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

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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 cingulated 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.

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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 Aβ peptides through interfering with amyloid precursor protein (APP) cleavage at the γ-secretase step. Importantly, lithium also blocked accumulation of Aβ 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


