Lithium Increases N-Acetyl-Aspartate in the Human Brain: In Vivo Evidence in Support of bcl-2’s Neurotrophic Effects?

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Background: Recent preclinical studies have shown that lithium (Li) robustly increases the levels of the major neuroprotective protein, bcl-2, in rat brain and in cells of human neuronal origin. These effects are accompanied by striking neuroprotective effects in vitro and in the rodent central nervous system in vivo. We have undertaken the present study to determine if lithium exerts neurotrophic/neuroprotective effects in the human brain in vivo.

Methods: Using quantitative proton magnetic resonance spectroscopy, N-acetyl-aspartate (NAA) levels (a putative marker of neuronal viability and function) were investigated longitudinally in 21 adult subjects (12 medication-free bipolar affective disorder patients and 9 healthy volunteers). Regional brain NAA levels were measured at baseline and following 4 weeks of lithium (administered in a blinded manner).

Results: A significant increase in total brain NAA concentration was documented ($p < .0217$). NAA concentration increased in all brain regions investigated, including the frontal, temporal, parietal, and occipital lobes.

Conclusions: This study demonstrates for the first time that Li administration at therapeutic doses increases brain NAA concentration. These findings provide intriguing indirect support for the contention that chronic lithium increases neuronal viability/function in the human brain, and suggests that some of Li’s long-term beneficial effects may be mediated by neurotrophic/neuroprotective events.

Introduction

Bipolar affective disorder (BD, manic-depressive illness) is a common, severe, chronic, and life-threatening illness (Goodwin and Jamison 1990). Despite the devastating impact that this illness has on the lives of millions, there is still a dearth of knowledge concerning its etiology and pathophysiology. The discovery of lithium’s efficacy as a mood-stabilizing agent revolutionized the treatment of patients with BD. Indeed, it is likely that the remarkable efficacy of lithium served to spark a revolution that has reshaped not only medical and scientific but also popular concepts of severe mental illnesses. After more than three decades of use in North America, lithium continues to be the mainstay of treatment for this illness, both for the acute manic phase and as prophylaxis for recurrent manic and depressive episodes (Goodwin and Jamison 1990). Interestingly, long-term lithium treatment not only reduces the excessive mortality from suicide observed in the illness but also reduces cardiovascular mortality (Baldessarini et al 1999). The effect on the broader community is highlighted by one estimation that the use of lithium saved the United States $4 billion in the period 1969–1979, by reducing associated medical costs and restoring productivity (Reifman and Wyatt 1980). Despite its role as one of psychiatry’s most important treatments (Goodwin and Jamison 1990), the biochemical basis for lithium’s therapeutic effects remains to be fully elucidated (Jope 1999; Manji et al 1995). It has been increasingly appreciated in recent years that the long-term treatment of complex neuropsychiatric disorders likely involves the regulation of gene expression in critical neuronal circuits. In this context it is noteworthy that a recent mRNA reverse transcription polymerase chain reaction differential display study has shown that chronic (4-week) lithium administration robustly increases the levels of the neuroprotective protein bcl-2 in rat frontal cortex (Chen et al 1999). Subsequent studies have shown that chronic lithium also increases the levels of bcl-2 in areas of hippocampus and striatum in vivo, as well as in...
rodent and human neuronal cells in culture (Chen and Chuang 1999; Manji et al 1999).

Bcl-2 is the acronym for the B-cell lymphoma/leukemia-2 gene; this gene was first discovered because of its involvement in B-cell malignancies, where chromosomal translocations activate the gene in the majority of follicular non-Hodgkin’s B-cell lymphomas (Adams and Cory 1998; Bruckheimer et al 1998 and references therein; Merry and Korsmeyer 1997). A role for bcl-2 in protecting neurons from cell death is now supported by abundant evidence; thus, bcl-2 has been shown to protect neurons from a variety of insults in vitro, including growth factor deprivation, glucocorticoids, ionizing radiation, and oxidant stressors, such as hydrogen peroxide, tert-butylhydroperoxide, reactive oxygen species, and buthionine sulfoxamine (Adams and Cory 1998; Bruckheimer et al 1998). In addition to these potent in vitro effects, bcl-2 has been shown to prevent cell death in vivo in a variety of experimental paradigms. In transgenic models, bcl-2 overexpression has been shown to prevent motor neuron death induced by facial nerve axotomy and sciatic nerve axotomy, and to protect from the deleterious effects of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine or focal ischemia; interestingly, neurons that survive ischemic lesions or traumatic brain injury in vivo show upregulation of bcl-2 (Chen et al 1997; Lawrence et al 1996; Merry and Korsmeyer 1997; Yang et al 1998, and references therein). Overexpression of bcl-2 has also recently been shown to prolong survival and attenuate motor neuron degeneration in a transgenic animal model of amyotrophic lateral sclerosis (Kostic et al 1997). Most recently, it has been clearly demonstrated that not only does bcl-2 overexpression protect against apoptotic and certain types of necrotic cell death, it can also promote regeneration of axons in the mammalian central nervous system (CNS), leading to the intriguing postulate that bcl-2 acts as a major regulatory switch for a genetic program that controls the growth of CNS axons (Chen et al 1997).

