Clinical 1H MRS Studies of Glutamatergic Neurotransmission in Bipolar Disorder

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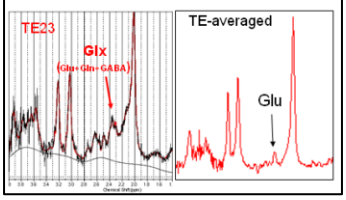
INTRODUCTION: Abnormal glutamate (Glu) neurotransmission has been suspected to underlie neuronal dysfunction in bipolar disorder (BD).[1] When studying Glu with short TE PRESS (Point RESolved Spectroscopy) spectra, the overlapping resonance signals presented as Glx around 2.35 ppm of chemical shift arise from Glu, glutamine (Gln), and γ-amino butyric acid, complicating the quantification of Glu. In contrast, TE-averaged spectra show an isolated Glu peak at 2.35 ppm of chemical shift with a flat baseline, which makes the quantification of Glu more reliable.[2] In this study we examined Glu levels in medication-free BD patients, lithium (Li)-treated BD patients and healthy volunteers using PRESS with short TE and TE-averaged methods (Figure 1). Our goal was to measure alterations of Glu in this condition, to extend previous reports of elevated Glx in BD.

METHODS: Eleven depressed BD patients were studied (5 medication free and 6 on Li treatment; 7F/4M; 27.5±8.1 yrs). The inclusion criteria for patients were: 1) met DSM-IV criteria for type I and II bipolar disorder, currently depressed; and 2) an index Young Mania Rating Scale total score <12 and Montgomery-Åsberg Depression Rating Scale ≥20. Six healthy volunteers (4F/2M; 25.0±7.5 yrs) were also studied for comparison. For healthy volunteers, the subjects had no history of any Axis I psychiatric disorder and also had no first-degree relatives with affective or psychotic disorders. All MR data were acquired on a Varian 4T whole-body MRI/MRS system, using a TEM head coil. A 3-D whole head image was first acquired using a MDEFT (Modified Driven Equilibrium Fourier Transform) pulse sequence for the purpose of MRS voxel positioning and tissue segmentation. Localized shimming was optimized using the automatic shimming method FASTMAP (Fast, Automatic Shimming Technique by Mapping Along Projections). The short TE PRESS spectra were acquired using TR/TE=2000/23ms, 128 averages with water suppression by VAPOR (variable pulse power and optimized relaxation delays) methods. For the TE-averaged spectrum acquisition, a modification of the PRESS method with 32 increments of 2.5 ms was used. To quantify the individual Glu level, a water reference spectrum was also acquired and used as an internal reference. The water reference spectrum, TE23 spectrum, and TE-averaged spectrum were acquired from the same brain regions, the left- and right- ventrolateral prefrontal cortex and anterior cingulated cortex (ACC). MRS data processing and quantification was accomplished using LCModel and jMRUI with tissue content correction. Statistical comparisons between the healthy volunteer group and the bipolar patient group were tested with the Mann-Whitney rank sum test. A *p* value of 0.05 or less was defined as statistically significant.

Figure 1.



RESULTS: In the TE-averaged data set, the medication-free patients' ACC Glu level (1.23±0.03) was significantly higher than the healthy volunteer values (0.73±0.12, p=0.002). The Glu level in ACC of the Li-treated patient group showed a strong trend of normalization compared with the medication-free patient group but was not statistically different from medication-free patients (Table 1, P=0.059*)*. We did not find any statistical difference between groups in TE-23 data set.

Table 1.

	Glu levels (arbitrary units vs. water signal)
Healthy volunteers	0.73±0.12
Patient, medication-free	1.23±0.03
Patient, Li-treated	0.81±0.42

DISCUSSION AND CONCLUSION: Elevated Glx has been reported in all phases of BD.[1] Our TE-averaged data show that increased Glu levels contribute to elevated Glx in medication-free depressed BD. Although the subject sample was small, the Glu of Li-treated patients show a strong trend toward normalization. Chronic, not acute, Li treatment robustly protected neurons against glutamate excitotoxicity.[3] A careful recruitment of Li-treated patients in future studies may provide results with statistical significance. The TE-23 spectra acquired at 4T demonstrated good signal-to-noise ratio but the rolling broadened baseline resulting from macromolecules remains a hurdle for the accurate Glu quantification. We suspect that this is the reason we did not find any significant difference in the TE-23 data in such a small study sample. A recently published study suggests the optimal TE to quantify Glu at 3T is 40 ms.[4] With the similarity between 3T and 4T, this study suggests the optimal TE for Glu measurement at 4T may be longer than 23 ms.

REFERENCES: 1). Prog Neuropsychopharmacol Biol Psychiatry. 2006;30(6):969. 2). MRM. 2004;51:435. 3). PNAS USA 1998;95:2642. 4). MRM. 2008;60:964. **ACKNOWLWDGEMENT:** We thank the National Alliance for Research on Schizophrenia and Depression (NARSAD) for funding support to this work (WJC).