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Neuroprotective Effects of Lithium Relevant to Its Therapeutic Actions

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Objective : Lithium has been used as a mood stabilizer for more than 50 years since its first use in the treatment of bipolar disorder. However, the mechanisms of its therapeutic actions remain unclear. Previous studies have shown neuroprotective and stress-attenuating effects of lithium which are thought to be related to its therapeutic actions. This article reviewed neuroprotective and stress-attenuating effects of lithium by searching data from previous studies.

Methods : The literature on neuroprotective and stress-attenuating effects of lithium was searched using PubMed.

Results : Lithium has the ability to protect neurons against a variety of insults. Lithium has been shown to prevent or attenuate the altered neural plasticity induced by stress at the molecular, structural, and behavioral levels, at least in animal studies. Neuroprotective effects of lithium have also been demonstrated in patients with bipolar disorder. The neuroprotective mechanisms of lithium include up-regulation of cytoprotective proteins, such as bcl-2, direct and indirect inhibition of glycogen synthase kinase 3-β, down-regulation of pro-apoptotic proteins, such as p38 and Bax, and activation of cAMP response element binding protein, with the resulting up-regulation of neurotrophic factors, such as brain-derived neurotrophic factor.

Conclusion : These neuroprotective and stress-attenuating effects may contribute to the therapeutic actions of lithium.

KEY WORDS : Lithium; Mood stabilizer; Bipolar disorder; Neurotrophic factors; Stress; Neuroprotection.

INTRODUCTION

Lithium has been used to treat acute manic episodes and to prevent relapses in bipolar disorder (BPD). Lithium is also used as an augmenting agent for some depressive patients. Although lithium is a leading mood stabilizer, the mechanism of its therapeutic actions remains unclear.

Previous studies have demonstrated that lithium regulates multiple target molecules in neuroprotective signaling pathways. The regulation of multiple targets involves modulation of receptor function, up-regulation of neuroprotective proteins, such as bcl-2 and brain-derived neurotrophic factor (BDNF), and down-regulation of pro-apoptotic proteins, such as Bax and p38.[1-6)]

As discussed below, lithium has been shown to prevent or attenuate stress-induced neural plasticity. Stress, which is thought to be related to mood disorders and post-traumatic stress disorder, induces altered neural plasticity at the molecular, structural, and behavioral levels.

The effects of stress on the hippocampus have been studied more extensively than its effects on other brain regions. Acute and chronic stresses have been shown to decrease BDNF expression in the rat hippocampus.[7)] Cellular atrophy and cell death have been shown to be induced in hippocampal subregions by repeated stress.[8-10)] Deficits in hippocampus-dependent memory were demonstrated in patients with post-traumatic stress disorder[11)] and in rats under chronic stress.[12)] Impairment of long-term potentiation (LTP) by acute and chronic stress, a manifestation of stress-induced synaptic plasticity, is well known.[13-15)]

Patients with BPD consistently show impairments in neural plasticity. Lowered serum or plasma BDNF levels are seen during depressive and manic episodes.[16,17)] Reduction in gray matter volume, a manifestation of altered structural plasticity, has been demonstrated in specific brain regions, such as the prefrontal cortex, hippocampus, and ventral striatum in patients with mood disorders.[18-20)] Moreover, chronic treatment with lithium was found to increase the total brain volume in patients with BPD.[21)]

The results of these studies suggested that lithium may exert its anti-bipolar properties at least through neuroprotective and anti-stress effects. Major findings concerning these neuroprotective and anti-stress effects are described in detail below.

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PROTECTION AGAINST EXCITOTOXICITY

Lithium is known to protect neurons against cholinergic and glutamatergic excitotoxicity. Ibotenic acid-induced cholinergic excitotoxicity in the nucleus basalis of the rat was attenuated by subchronic lithium treatment, as assessed by behavioral parameters and choline acetyltransferase activity.[22)]

