MAP kinase cascade also increases the expression of Bcl-2 via its effects on CREB. (1) Phosphodiesterase inhibitors increase the levels of pCREB. (2) MAP kinase modulators increase the expression of the major neurotrophic protein, Bcl-2. (3) Metabotropic glutamate receptors (mGluRs) II/III agonists modulate the release of excessive glutamate and BDNF. (6) N-methyl-D-aspartate (NMDA) antagonists such as ketamine and memantine enhance plasticity and cell survival. (7) Novel drugs to enhance glial release of trophic factors and clear excessive glutamate may have utility for the treatment of depressive disorders. (8) Corticotropin releasing factor (CRF). (9) Glucocorticoid antagonists attenuate the deleterious effects of hypercortisolemia, and CRH antagonists may exert other beneficial effects in the treatment of depression through non-HPA (hypothalamo–pituitary–adrenal) mechanisms. (10) Agents that upregulate Bcl-2 (e.g. pramipexole, shown to be effective in bipolar depression; Zarate et al 2004b) would be postulated to have considerable utility in the treatment of depression and other stress-related disorders. Reproduced with permission from Charney and Manji (2004): Sci STKE 225:re5.

AMPA potentiators, cAMP phosphodiesterase inhibitors, and GR antagonists. Some of these compounds are in early phases of clinical testing (e.g., corticotropin releasing factor [CRF] antagonists, rituxizole), and as such, the results will need to be confirmed in larger controlled studies.

Furthermore, an increasing number of strategies are being investigated to develop small molecule agents to regulate the activity of growth factors, MAP kinases cascades, and the Bcl-2 family of proteins. Finally, in addition to treating the core symptoms of bipolar disorder, next generation drugs might be able to target other important aspects of the illness (e.g., enhancing cognition independent of whether mood symptoms significantly improve; GR antagonists), prevent or reverse epigenetic factors that may have long-term negative impact on the course of the illness (e.g., histone deacetylase inhibitors), or reduce certain medical comorbidities (e.g., diabetes; GSK-inhibitors). This progress holds much promise for the development of novel therapies for the long-term treatment of severe, refractory mood disorders and for improving the lives of millions.

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