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Molecular actions and therapeutic potential of lithium in preclinical and clinical studies of CNS disorders

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Abstract

Lithium has been used clinically to treat bipolar disorder for over half a century, and remains a fundamental pharmacological therapy for patients with this illness. Although lithium's therapeutic mechanisms are not fully understood, substantial *in vitro* and *in vivo* evidence suggests that it has neuroprotective/neurotrophic properties against various insults, and considerable clinical potential for the treatment of several neurodegenerative conditions. Evidence from pharmacological and gene manipulation studies support the notion that glycogen synthase kinase-3 inhibition and induction of brain-derived neurotrophic factor-mediated signaling are lithium's main mechanisms of action, leading to enhanced cell survival pathways and alteration of a wide variety of downstream effectors. By inhibiting *N*-methyl-D-aspartate receptor-mediated calcium influx, lithium also contributes to calcium homeostasis and suppresses calcium-dependent activation of pro-apoptotic signaling pathways. In addition, lithium decreases inositol 1,4,5-trisphosphate by inhibiting phosphoinositol phosphatases, a process recently identified as a novel mechanism for inducing autophagy. Through these mechanisms, therapeutic doses of lithium have been demonstrated to defend neuronal cells against diverse forms of death insults and to improve behavioral as well as cognitive deficits in various animal models of neurodegenerative diseases, including stroke, amyotrophic lateral sclerosis, fragile X syndrome, as well as Huntington's, Alzheimer's, and Parkinson's diseases, among others. Several clinical trials are also underway to assess the therapeutic effects of lithium for treating these disorders. This article reviews the most recent findings regarding the potential targets involved in lithium's neuroprotective effects, and the implication of these findings for the treatment of a variety of diseases.

Keywords

apoptosis; brain-derived neurotrophic factor (BDNF); glycogen synthase kinase 3 (GSK-3); lithium; neurodegenerative diseases; neuroprotection

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1. Introduction

Lithium, a monovalent cation, has been the standard pharmacological treatment for bipolar disorder (BD) for more than 60 years. It remains recommended by many treatment guidelines as the first-line treatment against acute mania, and prophylactically for recurrent manic and depressive episodes. Clinically, lithium has been used adjunctively with other mood stabilizers, antidepressants, and antipsychotic medications to facilitate, enhance, or prolong both treatment response and remission (Goodwin, 2003; Lin et al., 2006). Lithium also has strong anti-suicidal properties (Tondo & Baldessarini, 2009). The clearance of lithium is exclusively dependent on renal excretion as a free ion and is considered to be decreased with aging (Grandjean & Aubry, 2009). Although lithium has a narrow therapeutic margin and well-known adverse effects, it is safe to use in the therapeutic dose range. Several minor side effects may occur at serum levels of lithium ranging from 0.6 to 1.2 mEq/L that have been demonstrated to be efficacious in the treatment of BD (Moscovich, 1993; Speirs & Hirsch, 1978). Symptoms associated with serum levels above 1.5 mEq/L are generally mild, including tremor, nausea, diarrhea, vertigo, and confusion (American Psychiatric Association, 2002). Nonetheless, lithium levels at 1.2 mM or higher in the plasma rarely cause persistent neurological deficits (Chen et al., 2004b). Lithium does not appear to be carcinogenic or mutagenic, but may lead to renal and liver damage at prolonged exposures to serum levels of 2 mM or more (American Psychiatric Association, 2002; Gould et al., 2003; Mazlo et al., 1983). Patients may experience more severe neurological complications such as seizures, coma, cardiac dysrrhythmia, and permanent neurological impairment with plasma levels of lithium greater than 2.5 mEq/L (American Psychiatric Association, 2002). Therefore, regular monitoring of serum concentrations is essential, particularly in elderly patients with lower clearance or preexisting neurological illness, to ensure optimal clinical efficacy and minimal adverse effects.

Given its long history of clinical use (Jope, 1999a), multiple actions associated with lithium's mood stabilizing effects have been recognized; nevertheless, the precise underlying biochemical mechanisms of this drug remain poorly defined. In addition, clinical use of lithium for the treatment of BD has declined in recent years due to its narrow therapeutic range and to the availability of alternative medications. However, the last decade has also seen significant attention focused on lithium's neurotrophic and neuroprotective effects. Loosely defined, *neurotrophic effects* encompass therapeutic strategies intended to augment proliferation, differentiation, growth, and regeneration. In contrast, *neuroprotective effects* are defined as those that halt or slow the progression of neuronal atrophy or cell death following the onset of insult or disease. Indeed, due to lithium's remarkable neuroprotective and neurotrophic properties, considerable research has been conducted on its efficacy as a novel therapeutic in various disease models.

Lithium is the lightest of all metals, with a density only half that of water. It induces multiple biochemical and molecular effects on neurotransmitter receptor-mediated signaling, signal transduction cascades, hormonal and circadian regulation, ion transport, and gene expression. These effects have been widely associated with the activation of neurotrophic pathways, and neuroprotection has been the most expected and replicated biological effect associated with lithium use in both human and preclinical studies. Growing evidence suggests that lithium has neuroprotective effects against a variety of insults, including glutamate-induced excitotoxicity, ischemia-induced neuronal damage, and other neurodegenerative conditions. Lithium's beneficial effects normally require long-term treatment to become evident, and are not immediately reversed after discontinuation of the drug. Therefore, it has been suggested that the therapeutic actions of lithium may involve signaling pathway and gene expression alterations in the central nervous system (CNS). In fact, recent research has recognized prominent molecular and cellular targets associated with

lithium's neuroprotective effects. These include its ability to inhibit intracellular signaling kinases and phosphatases, to protect against apoptosis induced by a variety of insults in cultured neurons and neurally related cell lines, to affect transcriptional activity and gene expression, and to promote cell proliferation and likely neurogenesis in the CNS. This article reviews the most recent findings regarding these potential targets involved in lithium's neuroprotective effects, and the implication of these findings for the treatment of a variety of diseases. Lithium is already FDA-approved for the treatment of BD; our conclusions support the notion that its clinical relevance can be expanded to include the treatment of several neurological and neurodegenerative-related diseases.

2. Mechanisms of lithium's neuroprotective actions

2.1 Lithium as a multi-functional neuroprotectant

Initial hypotheses that lithium has neuroprotective and neurotrophic effects were based on observations that chronic lithium treatment at therapeutic concentrations increases m3-muscarinic acetylcholine receptor-mediated second messenger production and c-Fos and m3-receptor expression in cultured rat cerebellar granule cells (CGCs) (Gao et al., 1993). In addition, lithium also increases the activity of two prominent transcription factors—activator protein-1 (AP-1) and cyclic AMP-response element binding protein (CREB)—in the same CGC cultures and in distinct brain areas (e.g., frontal cortex, amygdala, hippocampus, and cerebellum) of rats (Ozaki & Chuang, 1997). Although AP-1 activation may be either anti-apoptotic or pro-apoptotic depending on the nature of AP-1 binding components and the target genes induced (Karin, 1998; Mummery, 1975), it has been suggested that m3-muscarinic receptors and the DNA binding activities of AP-1 and CREB play prominent roles in regulating cell viability. Earlier pioneering studies noted that lithium promotes survival of gamma aminobutyric acid-releasing (GABAergic) neurons (Volonte et al., 1994) and mature CGCs (D'Mello et al., 1994), and accumulating evidence from various laboratories supports the view that lithium protects against diverse forms of death insults, suggesting that it is a multifunctional neuroprotectant.

Glutamate-induced excitotoxicity in discrete brain areas has been implicated in a variety of neurodegenerative diseases such as stroke, Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), brain trauma, cerebellar degeneration, spinal cord injury, and possibly Alzheimer's disease (AD) and Parkinson's disease (PD) (Friedlander, 2003; Mattson & Kroemer, 2003; Yuan & Yankner, 2000). Therefore, the neuroprotective effects of lithium against glutamate-induced excitotoxicity have been extensively studied in various cellular and animal models. In addition to glutamate excitotoxicity, lithium can also protect against other forms of insults in CNS neurons and neurally related cell lines (Chuang, 2004; 2005; Chuang et al., 2002; Chuang & Priller, 2006; Rowe & Chuang, 2004; Rowe et al., 2007). For example, lithium also protects against endoplasmic reticulum (ER) stress (Chen et al., 1999; Hiroi et al., 2005). The ER is the primary site for protein synthesis, folding, and trafficking. It also acts as an intracellular calcium repository and regulates calcium signaling. The ER is highly sensitive to perturbation of its intralumenal environment, and ER dysfunction has been linked to impaired synaptic plasticity and pathophysiology of diseases such as BD (Hough et al., 1999), AD (Mattson et al., 2000), and cerebral ischemia (Mattson et al., 2000). Thus, the neuroprotective effects of mood stabilizers against ER stress may also be clinically relevant.

The pathogenesis of a number of diseases involves aberrant cell death processes (Chuang et al., 2005; Ekshyyan & Aw, 2004). Cell death can occur via two morphologically distinct processes: apoptosis and necrosis. Increasing lines of evidence support the notion that excessive cell death may be involved in certain forms of neuropsychiatric illness and multiple forms of neurodegenerative diseases, such as stroke, AD, HD, and PD (Mattson,

2006; Shacka & Roth, 2005). In cultured neurons and neurally related cell lines, lithium has been shown to have neuroprotective effects against apoptosis induced by a variety of insults such as growth factor withdrawal (Bhat et al., 2000), β-amyloid (Aβ) (Alvarez et al., 2002), colchicine (Jorda et al., 2004; 2005), high potassium deprivation (D'Mello et al., 1994), heat shock exposure (Bijur et al., 2000), and supra-therapeutic concentrations of anticonvulsants (phenytoin and carbamazepine) (Nonaka et al., 1998b), in addition to glutamate-induced excitotoxicity. Figure 1 illustrates the proposed multiple signaling pathways and mechanisms of actions involved in the neuroprotective effects of this drug.

2.2 Inositol depletion

The cleavage of membrane inositol phospholipids, particularly phosphatidylinositol 4,5-bisphosphate (PIP_2) into diacylglycerol and inositol 1,4,5-trisphosphate (IP_3), is necessary for cell surface G protein-coupled receptors, as well as certain receptor tyrosine kinases, to convey signals intracellularly (Berridge et al., 1989; Fisher et al., 1987; Phiel & Klein, 2001). At therapeutic concentrations, lithium is a powerful inhibitor of various phosphoinositol phosphatases involved in inositol phosphate metabolism, such as inositol polyphosphate 1-phosphatase (IPPase) and inositol monophosphatase (IMPase) (Berridge et al., 1989; Gould et al., 2004c; Quiroz et al., 2004; Sherman et al., 1986). Accordingly, lithium blocks the recycle of inositol for the re-synthesis of inositol phospholipids (Fig. 2). This inhibitory action of lithium on inositol phosphate metabolism has led to the inositol depletion hypothesis of lithium's action, which posits that lithium's therapeutic effects may result from interfering with IP_3-mediated cell signaling caused by inositol depletion (Berridge et al., 1989). Via this inositol depletion mechanism, lithium was indeed found to inhibit the collapse of sensory growth cones in cultured sensory neurons and to increase these cone area (Williams et al., 2002); it was also found to suppress pilocarpine-induced reciprocal hind limb scratching in mice (Martinez & Raffa, 2002). Although several experiments found that the neuroprotective effects of lithium could not be mimicked by other potent IMPase inhibitors or prevented by excess inositol (Centeno et al., 1998; Nonaka et al., 1998a; 1998b), the ability of lithium to deplete free inositol was recently identified as a novel pathway for inducing autophagy (see section 2.11 below).

2.3 Inhibition of NMDA receptor-mediated signaling

Glutamate-induced excitotoxicity was found to be mediated by *N*-methyl-D-aspartate (NMDA) receptors, and was robustly reduced by chronic lithium treatment in cultured CNS neurons including rat CGCs, cerebral cortical, and hippocampal neurons (Nonaka et al., 1998a), partly via the inhibition of NMDA receptor-mediated calcium influx. This long-lasting neuroprotective effect, occurring at therapeutically relevant concentrations of lithium ($EC_{50} \approx 1$ mM), is time-dependent and requires six to seven days of pretreatment for maximum efficacy. This neuroprotection is also specific to lithium, since other monovalent ions including rubidium and cesium, as well as classic antidepressants such as imipramine, desipramine, clomipramine, and fluoxetine are ineffective (Hashimoto et al., 2002a). Furthermore, these neuroprotective effects appears to occur independently of lithium's inhibition of IMPase, given that co-addition of excessive myo-inositol fails to reverse lithium's neuroprotective effects (Nonaka et al., 1998b).

Levels of Tyr1472-phosphorylation of the NR2B subunit are positively correlated with NMDA receptor-mediated synaptic activity and excitotoxicity. Studies indicate that the mechanism of action underlying lithium's ability to inhibit NMDA receptor-mediated calcium influx results from the attenuation of constitutive phosphorylation at Tyr1472 of the NR2B subunit of the NMDA receptor, which is catalyzed by Fyn, a member of the Src tyrosine kinase family (Hashimoto et al., 2002a; 2003a). Neither total tyrosine protein kinase activity nor that of tyrosine protein phosphatase is affected by this drug, indicating the

selectivity of the modulation and its contribution to neuroprotection. In addition, lithium has also been shown to reduce excitotoxicity-related brain damage following ischemic events. Brain ischemia increases Src-mediated tyrosine phosphorylation of NR2A (Liu et al., 2001; Takagi et al., 1997), and the interaction of NR2A with Src and Fyn, which is mediated by postsynaptic density protein 95 (PSD-95) (Hou et al., 2002). Lithium blocks both the ischemia-induced increases in NR2A phosphorylation and PSD-95 interaction (Ma & Zhang, 2003). This suggests that chronic lithium treatment may be beneficial in treating brain damage induced by hypoxic insult. However, glutamate-induced excitotoxicity in cultured cortical neurons, that is diminished by treatment with either lithium or MK-801, can be blocked only partially by a Src kinase inhibitor, SU6656 (Hashimoto et al., 2003a). Lithium's neuroprotective effects against glutamate excitotoxicity also involve the blockade of apoptotic components and will be discussed in the following section (see section 2.4).

