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Neuroprotective action of lithium in disorders of the central nervous system

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De-Maw Chuang, Ph. D., professor of psychiatry and molecular neurobiology, has been mainly engaged in research involving neurodegenerative disorders for the past decades. His research has involved programmed cell death (apoptosis) of neurons, neurotransmitter receptor regulation, mechanisms and actions of mood stabilizers and psychotropic drugs. He has been involved in characterization of potential roles of lithium and HDACIs in neuropsychiatric disorders including mood and anxiety disorders and stroke. He was awarded as Academician of Academia Sinica of Taiwan in 2006, and wan the Distinguished Investigator Award of National Alliance for Research on Schizophrenia and Depression (NARSAD) in 2002, the National Institute of Mental Health (NIMH) Director's Mentor of the Year Award in 2010. He is currently the Chief of Molecular Neurobiology Section, National Institute of Mental Health (NIMH), National Institute of Health (NIH).

Abstract: Substantial in vitro and in vivo evidence of neurotrophic and neuroprotective effects of lithium suggests that it may also have considerable potential for the treatment of neurodegenerative conditions. Lithium's main mechanisms of action appear to stem from its ability to inhibit glycogen synthase kinase-3 activity and also to induce signaling mediated by brain-derived neurotrophic factor. This in turn alters a wide variety of downstream effectors, with the ultimate effect of enhancing pathways to cell survival. In addition, lithium contributes to calcium homeostasis. By inhibiting *N*-methyl-D-aspartate receptor-mediated calcium influx, for instance, it suppresses the calcium-dependent activation of pro-apoptotic signaling pathways. By inhibiting the activity of phosphoinositol phosphatases, it decreases levels of inositol 1,4,5-trisphosphate, a process recently identified as a novel mechanism for inducing autophagy. These mechanisms allow therapeutic doses of lithium to protect neuronal cells from diverse insults that would otherwise lead to massive cell death. Lithium, moreover, has been shown to improve behavioral and cognitive deficits in animal models of neurodegenerative diseases, including stroke, amyotrophic lateral sclerosis, fragile X syndrome, and Huntington's, Alzheimer's, and Parkinson's diseases. Since lithium is already FDA-approved for the treatment of bipolar disorder, our conclusions support the notion that its clinical relevance can be expanded to include the treatment of several neurological and neurodegenerative-related diseases.

Key words: brain-derived neurotrophic factor; CNS disorders; glutamate excitotoxicity; glycogen synthase kinase-3; lithium; neurodegenerative diseases; neuroprotection
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1 INTRODUCTION

For more than 60 years, lithium has been the standard pharmacological treatment for bipolar disorder (BD), a chronic mental illness characterized by cycling between moods of mania and depression[1]. In fact, current treatment guidelines frequently recommend lithium as the first-line treatment against acute mania and

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prophylactically for recurrent manic and depressive episodes. Clinically, lithium can be used adjunctively with other mood stabilizers, antidepressants, and antipsychotic medications to facilitate, enhance, or prolong both treatment response and remission[2]. While lithium's mood-stabilizing effects have been associated with a number of actions[3], the underlying biochemical mechanisms involved have yet to be defined.

Neuronal atrophy and reduced cellular density, as well as reduced grey matter volume were found in various brain regions of patients with BD[4], and MRI studies of the prefrontal cortex in patients with BD show abnormally low levels of the neuronal integrity marker N-acetyl-asparate (NAA)[5]. It is interesting to note that BD patients who receive chronic lithium treatments show consistently higher NAA levels and reduced loss of grey matter volume[6-8]. In fact, significant attention has focused on lithium's neurotrophic and neuroprotective effects during the last decade, and considerable research has been conducted on its efficacy as a novel therapeutic in various disease models.

The neuroprotective effects of lithium against glutamate-induced excitotoxicity have been extensively studied in various cellular and animal models. Glutamate excitotoxicity 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)[9-10]. Lithium has also been shown to protect against insults to neurons in the central nervous system (CNS) and neurally related cell lines; these insults include endoplasmic reticulum (ER) stress[11-12], apoptosis induced by withdrawal of growth factor[13], β-amyloid (Aβ)[14], or colchicines[15], high potassium deprivation[16], exposure to heat shock[17], and supratherapeutic concentrations of anticonvulsants (phenytoin and carbamazepine)[18]. This article reviews recent findings regarding potential targets involved in lithium's neuroprotective effects and their implications for the treatment of human disorders of the CNS.

