Published in final edited form as:

Biol Psychiatry. 2007 July 1; 62(1): 4–6.

In Search of the Holy Grail for the Treatment of Neurodegenerative Disorders: Has a Simple Cation Been Overlooked?

De-Maw Chuang and Hussein K Manji

Mood and Anxiety Disorders Program National Institute of Mental Health

In recent years, there has been considerable excitement about the possibility that the “molecular medicine revolution” would lead to identification of numerous putative targets designed to slow the atrophic/degenerative process in various neuropsychiatric disorders. Indeed, tremendous progress was made in the identification of cellular processes and pathways involved in numerous degenerative diseases; however, to date, proliferation of candidate drugs has not resulted in viable novel clinical treatments for these devastating disorders (Heemskerk et al., 2002). Ironically, the paper by Bearden and associates in this issue of the journal suggests that an old medication present in our therapeutic armamentarium for half a century, exerts neurotrophic effects *not only in animal models, but also in humans*. Bearden et al. used high-resolution magnetic resonance imaging and cortical pattern matching methods to map gray matter differences in 28 bipolar patients; 20 lithium-treated, and 28 healthy controls. Their results showed gray matter density was significantly greater in bipolar patients, compared with healthy subjects, in diffuse cortical regions, notably bilateral cingulate and paralimbic cortices, areas utilized in attention, motivation and emotion. Additionally, their data revealed greater gray matter density in the right anterior cingulate in lithium-treated patients relative to the bipolar subjects not taking lithium. Their lithium-treated sample included subjects who were on lithium for varying time durations, at different individual doses. The lack of difference in gray matter density between the untreated patients and healthy controls, as well as growing evidence that lithium exerts major effects on a number of cellular proteins and pathways (*vide infra*) known to regulate cell atrophy/death lends support to the view that gray matter enlargement is mediated through the trophic actions of lithium in the brain.

Lithium exerts major effects on cytoprotective pathways

Klein and co-workers made the seminal observation that lithium inhibited the action of glycogen synthase kinase-3 (GSK-3) (Klein and Melton, 2006). GSK-3 is known to regulate diverse functions in adult mammalian brain, and to exert major cytoprotective effects (reviewed in Grimes and Jope, 2001; Gurvich and Klein, 2002; Bachmann et al., 2005). Indeed, GSK-3 represents one of the kinases responsible for the aberrantly hyperphosphorylated form of the microtubule-associated protein, *tau*, a major constituent of neurofibrillary tangles (Hong et al., 1997). GSK-3 also plays a major role in amyloid deposition (Phiel et al., 2003); thus GSK-3 inhibition regulates the two major pathways implicated in the pathogenesis of Alzheimer’s disease.

Address Correspondence to: De-Maw Chuang, PhD, Molecular Neurobiology Section, Mood and Anxiety Disorders Program, National Institute of Mental Health, National Institutes of Health, Bldg. 10, Rm. 4C-206, 10 Center Dr. MSC 1363, Bethesda, MD 20892-1363, USA, Phone: (301) 496-4915, FAX: (301) 480-9290, Email: chuang@mail.nih.gov

Financial Disclosures: Dr. Chuang and Dr. Manji reported no biomedical financial interests nor potential conflicts of interest.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

In addition to its direct effects on GSK-3, chronic lithium administration, at therapeutically relevant concentrations, induces prominent neuroprotective and neurotrophic proteins, bcl-2 and brain-derived neurotrophic factor (BDNF) in rodents and cultured neurons (Chen et al., 1999;Chen and Chuang, 1999;Fukumoto et al., 2001;Hashimoto et al., 2002b;Einat et al., 2003). Bcl-2 is not only a major anti-apoptotic protein, but also stimulates axonal regeneration following injury (Huang et al., 2003), while BDNF has a critical role in cortical development, synaptic plasticity and neuronal survival. Induction of BDNF is also a possible mechanism underlying lithium-induced neurogenesis in the dentate gyrus of rat hippocampus (Chen et al., 2000).