Lithium is well known to prevent glutamate-induced excitotoxicity. Chuang and his colleagues demonstrated that lithium pretreatment for seven days dose-dependently prevented glutamate-induced apoptosis in primary cerebellar granule cell culture.[23)] Glutamate-induced apoptosis of cerebellar granule cells was blocked by NMDA receptor antagonists, and lithium also blocked apoptosis induced by direct exposure to NMDA.[24)] The protective effect of lithium against glutamate-induced excitotoxicity in cortical cells was more robust than that in cerebellar granule cells. The same group also demonstrated that lithium treatment for six days before glutamate stimulation prevented glutamate excitotoxicity in cortical cells, which was also time-dependent and mediated by NMDA receptors.[25)] Even at low concentrations (0.1−0.2 mM), lithium significantly prevented glutamate excitotoxicity, with a nearly complete block at 1 mM. This neuroprotective effect involves inhibition of NMDA receptor activity.

Pretreatment with lithium reduces the level of phosphorylation of the NMDA receptor NR2B subunit at Tyr1472 and Ca^{2+} influx, which were thought to contribute to the neuroprotective effect against glutamate excitotoxicity.[25)] The lithium-induced reduction of phosphorylation of NR2B at Tyr1472 was shown to be mediated by inhibition of phosphorylation of Src kinase by lithium pretreatment.[26)]

Other mechanisms involve activation of cell survival pathways. These include the phosphatidylinositol-3 kinase (PI3 kinase)/Akt signaling pathway,[27)] suppression of the pro-apoptotic proteins, p53 and Bax,[28,29)] and enhancement of expression of the cytoprotective protein, bcl-2.[6,30)]

Chronic lithium administration to cultured rat cerebral cortical neurons has been shown to inhibit glutamate-induced increases in intracellular free calcium concentration, lipid peroxidation, protein oxidation, DNA fragmentation, and cell death, without affecting the basal levels of these oxidative stress parameters or cell death.[31)] These findings suggest that inhibition of oxidative stress is another neuroprotective mechanism of action of lithium.

Neuroprotection against glutamate excitotoxicity also requires the involvement of BDNF and the TrkB receptor. Hashimoto *et al.*[32)] reported that lithium increased the cellular BDNF content. They showed that both lithium and BDNF protected cortical cells from glutamate excitotoxicity and that the protective effect of lithium disappeared in the presence of a BDNF neutralizing antibody and TrkB receptor antagonists. BDNF binding to its receptor, TrkB, causes TrkB receptor dimerization. The dimerized TrkB receptor then undergoes autophosphorylation, which recruits the adaptor protein, shc, which in turn activates the PI3 kinase/Akt and mitogen-activated protein kinase (MAPK)/extracellular signalregulated kinase (ERK) pathways.[33)] BDNF plays a central role in cell differentiation, survival, and neuronal plasticity, and is involved in LTP, memory, and learning.[33)] Activation of the PI3 kinase/Akt pathway suppressed p53-mediated apoptosis and enhanced the expression of bcl-2. In fact, Chen and Chuang[28)] reported that chronic lithium treatment dose-dependently decreased the expression of p53 mRNA and protein. Bax mRNA and protein expression were also decreased by chronic lithium treatment. On the other hand, bcl-2 mRNA and protein expression were increased by lithium.[28)] In a study by Chuang and colleagues[27)] that demonstrated an anti-apoptotic effect of lithium in cerebellar granule cells, lithium administration was shown to induce rapid activation of PI3 kinase followed by increased phosphorylation and activation of Akt; this Akt activation by lithium was blocked by PI3 kinase inhibitors.

Kang *et al.*[34)] reported that lithium exerted anti-apoptotic effects by activating PI3 kinase and consequently phospholipase Cγ (PLCγ) activation in cortical cells exposed to NMDA. These findings indicate that lithium-induced PI3 kinase activation follows at least two pathways in neuroprotection, involving Akt and PLCγ activation.