2 MECHANISMS UNDERLYING LITHIUM'S NEUROPROTECTIVE EFFECT

The fact that lithium's beneficial effects normally become evident only after long-term treatment and that these effects are not immediately reversed after discontinuation of the drug suggests that the drug works by altering signaling pathways and gene expression in the CNS. Fig. 1 shows the many signaling pathways and mechanisms of action implicated to date in lithium's neuroprotective effects.

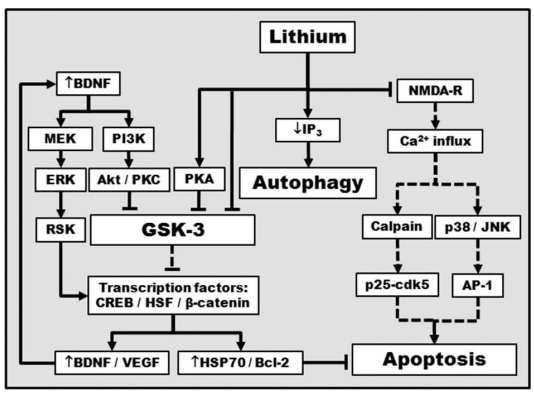

Fig. 1 A schematic illustration of proposed mechanisms underlying lithium's neuroprotective effects. Lithium can directly and indirectly inhibit constitutively activated glycogen synthase kinase-3 (GSK-3) by multiple mechanisms, leading to disinhibition of several transcription factors, including cyclic AMP-response element binding protein (CREB), heat-shock factor-1 (HSF-1), and β-catenin, and subsequent induction of major cytoprotective proteins such as brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF), heat shock protein (HSP)70, and B-cell lymphoma/leukemia-2 protein (Bcl-2). Lithium-induced neurotrophic factors such as BDNF, in turn, activate its cell surface receptor and the downstream phosphoinositide 3-kinase (PI3K)/Akt and MAP kinase kinase (MEK)/extracellular-signal regulated kinase (ERK) pathways. 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 protein kinase C (PKC) and cAMP-dependent activation of protein kinase A (PKA). The ability of lithium to decrease inositol 1,4,5-trisphosphate (IP3) levels is a novel route for inducing autophagy. Furthermore, lithium inhibits *N*-methyl-D-aspartate (NMDA) receptor-mediated calcium influx, which in turn decreases subsequent activation of c-Jun N-terminal kinase (JNK), p38 kinase, and transcription factor activator protein-1 (AP-1). Inhibition of intracellular calcium increase not only suppresses cellular stress, but also reduces the activity of calpain and calpain-mediated activation of pro-apoptotic cyclin-dependent kinase 5 (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.

2.1 Protection against glutamate-induced excitotoxicity

In cultured rat CNS neurons that included cerebellar granule cells (CGCs) and cerebral cortical and hippocampal neurons[19], chronic lithium treatment was found to robustly reduce glutamate-induced excitotoxicity mediated by NMDA receptors. This effect was at least partly due to lithium's ability to inhibit the influx of calcium, which mediates activity in NMDA receptors. Studies further indicate that the mechanism of action results from the attenuation of constitutive phosphorylation at Tyr1 472 of the NR2B subunit of the NMDA receptor, which is catalyzed by Fyn, a member of the Src tyrosine kinase family[20-21]. Brain ischemia is known to increase Src-mediated tyrosine phosphorylation of NR2A[22-23] and to increase the interaction of NR2A with Src and Fyn, which is mediated by postsynaptic density protein 95 (PSD-95)[24]. Lithium blocks increases in both ischemia-induced NR2A phosphorylation and PSD-95 interaction[25].