2.4 Anti-apoptotic actions

2.4.1 Suppression of the JNK/p38 MAP kinase pathways—The c-Jun N-terminal kinase (JNK) and p38 mitogen-activated protein (MAP) kinase are activated by site-specific phosphorylation in response to a variety of apoptotic insults (Mielke & Herdegen, 2000). These two kinases often act synergistically to enhance the DNA binding activity of AP-1, a dimeric transcription factor consisting of the Jun, Fos, CREB, and ATF subunits (Shaulian & Karin, 2002; Whitmarsh & Davis, 1996). AP-1 is also activated by a wide variety of stress factors and other cellular signals. Glutamate-induced, NMDA receptor-mediated apoptotic death in cultured rat CGCs requires the activation of both JNK and p38 MAP kinase, subsequently leading to a robust increase in AP-1 binding before apoptotic death (Chen et al., 2003). These glutamate-induced signaling events and apoptosis are prevented by long-term (seven days) treatment with therapeutic concentrations of lithium (0.5-2 mM) (Chen et al., 2003).

2.4.2 Downregulation of pro-apoptotic p53, Bax, caspase, and cytochrome c release—In cultured rat CGCs, glutamate-induced downregulation of the cytoprotective B-cell lymphoma/leukemia-2 (Bcl-2) protein and upregulation of pro-apoptotic proteins such as p53 and Bax are concentration-dependently reversed by long-term, but not acute, lithium pretreatment (Chen & Chuang, 1999). Studies using p53 inhibitors have implicated p53 in neuronal death induced by Aβ, ischemic and excitotoxic insults, and *N*-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a neurotoxin commonly used to reproduce PD-like phenotypes in animals (Culmsee et al., 2001; Duan et al., 2002). Glutamate exposure also triggers the release of cytochrome *c* from the mitochondria into the cytosol. Lithium pretreatment blocks glutamate-induced cytochrome *c* release and cleavage of lamin B1, a nuclear substrate for caspase-3 (Chen & Chuang, 1999). These results suggest that lithium-induced downregulation of p53 and Bax plays a prominent role in neuroprotection against excitotoxicity.

2.4.3 Inhibition of calpain/Cdk5 pathway—Cyclin-dependent kinase 5 (Cdk5), a serine/threonine kinase essential for brain development, is the only cyclin-dependent kinase not related to cell cycle regulation (Nguyen et al., 2002). Cdk5 also regulates NMDA receptor-mediated signaling by direct phosphorylation of the NR2B subunit or indirectly through phosphorylation of PSD-95 (Morabito et al., 2004; Zhang et al., 2008). Cdk5 activity is primarily regulated by its co-activator p35. However, when it binds to p25, the product of calpain-mediated cleavage of p35, Cdk5 will become pro-apoptotic and its activity becomes dysregulated (Camins et al., 2006; Lee et al., 2000; Patrick et al., 1999). Calpain is a non-lysosomal calcium-dependent intracellular cysteine protease, and uncontrolled calpain activity has been implicated in an increasing number of pathological conditions including ischemic brain injury, AD, multiple sclerosis, and PD (Camins et al.,

2009; Wang, 2000). Accordingly, p25 accumulation was observed in neurons in response to glutamate or oxidative stress, and in the brain of several animal models of neurodegenerative diseases. In addition, sustained activation of Cdk5 in neurons is believed to be involved in many neurodegenerative diseases (Cruz & Tsai, 2004; Dhariwala & Rajadhyaksha, 2008). In cultured rat CGCs, lithium pretreatment prevents colchicine-induced apoptosis and associated increases in Cdk5 expression and p35 to p25 fragmentation (Jorda et al., 2005).

In addition, intracellular calcium increase, calpain activity, Cdk5 activation, and cellular death induced by 3-nitropropionic acid (3-NP), a succinate dehydrogenase inhibitor used to induce striatal pathology similar to that observed in HD (Brouillet et al., 1999), are also reduced by pretreatment with lithium in cultured primary brain neurons (Crespo-Biel et al., 2009). In rats, lithium treatment reduces 3-NP-induced striatal neurodegeneration by preventing calpain activation and subsequent increases in Cdk5 activity (Crespo-Biel et al., 2009). These results indicate that calpain and Cdk5 are involved in lithium's neuroprotective effects, and suggest that this drug is a good alternative for modulating calpain action in different pathological disorders (Camins et al., 2009).

2.5 Induction of survival pathways

Apoptosis is also regulated by survival signaling pathways. Stimulation of cell-surface trophic factor receptors such as tyrosine receptor kinase B (TrkB), the receptor of brain-derived neurotrophic factor (BDNF) (Huang & Reichardt, 2003), insulin, and other growth factors, activates multiple survival pathways including the phosphoinositide 3-kinases (PI3K)/Akt pathway (Brunet et al., 2001; Franke et al., 2003) and the MAP kinase kinase (MEK)/extracellular-signal regulated kinase (ERK) pathway (Chang et al., 2003; Segal & Greenberg, 1996).

2.5.1 The PI3K/Akt pathway—Akt is a serine/threonine kinase regulated by PI3K-mediated signaling. Activation of Akt involves phosphorylation at residues of Thr308 and Ser473 (Alessi & Cohen, 1998; Jacinto et al., 2006). In cultured rat CGCs, lithium treatment rapidly normalizes glutamate-induced inactivation of Akt by activating PI3K and subsequently increasing the phosphorylation of Akt at Ser473 (Chalecka-Franaszek & Chuang, 1999). In turn, activated Akt affects on several anti-apoptotic targets including Bcl-2 associated death promoter (BAD) (a Bcl-2 family member), CREB, members of the forkhead family, and procaspase 9 (Huang & Reichardt, 2003; Neri et al., 2002; Nicholson & Anderson, 2002). In addition, this pathway also mediates the indirect inhibitory effects of lithium on glycogen synthase kinase-3 (GSK-3) isoform α through enhanced Ser21 phosphorylation (Chalecka-Franaszek & Chuang, 1999) (see section 2.6 and Fig. 3). However, the effects of lithium on the PI3K/Akt pathway may be cell-type-specific and time-dependent, as some studies in certain cell lines detected no changes in Akt phosphorylation levels at specific time points following lithium application (De Sarno et al., 2002; Zhang et al., 2003a).

2.5.2 The MEK/ERK pathway—The second signaling pathway affected by lithium is the MEK/ERK pathway. ERK regulates several effector systems such as the NF-κB pathway, and ribosomal S6 kinase (RSK) that in turn activates CREB and inhibits GSK-3β (Chang et al., 2003; Steelman et al., 2004). CREB, a transcription factor involved in learning and memory, plays a major role in mediating adaptive responses at glutamatergic synapses and cell survival by promoting the expression of cell-protective proteins such as BDNF and Bcl-2 (Finkbeiner, 2000). In CGCs, toxic concentrations (≥ 50 μM) of glutamate induce a rapid increase in MEK activity and NMDA receptor-dependent decreases in CREB phosphorylation at Ser133, as well as CREB-driven transcriptional activity (Kopnisky et al.,

2003); these latter processes are mediated by protein phosphatase 1. Commensurate with its neuroprotective effects, long-term but not acute lithium treatment potentiates glutamate-induced increases in MEK activity and suppresses glutamate-induced dephosphorylation of CREB, presumably by inhibiting protein phosphatase 1 as well as promoting MEK/ERK activity. It should be noted that lithium's effects on the MEK/ERK pathway may also be cell-type-specific, as lithium has been reported to have opposite effects on this pathway in different types of neural cells (Pardo et al., 2003).

2.6 Inhibition of GSK-3

GSK-3, a serine/threonine protein kinase, is a down-stream mediator of signaling pathways induced by various stimuli and is involved in a diverse array of cellular functions. In general, GSK-3 is pro-apoptotic and considered to be constitutively active under non-stimulated basal conditions. Growing evidence in the literature also indicates that GSK-3 is a major regulator of inflammation. Dysfunction of this enzyme has been implicated in the pathophysiology of mood disorders, schizophrenia, AD, diabetes, cancer, inflammatory and autoimmune diseases, among others (Beurel et al., 2010; Huang & Klein, 2006; Jope et al., 2007; Meijer et al., 2004). GSK-3 is evolutionarily conserved, with α and β isoforms. The main structural differences between them lie in the N- and C-terminal regions, while their sequences within the kinase domain are highly homologous. GSK-3 inhibition has recently attracted widespread attention as one of the critical therapeutic targets whereby lithium exerts its effects on mood stabilization, neurogenesis, neurotrophicity, neuroprotection, anti-inflammation, and others (Beurel et al., 2010; Rowe & Chuang, 2004; Rowe et al., 2007).

GSK-3 activity is regulated by a wide variety of kinases and systems including Akt, protein kinase A (PKA), protein kinase C (PKC), MAP kinases, and the Wnt pathway. Phosphorylation of GSK-3 α/β at a specific 21/9 serine residue negatively regulates its activity, while phosphorylation at a specific 279/216 tyrosine residue positively regulates its activity (Jope, 2003; Yukimasa et al., 2001). As a competitive inhibitor of magnesium, lithium was found to directly inhibit the adenosine triphosphate (ATP)-magnesium-dependent catalytic activity of GSK-3 (Klein & Melton, 1996; Ryves & Harwood, 2001; Stambolic et al., 1996) (Fig. 3). At concentrations similar to those in human plasma after therapeutic administration, lithium also indirectly inhibits GSK-3 activity through enhanced phosphorylation of GSK-3α at Ser21 and GSK-3β at Ser9. Multiple mechanisms have been identified which contribute to this effect, including the involvement of the 3′,5′-cyclic adenosine monophosphate (cAMP)-dependent activation of PKA (Jope, 1999a; 1999b), PI3K-dependent activation of PKC (Kirshenboim et al., 2004), and Akt (Chalecka-Franaszek & Chuang, 1999), as well as the auto-regulation resulting from enhanced inhibition of protein phosphatase-l through the action of inhibitor-2 complex (Zhang et al., 2003a). In general, lithium raises basal levels, but suppresses stimulus-induced increases, in cAMP and PKA activity. This bimodal action has been proposed as the biochemical basis underlying lithium's antidepressant and antimanic efficacy (Jope, 1999b).

Moreover, β-arrestin 2 (βArr2), a scaffolding protein associated with receptor desensitization and the termination of G protein-coupled receptor signaling (Ferguson et al., 1996; Lohse et al., 1989), is essential for regulating the Akt/GSK-3 signaling cascade (Beaulieu et al., 2005; 2007), and plays an important role in the expression of behavioral responses to drugs acting on dopamine neurotransmission (Beaulieu et al., 2005; Gainetdinov et al., 2004). In response to the stimulation of the dopamine D_2 receptor, Akt can be dephosphorylated/inactivated by the formation of a complex composed with βArr2 and protein phosphatase 2A (PP2A), consequently resulting in the concomitant activation of GSK-3β (Beaulieu et al., 2005). By disrupting this βArr2 signaling complex, lithium was found to indirectly inhibit GSK-3 by activated Akt and induce behavioral changes associated with GSK-3 inhibition in mice (Beaulieu et al., 2008). Moreover, recent studies have

discovered that lithium has novel effects on GSK-3 regulation. For example, GSK-3β transcription can be decreased by lithium treatment *in vitro* and *in vivo* (Mendes et al., 2009). In addition, the kinase activity of GSK-3 can be upregulated through its N-terminal cleavage by calpain (Goni-Oliver et al., 2007), a calcium dependent protease that is negatively regulated by lithium as described above.

Because GSK-3 activation has been linked to apoptotic cell death induced by multiple insults including glutamate excitotoxicity (Grimes & Jope, 2001), lithium's inhibition of GSK-3 undoubtedly constitutes part of the molecular mechanisms underlying its neuroprotective effects. Isoform-specific small interfering RNAs (siRNAs) that selectively silence the expression of targeted GSK-3 have recently been designed to distinguish the functional and regulatory differences between these two GSK-3 isoforms (Liang & Chuang, 2007). In cultured rat cerebral cortical neurons, RNA interference-induced depletion of either isoform is sufficient to block glutamate-induced excitotoxicity. Moreover, transfection with isoform-specific dominant-negative mutants of GSK-3 or treatment with other non-selective pharmacological GSK-3 inhibitors mimics lithium-induced neuroprotection against glutamate excitotoxicity. Although GSK-3α and GSK-3β may have distinct roles in transcriptional regulation and cell survival (Liang & Chuang, 2006; 2007), these results strongly suggest that both isoforms of GSK-3 are involved in the execution of glutamate-induced neuronal death and that both isoforms are initial targets of lithium-induced neuroprotection. However, the development of GSK-3 isoform-specific inhibitors remains crucial for therapeutic interventions in GSK-3-related neuropathological conditions and reductions of unwanted side effects.

Substrates phosphorylated by GSK-3 include metabolic, signaling, and structural proteins as well as transcription factors. The DNA binding activity of AP-1 is also reduced by GSK-3β-dependent phosphorylation of c-Jun (Boyle et al., 1991). Dysfunction of GSK-3-mediated phosphorylation of transcription factors is believed to be related to the pathophysiology of various pathological conditions. Inhibition of GSK-3 leads to activation of cell-survival transcription factors such as CREB, AP-1, β-catenin, heat-shock factor-1 (HSF-1) (Bijur & Jope, 2000), and inhibition of pro-apoptotic factors such as p53 (Grimes & Jope, 2001; Jope, 2003; Jope & Roh, 2006). Many of these effector systems in turn regulate members of the Bcl-2 protein family, thus serving as an intersection between survival and death receptors. Pharmacological inhibition of GSK-3 is also likely involved in the antidepressant and antimanic effects of lithium observed in rodent models (Beaulieu et al., 2004; Gould et al., 2004b; Kaidanovich-Beilin et al., 2004; O'Brien et al., 2004), whereas overexpression of this kinase in mice produces behavioral correlates of hyperactivity and mania (Prickaerts et al., 2006). These findings suggest GSK-3 as the therapeutic target of lithium in BD treatment (see section 3.1).

