Glutamate as a Marker of Cognitive Function in Schizophrenia: A Proton Spectroscopic Imaging Study at 4 Tesla

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Background: Cognitive deficits in schizophrenia may be related to glutamatergic dysfunction, but in vivo measurement of glutamate metabolism has been challenging. We examined the relationship between glutamate metabolism and cognitive function in schizophrenia.

Methods: Thirty subjects with DSM-IV schizophrenia and 28 healthy volunteers were studied using 4 Tesla proton echo planar spectroscopic imaging. Glutamate plus glutamine (Glx), N-acetylaspartate compounds, and Inositol concentrations in gray and white matter and broad neuropsychological function were assessed in all subjects.

Results: Glutamate plus glutamine was positively correlated with overall cognitive performance in the schizophrenia group ($p = .0006$), accounting for about 36% of the variance. No correlation was found in control subjects. Group-averaged Glx levels were similar in schizophrenia and control subjects. N-acetylaspartate compounds were reduced in cortical gray matter in the younger schizophrenia subjects (age < 30; $p = .04$) compared with age-matched control subjects. Inositol was increased in cortical gray ($p = .002$) and white matter ($p = .02$) in the older schizophrenia subjects (age > 30) compared with age-matched control subjects.

Conclusions: Although not reduced in schizophrenia as a group, lower Glx levels correlates with impaired cognition in the illness. This suggests heterogeneity in mechanisms that regulate glutamate function in schizophrenia. Patients with reduced glutamatergic reserves may be rendered into a more severe hypoglutamatergic state with cognitive consequences. Reduced cortical gray matter N-acetylaspartate compound concentration early in the illness with normalization in older subjects is consistent with a process of early dendritic retraction with subsequent increased neuronal packing. Later in the illness, Inositol elevation suggests glial involvement.

Key Words: Cognition, glutamate, 1H-MRS, inositol, N-acetylaspartate, schizophrenia

Schizophrenia is characterized by psychosis and functional deterioration. Cognitive impairments are also common, broad, and persistent and account for most of the variance in psychosocial deficits (1). Understanding the neurobiological underpinnings of functional deterioration in schizophrenia is crucial for the development of therapeutic strategies that go beyond the resolution of psychotic symptoms. It has been postulated that a glutamate-related process accounts for cognitive impairment in schizophrenia (2). However, in vivo measurement of glutamate metabolism has been challenging.

Proton magnetic resonance spectroscopy has been used to measure glutamate (Glu) and its glial metabolite glutamine (Gln) in the brain of schizophrenia patients (3–10). These studies used the single voxel method and results were largely inconsistent. In schizophrenia, a disease with subtle but broad gray and white matter involvement (11), proton magnetic resonance spectroscopic imaging (1H-MRSI) is potentially a more powerful tool, because it enables measurement in a much larger brain region, thereby reducing the bias of voxel selection that is intrinsic to single voxel studies. We used 1H-MRSI to examine glutamate plus glutamine (Glx) and myoinositol (Ins), as well as traditional peaks (N-acetylaspartate compounds [NAAc], creatine [Cr], and choline [Cho]) in schizophrenia and healthy control subjects. Because the disease may be more active (i.e., more frequent psychotic episodes and more pronounced social deterioration) during the initial 10 years (12,13), younger (< 30 years) and older (≥ 30 years) subjects were studied. We hypothesized Glx abnormalities in schizophrenia, as well as reduced NAAc. We also hypothesized that Glx, the measurable metabolite most clearly related to neuronal function (14), would relate to cognitive performance.

Methods and Materials

Subjects

Patients were from the University of New Mexico Hospitals. Inclusion criteria were 1) DSM-IV schizophrenia using the Structured Clinical Interview for DSM-IV; and 2) clinically stable on the same antipsychotic medications > 4 weeks. Exclusion criteria were neurological disorder or active substance use disorder. Healthy control subjects were excluded if they had 1) any DSM-IV Axis I disorder, determined by Structured Clinical Interview for DSM-IV; 2) first-degree relatives with any psychotic disorder; or 3) history of neurological disorder. The study was approved by the local Institutional Review Board and subjects gave informed consent.

Magnetic Resonance Studies

Acquisition. Studies were performed using a 4T scanner (Bruker, MedSpec, Ettlingen, Germany) with proton echoplanar spectroscopic imaging (PEPSI) methods previously described (15). Head position was fixed with a head mold. Axial T1 magnetization prepared rapid acquisition gradient echo images were acquired for PEPSI prescription and for tissue segmentation. The PEPSI data were acquired from a slice parallel to anterior commissure-poste-