Cdk5 also regulates signaling mediated by NMDA receptors, either directly through phosphorylation of the NR2B subunit or indirectly through phosphorylation of PSD-95[26-27]. Cdk5 activity is primarily regulated by its co-activator p35, but when it binds to p25 (the product of calpain-mediated cleavage of p35), Cdk5 becomes pro-apoptotic and its activity becomes dysregulated[28-29]. Sustained activation of Cdk5 in neurons is believed to be involved in many neurodegenerative diseases[30]. In cultured rat CGCs, lithium pretreatment prevents colchicine-induced apoptosis, associated increases in Cdk5 expression, and fragmentation of p35 to p25[31]. In cultured primary brain neurons and rat brains, moreover, pretreatment with lithium also reduces intracellular calcium increase, calpain activity, Cdk5 activation, and cellular death induced by 3-nitropropionic acid (3-NPA)[32]—a succinate dehydrogenase inhibitor used to induce striatal pathology similar to that observed in HD[33].

Using cultured rat CGCs as a model to investigate the mechanisms underlying human neuropathology, researchers have associated excitotoxicity with down-regulation of the cytoprotective Bcl-2 protein and also with up-regulation of pro-apoptotic proteins such as Bax and p53[34]. Apoptotic death in cultured rat CGCs, furthermore, was found to require activation of both JNK and p38 mitogen-activated protein kinase (MAP kinase), which led to a robust increase in AP-1 binding before apoptotic death[35]. Long-term treatment with therapeutic concentrations of lithium, however, was found to prevent both the signaling events and the sharp increase in apoptosis.

2.2 Inhibition of GSK-3 and stabilization of β-catenin

Under non-stimulated basal conditions, GSK-3, an enzyme with α and β isoforms that is pro-apoptotic and appears to be a major regulator of inflammation, is considered to be constitutively active. Dysfunction of this enzyme, moreover, has been implicated in the pathophysiology of mood disorders, AD, diabetes, cancer, and inflammatory and autoimmune diseases[36-37]. It has recently been suggested that lithium's mood-stabilizing, neurogenetic, neurotrophic, neuroprotective, and anti-inflammatory effects stem, at least in part, from its ability to inhibit the kinase activity of GSK-3[36, 38-39]. This ability arises from the fact that lithium is a competitive inhibitor of magnesium. Since GSK-3 catalysis is dependent on ATP-magnesium, lithium can inhibit its kinase activity directly[40-41].

Lithium also inhibits GSK-3 activity indirectly. At therapeutic concentrations, it has been shown to enhance phosphorylation of GSK-3α at Ser21 and GSK-3β at Ser9. Researchers have identified a number of mechanisms that contribute to this effect, including cAMP-dependent activation of PKA [3, 42], PI3K-dependent activation of PKC[43] and Akt[44], and auto-regulation involving inhibitor-2 complex activity, which enhances the inhibition of protein phosphatase-1[45]. Others have shown that in vitro and in vivo, lithium treatment can decrease GSK-3β transcription[46]. It also inhibits GSK-3 by negatively regulating the calcium-dependent protease calpain, whose N-terminal cleavage upregulates the activity of GSK-3β kinase[47]. The fact that GSK-3 activation has been linked to apoptotic cell death induced by a variety of neural insults including glutamate excitotoxicity[48] makes it highly likely that neuroprotective effect of lithium stems mainly from its ability to inhibit GSK-3. In fact, when RNA interference depletes either of the 2 GSK-3 isoforms in neurons cultured from the rat cerebral cortex, glutamate-induced excitotoxicity is blocked[49]. By the same token, transfection with isoform-specific dominant-negative mutants of GSK-3 or treatment with other non-selective pharmacological GSK-3 inhibitors also results in

lithium-like neuroprotection against glutamate excitotoxicity. Although GSK-3α and GSK-3β could have distinct roles in transcriptional regulation and cell survival[49-50], these results strongly suggest that both are involved in the execution of glutamate-induced neuronal death, and that both isoforms are initial targets of lithium-induced neuroprotection.

