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Therapeutic Potential of Mood Stabilizers Lithium and Valproic Acid: Beyond Bipolar Disorder

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***Abstract*——The mood stabilizers lithium and valproic acid (VPA) are traditionally used to treat bipolar disorder (BD), a severe mental illness arising from complex interactions between genes and environment that drive deficits in cellular plasticity and resiliency. The therapeutic potential of these drugs in other central nervous system diseases is also gaining support. This article reviews the various mechanisms of action of lithium and VPA gleaned from cellular and animal models of neurologic, neurodegenerative, and neuropsychiatric disorders. Clinical evidence is included when available to provide a comprehensive perspective of the field and to acknowledge some of the limitations of these treatments. First, the review describes how action at these drugs' primary targets—glycogen synthase kinase-3 for lithium and histone deacetylases for VPA—induces the transcription and expression of neurotrophic, angiogenic, and neuroprotective proteins. Cell survival signaling cascades, oxidative stress pathways, and protein quality control mechanisms may further underlie lithium and VPA's beneficial actions. The ability of cotreatment to augment neuroprotection and enhance stem cell homing and migration is also discussed, as are microRNAs as new therapeutic targets. Finally, preclinical findings have shown that the neuroprotective benefits of these agents facilitate anti-inflammation, angiogenesis, neurogenesis, blood-brain barrier integrity, and disease-specific neuroprotection. These mechanisms can be compared with dysregulated disease mechanisms to suggest core cellular and molecular disturbances identifiable by specific risk biomarkers. Future clinical endeavors are warranted to determine the therapeutic potential of lithium and VPA across the spectrum of central nervous system diseases, with particular emphasis on a personalized medicine approach toward treating these disorders.**

ABBREVIATIONS: Aβ, β-amyloid peptide; AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; AMD3100, 1,1′-[1,4-phenylenebis (methylene)]bis [1,4,8,11-tetraazacyclotetradecane]; AP-1, activator protein 1; APP, amyloid precursor protein; AR-A014418, *N*-(4-methoxybenzyl)-*N*′-(5-nitro-1,3-thiazol-2-yl)urea; BBB, blood-brain barrier; Bcl-2, B-cell-lymphoma 2; BD, bipolar disorder; BDNF, brain-derived neurotrophic factor; CGCs, cerebellar granule cells; CNS, central nervous system; CREB, cAMP response element-binding protein; CXCR4, CXC chemokine receptor 4; DG, dentate gyrus; FXS, fragile X syndrome; GDNF, glial cell line-derived neurotrophic factor; GM6001, *N*-[(2*R*)-2-(hydroxamidocarbonylmethyl)-4-methylpentanoyl]-L-tryptophan methylamide; GRP78, 78-kDa glucose-regulated protein; GSK-3, glycogen synthase kinase-3; HD, Huntington's disease; HDACs, histone deacetylases; HSF-1, heat shock factor-1; HSP70, heat shock protein 70; ITF2357, {6-[(diethylamino)methyl]naphthalen-2-yl}methyl [4-(hydroxycarbamoyl)phenyl]carbamate; LPS, lipopolysaccharide; LY294002, 2-(4-morpholinyl)-8-phenyl-4*H*-1-benzopyran-4-one; MCAO, middle cerebral artery occlusion; miRNA, microRNA; MMP, matrix metalloproteinase; MSCs, mesenchymal stem cells; mHtt, mutant huntingtin; NF-κB, nuclear factor-κB; NMDA, *N*-methyl-D-aspartate; PI3K, phosphatidylinositol 3-kinase; PSD-95, postsynaptic density-95; QA, quinolinic acid; ROS, reactive oxygen species; SB, sodium butyrate; SB216763, 3-(2,4-dichlorophenyl)-4-(1-methyl-1*H*-indol-3-yl)-1*H*-pyrrole-2,5-dione; SMA, spinal muscular atrophy; SOD, superoxide dismutase; SVZ, subventricular zone; TBI, traumatic brain injury; TSA, trichostatin A; U0126, 1,4-diamino-2,3-dicyano-1,4-bis[2-aminophenylthio]butadiene; UPS, ubiquitin-proteasome system; VEGF, vascular endothelial growth factor; VPA, valproic acid.

I. Introduction

The mood stabilizers lithium and valproic acid (VPA) are primarily used to treat bipolar disorder (BD), a common, severe, and chronic mental illness that affects approximately 1%–3% of the population and is one of the major causes of disability worldwide (for review, see Goodwin and Jamison, 2007). However, accumulating evidence indicates that these agents also hold promise for treating neurologic and/or neurodegenerative diseases via their diverse mechanisms of action. To provide a clear and comprehensive picture of the mechanisms that may underlie the beneficial effects of lithium and VPA, this review focuses on two primary targets: glycogen synthase kinase-3 (GSK-3) for lithium and histone deacetylases (HDACs) for VPA. Here, we propose that GSK-3 and HDAC inhibition are critical to the facilitation of the numerous molecular mechanisms that may be exploited for therapeutic use. We anticipate that novel therapies will emerge from characterizing the mechanisms used by lithium and VPA either as monotherapy or in combination; both will be considered in great detail in this review.

Although lithium and VPA have long been used to treat BD, the mechanisms underlying their therapeutic effects remain elusive. Furthermore, it is likely that the interactions of many different genetic, epigenetic, and environmental factors contribute to this complex and heterogeneous mood disorder. Although the etiology of BD remains poorly understood, it is believed to involve multiple factors, including dysregulation of signaling pathways and gene expression, loss of synaptic plasticity, decreased cellular resilience, reduced brain cell density, and abnormalities in neuroanatomical structure and function. Lithium may counteract some of these deficits via its neurotrophic effects; for example, it has been shown to affect brain derived neurotrophic factor (BDNF) levels in individuals with BD (Suwalska et al., 2010; de Sousa et al., 2011). In addition, lithium treatment has been shown to increase gray matter volume in patients with BD in whole brain, cortex, hippocampus, and anterior cingulate (Sassi et al., 2002; Bearden et al., 2007, 2008; Moore et al., 2000b, 2009). Lithium also increases brain volume in limbic structures, such as the hippocampus (Yucel et al., 2007, 2008), that are implicated in emotional regulation. Untreated patients with BD showed decreased left anterior cingulate volumes compared with either healthy control subjects or lithium-treated patients (Sassi et al., 2004). *N*-Acetyl-aspartate (NAA), a putative marker for neuronal viability and function, was also reported to be increased in the brain of patients with BD after lithium treatment (Moore et al., 2000a; Hajek et al., 2012). Of interest, increased gray matter volume was found in patients with BD who responded clinically to lithium, suggesting a therapeutic role for this neurotrophic effect in clinical response to lithium (Moore et al., 2009; Lyoo et al., 2010). Collectively, this indirect evidence suggests that lithium augments neurotrophic mechanisms in BD and warrants further investigation in other brain diseases.

This review discusses numerous mechanisms used by lithium and VPA that may be effective in treating other central nervous system (CNS) disorders. We scrutinize neurologic disease mechanisms implicated in stroke, traumatic brain injury (TBI), Huntington's disease (HD), Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), and Fragile X Syndrome (FXS). In particular, preclinical evidence of the mechanisms used by these mood stabilizers to thwart disease processes and achieve their beneficial effects will be presented. These include neurotrophism, neuroprotection, oxidative stress, protein quality control, anti-inflammation, stem cell migration, neurovascular remodeling, blood-brain barrier (BBB) integrity, and microRNA (miRNA) regulation. There are similarities and differences in the biologic processes affected by lithium and VPA (Gupta et al., 2012). Both lithium and VPA have multiple targets in addition to GSK-3 and HDACs; however, it is beyond the scope of this review to consider all of these. The interested reader is referred to several excellent reviews describing additional targets (Jope, 2003, 2011; Gould and Manji, 2005; Zarate et al., 2006; Hunsberger et al., 2009; Chiu and Chuang, 2010; Quiroz et al., 2010).

A. Lithium and GSK-3

For more than half a century, the monovalent cation lithium has been the primary drug used to treat BD. It is effective against acute mania, prophylactic for recurrent manic and depressive episodes, and reduces the risk of suicide (Geddes et al., 2004; Cipriani et al., 2005; Ohgami et al., 2009). It can also augment the efficacy of antidepressants commonly used for the treatment of major depressive disorder (MDD) (Crossley and Bauer, 2007). At therapeutic serum concentrations (0.6−1.2 mM), lithium is known to inhibit a group of phosphomonoesterases in mammals, including inositol polyphosphate 1-phosphatase, inositol monophosphate phosphatase, fructose 1,6-bisphosphatase, and bisphosphate nucleotidase, in addition to the metabolic enzyme phosphoglucomutase and GSK-3. Downstream effectors, such as adenylate cyclase, the phosphoinositol cascade, and metabolism of arachidonic acid, are also affected by lithium treatment (for a review, see Quiroz et al., 2004; Gould et al., 2004c; Rao and Rapoport, 2009). Although the mood-stabilizing effects of lithium may result from inhibiting these enzymes, the multifaceted protein GSK-3 is believed to be the main facilitator of lithium's mood stabilizing and neuroprotective effects, because of its array of cellular and physiologic functions (Fig. 1).

GSK-3 is an evolutionarily conserved, ubiquitous serine-threonine kinase consisting of α and β isoforms

(for a review, see Chiu and Chuang, 2010). GSK-3 dysfunction has been linked to the pathophysiology of mood disorders, schizophrenia, AD, diabetes, and others (reviewed in Meijer et al., 2004; Huang and Klein, 2006; Jope et al., 2007; Chiu and Chuang, 2010; Li and Jope, 2010). In rodent models, the pharmacological inhibition or gene knockout/knockdown of GSK-3 mimicked lithium's antidepressant and anti-manic effects (Kaidanovich-Beilin et al., 2004, 2009; O'Brien et al., 2004; Gould et al., 2004b; Rosa et al., 2008; Jope, 2011; Omata et al., 2011). Despite limited clinical data, some evidence from genetic and postmortem studies supports the role of GSK-3 in mood disorders (for a review, see Jope, 2011). For example, elevated GSK-3 activity was found in post mortem samples from individuals with MDD (Karege et al., 2007, 2011), whereas serine-phosphorylation of GSK-3 in peripheral blood mononuclear cells was identified to be decreased with disease and increased after therapy (Li et al., 2007, 2010b).

Lithium inhibits GSK-3 by binding directly to the enzyme's magnesium-sensitive site (Klein and Melton, 1996; Stambolic et al., 1996) and indirectly by enhancing phosphorylation of this kinase at specific serine residues. The phosphatidylinositol 3-kinase (PI3K)/Akt pathway was found to mediate the indirect inhibitory effects of lithium on this enzyme by elevating phosphorylation of GSK-3α at Ser21 (Chalecka-Franaszek and Chuang, 1999), providing the first evidence that lithium indirectly inhibits GSK-3 via enhanced phosphorylation. In addition, GSK-3β activity can also be negatively regulated by its phosphorylation at Ser9 (Jope, 2003). To date, multiple mechanisms have been identified that contribute to GSK-3 phosphorylation, including the 3′,5′-cyclic adenosine monophosphate (cAMP)–dependent activation of protein kinase A (PKA) (Jope, 1999); the PI3K-dependent activation of protein kinase C (PKC) (Kirshenboim et al., 2004); and the enhanced inhibition of protein phosphatase-l through the action of inhibitor-2 complex, which auto-regulates GSK-3 (Zhang et al., 2003). A mouse study further showed that lithium increased the serine phosphorylation of GSK-3 by disrupting the formation of β-arrestin 2/protein phosphatase 2A/Akt complex that dephosphorylated and inactivated Akt (Beaulieu et al., 2008). Because a complete analysis of the neurobiology of GSK-3′s action is beyond the scope of the current review, we refer interested readers to several excellent reviews on the subject (Jope, 2003, 2011; Meijer et al., 2004; Rowe and Chuang, 2004; Huang and Klein, 2006; Jope and Roh, 2006; Rowe et al., 2007; Chiu and Chuang, 2010; Li and Jope, 2010).

B. VPA and HDACs

Several anti-convulsants—VPA, carbamazepine, and lamotrigine—are also effective in treating BD (Yatham, 2004). Similar to lithium, VPA has strong anti-manic effects, but it is less effective against depressive episodes. It has been suggested that the efficacy of VPA in BD results from enhanced γ-aminobutyric acid (GABA) neurotransmission and the inhibition of enzymes involved in GABA metabolism, such as succinate semialdehyde dehydrogenase, succinate semialdehyde reductase, and GABA transaminase (for a review, see Gould et al., 2004c). In addition, the anti-convulsive action of VPA is thought to be mediated by its inhibitory effects on

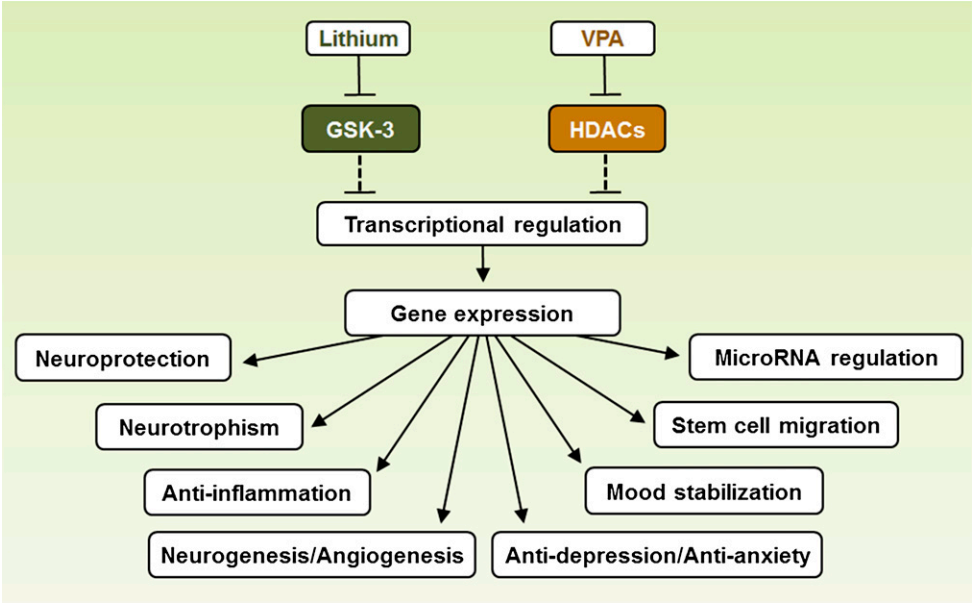

Fig. 1. A schematic illustration of the central hypothesis of molecular actions of mood stabilizers lithium and VPA. Through the inhibition of GSK-3 and HDACs, respectively, lithium and VPA are hypothesized to regulate the transcription and expression of factors critically involved in neuroprotective, neurotrophic, anti-inflammatory, neurogenic and angiogenic, mood-stabilizing, antidepressant-like, and anxiolytic effects, in addition to regulating stem cell migration and miRNAs. The underlying mechanisms of these actions have been elucidated by both in vitro and in vivo experimental settings and are discussed in this review. Lines with solid arrows represent stimulatory connections; lines with flattened ends represent inhibitory connections. Dashed lines represent pathways with reduced activity as a result of drug treatment.

the sodium channel at high frequencies (reviewed in Macdonald and Kelly, 1995). VPA also inhibits HDACs at therapeutic serum levels (0.4−0.8 mM) (Fig. 1).

Histone proteins organize DNA into nucleosomes, which are regular repeating structures of chromatin. This organization is required for the efficient packaging of large amounts of eukaryotic genomic DNA. In the process of deacetylation, HDACs remove charge-neutralizing acetyl groups from the lysine residues on tails of histones and favor a more transcriptionally inactive chromatin conformation. In contrast, histone acetyltransferases (HATs) increase acetylation and favor a more transcriptionally active chromatin conformation. Therefore, VPA inhibits HDACs to promote a more transcriptionally active chromatin structure.

HDACs fall into at least two major classes: class I contains isoforms 1–3 and 8, and class II contains isoforms 4–7 and 9–10 (Chuang et al., 2009). At clinically relevant levels, VPA effectively inhibits HDAC (Gottlicher et al., 2001; Phiel et al., 2001), making it valuable for investigations into the therapeutic role of chromatin remodeling in disorders of the CNS. VPA and its analogs inhibit the activity of HDAC isoforms from both classes, although it appears not to affect HDAC6 and 10 isoforms that belong to class IIb (Gurvich et al., 2004). VPA significantly inhibits class I and, to a lesser extent, class II HDACs (Gottlicher et al., 2001). However, a more recent work indicated that VPA's inhibition of class II HDACs might be attributable to the contaminating activities of class I HDACs (Fass et al., 2010). Additional studies are necessary to clarify this issue. The epigenetic control of genes through modification of histones and the resultant remodeling of chromatin has been shown to profoundly affect development, synaptic plasticity, learning, memory, drug abuse, alcoholism, circadian rhythm, and the efficacy of antidepressants (Abel and Zukin, 2008; McClung and Nestler, 2008; Chuang et al., 2009).

II. Neuroprotective Effects of Mood Stabilizers

Harnessing the ability of mood stabilizers to enhance neuroprotection has therapeutic implications for a wide range of CNS diseases. We begin by highlighting the critical signaling molecules and mechanisms that contribute to the neuroprotective actions of lithium and VPA, including selected neurotrophic, angiogenic, and anti-apoptotic factors; survival signaling cascades; oxidative stress pathways; and protein quality control mechanisms. We then discuss the augmented therapeutic effects of combined lithium and VPA treatment achieved in primary cultured neurons and stem cells and provide evidence for miRNAs as novel targets and facilitators of lithium and VPA.

A. Neurotrophic and Angiogenic Factors Modulated by Lithium and VPA

Neurotrophic and angiogenic factors play vital roles during neural development and synaptic plasticity. Most neurotrophic factors, which enhance the growth and survival of developing neurons and maintain the vitality of mature neurons, fall into one of three broad families as follows: 1) neurotrophins (Huang and Reichardt, 2001), 2) glial cell-line derived neurotrophic factor (GDNF) family ligands (Paratcha and Ledda, 2008), and 3) neuropoietic cytokines (Bauer et al., 2007). Angiogenic factors, which support the formation of new vasculature from preexisting blood vessels, have been implicated in numerous disease mechanisms (reviewed in Carmeliet, 2003). This section focuses on BDNF, GDNF, and angiogenic vascular endothelial growth factor (VEGF), three key factors augmented after the administration of lithium or VPA.

