Brain myo-inositol decreases, NAA is unchanged in healthy volunteers in response to lithium administration

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Introduction

Lithium salts are a mainstay in the treatment of individuals with bipolar disorder. Amongst its other effects, lithium is a non-competitive inhibitor of the enzyme myo-inositol-1-phosphatase (1), leading to marked decreases in brain myo-inositol and increases in myo-inositol-1-phosphate levels in animals treated with lithium salts. These observations, coupled with the important role of inositol phospholipids in signal transduction, have lead to an "inositol depletion" hypothesis of lithium's therapeutic action (ibid.). This theory is also supported by the recent report of decreased frontal lobe myo-inositol levels of post-mortem brain tissue from subjects with bipolar disorder(2).

To date, evidence for lithium-induced reduction of inositol levels in humans is mixed. Kofman and Belmaker (1993) have reported a decrease in the activity of myo-inositol-1-phosphatase in the erythrocytes of lithium treated bipolar patients. Inconsistent reports have appeared on the matter of whether cerebrospinal fluid levels of myo-inositol are decreased (Swann et al., 1987) or unchanged (Agam et al., 1993) by lithium treatment. Most recently, however, Moore, et al. have shown a 30% decrease in right frontal lobe myo-inositol levels using proton MRS 5-7 days after resumption of lithium treatment in bipolar subjects following a 2 week washout period (3).

Another factor that may be important in understanding lithium´s therapeutic efficacy is its apparent neurotrophic/neuroprotective effects (4). Recent *in vivo* MR studies have shown that after 4 weeks of lithium treatment, bipolar subjects show an increase in gray matter voxel content (5) and both bipolar subjects and healthy volunteers show an increase in NAA concentration (6).

Myo-inositol, NAA and lithium are all visible to MRS, and a multinuclear MRS study allows us to further elucidate the relationship between lithium and its effects in the brain.

Methods

In order to clarify the effects of lithium on brain myo-inositol and NAA levels in normal subjects, a study was conducted involving healthy volunteers. Ten subjects (mean age = 30 ± 6 years, 3 M, 7 F) were given a baseline structural MR exam, and a proton MRSI examination to measure brain myo-inositol in the anterior cingulate (STEAM, TR = 2 sec, TE = 30 ms, SW = 2000 Hz, 1024 points, 160 cm FOV, 16 x 16 matrix, and 2 cm slice thickness. Immediately following this scan, subjects began taking lithium carbonate at a low therapeutic dose of 900 mg/day for one week. After one week of treatment, the proton MRSI examination was repeated, and brain lithium concentrations were also assessed using whole-brain lithium MRS (using the method described in (7, 8)).

The spectra from each of the individual voxels in the anterior cingulate were fit using VARPRO/MRUI, and the resulting metabolite ratios were averaged. A student´s paired t-test was used to assess differences in metabolite ratios between the baseline and one week state.

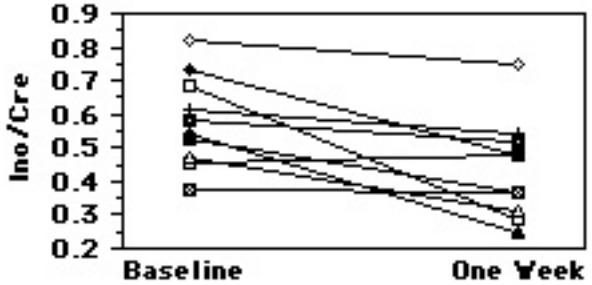

Figure 1 - Ino/Cre ratios before and after lithium treatment

Results

After seven days of treatment, serum lithium levels were 0.6 ± 0.2 mM (in the therapeutic range for patients treated with lithium). Brain lithium levels were lower (0.33± 0.16 mM, range 0.17-0.71 mM) and not significantly correlated with serum levels, in agreement with previous studies (5).

The proton metabolite ratios are consistent with a decrease in the inositol concentration from baseline to one week (Ino/Cre decreased 25%, $p<0.0072$; Ino/NAA decreased 26%, $p<0.011$; Ino/Cho decreased 15%, NS). No other metabolite ratios were altered significantly, although the trend in the choline containing ratios were indicative of an decrease in choline concentration (Cho/Cre decreased 14%, $p<0.105$).

Discussion

The myo-inositol results shown above are in good agreement with the findings of Moore et al (3). Moore showed a 30% decrease in right frontal lobe myo-inositol in subjects with bipolar disorder restarting lithium therapy after washout. These results are also consistent with the 31P results of Yildiz, et al., showing a significant 16% increase in PME following one week of lithium administration in healthy volunteers(9). The myo-inositol-1-monophosphate is a contributor to the phosphorous PME peak, and a decrease in myo-inositol due to lithium inhibition of myo-inositol-1-monophosphatase would be expected to accompany an increase in this resonance. Since the proton myo-inositol resonance consists not only of myo-inositol, but also myo-inositol-1-monophosphate (and glycine), it is probable that the actual decrease in myo-inositol is larger than that measured in our protocol.

Surprisingly, the decrease in myo-inositol was not significantly correlated to either brain or serum lithium level. Brain lithium level is a good predictor of treatment response in subjects with bipolar disorder; if lithium´s effect on myo-inositol were the primary mechanism of its action, we would expect a stronger correlation between these measures. This lack of correlation, the fact that a similar magnitude change is observed in controls and bipolar subjects, and Moore´s observation that the decrease in myo-inositol precedes any therapeutic effect of lithium, all support the contention that it is the secondary CNS effects resulting from the myo-inositol decrease, or other unrelated effects, that are responsible for lithium´s therapeutic action.

We observed no significant changes in the NAA resonance amplitudes in this study. There are most likely two reasons for this; first, the short duration of the experiment (one week) may not have been long enough for the neurotrophic effects of lithium to commence. Moore and colleagues only saw a 3-4% change in NAA in the frontal areas after 4 weeks of lithium treatment, so any changes in one week are most likely much smaller. Second, for the number of subjects studied, a change of this magnitude is not likely to be detectable.

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Table 1 - Metabolite ratios

	Baseline	One Week	Change	P value
Ino/Cre	0.58±0.14	0.43±0.15	-25%**	p<0.007
Ino/NAA	0.30±0.07	0.22±0.09	-26%*	p<0.011
Ino/Cho	0.59±0.18	0.51±0.17	-15%	p<0.261
NAA/Cre	1.96±0.20	2.03±0.33	4%	p<0.532
NAA/Cho	1.99±0.39	2.41±0.73	21%	p<0.174
Cho/Cre	1.02±0.22	0.88±0.16	-14%	p<0.105