Activation of the MAPK/ERK cascade is important in cell division, survival, and differentiation.[33)] Some MAPKs, such as c-Jun N terminal kinase (JNK) and p38 kinase, are thought to play roles in apoptosis.[24,35)] Glutamate-induced excitotoxicity can be suppressed by long-term lithium pretreatment or curcumin, a purported inhibitor of JNK signaling and AP-1 binding.[24)]

Chuang *et al.*[36)] reported that lithium also has the ability to protect against a variety of apoptotic insults in addition to glutamate excitotoxicity. Lithium protected cultured rat cerebellar granule cells against apoptosis induced by the anti-convulsants phenytoin and carbamazepine.[36)] Age-induced apoptosis in culture, a phenomenon in which cerebellar granule cells die abruptly after 15 or 16 divisions, is inhibited by lithium pretreatment. Lithium also suppressed apoptosis of cerebellar

granule cells exposed to low concentrations of extracellular potassium.[36]

NEUROPROTECTIVE ACTIONS OF LITHIUM AGAINST EXCITOTOXICITY IN ANIMAL DISEASE MODELS

Lithium is known to attenuate quinolinic acid (QA)-induced excitotoxicity, an animal model of Huntington's disease. Pretreatment with lithium for 1 or 16 days markedly diminished QA-induced loss of medium-sized spiny striatal neurons.[37] Lithium pretreatment also reduced QA-induced caspase 3 activation and DNA damage. Lithium pretreatment 24 hours prior to and one hour after QA infusion into the rat striatum also significantly reduced loss of medium-sized striatal neurons immunopositive for NeuN and reduced caspase 3 activation. Lithium pretreatment not only protected neurons against apoptosis, but also stimulated neuronal and astroglial progenitor proliferation in the injured striatum in the QA excitotoxicity model.[37]

Despite these neuroprotective effects, lithium actually potentiates a certain type of cell death. Lee *et al*.[38] demonstrated that lithium potentiated $FeCl_2$-induced necrosis in mouse cortical cell culture by increasing production of oxygen free radicals. However, the clinical implications of this finding are unclear, although such a necrosis-potentiating effect may be related to the toxic effects of lithium.

Neuroprotection is also seen at the spinal motor neuron level. A recent study demonstrated that lithium robustly inhibited Fas-mediated neuronal apoptosis and enhanced survival time and motor function in a model of amyotrophic lateral sclerosis in transgenic G93A mice.[39] However, lithium did not prevent oxidative stress, which is consistent with the results of an earlier study.[38]

Lithium reduced apoptotic cell death following focal cerebral ischemia. In the middle cerebral artery occlusion (MCAO) model, a 16-day pretreatment with lithium significantly reduced MCAO-induced neurological deficits and decreased the amount of brain damage.[40] In the MCAO/reperfusion model, a more pathophysiologically relevant model, lithium administration resulted in a reduction of infarct volume even after the onset of ischemic insult.[41] Lithium also up-regulated heat shock protein 70 (HSP 70) in the infarct area, which contributed to cellular resilience. Bax expression in glial cells of MCAO/reperfusion rats was decreased by lithium treatment, suggesting that apoptotic glial death resulting from MCAO was prevented by lithium.[41]

Lithium is known to be able to prevent β-amyloid-induced neuronal toxicity. β-amyloid- induced cell death in pheochromocytoma (PC 12) cells and cerebellar granule cells was inhibited by long-term (7 days), but not short-term (1 day), pretreatment with lithium. Up-regulation of bcl-2 was seen with lithium pretreatment, which may contribute to the prevention of this type of cell death.[42] Lithium has also been demonstrated to reduce hyperphosphorylation of tau protein. β-amyloid-induced hyperphosphorylation and cell death in rat cortical neurons were also inhibited by lithium.[43]

GLYCOGEN SYNTHASE KINASE-3β (GSK-3β) AND LITHIUM

Glycogen synthase kinase-3 (GSK-3) was first identified as a negative regulator of glycogen synthesis that phosphorylates and thus inhibits glycogen synthase.[44,45] Two isoforms have been identified to date, GSK-3β and GSK-3α.[46] GSK-3 is a unique kinase that is constitutively active and is deactivated by phosphorylation, whereas most kinases are inactive in cells and are often activated by phosphorylation.[45] Activation of the Wnt signaling pathway results in dissociation of GSK-3 from β-catenin, which prevents phosphorylation of β-catenin. Non-phosphorylated β-catenin can enter the nucleus and act as a transcription factor.[44,45] PI3 kinase and Akt activation lead to phosphorylation at a serine residue and the resulting inactivation of GSK-3. Other kinases that deactivate GSK-3 include protein kinase C, cAMP-dependent protein kinase, and ribosomal S6 kinase.[44,45]