1. BDNF. BDNF, which signals through the TrkB receptor to augment cortical development, synaptic plasticity, neurogenesis, and neuronal survival, is known to play a vital role in neuropsychiatric disorders (for a review, see Autry and Monteggia, 2012). Evidence also exists that the neuroprotective effects of lithium and VPA are facilitated, at least in part, by the induction of BDNF and activation of its receptor. Pretreatment with lithium or BDNF, for instance, protected primary cortical neurons against glutamate excitotoxicity (Hashimoto et al., 2002b), and conversely, use of a Trk tyrosine kinase inhibitor or BDNF-neutralizing antibody negated this neuroprotection. An extension of this study demonstrated that lithium treatment both increased BDNF protein levels and activated its receptor and that lithium-induced neuroprotection did not occur in cortical neurons derived from both homozygous and heterozygous BDNF-knockout mice.

Building on these findings, additional studies showed that both lithium and VPA increased levels of exon IV–containing BDNF mRNA and increased the activity of BDNF promoter IV in cortical neurons (Yasuda et al., 2009). In addition, GSK-3 inhibition contributed to the lithium-induced activation of BDNF promoter IV, whereas GSK-3 inhibitors mimicked this activation. Conversely, HDAC inhibition contributed to VPA-induced promoter IV activation. In hypoxia, chronic lithium treatment is known to be neuroprotective (as measured by cerebral glucose metabolic rate), apparently because it elevates levels of BDNF protein and phosphorylated cAMP response element binding protein (CREB) (Omata et al., 2008). In addition to its neuroprotective effects, BDNF has been found to enhance neurogenesis, contributing further to the therapeutic effects of lithium (Chen et al., 2000; Wexler et al., 2008) and VPA (Hao et al., 2004; Laeng et al., 2004). Clinically, lithium treatment augmented serum levels of BDNF in patients with early AD (Leyhe et al., 2009). These results support BDNF regulation in a clinical population and suggest considerable potential of this regulation for the treatment of neurodegenerative diseases.

2. GDNF. Lithium and VPA have been shown, in vivo and in vitro, to regulate GDNF, in which pleiotropic

functions include migration, chemo-attraction, and differentiation (on neuroblasts) and axonal growth, axonal guidance, survival, and synapse function (on neurons) (for a review, see Paratcha and Ledda, 2008). In rat models of depression, six weeks of lithium treatment increased GDNF protein levels in hippocampus, striatum, and prefrontal cortex, and these increases appeared to contribute to the drug's antidepressant-like effects (Angelucci et al., 2003). Both lithium and GDNF, moreover, protected against mitochondrial and endoplasmic reticulum (ER) stress-mediated apoptosis induced by aluminum (Savory et al., 2003).

VPA has also been shown, in primary neuronal-glial cocultures from rat midbrain, to protect against neurotoxicity induced by lipopolysaccharide (LPS), in part because of its inhibitory effects on pro-inflammatory factors (Peng et al., 2005). In a similar midbrain neuronal-glial coculture, astrocytes were shown to release GDNF and BDNF, which mediate VPA's neuroprotective effects on dopaminergic neurons (Chen et al., 2006). Other HDAC inhibitors have also been demonstrated to exert neuroprotective effects. In neuronal-glial cocultures, for instance, sodium butyrate (SB) and trichostatin A (TSA) protected dopaminergic neurons by inducing GDNF and, possibly, BDNF in astrocytes (Wu et al., 2008). Finally, after spinal cord injury, GDNF and BDNF may have contributed to the improvement of locomotion produced by VPA treatment (Lv et al., 2012).

3. VEGF. VEGF is a prominent angiogenic factor (Ferrara et al., 2003) that induces and promotes angiogenesis to increase trophic support through the formation of new blood vessels from existing vasculature. Angiogenesis then should be considered as an important mechanism that offers trophic and neuroprotective effects to neuronal and glial cells, in addition to enhancing neurogenesis and synaptic plasticity where VEGF has been implicated (Newton et al., 2003; Newton and Duman, 2004; Warner-Schmidt and Duman, 2007). VEGF's angiogenic signals are mediated through two primary receptors, VEGFR-1 and VEGFR-2, that play a variety of roles. These include inducing anti-apoptotic proteins (such as B-cell lymphoma 2 [Bcl-2]) to preserve endothelial cells and promoting monocyte chemotaxis in bone marrow–derived cells to induce vascular leakage (reviewed by Ferrara et al., 2003).

VEGF has been shown to modulate neurogenesis (Jin et al., 2002) and contribute to the behavioral actions of antidepressants (Warner-Schmidt and Duman, 2007). In addition to antidepressants, VEGF is also regulated by mood stabilizers. In cultured brain cells, for instance, treatment with lithium increased VEGF levels in both endothelial cells and astrocytes. This increase in endothelial cells, moreover, was associated with enhanced GSK-3β Ser9 phosphorylation, an effect mimicked by the GSK-3 inhibitor SB216763 (Guo et al., 2009) and blocked by the PI3K inhibitor LY294002. In contrast, SB216763 did not mimic, nor did LY294002 affect, lithium upregulation of VEGF in astrocytes, although LY294002 abolished lithium-induced GSK-3 phosphorylation, suggesting cell type–specific regulatory mechanisms.

In cultured endothelial cells, VPA enhanced VEGF-induced angiogenesis (Jin et al., 2011). Chronic post-insult treatment with VPA increased VEGF protein levels in the ischemic cerebral cortex (Wang et al., 2012). This VEGF upregulation was mediated by the transcription factor hypoxia inducible factor-1α (HIF-1α) and contributed to angiogenesis and functional recovery after ischemic stroke in rats (see section III.A).

B. Factors Affecting Apoptotic Signaling: Bcl-2, p53, Bax, Caspase Signaling, and HSP70

Apoptosis, or programmed cell death, involves numerous biochemical signaling cascades. Both lithium and VPA increased mRNA expression of the anti-apoptotic protein Bcl-2 in rat frontal cortex (Chen et al., 1999b). In a mouse model of ALS, VPA and two other HDAC inhibitors were shown to upregulate Bcl-2 mRNA in spinal cord (Rouaux et al., 2007). In primary brain neuronal cultures challenged with glutamate excitotoxicity mediated by *N*-methyl D-aspartate (NMDA) receptors, lithium increased the expression of Bcl-2, decreased the expression of the proapoptotic proteins p53 and Bax, and suppressed the mitochondrial release of glutamate-induced cytochrome *c* (Chen and Chuang, 1999). Pretreatment with lithium, moreover, prevented the activation of caspase-3 cleavage of lamin B1 that usually results from mitochondrial release of cytochrome *c*. In addition to modulating anti-apoptotic and proapoptotic proteins, lithium was found to modulate NMDA receptor–mediated synaptic activity and excitotoxicity by attenuating the constitutive phosphorylation at Tyr1472 of the NR2B subunit of the NMDA receptor, which is activated by the Src tyrosine kinase Fyn (Hashimoto et al., 2002a, 2003a).

Heat shock proteins (HSPs) are a group of molecular chaperones that assist in regulating protein folding and refolding of misfolded proteins, where they help restore cellular homeostasis and promote cell survival (see section II.E). Studies have found that HSPs, such as HSP70, exert a wide variety of neuroprotective effects against apoptosis (Takayama et al., 2003) through varied mechanisms, ranging from antagonizing apoptosis-inducing factors (Ravagnan et al., 2001), inhibiting the activation of nuclear factor-κB (NF-κB) by stabilizing IκB protein (Feinstein et al., 1996; Zheng et al., 2008), stabilizing Akt-1 protein (Gao and Newton, 2002), and preventing mitochondrial cytochrome *c* release and caspase activation (Beere et al., 2000). Of interest, HSP70 expression is regulated by heat shock factor-1 (HSF-1), a transcription factor negatively regulated by GSK-3β–dependent phosphorylation (Bijur

and Jope, 2000). The neuroprotective effects of lithium in a stroke model are in fact associated with a marked increase in the DNA binding activity of HSF-1 and subsequent elevations in the expression of HSP70 protein in the ischemic brain (Ren et al., 2003).

Findings from an experiment of SH-SY5Y cells challenged with the mitochondrial complex I inhibitor rotenone suggest that VPA's neuroprotective effects may also involve HSP70 and may be associated with reductions in the release of cytochrome *c* and the cleavage of caspase-3 and -9 (Pan et al., 2005). In rat cortical neuronal cultures, HSP70 participated in VPA neuroprotection against short-term glutamate excitotoxicity. This VPA-induced HSP70 was triggered by inhibition of class I HDACs, as well as acetylation and recruitment of the transcription factor Sp1 at the HSP70 promoter (Marinova et al., 2009). In addition, VPA-induced HDAC inhibition also altered methylation levels of histone (H3K4Me2) at the HSP70 promoter and caused its induction in both neurons and astrocytes (Marinova et al., 2011). In various animal models, overexpression of HSP70 has been recognized as a potential therapeutic target against ischemic neuronal injury and will be discussed in detail in the section III.A.

C. Cell Survival Signaling Cascades

Activated by the stimulation of trophic-factor receptors on the cell surface, the neuroprotective mechanisms of lithium and VPA involve multiple survival signaling cascades, including the PI3K/Akt pathway, Wnt/β-catenin pathway, and the MAP kinase-kinase (MEK)/extracellular-signal regulated kinase (ERK) pathway.

1. The PI3K/Akt Pathway. BDNF induction is an early and essential step in lithium's neuroprotection against glutamate excitotoxicity. BDNF's trophic action is likely to be involved in lithium-induced activation of the cell survival PI3K/Akt and MEK/ERK pathways. Activation of Akt, a serine/threonine kinase regulated by PI3K, involves phosphorylation at residues of Thr308 and Ser473 (Alessi and Cohen, 1998; Jacinto et al., 2006). In cultured rat cerebellar granule cells (CGCs), lithium treatment rapidly normalized glutamate-induced inactivation of Akt by activating PI3K and subsequently increasing the phosphorylation of Akt at its Ser473 residue (Chalecka-Franaszek and Chuang, 1999). After activation, Akt in turn affects several anti-apoptotic targets, including Bcl-2–associated death promoter, CREB, members of the forkhead family, and procaspase-9 (Neri et al., 2002; Nicholson and Anderson, 2002; Huang and Reichardt, 2003). In cultured human neuroblastoma cells, caspase-3 activation induced by neurotoxins that mimic neurochemical changes associated with Parkinson's disease was inhibited by lithium treatment in a PI3K-dependent manner (King et al., 2001). Against HIV-induced toxicity, both in vitro and in vivo, lithium-induced neuroprotection appears to be mediated through the PI3K/Akt pathways (Everall et al., 2002; Dou et al., 2005). However, because some studies detected no changes in Akt phosphorylation levels at specific time points after the application of lithium in certain cell lines, the effects of lithium on the PI3K/Akt pathway may be cell type–specific and time-dependent (De Sarno et al., 2002; Zhang et al., 2003).

Although considered to be an HDAC inhibitor, VPA has been reported to cause gradual increases in phosphorylation of Akt and GSK-3β at Ser473 and Ser9 residues, respectively, under some in vitro conditions (Chen et al., 1999a; De Sarno et al., 2002). Because lithium and VPA can both upregulate BDNF expression, VPA may increase GSK-3 phosphorylation via BDNF-mediated activation of the PI3K/Akt pathway. In fact, VPA has been implicated in the activation of both the PI3K/Akt and MEK/ERK cellular signaling pathways (Kostrouchova et al., 2007). In cultured cortical neurons, pretreatment with either a PI3K or Akt inhibitor attenuated VPA-induced upregulation of HSP70 (Marinova et al., 2009). In a rat cerebral ischemia model, injection with other HDAC inhibitors augmented HSP70 and reversed ischemia-induced downregulation of Akt phosphorylation (Kim et al., 2007). A recent study in cultured human neuroblastoma cells also demonstrated that the effect of VPA on monoamine oxidase A induction was mediated by the PI3K/Akt/forkhead signaling pathway (Wu and Shih, 2011).

*2. The Wnt/*β*-Catenin Pathway.* By controlling axon remodeling and synapse formation, the Wnt pathway plays an important role in regulating neuronal connectivity in the nervous system (Ciani and Salinas, 2005). GSK-3 activity is also negatively regulated by Wnt-stimulated activation of the Frizzled receptor in addition to the aforementioned protein kinases (e.g., PKA, PKC, and Akt). As a substrate of GSK-3, the transcription factor β-catenin is part of the Wnt pathway, and its cytoplasmic levels are decreased by GSK-3 through phosphorylation-dependent proteasomal degradation (Jope and Johnson, 2004; Takahashi-Yanaga and Sasaguri, 2007). In conjunction with T cell–specific transcription factor (Tcf)/lymphoid enhancer binding factor (Lef), increases in cytoplasmic accumulations of β-catenin facilitate its translocation into the nucleus and, subsequently, enhance the transcription of diverse genes, such as growth factors (Sinha et al., 2005; Silva et al., 2007) and those involved in apoptotic inhibition (Feng, 1979; Seidensticker and Behrens, 2000; Huelsken and Behrens, 2002). Activation of the canonical Wnt/β-catenin pathway has been shown to contribute to adult hippocampal neural progenitor cell proliferation triggered by lithium treatment (Wexler et al., 2008). At therapeutic concentrations, treatment with lithium was also found to increase β-catenin levels both in vitro (Stambolic et al., 1996; Chen and Chuang, 1999) and in vivo (O'Brien et al., 2004; Gould et al., 2004a) and to promote β-catenin–dependent

transcriptional events (Jope and Johnson, 2004; O'Brien et al., 2004; Marmol, 2008).

Of interest, knockdown of β-catenin protein in mouse brain resulted in a depression-like phenotype (Gould et al., 2008), and overexpression of β-catenin mimicked the antidepressant-like effects of lithium (Gould et al., 2007). In addition, β-amyloid peptide (Aβ) toxicity in hippocampal slices was associated with loss of Wnt signaling function (Inestrosa et al., 2000), whereas chronic lithium treatment protected against Aβ-induced hippocampal neurodegeneration by activating the Wnt/β-catenin pathway in rat brains (De Ferrari et al., 2003). Lithium also inhibited HIV replication in a Wnt/β-catenin–dependent manner (Kumar et al., 2008). As a result, the idea that lithium-induced accumulation of β-catenin may account for much of its neuroprotective and therapeutic effects has led some to propose elevated β-catenin as a novel therapeutic strategy for treating mood disorders.

VPA also alters Wnt signaling in cultured human and animal cells and induces Wnt-dependent gene expression at doses that cause developmental effects (Wiltse, 2005). Upregulation of the Wnt/β-catenin signaling pathway and the subsequent imbalance of oxidative homeostasis produced by VPA administration during early pregnancy may facilitate susceptibility to autism (Zhang et al., 2012a). However, as mediated through the β-catenin-Lef-Tcf–dependent transcriptional activity, cotreatment with VPA was found to potentiate lithium-induced neuroprotective effects against excitotoxicity in aging CGCs (Leng et al., 2008). In addition, VPA altered angiogenic processes in human umbilical vein endothelial cells by increasing the expression of β-catenin and enhancing spheroid sprout formation (Jin et al., 2011). It has been suggested, in fact, that VPA-induced increases in acetylation and the nuclear translocation of β-catenin largely account for its ability to protect neurons from hypoxia-induced apoptosis and to improve animal survival after hemorrhagic shock (Leng et al., 2008).

3. The MEK/ERK Pathway. Another signaling pathway mediating the trophic actions and effects of lithium and VPA is the MEK/ERK cascade. The finding that both K252a and the MEK inhibitor U0126 blocked antidepressant-like effects induced by BDNF (Shirayama et al., 2002) supports the involvement of TrkB in the activation of the MEK/ERK pathway.

ERK regulates several downstream effector systems, such as NF-κB and ribosomal S6 kinase (RSK), and in turn inhibits GSK-3β and activates CREB (Chang et al., 2003; Steelman et al., 2004). CREB is a transcription factor and a common downstream target of both PI3K/Akt and MEK/ERK pathways. When activated through phosphorylation, CREB is involved in cell survival by promoting the expression of cell-protective proteins, such as BDNF and Bcl-2 (Finkbeiner, 2000). Lithium treatment after ischemia was found to enhance ERK phosphorylation, whereas lithium-induced increases in BrdU-positive cells and improvement of cognitive function were prevented by U0126 (Yan et al., 2007). Because lithium has been reported to have opposite effects on the MEK/ERK pathway in different types of neural cells, it should be noted that lithium's effects on this pathway may also be cell type–specific (Pardo et al., 2003).

VPA activates the ERK pathway, and activation of this cascade has been associated with its neuroprotective effects in a variety of cell types. In fact, VPA treatment not only increases the expression of ERK-regulated genes (such as Bcl-2), it has also been shown to promote neurite growth and cell survival in primary neurons and in the cultured human neuroblastoma cell line SH-SY5Y (Yuan et al., 2001; Di Daniel et al., 2005). In human umbilical vein endothelial cells, activation of the MEK/ERK pathway mediated VPA-induced phosphorylation of Bcl-2 and inhibition of serum starvation-induced apoptosis (Michaelis et al., 2006); in peripheral Schwann cells, VPA used the same signaling pathway to mediate the evocation of cell proliferation (Fei et al., 2011). Moreover, in a sleep deprivation animal model of manic-like behavior, VPA treatment prevented the attenuation of ERK activation, CREB phosphorylation, and the expression of Bcl-2 and BDNF in the frontal cortex (Park et al., 2012).