Lithium exerts robust neuroprotective effects in preclinical paradigms

In view of its major effects on BDNF, bcl-2 and GSK-3, it is not surprising that recent studies investigated lithium's potential neuroprotective effects in a variety of preclinical paradigms in which the ion demonstrated robust neuroprotective properties against a variety of insults (reviewed in Manji et al., 2000;Bachmann et al., 2005;Chuang and Priller, 2006). Notably, lithium pretreatment protected cultured brain neurons from glutamate-induced, N-methyl-D-aspartate (NMDA) receptor-mediated apoptosis (reviewed in Chuang and Priller, 2006). Excessive NMDA throughput is likely involved in stress-induced hippocampal atrophy, and has been implicated in the pathogenesis of a variety of neurodegenerative diseases. In cultured neurons, lithium-induced neuroprotection against glutamate excitotoxicity occurred within the therapeutic concentration range of this drug, requiring 5–6 days pretreatment for maximal effects. The lithium neuroprotection involved BDNF induction and was associated with upregulation of anti-apoptotic protein bcl-2, downregulation of pro-apoptotic proteins p53 and Bax, and inhibition of caspase-3. Treatment of cultured neurons with other GSK-3 inhibitors or transfection with GSK-3 siRNA mimicked lithium's neuroprotective effects (Liang and Chuang, 2007), again suggesting a critical role of GSK-3 in mediating neuroprotection.

Lithium showed beneficial effects in some animal models of neurodegenerative diseases. For example, pre- or post-insult treatment with lithium suppressed cerebral ischemia-induced brain infarction, caspase-3 activation, and neurological deficits in rats, and these neuroprotective effects were associated with induction of heat shock protein 70 and decreased expression of Bax (Ren et al., 2003;Xu et al., 2003). Several independent studies demonstrated that lithium has neuroprotective effects in animal and cellular models of Alzheimer's disease, Huntington's disease, Parkinson's disease, retinal degeneration, spinal cord injury and HIV infection (reviewed in Chuang and Priller, 2006). Notably, Phiel and associates (2003) demonstrated that therapeutic concentrations of lithium, by acting on GSK-3, blocked the production of A β peptides through interfering with amyloid precursor protein (APP) cleavage at the γ -secretase step. Importantly, lithium also blocked accumulation of A β peptides in the brains of mice that overproduce APP. Similarly, lithium administration significantly lowers levels of phosphorylation at several epitopes of tau known to be hyperphosphorylated in Alzheimer's disease and to significantly reduce levels of aggregated, insoluble tau (Noble et al., 2005). Most recently, it was demonstrated that lithium is neuroprotective in APP tg mice (Rockenstein et al., 2007). Thus, mice treated with lithium displayed improved performance in the water maze, preservation of dendritic structure in frontal cortex and hippocampus, and decreased tau phosphorylation.

Human Evidence for the Neurotrophic Effects of Lithium

In view of lithium's robust effects on levels of cytoprotective protein bcl-2 in the anterior cingulate, Drevets and associates re-analyzed older data demonstrating ~ 40% reductions in subgenual prefrontal cortex (PFC) volumes in familial mood disorder subjects (Drevets, 2001). Consistent with neurotrophic/neuroprotective effects of lithium, they found that patients

treated with chronic lithium or valproate exhibited subgenual PFC volumes that were significantly higher than those in non lithium- or non valproate-treated patients, and not significantly different from controls. To investigate potential neurotrophic effects of lithium in humans more definitively, Moore and coworkers used proton magnetic resonance (MR) spectroscopy, showing that treatment of bipolar patients with lithium for 4 weeks increased N-acetyl-aspartate, a marker of neuronal viability, in the cerebral cortex (Moore et al., 2000a). A follow-up volumetric MRI study showed 4 weeks of lithium treatment also significantly increased *total gray matter content* in the human brain (Moore et al., 2000b). Most recently, a study of familial pediatric bipolar disorder revealed that subjects with bipolar disorder with past lithium or valproate exposure tended to have greater amygdalar gray matter volume than subjects with bipolar disorder without such exposure (Chang et al., 2005).

Are “antimanic concentrations” of lithium required for its neurotrophic effects?

The aforementioned exciting results suggest lithium may have utility in the treatment of a variety of neuropsychiatric disorders associated with cell atrophy/loss and impairments of cellular resilience. One obvious concern is lithium’s tolerability, especially in patients with neurodegenerative disorders. A series of studies were undertaken to determine if chronic administration of lithium at low doses also regulates bcl-2 expression. It was found that chronic (4 weeks) lithium administration, at doses that produce plasma levels of ~ 0.35 mM, robustly increases bcl-2 levels in rat frontal cortex and hippocampus (Goodwin and Jamison, 2007). Furthermore, 0.1–0.6 mM lithium robustly protects cultured cortical neurons from glutamate excitotoxicity (Hashimoto et al., 2002a). In middle cerebral artery occlusion, an *in vivo* model of stroke, lithium also provided significant protection at 0.5 mEq/kg (Ren et al., 2003). Overall, the data clearly suggest that considerably lower than “traditional antimanic” doses of lithium have neurotrophic and neuroprotective effects, and may have utility as adjunctive treatments for neuropsychiatric disorders associated with cell loss/atrophy.