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. After being phosphorylated by GSK-3, β-catenin undergoes proteasomal degradation[51]. Increases in cytoplasmic accumulations of β-catenin facilitate its translocation into the nucleus. There it conjoins with T-cell-specific transcription factor (Tcf)/lymphoid enhancer binding factor (Lef), enhances the transcription of growth factors[52-53], and enhances genes involved in apoptotic inhibition[54]. Results such as these have led some to propose elevating β-catenin as a novel therapeutic strategy for treating mood disorders. In support of this theory, treatment with lithium increases β-catenin levels both in vitro[11] and in vivo[55-56], and promotes β-catenin-dependent transcriptional events[51, 56]. These results indicate that lithium-induced accumulation of β-catenin could be relevant to its neuroprotective and therapeutic effects.

2.3 Induction of survival molecules in the brain

In addition to the prophylactic qualities described above, in rat brains and cultured CGCs chronic lithium treatment has been found to induce Bcl-2 expression in the frontal cortex[11, 34]. 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[57-58]. The ability to maintain calcium homeostasis in the ER is another cytoprotective action of Bcl-2[59-60]. We have associated chronic lithium's ability to induce upregulation of Bcl-2 in PC12 cells with its cytoprotective effects against Aβ peptide and thapsigargin-induced ER stress[12, 61]. In the rat brain, chronic treatment with valproate—a mood-stabilizing drug, anticonvulsant, and histone deacetylase inhibitor[62-64] often used in BD patients with poor response to lithium—also upregulates Bcl-2[11]. A recent study shows that, in SH-SY5Y cells, Bcl-2 translation is directly inhibited by expression of the specific microRNA miR-34a[65]. In the rat hippocampus and in primary cultures of hippocampal neurons, chronic treatment with lithium or valproate decreases levels of several microRNAs, including miR-34a[66], suggesting a common regulator shared by these structurally dissimilar mood stabilizers and indicating that a novel target accounts for their therapeutic efficacy.

BDNF, a major neurotrophin essential for cortical development, synaptic plasticity, and neuronal survival, is likely one of the mediators of the clinical efficacy of antidepressants and anxiolytics[67-68]. Long-term treatment of cultured cortical neurons with lithium induces BDNF, which in turn increases phosphorylation at the Tyr490 residue and activates its tyrosine receptor kinase B (TrkB) receptor[69]. Chronic treatment of rats with lithium also increases protein levels of BDNF in various brain regions, but without altering the expression of TrkB[70-71]. Recent study in cultured cortical neurons further reveals 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[72]. Notably, this effect can be mimicked by the pharmacological inhibition of GSK-3 or by the siRNA-mediated gene silencing of either the GSK-3α or GSK-3β isoform. By the same token, adding the Trk-tyrosine kinase inhibitor K252a, or a BDNF-neutralizing antibody, counteracts lithium's ability to protect neurons from excitotoxicity[69]. In cultured cortical neurons, heterozygous or homozygous knockout of the BDNF gene also blocks lithium's neuroprotective effects completely.

Researches in vitro and in vivo have further shown that lithium treatment increases the expression of VEGF[52, 73-74], in all probability by inhibiting GSK-3β and stabilizing β-catenin signaling. VEGF promotes cell proliferation[75], proneuronal differentiation of newly born cells[76], migration of immature neuroblasts[76-77], and neurovascular remodeling after stroke[74, 76, 78]. By upregulating VEGF, lithium treatment optimizes skeletal myoblast functions for cellular cardiomyoplasty in vitro[79] and prevents stress-induced reductions in VEGF levels[52], and promotes angiogenic and anti-apoptotic signaling in rat ischemic preconditioned myocardium[74].

HSPs are a group of molecular chaperones that promote the folding of proteins and refolding of misfolded proteins. They also inhibit protein aggregate formation and, through the ubiquitin-proteasome system, facilitate the degradation of abnormally folded

proteins[80-81]. Among HSPs, HSP70 exerts a wide variety of neuroprotective effects against apoptosis[82]. In various animal models, overexpression of HSP70 has been recognized as a potential therapeutic target against ischemic neuronal injury[83-85]. The expression of HSP70 is regulated by HSF-1[86], a transcription factor negatively regulated by GSK-3β-dependent phosphorylation[87]. Not surprisingly, therefore, GSK-3β activity correlates negatively with both DNA binding activity of HSF-1 and HSF-1-dependent transcription[86, 88]. In light of the fact that lithium's inhibition of GSK-3 is associated with the activation of HSF-1, upregulation of the heat-shock response may account for some part of the neuroprotective effect of lithium.