D. Oxidative Stress Pathways

Oxidative stress is caused by the imbalance between reactive oxygen species and the cell's ability to quench these free radicals, which can lead to ensuing damage of the cellular proteins, lipids, DNA, and organelles, such as the mitochondria; it can also activate numerous stress-sensitive signaling processes (reviewed in Droge, 2002). Some of these stress-sensitive signaling processes overlap with the aforementioned survival signaling pathways (e.g., the MAPK signaling cascade), and others involve autophagy and mitochondrial dysfunction (Lee et al., 2012a). It is beyond the scope of this review to delve into specific stress-sensitive signaling pathways; we will only briefly discuss some of the evidence that oxidative stress pathways are implicated in diverse CNS disorders and facilitated by mood stabilizers.

Mood stabilizers have been reported to produce antioxidant effects that may contribute to their neuroprotective properties. For instance, chronic treatment with lithium (1 mM) or VPA (0.6 mM) protected human neural (SH-SY5Y) cell lines against oxidative stress, but not glial (SVG and U87) cell lines (Lai et al., 2006). This elegant study demonstrated that, when oxidative stress was induced by either 5μM rotenone or 100 μM H_2O_2, lithium and VPA treatment attenuated release of cytochrome *c* and activation of caspase 3 in SH-SY5Y cells. On the other hand, ER stress induced by 1 μM thapsigargin was not protected by either lithium or VPA. This suggests that the intrinsic mitochondrial

apoptotic pathway may be important for these neuroprotective effects. In fact, the authors also reported that both lithium and VPA upregulated Bcl-2, an anti-apoptotic factor that can suppress release of cytochome *c*, during oxidative stress but not during ER stress in SH-SY5Y cells. However, another study found that chronic lithium or VPA treatment protected against thapsigargin-induced ER stress in PC12 cells (Hiroi et al., 2005). These discrepancies might be attributable to cell type differences and remain to be elucidated. GSK-3β inhibition was also neuroprotective after rotenone-induced oxidative stress but not H_2O_2-induced oxidative stress (Lai et al., 2006). Clearly, multiple mechanisms are at play to facilitate cell type–specific neuroprotection.

Oxidative stress mechanisms have also been evaluated in human B lymphoblast cell lines (BLCLs) from both healthy control subjects and patients with BD. In fact, increased reactive oxygen species (ROS) have been found in both plasma and serum samples from patients with BD (Kuloglu et al., 2002; Savas et al., 2006; Andreazza et al., 2009). These ROS can be sensed by a family of calcium-permeable ion channels, the transient receptor protein (TRP) family that has been implicated in the pathophysiology of BD-I (Xu et al., 2006, 2009; Andreopoulos et al., 2004; Perova et al., 2008). BLCLs were challenged with the oxidative stressor rotenone (2.5 and 10 μM), cell viability was monitored, and the expression and function of the TRP family ion channel (TRPM2 and TRPC3) were determined (Roedding et al., 2012). Cell viability was decreased after rotenone treatment, with BLCLs from individuals with BD-I found to be more susceptible to oxidative stress than control subjects. This study further implicates TRP family channels as contributing to the pathophysiology of BD, because of the changes in their regulation and functional response after oxidative stress.

Oxidative stress mechanisms have also been associated with manic episodes in BD. Elevated oxidative metabolism markers, including thriobarbituric acid reactive substances, superoxide dismutase (SOD), and catalase were found to be elevated in unmedicated manic patients when compared with both lithium-treated manic patients and control subjects (Machado-Vieira et al., 2007). Furthermore, in healthy control subjects treated with therapeutic doses of lithium (2–4 weeks), selective decreases in oxidative stress markers were observed, including SOD and H_2O_2 (Khairova et al., 2012). This supports the notion that lithium has neuroprotective properties in healthy subjects, suggesting that these benefits may extend to the treatment of CNS diseases beyond BD. Oxidative stress has also been reported to exacerbate the development of symptoms in numerous human CNS disorders, including BD (Andreazza et al., 2008), stroke (Chen et al., 2011), TBI (Ansari et al., 2008), HD (Klepac et al., 2007), AD (Perry et al., 2002), and ALS (Barber and Shaw, 2010), suggesting that the antioxidant effects of mood stabilizers, which enhance neuroprotective mechanisms, may have broad utility in the treatment of numerous CNS disorders.

E. Protein Quality Control Mechanisms

1. Induction of the Ubiquitin-Proteasome System and Autophagy. In eukaryotic cells, the ubiquitin-proteasome system (UPS) and autophagy-lysosomal pathway are two major intracellular quality control mechanisms for protein clearance against abnormal protein accumulation (Ross and Poirier, 2005). As noted above, treatment with either lithium or VPA alone increased HSP70 expression both in vitro and in vivo (Klionsky and Emr, 2000; Levine and Kroemer, 2008). Through the UPS and autophagy, HSPs promote the degradation of abnormally folded proteins (Hendrick and Hartl, 1993; Fink, 1999; Ma and Hendershot, 2001; Hartl and Hayer-Hartl, 2002; Ross and Poirier, 2005). However, short-lived proteins, in general, are predominantly degraded by proteasomes, whereas aggregation-prone proteins appear to be better substrates for autophagic-lysosomal degradation (Klionsky and Emr, 2000; Levine and Kroemer, 2008).

Autophagy induction is considered to be a potential neuroprotective mechanism. Rapamycin is currently the most commonly used pharmacological agent for inducing autophagy, which it does by inhibiting the mammalian target of rapamycin (mTOR). Of note, rapamycin has been shown to be beneficial in various models of neurodegenerative diseases (Ravikumar et al., 2004; Berger et al., 2006; Rubinsztein et al., 2007). The ability of lithium to deplete free inositol and subsequently decrease levels of inositol 1,4,5-trisphosphate (IP_3), through inhibiting inositol monophosphatase and inositol transporters (Phiel and Klein, 2001), was identified as a novel mTOR-independent route for inducing autophagy (Sarkar et al., 2005; Sarkar and Rubinsztein, 2006). VPA, carbamazepine, and other mood stabilizers that decrease IP_3 levels can also induce autophagy (Sarkar et al., 2005). At therapeutic concentrations, lithium not only facilitated the clearance of mutant huntingtin (mHtt) and α-synuclein (Sarkar et al., 2005) but also induced clearance of protease-resistant prion protein in prion-infected cells (Heiseke et al., 2009). This autophagy-inducing property of lithium has been demonstrated to be protective in ALS model mice (Fornai et al., 2008), and its use in combination with rapamycin has been proposed as a possible therapy in various animal models of HD (Sarkar et al., 2008). Together, these mechanisms are believed to be beneficial in neurodegenerative disorders characterized by the accumulation of misfolded proteins (Cuervo, 2004; Berger et al., 2006; Rubinsztein et al., 2007; Levine and Kroemer, 2008).

2. GRP78 Upregulation. The ER is the primary site for protein synthesis, folding, and trafficking. It acts as

an intracellular calcium repository and is highly sensitive to perturbation of its intraluminal environment. In addition to upregulating Bcl-2, lithium or VPA treatment was shown to protect against ER stress by upregulating a molecular chaperone of the HSP70 family, the 78-kDa glucose-regulated protein (GRP78) (Hiroi et al., 2005). GRP78 binds to calcium, participates in protein folding, plays a role in stress-induced autophagy, and protects cells from the deleterious effects of misfolded proteins in the ER (Katayama et al., 1999; Kaufman, 1999; Yu et al., 1999; Ni et al., 2011). GRP78 can be induced by various apoptotic insults, including the ER calcium-ATPase inhibitor thapsigargin (Aoki et al., 1997; He et al., 2000). Triggered by calcium release from the ER, transcription factor c-Fos (a component of the activator protein 1 [AP-1] heterodimeric transcription factor complex) appears to be involved in thapsigargin's induction of GRP78 (He et al., 2000), although the fact that the GRP78 promoter contains no recognizable AP-1–interacting sequence motifs (He et al., 2000) suggests that AP-1's role in regulating GRP78 is only indirect.

In addition to upregulating GRP78 (Wang et al., 2001; Hiroi et al., 2005; Shao et al., 2006), lithium similarly induced c-Fos expression and subsequent AP-1–binding activity (Kalasapudi et al., 1990; Gao et al., 1993; Ozaki and Chuang, 1997), but without affecting basal calcium levels (Hiroi et al., 2005). Accordingly, lithium pretreatment reversed thapsigargin-induced downregulation of the anti-apoptotic protein Bcl-2 in PC12 cells, and its cytoprotective effects included upregulation of c-Fos and GRP78 and attenuation of thapsigargin-triggered intracellular calcium release. These beneficial effects were blocked, moreover, by curcumin (Hiroi et al., 2005), an AP-1 inhibitor. On the other hand, VPA pretreatment also upregulated this ER stress protein (Wang et al., 1999, 2001; Bown et al., 2000; Hiroi et al., 2005), and induced similar protective effects against ER stress in PC12 cells (Hiroi et al., 2005), as well as oxidative damage in primary cultured rat cerebrocortical cells (Wang et al., 2003). Because ER dysfunction has been linked to impaired synaptic plasticity and to the pathophysiology of diseases, such as BD (Hough et al., 1999; Hayashi et al., 2009), AD (Mattson et al., 2000), and cerebral ischemia (Mattson et al., 2000), the induction of GRP78 by lithium and VPA against ER stress may well be clinically relevant. In support of GRP78's therapeutic relevance, it was recently implicated in protection against α-synuclein–induced neurotoxicity in a rodent model of Parkinson's disease (Gorbatyuk et al., 2012) and cell death caused by mHtt aggregates in a cell culture model of HD (Jiang et al., 2012).

F. Augmented Protective Effects by Lithium and VPA Cotreatment

As mentioned previously, lithium and VPA have diverse neuroprotective mechanisms, ranging from the augmentation of neurotrophic factors (such as BDNF) to the facilitation of anti-apoptotic factors (such as Bcl-2) and the regulation of numerous survival-signaling cascades (such as enhancing the PI3K/Akt signaling pathway). These diverse signaling effects are primarily mediated by inhibition of GSK-3 and HDAC. In the following section, we examine how combination treatment provides enhanced beneficial effects in different model systems.

1. Enhanced Neuroprotection by Cotreatment. As CGC neuronal cultures age, lithium loses its ability to enhance serine phosphorylation of GSK-3 and protect CGCs from glutamate-induced apoptosis. VPA also has little protective effect against glutamate-induced cell death in older CGCs. However, in the first study to demonstrate these drugs' synergistic neuroprotective effects, Leng and colleagues showed that cotreatment with lithium and VPA completely blocked glutamate excitotoxicity in aging CGCs (Leng et al., 2008). Gene silencing with siRNA to GSK-3α or GSK-3β mimicked the ability of lithium to induce this synergistic neuroprotection when used in combination with VPA. Conversely, treatment with other class I and II HDAC inhibitors or transfection with an HDAC1 isoform-specific siRNA in conjunction with lithium treatment also enhanced neuroprotection.

The neuroprotective effects elicited in intact neurons cotreated with lithium and VPA, moreover, are closely associated with a potentiation in GSK-3 inhibition, as revealed by augmented phosphorylation of both GSK-3α and β, and attenuated phosphorylation of tau protein, a major GSK-3 substrate. In a cell-free system of CGC lysate, combined treatment also induced a more than additive decrease in GSK-3β enzymatic activity (Leng et al., 2008). These observations suggest that GSK-3 inhibition is a likely molecular target for this enhanced neuroprotection, despite the fact that the role of HDAC-regulated genes has yet to be investigated. It is also important to note that although combination treatment with lithium and VPA was no more effective than lithium alone in preventing relapse in patients with BD-I (The BALANCE investigators and collaborators, 2010), recent data from preclinical HD and ALS models indicate that this combined treatment may be useful for treating these disorders (see sections III.C and III.E).

2. Enhancing the Homing and Migratory Capacity of Stem Cells. Over the past 20 years, stem cell therapy has been investigated as a potential treatment of neurodegenerative diseases (reviewed in Goldman, 2005; Lunn et al., 2011). After transplantation of stem cells, directing migration and ensuring survival and integration are essential for successful development of these therapies for clinical use.

Mesenchymal stem cells (MSCs) derived from bone marrow have been demonstrated to produce beneficial effects in diverse animal models of neurodegenerative

diseases (Joyce et al., 2010). Although MSCs can reach an injured brain region and release trophic factors to hasten endogenous repair and regeneration, it is increasingly recognized that the poor homing and migratory abilities of transplanted MSCs limit their effectiveness as a treatment strategy (Karp and Leng Teo, 2009). Enhancing the homing and migratory capacity of transplanted MSCs could therefore be expected to improve their therapeutic efficacy.

MSC migration toward ischemic brain lesions is mediated by the interaction between stromal cell–derived factor 1α (SDF-1α), a molecule endowed with potent chemotactic activity, and its specific α-chemokine receptor CXC-chemokine receptor 4 (CXCR4) (Wang et al., 2008), in which expression in hematopoietic stem cells is enhanced by VPA (Gul et al., 2009). Because MSC migration is regulated by the Wnt signaling pathway in which activation inhibits GSK-3β (Neth et al., 2006), lithium's ability to inhibit GSK-3β allows it to activate the Wnt downstream signaling pathway. For this reason, combined treatment with lithium and VPA additively enhanced MSC migration in vitro (Tsai et al., 2010).

Three-hour exposure of MSCs to 2.5 mM VPA markedly increased the mRNA and protein levels of CXCR4 (Tsai et al., 2010). This effect of VPA requires inhibition of HDACs and involves histone hyperacetylation at the CXCR4 gene promoter. VPA treatment also enhanced MSC migration mediated by SDF-1α, which was completely blocked by the CXCR4 antagonist AMD3100. On the other hand, MSCs treated with 2.5 mM lithium for one day showed selective elevation of mRNA and protein levels and enzymatic activity of matrix metalloproteinase-9 (MMP-9), effects mimicked by the pharmacological inhibition or gene silencing of GSK-3β. Lithium treatment also potentiated MSC migration across the extracellular matrix, which was mediated by SDF-1α and suppressed by the MMP-9 inhibitors doxycycline and GM6001. Significantly, where AMD3100 and GM6001 were both present, the additive enhancement of MSC migration induced by VPA and lithium cotreatment was completely blocked. These findings suggest that the two drugs operate through distinct targets and mediators to stimulate MSC migration: VPA through HDAC-CXCR4 and lithium through GSK-3β-MMP-9 (Tsai et al., 2010). For a discussion of VPA and lithium cotreatment in a model of ischemic stroke, see section III.A.

Hematopoietic stem cells (HSCs) from the peripheral blood have been shown to transdifferentiate into neurons and glial cells in the brain (Mezey et al., 2000; Cogle et al., 2004; Sigurjonsson et al., 2005). Circulating HSCs are decreased in early AD, and this decrease is significantly correlated with age (Maler et al., 2006). Transplantation of HSCs has been shown to promote angiogenesis and enhance neuroplastic effects in the ischemic brain (Shyu et al., 2006). Although HSCs have the potential for wide clinical application, insufficient cell numbers have limited their use. Attempts are now being made to amplify these stem cells in an uncommitted state, while maintaining their differentiation potential. The combination of VPA and lithium treatment has been shown to delay hematopoietic stem/progenitor cells (HSPCs) differentiation and to increase the potential for cell survival (Walasek et al., 2012). Specifically, VPA and lithium cotreatment preserved the immature cell phenotype of HSPCs in the hematopoietic differentiation-inducing culture and regulated transcription factor networks at the molecular level by preserving expression of stem cell–related genes and repressing genes involved in differentiation. These findings provide an ex vivo strategy to obtain sufficient autologous HSPCs before transplantation by using a combination of lithium and VPA. However, this study by Walasek et al. did not investigate whether this combination treatment would affect the transdifferentiating ability of HSPCs. Further investigation is warranted.

G. New Directions: miRNAs Targeted by Lithium and VPA

miRNAs are non–protein-coding RNAs of 21–24 nucleotides. Abundant in all multicellular organisms, they function in translational repression and mRNA degradation by binding either to the 3′−UTR of mRNAs (Lai, 2002) (predominantly) or to coding regions (Forman et al., 2008), where they have the potential to silence hundreds of genes. This mechanism allows miRNAs to modulate complex transcriptomic and proteomic networks and to play an important regulatory role in nervous system function. Brain-enriched miRNAs, for instance, have been reported to regulate spine development and synaptic plasticity (Schratt et al., 2006; Siegel et al., 2011).

The unique regulatory mechanisms used by miRNAs have also been used to elucidate transcriptional mechanisms used by mood stabilizers. In the rat hippocampus, in fact, chronic treatment with either lithium or VPA has been found to selectively modulate miRNAs (Zhou et al., 2009). It is particularly interesting to note that among those miRNAs regulated by mood stabilizers, three miRNAs (miR-24, -34a, -128) target six BD susceptibility genes: calpain 6, dipeptidyl-peptidase 10, estrogen-related receptor gamma, member A of family with sequence similarity 126, metabotropic glutamate receptor 7 (GRM7), and thyroid hormone receptor beta. Future studies are warranted to strengthen the association of these six BD susceptibility genes with both the pathophysiology of BD and their potential regulation via miRNA-mediated mechanisms. GRM7 regulation via miR-34a has been confirmed in vitro (Zhou et al., 2009). In vivo regulation of both miR-34a and GRM7 after long-term treatment with either lithium or VPA has also been reported (Zhou et al., 2009). Another study found that lithium regulates a select set of

miRNAs in human lymphoblastoid cells (Zhou et al., 2009). Of interest, some of these lithium-responsive miRNAs (miR-34a and miR-221) were identified in both rats and humans, suggesting that the transition from preclinical to clinical research will prove to be fruitful. For instance, a recent preliminary study with a small sample size correlating plasma miR-134 levels in successfully medicated manic patients with BD (Rong et al., 2011) further suggests an additional role for miRNAs in psychiatry, where they may be effective biomarkers to predict lithium response. Moreover, miR-134 has recently been reported to be dysregulated in schizophrenia in dorsolateral prefrontal cortex (Santarelli et al., 2011). Clearly additional studies are warranted to substantiate miRNA's potential as biomarkers, but these studies and others provide tantalizing hints in support of their exciting promise.

