Lithium Increases N-Acetyl-Aspartate (NAA) in the Human Brain: In Vivo Evidence In Support of Lithium-Induced CNS Bcl-2 Increases?

G.J. Moore, J.M. Bebchuk, G. Chen, K. Hasanat, I.B. Wilds, N. Seraji-Bozorgzad, M.W. Faulk, L. Jolkovsky, S. Koch, D. Glitz, and H.K. Manji
Department of Psychiatry and Behavioral Neurosciences, Wayne State University School of Medicine, Detroit, MI USA

INTRODUCTION

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

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, chronic lithium increases the levels of the neuroprotective/neurotrophic protein bcl-2 in the human brain leading to increased neuronal viability/function as evidenced by increased CNS levels of NAA in both healthy subjects and medication free bipolar disorder patients.

METHODS

Using quantitative proton magnetic resonance spectroscopy (STEAM TE30/TM 13.7/TR2000), NAA levels (a putative marker of neuronal viability and function) were investigated in 21 adult subjects (9 healthy volunteers, and 12 medication-free bipolar disorder patients). In all subjects, written institutional review board approved informed consent was obtained. Regional brain (frontal lobe, occipital lobe, parietal lobe, medial temporal lobe) NAA levels were measured at baseline and following 4 weeks of lithium administration (blinded) at therapeutic levels (0.8-1.2 meq/L). Quantitative analysis of MRS data included automated fitting of peak areas, referencing to brain water, and segmentation of voxels to correct for percent tissue content (gray, white, CSF).

RESULTS

Four weeks of lithium administration resulted in a small (~5%), but significant increase of total brain NAA concentration (RMANOVA, F=5.528, p =0.02) (see Fig 1). All brain regions investigated demonstrated an increase in NAA over the course of the study (Fig. 2). When regional brain NAA increases were examined together with the regional voxel image segmentation data, we noted a significant positive correlation between increased NAA and the voxel gray matter content (r=0.967, p=0.033), indicating that NAA increases were occurring primarily in CNS gray matter, consistent with the location of the Bcl-2 increases in the rat brain studies.

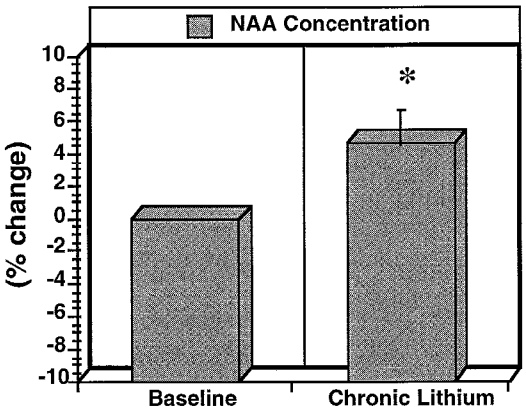

Figure 1. Relative increase in brain NAA levels following 4 weeks of Li administration * p=0.02

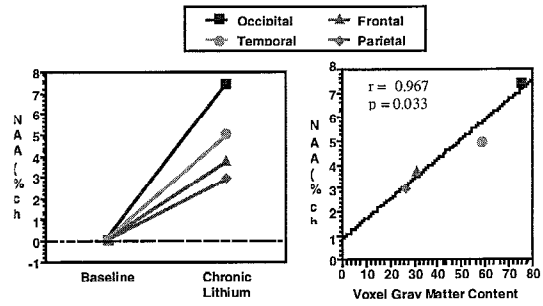

Figure 2. (left) % increase NAA levels in each brain region following 4 weeks of Li administration, (right) % NAA increase significantly (p=0.03) correlates with regional voxel gray matter content

DISCUSSION

We report here the novel observation that chronic lithium administration increases brain NAA levels. These findings provide intriguing indirect support for the contention that lithium also increases bcl-2 expression in the human brain, and suggests that *some* of Li's long term beneficial effects in bipolar disorder may be mediated by neurotrophic/ neuroprotective events. The increases in NAA levels, the robust increases in bcl-2 levels, as well as the clear evidence for neuroprotective effects in preclinical studies all suggest that the potential efficacy of lithium may have utility in the long term treatment of certain neurodegenerative disorders.