In conclusion, the paper by Bearden and associates in this issue of *Biological Psychiatry* adds to the growing body of data supporting the contention that lithium does indeed exert neurotrophic effects in humans. Although there have been some major breakthroughs in the identification of the genetic and pathogenic causes of many neurodegenerative diseases, the currently available therapies for nearly all these disorders are clearly quite inadequate. Increasing knowledge of etiology and pathogenesis will undoubtedly provide future opportunities to develop specific therapies aimed at protecting neurons from underlying degenerative processes. However, there is a mounting sense of urgency and desperation among patients and families to develop new “wonder drugs” for some of society’s most devastating illnesses. Ironically, the paper by Bearden and associates and the data reviewed in this commentary suggest that, in our efforts to develop novel “magic bullets”, we may have overlooked the potential of a simple monovalent cation that has been used therapeutically for bipolar disorder for decades (Angst et al., 2007; Nunes et al., 2007). Controlled clinical trials of low dose lithium for attenuating the rate of disease progression in atrophic/neurodegenerative illnesses are clearly warranted.

References

- Angst J, Gamma A, Gerber-Werder R, Zarate CA, Manji HK. Does long-term medication with lithium, clozapine or antidepressants prevent or attenuate dementia in bipolar and depressed patients? *Int J Psychiatry Clin Practice* 2007;11:2–8.
- Bachmann RF, Schloesser RJ, Gould TD, Manji HK. Mood stabilizers target cellular plasticity and resilience cascades: implications for the development of novel therapeutics. *Mol Neurobiol* 2005;32:173–202. [PubMed: 16215281]