Additional support exists for miRNA mechanisms underlying the therapeutic actions of mood stabilizers. For instance, alterations in the muscarinic acetylcholine receptor system are thought to be associated with BD (Goodwin and Jamison, 2007). Muscarinic M_1-receptor knockout mice exhibited mania-like behavioral deficits (e.g., hypersensitivity to amphetamine-induced hyperlocomotion), and lithium treatment normalized these behavioral deficits in part by enhancing M_1-receptor-ERK pathway signaling (Creson et al., 2011). This enhancement of M_1 was attributable in part to downregulation of a previously recognized lithium responsive miRNA (let-7b) (Zhou et al., 2009). Therefore, identifying the miRNA mechanisms that mood stabilizers use to achieve their therapeutic effects is likely to provide insight into another transcriptional layer of regulatory control that may identify numerous unrealized therapeutic targets.

In addition, miRNA dysregulation has been implicated in many different pathologic conditions, including neurodegenerative, neuropsychiatric, and neurologic diseases (Hebert and De Strooper, 2009; Eacker et al., 2009; Dinan, 2010; Kim et al., 2010; Moreau et al., 2011; Hunsberger et al., 2012). A very recent article reported miRNA regulation after ischemic stroke (e.g., miR-446f, miR-446h, miR-155, miR-1224, and miR-297a) and the potential for underlying the benefits of postinsult VPA treatment (e.g., miR-885-3p and miR-331) in a rat model of cerebral ischemia (Hunsberger et al., 2012). Collectively, this support suggests that miRNAs may underlie disease processes that contribute to numerous neurologic disorders. Furthermore, insight into the miRNA targets and pathways currently under investigation and the in silico analysis for predicted targets (Dweep et al., 2011) may provide critical knowledge for elucidating the complex signaling networks underlying fundamental disease processes. In addition, uncovering which miRNA binding sites in susceptibility genes are mutated in patients will help link miRNA mechanisms to genetic vulnerabilities and may help explain why some patients respond to treatment with mood stabilizers and others do not.

Because of the insights gleaned to date, miRNA research appears to hold great promise for the identification of currently unknown mechanisms of transcriptional regulation that contribute to the neurobiological effects of mood stabilizers and of dysregulated signaling networks that contribute to CNS disorders. Indeed, a recent article by Salmena and colleagues provides a unifying hypothesis detailing how mRNAs, transcribed noncoding pseudogenes, and long noncoding RNAs may communicate and interact using miRNA binding sites (Salmena et al., 2011). In accordance with this hypothesis, the presence of a noncoding pseudogene with miRNA response elements may compete for miRNAs and effectively switch from being a target to a sponge to dampen the effect of a particular miRNA. It has also been speculated that miRNAs in signaling networks act as key regulatory nodes (Inui et al., 2010). Theories such as these suggest that the ability to modulate key miRNAs could be used to repress disease pathology or activate the therapeutic mechanisms underlying mood stabilizers in a manner not currently achievable. A future challenge is how to integrate transcriptomic and proteomic data to evaluate how the myriad of regulatory controls (e.g., through miRNAs, epigenetics, and posttranslational modifications) contribute to therapeutic effects and to the dysregulation of brain processes associated with CNS disorders. Overcoming this challenge should provide unparalleled new insights into the complex mechanisms of pathophysiology and revolutionize current targets and methods of treatment of neuropsychiatric and neurodegenerative diseases.

III. Repurposing Mood Stabilizers for CNS Disorders Beyond BD

Loosely defined, drug repurposing is using known drugs to treat conditions for which they are not currently intended. Lithium and VPA have a long history of safe use in the treatment of BD and, in the case of VPA, epilepsy. Because of their numerous beneficial effects, they could be readily repurposed to treat other CNS diseases. Indeed, the largest study of its kind to date recently reported that long-term lithium treatment augmented the neuronal viability marker NAA in prefrontal cortex of patients with BD in a two center study (Hajek et al., 2012). Decreased NAA expression measured by noninvasive proton magnetic resonance spectroscopy has been reported in both neurologic and neurodegenerative conditions, where it has been associated with loss of neurons and axons. Clinical studies are now warranted to investigate the long-term treatment effects of lithium and VPA in CNS disorders beyond BD, perhaps with use of a methodology similar to that use by Hajek et al. (2012). Tables 1

and 2 list preclinical studies supporting the neuroprotective actions of lithium and VPA, respectively, in various animal models of CNS diseases. Below, we summarize evidence from selected models that support the translation of these findings into highly anticipated and needed clinical benefits.

A. Stroke

Stroke is the third leading cause of death in the United States and a major cause of serious long-term disability in adults. In addition, stroke victims are frequently burdened with vascular depression and dementia that is difficult to treat with conventional medicine. Of all strokes, 87% are ischemic and the rest are hemorrhagic (Roger et al., 2011). For acute ischemic stroke, thrombolysis with intravenous recombinant tissue plasminogen activator (rtPA) is the only treatment approved by the US Food and Drug Administration (FDA) to date. However, because of the narrow therapeutic window of less than 4.5 hours and risk of intracerebral hemorrhage, it is estimated that rtPA is used in only 1.8%–2.1% of patients with ischemic stroke (Barber et al., 2001; Kleindorfer et al., 2008).

Although there is clearly an urgent need to develop novel treatments for stroke, poststroke pathophysiology is complex and involves early- and late-phase processes (such as apoptosis, neuroinflammation, BBB breakdown, neurovascular repair, and neurovascular regeneration). Accumulating evidence demonstrates that lithium and VPA exert beneficial effects throughout this pathophysiological process (for a review, see Chuang et al., 2009, 2011; Wang et al., 2011b) and hold clinical potential for its treatment.

1. Lithium-Induced Effects in Experimental Stroke Models.

a. Neuroprotection and behavioral improvement. The neuroprotective effects of lithium against cerebral ischemia were first demonstrated in a rat model of permanent middle cerebral artery occlusion (pMCAO) (Nonaka and Chuang, 1998). This pioneering study showed that long-term pretreatment with lithium at therapeutically relevant doses decreased scores indicative of neurologic deficit and volume of brain infarct. Chronic lithium pretreatment also reduced apoptotic death in the penumbra of the ischemic cortex in a transient MCAO (tMCAO) model (Xu et al., 2003). In addition to pretreatment, subcutaneous injection of therapeutic doses of lithium into tMCAO rats three hours after the onset of occlusion markedly decreased infarct volume and suppressed neurologic deficits, as measured by sensory, motor, and reflex tests (Ren et al., 2003). Lithium pretreatment in gerbils after global cerebral ischemia was also found to suppress most ischemia-induced changes in exploratory behavioral and memory impairments (Bian et al., 2007). These behavioral benefits in gerbils were associated with an increased number of viable cells and a decrease in apoptotic cells in the CA1 hippocampal ischemic area.

b. Anti-excitotoxic and anti-apoptotic effects. In a rat model of global cerebral ischemia, lithium was reported to inhibit ischemia-induced hyperactivation of the NMDA receptor by inhibiting phosphorylation of the NMDA subunit 2A tyrosine and its interactions with Src and Fyn through PSD-95 in the rat hippocampus (Ma and Zhang, 2003). In a tMCAO model, postischemic lithium treatment (presumably through GSK-3 inhibition) upregulated heat shock responses, including activation of HSF-1 and induction of HSP70 in the cortical penumbra (Ren et al., 2003). In addition, in organotypic cultures of rat hippocampus subjected to oxygen and glucose deprivation, lithium was neuroprotective in conjunction with HSP27 activation (Cimarosti et al., 2001). In the mouse brain, lithium also attenuated hypoxia-induced serine dephosphorylation of GSK-3α and β (Roh et al., 2005). These findings suggest that lithium protection against ischemia-induced injury involves multiple mechanisms, including GSK-3 inhibition. In addition to inducing anti-apoptotic HSP70, lithium-induced neuroprotection was also accompanied by downregulation of proapoptotic p53 in the CA1 but upregulation of anti-apoptotic Bcl-2 in the global ischemic brain of gerbils (Bian et al., 2007).

c. Anti-inflammation. It is now generally acknowledged that ischemia-induced brain injury results at least in part from neuroinflammation mediated by microglia, monocytes, or macrophages. To date, lithium's anti-inflammatory effects have been demonstrated in rat models of neonatal hypoxia-ischemia and hemorrhagic stroke, but not in ischemic stroke. Under neonatal hypoxia-ischemia conditions, postinsult treatment with lithium suppressed microglial activation and attenuated overexpression of proinflammatory cytokines and chemokines (Li et al., 2011). Pretreatment of intracerebral hemorrhagic rats with lithium for three days suppressed the expression of cyclooxygenase-2 (COX-2) and reactive microglia in the perihematomal regions (Kang et al., 2012), and this was associated with decreased cell death and improved sensorimotor recovery, underscoring lithium's anti-inflammatory effects. Because GSK-3 inhibition is known to reduce neutrophil infiltration and decrease the expression of proinflammatory factors in a rat tMCAO model (Koh et al., 2008), inhibition of this kinase may also be involved in mediating lithium's anti-inflammatory effects in the context of stroke.

d. Angiogenesis. One key component of poststroke neurovascular remodeling is angiogenesis, a process in which new capillaries are formed on existing blood vessels through directed proliferation and the migration of endothelial progenitor cells. Poststroke angiogenesis increases collateral circulation and restores

TABLE 1
Beneficial effects of the mood stabilizer lithium in multiple models of CNS disorders
Preclinical studies supporting the repurposing of lithium as a modulator of neuroprotection in various animal models of CNS diseases.

Disease	Experimental models	References
Ischemic stroke	Rat and mouse MCAO models; gerbil and rat global ischemia model; hippocampal organotypic cultures	Nonaka and Chuang, 1998; Cimarosti et al., 2001; Ma and Zhang, 2003; Ren et al., 2003; Xu et al., 2003; Roh et al., 2005; Bian et al., 2007; Yan et al., 2007; Kim et al., 2008; Li et al., 2010a, 2011; Tsai et al., 2011;
Hemorrhagic stroke	Rat intracerebral hemorrhagic model	Kang et al., 2012
TBI	Rat and mouse models of controlled cortical impact	Shapira et al., 2007; Zhu et al., 2010; Dash et al., 2011; Yu et al., 2012a,b
HD	Rat excitotoxic model; rat corticostriatal slices; transgenic mice; neuroblastoma cells	Wei et al., 2001; Carmichael et al., 2002; Wood and Morton, 2003; Senatorov et al., 2004; Berger et al., 2005; Senatorov and Chuang, 2007; Sarkar et al., 2008; Crespo-Biel et al., 2009; Chiu et al., 2011
AD	Cultured cells and hippocampal slices; rabbits and rats; transgenic mice; *Drosophila*	Hong et al., 1997; Munoz-Montano et al., 1997; Alvarez et al., 1999, 2002; Inestrosa et al., 2000; Wei et al., 2000; Sang et al., 2001; Sun et al., 2002; De Ferrari et al., 2003; Ghribi et al., 2003; Perez et al., 2003; Phiel et al., 2003; Tsuji et al., 2003; Mudher et al., 2004; Rametti et al., 2004, 2008; Su et al., 2004; Nakashima et al., 2005; Noble et al., 2005; Scali et al., 2006; Rockenstein et al., 2007; Martin et al., 2009; Leroy et al., 2010; Sofola et al., 2010; Sy et al., 2011; Zhang et al., 2011a
ALS	Transgenic mice	Shin et al., 2007; Feng et al., 2008; Fornai et al., 2008; Ferrucci et al., 2010; Fulceri et al., 2011;
FXS	Transgenic *Drosophila* and mouse models	McBride et al., 2005; Min et al., 2009; Choi et al., 2010; Mines et al., 2010; Mines and Jope, 2011; Liu et al., 2011, 2012b
PD	Cellular, rat and mouse MPTP models; 6-hydroxydopamine models	King et al., 2001; Chen et al., 2004; Youdim and Arraf, 2004; Koh et al., 2008; Duka et al., 2009; Kim et al., 2011; Arraf et al., 2012; Castro et al., 2012
Retinal degeneration	Retinal ganglion cells in vivo and in vitro; retinal neurocytes in vitro	Huang et al., 2003; Huang and Klein, 2006; Schuettauf et al., 2006; Cho and Chen, 2008; Zhuang et al., 2009
Multiple sclerosis	Mouse experimental autoimmune encephalomyelitis	De Sarno et al., 2008
Spinal cord injury	Adult rats	Shimizu et al., 2000; Yick et al., 2004; Su et al., 2007; Dill et al., 2008
Alcohol-induced degeneration	Cultured neurons; neural stem cells; infant mice and *Drosophila*	Zhong et al., 2006; Chakraborty et al., 2008; Ishii et al., 2008; French and Heberlein, 2009; Liu et al., 2009; Luo, 2010; Saito et al., 2010
Down syndrome	Transgenic mice	Huang et al., 2000; Dou et al., 2005; Bianchi et al., 2010;
Spinocerebellar ataxia-1	Transgenic mice	Watase et al., 2007
HIV-associated neurotoxicity	Mouse model of encephalitis; cultured neurons	Maggirwar et al., 1999; Everall et al., 2002;

blood flow to injured tissue. These new vessels also provide neurotrophic support for concurrent neurogenesis and synaptogenesis, ultimately leading to functional recovery (Beck and Plate, 2009). For these reasons, enhancing angiogenesis after stroke may hold great promise for the treatment. Neurovascular remodeling in the chronic phase of stroke determines the ultimate extent of recovery. A functional MRI study in tMCAO rats demonstrated the neurohemodynamic aspects of lithium-induced recovery from ischemia. In this study, a delayed lithium injection (12 hours after ischemic onset), followed by daily injections, significantly enhanced the ratios of mean activated volume and total activation of magnitude for both blood oxygen level dependence and functional cerebral blood volume on day 15 (Kim et al., 2008). Lithium elevated levels of CD31 staining, a marker of microvasculature, and functional cerebral blood volume in the peri-infarct regions, suggesting possible vascular transformation (Kim et al., 2008). An increase in MMP-9 staining and its colocalization with CD31 further suggest that neurovascular remodeling depends on MMP-9 in the recovering brain area. Treatment of rat brain endothelial cells with lithium was also found to increase protein levels of VEGF, apparently through the PI3K and GSK-3 signaling pathways (Guo et al., 2009). Because VEGF has been linked to angiogenesis, neurogenesis, and neuroprotection (Fan and Yang, 2007), VEGF overexpression may contribute to lithium's ability to promote neurovascular remodeling and functional recovery after ischemic stroke.

e. Neurogenesis. Neurogenesis, which includes cell proliferation, migration, and differentiation, is the process of forming integrated neurons from progenitor cells (Kornack and Rakic, 2001). In the adult brain, neurogenesis usually occurs in the subventricular zone (SVZ) and hippocampal dentate gyrus (DG). The neural stem cells in the SVZ migrate into the olfactory bulb and then differentiate into interneurons, and new neurons in the subgranular zone migrate into the adjacent DG granule cell layer. It is known that cerebral ischemia enhances neurogenesis in regions that are traditionally neurogenic and nonneurogenic, perhaps as part of the self-repair system of ischemic

TABLE 2
Beneficial effects of the mood stabilizer VPA in multiple models of CNS disorders
Preclinical studies supporting the repurposing of VPA as a modulator of neuroprotection in various animal models of CNS diseases.

Disease	Experimental models	References
Ischemic stroke	Rat and mouse MCAO models; rat global ischemia model	Ren et al., 2004; Kim et al., 2007; Qian et al., 2010; Tsai et al., 2011; Wang et al., 2011a, 2012; Xuan et al., 2012
Hemorrhagic stroke	Rat intracerebral hemorrhagic model	Sinn et al., 2007
TBI	Rat model of controlled cortical impact	Dash et al., 2010
HD	Transgenic mice	Zadori et al., 2009; Chiu et al., 2011;
AD	Cultured cells and hippocampal slices; transgenic mice; *Drosophila*	Su et al., 2004; Qing et al., 2008; Smith et al., 2010; Hu et al., 2011
ALS	Transgenic mice	Sugai et al., 2004; Rouaux et al., 2007; Feng et al., 2008
FXS	FXS lymphoblastoid cell lines	Tabolacci et al., 2005, 2008
PD	LPS-treated midbrain neuron-glia co-cultures; cellular, rat and mouse MPTP models; rotenone-challenged cellular and rat models	Peng et al., 2005; Chen et al., 2006, 2007; Wu et al., 2008; Castro et al., 2012; Kidd and Schneider, 2010, 2011; Monti et al., 2010; Xiong et al., 2011
Retinal degeneration	Rat retinal ganglion cells; rat retinal ischemia model; optic nerve crush; mice	Biermann et al., 2010, 2011; Zhang et al., 2011b, 2012b
Spinal cord injury	Adult rats and mice; organotypic culture of spinal cord	Abematsu et al., 2010; Lv et al., 2011, 2012; Penas et al., 2011; Lee et al., 2012b
Spinal muscular atrophy	SMA fibroblast cell lines; transgenic mice	Sumner et al., 2003; Tsai et al., 2006, 2008; Harahap et al., 2012
HIV-associated neurotoxicity	Mouse model of encephalitis; cultured neurons	Dou et al., 2005

injury (Arvidsson et al., 2002). In a rat model of transient global ischemia with four-vessel occlusion, chronic lithium treatment improved spatial learning and memory deficits and increased the survival and generation of newborn cells in the DG, thereby potentiating hippocampal neurogenesis (Yan et al., 2007). It has been suggested that postischemic neurogenesis involves growth factor–induced activation of receptor tyrosine kinases and subsequent stimulation of PI3K/Akt and ERK signaling pathways (Shioda et al., 2009). Consistently, lithium treatment enhanced ERK phosphorylation after ischemia, whereas the ERK inhibitor U0126 abolished the effects of lithium on neurogenesis and behavioral improvement (Yan et al., 2007).

f. Effects on MSC migration after transplantation. Lithium- or VPA-primed MSCs transplanted by tail vein injection into tMCAO rats 24 hours after ischemic onset significantly increased the number of MSCs homing to brain infarct regions, such as the cortex and striatum, as measured two weeks after transplantation (Tsai et al., 2011). For a more detailed discussion of how priming with lithium and/or VPA affects MSC migration, see section II.F. MCAO rats receiving lithium- and/or VPA-primed MSCs exhibited improved functional recovery, reduced infarct volume, and enhanced angiogenesis in the penumbra regions. Of note, MSCs that have been coprimed with lithium and VPA showed further improvement in homing ability, angiogenesis, and functional recovery after transplantation into ischemic rats. Of significance, pharmacological inhibition of MMP-9 reversed these beneficial effects of lithium priming, and inhibition of CXCR4 reversed the benefits of VPA priming, suggesting that the mechanisms underlying these benefits likely involve lithium-induced MMP-9 upregulation and VPA-induced CXCR4 overexpression. These findings indicate a potential for enhancing MSC migration and homing capacity after transplantation into stroke victims by priming them with GSK-3 and HDAC inhibitors.