Consistent with the robust increases in bcl-2 levels, lithium has recently been shown to protect neurons from the deleterious effects of a variety of insults both in vitro and in vivo. Thus, lithium robustly protects against the toxic effects of glutamate, N-methyl-D-aspartate (NMDA) receptor activation, low potassium, serum/nerve growth factor deprivation, thapsigargin, and 1-methyl-4-phenylpyridinium-induced cell death (reviewed in Chen and Chuang 1999; Manji et al 1999 and references therein; Nonaka et al 1998a). Lithium’s protective effects against the deleterious effects of glutamate and NMDA receptor activation have also been demonstrated to occur in hippocampal and cortical neurons in culture, and in addition to these “harsh insults,” lithium has been shown to exert protective effects in a more “naturalistic” paradigm, age-induced cerebellar granule cell death (Nonaka et al 1998b). Most recently, chronic lithium was shown to exert dramatic protective effects against middle cerebral artery occlusion, reducing not only the infarct size (56%), but also the neurological deficits (abnormal posture and hemiplegia) (Nonaka and Chuang 1998).

Our study was undertaken to determine if lithium may also exert neurotrophic/neuroprotective effects in the human brain in vivo. Proton magnetic resonance spectroscopy (MRS) is a tool which provides a noninvasive window to functional brain neurochemistry. N-Acetyl-aspartate (NAA) is one of the many neurochemical compounds that can be quantitatively assessed via MRS. NAA is the predominant resonance in the proton MRS spectrum of the normal adult human brain, and although the functional role of this amino acid has not been definitively determined, NAA is a putative neuronal marker (Birken and Oldendorf 1989), localized to mature neurons and not found in mature glial cells, cerebrospinal fluid (CSF), or blood. A relative decrease in this compound may reflect decreased neuronal viability, neuronal function, or neuronal loss (for an excellent recent review of NAA see Tsai and Coyle 1995). In this prospective longitudinal study, we have utilized quantitative in vivo proton MRS to test the hypothesis that similar to the preclinical findings in the rodent brain and in human neuronal cells in culture, chronic lithium increases neuronal viability/function in the human brain in vivo, as evidenced by increased CNS levels of NAA in both medication-free BD patients and healthy subjects.

Methods and Materials

Subjects

BIPOLAR DISORDER PATIENTS (N = 12). Adult patients who gave written informed consent as approved by the institutional review board were eligible for this study. In addition, all eligible patients were required to meet diagnostic criteria for Bipolar Mood Disorder Most Recent Episode Depressed. The diagnosis was determined using the structured interview for DSM-IV (SCID). Patients were excluded if they met diagnostic criteria for any other DSM-IV Axis I disorder during the 2½ years preceding the index episode. In addition, patients with Psychoactive Substance Abuse or Dependence within 1 year of the index episode were excluded. Patients were also excluded from the study if they had any of the following medical conditions, which may put them at greater risk for side effects from lithium: 1) renal disease; 2) hepatic disease; 3) hematological disease; or the MRS procedure: 1) a cardiac pacemaker; 2) brain surgery for an aneurysm; 3) recent major surgery; 4) the presence of ferromagnetic implanted devices, such as neurostimulators; or 5) metal fragments in or near the eye or brain.

The effects of lithium on regional brain NAA levels were investigated in 12 patients (mean age 36.3 years, range 22–56
years, seven female, five male) who met the criteria outlined above. Eleven of these patients had a diagnosis of Bipolar I (history of Major Depression plus Mania) and one had a diagnosis of Bipolar II (history of Major Depression and Hypomania). Upon admission to the inpatient research unit, the subjects were administered blinded research capsules four times per day, tapered off any previous medications (through these capsules), and underwent a minimum 14-day drug washout period (depending on the half-lives of the previous treatment medications). On completion of the washout period, the patients had their affective symptomatology reassessed with the Hamilton Depression Rating Scale (HAM-D; Hamilton 1967) by trained blinded raters. All patients remained depressed following the washout period (HAM-D mean 18.75, range 11–29). The patients then underwent a baseline MRS scan (see neuroimaging methods described below) prior to the initiation of lithium treatment again through blinded research capsules. Lithium treatment was initiated and titrated to obtain a therapeutic plasma level (∼0.8 meq/L) over the first week of treatment. Quantitative proton (1H) MRS was utilized to measure brain NAA levels in the patients at baseline and after chronic (∼4 weeks) blinded lithium administration.

