The Use of Mood Stabilizers as Plasticity Enhancers in the Treatment of Neuropsychiatric Disorders


Mood disorders have traditionally been conceptualized as neurochemical disorders, but there is now evidence from a variety of sources demonstrating regional reductions in central nervous system (CNS) volume, as well as reductions in the numbers and/or sizes of glia and neurons in discrete brain areas. Although the precise cellular mechanisms underlying these morphometric changes remain to be fully elucidated, the data suggest that severe mood disorders are associated with impairments of structural plasticity and cellular resilience. It is thus noteworthy that lithium and valproate have recently been demonstrated to robustly increase the expression of the cytoprotective protein bcl-2 (an abbreviation for the B-cell lymphoma/leukemia-2 gene) in the CNS in vivo and in cells of human neuronal origin. Lithium and valproate also robustly activate a signaling cascade utilized by endogenous growth factors—the extracellular signal-regulated kinase (ERK) mitogen-activated protein (MAP) kinase pathway. Complementary human studies have shown that chronic lithium administration significantly increases gray matter content in a regionally selective manner, suggesting a reversal of illness-related atrophy and an increase in the volume of the neuropil. These unique and unexpected properties of lithium and valproate suggest that they may have broader utility as adjunctive agents in the treatment of a variety of neuropsychiatric disorders associated with cell atrophy or loss. The adjunctive use of these agents—at low doses—may provide the trophic support necessary to restore, enhance, and maintain normal synaptic connectivity, thereby allowing the chemical signal to reinstate the optimal functioning of critical circuits necessary for normal functioning.

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dysregulation of limbic and limbic-associated function also offers the potential to delineate the underlying etiology/pathophysiology of BD. Recognition of the significant morbidity and mortality of the severe mood disorders, as well as the growing appreciation that a significant percentage of patients respond poorly to existing treatments, has made the task of discovering new therapeutic agents that work quickly, potently, specifically, and with few side effects increasingly more important. Indeed, in a recent article discussing the major impact this monovalent cation has had on psychiatry, Schou expressed disappointment that we have yet to fully elucidate the mechanisms by which lithium exerts its therapeutic effects.

A recognition of the clear need for better treatments and the lack of significant advances in our ability to develop novel, improved therapeutics for these devastating illnesses has led to the investigation of the putative roles of intracellular signaling cascades and non-aminergic systems in the pathophysiology and treatment of mood disorders. Consequently, recent evidence demonstrating that impairments of neuroplasticity and cellular resilience may underlie the pathophysiology of mood disorders, and that antidepressants and mood stabilizers exert major effects on signaling pathways that regulate neuroplasticity and cell survival, has generated considerable excitement among the clinical neuroscience community and is reshaping views about the neurobiological underpinnings of these disorders.

“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 central nervous system (CNS) have been characterized as including alterations of dendritic function, synaptic remodeling, long-term potentiation and depression, axonal sprouting, neurite extension, synaptogenesis, and even neurogenesis. Although the potential relevance of neuroplastic events for the pathophysiology of psychiatric disorders has been articulated for some time, recent morphometric studies of the brain (both in vivo and postmortem) are beginning to lead to a fuller appreciation of the magnitude and nature of the neuroplastic events involved in the pathophysiology of mood disorders. In this article, we review these data and discuss their implications not only for changing existing conceptualizations regarding the pathophysiology of severe, recurrent mood disorders, but also for the strategic development of improved therapeutics.

**EVIDENCE FOR IMPAIRMENTS OF STRUCTURAL PLASTICITY AND CELLULAR RESILIENCE IN MOOD DISORDERS**

Positron emission tomography imaging studies have revealed multiple abnormalities of regional cerebral blood flow and glucose metabolism in limbic and prefrontal cortical (PFC) structures in mood disorders. These abnormalities implicate limbic-thalamic-cortical and limbic-cortical-striatal-pallidal-thalamic circuits, involving the amygdala, orbital and medial PFC, and anatomically related parts of the striatum and thalamus in the pathophysiology of mood disorders. Interestingly, recent morphometric magnetic resonance imaging (MRI) and postmortem investigations have also demonstrated abnormalities of brain structure that persist independently of mood state and may contribute to the corresponding abnormalities of metabolic activity (as discussed elsewhere).

Structural imaging studies have demonstrated reduced gray matter volumes in areas of the orbital and medial PFC, ventral striatum, and hippocampus and enlargement of the third ventricle in mood disordered relative to healthy control samples, which has been reviewed. Also consistent is the presence of white matter hyperintensities (WMH) in the brains of elderly depressed patients and patients with BD; these lesions may be associated with poor treatment response. There is a growing awareness of the genetic influences on WMH, and their possible impact on neuropsychological functioning, but WMH may have multiple causes, including cerebrovascular accidents, demyelination, loss of axons, dilated perivascular space, minute brain cysts, and necrosis. In this context, it is noteworthy that recent studies have used diffusion tensor imaging of brain tissue to study possible white matter tract disruption in mood disorders. This procedure measures diffusion of water as influenced by tissue structure, providing a measure of the integrity of fiber tracts. These authors showed that WMH showed a higher apparent diffusion coefficient and lower anisotropy than normal regions, with gray matter showing similar trends. Together, these results support the contention that WMH damage the structure of brain tissue and most likely disrupt the neuronal connectivity necessary for normal affective functioning. Although the cause of WMH in mood disorders is unknown, their presence—particularly in the brains of young bipolar patients—suggests importance in the pathophysiology of the disorder.

Complementary postmortem neuropathologic studies have shown abnormal reductions in cortex volume, glial cell counts, and/or neuron size in the subgenual PFC, orbital cortex, dorsal anterolateral PFC, and amygdala (Table 1; recently reviewed). 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. Understanding these issues will partly depend on experiments that delineate the onset of such abnormalities within the illness course and determine whether they antedate depressive episodes in individuals at high familial risk for mood disorders. While there is not total reproducibility among either the neuroimaging or postmortem studies, the differences most likely represent variations of experimental design (including medication effects, vide infra) and, as would be expected in heteroge-
neous disorders such as mood disorders, in patient populations. Thus, research is required in order to understand if more rigorously defined subtypes of depression, or mood disorders, are associated with any particular abnormality. Nevertheless, the marked reduction in glial cells in these regions has been particularly intriguing in view of the growing appreciation that glia play critical roles in regulating synaptic glutamate concentrations and CNS energy homeostasis and in releasing trophic factors that participate in the development and maintenance of synaptic networks formed by neuronal and glial processes. Abnormalities of glial function could thus prove integral to the impairments of structural plasticity and overall pathophysiology of mood disorders.