Lithium is a selective GSK-3β inhibitor. GSK-3β inhibits the activation of several transcription factors that are important in cell survival.[47] Lithium and valproate administered to rats for 9 days increased cytosolic β-catenin in the frontal cortex, a marker of *in vivo* GSK-3 activity.[48] GSK-3β plays a regulatory role in neuronal apoptosis. Overexpression of GSK-3β has been shown to induce apoptosis of PC 12 cells[49] and to potentiate staurosporine-induced caspase activation.[50]

Human SH-SY5Y neuroblastoma cells with GSK-3β overexpression are sensitive to stress-induced apoptosis, but spontaneous cell death does not occur. Lithium treatment was shown to attenuate GSK-3β-induced apoptosis.[47]

Yoshida *et al*.[51] reported that the cold water stress-induced increase in tau phosphorylation in the mouse hippocampus was attenuated by lithium pretreatment and that cold water stress increased the level of the active form of GSK-3β. These observations suggest that inhibition of GSK-3β by lithium may contribute to its neuroprotective effects.

The concept of altered GSK-3β activity has also been

used in animal models of mania. Pharmacological inhibition of GSK-3 resulted in antidepressant-like effects in rodents.[52] Transgenic mice constitutively expressing an active mutated form of GSK-3β (GSK-3β[S9A]) show hyperactivity and decreased habituation, expressed as reduced immobility in the forced swim test and an increased startle response respectively.[53] These mice also show reduced food and water intake. All these features are reminiscent of the manic phase of BPD. Locomotor hyperactivity was associated with mania and activation of the mesolimbic dopaminergic system in an animal model.[53] Lithium, a GSK-3β inhibitor, and the selective GSK-3β inhibitor, AR-A014418, reduced locomotor hyperactivity induced by amphetamine.[52] At least partially consistent with these findings, treatment with lithium and valproate before and during amphetamine administration prevented and reversed amphetamine-induced hyperactivity and the production of amphetamine-induced reactive oxygen species.[54]

PREVENTION OF STRESS-INDUCED NEURAL PLASTICITY

Stress-Induced Neural Plasticity

Stress causes altered neural plasticity at the molecular, structural, and behavioral levels. The effects of stress on neural plasticity have been studied most extensively in the hippocampus. It has been established that a variety of stresses reduce the expression of BDNF in the hippocampus.[7,55-59] Stress also alters neuronal morphology and neurogenesis in the hippocampus.

Chronic exposure to stress resulted in atrophy of CA3 neurons in the rodent hippocampus. Atrophy of apical dendrites of CA3 neurons was observed after daily restraint stress for 21 days. This effect was also seen after administration of glucocorticoids, doses of which approximated the levels induced by stress.[8] Psychosocial stress also caused atrophy of apical dendrites of CA3 neurons.[8-10] In the case of severe stress, death of CA3 neurons occurred. This stress effect on CA3 neurons is thought to be mediated by decreased glucose uptake, increased glutamate and Ca^{2+} excitotoxicity, and decreased BDNF expression.[60]

Adult neurogenesis of granule neurons is observed in rodents, non-human primates, and humans.[61,62] Stress also decreases neurogenesis of dentate gyrus granule neurons. Acute stress or exposure to high concentrations of glucocorticoids decreased neurogenesis in granule neurons.[63,64] Stress also caused deficits in synaptic plasticity. Impairments in LTP in the hippocampus have been observed after exposure to acute and chronic stress.[13-15]

Anti-Stress Effects of Lithium

Previous studies have demonstrated that lithium attenuates or prevents stress-induced neural plasticity. Chronic lithium treatment has been demonstrated to increase BDNF expression in the hippocampus.[65-67] It has also been demonstrated that chronic lithium treatment increases neurogenesis in the hippocampus, with accompanying increases in levels of cytoprotective or neurotrophic molecules, such as bcl-2 and BDNF.[68,69]

Given that stress down-regulated BDNF expression and neurogenesis in the hippocampus, this lithium-induced up-regulation of BDNF expression and neurogenesis may confer anti-stress effects.