2.7 Stabilizing β-catenin

The transcription factor β-catenin is a substrate of GSK-3 and is part of the Wnt pathway. Its cytoplasmic levels are negatively regulated by constitutively active GSK-3 as described above. After being phosphorylated by GSK-3, β-catenin undergoes proteasomal degradation (Jope & Johnson, 2004; Takahashi-Yanaga & Sasaguri, 2007). Increases in cytoplasmic accumulations of β-catenin facilitate its translocation into the nucleus and, in conjunction with T-cell-specific transcription factor (Tcf)/lymphoid enhancer binding factor (Lef), subsequently enhance the transcription of diverse genes such as growth factors (Silva et al., 2007; Sinha et al., 2005), and those involved in apoptotic inhibition (Feng, 1979; Huelsken & Behrens, 2002; Seidensticker & Behrens, 2000).

As a result, elevating β-catenin has been suggested as a novel therapeutic strategy for treating mood disorders. As expected, treatment with therapeutic concentrations of the

GSK-3 inhibitor lithium increases β-catenin levels both *in vitro* (Chen et al., 1999; Stambolic et al., 1996) and *in vivo* (Gould et al., 2004a; O'Brien et al., 2004), and promotes β-catenin-dependent transcriptional events (Jope & Johnson, 2004; Marmol, 2008; O'Brien et al., 2004). In addition, overexpression of β-catenin in mouse brain mimics the antidepressant-like effects of lithium (Gould et al., 2007), whereas knockdown of this protein in mice results in a depression-like phenotype (Gould et al., 2008). These results indicate that lithium-induced accumulation of β-catenin could be relevant to its neuroprotective and therapeutic effects.

2.8 Negative regulation of Smad3/4-dependent transcription

The transcription factor Smad3/4, a downstream mediator of the signaling pathway triggered by transforming growth factor-β (TGF-β) (Derynck & Zhang, 2003), plays a prominent role in regulating the expression of proteins involved in neuronal survival or death, differentiation, and synaptic plasticity (Gomes et al., 2005; Sanyal et al., 2004). The TGF-β signaling pathway has been implicated as a therapeutic target in neurodegeneration (Wyss-Coray, 2006). Smad3/4 was recently identified as a novel target for GSK-3 in neurons (Liang & Chuang, 2006). Using siRNA or dominant negative mutants specific to GSK-3 isoforms, GSK-3α inhibition was found to upregulate Smad3/4-dependent transactivation and protein levels of plasminogen activator inhibitor-1 (PAI-1), one of the Smad3/4-regulated protein targets (Liang et al., 2008); in contrast, GSK-3β inhibition downregulates the same processes (Liang & Chuang, 2006). Treating cultured cortical neurons with lithium at therapeutically relevant concentrations significantly decreases Smad3/4-dependent transactivation and protein levels of PAI-1 (Liang et al., 2008). Lithium's effects on Smad3/4 likely result from the cross-talk between CRE-dependent, cAMP/PKA, and PI3K/Akt/GSK-3β signaling pathways and depend on increased CREB activation and subsequent complex formation with p300 (Liang et al., 2008) (Fig. 4). This suppression of Smad3/4-dependent transactivation by lithium may be beneficial, because elevated levels of PAI-1 have been associated with the pathogenesis of mood disorders (Eskandari et al., 2005; Higgins, 2006; Tsai, 2006).

2.9 Altered AP-1 DNA binding activity

AP-1 activation can be either neuroprotective or neurodegenerative and in this regard plays a complex role in neuroprotection and apoptosis. As described above, DNA binding activity of the AP-1 complex can be positively or negatively regulated by the JNK/p38 pathway and GSK-3, respectively. Therefore, binding activity of AP-1 may be decreased via inhibition of the JNK/p38 pathway, and/or increased via inhibition of GSK-3 due to lithium treatment. Indeed, the fact that AP-1 can be either neuroprotective or neurodegenerative correlates well with evidence that lithium inhibits stimulus-induced AP-1 activity, but can also increase basal AP-1 activity (Asghari et al., 1998; Chen et al., 2003; Hiroi et al., 2005; Hongisto et al., 2003; Ozaki & Chuang, 1997; Song et al., 2002).

2.10 Induction of survival molecules

2.10.1 Bcl-2 upregulation—In contrast to pro-apoptotic proteins such as Bax and Bak, Bcl-2 is an anti-apoptotic protein that inhibits the release of cytochrome *c* from mitochondria by regulating the permeability of the mitochondrial outer membrane (Maiuri et al., 2007; Youle & Strasser, 2008). The ability to maintain calcium homeostasis in the ER is another cytoprotective action of Bcl-2 (He et al., 1997; Lam et al., 1994). Chronic lithium treatment has been found to induce Bcl-2 expression in the frontal cortex of rat brains (Chen et al., 1999) and in cultured CGCs (Chen et al., 1999; Chen & Chuang, 1999). In cultured neurons, lithium-induced Bcl-2 expression is paralleled by downregulation of the pro-apoptotic molecules p53 and Bax, and blockade of glutamate-induced cytochrome *c* release

as well as caspase activation (Chen & Chuang, 1999). In PC12 cells, chronic lithium-induced upregulation of Bcl-2 is closely associated with the cytoprotective effects of this drug against Aβ peptide (Chen et al., 1999; Wei et al., 2000) and thapsigargin-induced ER stress (Chen et al., 1999; Hiroi et al., 2005). Notably, gene transfer-mediated Bcl-2 overexpression has been shown to protect against thapsigargin-induced apoptosis in neuronal cell lines (Wei et al., 1998) and increase neuronal survival in various animal models of neurodegenerative diseases such as stroke (Kitagawa et al., 1998), AD (Rohn et al., 2008), PD (Offen et al., 1998; Vila et al., 2001), and HD (Zhang et al., 2003c). These results strongly suggest that lithium-induced Bcl-2 upregulation plays a prominent role in lithium's neuroprotective effects. It is interesting to note that chronic treatment with another mood stabilizing drug, valproate, a histone deacetylase inhibitor (Chuang et al., 2009; Gottlicher et al., 2001; Phiel et al., 2001) as well as an anticonvulsant drug that is often used in BD patients with poor response to lithium, also upregulates Bcl-2 in the brain of rats (Chen et al., 1999). MicroRNAs are 17-19 nucleotide non-protein coding RNAs that can inhibit the translation of their target genes. A recent study in SH-SY5Y cells shows that Bcl-2 translation is directly inhibited by the expression of a specific microRNA, miR-34a (Wang et al., 2009). Chronic treatment with lithium or valproate decreases the levels of several microRNAs in the hippocampus of rats as well as in the primary cultures of hippocampal neurons, including miR-34a (Zhou et al., 2009), suggesting a common regulator shared by these structurally dissimilar mood stabilizers and indicating a novel target for lithium's effects.

2.10.2 BDNF upregulation—BDNF, one of the major neurotrophins, is essential for cortical development, synaptic plasticity, and neuronal survival, and is likely one of the mediators of the clinical efficacy of antidepressants and anxiolytics (Manji et al., 2003; Woo & Lu, 2006). The necessity of protracted lithium pretreatment in order for maximum neuroprotective effects to become apparent suggests the involvement of gene expression. Indeed, long-term treatment of cultured cortical neurons with lithium induces BDNF; this, in turn, activates its receptor, TrkB, by increasing phosphorylation at the Tyr490 residue (Hashimoto et al., 2002b). Without altering the expression of TrkB, chronic treatment of rats with lithium also increases protein levels of BDNF in various brain regions (Fukumoto et al., 2001; Jacobsen & Mork, 2004).

Recent studies in cultured cortical neurons further reveal that treatment with lithium or valproate at therapeutic concentrations for 48 hours selectively increases the levels of exon IV (formerly rat exon III)-containing BDNF mRNA, and the activity of BDNF promoter IV (Yasuda et al., 2009). Notably, this effect can be mimicked by pharmacological inhibition of GSK-3 or siRNA-mediated gene silencing of either the GSK-3α or GSK-3β isoform. In addition, lithium-induced neuroprotection against excitotoxicity can be prevented by a Trk tyrosine kinase inhibitor, K252a, or by a neutralizing antibody against BDNF (Hashimoto et al., 2002b). Lithium's neuroprotective effects are also completely blocked by either heterozygous or homozygous knockout of the BDNF gene in cultured cortical neurons. Taken together, these results suggest that TrkB-stimulated upregulation of BDNF plays a central role in mediating many of the reported downstream effectors associated with lithium's neuroprotective effects. This trophic action is likely involved in lithium-induced activation of survival PI3K/Akt and MEK/ERK pathways as described above. Through phosphorylation, activation of CREB, a common downstream target of both pathways, increases the expression of BDNF (Finkbeiner, 2000). Moreover, the findings that BDNF-induced antidepressant-like effects are blocked by either K252a or a MEK inhibitor, U0126 (Shirayama et al., 2002), further support the involvement of TrkB-mediated activation of the MEK/ERK pathway.

One of the BDNF-regulated transcription factors is forkhead box class O3a (FoxO3a). FoxO3a is a member of the mammalian FoxO family and plays a prominent role in regulating cell fate, differentiation, survival, and stress response (Greer & Brunet, 2005). BDNF-dependent activation of PI3K and Akt leads to phosphorylation of FoxO3a, resulting in redistribution of the transcription factor from the nucleus to the cytosol and a loss of transcriptional activity (Brunet et al., 1999). Levels of active FoxO3a are increased in the brain after ischemia (Fukunaga et al., 2005). Chronic lithium treatment of mice with a therapeutically-relevant dose decreases FoxO3a protein levels in the hippocampus (Mao et al., 2007). Interestingly, FoxO3a protein levels are decreased in both cytosol and nucleus to reduce FoxO3a transcriptional activity via an Akt-dependent mechanism. In light of a more recent report noting that FoxO3a-deficient mice display antidepressant-like behaviors (Polter et al., 2009), it is possible that lithium-induced downregulation of FoxO3a might contribute to both its neuroprotective and mood stabilizing effects.

2.10.3 VEGF upregulation—Lithium treatment also increases the expression of vascular endothelial growth factor (VEGF) *in vitro* and *in vivo* (Du et al., 2009; Guo et al., 2009; Kaga et al., 2006; Silva et al., 2007), an effect that most likely occurs via inhibition of GSK-3β and stabilization of β-catenin signaling. VEGF is widely expressed throughout the CNS and can function as a potent angiogenic/neurotrophic factor for multiple types of neurally related cells including astrocytes (Heine et al., 2005), neurons (Kutcher et al., 2004), and neuronal progenitor cells (Maurer et al., 2003). VEGF has been shown to promote cell proliferation (Jin et al., 2002), proneuronal differentiation of newly born cells (Meng et al., 2006), migration of immature neuroblasts (Zhang et al., 2003b), and neurovascular remodeling after stroke (Chen et al., 2005; Kaga et al., 2006). By upregulating VEGF, lithium treatment optimizes skeletal myoblast functions for cellular cardiomyoplasty *in vitro* (Du et al., 2009), prevents stress-induced reductions in VEGF levels (Silva et al., 2007), and promotes angiogenic and anti-apoptotic signaling in rat ischemic preconditioned myocardium (Kaga et al., 2006). These data support the notion that VEGF plays a role in the neuroprotective actions of lithium.

2.10.4 HSP70 upregulation—Heat shock proteins (HSPs) are a group of molecular chaperones that promote protein folding as well as refolding of misfolded proteins, inhibit aggregate formation, and facilitate degradation of abnormally folded proteins through the ubiquitin-proteasome system (Fink, 1999; Hartl & Hayer-Hartl, 2002; Hendrick & Hartl, 1993; Ma & Hendershot, 2001). Indeed, the induction of HSPs that help restore cellular homeostasis is one of the important regulators of cellular survival in response to stress or to the accumulation of misfolded proteins in cells (Lindquist, 1986). Studies have found that among HSPs, HSP70 exerts a wide variety of neuroprotective effects against apoptosis (Takayama et al., 2003). These occur by antagonizing apoptosis-inducing factors (Ravagnan et al., 2001), inhibiting the activation of NF-κB by stabilizing IκB protein (Feinstein et al., 1996; Yenari & Han, 2006), stabilizing Akt-1 protein (Gao & Newton, 2002), preventing mitochondrial cytochrome *c* release and caspase activation (Beere et al., 2000), and suppressing JNK activation (Mosser et al., 2000). In various animal models, overexpression of HSP70 has been recognized as a potential therapeutic target against ischemic neuronal injury (Hoehn et al., 2001; Majda et al., 2001; Rajdev et al., 2000; Tsuchiya et al., 2003).

The expression of HSP70 is regulated by HSF-1 (Bijur & Jope, 2000), a transcription factor negatively regulated by GSK-3β-dependent phosphorylation (Chu et al., 1996). Both DNA binding activity of HSF-1 and HSF-1-dependent transcription are negatively correlated with GSK-3β activity (Bijur & Jope, 2000; Xavier et al., 2000). In light of the fact that lithium's inhibition of GSK-3 is associated with activation of HSF-1 (Bijur & Jope, 2000), upregulation of heat-shock response may be part of the neuroprotective mechanisms produced by lithium treatment. In fact, the neuroprotective effects of lithium in a stroke

model are 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).

2.10.5 GRP78 upregulation—The 78 kDa glucose-regulated protein (GRP78) is a molecular chaperone of the HSP70 family that binds to calcium and protects cells from the deleterious effects of misfolded proteins in the ER (Katayama et al., 1999; Kaufman, 1999; Yu et al., 1999). Various apoptotic insults, including the ER calcium-ATPase inhibitor thapsigargin, induce the expression of GRP78 mRNA (Aoki et al., 1997; He et al., 2000). It has been suggested that transcription factor c-Fos is involved in the induction of GRP78 by thapsigargin, and that the c-Fos-dependent induction is likely triggered by thapsigargin-induced release of calcium from the ER (He et al., 2000). c-Fos associates with c-Jun to form a heterodimeric AP-1 transcription factor complex that regulates the expression of a large number of genes. However, regulation of GRP78 expression via the AP-1 complex seems to be indirect, given that no recognizable AP-1 interacting sequence motifs are present in the GRP78 promoter (He et al., 2000).