BCL-2 AS A THERAPEUTICALLY RELEVANT TARGET FOR THE ACTIONS OF LITHIUM AND VALPROATE: THE SUCCESSFUL APPLICATION OF A CONCERTED mRNA DIFFERENTIAL DISPLAY STRATEGY TO IDENTIFY NOVEL TARGET GENES

It has become increasingly appreciated in recent years that the long-term treatment of mood disorders most likely involves the strategic regulation of signaling pathways and gene expression in critical neuronal circuits. In this context, several independent laboratories have now demonstrated that lithium and valproate, at therapeutically relevant concentrations, produce complex alterations in basal and stimulated DNA binding to activator protein 1 (AP-1) transcription factors. Together, these data suggest that lithium and valproate, via their effects on the AP-1 family of transcription factors, may bring about strategic changes in gene expression in critical neuronal circuits, effects that may ultimately underlie its efficacy in the treatment of a very complex neuropsychiatric disorder. Although many genes that are the targets of long-term lithium and valproate treatment have indeed been identified, it has been estimated that 10,000 to 15,000 genes may be expressed in a given cell at any time, and thus additional, novel methodologies are clearly required to study the complex pattern of gene expression changes induced by chronic drug treatment.

One methodology that has been successfully utilized to identify the differential expression of multiple genes (e.g., in pathologic vs. normal tissue or in control vs. treated tissue) is reverse transcription polymerase chain reaction mRNA differential display. Using this method, Wang and Young were the first to make the novel observation that lithium increased 2,3'-cyclic nucleotide 3'-phosphodiesterase mRNA levels in C6 glioma cells. Subsequent studies have also utilized this methodology to identify novel genes that may be the targets for the actions of mood stabilizers. A major problem inherent in neuropharmacologic research, however, is the dearth of phenotypic changes clearly associated with treatment response, particularly for mood-stabilizing agents. In the absence of clear-cut phenotypic changes, we have attempted to overcome this experimental hurdle by utilizing paradigms that involve the identification of common long-term molecular targets of structurally dissimilar mood-stabilizing agents (lithium and valproate) when administered chronically in vivo. These 2 distinct agents undoubtedly also exert a variety of dissimilar effects. However, the identification of genes affected by both agents, when administered in a therapeutically relevant paradigm, suggests that such molecular changes may play a role in the common therapeutic effects of these agents.

One of the genes whose expression was markedly increased by the treatments is the transcription factor polyoma enhancer binding protein (PEBP2β; GenBank Accession Number: AF087437). It was further demonstrated that the function of PEBP2β (DNA binding of the PEBP2β complex) was also clearly increased in frontal cortex by both lithium and valproate, but not by chronic amphetamine or benzodiazepine. One critical gene whose expression is known to be regulated by PEBP2β is the major neuroprotective protein bcl-2 (an abbreviation for the B-cell lymphoma/leukemia-2 gene); it was subsequently demonstrated that chronic treatment of rats with both

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Table 1. Postmortem Morphometric Brain Studies in Mood Disorders Demonstrating Cellular Atrophy and/or Loss

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<th>Reduced volume/cortical thickness</th>
<th>Cortical thickness rostral orbitofrontal cortex in MDD</th>
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<tr>
<td>Laminnar cortical thickness in layers III, V, and VI in subgenual anterior cingulate cortex (area 24) in BD</td>
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<tr>
<td>Volume of subgenual prefrontal cortex in familial MDD and BD</td>
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<td>Volumes of nucleus accumbens (left), basal ganglia (bilateral) in MDD and BD</td>
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<td>Parahippocampal cortex size (right) in suicide</td>
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<td>Reduced neuronal size and/or density</td>
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<td>Pyramidal neuronal density, layers III and V in dorsolateral prefrontal cortex in BD and MDD</td>
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<td>Neuronal size in layer V (~14%) and VI (~18%) in prefrontal cortex (area 9) in BD</td>
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<td>Neuronal size in layer VI (~20%) in prefrontal cortex (area 9) in MDD</td>
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<td>Neuronal density and size in layers II through IV in rostral orbitofrontal cortex, in layers V/VI in caudal orbitofrontal cortex, and in supragranular and infragranular layers in dorsolateral prefrontal cortex in MDD</td>
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<td>Neuronal size in layer VI (~23%) in anterior cingulate cortex in MDD</td>
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<td>Neuronal density in layers III, V, and VI in subgenual anterior cingulated cortex (area 24) in BD</td>
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<td>Layer-specific interneurons in anterior cingulate cortex in BD and MDD</td>
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<td>Non-pyramidal neuronal density in layer II (~27%) in anterior cingulate cortex in BD</td>
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<td>Non-pyramidal neuronal density in the CA2 region in BD</td>
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<td>Reduced glia</td>
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<td>Density/size of glia in dorsolateral prefrontal cortex and caudal orbitofrontal cortex in MDD and BD—layer specific</td>
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<td>Gial cell density in sublayer IIc (~19%) (and a trend to decrease in layer Va) in dorsolateral prefrontal cortex (area 9) in BD</td>
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<td>Gial number in subgenual prefrontal cortex in familial MDD (~24%) and BD (~41%)</td>
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<td>Gial cell density in layer V (~30%) in prefrontal cortex (area 9) in MDD</td>
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<td>Gial cell density in layer VI (~22%) in anterior cingulate cortex in MDD</td>
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<td>Gial cell counts, glial density, and glia-to-neuron ratios in amygdala in MDD</td>
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Modified and reproduced with permission from Manji and Duman, with additional information from references 24–28. Abbreviations: BD = bipolar disorder, MDD = major depressive disorder.
agents resulted in a doubling of bcl-2 levels in frontal cortex. Furthermore, immunohistochemical studies showed that chronic treatment of rats with lithium or valproate resulted in a marked increase in the number of bcl-2 immunoreactive cells in layers II and III of frontal cortex. Interestingly, the importance of neurons in layers II through IV of the frontal cortex in mood disorders has recently been emphasized, since primate studies have indicated that these are important sites for connections with other cortical regions and major targets for subcortical input. Chronic lithium also markedly increased the number of bcl-2 immunoreactive cells in the dentate gyrus and striatum (Figure 1); detailed immunohistochemical studies following chronic valproate treatment are currently underway. We have subsequently demonstrated that lithium also increases bcl-2 levels in C57BL/6 mice and in human neuroblastoma SH-SY5Y cells in vitro; our demonstration of a lithium-induced increase in bcl-2 levels has also been convincingly replicated in rat cerebellar granule cells in a recent study.