2. VPA-Induced Effects in Experimental Stroke Models.

a. Neuroprotective effects and behavioral benefits. VPA's protective effects against brain ischemic injury are well established. Initial studies using tMCAO found that subcutaneous injection with VPA (300 mg/kg) immediately after the onset of tMCAO, followed by twice-daily injections thereafter, markedly decreased infarct size, suppressed ischemia-induced apoptosis, and reduced neurologic deficits (Ren et al., 2004). VPA treatment in MCAO rats increased histone H3 acetylation and HSP70 upregulation in both ipsilateral and contralateral brain hemispheres, suggesting the involvement of HDAC inhibition and HSP70 induction in mediating VPA-induced neuroprotection. Postinsult treatment with VPA or other HDAC inhibitors (such as SB or TSA) within at least three hours of ischemic onset in a rat pMCAO model also significantly decreased infarct volume and induced long-term improvement in neurologic performance (Kim et al., 2007). Of note, it has been recently shown that treatment with 100 mg/kg VPA for seven days starting 24 hours after pMCAO in rats significantly improved neurologic performance of foot fault test, adhesive test, and neurologic severity score measured 7–28 days after ischemia, although this treatment did not reduce infarct volume (Liu et al., 2012a). These findings suggest that the beneficial effects of VPA on neurologic outcomes may be independent of the infarct volume reduction.

b. Anti-inflammation. In a rat pMCAO model, VPA treatment markedly reduced the number of both

activated microglia and infiltrating monocytes/macrophages and suppressed ischemia-induced upregulation of proinflammatory factors, inducible nitric oxide synthase, and COX-2 (Kim et al., 2007). The anti-inflammatory effects of VPA have also been demonstrated in vitro. In rat midbrain neuron-glia cocultures, for example, the neuroprotection of VPA against LPS-induced dopaminergic neurotoxicity was, at least in part, found to be attributable to a decrease in levels of proinflammatory factors released from activated microglia (Peng et al., 2005). Specifically, pretreating cocultures with VPA markedly reduced LPS-induced increases in the release of tumor necrosis factor-α (TNF-α), nitric oxide, and intracellular ROS. These anti-inflammatory effects correlate with a decrease in the number of microglia. Treatment of rat microglia-enriched cultures with VPA induced microglial death with multiple hallmarks of apoptosis (Chen et al., 2007). VPA-induced microglial apoptosis was also accompanied by disrupted mitochondrial membrane potential and hyperacetylation of histone H3—effects mimicked by treatment with other HDAC inhibitors. This HDAC inhibition-dependent microglial apoptosis induced by VPA provides a novel mechanism of protection against neuroinflammation.

Experiments with animal models of brain ischemia have further shown that HDAC inhibitors other than VPA (such as vorinostat, SB, and TSA) also super-induced HSP70 (Ren et al., 2004; Faraco et al., 2006; Kim et al., 2007). In a mouse tMCAO model, HSP70 overexpression inactivated the key inflammatory transcription factor NF-κB and prevented nuclear translocation of activated NF-κB subunits (Zheng et al., 2008). In addition, postinsult VPA treatment in a rat model of intracerebral hemorrhagic stroke was found to reduce the number of terminal deoxynucleotidyl transferase (TdT)-mediated dUTP nick end labeling (TUNEL)-positive cells, upregulate Bcl-2/Bcl-xl, downregulate Bax, and inhibit caspase activity (Sinn et al., 2007). VPA further mitigated cerebral inflammation by inhibiting neutrophil infiltration, suppressing microglial activation, and downregulating proinflammatory factors. Thus, suppression of neuroinflammation and apoptosis appears to be mediated by HDAC inhibition and comprises multiple mechanisms that contribute to the neuroprotective effects induced by VPA. Accordingly, VPA-induced inhibition of HDACs has been shown to suppress microglial activation, reduce levels of proinflammatory factors, and induce HSP70—anti-inflammatory effects that may mediate neuroprotection against hippocampal neuronal loss and cognitive deficits in rat models of transient global ischemia (Xuan et al., 2012).

c. BBB protection. Disruption of the BBB is critical to the pathogenesis of brain ischemia and other neurologic disorders, allowing intravascular proteins and fluid to penetrate into the cerebral parenchymal extracellular space, followed by leukocyte infiltration, vasogenic edema, and hemorrhage. One study found that postinsult treatment with VPA (200 and 300 mg/kg i.p.) robustly attenuated tMCAO-induced BBB disruption and brain edema (Wang et al., 2011a). Of note, VPA-induced BBB protection was dose-dependent and persisted for at least 72 hours after transient ischemia.

The BBB can be disrupted by abnormal activity of MMPs, a family of zinc-dependent endopeptidases known to perform multiphasic roles in ischemic stroke (Rosell and Lo, 2008). The abnormal upregulation of both MMP-2 and -9 induced by ischemia, for instance, is linked to BBB disruption by degrading tight junctions and basal lamina proteins and disrupting cell-matrix homeostasis. VPA strongly reduced MCAO-induced MMP-9 activity and protein elevation and concomitantly restored protein levels of tight junctions, claudin-5 and ZO-1, which are degraded 24 hours after MCAO (Wang et al., 2011a). MMP-9 expression has been shown to be regulated by NF-κB (Van den Steen et al., 2002), in which activation may be inhibited by VPA through upregulation of HSP70, as mentioned above. Consistent with this notion, treatment with VPA or SB completely blocked MCAO-induced nuclear translocation of the NF-κB p65 subunit (Wang et al., 2011a). Taken together, the evidence suggests that VPA's ability to protect the BBB likely involves the initial inhibition of HDACs, followed by suppression of MCAO-induced NF-κB activation, MMP-9 overexpression, and tight junction degradation.

d. Angiogenesis. As measured on day 14 after tMCAO, long-term postinsult administration of VPA (200 mg/kg i.p.) markedly reduced infarct volume and improved functional recovery (Wang et al., 2012). Concurrently, VPA treatment enhanced postischemic angiogenesis by increasing microvessel density, facilitating endothelial cell proliferation and upregulating regional cerebral blood flow in the ipsilateral cortex. In addition, ischemia is followed by an increase in levels of three key proangiogenic factors: VEGF, MMP-2, and MMP-9. These molecules are regulated by HIF-1, a transcription factor responsible for gene transcription that facilitates adaptation and survival after hypoxia or ischemia (Ke and Costa, 2006). As measured on days 7 and 14 after MCAO, VPA treatment was shown to potentiate MCAO-induced HIF-1α accumulation and to upregulate downstream levels of VEGF and MMP-2/9 activity in the ipsilateral cortex. Inhibition of HIF-1α, moreover, reversed the elevated postischemic angiogenesis and functional recovery induced by VPA.

Taken together, these findings indicate that long-term VPA treatment enhances postischemic angiogenesis and promotes long-term functional recovery in an experimental model of ischemic stroke. The findings are further supported by reports from an in vitro study that the HDAC inhibitors VPA and vorinostat

enhanced VEGF-induced spheroid sprout formation in human umbilical vein endothelial cells and that VPA displayed a trend toward increasing endothelial cell migration (Jin et al., 2011). Of note, VPA appeared to play a dual role in preserving postischemic endothelial cell function: it limited cell damage by inhibiting MMP-9 and VEGF in the acute phase but enhanced angiogenesis by upregulating VEGF and MMP-2/9 in the later recovery phase (Wang et al., 2012). To date, little is known about the mechanisms underlying this time-dependent switch in VPA-induced activity after MCAO. Further investigation is certainly warranted.

e. Neurogenesis. When studied in vitro and in vivo, VPA has been shown to promote hippocampal neurogenesis (Hsieh et al., 2004; Yu et al., 2009). In addition, even under conditions of favored lineage-specific differentiation, VPA was also found to inhibit the differentiation of astrocytes and oligodendrocytes (Hsieh et al., 2004). In fact, VPA-induced inhibition of HDAC has been shown to upregulate several regulatory factors favoring neurogenic transcription (such as NeuroD, Ngn1, Math1, and p15). Chromatin immunoprecipitation analysis further showed that, in neuronal differentiation of both hippocampal neural progenitor cells and adult hippocampal neurogenesis, acetylated histone H4 was associated with the promoter of Ngn1 (Yu et al., 2009). In a rat pMCAO model, delayed VPA treatment promoted white matter repair by increasing survival of oligodendrocytes and differentiation of oligodendrocyte progenitor cells and enhanced neurogenesis by increasing the number of newly formed neuroblasts in the ischemic boundary zone 28 days after ischemia (Liu et al., 2012a). In addition, VPA increased acetylated histone H4 levels in neuroblasts and neural progenitor cells, suggesting the involvement of HDAC inhibition in VPA's proneurogenic effects. The HDAC inhibitors SB and TSA, which are structurally similar and dissimilar to VPA, respectively, were also found to exert postischemic proneurogenic effects in a rat pMCAO model (Kim et al., 2009). In addition, postinsult treatment with SB of rats undergoing pMCAO was shown to stimulate BrdU incorporation in the SVZ, DG, striatum, and frontal cortex; post-MCAO treatment with SB or TSA was also shown to increase the population of cells expressing nestin, GFAP, CREB, BDNF, and polysialic acid-neural cell adhesion molecule (PSA-NCAM), a neuroblast marker with important neurobiological functions. After treatment with HDAC inhibitors, moreover, extensive colocalization of BrdU and PSA-NCAM was noted in multiple brain regions. BDNF and phospho-CREB, which are known to regulate neurogenesis, were robustly upregulated by treatment with SB or TSA. It is noteworthy that intraventricular injection of the TrkB antagonist K252a markedly suppressed SB-induced cell proliferation detected by BrdU and Ki67 in the ipsilateral SVZ, DG, and other brain regions. It also blocked nestin expression and CREB activation and attenuated the long-lasting behavioral benefits of SB. Together, these results suggest that proliferation, migration, and differentiation induced by HDAC inhibition require BDNF-TrkB signaling, which therefore, contributes to long-term behavioral improvement after stroke.

Overall, these findings highlight the ability of lithium and VPA to improve functional outcomes, suppress cell death, attenuate neuroinflammation, enhance migration of transplanted MSCs, and promote angiogenesis and neurogenesis in diverse animal models of cerebral ischemia. Figure 2 is a proposed model of how these two mood stabilizers induce multiple neurobiological effects in the MCAO ischemic model. These beneficial effects further confirm the considerable therapeutic potential of these mood-stabilizing drugs in the treatment of certain conditions of human stroke. Nevertheless, caution is warranted because of the limited therapeutic window of both lithium and VPA dosing, because adverse effects arise rapidly at toxic doses. These adverse effects can significantly negate the beneficial outcomes of long-term treatment. Therefore, appropriate dosing for both of these drugs is essential for their therapeutic potential to be realized, particularly because effective dosing for stroke and other neurodegenerative diseases is currently lacking. We anticipate that combining treatment of lithium and VPA may also provide unique advantages toward reducing harmful adverse effects by requiring lower doses for clinical benefit.

B. TBI

TBI is characterized by initial injury to neurons, glia, and vascular structures, followed by secondary injury from excitotoxicity, BBB breakdown, brain edema, neuroinflammation, and neurodegeneration. Secondary injury is often accompanied by behavioral and cognitive deficits and neuropsychiatric disturbances (such as depression, anxiety, and posttraumatic stress disorder) (for a review, see Ursano et al., 2010). Since 2001, more than 200,000 military personnel in the United States have sustained TBI, which is increasingly considered to be a signature wound of the wars in Iraq and Afghanistan. In addition, in developed countries, TBI is one of the leading causes of mortality and disability among young persons, and its incidence is rapidly increasing. Moreover, despite extensive research aimed at developing therapies for TBI, no FDA-approved drug yet exists for its treatment. Because of TBI's complex pathology, any effective therapy will need drugs that can act on multiple cell survival and death pathways, either alone or in combination (Margulies et al., 2009); in this regard, accumulating evidence indicates that lithium and VPA are both strong candidates.

1. Lithium-Induced Effects on Neurodegeneration, Neuroinflammation, Behavioral Improvement, and Aβ Accumulation in Models of TBI. In cases of mild TBI in mice, pretreatment with lithium (or another GSK-3

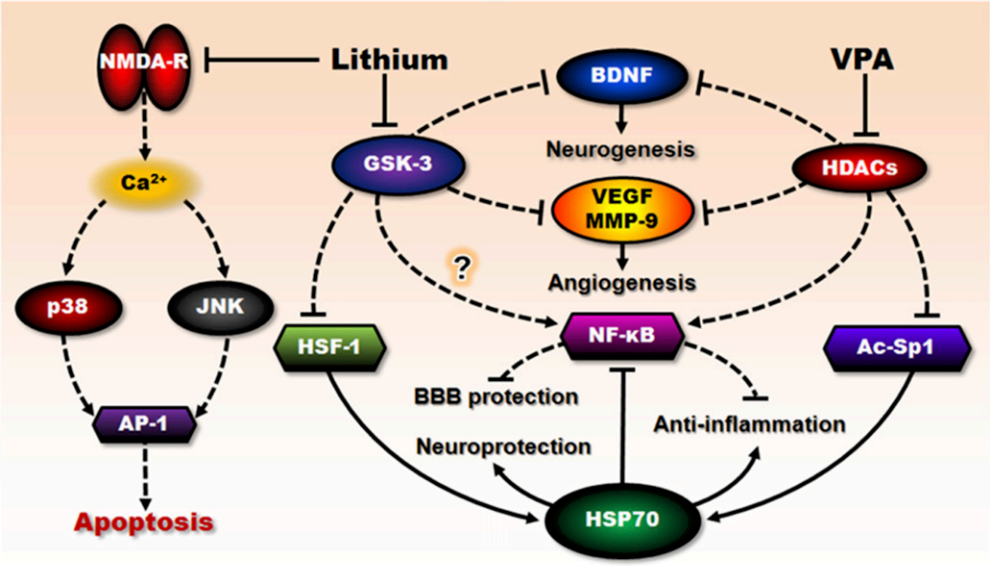

Fig. 2. A proposed model to demonstrate the molecular actions of lithium and VPA in preclinical models of cerebral ischemia. By inhibiting GSK-3 and HDACs, respectively, lithium and VPA induce transcriptional activation of diverse neuroprotective and neurotrophic genes in the ischemic brain. HSP70 expression is enhanced by mechanisms involving lithium-induced HSF-1 activation and VPA-induced Sp1 activation by acetylation. HSP70 is neuroprotective and anti-inflammatory, presumably because it inhibits NF-κB, in which activity is inhibited by VPA and, possibly, by lithium. NF-κB inhibition also contributes to protection against BBB breakdown by downregulating MMP-9 shortly after ischemia. VEGF and MMP-9 are induced by long-term lithium or VPA treatment and are key protein molecules involved in potentiating angiogenesis. In addition, BDNF is transcriptionally activated by lithium and VPA, and BDNF-TrkB signaling is essential for enhancing neurogenesis. BDNF and VEGF also contribute to neuroprotection and the behavioral benefits of mood stabilizers. Furthermore, ischemia-induced NMDA receptor overstimulation and calcium overflow in the ischemic brain are inhibited by lithium treatment through inhibition of NR2 subunit tyrosine phosphorylation. This could suppress excitotoxicity-induced p38 and Jun N-terminal kinase (JNK) and subsequent activator protein 1 (AP-1) activation to block neuronal apoptosis. Lines with solid arrows represent stimulatory connections; lines with flattened ends represent inhibitory connections. Dashed lines represent pathways with reduced activity as a result of lithium or VPA treatment.

inhibitor) 30 minutes before injury alleviated depressive behavior 24 hours after mild TBI (Shapira et al., 2007). In the hippocampus, mild TBI increased phosphorylation of Akt, phosphorylation of GSK-3β at Ser9, and accumulation of downstream β-catenin, suggesting the activation of this prosurvival cascade. The evidence thus suggests that inhibiting GSK-3β may be beneficial in TBI. In a mouse model of moderate TBI produced by controlled cortical impact, a method widely used for the accurate control of mechanical input, chronic lithium pretreatment for 14 days attenuated the loss of hemispheric tissue, brain edema, IL-1β expression, and hippocampal neuronal degeneration. In addition, these effects of lithium pretreatment in moderate TBI mice were associated with improved spatial learning and memory (Zhu et al., 2010).

Postinsult treatment with lithium also exerts robust neuroprotective effects in TBI. With a therapeutic window of 3–6 hours after injury, lithium treatment was recently reported to reduce controlled cortical impact–induced lesion volume in a TBI mouse model, when assessed at three days and three weeks after injury (Yu et al., 2012a). This postinsult lithium treatment attenuated TBI-induced neuronal death, microglial activation, COX-2 induction, and MMP-9 expression and preserved the integrity of the BBB, in addition to normalizing TBI-induced hyperlocomotor activity, anxiety-like behavior, and motor coordination. Under these experimental conditions, lithium also robustly increased GSK-3β phosphorylation at Ser9, suggesting that inhibition of this kinase is involved in mediating the drug's beneficial effects. In another study, controlled cortical impact–induced TBI was also found to cause a delayed increase in GSK-3β Ser9 phosphorylation. In contrast, postinsult (30 minutes after injury) lithium administration for five days was associated with elevated phosphorylation of this kinase and subsequent β-catenin accumulation with reduced hippocampal CA3 neuron loss and with lower deficits in hippocampus-dependent learning and memory, as measured at 14–28 days after injury (Dash et al., 2011). That lithium's behavioral benefits are partially mimicked by the GSK-3 selective inhibitor SB-216763 supports the theory that lithium's protective effects against TBI involve GSK-3 inhibition. Of note, however, lithium treatment may well have other targets that contribute to its beneficial effects.