Lithium has been shown to induce c-Fos expression, AP-1 binding activity (Gao et al., 1993; Kalasapudi et al., 1990; Ozaki & Chuang, 1997), and upregulation of GRP78 (Hiroi et al., 2005, Shao et al., 2006; Wang et al., 2001). In PC12 cells, protracted lithium pretreatment is cytoprotective against thapsigargin-induced cytotoxicity resulting from ER stress (Hiroi et al., 2005). This protection is concomitant with attenuation of thapsigargin-triggered intracellular calcium release and upregulation of c-Fos and GRP78. Lithium alone does not affect basal calcium levels, suggesting that distinct mechanisms are likely involved in its ability to trigger c-Fos and GRP78 induction. Valproate pretreatment also upregulates this ER stress protein (Bown et al., 2000; Hiroi et al., 2005; Wang et al., 1999; 2001), and induces similar protective effects against ER stress in PC12 cells (Hiroi et al., 2005) and oxidative damages in primary cultured rat cerebrocortical cells (Wang et al., 2003). In addition, lithium pretreatment reverses thapsigargin-induced downregulation of the anti-apoptotic protein Bcl-2. Lithium's cytoprotective effects against thapsigargin cytotoxicity are blocked by curcumin (Hiroi et al., 2005), an inhibitor of transcription factor AP-1; this suggests that induction of GRP78 and Bcl-2, as well as activation of AP-1, may contribute to lithium-induced protection against cytotoxicity resulting from ER stress.

2.10.6 tPA upregulation—Tissue-type plasminogen activator (tPA) is negatively regulated by PAI-1 (Wind et al., 2002), a Smad3/4-regulated protein target discussed in greater detail above (see section 2.8). The protein tPA is multifaceted, and believed to play multiple roles in the CNS, ranging from neural organization to the pathogenesis of brain disorders (Samson & Medcalf, 2006; Vivien & Ali, 2006). It is interesting to note that in the amygdala, tPA appears to be critical for stress-induced neuronal remodeling and for the development of anxiety-like behaviors that can subsequently be inhibited by PAI-1 (Pawlak et al., 2003). The tPA-plasminogen proteolytic cascade accelerates the clearance of fibrin and protects the brain from damage in stroke models, or when the blood-brain barrier breaks down (Akassoglou et al., 2003; Tabrizi et al., 1999); it also contributes to Aβ degradation (Melchor et al., 2003). These observations suggest that tPA may play a protective role in the neurodegenerative progression of AD.

In cultured cortical neurons, lithium increases protein levels of tPA by affecting PAI-1-dependent transcriptional suppression (Liang, M. H., & Chuang, D. M., unpublished observations). In addition, the neuroprotective effects of lithium against ER and oxidative stresses, induced respectively by thapsigargin and hydrogen peroxide, are also prevented by specific siRNA-induced tPA silencing. Conversely, exogenous or overexpression of tPA completely blocks the damaging effects of ER and oxidative stresses, but only weakly

suppresses the neuronal death induced by glutamate or staurosporine (Liang, M. H., & Chuang, D. M., unpublished observations). Together, these data demonstrate that tPA overexpression is critical to lithium-induced neuroprotection, especially protection against ER and oxidative stresses.

2.11 Induction of autophagy

Macroautophagy, usually referred to as autophagy, is a key physiological process for the bulk degradation of cytoplasmic proteins or organelles, and has recently been recognized as one of the principal responses to cellular stress as well as one of the important regulators of neuronal survival and function. The process of autophagy is initiated with the formation of double-membrane structures called autophagosomes that fuse with lysosomes to form autolysosomes and ultimately degrade their contents by lysosomal hydrolytic enzymes (Rubinsztein et al., 2007). Autophagy is responsible for the recycling of cytosolic components during normal conditions, as well as the recycling of nutrients necessary for cell survival under starvation conditions (Maiuri et al., 2007; Melendez & Neufeld, 2008). The autophagy-lysosomal pathway and the ubiquitin–proteasome system (UPS) are two major intracellular mechanisms for protein clearance against abnormal protein accumulation and damage to cytoplasmic organelles in eukaryotic cells. In general, short-lived proteins are predominantly degraded by proteasomes, whereas aggregation-prone proteins with long half-lives appear to be better substrates for autophagic-lysosomal degradation (Klionsky & Emr, 2000; Levine & Kroemer, 2008). Accordingly, this quality control function of autophagy is believed to be beneficial in several neurodegenerative disorders characterized by the accumulation of misfolded disease-causing proteins; these include AD, PD, ALS, spinocerebellar ataxia type 3, and HD (Berger et al., 2006; Cuervo, 2004; Levine & Kroemer, 2008; Nixon, 2005; Ravikumar et al., 2002; Ravikumar et al., 2004; Rubinsztein et al., 2007; Shibata et al., 2006; Webb et al., 2003).

Several signaling pathways and targets have been identified that regulate autophagy, including the mammalian target of rapamycin, mTOR, as a negative regulator. By inhibiting mTOR, rapamycin is currently the most suitable pharmacological agent for upregulating autophagy in mammalian cells, and has been shown to be beneficial in various models of neurodegenerative diseases (Berger et al., 2006; Ravikumar et al., 2004; Rubinsztein et al., 2007). In contrast to rapamycin which enhances autophagy, inhibition of GSK-3β downregulates autophagy by activating mTOR (Sarkar et al., 2008). Autophagy is also induced via mTOR-independent mechanisms. By inhibiting IMPase and inositol transporters (Phiel & Klein, 2001), the ability of lithium to deplete free inositol and subsequently decrease IP_3 levels was recently identified as a novel mTOR-independent route for inducing autophagy (Sarkar et al., 2005; Sarkar & Rubinsztein, 2006). Other mood stabilizers that decrease IP_3 levels, such as valproate and carbamazepine, can also induce autophagy (Sarkar et al., 2005).

Lithium independently inhibits both GSK-3β and IMPase. Interestingly, lithium inhibits IMPase at lower doses that induce autophagy (Ki ≈ 0.8 mM) (Sarkar et al., 2005); in contrast, it inhibits GSK-3β at higher doses that suppress autophagy (Ki ≈ 2 mM) (Stambolic et al., 1996). Nevertheless, induction of autophagy is considered a potential underlying mechanism of lithium that contributes to its neuroprotective effects. At therapeutic concentrations, lithium facilitates the clearance of known autophagy substrates such as mutant forms of huntingtin and α-synuclein (Sarkar et al., 2005), and induces clearance of protease-resistant prion protein in prion-infected cells (Heiseke et al., 2009). Lithium's autophagy-inducing properties have also been hypothesized to contribute to its protective effects in ALS (Fornai et al., 2008), and its use in combination with rapamycin has been proposed as a rational therapy in various models of HD (Sarkar et al., 2008). Given that lithium has been used clinically for decades to treat BD and is known to pass the blood-

brain barrier (Manji & Lenox, 1998), the autophagy induction properties of lithium—in addition to its other beneficial effects—underscore the potential clinical use of this drug in the treatment of neurodegenerative conditions associated with aggregate-prone proteins.

2.12 Induction of neurogenesis

Neurogenesis denotes the birth of progenitor cells that proliferate and differentiate into functional new neurons and, in turn, replace neurons in particular brain regions. This process is evident during development and continues into adulthood, and occurs particularly in the hippocampal dentate gyrus and olfactory bulb (Gage, 2000). Increasing evidence has indicated that several brain disorders are associated with reductions in volume of certain brain areas and the loss of neuronal cells. The proliferation of neuronal precursor cells is markedly enhanced by several growth factors, but attenuated by glutamate and glucocorticoids (Gage, 2000).

Lithium was found to stimulate progenitor proliferation in cultured brain neurons and to prevent the loss of proliferation induced by glutamate or glucocorticoids (Hashimoto et al., 2003b). In addition, chronic lithium treatment not only enhances neurogenesis in the hippocampus of normal mice (Chen et al., 2000), but also restores neurogenesis in the brain in an animal model of Down syndrome (Bianchi et al., 2009). Multiple mechanisms have been shown to mediate lithium's effects on neurogenesis. In primary rat hippocampal progenitor cultures, long-term lithium treatment promotes the conversion of these progenitors into neurons through the GSK-3β inhibition/β-catenin activation pathway (Boku et al., 2009; Wexler et al., 2008). In a rat model of stroke, chronic lithium treatment upregulates the generation and survival of newborn cells in the hippocampus by the ERK pathway, and improves the behavioral performance of rats after transient global cerebral ischemia (Yan et al., 2007a). Chronic lithium-induced hippocampal neurogenesis in the dentate gyrus of rats occurs independently of long-term potentiation (LTP). However, chronic lithium treatment only enhances neurogenesis in the brains of adult (Son et al., 2003), but not aged, rats (Yu et al., 2003). One possible common downstream event related to neurogenesis is lithium-induced upregulation of BDNF, which is necessary for hippocampal neurogenesis (Rossi et al., 2006). This ability of lithium to promote neurogenesis and reduce proliferation deficits induced by various insults suggests that lithium has profound neurophysiological significance for the treatment of neurodegenerative and neuropathological conditions.

3. Lithium in models of CNS disorders and its clinical implications and applications

3.1 Bipolar disorder (BD)

BD is a common and chronic mental illness characterized by mood cycling between states of mania and depression (Manji & Lenox, 1998), and is one of the major causes of disability worldwide (Manji et al., 2003; Zarate, Jr. et al., 2006). Because lithium has been the mainstay of treatment for this disorder, its neuroprotective effects may provide novel insights into the potential causes of this disease. For instance, it is interesting to note that, with very few exceptions, neuroprotection is a common feature of drugs prescribed to treat BD (Ketter et al., 2003; Li et al., 2002; Manji & Duman, 2001). Consistent with this view, magnetic resonance imaging (MRI) studies indicate lower levels of *N*-acetyl-asparate (NAA), a neuronal integrity marker, in the prefrontal cortex of individuals with BD (Brambilla et al., 2004; 2005). In addition, patients with BD showed neuronal atrophy and reduced cellular density, as well as reduced grey matter volume, in various brain regions (Chang et al., 2005b; Sassi et al., 2004). Notably, chronic lithium treatment was found to reduce the decrease in NAA levels and the loss of grey matter volume in the brains of

individuals with BD (Bearden et al., 2007; Chang et al., 2005a; 2005b; Chuang & Manji, 2007; Drevets, 2001; Manji et al., 2001; Moore et al., 2000a; 2000b). It should be noted that several species of microRNAs are common targets of lithium and valproate; these include let-7b, let-7c, miR-128a, miR-24a, miR-30c, miR-34a, miR-221, and miR-144 (Zhou et al., 2009). The predicted effectors of these microRNAs are involved in neurite outgrowth, neurogenesis, and signaling of ERK and Wnt/β-catenin pathways. Many of these effector-coding genes are also genetic risk factors for BD, suggesting that microRNAs and their predicted effectors are also targets of the action of mood stabilizers. These findings not only strongly imply that insufficient neuroprotection is relevant to the pathophysiology of BD, but also suggest that lithium's neuroprotective effects contribute to the multiple mechanisms underlying its therapeutic efficacy in treating this disease.

As mentioned earlier in section 2.6, inhibition of GSK-3 is also likely involved in the antidepressant and antimanic effects of lithium. For example, both lithium (Beaulieu et al., 2004) and selective GSK-3 inhibitor (Gould et al., 2004b) reduce hyperactivity, while overexpression of GSK-3β produces hyperactivity and mania-like behaviors in mice (Prickaerts et al., 2006). On the other hand, both lithium (O'Brien et al., 2004) and GSK-3 inhibitors (Kaidanovich-Beilin et al., 2004; Rosa et al., 2008) produce antidepressant-like effects in mice, and target deletion of GSK-3β gene to produce heterozygous GSK-3$\beta^{+/-}$ mice induces behavioral effects similar to the antidepressant-like effects of lithium (O'Brien et al., 2004). Inactivation of GSK-3β, using pharmacological or genetic approaches, alleviates the depressive behaviors in mice expressing a mutant form of the brain serotonin synthesis enzyme (Beaulieu et al., 2008). Administration of lentiviral-mediated GSK-3β shRNA into the dentate gyrus causes antidepressant-like effects in mice subjected to chronic stress (Omata et al., 2010). In addition to GSK-3β, genetic inactivation of the GSK-3α in mice also produces antidepressant-like behaviors such as decreased immobility time and reduced aggressive behavior (Kaidanovich-Beilin et al., 2009). A recent study further reveals that mice deficient in the inhibitory serine-phosphorylation of GSK-3 increases susceptibility to mood disturbances, and serine-phosphorylation of GSK-3 is reduced during both stress-related behavioral responses in wild-type mouse brain and in blood cells from patients with BD (Polter et al., 2010). It is interesting to note that, in addition to lithium, other compounds used to treat BD such as valproate and lamotrigine, also enhance serine phosphorylation of GSK-3 (Jope, 2003; Rowe et al., 2007). These findings not only support the hypothesis that inhibition of GSK-3 is the therapeutic target of lithium in the treatment of BD, but also indicate that targeting GSK-3-linked pathways is a rational strategy for developing novel therapeutics to treat this disorder.

3.2 Stroke

Stroke, the most common form of acute brain trauma, is a major global cause of disability and mortality in adults and the third leading cause of death in the United States. Most stroke cases are caused by the interruption of blood supply to the brain, *i.e*. cerebral ischemia. It is becoming increasingly clear that a large proportion these injuries are induced by excessive increases in extracellular glutamate in the brain following ischemia and subsequent overstimulation of glutamate receptors, notably NMDA receptors (Lipton, 1999). In addition, intracellular mechanisms such as inflammation, oxidative stress, calcium overloading, and caspase activation have also been identified as contributing to the neural damage induced by ischemia (White et al., 2000). Stroke is frequently associated with vascular depression and dementia that are difficult to treat with conventional medications and, unfortunately, no satisfactory treatments are available for preventing neural cell death and associated long-term neurological deficits in stroke victims.