**HEALTHY VOLUNTEERS (N = 9).** Healthy adult subjects who gave written informed consent as approved by the institutional review board were eligible for this study. Subjects were free of any personal or family history of psychiatric disorders, including psychoactive substance abuse or dependence. In addition, they were healthy and free of any significant neurological, cardiovascular, respiratory, or endocrine disorders and had no history of head trauma. The subjects were free of all medications (including health food supplements) for at least 2 weeks before beginning the study and had no factors (described above) that would preclude lithium administration or MR scanning. A total of nine healthy adults (mean age 27.1 years, range 18–48 years, 6 female, 3 male) completed the identical lithium administration and MRS scanning protocol with the timetable described above.

**MRS Protocol**

Quantitative single voxel 1H MRS exams were performed using a 1.5T clinical scanner (GE Signa/Horizon 5.7, Milwaukee, WI). A Stimulated Echo Acquisition Mode (STEAM) pulse sequence (Frahm et al 1987) was used to acquire spectra using the following acquisition parameters and also included unsuppressed water reference scans for neurochemical quantification: an echo time of 30 msec, a modulation time of 13.7 msec, a repetition time of 2 sec, 8 step phase cycle, 2048 points, a spectral width of 2500 Hz, and 128 averages for a total acquisition time of approximately 5 min. Spectra were acquired from approximately 8 mL regions of interest (ROIs) in the right frontal, left temporal, central occipital, and left parietal lobes (see Figure 1). Special care was taken to place the ROIs in identical locations for the exams (baseline and 4 weeks of lithium) using a systematic approach that referenced voxel position to readily identifiable anatomical gyral landmarks within the brain.

Additional procedures were undertaken to evaluate the precision of the voxel placement from scan to scan in this longitudinal study and to control for potential partial voluming effects, which may potentially confound any MRS findings. We utilized a simple robust semi-automated image segmentation approach to determine the relative percentage of the various components, namely gray matter (GM), white matter (WM), and CSF making up the voxel (Moore et al, in press).

**Quantitative MRS Analysis**

The NAA resonance at 2.02 ppm, which also includes a minor contribution from N-acetyl-aspartyl-glutamate (Koller et al 1984), was identified in each of the spectra. The area under the resonance is proportional to the concentration of the compound. Individual peak areas were fit using time domain analysis software (deBeer et al 1992; van den Boogaart et al 1994) and the concentration of NAA is reported in arbitrary quantitative units as a ratio to brain water concentration (×10^4/water). This water referencing method has been used in the field for over a decade and has been validated by a number of research groups (Barker et al 1993; Christiansen et al 1993; Frahm et al 1990; Hennig et al 1992; Hetherington et al 1996; Klose 1990; Soher et al 1996; Thulborn and Ackerman 1983). The analysis software is publicly available (http://carbon.uab.es/mruiwww) and eliminates much of the subjectivity previously involved in determining spectral peak areas.

Briefly, the software performs an automated fit of the unsuppressed water peak to determine its peak area and also uses the phase of the water peak to apply an automated zero order phase correction to the metabolite data. Following this, the user enters a priori information regarding the neurochemical data, to give the software starting values for its fitting process. The a priori information given includes the expected chemical shifts for each of the major chemical compounds appearing in the typical proton brain spectrum as well as a starting linewidth determined by the corresponding water linewidth. The chemical shift values given to the program are based on literature values (Barker et al 1994; Frahm et al 1989; Kreis et al 1993; Michaelis et al 1993; Narayana et al 1989). With this input, the software then attempts to fit the spectrum and then displays the results both visually and in a file that can then be pasted into a spreadsheet analysis program. The visual and quantitative results are inspected for goodness of fit and either accepted or reiterated for improvement. Most spectra (approximately 80%) required only one iteration to achieve a satisfactory fit, with the majority of the others being successful after two iterations. The analyzers were trained to accept a fit if the residual showed predominately unstructured noise. The areas of the water peak and neurochemical peaks are then entered into a spreadsheet for analysis, and quantitative neurochemical concentrations are then reported in arbitrary units relative to brain water concentration. We specifically did not attempt to correct for water and neurochemical relaxation effects with this technique, as obtaining these values on each of our subjects would have been time prohibitive (measurement time would take an additional 2 hours in each subject). We have, however, utilized acquisition parameters that minimize the uncertainty in our neurochemical concentration estimates due to relaxation effects. Specifically, we used a short echo time of 30 msec to minimize T2 signal decay and a standard repetition time
of 2 sec to minimize T1 error resulting from collecting spectra under less than fully relaxed conditions. This is a common trade-off in clinical research studies.