The latter study was undertaken to investigate the molecular and cellular mechanisms underlying the neuroprotective actions of lithium against glutamate excitotoxicity (vide infra). These investigators found that lithium produced a remarkable increase in bcl-2 protein and mRNA levels. Moreover, lithium has recently been demonstrated to reduce the levels of pro-apoptotic protein (p53) both in cerebellar granule cells and SH-SY5Y cells. Thus, overall, the data clearly show that chronic lithium robustly increases the levels of the neuroprotective protein bcl-2 in areas of rodent frontal cortex, hippocampus, and striatum in vivo and in cultured cells of both rodent and human neuronal origin in vitro; furthermore, at least in cultured cell systems, lithium has also been demonstrated to reduce the levels of p53.

Bcl-2 was the first identified member of a large family of cellular and viral apoptosis-regulating proteins. The bcl-2 family is the best-characterized protein family involved in the regulation of apoptotic cell death and consists of both anti-apoptotic (e.g., bcl-2 and bcl-XL) and pro-apoptotic members (e.g., BAX and BAD), several of which are expressed in the rodent and mammalian CNS. Bcl-2 attenuates apoptosis by sequestering proforms of death-driving cysteine proteases (called “caspases”); by preventing the release of mitochondrial apoptogenic factors such as calcium, cytochrome c, and apoptosis-inducing factor into the cytoplasm; and by enhancing mitochondrial calcium uptake (recently reviewed). Increasing evidence suggests a critical role for mitochondria in the process of apoptosis, and studies have shown that mitochondria undergo major changes in membrane integrity before classical signs of apoptosis become manifest, leading to a disruption of the inner transmembrane potential (Δψm) and the release of intermembrane proteins through the outer membrane. Chemically induced opening or closing of the permeability transition pore (also called “mitochondrial megachannel”) can induce or prevent apoptosis, respectively. Bcl-2 acts on mitochondria to stabilize membrane integrity and to prevent opening of the permeability transition pore, and has been shown to protect neurons from a variety of insults both in vitro and in vivo. Overexpression of bcl-2 in transgenic mice has been shown to prevent motor neuron and retinal ganglion death, to protect cells from the deleterious effects of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) or focal ischemia, to protect photoreceptor cells from inherited retinal degeneration, and to prolong survival and attenuate motor neuron degeneration in a transgenic animal model of amyotrophic lateral sclerosis.

Accumulating data suggest that not only is bcl-2 neuroprotective, but it also exerts neurotrophic effects and promotes neurite sprouting, neurite outgrowth, and axonal regeneration. Moreover, a recent study demonstrated that severe stress exacerbates stroke outcome by suppressing bcl-2 expression. In this study, the stressed mice expressed ≈ 70% less bcl-2 mRNA than unstressed mice after ischemia. Furthermore, stress greatly exacerbated infarct in control mice but not in transgenic mice that constitutively express increased neuronal bcl-2. Finally, high corticosterone concentrations were significantly correlated with larger infarcts in wild-type 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 and suggests that pharmacologically induced up-regulation of
bcl-2 may have considerable utility in the treatment of a variety of disorders associated with endogenous or acquired impairments of cellular resilience (vide infra). Overall, it is clear that the neurotrophic factor/mitogen-activated protein (MAP) kinase/bcl-2 signaling cascade plays a critical role in cell survival in the CNS and that there is a fine balance maintained between the levels and activities of cell survival and cell death factors; modest changes in this signaling cascade or in the levels of the bcl-2 family of proteins (potentially due to genetic-, illness-, or insult-related factors) may therefore profoundly affect cellular viability.

THE ROLE OF GENE EXPRESSION PROFILING IN PSYCHIATRIC RESEARCH

As described above, differential display (DD) technology was used to discover the up-regulation of bcl-2 by lithium and valproate (via the identification of the up-regulation of a transcription factor known to regulate bcl-2—PEBP2β). The discovery of this unexpected target, which has had a major influence on our thinking about the long-term cellular effects of mood stabilizers, illustrates the importance of hypothesis-generating (as opposed to hypothesis-dependent) techniques. Microarrays are another example of this type of research tool and have already proved quite valuable in the study of psychiatric drugs. As the technology improves, current problems are eliminated, and new applications are developed, microarrays are likely to become an essential, indispensable tool for the neuroscience-psychiatric community. The methodological issues of microarray experiments have been extensively reviewed, but are discussed here briefly.

It is important to note that microarray technology should not necessarily be considered to be superior to, or a replacement of, DD. Rather, each technique has unique advantages and disadvantages. Perhaps most obvious is the identification of transcripts: using a cDNA microarray, one is relatively certain what each differentially regulated mRNA is; with DD, on the other hand, one must clone and identify the transcript in question. While both methodologies require further validation to eliminate false-positives, the immediate identification of the differentially expressed transcripts by the microarray methodology translates into a major savings in terms of time and labor. However, this very advantage of the microarray technology is also one of its weaknesses compared with the DD methodology; the microarray methodology allows for the identification of known transcripts only (which the array in question is composed of); by contrast, DD allows for the detection of entirely novel mRNA transcripts and is thus truly unbiased. Oligonucleotide arrays are more like DD, in that novel targets may be identified and the identity of the transcript binding to a given oligo must be determined. For further comparison of DD and microarray technologies, the reader is referred to Liang’s recent review.

One key difficulty in the use of microarrays lies in the signal-to-noise ratio. Particularly for transcripts of low abundance, the test-retest reliability of microarray results can be dismal. For this reason, repetition is of obvious importance; noise can be filtered, and variance can be used to assess the validity of results. Unfortunately, the high cost of microarrays often forces researchers to forgo replication entirely and thereby jeopardize the usefulness of their results. Likewise, the commonly used approach of establishing a threshold of the magnitude of expression ratio that constitutes a significant change fails to address the issue of deviation and error. As the reliability increases, and the cost decreases, microarray data will hopefully become subject to more statistically rigorous analyses.

Even given the importance of replication, the usefulness of conventional statistical measures, such as the t test, is another concern. In a set of 10,000 transcripts, it is clear that one can expect ≈ 500 false-positives, if one uses a p < .05 cutoff. On the other hand, if one uses Bonferroni correction for repeated analyses, one is all but guaranteed to find no significantly regulated mRNA, and thus to acquire numerous false-negatives.