The therapeutic potential of lithium has been investigated in various animal models of stroke. Long-term pretreatment with lithium has been reported to decrease infarct volume

and reduce neurological deficits not only in a model induced by permanent middle cerebral artery occlusion (MCAO) (Nonaka & Chuang, 1998), but also in transient MCAO models followed by reperfusion (Xu et al., 2003), which more closely approximates the pathophysiology of acute stroke. Mechanisms underlying lithium-induced neuroprotection are complex and may include inactivation of NMDA receptors (Ma & Zhang, 2003; Ma et al., 2004); reduction in apoptotic cell death (Xu et al., 2003) through downregulation of pro-apoptotic p53 but upregulation of anti-apoptotic Bcl-2 and HSP70 (Bian et al., 2007); activation of the PI3K/Akt cell survival pathway (Chalecka-Franaszek & Chuang, 1999); and inhibition of hypoxia-induced activation of GSK-3 (Roh et al., 2005). Studies in a gerbil model of global ischemia further demonstrate that the neuroprotection afforded by long-term lithium pretreatment is associated with an increase in viable cells and a decrease in apoptotic cells in the hippocampal CA1area, which in turn largely suppresses ischemia-induced behavior deficits and memory impairments (Bian et al., 2007). In rats after transient global cerebral ischemia, lithium facilitates hippocampal neurogenesis via the ERK pathway and improves the recovery of spatial learning as well as memory and behavioral deficits (Yan et al., 2007a; 2007b). Co-treatment with lithium also potentiates the anti-ischemic actions of prostaglandin A1 (Xu et al., 2006; 2007) and E1 (Han et al., 2008) by upregulating HSPs in rats subjected to permanent MCAO. Moreover, in an animal model of salt-loaded, stroke-prone spontaneously hypertensive rats, the addition of low-dose lithium to captopril prevents stroke and dramatically prolongs the effects of this angiotensin-converting enzyme inhibitor on survival through an effect independent of the reduction in blood pressure (Xu et al., 2005).

Two-day pretreatment with lithium was reported not to protect brain tissue against transient ischemia in gerbils (Yoshida et al., 1991), suggesting that long-term pretreatment is a prerequisite for lithium's protective effects. However, post-insult treatment with therapeutic doses of lithium (~1.0 mEq/kg of body weight, subcutaneously), when administered up to three hours after the onset of ischemia, also markedly decreases infarct volume and suppresses neurological deficits measured by sensory, motor, and reflex tests in a rat model of transient MCAO (Ren et al., 2003). These beneficial effects are associated with HSF-1 activation and induction of the cytoprotective protein HSP70 in ischemic brain hemispheres. Recently, the neurohemodynamic aspects of lithium-induced recovery were further investigated in this transient MCAO model using functional MRI. This study found that delayed chronic lithium treatment—administered up to 12 hours after the onset of ischemia and followed by daily injections for two weeks—significantly improves blood oxygenation level dependence functional MRI response magnitude and influences vascular formation (Kim et al., 2008). The ability of lithium to affect neurovascular remodeling may be related to its ability to increase protein levels of matrix metallopeptidase 9 (MMP-9) and VEGF (Guo et al., 2009); the latter has been linked to angiogenesis, neurogenesis, and neuroprotection (Fan & Yang, 2007).

Taken together, the benefits of lithium observed in various animal models of stroke suggest that lithium pretreatment might be advantageous in controlling conditions that carry a high risk of predictable stroke, such as cardiac surgery, carotid endarterectomy, and transient ischemic attack. In addition, and of equal importance, is the finding that post-insult treatment with lithium is also effective within a time frame during which it could realistically be administered to human victims. These results raise the possibility that lithium has putative utility as a clinical tool for both prevention and treatment of patients with acute stroke.

3.3 Huntington's disease (HD)

HD is an inherited autosomal dominant neurodegenerative disease characterized by progressive memory loss, cognitive decline, and psychiatric disturbances such as

aggressiveness and depression, in addition to the impaired movement that is the main feature of this disease (Martin & Gusella, 1986). HD leads to death about 10 to 20 years after the initial symptoms occur (Vonsattel & DiFiglia, 1998), and currently there is no proven treatment to arrest or reverse the course of this disease. HD belongs to the polyglutamine disorders family and is caused by an abnormal expansion of a trinucleotide CAG repeat in the gene that encodes a polyQ stretch to more than 35 glutamines in the N-terminus of the disease-causing protein termed huntingtin (MacDonald et al., 1993). This abnormal expansion results in a selective loss of neurons in the brain, particularly the medium-sized spiny neurons in the striatum and, to a lesser extent, in the cortex (Friedlander, 2003; Hickey & Chesselet, 2003). Mutant huntingtin might cause neurotoxicity both through a toxic gain of function and a loss of wild-type huntingtin protein (Zuccato et al., 2001). Transcriptional dysregulation also plays a central role in the pathogenesis/pathophysiology of HD (Hodges et al., 2006; Sugars & Rubinsztein, 2003). HD pathogenesis is modeled frequently with the expression of mutant huntingtin that causes aggregate formation and toxicity in cell models and *in vivo* (Rubinsztein, 2002).

The protective properties of lithium against glutamate toxicity seem ideally suited to treat HD, particularly because supersensitivity or hyperactivation of NMDA receptors appears to contribute to the pathophysiology of HD (Taylor-Robinson et al., 1996). Initial research in animal models of HD found that lithium neuroprotection is mediated through Bcl-2 induction and GSK-3β inhibition. The striatal infusion of quinolinic acid (QA), a neuronal excitotoxin that causes the death of medium-sized spiny neurons by activating NMDA receptors, and produces many of the neuroanatomical changes found in HD, has been frequently used as an animal model for investigating this disease (Foster et al., 1983; Schwarcz & Whetsell, Jr., 1982). In this rat excitotoxic model of HD, lithium treatment at doses within the therapeutic range (0.5 and 1.0 mEq/kg) markedly reduces the size of QA-induced striatal lesions (Wei et al., 2001) and the loss of striatal medium-sized neurons (Senatorov et al., 2004). This lithium protection is correlated with upregulation of cytoprotective Bcl-2 and downregulation of caspase-3 activation.

Furthermore, the anti-apoptotic properties of lithium in HD may also be mediated through GSK-3β inhibition. For example, in a cell model of HD, the protective effects of lithium in reducing mutant huntingtin aggregates and cell death are mimicked by either 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 is mimicked by AR-A014418, a GSK-3β inhibitor (Berger et al., 2005). In addition to its ability to inhibit apoptosis, lithium pretreatment also stimulates the proliferation of striatal cells near the site of QA-induced injuries, and some of these replicating cells have the phenotype of neurons or astroglia (Senatorov et al., 2004). Thus it appears that both the cell-proliferating and anti-apoptotic properties of lithium may underlie its neuroprotective effects in HD models.

Abnormal proteolytic processing of mutant huntingtin has been implicated as a critical step in the onset of HD, and the cleavage of huntingtin in human HD tissue is believed to be mediated in part by calpain, a calcium-activated neutral protease whose activity has been shown to be elevated in the caudate of human HD tissues (Gafni & Ellerby, 2002). As mentioned above, the succinate dehydrogenase inhibitor 3-NP has been used to induce striatal pathology similar to that observed in HD (Brouillet et al., 1999). In a rat 3-NP model of HD, lithium treatment reduces striatal neurodegeneration by preventing calpain and, subsequently, Cdk5 activation (Crespo-Biel et al., 2009). Moreover, it was reported that eliminating mutant huntingtin expression not only halts symptomatic progression, but also leads to regression of disease-like symptoms (Yamamoto et al., 2000), suggesting that improving clearance of the mutant protein is expected to prevent cellular dysfunction and

neurodegeneration in HD. In *Drosophila* and R6/2 mouse models of HD, inhibition of mTOR by systemic administration of rapamycin induces autophagy and reduces toxicity of polyglutamine expansions (Ravikumar et al., 2004). Because it is an autophagy inducer, lithium in combination with rapamycin shows greater protection against neurodegeneration than either pathway alone in cellular and *Drosophila* models of HD (Sarkar et al., 2008). Some behavioral benefits have been shown with lithium in transgenic mouse models of HD. R6/2 mice, the most frequently studied model of HD, carry a 145 CAG repeat expansion in huntingtin and show behavioral motor deficits as early as five to six weeks of age. In this model, post-, but not pre-symptomatic lithium treatment significantly improves rotarod performance but has no overall effect on survival (Wood & Morton, 2003). However, in the N171-82Q and YAC128 mouse models of HD, pre-symptomatic co-treatment with lithium and valproate, another mood stabilizer, produces more robust improvements in motor deficits and stronger anxiolytic as well as antidepressant-like effects than either drug alone (Chiu et al., 2009). Consistent with these results, synergistic neuroprotective effects of lithium and valproate have also been recently reported *in vitro* using rat CGCs exposed to glutamate (Leng et al., 2008). This neuroprotective synergy by combinatory treatment in CGCs is due, at least in part, to enhanced inhibition of GSK-3.

The clinical use of lithium in HD patients was explored decades ago, even before its neuroprotective properties were discovered. Lithium treatment of HD patients strikingly reduces chorea, and markedly improves voluntary movements (Dalen, 1973) and motor function (Mattsson, 1973). One study suggests that patients in the early disease stages might be more likely to benefit from lithium treatment (Foerster & Regli, 1977). Interestingly, some of these patients also experienced beneficial mood- and temper-stabilizing effects. Combined therapy with lithium and neuroleptics also proved beneficial in several HD patients (Anden et al., 1973; Leonard et al., 1974; 1975; Manyam & Bravo-Fernandez, 1973; Schenk & Leijnse-Ybema, 1974). However, some other reports showed that lithium exerted no beneficial effects in HD patients (Aminoff & Marshall, 1974; Vestergaard et al., 1977). In some instances, lithium treatment even worsened motor and cognitive performance, particularly when used as the sole therapeutic agent (Carman et al., 1974; Leonard et al., 1974). Nonetheless, it should be noted that the number of patients included in those trials was small, and the duration of lithium treatment was also too short to assess the potential benefit of this drug. Given that potential HD patients can be identified by genetic testing prior to the onset of symptoms, recent evidence of lithium's neuroprotective properties in various models of HD still suggest its possible utility in treating HD, especially when administered in combination with other medications.

3.4 Alzheimer's disease (AD)

In 2009, AD was the seventh leading cause of death in the US. Clinically, it is characterized by progressive memory loss and personality changes, ultimately leading to dementia. Although the pathogenesis of AD is not well understood, the neuropathological hallmarks of AD are an abnormal accumulation of Aβ resulting from an imbalance between Aβ production and clearance, and neurofibrillary tangles (tauopathies) resulting from hyper-phosphorylation of tau, a microtubule-binding protein (Selkoe, 2001). Accumulation of Aβ in the brain has been suggested as the primary cause of AD (Hardy & Selkoe, 2002). Hyper-phosphorylation of tau has also been implicated early in the development of the neurofibrillary pathology associated with AD and other neurodegenerative diseases (Lee et al., 2001; Planel et al., 2001). Therefore, Aβ and tau are considered as the primary targets in the treatment of AD.

Abnormal increases in GSK-3 levels and activity are associated with pathogenesis and neuronal death in the brain of individuals with AD (Bhat et al., 2004; Munoz-Montano et al., 1999), suggesting that lithium may have therapeutic benefits in treating this disorder (Huang

& Klein, 2006). In fact, pioneering studies have demonstrated that lithium antagonizes AD toxicity by inhibiting GSK-3. For example, lithium reduces tau phosphorylation by inhibiting GSK-3 *in vivo* and *in vitro* (Hong et al., 1997; Munoz-Montano et al., 1997; Sang et al., 2001). In addition, levels of tau phosphorylation are also regulated by PP2A (Tanaka et al., 1998), and reduced PP2A activity has been reported in the brain of individuals with AD (Trojanowski & Lee, 1995). Inhibition of PP2A prevents tau dephosphorylation, a process that precedes and is required for its cleavage and degradation (Rametti et al., 2004). Cleavage and degradation of hyper-phosphorylated tau may reduce its accumulation and aggregation. Lithium treatment not only increases the activity of PP2A in the rat brain (Tsuji et al., 2003), but also decreases tau phosphorylation and in turn facilitates its destruction (Rametti et al., 2004), suggesting the involvement of PP2A in lithium's action. This is supported by the finding that blockade of PP2A activity reverses lithium-induced downregulation of total tau proteins mediated by GSK-3β inhibition in cultured neurons (Martin et al., 2009). Furthermore, it was recently shown that lithium downregulates tau transcription in cultured cortical neurons (Rametti et al., 2008).

Chronic lithium treatment also blocks Aβ production through GSK-3 inhibition (Sun et al., 2002). Aβ peptide is derived from amyloid precursor protein (APP) by sequential secretase-dependent proteolytic processing. In the brains of mice overproducing APP, chronic lithium treatment blocks Aβ accumulation, presumably by interfering with the reaction of γ-secretase (Phiel et al., 2003). This effect of lithium in Chinese hamster ovarian cells is mimicked by transfection with siRNA of GSK-3α, but not GSK-3β (Phiel et al., 2003). However, the results from another study in HEK 293 cells show that GSK-3β inhibition can also mimic the ability of lithium or valproate to suppress the process of Aβ formation from APP (Su et al., 2004). In cultured neurons and neurally related cells, chronic lithium treatment largely suppresses exogenous Aβ-induced hyper-phosphorylation of tau, downregulation of Bcl-2, and neuronal death (Alvarez et al., 1999; 2002; Hong et al., 1997; Wei et al., 2000). In addition, lithium treatment prevents acetylcholinesterase-promoted Aβ toxicity and associated loss of function of Wnt signaling components in hippocampal slices (Inestrosa et al., 2000). It is interesting to note that the protein level of Bcl-2 in the brains of a mouse model of AD is inversely correlated with the expression of miR-34a (Wang et al., 2009), a microRNA that has recently emerged as common target for lithium and valproate (Zhou et al., 2009). These findings suggest a novel mechanism for lithium's protective effects in AD by which it can upregulate Bcl-2 indirectly via downregulation of miR-34a.