Two research assistants trained in nuclear magnetic resonance spectral analysis using this protocol evaluated the data in this study. The individuals were blind to the study information and to each others’ results. Intra-class correlation coefficient analysis revealed an inter-rater reliability of greater than 98% for in vivo quantitative measurement of brain NAA concentration.

Data Analysis

Changes in the NAA concentration with lithium administration were assessed using a within-subjects repeated measures analysis of variance design (RM-ANOVA). Reported p values are two tailed. N-Acetyl-aspartate values were normalized to baseline to control for individual differences among subjects and diagnostic groups and the known regional variability of NAA in the different brain regions (Kreis et al 1993). N-Acetyl-aspartate changes are reported as a percent difference compared to baseline values for all analyses. Comparisons among groups were performed using t tests.

Results

Of the 168 potential in vivo proton brain spectra (four brain regions at two time points for each of the 21 subjects), 146 (87%) were available and judged to be of adequate quality to undergo quantitative analysis. Two subjects (both BD patients) failed to complete the chronic time point scans (loss of eight spectra), and 14 other spectra were discarded because of poor quality due to inadequate water suppression, subject motion during the scan, or magnetic susceptibility artifacts. The output of the spectral analysis program and a typical MR spectrum is shown in Figure 2. Voxel content within each ROI remained stable across the two time points, repeated measures analysis of variance revealed there was no significant differences over time for GM, WM, or CSF. Individual analysis of the combined data for voxel tissue content over time demonstrated that voxel content was highly correlated and highly significant (baseline vs. chronic r = 0.93, p < .0001).

No significant differences in baseline NAA concentra-
tion were found between the healthy volunteer and patient
groups (using unnormalized NAA concentrations), so data
from both groups were combined to increase the power of
the study. Four weeks of lithium administration resulted in
a small (5%) but significant increase of total brain NAA
concentration (RM-ANOVA, $F = 5.528, p = .0217$; see
Figure 3). There was no correlation between lithium levels
and NAA increases. All brain regions investigated dem-
strated an increase in NAA over the course of the study
(Figure 4).

When regional brain NAA increases were examined
in conjunction with the regional voxel image segmentation
data, we noted a significant positive correlation between in-
creased NAA and the voxel gray matter content ($r = 0.967, p = .033$; Figure 4), indicating that NAA increases
were occurring primarily in CNS gray matter. The per-
centage of the NAA increase with lithium administration
was not significantly different between the volunteer and
patient groups either on a total brain or regional basis. Of
the 19 completing both the acute and chronic scans, 14
(74%) had increased NAA levels, 1 (5%) showed no
change (±1%), and 4 (21%) showed a small decrease.
Examining data on a regional basis again together with
voxel gray matter content segmentation results, revealed
an interesting finding that the percentage of NAA increase
per voxel gray matter content was highest in the frontal
lobe region. Furthermore, examining the BD patient data
separately revealed an NAA increase per voxel gray
matter content two-fold higher in both the frontal and
temporal lobe regions compared to the parietal and occip-
tal regions; however, these regional findings should be
considered speculative as they failed to reach statistical
significance in this small sample.

Discussion

This study demonstrates for the first time that chronic Li
administration at therapeutic doses increases NAA con-
centration in the human brain in vivo. These findings
provide intriguing indirect support for the contention that,
similar to the findings observed in the rodent brain and in
human neuronal cells in culture, chronic lithium increases
neuronal viability/function in the human brain, and sug-
gests that some of Li’s long-term beneficial effects may be
mediated by neurotrophic/neuroprotective events.

Although the magnitude of the increase in brain NAA
with lithium administration over the course of this 4-week
trial is small (5%), a recent in-depth study by Brooks
and colleagues (Brooks et al 1999) investigating the
reproducibility of in vivo proton MRS in repeated scans
convincingly documented that with 20 subjects, in vivo
proton MRS can reliably detect a mean change in NAA
concentration of 3% between two scans. The acquisition
protocol and data processing used in the Brooks study are
identical to the protocols used in this study, and we have
obtained similar or greater reliability measures in our own
test-retest quality assurance measurements both in phantoms and in normal volunteers.