In this light, the stringency with which microarray data are analyzed becomes a much fuzzier matter and may be adjusted to address the specific question under investigation. While at first glance one may question the scientific rigor of such an approach, it needs to be emphasized that the microarray methodology is only a screening technique, and the results require much more independent validation. Thus, the cutoff threshold criteria should be determined by not only statistical considerations, but also the stringency and rigor of the experimental paradigm (e.g., identifying common targets of structurally highly dissimilar drugs) and the ability/willingness to subsequently validate positive results with independent methodologies. For example, if an experimenter hopes to discover single genes that are the target of the manipulation, high stringency is probably warranted (e.g., p < .01 and effect size of 2-fold). This ensures that less time will be wasted on false-negatives at the polymerase chain reaction and/or protein validation stage. If, on the other hand, the goal is to find groups of related genes that are affected, or common targets of multiple agents, lower stringency may be more desirable. For example, if all 12 subtypes of a given receptor are up-regulated 30% with p values ≤ .10, it may represent a very important finding that would have been discarded with higher stringency.

Aside from the t test and fold-difference comparisons, more powerful means of analyzing microarray data are emerging. Clustering is a fairly common technique in which transcripts are associated based on their co-regulation across a number of samples. “Fingerprinting” refers to the association of a general pattern of microarray results with a particular variable. For example, this technique has already begun to show usefulness in oncology, where patterns in microarray data from biopsies may help predict treatment...
response and outcome. Likewise, ex vivo gene expression data from psychiatric patients may one day predict optimal treatment strategies, risk of relapse, or other important clinical variables.

The Use of Microarrays to Ascertaining the Actions of Mood Stabilizers

To maximize the meaningfulness of our microarray data, we have included a number of important design features in our experiments. As a first step in this important series of studies, we have utilized human neuroblastoma SH-SY5Y cells. These cells were selected for a number of reasons, including the following:

1. They are human cells with a neuronal phenotype.
2. They provide a very homogeneous population of cells and the ability to control most experimental conditions—critical to accurately identifying the test/retest stability of results, stability over time, and inter- and intra-assay coefficients of variations for the microarray methodology.
3. They have previously been shown to produce treatment-induced changes that are very similar to those that have been observed in critical areas of rodent brain during chronic in vivo treatment with mood stabilizers, including changes in protein kinase C isozymes, the extracellular signal-regulated kinase (ERK) MAP kinase cascade, the glycogen synthase kinase (GSK-3)/β-catenin pathway, bcl-2, and AP-1 DNA binding activity. 40,62–64

For SY5Y experiments, 4 independent replicate control/experimental pairs were used for both lithium and valproate. Cells were treated for 5 days prior to mRNA extraction. For each pair, 2 slides were hybridized, reversing the Cy3/Cy5 labeling. This procedure corrects for the oft-encountered problem of gene-label interaction. 65 To model the requirement for chronic, systemic administration, rats were given lithium- or valproate-containing chow for 4 weeks, and hippocampi were collected bilaterally for mRNA extraction. Only animals with plasma drug levels within the therapeutic range were used for microarray analysis (lithium: 0.5–1.2 mM, valproate: 0.3–0.9 mM). Again, mRNA from each pair was hybridized to 2 slides, reversing the labels to control for gene-label interaction. Rat and SY5Y slides were read using the ScanArray 5000 (PerkinElmer Life Sciences, Boston, Mass.), and data were filtered and analyzed using QuantArray (PerkinElmer Life Sciences, Boston, Mass.) and Microsoft Excel (Microsoft, Redmond, Wash.). Replicates were tested for significance using a 2-tailed paired-samples t test.

The investment our laboratory has put into this intensive strategy has been rewarded. While specific reports are in progress and will appear elsewhere, some general trends are notable. A constellation of transcripts involved in apoptotic signaling have been found, in agreement with the large body of data supporting the cytoprotective effects of lithium and valproate. Therefore, it is a tempting hypothesis that mood stabilizers are inducing a cellular resilience program, which includes the host of alterations observed.

Interestingly, a number of genes involved in cytoskeletal functions were also dysregulated by lithium and valproate in SY5Y cells. Given the documented effects of lithium and valproate on processes like neurite outgrowth and synaptic plasticity, 66–68 these results come as no surprise. Again, it is conceivable that the array of changes seen in cytoskeletal functions and gene expression represent the activation/suppression of cellular programs.

LITHIUM AND VALPROATE ROBUSTLY ACTIVATE A SIGNALING CASCADE UTILIZED BY ENDOGENOUS GROWTH FACTORS: THE ERK MAP KINASE CASCADE

Neurotrophic Signaling Cascades: A Focus on Brain-Derived Neurotrophic Factor

Neurotrophins are a family of regulatory factors that mediate the differentiation and survival of neurons, as well as the modulation of synaptic transmission and synaptic plasticity. The neurotrophin family now includes, among others, nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin 3 (NT3), NT4/5, and NT6. These various proteins are closely related in terms of sequence homology and receptor specificity. They bind to and activate specific receptor tyrosine kinases belonging to the Trk family of receptors, including TrkA, TrkB, TrkC, and a pan-neurotrophin receptor, p75. 69 Additionally, there are 2 isoforms of TrkB receptors: the full-length TrkB and the truncated form of TrkB, which does not contain the intracellular tyrosine kinase domain. 70 The truncated form of TrkB can thus function as a dominant-negative inhibitor for the TrkB receptor tyrosine kinase, thereby providing another mechanism to regulate BDNF signaling in the CNS. 71 Neurotrophins can be secreted constitutively or transiently, and often in an activity-dependent manner. Recent observations support a model wherein neurotrophins are secreted from the dendrite and act retrogradely at presynaptic terminals where they act to induce long-lasting modifications. 89 Within the neurotrophin family, BDNF is a potent physiologic survival factor that has also been implicated in a variety of pathophysiologic conditions. The cellular actions of BDNF are mediated through 2 types of receptors: a high-affinity tyrosine receptor kinase (TrkB) and a low-affinity pan-neurotrophin receptor (p75). TrkB is preferentially activated by BDNF and NT4/5 and appears to mediate most of the cellular responses to these neurotrophins.