- Chang K, Barnea-Goraly N, Karchemskiy A, Simeonova DI, Barnes P, Ketter T, et al. Cortical magnetic resonance imaging findings in familial pediatric bipolar disorder. *Biol Psychiatry* 2005;58:197–203. [PubMed: 16084840]
- Chen G, Zeng WZ, Yuan PX, Huang LD, Jiang YM, Zhao ZH, et al. The mood-stabilizing agents lithium and valproate robustly increase the levels of the neuroprotective protein bcl-2 in the CNS. *J Neurochem* 1999;72:879–882. [PubMed: 9930766]
- Chen G, Rajkowska G, Du F, Seraji-Bozorgzad N, Manji HK. Enhancement of hippocampal neurogenesis by lithium. *J Neurochem* 2000;75:17291734.
- Chen R-W, Chuang D-M. Long term lithium treatment suppresses p53 and Bax expression but increases Bcl-2 expression: a prominent role in neuroprotection against excitotoxicity. *J Biol Chem (Communication)* 1999;274:6039–6042.
- Chuang, D-M.; Priller, J. Potential use of lithium in neurodegenerative disorders. In: Bauer, M.; Grof, P.; Muller-Oerlinghausen, B., editors. *Lithium in neuropsychiatry The comprehensive guide*. Abingdon, Oxon: Informa UK Ltd; 2006. p. 381-398.
- Drevets WC. Neuroimaging and neuropathological studies of depression: implications for the cognitive-emotional features of mood disorders. *Cur Opin Neurobiol* 2001;11:240–249.
- Einat H, Yuan PX, Gould TD, Li J, Du JH, Zhang L, et al. The role of the extracellular signal-regulated kinase signaling pathway in mood modulation. *J Neurosci* 2003;23:7311–7316. [PubMed: 12917364]
- Fukumoto T, Morinobu S, Okamoto Y, Kagaya A, Yamawaki S. Chronic lithium treatment increases the expression of brain-derived neurotrophic factor in the rat brain. *Psychopharm* 2001;158:100–106.
- Goodwin, FK.; Jamison, KR. *Manic-Depressive Illness: Bipolar and Recurrent Unipolar Disorders*. 2. New York: Oxford University Press; 2007.
- Grimes CA, Jope RS. The multifaceted roles of glycogen synthase kinase 3 β in cellular signaling. *Prog Neurobiol* 2001;65:391–426. [PubMed: 11527574]
- Gurvich N, Klein PS. Lithium and valproic acid: parallels and contrasts in diverse signaling contexts. *Pharmacol Ther* 2002;96:45–66. [PubMed: 12441177]
- Hashimoto R, Hough C, Nakazawa T, Yamamoto T, Chuang D-M. Lithium protection against glutamate excitotoxicity in rat cerebral cortical neurons: involvement of NMDA receptor inhibition possibly by decreasing NR2B tyrosine phosphorylation. *J Neurochem* 2002a;80:589–597. [PubMed: 11841566]
- Hashimoto R, Takei N, Shimazu K, Christ L, Lu B, Chuang D-M. Lithium induces brain-derived neurotrophic factor and activates TrkB in rodent cortical neurons: an essential step for neuroprotection against glutamate excitotoxicity. *Neuropharm* 2002b;43:1173–1179.
- Heemskerk J, Tobin AJ, Ravina B. From chemical to drug: neurodegeneration drug screening and the ethics of clinical trials. *Nat Neurosci* 2002;5(Suppl):1027–1029. [PubMed: 12403977]
- Hong M, Chen DCR, Klein PS, Lee VMY. Lithium reduces tau phosphorylation by inhibition of glycogen synthase kinase-3. *J Biol Chem* 1997;272:25326–25322. [PubMed: 9312151]
- Huang X, Wu D-Y, Chen G, Manji H, Chen DF. Support of retinal ganglion cell survival and axon regeneration by lithium through a Bcl-2-dependent mechanism. *Invest Ophthalmol Vis Sci* 2003;44:347–354. [PubMed: 12506095]
- Klein PS, Melton DA. A molecular mechanism for the effect of lithium on development. *Proc Natl Acad Sci USA* 1996;93:8455–8459. [PubMed: 8710892]
- Liang M-H, Chuang D-M. Regulation and function of glycogen synthase kinase-3 isoforms in neuronal survival. *J Biol Chem* 2007;282:3904–3917. [PubMed: 17148450]
- Manji HK, Moore GJ, Chen G. Clinical and preclinical evidence for the neurotrophic effects of mood stabilizers: implications for the pathophysiology and treatment of manic-depressive illness. *Biol Psychiatry* 2000;48:740–754. [PubMed: 11063971]
- Moore GJ, Bebchuk JM, Hasanat K, Chen G, Seraji-Bozorgzad N, Wilds IB, et al. Lithium increases N-acetyl-aspartate in the human brain: In vivo evidence in support of bcl-2's neurotrophic effects? *Biol Psychiatry* 2000a;48:1–8. [PubMed: 10913502]
- Moore GJ, Bebchuk JM, Wilds IB, Chen G, Manji HK. Lithium-induced increase in human brain grey matter. *Lancet* 2000b;356:1241–1242. [PubMed: 11072948]

- Noble W, Planel E, Zehr C, Olm V, Meyerson J, Suleman F, et al. Inhibition of glycogen synthase kinase-3 by lithium correlates with reduced tauopathy and degeneration in vivo. *Proc Natl Acad Sci U S A* 2005;102:6990–6995. [PubMed: 15867159]
- Nunes PV, Forlenza OV, Gattaz WF. Lithium and risk for Alzheimer's disease in elderly patients with bipolar Disorder. *Br J Psychiatry* 2007;190:359–360. [PubMed: 17401045]
- Phiel CJ, Wilson CA, Lee VMY, Klein PS. GSK-3 α regulates production of Alzheimer's disease amyloid- β peptides. *Nature* 2003;423:435–439. [PubMed: 12761548]
- Ren M, Senatorov VV, Chen R-W, Chuang D-M. Post-insult treatment with lithium reduces brain damage and facilitates neurological recovery in a rat ischemia/reperfusion model. *Proc Natl Acad Sci USA* 2003;100:6210–6215. [PubMed: 12732732]
- Rockenstein E, Torrance M, Adame A, Mante M, Bar-on P, Rose JB, et al. Neuroprotective effects of regulators of the glycogen synthase kinase-3 β signaling pathway in a transgenic model of Alzheimer's disease are associated with reduced amyloid precursor protein phosphorylation. *J Neurosci* 2007;27:1981–1991. [PubMed: 17314294]
- Xu JH, Culman J, Blume A, Brecht S, Gohlke P. Chronic treatment with a low dose of lithium protects the brain against ischemic injury by reducing apoptotic death. *Stroke* 2003;34:1287–1292. [PubMed: 12677021]