Of note, TBI has been identified as a major risk factor for developing AD. Memory impairments are frequent in both patients with TBI and animal models (Spikman et al., 2012), and Aβ levels were found to be elevated in CSF and postmortem brain samples from patient with TBI (Uryu et al., 2007). Hyperactivity of GSK-3 has been implicated in the pathogenesis of AD (Hooper et al., 2008), an idea supported by the fact that lithium treatment produces many benefits in various

models of this disease (see section III.D). In recent findings from our laboratory, lithium treatment in the corpus callosum and hippocampus robustly reduced a number of molecules and processes induced by TBI, including Aβ load, amyloid precursor protein (APP), tau hyperphosphorylation, and overexpression of β-APP–cleaving enzyme-1 (Yu et al., 2012b). Of importance, lithium also ameliorated TBI-induced deficits in spatial learning and memory, as assessed by the Morris water-maze and Y-maze tests; these effects were associated with increased hippocampal preservation. Together, these findings demonstrate multiple beneficial effects of lithium in TBI and underscore the continued need for its clinical investigation.

2. VPA-Induced Effects on Neurodegeneration, Neuroinflammation, and Functional Recovery in Models of TBI. Although less is known about the therapeutic potential of VPA in TBI, preclinical animal studies have similarly revealed beneficial effects. In a rat model of TBI, postinjury systemic VPA administration reduced cortical contusion volume, decreased BBB permeability, and, of most importance, improved motor function and spatial memory (Dash et al., 2010). VPA also dose-dependently increased histone acetylation and reduced GSK-3 activity in the hippocampus. Similar results were observed in a previous study from the same group using another HDAC inhibitor, SB, in combination with behavioral training (Dash et al., 2009). In addition, HDAC inhibition also reduced TBI-induced microglial inflammatory response in rats (Zhang et al., 2008). In a mouse model of closed head injury, a single dose of the HDAC inhibitor ITF2357 given 24 hours after injury significantly increased levels of acetylated histone H3, HSP70, and phosphorylated Akt (Shein et al., 2009). Other benefits included reduced neurologic deficits, attenuated neuronal degeneration, and reduced lesion volume. These results confirm the hypothesis that VPA's effects are mediated through HDAC inhibition and that VPA merits further investigation as a potential treatment of TBI.

3. Clinical Trials of VPA Treatment in TBI. In a two-year randomized double-blind trial, VPA treatment began within 24 hours after injury and lasted for one or six months. VPA substantially reduced the rate of early seizure, although this benefit was not significant, compared with short-term (one week) treatment with phenytoin; neither drug prevented late seizures (Temkin et al., 1999). In addition, no significant adverse or beneficial effects were associated with VPA in another clinical study, as assessed by a battery of neuropsychological measurements administered 1, 6, and 12 months after TBI (Dikmen et al., 2000). On the basis of this trial, it was suggested that VPA should not be used for prophylaxis of posttraumatic seizures. Although VPA showed no benefit over phenytoin, it is possible that treatment could be optimized by shortening the treatment time window, controlling the dropout rate, and including a placebo group. Because these two clinical trials were conducted over a decade ago and evidence is accumulating for VPA's robust benefits in preclinical TBI models, there is a need to re-examine the clinical effects of VPA and other HDAC inhibitors in patients with TBI. A recent study showed that VPA treatment caused an acute ischemic stroke in a patient with a mutation of methylenetetrahydrofolate reductase (Varoglu, 2009). Mutation of this enzyme results in a decrease in its activity and induces hyperhomocysteinemia, a possible risk factor for epilepsy and occlusive vascular disease. The use of VPA could exacerbate hyperhomocysteinemia by reducing folic acid and vitamin B12 levels. Therefore, genetic examination or the determination of plasma levels of homocysteine may prevent these risks associated with VPA treatment.

C. HD

HD is a devastating inherited neurodegenerative disease. It is estimated by the World Health Organization (WHO) that HD affects 180,000 Americans, 30,000 of whom currently have the disease and 150,000 of whom have a 50% chance of developing it. A member of the polyglutamine (polyQ) family of disorders, HD is caused by a trinucleotide CAG-repeat in the gene that encodes a polyQ stretch to an unnaturally high number ($\geq$35) of glutamines in the N terminus of the disease-causing huntingtin (Htt) protein (Macdonald, 1993). This abnormally expanded mutant Htt (mHtt) causes neurotoxicity, possibly through both a toxic gain of function and a loss of wild-type Htt protein (Zuccato et al., 2001). The presence of mHtt ultimately results in the selective loss of neurons in the brain that particularly affects medium-sized spiny neurons in the striatum and, to a lesser extent, neurons in the cortex (Friedlander, 2003; Hickey and Chesselet, 2003). Clinically, patients with HD experience various cognitive, psychiatric, and physical symptoms, such as memory loss, changes in personality, emotional deterioration, and uncontrollable jerky movements. HD is lethal, with death occurring ~15 years after the initial symptoms (Martin and Gusella, 1986; Vonsattel and DiFiglia, 1998; Ross and Tabrizi, 2011). No cure for HD presently exists, nor are there effective treatments to halt disease progression. The search for neuroprotective agents to combat this dreaded disease is therefore of critical importance.

1. Lithium-Induced Effects on Apoptosis, Cell Proliferation, and Neuroprotection in Excitotoxic Models of HD. Both preclinical and clinical studies have implicated excitotoxicity, a mechanism of neuronal death caused by supersensitivity to (or hyperactivation of) excitatory amino acid receptors, in the neuropathology of HD (Taylor-Robinson et al., 1996; Levine et al., 1999; Zeron et al., 2001, 2002). The development of an excitotoxic animal model of HD was based on the fact

that intrastriatal injection with kainic or quinolinic acid (QA), both glutamate receptor agonists, mimicked the loss of medium-sized spiny neurons and produced many of the neuroanatomical changes found in the brain of patients with HD (Coyle and Schwarcz, 1976; Schwarcz and Whetsell, 1982; Foster et al., 1983; Beal et al., 1986). QA is also endogenously produced, among other toxic substances, by activated microglia and macrophages. Infusion of this compound into the striatum has been reported to downregulate cytoprotective Bcl-2 and upregulate proapoptotic p53 and c-Myc (Liang et al., 2005). Furthermore, it has been hypothesized that QA-induced striatal neuronal apoptosis may be the result, at least in part, of a failed cell cycle attempt (Liang et al., 2007). Administration of the succinate dehydrogenase inhibitor 3-nitropropionic acid (3-NP) also mimics striatal HD pathology (Brouillet et al., 1999). The excitotoxic features of HD suggest that lithium and VPA could be useful for its treatment.

Initial research in the rat excitotoxic model of HD found that lithium pretreatment, at doses within the therapeutic range, markedly reduced the size of QA-induced striatal lesions and the loss of striatal medium-sized neurons (Senatorov et al., 2004). Lithium's protective effects correlated with upregulation of Bcl-2, downregulation of Bax, and suppression of caspase-3 activation. In addition, the ability of lithium to protect against QA-induced excitotoxicity was further confirmed in mature rat corticostriatal organotypic cultures (Senatorov and Chuang, 2007). This preparation has the advantages of both in vivo and in vitro approaches, because it preserves organotypic organization and interneuronal connections. Lithium pretreatment stimulated the proliferation of striatal cells near the site of QA-induced injuries, and some of these replicating cells had the phenotype of neurons or astroglia (Senatorov et al., 2004). These observations were corroborated by reports that lithium increased neurogenesis in the rat hippocampus in vivo (Chen et al., 2000). In rat cortical neuronal cultures, lithium stimulated the proliferation of neuroblasts and antagonized glutamate or corticosterone-induced loss of neuroblast proliferation (Hashimoto et al., 2003b). These studies demonstrate lithium's anti-apoptotic, cell-proliferating, and neuroprotective effects in different models of HD.

2. Investigating Mood Stabilizers in Transgenic Models of HD. HD pathogenesis is frequently modeled through the transgenic expression of mHtt, which causes aggregate formation and toxicity in cell models and in vivo (Carmichael et al., 2002). In the brains of N171-82Q and YAC128 transgenic mouse models of HD, GSK-3 and HDAC hyperactivity has been associated with the onset of behavioral symptoms of the disease (Chiu et al., 2011). As discussed above, GSK-3 dysfunction has been implicated in many neuropsychiatric disorders, and activation of this kinase has been linked to apoptotic cell death induced by multiple insults. In a neuroblastoma cellular model of HD, the protective effects of lithium in reducing mHtt aggregates and cell death were mimicked either by treatment with a GSK-3β inhibitor or overexpression of a dominant-negative GSK-3β mutant (Carmichael et al., 2002). In *Drosophila,* lithium-induced protection against the toxicity of aggregate-prone proteins was mimicked by AR-A014418, a GSK-3β inhibitor (Berger et al., 2005). HDACs, on the other hand, play a key role in the homeostasis of histone acetylation of chromatin and regulation of transcription. Imbalances in protein acetylation and transcription are associated with a wide variety of brain disorders, as discussed above. In HD, moreover, mHtt has been shown to affect diverse transcriptional regulatory pathways (Cha, 2007). Transcriptional dysregulation is in fact an early and progressive event in HD and is an important causative factor in the disease (Sugars and Rubinsztein, 2003; Hodges et al., 2006).

Wild-type Htt has been shown to activate transcription of the BDNF gene (Zuccato et al., 2001), whereas mHtt represses it (Zuccato et al., 2003, 2007); of note, BDNF is a neurotrophin essential for striatal neuron survival (Nakao et al., 1995; Ventimiglia et al., 1995). BDNF plays a central role in cortical development and synaptic plasticity. Accordingly, in HD, loss of this trophic support from the cortex is considered to be one of the causal factors of striatal death, and decreased BDNF has been reported both in animal models of HD (Duan et al., 2003, 2008) and in the striatum of patients with HD (Ferrer et al., 2000; Zuccato et al., 2001). In contrast, enhanced BDNF expression has been shown to protect neurons from neurochemical insults associated with HD, both in cultured cells (Saudou et al., 1998) and in rodents (Bemelmans et al., 1999; Canals et al., 2004; Kells et al., 2004). Emerging evidence indicates that treatment with lithium and VPA affects both transcriptional activity and gene expression. Long-term treatment with either of these two drugs increased BDNF expression in the rat brain (Fukumoto et al., 2001). As reported above, moreover, both lithium inhibition of GSK-3β and VPA inhibition of HDACs activate BDNF promoter IV in cortical neurons (Yasuda et al., 2009). In various in vitro and in vivo models of HD, however, treatment with lithium or VPA has had mixed results in protecting against mHtt toxicity (Wei et al., 2001; Carmichael et al., 2002; Wood and Morton, 2003; Zadori et al., 2009).

3. Effects of Mood Stabilizers on Clearance of mHtt. Abnormal proteolytic processing of mHtt is believed to be another critical step in the onset of HD. This cleavage of mHtt in human HD tissue was found to be partially mediated by calpain, a calcium-activated neutral protease in which activity is elevated in the caudate of human HD tissues (Gafni and Ellerby,

2002). In both cultured primary brain neurons and a rat 3-NP model of HD, pretreatment with lithium attenuated 3-NP–induced cellular death and striatal neurodegeneration by preventing calpain and subsequent activation of cyclin-dependent kinase 5 (Cdk5) (Crespo-Biel et al., 2009). Eliminating mHtt expression, moreover, not only halted symptom progression but also led to a regression of disease-like symptoms (Yamamoto et al., 2000). These results suggest that improved clearance of the mutant protein can prevent cellular dysfunction and neurodegeneration in HD.

As described in section II.E, the UPS and autophagy are two major intracellular mechanisms for the clearance of abnormal protein accumulation. These mechanism are therefore believed to be particularly beneficial in those neurodegenerative disorders (such as HD) characterized by the accumulation of misfolded, disease-causing proteins (Luo and Le, 2010; Hegde and Upadhya, 2011; Li and Li, 2011; Nijholt et al., 2011). Because both lithium and VPA induce autophagy independent of mTOR activation, lithium in combination with rapamycin has been proposed as a rational HD therapy and has been tested in various models of the disease (Sarkar et al., 2008). This autophagy-inducing property has also been hypothesized to contribute to lithium's protective effects in ALS (Fornai et al., 2008).

In HD models, overexpression of HSPs, molecular chaperones that promote the degradation of abnormally folded proteins, has been shown to reduce the formation of Htt aggregates and to suppress the neurodegeneration and toxicity associated with this disease (Chan et al., 2000; Jana et al., 2000; Fujimoto et al., 2005). The brains of HD animal models, however, show a decrease in HSP70 and its cochaperone HSP40 (Hay et al., 2004; Chiang et al., 2007; Duan et al., 2008; Yamanaka et al., 2008), which have been found to colocalize with Htt aggregates (Jana et al., 2000). Of significance, in cultured neurons and rats subjected to cerebral ischemia, after treatment with either lithium or VPA, expression of HSP70 was found to increase (Ren et al., 2003, 2004; Kim et al., 2007; Marinova et al., 2009, 2011).

4. Effects of Combined Lithium and VPA Treatment on Behavior in Transgenic Models of HD. The most frequently studied transgenic mouse model of HD is the R6/2, which carries a 145 CAG repeat expansion and shows behavioral motor deficits as early as 5–6 weeks of age. In this model, postsymptomatic lithium treatment significantly improved rotarod performance but had no overall effect on survival (Wood and Morton, 2003). However, because cotreatment with lithium and VPA synergistically protected cultured brain neurons from glutamate excitotoxicity (Leng et al., 2008), combination therapy is expected to provide additional benefits in neurodegenerative conditions. Figure 3 shows a hypothetical working model of the molecular actions of combined lithium and VPA treatment in preclinical models of HD.

The therapeutic potential of combined treatment with lithium and VPA was recently assessed (Chiu et al., 2011) in two transgenic mouse models of HD with distinct genetic backgrounds and disease progressions: N171-82Q and YAC128 (Schilling et al., 1999; Slow et al., 2003). Although neither additive nor synergistic in every aspect of this disease, combined lithium and VPA treatment produced overall reliable behavioral benefits in both models. This combined treatment alleviated impaired locomotion and depressive-like behaviors more strongly than treatment with either drug alone. Combination therapy was also more successful than single-drug therapy at improving motor skill learning and coordination in N171-82Q mice and at suppressing anxiety-like behaviors in YAC128 mice.

In addition to motor and cognitive impairments, patients with HD frequently experience psychiatric disturbances, such as anxiety and depression (Di Maio et al., 1993), that severely reduce their daily functioning and quality of life (Hamilton et al., 2003; Wheelock et al., 2003). In the brains of HD mice treated with lithium and VPA together, the activity of GSK-3β and HDACs was consistently decreased, and expression of BDNF and HSP70 was rapidly elevated and sustained (Chiu et al., 2011). Because BDNF is considered a key mediator of the clinical efficacy of antidepressants and anxiolytic drugs (Woo and Lu, 2006), these actions have particular relevance for the drugs' behavioral effects. Perhaps of more importance, in N171-82Q mice, cotreatment markedly prolonged survival. Taken together, the data suggest that combined lithium and VPA treatment could be even more effective against HD if administered early in the course of the disease (Chiu et al., 2011). Potential patients with HD can be identified by genetic testing before the onset of symptoms; thus, these data provide a strong rationale for using a combination of lithium and VPA to treat HD.

5. Clinical Trials of Lithium and VPA Treatment in HD. Before their neuroprotective properties were discovered, the clinical use of lithium or VPA in patients with HD was explored decades ago. In patients with HD, lithium strikingly reduced chorea and markedly improved voluntary movements (Anden et al., 1973) and motor function (Mattsson, 1973). One study found that patients in the early stages of the disease were more likely to benefit from lithium treatment (Foerster and Regli, 1977); in that study, lithium conferred beneficial mood- and temper-stabilizing effects. Combined therapy with lithium and neuroleptics has also proven to be beneficial in several patients with HD (Anden et al., 1973; Manyam and Bravo-Fernandez, 1973; Leonard et al., 1974, 1975; Schenk and Leijnse-Ybema, 1974). On the other hand,

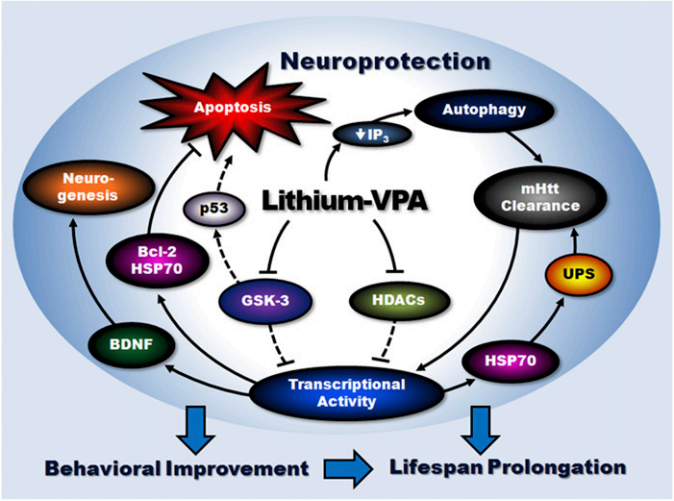

Fig. 3. A hypothetical working model to demonstrate molecular actions of combined lithium and VPA treatment in preclinical models of HD. In HD, the expression of mHtt affects a diverse set of transcriptional regulatory pathways and produces aggregates and toxicity in the striatal neurons. Transcriptional dysregulation, an early and progressive event in HD, is an important causative factor in this disease. Combined lithium and VPA treatment, by more consistently inhibiting both GSK-3 and HDACs, disinhibits several transcription factors, and subsequently elevates the expression of cytoprotective proteins, such as BDNF, HSP70, and Bcl-2. Suppressed GSK-3 activity further reduces the activity of the proapoptotic protein p53 and its negative regulatory effect on Bcl-2. Superinduction of HSP70 together with upregulated Bcl-2 and downregulated p53 attenuate apoptosis. As a molecular chaperone, HSP70 can also facilitate degradation of misfolded proteins via the ubiquitin-proteasome system (UPS). On the other hand, by decreasing inositol 1,4,5-trisphosphate (IP_3) levels, lithium and VPA induce autophagy, a key physiologic process for the bulk degradation of cytoplasmic proteins that has recently been recognized as one of the important regulators of neuronal survival and function. Induction of these intracellular protein quality control mechanisms enhances the clearance of mHtt and, thus, reduces mHtt-induced transcriptional dysregulation and toxicity. Moreover, increased expression of BDNF, an important neurotrophic support for striatal neurons, further protects against neurochemical insults associated with HD and promotes neurogenesis. These neuroprotective effects after lithium and VPA coadministration contribute to behavioral improvement and prolong the lifespan of transgenic HD mice. Lines with solid arrows represent stimulatory connections; lines with flattened ends represent inhibitory connections. Dashed lines represent pathways with reduced activity as a result of combined treatment.