BDNF and other neurotrophic factors are necessary for the survival and function of neurons, 72 implying that a sustained reduction of these factors could affect neuronal viability. However, what is sometimes less well appreciated is the fact that BDNF also has a number of much more acute
effects on synaptic plasticity and neurotransmitter release and facilitates the release of glutamate, γ-aminobutyric acid (GABA), dopamine, and serotonin. In this context, BDNF has been shown to potentiate both excitatory and inhibitory transmission, albeit via different mechanisms; BDNF strengthens excitation primarily by augmenting the amplitude of α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor-mediated miniature excitatory postsynaptic current, but enhances inhibition by increasing the frequency of miniature inhibitory postsynaptic current and increasing the size of GABAergic synaptic terminals. Furthermore, full-length TrkB receptor immunoreactivity has been found not only in glutamatergic pyramidal and granule cells, but also in some interneuron axon initial segments, axon terminals forming inhibitory-type synapses onto somata and dendritic shafts, and excitatory-type terminals likely to originate extrahippocampally. Together, these results suggest that TrkB is contained in some GABAergic interneurons, neuromodulatory (e.g., cholinergic, dopaminergic, and noradrenergic) afferents, and/or glutamatergic afferents.

As discussed already, BDNF is best known for its long-term neurotrophic and neuroprotective effects, which may be very important for its putative role in the pathophysiology and treatment of mood disorders (vide infra). In this context, it is noteworthy that although endogenous neurotrophic factors have traditionally been viewed as increasing cell survival by providing necessary trophic support, it is now clear that their survival-promoting effects are mediated in large part by an inhibition of cell death cascades. It is believed that neurotrophic factors inhibit cell death cascades by activating the MAP kinase signaling pathway and the phosphatidylinositol (PI) 3-kinase/Akt pathway. One important mechanism by which the MAP kinase signaling cascade inhibits cell death is by increasing the expression of the anti-apoptotic protein bcl-2.

**Lithium and Valproate Activate the ERK Signaling Cascade**

In view of the important role of the ERK signaling cascade in mediating long-term neuroplastic events, a series of studies have been undertaken to investigate the effects of lithium and valproate on this signaling cascade. These studies have shown that lithium and valproate, at therapeutically relevant concentrations, robustly activate the ERK MAP kinase cascade in human neuroblastoma SH-SY5Y cells. Follow-up studies have recently shown that, similar to the effects observed in neuroblastoma cells in vitro, chronic lithium or valproate also robustly increases the levels of activated ERK in areas of brain that have been implicated in the pathophysiology and treatment of BD—the frontal cortex and hippocampus. In addition to finding that valproate and lithium activate ERK, we have also found that downstream targets of the ERK pathway such as p90 ribosomal S6 kinase (RSK) and cyclic adenosine monophosphate response element binding protein (CREB) are activated, while the pro-apoptotic protein BAD is deactivated. Furthermore, an inhibitor of the enzyme that phosphorylates ERK, MAP kinase/ERK, attenuates the valproate-induced increase in ERK and RSK1 phosphorylation (G. Chen, M.D.; P. Yuan, M.D., Ph.D.; H.K.M.; unpublished observations, June 2002). Thus, recent evidence suggests that both lithium and valproate activate the ERK MAP kinase pathway and the transcription of downstream molecules bcl-2 and BDNF.

**DOES INHIBITION OF GLYCOGEN SYNTHASE KINASE 3B PLAY A ROLE IN THE THERAPEUTIC EFFECTS OF LITHIUM?**

While older literature suggests that lithium interacts with glycogen synthase, it was not until 1996, when Klein and Melton made the seminal observation that lithium inhibited the action of GSK-3, that the direct inhibition of this enzyme by lithium was identified. GSK-3 is a highly conserved enzyme in evolution and is found in 2 nearly identical isoforms in mammals, α and β. This enzyme was first discovered (and named) on the basis of its ability to phosphorylate, and thereby inactivate, the enzyme glycogen synthase, an action that led to a decrease in the synthesis of glycogen. However, as we discuss below, GSK-3 is now known to regulate diverse functions in the adult mammalian brain. GSK-3 is unique among kinases in that it is constitutively active. Thus, most intracellular signals to GSK-3 inactivate the enzyme. Signals deactivating GSK-3 arise from insulin stimulation, numerous growth factors (for example, PI 3-kinase), and developmental signals. A number of endogenous growth factors (e.g., NGF and BDNF) utilize the PI 3-kinase signaling cascade as a major effector system. Thus, growth factors may bring about many of their neurotrophic/neuroprotective effects, at least in part, by GSK-3 inhibition. GSK-3 phosphorylates—and thereby inactivates—many targets, including transcription factors and cytoskeletal proteins such as the Alzheimer’s protein tau (a previous name for GSK-3 was tau kinase). Inhibition of GSK-3 thus results in the release of this inhibition and activation of multiple cellular targets.

Lithium’s inhibition of GSK-3 appears to be by competition with magnesium for a binding site. Thus, magnesium binding increases the activity of GSK-3 when it is not inhibited by lithium. As mentioned, in 1996, Klein and Melton first identified lithium as a direct inhibitor of GSK-3 activity and suggested that this finding may be relevant to lithium’s efficacy in treating BD. Three years later, valproic acid, another mood stabilizer commonly used in clinical practice, was also identified as an inhibitor of GSK-3, further suggesting the importance of this enzyme in BD research. While lithium inhibits GSK-3 by direct competition with magnesium, the precise mechanisms by which valproic acid exerts its action are still uncertain.
GSK-3 plays a critical role in the survival of neurons, and this role has been postulated to be the target of lithium and valproic acid. As discussed elsewhere in this review, a large amount of data describe neuroprotective effects of lithium in many preclinical models. It is possible that the effect of lithium on GSK-3 plays a major role in these observations. Thus, a rapidly increasing amount of evidence suggests that GSK-3 plays important roles in regulating neuroplasticity and cellular resilience. Studies have suggested that changes in GSK-3-mediated microtubule-associated protein 1B (a cytoskeletal protein) phosphorylation are associated with the loss and/or unbundling of stable axonal microtubules. Furthermore, glycogen synthase kinase 3β (GSK-3β) inhibition results in the accumulation of synapsin I, a protein involved in synaptic vesicle docking and release, as well as neurite outgrowth, at growth cone–like areas.

In addition to the putative role of GSK-3 in regulating synapse formation and axonal growth, there is considerable excitement regarding both its role in regulating cell death in mature neuronal tissue and the development of GSK-3 inhibitors as novel therapeutic agents for BD and classical neurodegenerative diseases. Although it was initially reported 10 years ago, in 1993, that GSK-3 activity was required for β-amyloid–induced neurotoxicity in primary hippocampal neurons, these observations were not followed up until very recently. More recent studies have demonstrated that GSK-3 may regulate cell death beyond its role in β-amyloid–induced toxicity. For example, GSK-3 overexpression induces apoptosis in cultured cells, a finding that is prevented by dominant negative GSK-3 mutants. Furthermore, the expression of frequently rearranged in advanced T-cell lymphomas 1 (Frat1), a protein that inhibits GSK-3, also rescues primary sympathetic neurons from PI 3-kinase inhibition–induced cell death. Finally, serum deprivation or PI 3-kinase–induced apoptosis is attenuated by either a dominant negative form of GSK-3 or an inhibitory GSK-3 binding protein.