More direct stress-attenuating effects of lithium have consistently been demonstrated in animal studies. Chronic treatment with lithium for 7 weeks reduced acute restraint-induced AP-1 DNA-binding activity in the rat frontal cortex and hippocampus.[70] Wood *et al*.[71] reported chronic stress effects in the hippocampus and the ability of lithium to counteract these effects. They demonstrated that 21 days of restraint stress caused atrophy of the apical dendrites of CA3 pyramidal cells, which was prevented by chronic lithium treatment. Chronic stress increased molecular markers of glutamatergic activity, glial glutamate transporter-1 mRNA, and phospho-CREB levels in the CA3 area and the dentate gyrus, which were also prevented by chronic lithium treatment.

Vasconcellos *et al*.[12] reported that a variety of stresses over a period of 40 days (chronic stress model) caused impairments in spatial memory that were dependent on the hippocampus; these impairments were attenuated by chronic lithium treatment. The same group also demonstrated the consistent finding that chronic treatment with lithium reversed chronic variable stress-induced impair-ments in spatial memory with concomitant decrease in Na^+, K^+-ATPase activity.[72]

Enhancement of LTP has been observed in the hippocampus by chronic[69,73] and subchronic[74] lithium treatment. Son *et al*.[69] demonstrated that acute (2 days) or chronic (28 days) treatment with lithium enhanced LTP in the dentate gyrus. They observed that LTP enhancement was accompanied by elevated levels of calcium and calmodulin-dependent protein kinase II, and phosphorylated forms of Elk, MAPK, and CREB. These properties suggest that lithium may attenuate or prevent stress-induced impairment of LTP. Indeed, it was suggested that lithium has a restoring effect on stress-induced impairment in LTP induction. <check: does his also refer to the Lim *et al*. paper (ref.75)?> Addition of lithium to artificial cerebrospinal fluid (aCSF) at therapeutic concentrations restored acute immobilization stress-induced

impairment of LTP induction in the CA1 region.[75] However, it remains poorly understood how acute addition of lithium to aCSF ameliorates the impairment of LTP induction.

Lithium is also able to counteract the early life stress-induced effect.[76] Subjection of rats to maternal deprivation for three hours per day during the period from postnatal day 2−14 reduced neuropeptide Y-like immunoreactivity (NPY-LI) in the hippocampus and striatum and increased NPY-LI and corticotrophin-releasing hormone-like immunoreactivity (CRH-LI) in the hypothalamus. Lithium treatment on postnatal days 50−83 counteracted the effects of maternal deprivation in the hippocampus and striatum by increasing NPY-LI. In the hypothalamus, lithium decreased CRH-LI.[76] These observations suggest that the anti-stress effects of lithium are mediated at least in part by increasing brain NPY. Lithium is also known to modulate stress-induced alterations in polyamine enzymes.[77] These findings suggest that lithium restores altered stress-induced neural plasticity through regulation of a variety of molecules in signaling pathways.

EFFECTS OF LITHIUM ON BDNF AND EXTRACELLULAR SIGNAL-REGULATED KINASE (ERK) PATHWAY

It is well known that chronic lithium and valproate treatment increase BDNF expression in the brain.[66,67] Lithium[67] and valproate[78] activate the ERK pathway, a major downstream pathway, in response to BDNF activation. Einat *et al.*[67] demonstrated the involvement of the ERK pathway in mood regulation. Their study demonstrated increased levels of phosphorylated molecules in the ERK pathway on treatment with lithium and valproate. They also demonstrated that the mitogen-activated protein/ERK (MEK) kinase inhibitor, SL327, which penetrates the blood-brain barrier, reduced the immobility time and increased the swimming time in the forced swim test. SL327 also induced locomotor hyperactivity in an open field test, and this effect was normalized after chronic lithium treatment. These SL327-induced changes were similar to those induced by amphetamine.[79]

Heterozygous BDNF (+/−) mutant mice showed increased activity in an open field test, increased aggression, increased food consumption, increased time spent in the center of a large open field (a measure of risk-taking behavior),[79,80] and an increased response to amphetamine.[81] TrkB gene knock-out mice also showed similar features of increased activity.[82] Taken together, these findings suggest that BDNF and the ERK pathway are involved in mood regulation and in the therapeutic actions of mood stabilizers, including lithium.