VPA has been suggested as a rational choice as a neuroleptic therapy in HD treatment (Tremolizzo et al., 2007). A case study showed that VPA dose-dependently improved myoclonic hyperkinesia in eight patients with HD (Saft et al., 2006). When given in combination with olanzapine, VPA at the lowest effective dose (60–80 μg/ml in plasma) also appeared to be beneficial for relieving both psychosis and movement symptoms in patients with HD (Grove et al., 2000).

Other reports showed that lithium had no beneficial effects in patients with HD (Aminoff and Marshall, 1974; Vestergaard et al., 1977). In some instances, lithium treatment, particularly when used as the sole therapeutic agent, even worsened motor and cognitive performance (Carman et al., 1974; Leonard et al., 1974). VPA has also been reported to have no beneficial effects (Symington et al., 1978) or to lead to a state of tolerance (Tan et al., 1976) on involuntary movements in patients with HD. In these ancient trials reporting no effect, however, the patient samples were small and the duration of drug treatment was short. Large-scale new clinical trials with long treatment duration are necessary to resolve these discrepancies and assess the potential benefits of using mood-stabilizing drugs to treat HD. Lithium and VPA are already FDA-approved medications with a long history of safe use in humans, and in light of results from recent promising preclinical studies, combined treatment with lithium and VPA or other neuroprotective drugs is recommended for future clinical investigation. Because the symptoms of this disease are devastating and worsen progressively without remission until death, the potential effects on behaviors may significantly improve quality of life for individuals with HD and their caregivers.

D. AD

In 2011, AD affected an estimated 5.4 million Americans and was the sixth leading cause of death. Clinically, it is characterized by progressive memory loss, personality changes, and ultimately, dementia. There is essentially no treatment available to arrest or reverse the deterioration of neurons in AD, although the FDA has approved five drugs that can temporarily slow disease progression (Tariot et al., 2011). The pathogenesis of AD is not well understood; however, the accumulation of Aβ in the brain is believed to be the primary cause (Hardy and Selkoe, 2002). This neuropathological hallmark of AD presumably results from an imbalance between Aβ production and clearance. The hyperphosphorylation of tau, a microtubule-binding protein (Selkoe, 2001), has also been implicated in the early development of neurofibrillary pathology (tauopathies) associated with AD and other neurodegenerative diseases (Lee et al., 2001; Planel et al., 2001).

Therefore, in the treatment of AD, Aβ accumulation and tau hyperphosphorylation are the primary treatment targets. It is well-established that GSK-3 acts as an Aβ production regulator (Phiel et al., 2003; Su et al.,

2004; Rockenstein et al., 2007) and a tau kinase (Hanger et al., 1992; Lovestone et al., 1994; Brownlees et al., 1997). Because abnormal increases in GSK-3 levels and activity are associated with pathogenesis and neuronal death in the brain of individuals with AD (Munoz-Montano et al., 1999; Bhat et al., 2004), the mood stabilizers lithium and VPA, which have been shown to inhibit GSK-3, could have potential therapeutic use in treating this disorder.

1. Effects of Mood Stabilizers on GSK-3 Inhibition in AD Models. Aβ peptide is derived from APP by sequential secretase-dependent proteolytic processing. Through GSK-3 inhibition, chronic treatment with lithium or VPA has been reported to block Aβ production. For example, chronic lithium treatment was found to block Aβ accumulation in the brains of mice overproducing APP (Phiel et al., 2003), presumably by interfering with the reaction of γ-secretase. As discussed in section III.B.1, lithium could also decrease Aβ burden by inhibiting APP processing through BACE-1 inhibition in the brain of TBI mice (Yu et al., 2012b). Although this effect of lithium in vitro was mimicked by transfection with siRNA of GSK-3α but not GSK-3β (Phiel et al., 2003), other in vitro and in vivo studies found that GSK-3β inhibition also mimicked the ability of lithium or VPA to suppress the process of Aβ formation from APP (Su et al., 2002, 2004; Qing et al., 2008). A recent study in an adult-onset *Drosophila* model of AD demonstrated a novel mechanism, whereby GSK-3 directly regulated Aβ42 levels in the absence of any effects on APP processing (Sofola et al., 2010).

By inhibiting GSK-3, moreover, lithium has been demonstrated, both in vivo and in vitro, to reduce tau phosphorylation (Hong et al., 1997; Munoz-Montano et al., 1997; Sang et al., 2001). In transgenic mouse models of AD, chronic lithium treatment decreased mutant tau protein aggregation (Perez et al., 2003) and arrested the development of neurofibrillary tangles (Leroy et al., 2010). In mouse models of tauopathies, chronic lithium treatment not only inhibited tau phosphorylation and neuronal degeneration mediated by GSK-3 (Noble et al., 2005), but also promoted ubiquitination, thereby decreasing tau-induced lesions (Nakashima et al., 2005). In addition to GSK-3, tau phosphorylation was also regulated by PP2A (Tanaka et al., 1998). It has been reported that the activity of PP2A is reduced in the brain of individuals with AD (Trojanowski and Lee, 1995). PP2A inhibition prevented tau dephosphorylation, a process that precedes and is required for tau cleavage and degradation (Rametti et al., 2004). In cultured cortical neurons, lithium was found to down-regulate tau transcription (Rametti et al., 2008). In the rat brain, lithium treatment not only increased PP2A activity (Tsuji et al., 2003), but also decreased tau phosphorylation, which in turn, facilitated tau destruction (Rametti et al., 2004). Finally, the fact that blockade of PP2A activity in cultured neurons reversed lithium-induced down-regulation of total tau proteins mediated by GSK-3β inhibition (Martin et al., 2009) suggests that PP2A is involved in lithium's action.

2. Effects of Mood Stabilizers on Other Molecular Targets in AD Models. In addition to inhibiting GSK-3, lithium and VPA have other protective effects relevant to the pathogenesis of AD. In hippocampal slices, lithium treatment prevents acetylcholinesterase-promoted Aβ toxicity and associated loss of function of Wnt signaling components (Inestrosa et al., 2000). By rescuing β-catenin levels in rat brains, long-term lithium treatment was found to be neuroprotective against Aβ-induced hippocampal neurodegeneration (De Ferrari et al., 2003). It was also found that induction of Dickkopf protein 1 (DKK1), a Wnt pathway inhibitor (Krupnik et al., 1999), was associated with neurodegeneration in the brains of individuals with AD (Caricasole et al., 2004). Researchers demonstrated that, in the CA1 region of the rat hippocampus, systemic administration of lithium reversed local infusion of DKK1-induced neuronal cell death and astrocytosis (Scali et al., 2006). Lithium has further been shown to protect against Aβ-induced ER stress and the subsequent activation of caspases and NF-κB in the hippocampus of rabbits (Ghribi et al., 2003). This effect presumably comes from the induction of the chaperone protein GRP78 (Hiroi et al., 2005), as discussed in section II.E.2.

VPA, on the other hand, has been shown to enhance microglial phagocytosis of Aβ in vitro (Smith et al., 2010). In human astrocytes, moreover, VPA (but not lithium) has been shown to act as a potent inducer of clusterin expression and secretion (Nuutinen et al., 2010). Clusterin is a small, HSP-like molecular chaperone, in which secretion is induced by stress. Expression of clusterin is increased in AD (May et al., 1990); it is present in neuritic plaques and binds to and enhances the clearance of Aβ in the brain (Nuutinen et al., 2009). VPA's ability to induce clusterin expression and secretion is therefore a distinct protective mechanism. Chronic lithium treatment also largely suppressed exogenous Aβ-induced downregulation of Bcl-2 and neuronal death in vitro (Hong et al., 1997; Alvarez et al., 1999, 2002; Wei et al., 2000). Of note, Bcl-2 protein levels in the brains of a mouse model of AD were inversely correlated with miR-34a expression (Guan et al., 2009), a miRNA that has recently emerged as a common target for lithium and VPA (Zhou et al., 2009). These findings suggest that miRNA regulation may be a novel mechanism for the protective effects of these mood stabilizers in AD.

3. Effects of Mood Stabilizers on Recovery of Cognitive Function in AD Models. In *Drosophila* models of tauopathies, lithium is known to reverse axonal transport and locomotor deficits by inhibiting

GSK-3β (Mudher et al., 2004). In normal healthy rats, long-term lithium treatment improved learning and memory (Nocjar et al., 2007), and it ameliorated spatial learning deficits in rats injected with preformed Aβ fibrils (De Ferrari et al., 2003). By inhibiting GSK-3β signaling, lithium treatment of 3 months also reduced Aβ burden and tau hyperphosphorylation, prevented neurodegeneration in the cortex and hippocampus, and normalized memory deficits in transgenic mice overexpressing human APP (Rockenstein et al., 2007).

Because dysregulation of histone acetylation is also implicated in the memory impairment and pathogenesis of neurodegenerative diseases, using HDAC inhibitors to control the elevation of histone acetylation could be another novel approach for the treatment of memory deficits in AD. HDAC2 is known to negatively regulate memory formation and synaptic plasticity (Guan et al., 2009), and its expression has been found to be increased in experimental AD models and patients (Graff et al., 2012). In a mouse model of neurodegeneration, shRNA-induced knockdown of HDAC2 restored structural and synaptic plasticity and abolished memory impairments (Graff et al., 2012). In transgenic AD mice, relatively low doses of the HDAC inhibitor VPA significantly reduced the formation of neuritic plaques and improved memory deficits (Qing et al., 2008). In animal models of this disease, moreover, injections of other HDAC inhibitors (such as SB, phenylbutyrate, or vorinostat) completely restored contextual memory (Kilgore et al., 2010; Ricobaraza et al., 2012). A recent study using SB in AD mice indicated, in fact, that HDAC inhibitors may be therapeutically beneficial even when administered at an advanced stage of the disease (Govindarajan et al., 2011). In contrast, another preclinical animal study showed that, although administering a low dose of VPA (30 mg/kg) at a later stage could affect neuropathological changes, cognitive deficits could only be reduced by early intervention; this effect was attributed to GSK-3 inhibition (Qing et al., 2008). The role of HDAC inhibition in this low-dose VPA-induced effect requires further investigation.

4. Clinical Trials of Lithium and VPA Treatment in AD. The use of lithium and VPA in the treatment of AD has already been investigated clinically. Studies of individuals with BD found that patients with a history of lithium treatment had significantly better cognition and memory scores than did patients receiving other treatments (Terao et al., 2006). Long-term lithium treatment was also found to reduce the prevalence of AD in older patients with BD (Nunes et al., 2007). A 10-year Danish study reported that patients receiving continued lithium treatment had a reduced rate of dementia, compared with those who received only one prescription of lithium, and this rate was equal to that in the general population (Kessing et al., 2008); it should be noted, however, that the study did not specify the indication for the lithium prespcription. In addition, a recent study showed that long-term treatment (12 months) with lithium (0.25−0.5 mM) decreased phospho-tau levels in CSF and improved cognitive performance on the AD Assessment Scale (Forlenza et al., 2011). Moreover, lithium tolerability was excellent, with a 91% adherence rate. In contrast, a trial in which 33 patients with AD received 10 weeks of lithium treatment reported no effect on GSK-3 activity or cognitive performance (Hampel et al., 2009), and other studies with small samples and short duration have similarly reported no therapeutic effect of lithium treatment in patients with AD (Brinkman et al., 1984; Macdonald et al., 2008).

As with lithium, VPA clinical trials conducted on patients with AD have produced mixed results. A recent case study suggested that low-dose divalproex may reduce the risk of adverse effects and led to behavioral improvement in patients with AD with agitation (Dolder and McKinsey, 2010). A 10-week safety and tolerability study with a sample of 20 outpatients with probable AD revealed that the maximum tolerated dosage of divalproex sodium was $<$1000 mg/day, whereas the most common adverse effects were sleepiness and tiredness (Profenno et al., 2005). In patients with mild to moderate AD, divalproex treatment (10–12 mg/kg/day) did not delay the emergence of agitation and cognitive impairment and, more alarmingly, was found to accelerate brain volume loss with significant toxic effects (Tariot et al., 2011). VPA treatment was also found to be ineffective for the management of agitation and aggression in older patients with moderate to severe AD (Herrmann et al., 2007). Of note, most of these reports used fixed doses and had few data on VPA's effects on the pathogenesis or neuropathology of AD. Taken together, these preliminary results suggest that studies with longer treatment phases and larger groups of patient with AD are needed to observe the potential benefits of lithium. With regard to potential improvement of pathologic and cognitive impairments, VPA treatment should be administered with flexible dosing and in the early stages of AD.

E. ALS

ALS is an adult-onset neurodegenerative disease characterized by progressive loss of motor neurons in the motor cortex and spinal cord, resulting in generalized weakness, muscle atrophy, paralysis, and death within five years after disease onset (Rowland, 1994). Damage to surrounding glial cells, muscle cells, interneurons, and Renshaw inhibitory neurons have also been reported, in addition to the loss of motor neurons (Boillee et al., 2006; Dobrowolny et al., 2008; Fornai et al., 2008). Most ALS cases occur sporadically, with no family history of the disease (Boillee et al., 2006; Wijesekera and Leigh, 2009). Sporadic and

autosomal-dominant familial forms of ALS are, however, clinically similar. Approximately 20% of familial ALS is attributed to gain-of-function mutations in the gene encoding Cu/Zn superoxide dismutase 1 (SOD1), a key antioxidant enzyme (Rosen et al., 1993; Andersen and Al-Chalabi, 2011). Mice expressing mutant Cu/Zn SOD1 exhibit ALS-like phenotypes, including premature death, behavioral abnormalities, and the formation of intracellular aggregates of SOD1 in the brain and spinal cord.

1. Effects of Lithium Treatment in ALS. Lithium's neuroprotective mechanisms have been suggested as a possible treatment of ALS, particularly because upregulation of GSK-3β, hyperphosphorylation of β-catenin (Yang et al., 2008) and downregulation of VEGF and its receptors (Brockington et al., 2006) have all been identified in postmortem tissue samples from patients with ALS. As described above, lithium treatment increased the expression of VEGF, a growth factor that has been shown to prolong survival in ALS mice (Wang et al., 2007), and to protect motor neurons against excitotoxicity (Tolosa et al., 2008). In organotypic slice cultures of spinal cord, long-term treatment with lithium dose-dependently inhibited the GSK-3β signaling pathway and, thereby, prevented excitotoxic cell death of motor neurons (Caldero et al., 2010). Treatment with lithium alone or in conjunction with an antioxidant also improved motor function and slowed disease progression in a mouse model of ALS (Shin et al., 2007; Fornai et al., 2008; Ferrucci et al., 2010). Because defective autophagy has been found in diseased motor neurons (Venkatachalam et al., 2008), the autophagy-inducing properties of lithium are also believed to contribute to its protective effects in ALS (Fornai et al., 2008; Fulceri et al., 2011). However, one recent study in a female mouse ALS model found that lithium had no beneficial or neuroprotective effects (Pizzasegola et al., 2009). Although differences in sex and the genetic background of the mice cannot be excluded, the remarkably low serum steady-state lithium level (0.05–0.07 mM) found in these female mice from the latter study may account for this discrepancy.

2. Effects of VPA Treatment in ALS. Alteration in the gene that encodes the survival motor neuron (SMN) protein is responsible for spinal muscular atrophy (SMA) (Lefebvre et al., 1995). This gene is present as two homologous copies in the human genome: the telomeric *SMN1* and the centromeric *SMN2*. Homozygous deletion or point mutation of *SMN1* causes SMA, whereas differential copy numbers of *SMN2* modulate the phenotype of this disease (Rochette et al., 1997; Gavrilov et al., 1998). Of interest, abnormal copy numbers of *SMN1* (single and triple) have been implicated as a risk factor in sporadic ALS (Corcia et al., 2002, 2006, 2009; Blauw et al., 2012).

Although the roles of *SMN2* were reported to be inconclusive (Veldink et al., 2001; Blauw et al., 2012; Corcia et al., 2012), genetic studies suggest that SMN expression helps to modify disease severity in both SOD1 mouse models (Kunst et al., 2000) and patients with sporadic ALS (Veldink et al., 2001). Lower *SMN2* copy numbers and lower SMN protein levels were found to be associated with an increased susceptibility to and severity of ALS (Turner et al., 2009; Veldink et al., 2005). In SMA fibroblast cultures, VPA administration activated *SMN2* transcription, modulated the expression of splicing factors (Harahap et al., 2012), and increased the expression of SMN protein (Sumner et al., 2003). The upregulated level of SMN protein has also been shown to depend on the number of *SMN2* copies (Brichta et al., 2003). Although further exploration is required, these results suggest that VPA may have therapeutic potential in the treatment of ALS.

In ALS mice, CREB-binding protein, a transcriptional coactivator with histone acetyltransferase activity, was specifically reduced in motor neurons of the lumbar spinal cord. Consistently, decreased histone acetylation levels were observed in degenerating motor neurons (Rouaux et al., 2003). Numerous studies have reported the beneficial effects of HDAC inhibitors on different aspects of neurodegeneration (Guo et al., 2009). Although results are inconsistent in ALS mice, treatment with VPA maintained histone acetylation in the spinal cord, restored CREB-binding protein levels in motor neurons, and slowed the degeneration of motor neurons (Rouaux et al., 2007; Crochemore et al., 2009). Although treatment with VPA was found to protect motor neurons against glutamate toxicity in an organotypic culture of spinal cord and, in one study, prolonged lifespan in a G93A mouse model of ALS (Sugai et al., 2004), another study using the same mouse model found that long-term dietary VPA administration protected motor neurons but did not significantly affect lifespan (Crochemore et al., 2009).

