No significant change of brain myo-inositol is observed in bipolar affective disorder after sodium valproate medication by in vivo proton MR spectroscopy

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Introduction
Bipolar disorder is a severe psychiatric illness. Mood stabilizers such as lithium and sodium valproate have had a remarkable beneficial effect on the lives of millions suffered from bipolar affective disorder. Yet, the cellular and molecular basis for mood stabilizers' therapeutic effects remains to be fully elucidated. One widely accepted hypothesis proposes that lithium blocks inositol monophosphatase and causes an accumulation of inositol monophosphates and a corresponding depletion of myo-inositol. This theory is supported by in vitro MRS studies in rat brain extracts (1, 2). However, human MRS studies to date have been less clear, showing both higher ratios of myo-inositol / creatine (3) and lower myo-inositol concentrations (4) after lithium medication.

In addition to lithium, sodium valproate is now also commonly used as an effective mood stabilizer. Nonetheless, it was felt to have a different mechanism of action since sodium valproate does not appear to inhibit inositol monophosphatase (5). However, interestingly, in a recent animal study we have shown that both sodium valproate and lithium affected the PI-cycle in the same manner, therefore possibly sharing a common mechanism of action in the treatment of bipolar disorder (1). The purpose of the present study was to quantitatively measure the concentration of metabolites in both frontal and temporal lobes after sodium valproate medication in bipolar patients to determine if these were altered in any way from controls.

Methods
We studied 8 adult patients with bipolar disorder and 11 healthy volunteers. Among the patients, there were six women and two men with an mean age of 43 years. All the patients took sodium valproate 1,000 mg daily as the sole medication. Five female and six male volunteers with a mean age of 37 years were included. None of the volunteers was taking any medication.

MR experiments were performed by using a Magnex 3 T scanner, and spectrometer control was provided by an SMIS console. After axial and coronal scout brain images were collected, the PRESS sequence was used to acquire proton MRS data with TE1=25 msec, TE2=25 msec, TR=3000msec, and 128 scan averages. The MRS data were acquired from three square voxels (2x2x2 cm3 ) placed in the cortex of frontal lobe, the cortex of temporal lobe, and external standard solution. The external standard was a 125ml glass sphere filled with physiological saline containing NAA, GABA, Glutamine, Glutamate, creatine, choline, and myo-inositol. In order to measure T1 and T2 values of the metabolites in the brain and standard solution, MRS data were collected with different TE values at a constant TR and different TR values at a constant TE both in human subjects and standard solution (6).

After phase and baseline correction for MRS data, Marquardt functions were used to fit the resonance peaks of NAA, total creatine, choline, and myo-inositol, and their respective peak areas were measured using PERCH program. To obtain accurate brain metabolite concentrations, following equation was used:

Where the subscripts s and b represent standard solution and brain, respectively (6,7). The two-tailed unpaired t test was used for determining the significance of different means.

Results
Table 1 lists the means and SD of brain metabolite concentrations in both frontal and temporal lobes and in both patient and volunteer groups. Compared with the volunteers, the patients had no significantly lower levels of myo-inositol (P=0.77 in frontal lobe and P=0.67 in temporal lobe). Also, there were no significant differences for choline, total creatine and NAA between volunteer and patient groups.

Discussion
Our results show a small, but non-significant, decrease in the mean values of brain myo-inositol concentration in the patients with bipolar disorder compared to in volunteers. There were also no statistically significant differences for choline, total creatine and NAA.

These results do not suggest that sodium valproate administration significantly alters baseline concentrations of myo-inositol in euthymic bipolar patients. These findings are consistent with those from previous studies of lithium, in which myo-inositol concentrations have been altered only in patients who have an active mood disorder. One of the potential problems with measuring myo-inositol with MRS is that both the 3.65 ppm and 3.56 ppm myo-inositol peaks contain contribution from inositol monophosphates and 3.56 ppm peak is also contaminated with signal from glycine. In human brain, the myo-inositol peaks can be influenced by the signal contribution from macro molecules. The accuracy of myo-inositol concentration may thus be obscured by the contributions from inositol monophosphates, glycine and macro molecules, especially when there is an increase of inositol monophosphates and glycine after mood stabilizer medication.

References