2.4 Induction of autophagy

Autophagy—a physiological process for degrading cytoplasmic proteins or organelles in bulk—has recently been recognized as a principal response to cellular stress and an important regulator of neuronal function and survival. As a 'quality control' process, autophagy is believed to be particularly beneficial in neurodegenerative disorders (AD, PD, ALS, spinocerebellar ataxia type 3, and HD) characterized by the accumulation of misfolded disease-causing proteins[89-92]. Authophagy appears to be negatively regulated by the mammalian target of rapamycin (mTOR). By inhibiting mTOR, rapamycin upregulates autophagy and this has been shown to be beneficial in various models of neurodegenerative diseases[89-91]. Other mechanisms for inducing autophagy include inhibiting inositol monophosphatase and inositol transporters[93]. Lithium's ability to deplete free inositol and subsequently decrease IP3 levels was recently identified as a novel route (independent of mTOR) for inducing autophagy[94-95] and its attendant benefits.

2.5 Induction of neurogenesis

Lithium was found to stimulate progenitor proliferation in cultured brain neurons and to prevent the loss of proliferation induced by glutamate or glucocorticoids[96]. In addition, chronic lithium treatment not only enhances neurogenesis in the hippocampus of normal mice[97], but also restores neurogenesis in the brain in an animal model of Down syndrome[98].

In primary rat hippocampal progenitor cultures, long-term lithium treatment promotes the conversion of these progenitor cells into neurons through the GSK-3β inhibition/β-catenin activation pathway[99-100]. 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[101]. One possible common downstream event related to neurogenesis is lithium-induced upregulation of BDNF, which is necessary for hippocampal neurogenesis[102].

3 CLINICAL IMPLICATIONS AND APPLICATIONS

3.1 BD

Because lithium has been the mainstay of treatment for bipolar disorder, understanding the mechanisms underlying its neuroprotective effects could well provide insights into potential causes of the disease. With few exceptions, for instance, drugs prescribed to treat BD work by conferring some measure of neuroprotection[103-104]. As observed in rodent models, the antidepressant and antimanic effects of lithium are most likely due to the inhibition of the kinase GSK-3[56, 105-106], whose overexpression in mice produces behavioral correlates of hyperactivity and mania[107]. Drugs or genetic approaches that inactivate GSK-3β also alleviate depressive-like behaviors in mice expressing a mutant form of the brain serotonin-synthesizing enzyme[108], while administering lentiviral-mediated GSK-3β shRNA into the dentate gyrus of mice subjected to chronic stress appears to have an antidepressant-like effect[109]. By the same token, genetic inactivation of GSK-3α in mice appears to have a similar antidepressant-like effect, as measured by decreased immobility time and fewer aggressive-like behaviors in behavioral tests[110]. 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[111]. It is also interesting to note that lithium, valproate, and lamotrigine all enhance the serine phosphorylation of GSK-3[39, 112]. These findings not only support the hypothesis that lithium's therapeutic effects stem primarily from its inhibition of GSK-3, they also support

the targeting of GSK-3-linked pathways in our search for new ways to treat BD.

