^{1}H MRS Provides Evidence of Altered Frontal Cortex GABA and Glutamate-Glutamine in Schizophrenia In Vivo

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Background: Abnormalities in the neurotransmitters glutamate (Glu) and GABA have been implicated in schizophrenia. Alterations have been found in postmortem studies in the anterior cingulate cortex (ACC) and the dorsolateral prefrontal cortex (DLPFC) that suggest transmission deficits in fast-spiking GABAergic interneurons. The NMDA receptor hypofunction hypothesis of schizophrenia suggests Glu elevations in these regions, and in vivo magnetic resonance spectroscopy (MRS) studies have begun to report Glu abnormalities. The goal of this study was to assess GABA and combined glutamate-glutamine (Glx) levels in these regions in vivo in schizophrenia.

Methods: We enrolled 30 patients with schizophrenia (age 32 ± 10 y) and 24 matched healthy controls (age 33 ± 8 y). Fifteen patients were on stable doses of antipsychotic medication for at least 4 weeks, and 15 were unmedicated for at least 14 days. MRS data were acquired from the left DLPFC (9.6 cc voxel) and ACC (18.8 cc voxel, Fig. 1). All spectra were recorded on a 3T GE 'EXCITE' MR system using an 8-channel phased-array head coil. The J-edited spin echo difference technique followed by a frequency-domain nonlinear least-squares spectral fitting procedure were used to determine the two main outcome measures, GABA and Glx, which were normalized to each voxel's tissue water signal recorded simultaneously. We previously showed that test-retest reliability using these methods was high (percent coefficient of variation or %CV was 5.2%, and intraclass correlation coefficient or ICC was 0.84 for GABA/water). Voxel volumes were segmented to derive the proportions of gray and white matter and cerebrospinal fluid, which were compared to account for the potential effect of brain matter heterogeneity on the measured GABA and Glx levels.

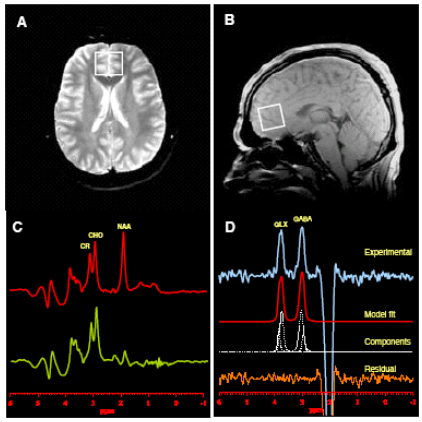

Fig. 1. [A] axial and [B] sagittal images showing ACC voxel size and location; [C] PRESS ^{1}H MR spectra with editing rf pulse [a] off and [b] on. [D] The difference of the spectra in [C] showing (a) the detected GABA and Glx peaks, with (b-d) best-fit model curves and residuals

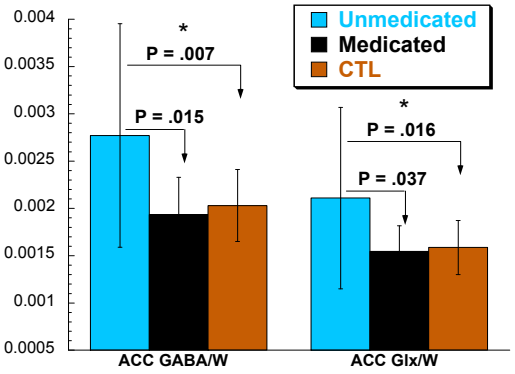

Fig. 2. Comparisons of ACC GABA and Glx group means

Results: We found regionally selective GABA and Glx abnormalities in the unmedicated patients: both measures were elevated in the ACC relative to controls and to medicated patients (Fig. 2), but both measures showed no group differences in the DLPFC. Mean ACC GABA/water was 2.8 ± 1.2, 1.9 ± 0.4, and 2.0 ± 0.4 (x 10^{-3} for all) in unmedicated patients, medicated patients, and controls, respectively. P values were .015 and .007 for unmedicated patients compared to medicated patients and to controls, respectively. ACC Glx/water gave P values of .037 and .016 for these comparisons. All comparisons of medicated patients to controls showed no significant differences, as did all measures in the DLPFC. Voxel tissue heterogeneity did not affect these findings.

Discussion: These results suggest regionally selective GABA and glutamate elevations in patients in the unmedicated state compared with healthy controls. The GABA abnormalities are opposite to the deficits seen in major depressive disorder [1,2]. The findings also suggest that antipsychotic medication may significantly lower ACC GABA and glutamate levels to the normal range. Relationships of these MRS data to postmortem GABA findings and significance for the GABA and the NMDA receptor hypofunction hypotheses of schizophrenia will be discussed. Additional studies with longitudinal within-subject assessment of medication effects will be needed to further investigate these findings.

References

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