Although the study of the effects of selective small molecule GSK-3 inhibitors is still in its infancy, the available data suggest that pharmacologic inhibition of GSK-3β also exerts neuroprotective effects. For example, 2 novel inhibitors of GSK-3 have been demonstrated to protect primary sensory and granule neurons from potassium deprivation or PI 3-kinase–induced cell death.

A second putative target pathway resultant from GSK-3 inhibition is suggested by research exploring the underlying circadian cycle of Drosophila. The Drosophila orthologue of GSK-3 (SHAGGY) regulates circadian rhythms in this species. A decrease in SHAGGY activity results in an increase in circadian period length, precisely the effect (increase in circadian period) that has been noted in numerous species, including Drosophila, after treatment with lithium. While there are many differences between the molecular components of circadian cycles in mammals and Drosophila, there are also many similarities. It is thus interesting to speculate that GSK-3 has a similar general action in the function of the mammalian circadian clock. This putative function of GSK-3 in mammals thus represents another possible therapeutic target for the actions of lithium on GSK-3.

Thus, GSK-3 may play important roles in regulating processes such as synaptic plasticity, cell survival, and circadian rhythms in the mature CNS. It is interesting that all of these processes have been implicated in the pathophysiology and treatment of BD. Since GSK-3 is also a tau kinase, many pharmaceutical companies are developing CNS-penetrant small molecule GSK-3 inhibitors for the treatment of Alzheimer’s disease. It is anticipated that these drugs will also undergo trials in BD.

**NEUROPROTECTIVE EFFECTS OF LITHIUM: COMPELLING PRECLINICAL EVIDENCE**

Lithium’s robust effects on bcl-2, ERK MAP kinase, and GSK-3β in the mature CNS suggest that it may possess significant neuroprotective properties. Indeed, several studies conducted before the identification of bcl-2 or GSK-3β as targets for lithium’s actions had already demonstrated neuroprotective properties of lithium. The protective effects of lithium have been investigated in a number of in vitro studies, in particular using rat cerebellar granule cells, pheochromocytoma (PC12) cells, and human neuroblastoma SH-SY5Y cells. In these studies, lithium has been shown to protect against the deleterious effects of glutamate, N-methyl-D-aspartate receptor activation, low potassium, and toxic concentrations of anticonvulsants (Table 2). Lithium also protects PC12 cells from serum/NF deprivation and protects both PC12 cells and human neuroblastoma SH-SY5Y cells from ouabain toxicity. Most recently, lithium has been shown to protect cultured neurons from β-amyloid–induced cell death and to protect against the deleterious effects of GSK-3β overexpression coupled to staurosporine addition.

In addition to these demonstrations of protective effects in vitro, a number of studies have investigated lithium’s neuroprotective effects in vivo. In this context, studies have investigated the effects of lithium on the biochemical and behavioral manifestations of excitotoxic lesions of the cholinergic system. These studies have demonstrated that lithium pretreatment attenuates both the behavioral deficits (passive avoidance and ambulatory behavior) and the reduction in choline acetyltransferase (ChAT) activity by forebrain cholinergic system lesions. In a study that may have implications for the treatment of Alzheimer’s disease, rats received ibotenic acid lesions of cholinergic basal forebrain nuclei, resulting in a 30% to 40% depletion of both cortical ChAT and acetylcholinesterase (AChE) activity. Lithium as well as tetrahydroaminoacridine, given separately either prior or subsequently to the development of the
Table 2. Neurotrophic and Neuroprotective Effects of Lithium

<table>
<thead>
<tr>
<th>Protects cultured cells of rodent and human neuronal origin in vitro from</th>
<th>Glutamate</th>
<th>High concentrations of calcium</th>
<th>MPP⁺</th>
<th>β-Amyloid</th>
<th>Aging-induced cell death</th>
<th>HIV regulatory protein, Tat</th>
<th>HIV gp120 envelope protein</th>
<th>Glucose deprivation</th>
<th>Growth factor or serum deprivation</th>
<th>Toxic levels of anticonvulsants</th>
<th>Platelet activating factor</th>
<th>Aluminum toxicity</th>
<th>Low potassium concentrations</th>
<th>C2-ceramide</th>
<th>Ouabain</th>
<th>GS-K-β</th>
<th>Bungarotoxin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protects rodent brain in vivo from</td>
<td>Cholinergic lesions</td>
<td>Radiation injury</td>
<td>Middle cerebral artery occlusion (model of stroke)</td>
<td>HIV gp120 envelope protein injection (model of HIV-associated dementia)</td>
<td>Quinolinic acid infusion (model of Huntington’s disease)</td>
<td>Aluminum maltolate</td>
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<tr>
<td>Human effects</td>
<td>No subgenual PFC gray matter volume reductions in cross-sectional MRI studies</td>
<td>No reductions in amygdala glial density in postmortem cell counting studies</td>
<td>Increased total gray matter volumes on MRI compared with untreated BD patients in cross-sectional studies</td>
<td>Increased NAA (marker of neuronal viability) levels in BD patients in longitudinal studies</td>
<td>Increased gray matter volumes in BD patients in longitudinal studies</td>
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Adapted from Manji et al. (See also recent reviews by Li et al. and Chuang et al.).