Lithium was also found to have beneficial effects in various animal models of AD. In *Drosophila* models of tauopathies, lithium reverses axonal transport and locomotor deficits by inhibiting GSK-3β (Mudher et al., 2004). In mouse models of tauopathies, chronic lithium treatment not only inhibits GSK-3 mediated tau phosphorylation and neuronal degeneration (Noble et al., 2005), it also decreases tau lesions by promoting ubiquitination (Nakashima et al., 2005). In rat brains, chronic lithium treatment protects against Aβ-induced hippocampal neurodegeneration by activating the Wnt/β-catenin pathway (De Ferrari et al., 2003). It was found that induction of Dickkopf protein 1 (DKK1), a Wnt pathway inhibitor (Krupnik et al., 1999), is associated with neurodegeneration in the brains of individuals with AD (Caricasole et al., 2004). Accordingly, systemic administration of lithium reverses local infusion of DKK1-induced neuronal cell death and astrocytosis in the CA1 region of the rat hippocampus (Scali et al., 2006). In the hippocampus of rabbits, lithium prevents Aβ-induced ER stress and the subsequent activation of caspase-12 and -3, NF-κB activation, and GSK-3 nuclear translocation (Ghribi et al., 2003). This action of lithium against ER stress might be related to its ability to induce the chaperone protein GRP78 (Hiroi et al., 2005), or the tPA-plasminogen proteolytic cascade (Melchor et al., 2003) as described above (see sections 2.10.5 and 2.10.6). Chronic lithium treatment not only decreases mutant tau protein aggregation in a transgenic mouse model (Perez et al.,

2003a), it also arrests the development of neurofibrillary tangles in mutant tau transgenic mice with advanced neurofibrillary pathology (Leroy et al., 2010).

With regards to its behavioral effects, chronic lithium treatment was found to improve learning and memory in normal rats (Nocjar et al., 2007), as well as improve spatial learning deficits in rats injected with preformed Aβ fibrils (De Ferrari et al., 2003). In transgenic mice overexpressing human APP, chronic (3-month) lithium treatment reduces the Aβ burden, tau hyper-phosphorylation, and neurodegeneration in the cortex and hippocampus, and normalizes deficits in water-maze performance by inhibiting GSK-3β signaling (Rockenstein et al., 2007). Taken together, these results from various cell and animal models of AD suggest a promising therapeutic role for lithium in the treatment of AD.

Lithium use in the treatment of AD has also been investigated clinically. One preliminary clinical study in individuals with BD found that a history of lithium treatment resulted in significantly better cognition and memory scores compared with individuals who had received other treatments (Terao et al., 2006). Chronic lithium treatment was further shown to reduce the prevalence of AD in elderly patients with BD (Nunes et al., 2007). A ten-year study in Denmark also found that continued lithium treatment of patients with dementia is associated with reduced rate of dementia to the same level as that for the general population (Kessing et al., 2008). Surprisingly, a German study found that lithium treatment of AD patients for 10 weeks significantly increases serum levels of BDNF, and that the diminution of cognitive impairment is inversely correlated with lithium serum concentrations (Leyhe et al., 2009). However, another trial of 33 AD patients reported no effect on GSK-3 activity or cognitive performance after 10 weeks of lithium treatment (Hampel et al., 2009). Similar reports with either small numbers of patients or short duration of treatment also indicate no therapeutic effect of lithium treatment in AD patients (Brinkman et al., 1984; Macdonald et al., 2008). Although lithium treatment in elderly people with AD was reported to have relatively few adverse effects (Macdonald et al., 2008), lithium levels in elderly patients still need to be carefully monitored due to reduced renal secretion of lithium (Williams, 1989). These preliminary results suggest that studies with longer treatment phases and larger patient groups are needed to observe the potential benefits of lithium in AD patients.

3.5 Parkinson's disease (PD)

PD is a prevalent neurodegenerative disease characterized by resting tremor, muscular rigidity, bradykinesia, and postural instability associated with a relatively selective loss of dopaminergic neurons, preferentially in the substantia nigra. Most cases of PD occur sporadically and primarily in older populations (age 65 or higher). PD is another neurodegenerative condition characterized by aggregates of mutant protein (Lewy bodies), mainly α-synuclein (Kruger et al., 1998; Polymeropoulos et al., 1997), a cytosolic protein essential for presynaptic regulatory function (Abeliovich et al., 2000). Although α-synuclein is degraded by both autophagy and the proteasome, the clearance of these mutant forms is retarded when autophagy is inhibited (Cuervo et al., 2004; Webb et al., 2003). Neurotoxins such as rotenone, 6-hydroxydopamine (6-OHDA), l-methyl-4-phenylpyridinium (MPP^+), and the MPP^+ precursor, MPTP, are widely used as parkinsonism-inducing neurotoxins to trigger PD-associated neurochemical changes in animal models.

Several lines of evidence support the therapeutic potential of lithium in PD. In cultured human neuroblastoma cells, caspase-3 activation induced by the mitochondrial complex I inhibitor rotenone or MPP^+ is facilitated by GSK-3β activation, and inhibited by lithium treatment in a PI3K-dependent manner (King et al., 2001). GSK-3β activation in PD seems to depend on the presence of α-synuclein, since MPP^+ or MPTP-induced tyrosine phosphorylation of GSK-3β is absent in cells lacking α-synuclein or from α-synuclein knockout mice (Duka et al., 2009). In cultured neurons, lithium prevents 6-OHDA (Chen et

al., 2004a) and MPP^+-induced (Kramer et al., 2010) neuronal death. In addition, chronic lithium treatment not only prevents MPTP-induced neurotoxicity in mice, it also normalizes the downregulation of Bcl-2 and upregulation of Bax elicited by MPTP in the striatum of the mouse brain (Youdim & Arraf, 2004). A recent study further indicates that lithium treatment, via GSK-β inhibition, prevents high concentrations of L-3,4-dihydroxyphenylalanine (L-DOPA)-induced neuronal cell death (Koh et al., 2008).

As with HD, clinical trials of lithium in PD patients were performed decades ago, before its neuroprotective properties were discovered. Lithium was used adjunctively to address the side effects of L-DOPA therapy, namely the on-off phenomenon (alternating periods of dyskinesia and akinesia) and L-DOPA-induced hyperkinesias associated with its early use. Despite experimental results suggesting that lithium may prevent striatal dopamine receptor desensitization, PD-like symptoms were reported in association with lithium treatment (Holroyd & Smith, 1995; Karcher et al., 1969). Case studies addressing the effects of lithium on L-DOPA-induced hyperkinesia remain contradictory (Karcher et al., 1969; McCaul & Stern, 1974; Van Woert & Ambani, 1973). On the other hand, lithium did prove beneficial in the management of the on-off phenomenon associated with L-DOPA therapy. In a double-blind crossover study and one case report, lithium was found to significantly reduce akinesia (Coffey et al., 1982; Ross et al., 1981), whereas lithium also increased dyskinesia (Coffey et al., 1982), or failed to improve the on-off phenomenon (Lieberman & Gopinathan, 1982). Nonetheless, the experimental evidence indicates that lithium is associated with protective properties that may encourage the use of this drug to treat PD patients; new, long-term trials are needed to fully explore this issue.

3.6 Retinal degeneration

Several hypotheses suggest that lithium alters circadian rhythms in individuals with BD by reducing sensitivity to light at the retinal level (Seggie, 1988). However, an early study of BD patients observed that chronic lithium use is not associated with differences in retinal light sensitivity, nor is there evidence for retinal toxicity after long-term lithium administration (Lam et al., 1997).

In contrast, in retina-brain slice co-cultures, lithium was found to support both the survival of retinal ganglion cells (RGCs) and regeneration of their axons through a Bcl-2-dependent mechanism (Huang et al., 2003). Lithium's Bcl-2-dependent effects were later confirmed *in vivo;* in rats, lithium protects RGCs from partial optic nerve crush (Schuettauf et al., 2006). Co-application of lithium and astrotoxin, a glutamate analogue that selectively kills astrocytes with minimal effects on surrounding neurons, induces more robust optic nerve regeneration in adult mice (Cho & Chen, 2008). Lithium is also protective in cultured primary retinal neurocytes, where it promotes neurite outgrowth and DNA non-homologous end-joining following nutrient deprivation, an *in vitro* condition mimicking cell death in glaucoma (Zhuang et al., 2009). In addition, activation of the canonical Wnt pathway is necessary for the normal development of anterior eye structures (Liu et al., 2007), and plays a role in retinal development and homeostasis (Liu et al., 2006). In retinoblastoma, the cancer stem-like cell population is also regulated by the canonical Wnt pathway (Silva et al., 2010). All of these events are normalized by lithium treatment, suggesting that this drug may be beneficial for the treatment of RGC degeneration.

3.7 Fragile X syndrome (FXS)

FXS is the most common inherited single-gene disorder associated with mental retardation. It is caused by abnormal expansion of the trinucleotide (CGG) repeat-mediated transcriptional silencing of the fragile X mental retardation-1 (*FMR1*) gene (Crawford et al., 2002; Pieretti et al., 1991) that encodes the fragile X mental retardation protein (FMRP)

(Garber et al., 2006). The discovery of the *FMR1* gene, the first identified autism-related gene (Hagerman et al., 2005), led to the development of *FMR1* gene knockout animals as models of FXS in order to improve our understanding of the pathophysiological mechanisms of autism and the development of effective therapeutics to treat this disorder. It has been suggested that the absence of FMRP causes enhanced metabotropic glutamate receptor (mGluR) signaling resulting from unchecked activation of neuronal mGluR5 and consequent enhanced mGluR-activated long-term depression in the brain of individuals with FXS (Bear et al., 2004; Dolen et al., 2007); this suggests that mGluR antagonists may ultimately be useful in treating this disorder. In addition, a recent study found that the inhibitory serine-phosphorylation of GSK-3 is impaired in FVB/NJ *FMR1* knockout mice (Min et al., 2009), suggesting elevated GSK-3 activity in FXS. Recent studies demonstrate that lithium, which inhibits GSK-3, may be therapeutically useful for treating FXS (Berry-Kravis et al., 2008; Choi et al., 2009; McBride et al., 2005; Min et al., 2009; Yan et al., 2005).

In a *Drosophila* model of FXS, behavioral and cognitive deficits measured by the naive and conditioned courtship behaviors, respectively, are rescued by treatment with mGluR antogonists administered during development alone, during adulthood alone, or during both time periods (McBride et al., 2005). Lithium treatment in adulthood, presumably through modulating signaling in a manner similar to the downstream effects of mGluR antagonists, also increases naive courtship and restores short-term memory in FXS flies (McBride et al., 2005). A recent study further indicates that age-related cognitive impairments in the *Drosophila* model of FXS are also prevented by treatment with mGluR antagonists or lithium, and continuous treatment during aging effectively rescues all of these phenotypes (Choi et al., 2009). Mouse models of FXS display certain FXS- and autism-relevant behavioral phenotypes such as hyperactivity and impaired memory and social behavior (Liu & Smith, 2009; Qin et al., 2002; Spencer et al., 2005; The Dutch-Belgian Fragile X Consortium, 1994), and lithium treatment ameliorates several behavioral deficits in these mouse models of FXS (Min et al., 2009; Yuskaitis et al., 2010). In addition, the aberrant dendritic spine morphology, reduced anxiety levels, deficient social interactions, and impaired learning ability observed in FXS mice are also largely blocked by chronic lithium treatment (Liu, Z. H., Chuang, D. M., & Smith C. B., resubmitted for publication). These beneficial effects of lithium are associated with normalization of hypo-phosphorylation of GSK-3β at Ser9 in the brain of FXS mice. Activation of mGluR5 receptors inhibits GSK-3 activity in wild-type mice (Liu et al., 2005), whereas the levels of serine-phosphorylation of GSK-3 were found to be increased by 2-methyl-6-phenylethynyl-pyridine (MPEP), an mGluR5 antagonist, in the brain of FXS mice (Min et al., 2009; Yuskaitis et al., 2010). Moreover, the combination of an mGluR5 antagonist with a GSK-3 inhibitor does not produce additive therapeutic effects in FXS mice (Min et al., 2009). Collectively, these findings suggest that GSK-3 may be a fundamental component of the pathology of FXS, and support the therapeutic potential of lithium in FXS. Recent results from a pilot clinical study show that the effects of lithium are consistent with preclinical results; in FXS patients 6 to 23 years of age, lithium exerts positive effects on behavior, adaptive skills, and cognitive measures (Berry-Kravis et al., 2008).

3.8 Amyotrophic lateral sclerosis (ALS)

ALS is an adult-onset neurodegenerative disease characterized by progressive loss of motor neurons (MNs) in the brain, brain stem, and spinal cord, resulting in generalized weakness, muscle atrophy, paralysis, and eventual mortality within five years of disease onset (Rowland, 1994). Most ALS cases occur sporadically, with only about 10% of the patients categorized as having a familial form (Boillee et al., 2006; Wijesekera & Leigh, 2009). Of these, approximately 20% are attributed to gain-of-function mutations in the gene encoding Cu/Zn superoxide dismutase 1 (SOD1), a key antioxidant enzyme (Rosen et al., 1993).

However, sporadic and familial forms of ALS produce similar pathological hallmarks. Mice expressing mutant Cu/Zn SOD1 exhibit ALS-like phenotypes, including the formation of intracellular aggregates of SOD1 in the brain and spinal cord, behavioral abnormalities, and premature death. In addition to MNs, damage to surrounding glial cells, muscle cells, interneurons, and Renshaw inhibitory neurons have also been reported in ALS (Boillee et al., 2006; Dobrowolny et al., 2008; Fornai et al., 2008).

Defective autophagy has been found in diseased MNs (Venkatachalam et al., 2008). In addition, upregulated GSK-3β (Yang et al., 2008), hyper-phosphorylated β-catenin (Yang et al., 2008), and downregulated VEGF and its receptors (Brockington et al., 2006) have also been observed in the postmortem tissue of ALS patients. VEGF prolongs survival in ALS mice (Wang et al., 2007) and protects MNs against excitotoxicity (Tolosa et al., 2008). These findings suggest that the neuroprotective mechanisms of lithium may be suitable for treating ALS. In fact, treatment with either lithium alone or in conjunction with an antioxidant has been shown to improve motor function and slow disease progression in a mouse model of ALS (Ferrucci et al., 2010; Fornai et al., 2008; Shin et al., 2007). In organotypic slice cultures of spinal cord, chronic treatment with lithium dose-dependently prevents excitotoxic cell death of MNs by inhibiting the GSK-3β signaling pathway (Caldero et al., 2010).