SUMMARY

The therapeutic properties of lithium have been attri-

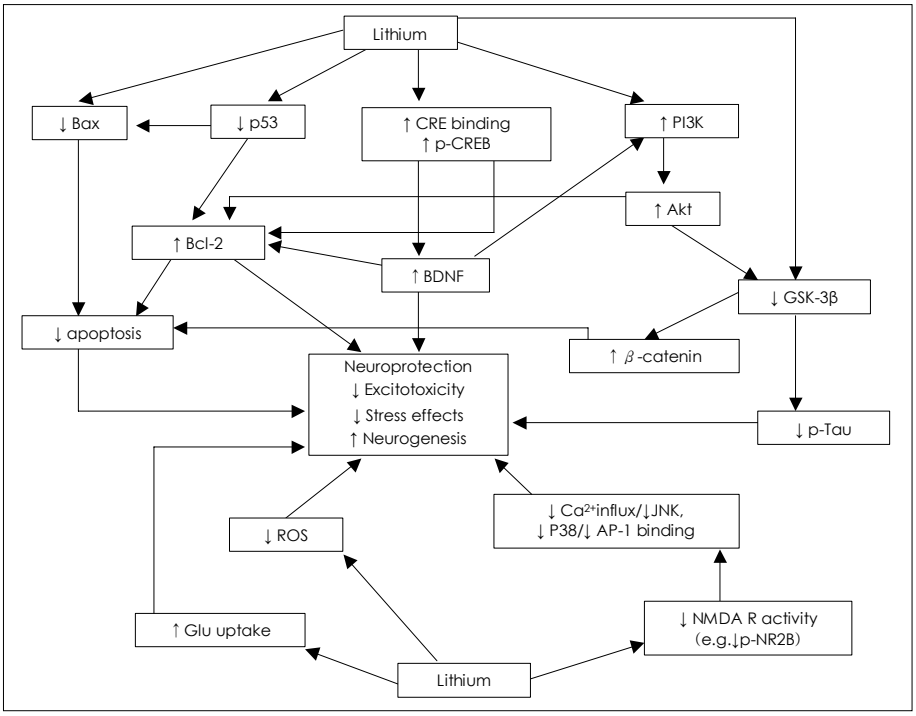

Fig. 1. Schematic representation of lithium-induced effects on signaling molecules. This figure is, in part, based on the study of Chuang *et al*.[24] ↑: Increase or activation of target molecules. ↓: Decrease or inhibition of target molecules. BDNF can increase the Bcl-2 level through activation of ribosomal S6 kinase (Rsk) in the BDNF-ERK pathway. Rsk can phosphorylate CREB, thus increasing the expression of Bcl-2.[5] CRE, cAMP response element; CREB, cAMP response element binding protein; Glu, glutamate; JNK, c-Jun N-terminal kinase; NMDA R, N-methyl-D-aspartate receptor; p-CREB, phosphorylated CREB; PI3K, phosphatidylinositol 3 kinase; p-NR2B, phosphorylated NR2B subunit of NMDA receptor; p-Tau, phosphorylated tau; ROS, reactive oxygen species.

buted to its neuroprotective effects, which include protection of neurons from diverse apoptotic insults and attenuation of stress-induced neural plasticity. Lithium mediates these neuroprotective effects through neuroprotective signaling pathways, involving NMDA receptor inactivation, inhibition of GSK-3β, and consequent inhibition of pro-apoptotic proteins, activation of cytoprotective proteins, and activation of the BDNF and ERK pathways. Fig. 1 presents a summary of the neuroprotective actions of lithium.

The suggestion that the neuroprotective activities of lithium are responsible for its therapeutic effects is further supported by the results of studies in bipolar patients. Patients with bipolar disorder show altered neural plasticity. Gray matter volume reduction in specific brain regions has been observed in such patients, and this volume reduction can be reversed by chronic treatment with lithium.[21] The N-acetyl aspartate level is reduced in bipolar disorder, and is also normalized after chronic treatment with lithium.[83]

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