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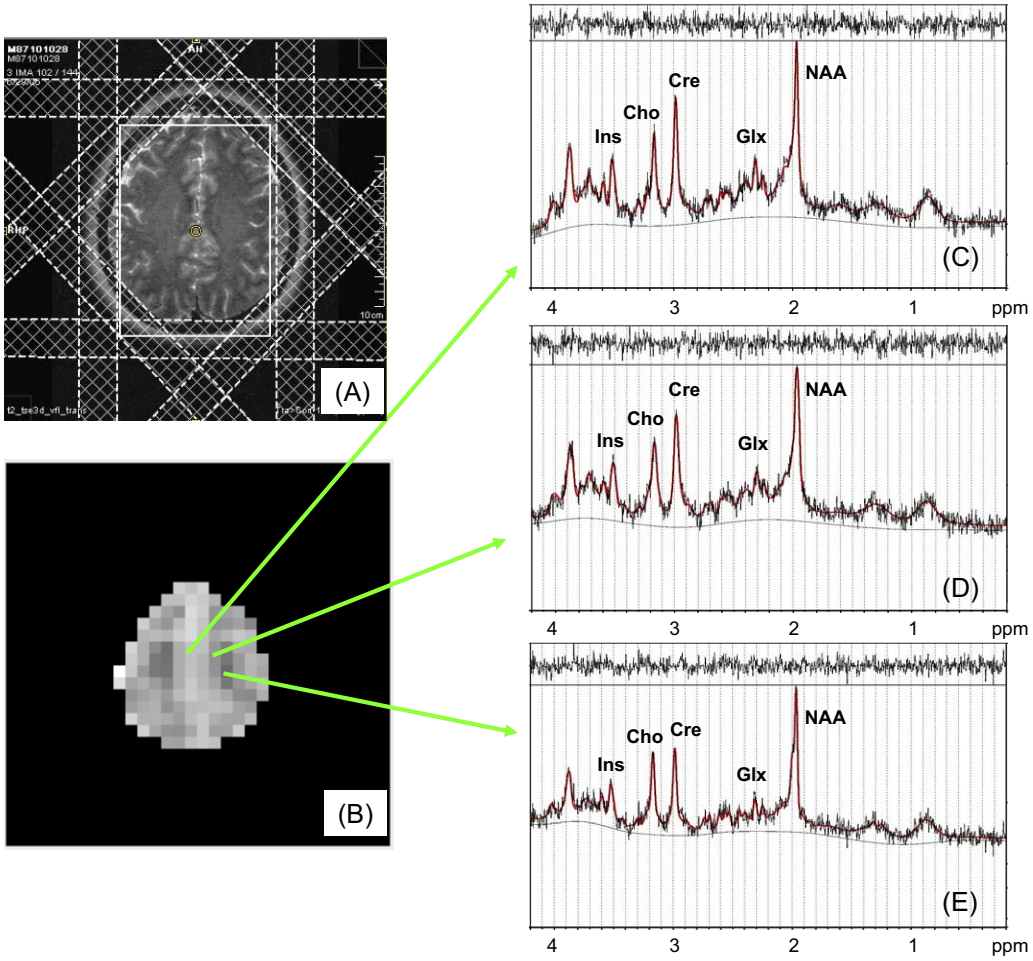

Figure 1. Slice selection for proton echoplanar spectroscopic imaging placement on axial T2-weighted magnetic resonance image **(A)**, with corresponding image composed from glutamate plus glutamine LCModel fitted concentrations **(B)** and examples of spectral resolution and fitting from voxels of mainly gray **(C)**, mixed gray/white **(D)**, and white matter **(E)**. Cho, choline; Cre, creatine + phosphocreatine; Glx, glutamate plus glutamine; Ins, myoinositol; NAA, N-acetylaspartate; ppm, parts per million.

rior commissure immediately superior to the lateral ventricles. This location has broad coverage of gray/white matter in bilateral frontal and parietal regions, where metabolic (16), structural (11), and functional abnormalities (17) have been reported in schizophrenia. The PEPSI used these parameters: echo time = 15 msec, repetition time = 2 sec, 32 × 32 matrix, field of view = 256 mm, slice thickness = 15 mm, resulting in a nominal voxel size of 1 cc. Outer volume suppression consisted of eight manually prescribed 25-mm thick presaturation slices positioned octagonally along the contours of the brain (Figure 1A). A water suppressed dataset with eight signal averages and a nonwater suppressed reference dataset with single signal average were collected in 10 min. Raw spectral data were automatically processed with an Interactive Data Language based in-house developed reconstruction software (ITT Visual Information Solutions, Denver, Colorado) (15).

Spectral Fitting. Localized spectra were quantified using LCModel fitting (version 6.1; Provencher, Ontario, Canada) (18). Simulated basis sets for sequence parameters included the following metabolites: aspartate, total Cho, Cr, gamma-aminobutyric acid, Gln, glutathione, Glu, Ins, glucose, lactate, N-acetylaspartate (NAA), N-acetylaspartylglutamate (NAAG), phosphocreatine, phosphoethanolamine, scyllo-inositol, and taurine. The following sums were also reported by the fitting program: creatine + phosphocreatine (Cre), Gln + Glu (Glx), and NAA + NAAG (NAAc). Spectra were fitted in reference to the nonwater suppressed reference dataset using water scaling.

We automatically selected spectra with the following quality control parameters—full width at half maximum (ppm) < .06 and signal-to-noise ratio (S/N) > 5—and also restricted to individual metabolite spectra with goodness of fit, as measured by the Cramer-Rao Lower Bound (CRLB), of < 20 in all selected voxels. Because reliable fits for NAAG and Gln were not generally achieved, all the analyses presented below focus on NAAc and Glx (for exploratory analyses that attempt to separate Gln from Glu, see Supplement 1). Hence, we obtained a contiguous area of about 130 voxels per subject with consistent fit quality for NAAc, Ins, Cre, Cho, and Glx (Figure 1B–E; no group differences between the number of voxels selected).

Partial Volume Correction. T1 images were segmented with SPM2 (The Wellcome Department of Imaging Neuroscience, London, United Kingdom). The cerebrospinal fluid (CSF), gray matter (GM), and white matter (WM) maps were resampled and filtered using statistical parametric mapping to match the point spread function, slice thickness, and field of view of the PEPSI data. The resulting low-resolution maps of GM, WM and CSF were converted into water concentration maps and corrected for the concentration of magnetic resonance visible water in the three compartments using literature values (19). Re-