In addition, the autophagy-inducing properties of lithium are also believed to contribute to its protective effects in ALS (Fornai et al., 2008). A recent study found that combined treatment of ALS mice with lithium and valproate produces a greater and more consistent effect in delaying the onset of disease symptoms, decreasing neurological deficit scores, and prolonging life span than monotreatment with either drug (Feng et al., 2008). Moreover, a 15-month pilot clinical trial in randomized ALS patients found that lithium and riluzole cotreatment markedly reduced mortality when compared with matched control patients treated with riluzole alone (Fornai et al., 2008). However, it should be noted that inconsistent results have also been reported. In a sibling-matched, gender-balanced, investigator-blinded trial, chronic lithium treatment was found to be ineffective on any treatment measure (Gill et al., 2009). Another study also found no therapeutic or neuroprotective effects of lithium in female ALS mice (Pizzasegola et al., 2009). Moreover, a very recent study showed that lithium in combination with riluzole did not slow the progression of ALS more than riluzole alone (Aggarwal et al., 2010). Future studies are needed to clarify these discrepancies (Bedlack et al., 2008; Vanacore & Galeotti, 2008). Accordingly, an international effort is already underway to initiate larger, randomized trials to verify lithium’s effect in ALS patients (Meininger et al., 2008).

3.9 Multiple sclerosis (MS)

MS is the most common inflammatory demyelinating disease of the CNS, in which focal lymphocytic infiltration leads to damage of myelin sheaths around the axons of the brain and spinal cord, and results in demyelination and neurodegeneration with lesions predominantly in the white matter (Hafler, 2004; McFarland & Martin, 2007; Sospedra & Martin, 2005). MS is more prevalent in females and usually occurs in young adults in either relapsing or progressive form characterized by a broad spectrum of symptoms, including muscle weakness, motor incoordination, and cognitive impairments (Compston & Coles, 2008). Although MS has been widely thought to be an autoimmune disease, the etiology of this disease remains elusive and there is no cure at this time. Current therapeutic strategies for MS focus on slowing the disease progression and controlling the symptoms.

Experimental autoimmune encephalomyelitis (EAE) (Noseworthy et al., 2000) in animals is the most frequently used animal model of MS, and it has directly led to the development of three medications for treatment of MS, glatiramer acetate, mitoxantrone and natalizumab

(Steinman & Zamvil, 2006). EAE recapitulates many of the clinical, immunological, and neuropathological aspects of human MS (Denic et al., 2010; Steinman & Zamvil, 2005), and it can be induced by systemic injection of an emulsion that contains synthetic peptides derived from myelin proteins, such as myelin oligodendrocyte glycoprotein (MOG), myelin basic protein, or proteolipid protein, in a variety of mammal species (Baxter, 2007). Activation of the immune system and subsequent infiltration of peripherally activated immune cells together with resident glia amplify neuroinflammation, and cause demyelination and loss of neuronal function in the CNS (Hafler, 2004; Kuchroo et al., 2002). A recent study demonstrates that EAE is more severe and develops more rapidly in knock-in mice expressing constitutively active GSK-3 (De Sarno et al., 2008), suggesting that this kinase is a potential therapeutic target for the treatment of MS.

Administration of GSK-3 inhibitors has been shown to control several inflammatory and immune conditions in both the periphery and the CNS (Beurel et al., 2010). For example, GSK-3 inhibition ameliorates arthritis, peritonitis, and colitis in rodents (Cuzzocrea et al., 2006; Dugo et al., 2005; Whittle et al., 2006), and increases the production of anti-inflammatory IL-10 by memory $CD4^+$ T cells (Garcia et al., 2008) and B cells (Lambert & Martinez, 2007). Notably, lithium pretreatment at therapeutically relevant doses not only abolishes the onset of EAE, but also greatly reduces demyelination, microglia activation, and leukocyte infiltration in the spinal cord of mice (De Sarno et al., 2008). Although the disease rapidly relapses after lithium withdrawal, lithium also promotes recovery and prevents relapse episodes of EAE when administered postimmunization (after the first relapse episode). In addition, lithium treatment suppresses MOG peptide-induced immune responses *in vitro* and decreases the production of several proinflammatory cytokines by splenocytes stimulated with MOG peptide after isolation from EAE mice. These results suggest that GSK-3 is the most likely target mediating lithium's beneficial effects in EAE, and lithium may be useful for therapeutic intervention in autoimmune and inflammatory diseases afflicting the CNS such as MS. However, it should be noted that numerous therapeutical approaches that showed promising results in EAE turned out to be either ineffective or even harmful in human MS (Sriram & Steiner, 2005). Therefore, the potential use of lithium as a novel therapeutic for this disease requires more studies to gain better insight into the mechanisms of action.

3.10 Other neurological conditions

3.10.1 Spinal cord injury—In a spinal cord injury model of rats induced by unilateral hemisection, combined lithium with chondroitinase was reported to have synergistic effects in increasing axonal regeneration of the rubrospinal tract and in improving forelimb movement (Yick et al., 2004). Intrathecal injection of lithium also reduces neuropathic pain responses in rats subjected to chronic constrictive injury to the sciatic nerve (Shimizu et al., 2000), raising its potential utility in neuropathic pain syndromes resulting from peripheral nerve injury. In addition, chronic lithium treatment, presumably through the secretion of BDNF (Su et al., 2009), enhances proliferation and neuronal differentiation of neural progenitor cells *in vitro* and after transplantation into the adult rat spinal cord with reduced activation of microglia and macrophages (Su et al., 2007). Systemic application of a therapeutic dose of lithium suppresses the activity of GSK-3 around the lesion sites of spinal cord-lesioned rats, and promotes axonal growth and recovery in rats with thoracic spinal cord transection or contusion injuries (Dill et al., 2008). Taken together, these preliminary results provide evidence that GSK-3 signaling is an important therapeutic target for promoting functional recovery, and that lithium may have therapeutic potential in cell replacement strategies for CNS injury due to its ability to suppress the host immune response.

3.10.2 HIV infection—Murine acquired immune deficiency syndrome (MAIDS), a mouse-related syndrome with extensive similarities to human immunodeficiency virus (HIV) infection, is caused by a defective murine leukemia virus. Lithium has been shown to have immune-enhancing properties in peripheral blood mononuclear cells obtained from normal subjects and patients with AIDS-related complex (ARC) (Sztein et al., 1987). MAIDS mice treated with lithium show a marked reduction in the development of lymphadenopathy and splenomegaly (Gallicchio et al., 1993). In rat CGCs, lithium abolishes HIV-1 transactivator protein (Tat)-induced increases in GSK-3β activity and enhances neuronal survival following exposure to Tat or prenatal platelet activating factor (PAF), a protein produced from HIV-1-infected brain-resident macrophages (Maggirwar et al., 1999). Lithium also reverses PAF-induced GSK-3β overactivation, as well as cell migration and death in cultured CGCs (Tong et al., 2001). In addition, noncytotoxic/noncytostatic concentrations of lithium inhibit the replication of HIV in a Wnt/β-catenin-dependent manner (Kumar et al., 2008). A study notes that lithium pretreatment protects the hippocampus of mice from HIV-gp120-induced toxicity (Everall et al., 2002). Similarly, pre- but not post-exposure of human neuroblastoma cells to lithium reduces gp120-induced neurotoxicity, and this protective effect is blocked by a PI3K inhibitor. The neuroprotective mechanisms of lithium in murine HIV-1 encephalitis identified *in vivo*, appear to be mediated through the classic PI3K/Akt and GSK-3β pathways (Dou et al., 2005). These results are compatible with the view that prophylactic treatment with lithium may prevent or delay the onset and progression of HIV-associated cognitive impairments. Indeed, lithium has already been safely used to improve HIV-associated neurocognitive impairment in diagnosed patients (Letendre et al., 2006; Schifitto et al., 2009).

3.10.3 Prion diseases—Transmissible spongiform encephalopathies, also known as prion diseases, are a group of unusual, fatal, neurodegenerative disorders. Prion diseases are caused by aggregates of a proteinase-resistant, abnormal isoform of the native prion protein (PrP) that induces neuronal cell death and glial proliferation (Collinge, 2001; Prusiner, 1998). Creutzfeldt-Jakob disease is the most prevalent human prion disease with possible sporadic, genetic, and acquired etiologies. Several studies indicate that serotonergic dysregulation are likely to associate with high frequency of neuropsychiatric symptoms in prion diseases, and that prion-mediated cytotoxicity may be blocked by NMDA receptor antagonists (Appleby, 2009). Notably, PrP-induced neuronal cell death in both primary neuronal cultures and neuroblastoma cells is mediated through a pathway involving GSK-3 and is blocked by lithium (Perez et al., 2003b). Lithium significantly reduces the amount of pathological PrP in prion-infected neuronal and cultured non-neuronal cells by inducing autophagy (Fornai et al., 2006; Heiseke et al., 2009). Co-treatment with lithium and rapamycin has an additive effect on pathological PrP clearance compared to treatment with either drug alone (Heiseke et al., 2009). These data indicate that lithium has potential utility in treating these diseases.

3.10.4 Alcohol-induced neurodegeneration—The developing nervous system is vulnerable to ethanol toxicity. Lithium protects cultured CGCs from ethanol-induced apoptosis and caspase-3/9 activation, but neither ethanol nor lithium significantly affects the phosphorylation of Akt at ser473 or GSK-3β at ser9 (Zhong et al., 2006). Since lithium-induced activation of Akt in CGCs is transient (Chalecka-Franaszek & Chuang, 1999), these data cannot exclude the involvement of the Akt/GSK-3β pathway. Lithium also protects infant mice against ethanol-induced apoptotic cell death as well as caspase-3 activation in the brain (Chakraborty et al., 2008; Zhong et al., 2006). Notably, Akt, GSK-3β, and 5′ adenosine monophosphate-activated protein kinase (AMPK) have been shown to be involved in ethanol-induced neurodegeneration and the neuroprotective effects of lithium in an *in vivo* study (Chakraborty et al., 2008).

3.10.5 Down syndrome (DS)—DS is a high-incidence genetic disorder in which an extra portion of chromosome 21 leads to brain hypoplasia, mental retardation, and high prevalence of dementia. Segmental trisomy Ts65Dn mice, the most widely used model for DS, have elevated levels of brain myo-inositol, one of the metabolites that has been investigated in relation to the mental retardation associated with DS. Studies found that this elevated myo-inositol in the brain of DS mice is decreased by lithium treatment (Huang et al., 2000). In addition, emerging evidence suggests that reduced neurogenesis may be a major determinant of brain underdevelopment in DS. The Ts65Dn mice exhibit severe proliferation impairment and lithium restores neurogenesis in the subventricular zone of these DS mice (Bianchi et al., 2009). These data suggest that lithium may potentially improve neurogenesis in patients with DS.

3.10.6 Spinocerebellar ataxia type 1 (SCA1)—Spinocerebellar ataxia type 1 (SCA1), one of the nine polyglutamine disorders, is caused by the expansion of a CAG repeat that encodes polyglutamine in the respective disease protein ataxin-1 (Gatchel & Zoghbi, 2005). SCA1 is a dominantly inherited neurodegenerative disorder characterized by progressive motor and cognitive dysfunction. The pathogenesis of this disease includes the misfolding of ataxin-1 and consequent transcriptional dysregulation, and is characterized by degeneration of cerebellar Purkinje cells and brain stem neurons (Burk et al., 2003; Zoghbi & Orr, 1995). One study in a knock-in mouse model of SCA1 found that dietary lithium supplementation attenuates the reduction of dendritic branching in mutant hippocampal pyramidal neurons, and results in improvement of motor coordination, learning, and memory in these SCA1 mice. Importantly, motor improvement is achieved by either pre- or post-symptomatic lithium treatment (Watase et al., 2007). These results suggest that lithium is an excellent treatment candidate for human SCA1 patients. A clinical trial assessing the side effects and tolerability of lithium in SCA1 patients (18 to 65 years of age) has recently been completed by the National Institutes of Health, USA, and data analyses are ongoing.

3.10.7 Tardive dyskinesia (TD)—TD is clinically characterized by involuntary choreiform movements—mostly of the mouth, tongue, and face—that disappear during sleep. TD is hypothesized to result from dopaminergic supersensitivity associated with the prolonged use of typical antipsychotic medications. Early studies using animal models of TD found that lithium treatment prevents supersensitivity to apomorphine, a non-selective dopamine receptor agonist (Klawans et al., 1977; Pert et al., 1978), underscoring its potential prophylactic and therapeutic usefulness in TD. Numerous case reports also suggest that the lithium salt is beneficial in the treatment of drug-induced TD, particularly in combination with antidepressants (Dalen, 1973; Pickar & Davies, 1978; Reda et al., 1975; Rosenbaum et al., 1977; Simpson et al., 1976). However, other studies indicate that lithium only improves a subpopulation of patients (Gerlach et al., 1975; Jus et al., 1978), or fails to show a therapeutic effect in older TD patients (Simpson et al., 1976). Although a previous Cochrane review did not recommend lithium for everyday use in TD (Soares-Weiser & Joy, 2003), a recent nine-year follow-up study suggests a beneficial effect of lithium on TD in some patients using long-term antipsychotics (van Harten et al., 2008).

3.10.8 Schizophrenia—Based on the co-administration of second generation antipsychotics with mood stabilizers for BD, mood stabilizers such as lithium or anticonvulsants have been used together with antipsychotics as adjunctive medication for the treatment of schizophrenia, for the same purpose of producing potential synergistic or enhanced responses (Citrome et al., 2005; Johannessen, 2008). Although adjunctive lithium treatment in early studies seemed to be somewhat beneficial (Carman et al., 1981; Kellams et al., 1976; Small et al., 1975), later, well-designed trials found that this treatment strategy did not produce robust evidence of improvement. Therefore, this application has not been

approved by regulatory agencies. While the reasons underlying lithium's lack of conclusive effects in individuals with schizophrenia are unclear, it is interesting to note that the expression of GSK-3β protein and mRNA are decreased in both schizophrenic patients and in a rat model of this disease (Kozlovsky et al., 2005).

4. Conclusion and future directions

In recent years, accumulating evidence has focused on the neuroprotective and neurotrophic properties of lithium, rekindling interest in this drug for the treatment of a wide variety of disorders. Studies from various laboratories support the notion that lithium has robust neuroprotective effects in a vast number of cellular and animal models of brain disorders. Indeed, neuroprotection is the most consistent biological outcome associated with lithium treatment in both preclinical and clinical experimental settings. It is becoming clear that GSK-3 hyperactivity is involved in the cell death and pathophysiology of many neurodegenerative conditions, and that GSK-3 inhibition is an important target for lithium to induce neuroprotective and neurotrophic actions.