Abbreviations: BD = bipolar disorder, GSK-3β = glycogen synthase kinase 3β, HIV = human immunodeficiency virus, MPP⁺ = 1-methyl-4-phenylpyridinium ion, MRI = magnetic resonance imaging, NAA = N-acetyl-aspartate, PFC = prefrontal cortex.

lesion, had small but significant effects on the recovery of cortical ChAT and AChE activity. Intriguingly, when applied in combination, the drugs clearly showed synergistic effects. However, considerable caution is required in the extrapolation of these results to the treatment of humans, since the coadministration of lithium and cholinesterase inhibitors has been shown to be capable of inducing seizures. In another study investigating lithium’s effects against excitotoxic insults, it was demonstrated that lithium attenuated the kainic acid–induced reduction in glutamate decarboxylase levels and [3H]β-aspartate uptake. Chronic lithium has also been shown to exert dramatic protective effects against middle cerebral artery occlusion, reducing not only the infarct size (56%), but also the neurologic deficits (abnormal posture and hemiplegia). Most recently, the same research group has demonstrated that chronic in vivo lithium treatment robustly protects neurons in the striatum from quinolinic acid–induced toxicity, in a putative model of Huntington’s disease. Table 2 summarizes some of the most robust experimental evidence demonstrating neuroprotective effects of lithium in vitro and in vivo. In addition to lithium’s effects on bcl-2 and GSK-3β, its effects on other signaling pathways and transcription factors may also contribute to its neuroprotective effects. In this context, it is noteworthy that recent studies have shown that modulation of Akt-1 activity is involved in glutamate excitotoxicity and may play a role in lithium’s neuroprotective effects in rat cerebellar granule cells. Furthermore, Datta and colleagues have demonstrated that Akt phosphorylation of BAD (a pro-apoptotic member of the bcl-2 family) blocks BAD-induced death of primary neurons. These results suggest that lithium’s effects on Akt-1 may also contribute to neuroprotective effects; however, such a contention awaits the demonstration of lithium-induced activation of Akt-1 in the CNS in vivo.

Does Lithium Affect Neurogenesis?

As discussed already, utilizing a method for labeling cell division directly in the adult human brain, it has been shown that the dentate gyrus (an area where robust lithium-induced increases in bcl-2 levels are observed) can produce new neurons during adulthood in humans. A large number of the newborn daughter cells are known to die rapidly, most likely via apoptosis. Thus, increasing bcl-2 levels could enhance the survival of the newborn cells, allowing them to differentiate into neurons. Additionally, bcl-2 has been shown to have robust effects on the regeneration of CNS axons. In view of bcl-2’s major neuroprotective and neurotrophic role, a study was undertaken to determine if lithium, administered at therapeutically relevant concentrations, affects neurogenesis in the adult rodent brain. Kempermann and Gage have suggested the use of the word neurogenesis to refer to a series of events (including proliferation of a neuronal precursor or stem cell, and survival of the daughter cells) that results in the appearance of a new neuron. To investigate the effects of chronic lithium on neurogenesis, mice were treated with “therapeutic” lithium (mean ± SD plasma levels = 0.97 ± 0.20 mM), for ∼ 4 weeks. After treatment with lithium for 14 days, the mice were administered single doses of bromodeoxyuridine (BrdU, a thymidine analog that is incorporated into the DNA of dividing cells) for 12 consecutive days. Lithium treatment continued throughout the duration of the BrdU administration. Following BrdU immunohistochemistry, 3-D cell counting was performed using a computer-assisted image analysis system. This system is based on the optical disector method and estimates the number of cells independent of section thickness and cell shape. We found that chronic lithium administration does, indeed, result in an increase in the number of BrdU-positive cells in the dentate gyrus (Figure 2). Moreover, approximately two thirds of the BrdU-positive cells also double-stained with the neuronal marker NeuN, confirming their neuronal identity. Double-staining of BrdU and bcl-2 was also seen, and studies using bcl-2 transgenic animals are currently underway.
to delineate the role of the observed bcl-2 overexpression in the enhanced hippocampal neurogenesis.

HUMAN EVIDENCE FOR THE NEUROTROPHIC EFFECTS OF LITHIUM

While the body of preclinical data demonstrating neurotrophic and neuroprotective effects of mood stabilizers is striking, considerable caution must clearly be exercised in extrapolating to the clinical situation with humans. In view of lithium’s robust effects on the levels of the cytoprotective protein bcl-2 in the frontal cortex, Drevets reanalyzed older data that demonstrated ≈ 40% reductions in subgenual PFC volumes in familial mood disorder subjects. Consistent with neurotrophic/neuroprotective effects of lithium, the results revealed that the patients treated with chronic lithium or valproate exhibited subgenual PFC volumes that were significantly higher than the volumes in patients not treated with lithium or valproate and not significantly different from control. In a more recent study, Bowley and colleagues have investigated glial cell densities in mood disorder patients. Although the sample sizes are quite small, the authors made the intriguing observation that unipolar patients exhibited reduced glial cell densities, whereas only the bipolar patients off chronic lithium or valproate treatment exhibited similar reductions.

Although the results of the aforementioned studies suggest that mood stabilizers may have provided neuroprotective effects during naturalistic use, considerable caution is warranted in view of the small sample size and cross-sectional nature of the studies. To investigate the potential neurotrophic effects of lithium in humans more definitively, a longitudinal clinical study was recently undertaken using proton magnetic resonance spectroscopy (MRS) to quantify N-acetyl-aspartate (NAA, a putative marker of neuronal viability) levels. Four weeks of lithium treatment produced a significant 25% increase in BrdU immunolabeling in both right and left dentate gyrus (p < .05).

Lithium Increases Gray Matter in the Human Brain

A follow-up volumetric MRI study has demonstrated that 4 weeks of lithium treatment also significantly increased total gray matter content in the human brain, suggesting an increase in the volume of the neuropil (the mossy fiber layer composed of axonal and dendritic fibers that occupies much of the cortex gray matter volume; Figure 3). A finer-grained subregional analysis of these brain-imaging data is ongoing and clearly shows that lithium produces a regionally selective increase in gray matter, with prominent effects being observed in hippocampus and caudate. Furthermore, no changes in overall gray matter volume are observed in healthy volunteers treated chronically with lithium, suggesting that lithium is truly producing a reversal of
illness-related atrophy, rather than nonspecific gray matter increases.

**ARE TRADITIONAL “ANTIMANIC LEVELS” OF LITHIUM REQUIRED FOR NEUROTROPHIC/NEUROPROTECTIVE EFFECTS?**

It is striking that lithium has such robust effects on the cytoprotective protein bcl-2, exerts neuroprotective effects in a variety of paradigms, and actually increases gray matter volumes in humans. These exciting results suggest that lithium may have utility in the treatment of a variety of neuropsychiatric disorders that are associated with cell atrophy/loss and impairments of cellular resilience. One obvious concern is lithium’s tolerability, especially in patients with neurodegenerative disorders. Our laboratory has therefore undertaken a series of studies to determine if the chronic administration of lithium at low doses also regulates bcl-2 expression. We have found that chronic (4-week) lithium administration, at doses that produce plasma drug levels of ≈ 0.35 mM, robustly increases bcl-2 levels in rat frontal cortex (Figure 4) and hippocampus. Furthermore, there is accumulating evidence from other groups suggesting that lithium exerts neuroprotective effects at lower doses. Thus, 0.5 mM of lithium has been shown to protect cultured cerebellar granule cells from glutamate excitotoxicity and to decrease levels of the pro-apoptotic protein p53. In middle cerebral artery occlusion, an in vivo model of stroke, lithium has also been shown to offer significant protection at 0.5 mEq/kg. Of particular interest, a recent study demonstrated that cortical neurons are even more potently protected from excitotoxicity, with significant increases in viability occurring with lithium doses as low as 0.1 mM. Overall, the data clearly suggest that doses of lithium lower than “traditional antimanic” doses have neurotrophic and neuroprotective effects and may thus have utility as adjunctive treatments for neuropsychiatric disorders associated with cell loss/atrophy.