3.2 Stroke

Most strokes are caused by cerebral ischemia, which is the interruption of blood supply to the brain. 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)[113], but also in transient MCAO models followed by reperfusion[114], which more closely approximate the pathophysiology of acute stroke. The complex mechanisms underlying lithium's neuroprotective effects may include inactivation of NMDA receptors[25], downregulation of pro-apoptotic p53 and upregulation of anti-apoptotic Bcl-2 and HSP70[115], resulting in reduced apoptotic cell death[114], activation of the PI3K/Akt cell survival pathway[44] and inhibition of hypoxia-induced activation of GSK-3[116]. When administered up to three hours after the onset of ischemia, post-insult treatment with therapeutic doses of lithium also markedly decreases infarct volume. In a rat model of transient MCAO, lithium has been shown to suppress neurological deficits as measured by sensory, motor, and reflex tests[117]. These beneficial effects are associated with the activation of HSF-1 and induction of the cytoprotective protein HSP70 in ischemic brain hemispheres. A functional MRI study further showed that even delayed chronic lithium treatment (administered up to 12 hours after the onset of ischemia and followed by daily injections for 2 weeks) significantly improved functional MRI response magnitude, which is dependent on blood oxygenation levels, and vascular formation[118]. The ability of lithium to affect neurovascular remodeling may be related to its ability to increase protein levels of matrix metalloproteinase 9 (MMP-9) and VEGF[73]. VEGF has, in fact, been linked to angiogenesis, neurogenesis, and neuroprotection[119]. These preliminary demonstrations of lithium's pre- and post-insult beneficial effects suggest that it may ultimately become a valuable clinical tool for both the prevention and treatment of acute stroke.

3.3 HD

HD is an inherited, autosomal-dominant, neurodegenerative disease characterized by irreversible physical and mental deterioration[120]. It is caused by abnormal expansion of a trinucleotide CAG-repeat in the gene that encodes a polyglutamine stretch in the N-terminus of huntingtin, the disease-causing protein[121]. This abnormal expansion results in a selective loss of neurons in the striatum and cortex[9, 122]. Transcriptional dysregulation also plays a central role in the pathogenesis and pathophysiology of this disease[123]. HD is lethal, and currently there is no treatment proven to arrest or reverse its course.

Because the supersensitivity (or hyperactivation) of NMDA receptors appears to contribute to the pathophysiology of HD[124], lithium's protective properties against glutamate toxicity would seem to make it ideally suited to treat this disease. In the rat excitotoxic model induced by quinolinic acid (QA), lithium treatment markedly reduces the size of QA-induced striatal lesions[61] and the loss of striatal medium-sized neurons[125]. This lithium protection is correlated with upregulation of cytoprotective Bcl-2 and downregulation of caspase-3 activation. In a cell model of HD, the protective effects of lithium in reducing mutant huntingtin aggregates and cell death are mimicked, either by treatment with a GSK-3β inhibitor or by overexpression of a dominant-negative GSK-3β mutant[126]. In *Drosophila*, a GSK-3β inhibitor mimics lithium-induced protection against the toxicity of aggregate-prone proteins[127]. 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[125]. In a rat 3-NP model of HD, lithium treatment reduces striatal neurodegeneration by preventing the activation of calpain and Cdk5[33]. In *Drosophila* and R6/2 mouse models of HD, systemic administration of rapamycin induces autophagy and reduces toxicity of polyglutamine expansions[90]. Moreover, in cellular and *Drosophila* models of HD, lithium combined with rapamycin induces autophagy and shows greater protection against neurodegeneration than either pathway alone[128]. In R6/2 mice, although lithium treatment administered post- (but not pre-) symptomatically significantly improves rotarod performance, it appears to have no effect on survival overall[129]. However, in the N171-82Q and YAC128 mouse models of HD, pre-symptomatic cotreatment with lithium and valproate produces more robust improvements in motor deficits and stronger anxiolytic and antidepressant-like effects than either drug alone[130]. Evidence of these neuroprotective properties in models of HD suggests that lithium, es-

pecially in combination with other medications, may prove useful as a treatment for HD.

3.4 AD

AD is characterized by progressive memory loss and personality changes, ultimately leading to dementia. The neuropathological hallmarks of AD are an abnormal accumulation of Aβ and neurofibrillary tangles (tauopathies) resulting from hyper-phosphorylation of *tau*, a microtubule-binding protein[131]. The association of pathogenesis and neuronal death in AD with abnormal increases in GSK-3 levels and activity[132] suggests a possible role for lithium in treating this disorder[133]. In vivo and in vitro, lithium reduces *tau* phosphorylation by inhibiting GSK-3[134-135]. *Tau* phosphorylation levels are also regulated by protein phosphatase 2A (PP2A)[136], and reduced PP2A activity in the brain has been reported in individuals with AD[137]. In rats, lithium treatment has been shown to increase PP2A activity[138], decrease *tau* phosphorylation, and facilitate its destruction[139]. In cultured cortical neurons, lithium was also recently shown to downregulate *tau* transcription[140]. Chronic lithium treatment also blocks Aβ production through GSK-3 inhibition[141]. 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[142]. 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[14, 134, 143]. It is further 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[65], a microRNA that has recently emerged as a common lithium and valproate target[66]. These findings suggest a novel mechanism for lithium's protective effects against AD in which the downregulation of miR-34a indirectly upregulates Bcl-2.