GSK-3 is inhibited by lithium via multiple mechanisms, and this GSK-3 inhibition plays a prominent role in activating a wide spectrum of signaling pathways, and inducing various anti-apoptotic and neurotrophic proteins. Furthermore, lithium-induced inhibition of phosphoinositide metabolism and IP_3 production appears to be involved in upregulation of autophagy, and lithium's effects on this process may be critical to the clearance of protein aggregates associated with neurodegenerative diseases. Emerging evidence suggests that specific microRNAs are targets of lithium and another mood stabilizer, valproate, and are involved in the regulation of expression of anti-apoptotic proteins and could have a role in the pathophysiology of some brain disorders. Further investigations in the area of microRNA research may provide new insights into the etiology of diseases and mechanisms of action of lithium.

As reviewed above, lithium treatment has been shown to be beneficial in an increasing list of animal models of CNS disorders. Decreased neurodegeneration, enhanced neurogenesis, improved behavioral performance and cognitive function, and prolonged survival time have all been reported in many preclinical studies. In addition, co-treatment of lithium with other drugs such as valproate has sometimes been found to produce more robust and consistent neuroprotective effects and behavioral improvements *in vitro* and *in vivo*. Thus, combinatory treatment to enhance the beneficial effects of lithium seems to be warranted. As a result of these promising preclinical evidences, and because of its long history of safe use in humans, a number of clinical trials using lithium to treat a variety of brain disorders are now underway. While some clinical studies show promising positive results, others indicate no improvement or response after lithium treatment. Large-scale clinical trials with long treatment durations are necessary to resolve these discrepancies. In light of the results from recently completed preclinical studies, combinatory treatment with lithium and other neuroprotective drug(s) is also recommended for future clinical investigation.

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Abbreviations

3-NP	3-nitropropionic acid

Aβ	β-amyloid
AD	Alzheimer's disease
ALS	amyotrophic lateral sclerosis
AP-1	activator protein-1
βArr2	β-arrestin 2
Bcl-2	B-cell lymphoma/leukemia-2 protein
BD	bipolar disorder
BDNF	brain-derived neurotrophic factor
Cdk5	cyclin-dependent kinase 5
CGCs	cerebellar granule cells
CNS	central nervous system
CREB	cyclic AMP-response element binding protein
DS	Down syndrome
EAE	experimental autoimmune encephalomyelitis
ER	endoplasmic reticulum
ERK	extracellular-signal regulated kinase
FoxO3a	forkhead box class O3a
FXS	fragile X syndrome
GRP78	glucose-regulated protein 78
GSK-3	glycogen synthase kinase-3
HD	Huntington's disease
HIV	human immunodeficiency virus
HSF-1	heat-shock factor-1
HSP	heat shock protein
IMPase	inositol monophosphatase
IP_3	inositol 1,4,5-trisphosphate
JNK	c-Jun N-terminal kinase
L-DOPA	L-3,4-dihydroxyphenylalanine
MAP kinase	mitogen-activated protein kinase
MCAO	middle cerebral artery occlusion
MEK	MAP kinase kinase
mGluR	metabotropic glutamate receptor
MNs	motor neurons
MPTP	*N*-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MS	multiple sclerosis
mTOR	the mammalian target of rapamycin

NMDA	*N*-methyl-D-aspartate
PAI-1	plasminogen activator inhibitor-1
PD	Parkinson's disease
PI3K	phosphoinositide 3-kinase
PKA	protein kinase A
PKC	protein kinase C
PP2A	protein phosphatase 2A
tPA	tissue-type plasminogen activator
SCA1	spinocerebellar ataxia type 1
siRNA	small interfering RNA
TD	tardive dyskinesia
TrkB	tyrosine receptor kinase B
VEGF	vascular endothelial growth factor

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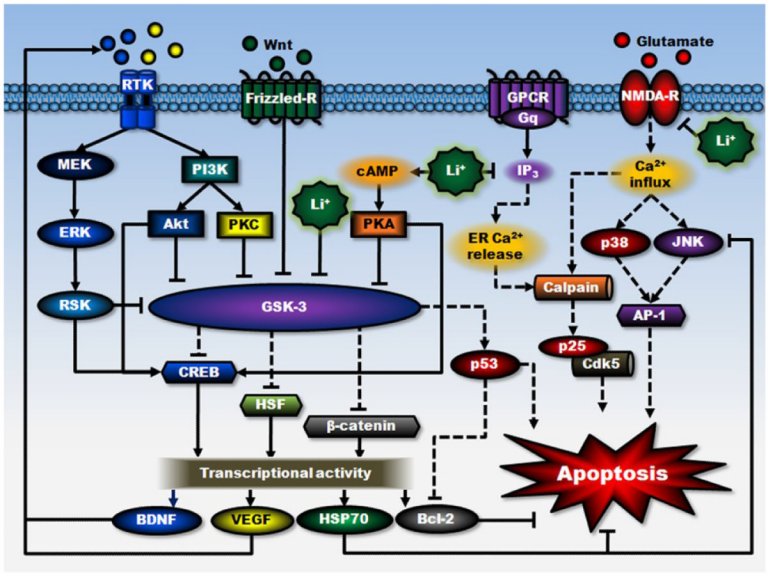

Figure 1. An overview of proposed signaling mechanisms underlying lithium's neuroprotective effects

The neuroprotective effects of lithium against glutamate excitotoxicity are proposed to result from its interactions with cell survival and apoptotic machinery, as well as inhibition of receptor-mediated calcium entry. First, lithium can directly and indirectly reduce the activity of constitutively activated GSK-3 by multiple mechanisms, leading to disinhibition of several transcription factors, including CREB, HSF-1, and β-catenin, and subsequent induction of major cytoprotective proteins such as BDNF, VEGF, HSP70, and Bcl-2. GSK-3 is negatively regulated by Wnt-stimulated activation of the Frizzled receptor and decreased GSK-3 activity further reduces the activity of pro-apoptotic protein p53 and its downregulating effect on Bcl-2. Second, lithium-induced neurotrophic factors such as BDNF, in turn, activates its cell surface receptor and the downstream PI3K/Akt and MEK/ERK pathways. Both pathways are strongly associated with neuroprotective effects, which stimulate CREB and inhibit GSK-3. BDNF induction is an early and essential step for neuroprotection against glutamate excitotoxicity and may contribute to lithium-induced neurogenesis. Lithium also indirectly inhibits GSK-3 activity via PI3K-dependent activation of PKC and cAMP-dependent activation of PKA. Third, lithium inhibits NMDA receptor-mediated calcium influx, which in turn decreases subsequent activation of JNK, p38 kinase, and transcription factor AP-1. This NMDA receptor-mediated signaling plays a critical role in mediating glutamate-induced caspase activation and apoptosis. JNK activity is also inhibited by overexpression of HSP70. In addition, through inositol depletion, lithium reduces IP_3-mediated calcium release from the ER. Inhibition of intracellular calcium increase not only suppresses cellular stress, but also reduces the activity of calpain and calpain-mediated activation of pro-apoptotic Cdk5/p25 kinase. 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 treatment. Frizzled-R, Frizzled receptor; GPCR, G protein-coupled receptor; NMDA-R, NMDA receptor; RTK, receptor tyrosine kinase.

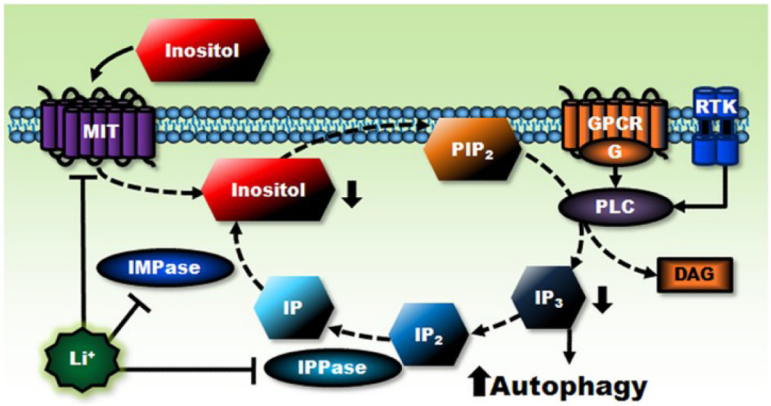

Figure 2. Lithium's actions on inositol depletion and autophagy induction

Extracellular signal binding to its cell surface receptor, either GPCR or RTK, activates phospholipase C (PLC), which hydrolyzes the phospholipid PIP_2 to yield second messengers IP_3 and diacylglycerol (DAG). IP_3 is recycled by enzymes IPPase and IMPase and converted to inositol (mainly myo-inositol), which is required for PIP_2 re-synthesis. Lithium decreases intracellular inositol levels by directly inhibiting IPPase, IMPase, and inositol transporter (MIT) that uptakes extracellular inositol. Decreased intracellular inositol levels are expected to subsequently reduce PIP_2 and prevent the formation of IP_3 and DAG, thus blocking transmembrane signaling and trigging the induction of autophagy. 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 treatment. DAG, diacylglycerol; IP, inositol monophosphate; IP_2, inositol bisphosphate; MIT, inositol transporter; PLC, phospholipase C.

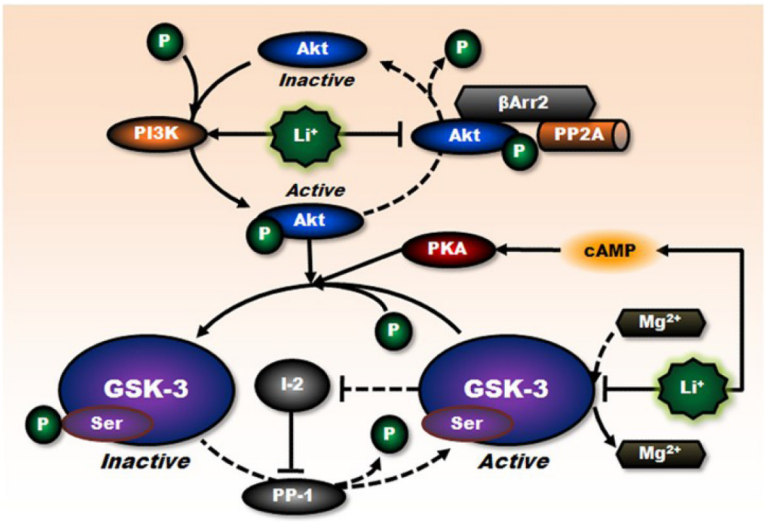

Figure 3. Inhibitory regulation of GSK-3 activity by lithium

Lithium regulates the activity of constitutively activated GSK-3 through multiple mechanisms. First, lithium is a competitive inhibitor of magnesium that directly inhibits ATP-magnesium-dependent catalytic activity of GSK-3. Second, lithium can indirectly increase serine phosphorylation of GSK-3 through PI3K-mediated phosphorylation/activation of Akt. The activity of GSK-3 is reduced by phosphorylation at this specific serine residue. Third, lithium can also disrupt the formation of the βArr2/PP2A/Akt complex that dephosphorylates/inactivates Akt, thereby increasing the serine phosphorylation of GSK-3. In addition, lithium can negatively regulate GSK-3 activity through other protein kinases including cAMP-dependent activation of PKA and PI3K-mediated activation of PKC (not shown), and through other mechanisms including downregulation of GSK-3 (not shown). Moreover, direct inhibition of GSK-3 by lithium interrupts the auto-regulation of GSK-3, by disinhibiting the inhibitory action of inhibitor-2 (I-2) on protein phosphatase-l (PP-1) that dephosphorylates GSK-3 at serine residues, and further decreases GSK-3 activity. 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 treatment. I-2, inhibitor-2; PP-1, protein phosphatase-l.

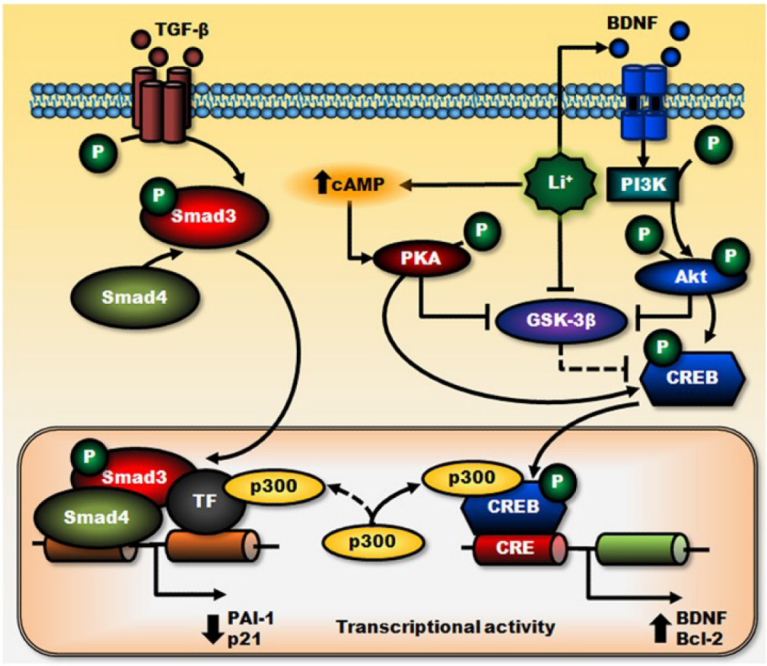

Figure 4. Negative regulation of Smad3/4-dependent transcription by lithium

Through stimulation of their cell surface receptors, TGF-β- and BDNF-triggered transcriptional activations are mediated by Smad3/4- and PI3K/Akt-dependent pathways, respectively. Lithium treatment reduces GSK-3β activity directly and indirectly via cAMP-dependent activation of PKA and BDNF-stimulated activation of PI3K/Akt pathways. These effects of lithium potentiate BDNF-induced phosphorylation/activation of CREB and increase cAMP response element (CRE)-mediated transactivation and expression of survival factors such as BDNF and Bcl-2. Increased BDNF-induced gene transcription causes sequestration of transcriptional co-activator p300, which suppresses Smad3/4-dependent transactivation and subsequently decreases the expression of TGF-β-responsive genes, PAI-1, and p21. 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 treatment. CRE, cAMP response element.