Does low-dose lithium have utility in the treatment of mood disorders? While the data overall are not conclusive, there is considerable suggestive evidence to support such a contention. In this context, it is noteworthy that a recent demonstration of the potential usefulness of low-dose lithium was provided by Perlis et al. Reanalyzing data from an earlier randomized, blinded study that determined that patients treated with low doses of lithium were more likely to relapse, the newer study determined that it was the abrupt drop in lithium levels, rather than the absolute dose...
per se, that increased risk of new episodes. Patients who had been receiving similarly low doses before and after randomization were no more likely to relapse than those who were receiving high doses before and after randomization. Likewise, in a 12-month, double-blind, crossover study of high- and low-dose lithium, patients experienced more episodes during treatment with the low dose, but primarily in the first month following dose readjustment. Longer studies have found low-dose lithium to be as effective as standard doses, although there are conflicting reports.

While the data are mixed, there is also substantial evidence suggesting that low-dose lithium is an effective potentiatior of antidepressant action. In their review, Rouillon and Gorwood discuss both case reports and larger trials and suggest that lithium augmentation should begin with a low dose, increasing only if necessary. It has been unequivocally established in controlled studies that about half of all treatment-refractory depressed patients respond to an addition of lithium to their ongoing antidepressant regimen. Although lithium potentiation is more efficacious in bipolar patients, it also has clear efficacy in the treatment of unipolar depressive patients. The lithium augmentation strategy derived from de Montigny and colleagues heuristic proposal that the enhancement of ascending presynaptic serotoninergic function would translate into potentiation of antidepressant efficacy. However, the data reviewed here clearly show that lithium—even at lower doses—has major effects on neurotranscital signaling cascades, and it is our contention that these effects may also underlie its antidepressant potentiating efficacy. Finally, recent studies of elderly depressed patients suggest that low-dose lithium may be particularly useful in this population. It is thus clear that longitudinal studies using low-dose lithium as a “plasticity enhancer” are clearly warranted.

CONCLUDING REMARKS

As discussed, there is a considerable body of evidence to suggest both conceptually and experimentally that impairments in neuroplasticity and cellular resilience may play an important role in the pathophysiology of recurrent mood disorders. Furthermore, we contend that for many re- fractory depression patients, new drugs that simply mimic many “traditional” drugs that directly or indirectly alter neurotransmitter levels and those that bind to cell surface receptors may be of limited benefit. This is because such strategies implicitly assume that the target circuits are functionally intact and that altered synaptic activity will thus be transduced to modify the postsynaptic “throughput” of the system. However, the evidence presented here suggests that, in addition to neurochemical changes, many patients also have pronounced structural alterations (e.g., reduced spine density, neurite retraction, overall neuropil reductions) in critical neuronal circuits. Thus, optimal treatment may be attained only by providing both trophic and neurochemical support; the trophic support would be envisioned as enhancing and maintaining normal synaptic connectivity, thereby allowing the chemical signal to reinstate the optimal functioning of critical circuits necessary for normal affective functioning. Indeed, preliminary studies have suggested that regional structural brain changes in patients with mood disorders may be associated with not only illness severity/duration, but also altered treatment response.

Does the long-term administration of these agents actually retard disease- or affective episode–induced cell loss or atrophy? As articulated, the distinction between disease progression and affective episodes per se is an important one, since it is quite possible that the neurotrophic effects of lithium or valproate may even be independent of their ability to treat or prevent affective episodes. There are presently no longitudinal studies that we are aware of that can fully address this question, but this is clearly a very important and fundamental issue worthy of investigation. The findings that lithium administration increases brain NAA levels and gray matter volumes, as well as the cross-sectional study demonstrating “normalized” subgenual PFC volumes in lithium- and valproate-treated patients, do provide indirect support for such a contention. Longitudinal studies investigating the potential long-term neurotrophic effects (using serial volumetric MRI scans or MRS quantification of regional NAA levels, for example) of mood stabilizers are clearly warranted. The evidence also suggests that early and potentially sustained treatment may be necessary to adequately prevent many of the deleterious long-term sequelae associated with mood disorders. While data suggest that hippocampal atrophy in depression is related to illness duration, it is not presently clear if the
While lithium and valproate are clearly not going to "cure" neurodegenerative disorders, it is our contention that their adjunctive use early in the course of these disorders has the potential to play an important role in slowing down disease progression by enhancing neuroplasticity and cellular resilience; clinical studies are thus clearly warranted.

Drug name: valproic acid (Depakene and others).

Disclosure of off-label usage: The authors of this article have determined that, to the best of their knowledge, valproic acid is not approved for neurodegenerative disorders.

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Table 3. Summary of the Differences in the Neurotrophic Properties of Antidepressants and Lithium: Evidence From Current Studies

<table>
<thead>
<tr>
<th>Antidepressants exert major effects on CREB and BDNF expression in rat hippocampus.</th>
<th>Lithium exerts major effects on ERK activation in rat frontal cortex and hippocampus.</th>
<th>Longitudinal studies show that chronic lithium increases the levels of NAA in areas of brain in bipolar patients; there are no similar published studies with valproic acid or antidepressants.</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Antidepressants may exert modest effects on CREB and BDNF expression in rat hippocampus.</td>
<td>Cross-sectional neuroimaging studies suggest that patients treated with chronic lithium or valproic acid do not show subgenual prefrontal cortex atrophy; patients treated with SSRIs show atrophy similar to that of untreated patients.</td>
<td>Longitudinal studies show that chronic lithium increases gray matter volumes in bipolar patients; there are currently no similar published studies with antidepressants.</td>
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</tr>
</tbody>
</table>

Abbreviations: BDNF = brain-derived neurotrophic factor, CREB = cyclic adenosine monophosphate response element binding protein, ERK = extracellular signal-regulated kinase, NAA = N-acetylaspartate, SSRI = selective serotonin reuptake inhibitor.


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