Experiments with various animal models of AD have shown a number of other benefits from lithium. In mouse models of *tau*opathies, chronic lithium treatment not only inhibits *tau* phosphorylation and neuronal degeneration mediated by GSK-3[144], it also decreases *tau* lesions by promoting ubiquitination[145]. In addition, in mutant *tau* transgenic mice with advanced neurofibrillary pathology, chronic lithium treatment decreases aggregation of mutant *tau* proteins[146] and arrests the development of neurofibrillary tangles[147]. Chronic lithium treatment in rats has also been shown to activate the Wnt/β-catenin pathway, and thereby to protect against Aβ-induced hippocampal neurodegeneration[148]. With regard to lithium's behavioral effects, *Drosophila* models of tauopathies show that its inhibition of GSK-3β reverses locomotor deficits[149]. In rats injected with preformed Aβ fibrils, chronic lithium treatment improves spatial learning deficits[148]. In transgenic mice overexpressing human APP, 3 months of treatment with lithium have been shown to reduce the burden of Aβ, *tau* hyper-phosphorylation, and neurodegeneration in the cortex and hippocampus. In addition, the inhibition of GSK-3β signaling normalizes deficits in water-maze performance[150]. Clinically, a preliminary study in individuals with BD found that a history of lithium treatment resulted in significantly better cognition and memory scores compared with individuals receiving other treatments[151]. In elderly BD patients, moreover, chronic lithium treatment reduced the prevalence of AD[152]. Taken together, these results suggest a promising therapeutic role for lithium in the treatment of AD.

3.5 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 in the substantia nigra. PD is another neurodegenerative condition characterized by aggregates of mutant protein (Lewy bodies), mainly α-synuclein[153-154]. In animal models, neurotoxins such as rotenone, 6-hydroxydopamine (6-OHDA), 1-methyl-4-phenylpyridinium (MPP^+), and the MPP^+ precursor N-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) can trigger PD-associated neurochemical changes. In these models, therapeutic concentrations of lithium have been shown to facilitate clearance of the mutant form of α-synuclein, an autophagy substrate[94]. In cultured human neuroblastoma cells, GSK-3β activation facilitates the activation of caspase-3 induced by rotenone, a mitochondrial complex I-inhibitor, or by MPP^+. By the same token, lithium treatment inhibits the activation of caspase-3 in a PI3K-dependent manner[155]. In cultured neurons, it prevents 6-OHDA[156] and MPP^+-

induced neuronal death. In addition, chronic lithium treatment in mice prevents MPTP-induced neurotoxicity, normalizes the downregulation of Bcl-2, and normalizes the upregulation of Bax elicited by MPTP in the striatum of the mouse brain[157]. Experimental evidence of these protective effects suggests that lithium may have substantial therapeutic potential in the treatment of PD.