3. Clinical Trials of Lithium and VPA Treatment in ALS. Although results from the aforementioned preclinical studies raise the possibility that lithium and VPA have putative utility for the treatment of ALS, clinical trials of these mood stabilizers have, to date, provided controversial results. A 15-month pilot clinical trial in randomized patients with ALS found that, when compared with matched control patients treated with riluzole alone, cotreatment with riluzole and lithium markedly reduced mortality (Fornai et al., 2008). However, another randomized, double-blind, controlled clinical trial found that this combined treatment did not slow the progression of sporadic ALS more than riluzole plus placebo (Aggarwal et al., 2010). In a sibling-matched, sex-balanced, investigator-blinded trial, long-term lithium treatment was found to be ineffective on any treatment measure (Gill et al., 2009). Three of the latest trials also refute any beneficial effect of lithium treatment in patients with ALS (Chio et al., 2010; Miller et al., 2011; Verstraete et al., 2012), and a randomized sequential trial using

a fixed dose of VPA found it to be equally ineffective in patients with ALS (Piepers et al., 2009).

Because of these disappointing results, future independent and competitive trials may not be conducted (de Carvalho and Pinto, 2011). Nevertheless, preclinical studies in ALS mice suggest that combined treatment with lithium and VPA produces a greater and more consistent effect in delaying the onset of disease symptoms, decreasing neurologic deficit scores and prolonging lifespan, compared with monotherapy with either drug (Feng et al., 2008). As with HD, this preclinical evidence encourages future clinical trials using this combined treatment, which may lead to potential additive or synergistic protective effects that may also reduce the required dosages of both drugs, thereby minimizing their adverse effects. We suggest that future trials be conducted with a larger number of subjects early in the disease course, longer duration of treatment, and various doses of drug to clarify treatment discrepancies and the efficacy of these mood stabilizers in ALS.

F. FXS

FXS is caused by a full mutation of the fragile X mental retardation-1 (*FMR1*) gene with an abnormal expansion of more than 200 CGG repeats within the gene promoter (Verkerk et al., 1991). This expansion triggers hypermethylation of cytosines in the CpGs of the gene and hypoacetylation of associated histones, resulting in transcriptional silencing of *FMR1* (Verkerk et al., 1991; Sutcliffe et al., 1992; Hornstra et al., 1993). This gene encodes the fragile X mental retardation protein (FMRP), an RNA-binding protein that negatively regulates translation at synapses (Garber et al., 2006).

FXS is the most common inherited single-gene disorder associated with mental retardation. Patients with FXS exhibit cognitive impairments, seizures, hyperactivity, and autistic behaviors. Another significant problem for many affected young individuals is symptomatic attention deficit hyperactivity disorder (Baumgardner et al., 1995). The discovery of this autism-related gene led to the development of FMRP knockout animals, which not only serve as animal models of FXS but have also improved our understanding of the pathophysiological mechanisms of autism (Hagerman et al., 2005). No cure presently exists for FXS; current medical treatments are focused on behavioral improvement.

1. Therapeutic Potential of Lithium Treatment in FXS. It has been suggested that the absence of FMRP in the brain of individuals with FXS enhances the activation of the metabotropic glutamate receptor (mGluR), which results in long-term depression (Bear et al., 2004; Dolen et al., 2007). If so, the use of mGluR antagonists may prove to be effective for treating this disorder. In a *Drosophila* model of FXS that measured naive and conditioned courtship behaviors after treatment, mGluR antagonists were found to rescue both behavioral and cognitive deficits (McBride et al., 2005). Lithium treatment, which modulates signaling in a manner similar to mGluR antagonists, also increased naive courtship and restored short-term memory in FXS flies (McBride et al., 2005). A later study further found that treatment with mGluR antagonists or lithium effectively prevented age-related cognitive impairments in this *Drosophila* model of FXS (Choi et al., 2010).

In the brain of FXS mice, the inhibitory serine-phosphorylation of GSK-3 was found to be impaired (Min et al., 2009, 2010). Although levels of this GSK-3 phosphorylation can be increased by 2-methyl-6-phenylethynyl-pyridine (MPEP), an mGluR5 antagonist (Min et al., 2009; Mines et al., 2010), the combination of an mGluR5 antagonist with a GSK-3 inhibitor did not produce additive therapeutic effects in FXS mice (Min et al., 2009). These findings suggest that GSK-3 is the fundamental component of FXS pathology and indicate that GSK-3 is a potential therapeutic target. In fact, recent studies using mouse models of FXS demonstrated that lithium, a potent GSK-3 inhibitor, may be therapeutically useful for treating the disease (Mines and Jope, 2011). These studies showed that, in FXS mouse models, lithium treatment not only corrected hypophosphorylation of GSK-3 but also ameliorated aberrant dendritic spine morphology, deficient social interactions, and impaired learning ability (Min et al., 2009, 2010; Liu et al., 2011). In addition, the increased rate of cerebral protein synthesis observed in FXS mice, presumably a consequence of FMRP deficiency, was also significantly reversed by long-term lithium treatment (Liu et al., 2012b). Consistent with preclinical findings, lithium treatment in a pilot clinical study showed positive effects on behavior, adaptive skills, and cognitive measures in 15 FXS patients aged 6–23 years (Berry-Kravis et al., 2008).

2. Therapeutic Potential of VPA Treatment in FXS. Increasing histone acetylation has been identified as an epigenetic alteration to facilitate gene transcription. In cells from normal individuals, *FMR1* was associated with acetylated histone H3 and H4, whereas in the cells of patients with FXS, reduced acetylation was observed (Coffee et al., 1999). Because the loss of transcriptional activity of *FMR1* appears to be the major cause of FXS, pharmacological reactivation of this gene may serve as a possible therapeutic approach. As both a mood stabilizer and HDAC inhibitor, VPA may have dual beneficial effects in FXS: ameliorating behavior and reactivating *FMR1*.

Treatment of Fragile X cells with 5-aza-2-deoxycytidine, a DNA demethylating agent, resulted in reassociation of acetylated histone H3 and H4 with *FMR1* promoter and transcriptional reactivation (Tabolacci et al., 2005). In addition, a clinical study found that

treatment with L-acetylcarnitine, which regulates *FMR1* activity (possibly via increased histone acetylation; Tabolacci et al., 2005), effectively ameliorated the symptoms of attention deficit hyperactivity disorder in children with FXS (Torrioli et al., 2008). VPA alone was found to produce only modest reactivation of *FMR1* in different FXS lymphoblastoid cell lines (Tabolacci et al., 2008) and had no effect on DNA demethylation. Of note, the effect of VPA on reactivation of the *FMR1* gene in other types of tissue may be varied and still remains unclear. In addition, VPA has already been proven to be an effective treatment of behavioral and psychiatric symptoms in patients with autism or FXS (Sovner, 1989; Hagerman et al., 1999; Torrioli et al., 2010). For these reasons, using VPA to treat FXS cannot be excluded, although further research on its basic mechanisms is needed.

IV. Limitations for Lithium and VPA Treatment

As the aforementioned evidence suggests, lithium and VPA have tremendous potential for the treatment of a variety of CNS and neurodegenerative disorders. Nevertheless, their use is associated with numerous concerns relating to toxicity, teratogenicity, dosing, patient age, comorbidites, and patient stability, and these must be addressed.

The toxicity of lithium was recently and systematically reviewed by McKnight and colleagues (2012). This review examined 385 studies (from the 1950s to the present) and included 33 studies examining renal function, 77 studies examining thyroid function, 60 studies examining parathyroid function, 24 studies examining hair, 77 studies examining skin, 55 studies examining weight, and 62 studies examining teratogenicity (McKnight et al., 2012). The main conclusions drawn from this comprehensive meta-analysis were that lithium increased the risk of polyuria, hypothyroidism, hyperparathyroidism, and weight gain; of surprise, little clinical support was found for the notion that lithium significantly impaired renal function in most patients (0.53% in patients treated with lithium, compared with 0.2% in the general population). The review also concluded that the risk of teratogenicity in infants exposed to lithium was not significantly different when compared with control subjects; however, there is still some uncertainty of risk to women who wish to become pregnant, suggesting that patients, in conjunction with their doctors, must balance these risks between harm to the infant and maternal mental health before continuing or discontinuing lithium treatment.

The review also noted that acute lithium toxicity (doses above 1.2 mM) did occur, particularly in patients made susceptible after surgery, renal failure, heart failure, or even severe illness resulting in diarrhea and vomiting. Therefore, to avoid lithium toxicity, monitoring serum lithium levels every three months is recommended, along with daily dosing rather than multiple daily dosing (Malhi and Tanious, 2011). Among the potential limitations of this exhaustive review are as follows: 1) lack of many long-term randomized or controlled cohort studies, 2) relatively small sample sizes, 3) lithium doses considered to be mainly in therapeutic range (0.4–1.0 mM) rather than at concentrations of toxicity (above 1.2 mM), 4) incomplete dosing information reported, 5) exclusion of patients with a history of lithium toxicity or sparse information to monitor these individuals and evaluate their clinical response to lithium treatment, and 6) tendency for a high dropout rate in important cohort studies, with little information regarding the cause of removal from the study. Even with these limitations, the authors provide an extensive systematic quantification of the potential risks associated with lithium treatment.

For current recommendations on optimal plasma lithium levels (0.4–1.0 mM) in treating BD and the risks associated with lithium treatment, the interested reader is referred to a practical guide (Malhi et al., 2011). These authors developed a lithiumeter, a visual scale for optimal lithium plasma levels for the treatment of BD. Future investigations may develop this scale further to assess optimal lithium plasma levels in combination therapies with VPA and also for dosing considerations based on factors, such as patients' comorbidities, age, and sex. Although a careful study showing efficacy, tolerability, and safety of lithium in older patients with BD is currently unavailable, a recent review reported that lithium use in late-life BD was not only effective in treating manic and depressive symptoms, it also provided the benefit of reducing cognitive impairment and suicide rates (D'Souza et al., 2011). However, caution is warranted when monitoring dosing in older patients, because lithium plasma and brain levels do not correlate in older patients in the same manner as in younger patients (Forester et al., 2009). Moreover, higher brain lithium levels were found to correlate with both frontal lobe dysfunction and increased depressive symptoms in older adults with BD.

VPA toxicity was also recently reviewed (Chateauvieux et al., 2010). Adverse effects after treatment included weight gain (Grosso et al., 2009; Wirrell, 2003), decreased reproductive potential (Isojarvi, 2008; Verrotti et al., 2011), and a three-fold increase in birth defects (spina bifida, anencephaly, cardiac defects, dysmorphic features, valproate syndrome, and craniofacial, skeletal, or limb defects) (Clayton-Smith and Donnai, 1995; Genton et al., 2006; Ornoy, 2009). In a recent review surveying drug treatments for mood disorders during pregnancy, it was reported that the use of VPA, in addition to chlorimipramine, paroxetine, and atypical antipsychotics, should be avoided (Gentile, 2011); in contrast, lithium was associated with no significant teratogenic risks, making it

potentially appropriate for treating pregnant patients (Gentile, 2012).

Additional adverse effects from VPA treatment include decreasing IQ in children after fetal exposure (Bromley et al., 2009; Meador et al., 2009) and some neurologic adverse effects (inducing ischemic stroke and exacerbating epilepsy) (Buechler and Buchhalter, 2007; Varoglu, 2009). The studies correlating VPA treatment with neurologic adverse effects were case reports and require additional randomized and controlled studies to substantiate these potential risks in a larger sample size. There have also been reports of hepatotoxicity and hematopoietic damage (thrombocytopenia, platelet dysfunction, factor XIII deficiency, hypofibrinogenemia, and vitamin K-dependent factor deficiency) after VPA treatment (Koenig et al., 2006; McFarland et al., 2008). Of interest, lithium was suggested to be used in treating hematopoietic deficits via increasing colony-stimulating factor (reviewed in Focosi et al., 2009). VPA was also reported to increase prevalence of von Wilbrant disease (Serdaroglu et al., 2002; Koenig et al., 2008), a coagulation abnormality presenting with increased bleeding tendency in the form of easy bruising, nosebleeds, and bleeding gums, and a nine-fold increase in aplastic anemia (Handoko et al., 2006), a condition in which a patient has lower red blood cells, white blood cells, and platelets because of bone marrow not producing sufficient new cells. Clearly, precautions are warranted with both lithium and VPA treatments, and the risks must be weighed against the benefits.

A final consideration of the limitations on these two drugs to develop them into successful clinical treatments beyond BD is the lack of financial incentive for unpatentable drugs. This is based on problems with the current patent-based drug development process. Currently, market demand and novelty are rewarded over the reduction in global disease burden. A revised disease burden incentive system would reward actual performance of a new drug based on reducing the number of patients with a specific disease or improving quality of life (Barton and Emanuel, 2005). Without imposing monetary incentives to favor such a prize-based system that focuses on the social value of health benefits to inspire drug innovation (Gandjour and Chernyak, 2011), developing these unpatentable therapies will prove to be difficult where large-scale randomized trials are required to determine efficacy and tolerability.

V. Conclusions and Future Directions

The past decade has seen remarkable growth in our understanding of the mechanisms of action of lithium and VPA. In vitro studies have revealed that both of these mood-stabilizing drugs have robust neuroprotective effects against glutamate-induced excitotoxicity and a number of other insults in experimental settings. In diverse preclinical animal models of CNS disorders (including stroke, HD, AD, ALS, and others), lithium and VPA have also been shown to improve behavioral and cognitive performance, suppress neurodegeneration and neuroinflammation, enhance neurogenesis and angiogenesis, and prolong cell survival. When considering these drugs' therapeutic potential, it is advisable to address common mechanisms that may underlie these benefits and thwart disease pathology.

Characterizing the unifying mechanisms that are common to different diseases will provide clear targets for facilitating beneficial effects across diverse CNS disorders. This review focused on GSK-3 and HDAC, two primary targets of lithium and VPA, respectively, in which dysregulation has been implicated in diverse neuropathological conditions. Although both drugs induce neuroprotective and neurotrophic effects, they use different molecular signaling pathways to regulate transcriptional activation of cell survival signaling cascades, oxidative stress pathways, protein quality control mechanisms, and numerous other beneficial effects. In promoting cell survival, lithium and VPA appear to affect many different downstream molecules (such as the neurotrophins BDNF and GDNF and angiogenic VEGF) and anti-apoptotic proteins (such as HSP70, Bcl-2, and Bcl-xl). In promoting cellular plasticity and resiliency, lithium and VPA affect similar downstream molecules, such as BDNF and Bcl-2; however, the associated changes in physiologic function are different from that of promoting cell survival mechanisms. These differences may provide critical distinctions between impaired cellular plasticity and different phases of neurodegeneration and cell death when treating diverse CNS indications.

Further investigation is clearly warranted to establish the core cellular and molecular disturbances that characterize the degree of impaired cellular plasticity and neurodegeneration and ultimately determine the associated changes in physiologic function (e.g., presymptomatic, early, and late symptoms) that lead to disease. This type of careful characterization will allow for personalized treatments to be timed for specific disease stages to slow or halt the progression from impaired cellular resilience to a breakdown in the maintenance of cellular integrity. In addition to timing treatment, combing the use of effective and specific risk biomarkers (genetic, molecular, cellular, and neuroimaging based) may prove to be helpful for paving the way for personalize medicine by targeting at-risk individuals before symptoms arise. Additional considerations may include targeting specific cell types and CNS regions. Keeping in mind these numerous considerations and the limitations associated with both agents, long-term clinical trials on a large scale are now warranted to repurpose lithium and VPA for therapeutic use in diverse new indications, ranging from stroke to neurodegenerative diseases.

In this respect, it is important to reiterate that in some experimental conditions in which treatment with lithium or VPA alone was either ineffective or only marginally beneficial, enhanced neuroprotection was observed as a result of cotreatment with both agents. This augmented neuroprotection was associated with potentiating GSK-3 inhibition and may involve particular miRNA mechanisms currently under investigation, although understanding the precise underlying mechanisms in detail will require future study. The benefits of cotreatment also extend to enhancing MSC migration via the upregulation of MMP-9 and CXCR4 by lithium and VPA, respectively. In addition, in transgenic mouse models of ALS and HD, cotreatment with lithium and VPA more robustly and consistently delayed disease syndrome progression, decreased behavioral deficits, and increased lifespan. These preclinical studies confirmed that using lithium and VPA together is a rational strategy with significant potential for treating neurodegenerative and neurologic diseases; indeed, we speculate that combination treatment may more effectively enhance neurotrophic and neuroprotective mechanisms. Future studies are required to confirm this hypothesis and to identify common targets to discover new treatment opportunities. Furthermore, despite their long history of safe clinical use, both lithium and VPA have adverse effects, especially at high doses. However, future clinical investigations that combine treatment with VPA and lithium could thus use lower doses of both drugs, which would reduce undesirable adverse effects and still achieve enhanced therapeutic actions.

In view of the many recent findings summarized above, we expect that future studies will shed considerable new light on how to more effectively target the mechanisms contributing to neurologic and neurodegenerative pathologies. New avenues of research into mechanisms mediated by miRNAs, for instance, are expected to reveal another layer of regulatory control and identify network nodes capable of modulating multiple signaling cascades. Validating miRNAs involved in fundamental disease processes (neuroinflammation, BBB integrity, and apoptosis) may also lead to the development of novel and more efficacious treatments capable of regulating multiple signaling networks. Finally, we predict that identifying the mechanisms regulated by lithium and VPA will steer genetic studies to identify susceptibility and protective genes for both neurologic and neurodegenerative diseases in which miRNA-mediated mechanisms may provide one of the unifying links among patient treatment response, therapeutic targets, and genetics.

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