A number of studies have now shown that initial abnormally low brain NAA measures may increase and even normalize with remission of CNS symptoms in disorders such as demyelinating disease, amyotrophic lateral sclerosis, mitochondrial encephalopathies, and human immunodeficiency virus (HIV) dementia. (Davie et al 1994; De Stefano et al 1995a, 1995b; Ellis et al 1997; Holshouser et al 1995; Kalra et al 1998; Pavlakis et al 1998; Salvan et al 1997; Takanashi et al 1997; Vion-Dury et al 1995). In the case of temporal lobe epilepsy in which proton MRS often reveals abnormal NAA measures in the contralateral hippocampus, several studies have shown normalization of these measures following successful neurosurgical removal of the ipsilateral anterior temporal lobe to control seizures (Cendes et al 1997; Da Silva et al, unpublished data, 1999; Hugg et al 1996). In the majority of these studies, the magnitude of increase in NAA reported is quite similar to that reported in our study.

There is now considerable literature support from a variety of sources demonstrating significant reductions in regional CNS volume and cell numbers (both neurons and glia) associated with mood disorders. Thus, volumetric neuroimaging studies have demonstrated reduced basal ganglia volume and reduced temporal lobe volume (including the hippocampus) in mood disorders (reviewed in Ketter et al 1997; Da Silva et al, unpublished data, 1999; Hugg et al 1996). Within the frontal lobe, volumetric neuroimaging studies have also consistently shown reduced volumes in mood disorders. In particular, recent volumetric MRI studies in familial bipolar depressives and familial unipolar depressives have demonstrated reductions in the mean gray matter volume of approximately 40% in the prefrontal cortex ventral to the genu of the corpus callosum (Drevets et al 1997). Intriguingly, lithium-treated subjects demonstrate smaller reductions in prefrontal cortical volumes (personal communication from W. Drevets to H.K. Manji, March 1999). In addition to the accumulating neuroimaging evidence, recent postmortem studies of the prefrontal cortex have also demonstrated reduced CNS volume and cell numbers in mood disorders. Rajkowska (1997) has used three-dimensional cell counting and morphological techniques to demonstrate significantly reduced sizes and densities of both neurons and glia in several distinct areas in mood disorder subjects (Rajkowska et al 1999). Intriguingly, neuronal dimunition was especially pronounced in layer II of the rostral orbitofrontal region (Rajkowska et al 1999), an area where we have observed among the largest lithium-induced increases in bcl-2 immunoreactivity (Chen et al 1999; Manji et al 1999). Also in the prefrontal cortex, Ongur and colleagues (Ongur et al 1998) have recently reported a histological study examining the cellular composition of area sg24 located in the subgenual prefrontal cortex. They found striking reductions in glial cell numbers in patients with familial major depression (24% reductions) and BD (41% reductions), compared to controls. This is a particularly striking finding, as it is consistent with neuroimaging findings showing cortical volume loss in this same region on volumetric magnetic resonance imaging in a similar diagnostic group (Drevets et al 1997). Together, the preponderance of the data from the neuroimaging studies and the growing body of postmortem evidence presents a convincing case that there is indeed a reduction in regional CNS volume, accompanied by cell atrophy/loss, in mood disorders; these findings, along with the results of our study, raise the possibility that chronic lithium may exert some of its long term benefits.

Figure 4. $N$-Acetyl-aspartate (NAA) increases on a regional basis (left); NAA increase positively correlates with percent voxel gray matter content (right). ●, occipital; ○, temporal; ▲, frontal; ●, parietal.
via hitherto underappreciated neurotrophic/neuroprotective effects.

Interestingly, recent findings from Duman and associates have demonstrated that chronic administration of a variety of antidepressants increases the expression of BDNF (brain derived neurotrophic factor), and its receptor trkB in certain populations of neurons in the hippocampus (Duman et al 1997). Moreover, Smith and associates (Smith et al 1995) have also recently demonstrated that antidepressants increase the locus coeruleus expression of another neurotrophic factor, neurotrophin 3.

In conclusion, we report here the novel observation that chronic lithium administration increases brain NAA levels. Clearly a larger longitudinal study with a follow-up of BD patients over a period of years will be required to determine if lithium indeed has a long term neurotrophic/neuroprotective effect in BD patients. The increases in NAA levels, the robust increases in bcl-2 levels, as well as the clear evidence for neuroprotective effects in preclinical studies also suggest that lithium may have utility in the long term treatment of certain neurodegenerative disorders.

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