3.6 Fragile X syndrome (FXS)

FXS is caused by abnormal expansion of the trinucleotide (CGG) repeat-mediated transcriptional silencing of the fragile X mental retardation-1 (*FMR1*) gene[158] that encodes the fragile X mental retardation protein (FMRP)[159]. A recent study found that in FVB/NJ *FMR1* knockout mice, the inhibitory serine-phosphorylation of GSK-3 is impaired[160], suggesting a possible therapeutic role for lithium. In a *Drosophila* model of FXS, adulthood lithium treatment increases naive courtship and restores short-term memory[161]. Moreover, in the *Drosophila* model, treatment with metabotropic glutamate receptor (mGluR) antagonists or lithium prevents age-related cognitive impairments, and continuous treatment during aging effectively rescues these deficits[162]. Mouse models of FXS display certain FXS- and autism-relevant behavioral phenotypes[163-165], several of which are ameliorated with lithium treatment[160, 166]. Chronic lithium treatment of FXS mice largely blocks aberrant dendritic spine morphology and reduces anxiety levels, deficient social interactions and impaired learning ability[167]. Lithium's beneficial effects on FXS mouse brains are associated with normalization of hypo-phosphorylation of GSK-3β at Ser9. A pilot clinical study has confirmed similar benefits from lithium treatment in FXS patients aged 6 – 23 years, who showed improvements in behavior, adaptive skills, and cognition[168].

3.7 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 5 years of disease onset[169]. Mice expressing mutant Cu/Zn superoxide dismutase 1 (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 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[170]. 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[171-173]. Combined treatment of ALS mice with lithium and valproate produces a greater and more consistent effect than monotreatment with either drug in delaying the onset of disease symptoms, decreasing neurological deficit scores, and prolonging life span[174]. Moreover, a 15-month pilot clinical trial in randomized ALS patients found that patients treated with lithium and riluzole together showed markedly reduced mortality than patients treated with riluzole alone[172]. Since inconsistent results have also been reported[175-177], however, further studies are needed to clarify these discrepancies.

3.8 Multiple sclerosis (MS)

MS is the most common inflammatory demyelinating disease of the CNS, which causes demyelination and neurodegeneration with lesions predominantly in the white matter[178]. The most frequently used animal model of MS is experimental autoimmune encephalomyelitis (EAE)[179] induced in mammals by systemic injection of myelin oligodendrocyte glycoprotein (MOG), myelin basic protein, or proteolipid protein[180]. A recent study demonstrates that in knock-in mice expressing constitutively active GSK-3, EAE develops more rapidly and is more severe[181], suggesting that GSK-3 kinase may be a potential therapeutic target for the treatment of MS. Administration of GSK-3 inhibitors in mice has been shown to control several inflammatory and immune conditions in both the periphery and the CNS[36]. 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[181]. 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 lithium may be useful for therapeutic intervention in autoimmune and inflammatory diseases such as MS, which afflict the CNS.

4 CONCLUSION

Studies from various laboratories confirm that, in a vast number of cellular and animal models of brain disorders, lithium has robust therapeutic effects. It is also becoming increasingly clear that lithium's inhibition of GSK-3, whose hyperactivity is involved in cell death and the pathophysiology of many neurodegenerative conditions, accounts for much of its ability to protect and even increase neurons. GSK-3 inhibition plays a prominent role in activating signaling pathways and inducing anti-apoptotic and neurotrophic proteins. The lithium-induced inhibition of the metabolism of phosphoinositide and production of IP3 also appears to be involved in upregulating autophagy—a process critical for the clearance of protein aggregates associated with neurodegenerative diseases. Emerging evidence suggests that the mood-stabilizers lithium and valproate target specific microRNAs that regulate the expression of anti-apoptotic proteins and are perhaps involved in the pathophysiology of brain disorders. Further microRNA research is therefore needed to investigate the etiology of these diseases and elucidate lithium's mechanisms of action.

As can be seen from the review provided above, research with animal models has confirmed the beneficial effects of lithium treatment in an increasing number of CNS disorders. Many preclinical studies report evidence of significantly decreased neurodegeneration, enhanced neurogenesis, improved behavioral performance, improved cognitive function, and prolonged survival. Based on promising preclinical results and its long history of safe clinical use in humans, lithium is currently being tested as a treatment for a variety of human brain disorders. Results to date are mixed. While some clinical studies report promising improvement, others indicate no treatment response. Resolving discrepancies such as these requires large-scale clinical trials of long duration—an expensive undertaking difficult to envision in this era of restricted budgets. Yet, in light of the results from recently completed preclinical studies, combined treatment with lithium and other neuroprotective drug(s) is recommended for adequate clinical testing to ameliorate the devastating effects of neurodegenerative diseases and psychiatric disorders that currently exact so great a human toll.

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