N-acetyl-aspartyl-glutamate in first-episode psychosis

Anouk Marsman[1], Subechhya Pradhan[1], Candice Ford[2], Ashley Lloyd[2], Teppei Tanaka[2], Akira Sawa[2], and Peter B. Barker[1]
[1]*Russell H. Morgan Department of Radiology and Radiological Science, Johns Hopkins University School of Medicine, Baltimore, Maryland, United States,*
[2]*Department of Psychiatry, Johns Hopkins University School of Medicine, Baltimore, Maryland, United States*

Target audience

Scientists and clinicians interested in the neurobiology of schizophrenia and/or measurement of neurometabolite levels *in vivo* using 7T ^{1}H-MRS.

Figure 1: CSO voxel.

Purpose

It has been increasingly recognized that the glutamatergic system plays a role in the pathophysiology of schizophrenia [1,2]. N-acetyl-aspartyl-glutamate (NAAG) modulates the glutamatergic system and may therefore be implicated in schizophrenia [3]. Preliminary data of an ongoing study were obtained to determine metabolite levels in first-episode psychosis (FEP) subjects and healthy controls.

Methods

Participants: 17 FEP subjects (age 21.6±5.3, M/F=11/6) and 37 matched healthy controls (age 24.0±3.9, M/F 19/18) have participated in this study to date. FEP subjects were diagnosed with a psychotic disease (59% schizophrenia) and recruited within the first two years after onset. All FEP subjects were on antipsychotic medication at the time of the scan.

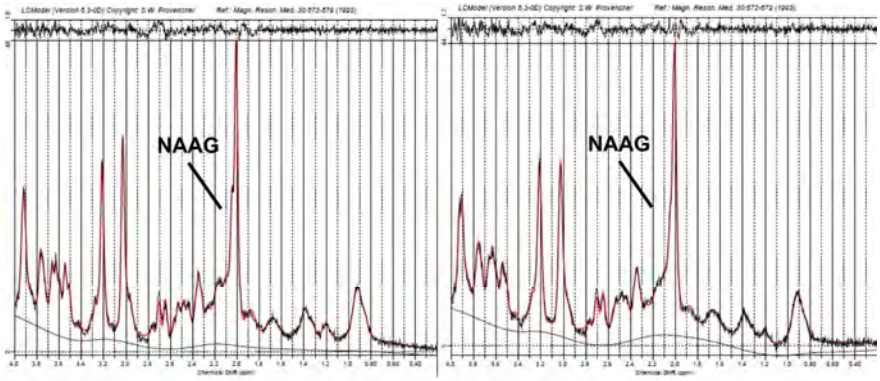

Figure 2: Typical CSO spectra for controls (left) and FEP subjects (right).

MR acquisition: All investigations were performed on a 7T whole body MR scanner (Philips, Cleveland, OH, USA) with a birdcage transmit head coil in combination with a 32-channel receive coil (both Nova Medical Inc., Burlington, MA, USA). Spectroscopic voxels were positioned in the anterior cingulate cortex (ACC; 30x20x20 mm^3), left centrum semiovale (CSO; 40x20x15 mm^3) (Figure 1), left dorsolateral prefrontal cortex (DLPFC; 25x20x20 mm^3), left orbitofrontal cortex (OFC; 20x20x20 mm^3), and bilateral thalamus (20x30x15 mm^3). Spectra were acquired using a STEAM sequence (TR/TE/TM=3000/14/33 ms, 128 averages with water suppression, 16 averages without water suppression). Water suppression was achieved using VAPOR.
Spectral fitting and quantification: Spectra were analyzed using LCModel version 6.3 [4] (Figure 2). Metabolite concentration uncertainties that exceeded a CRLB of 20% for NAA, NAAG, tNAA, tCr, tCho, Gln, Glu and mI, and 50% for GABA and GSH, were excluded from the study.

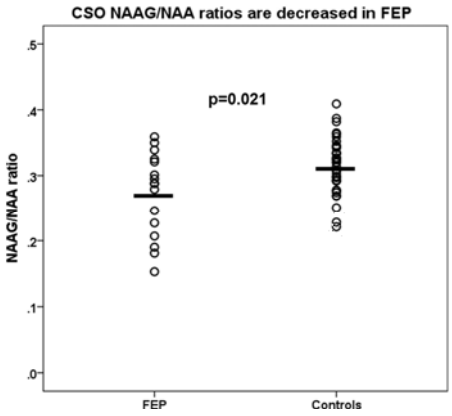

Figure 3: Left CSO NAAG/NAA ratios are lower in FEP subjects as compared to controls. The horizontal bars indicate the group means.

Results

Interim analyses (Student's t-tests) revealed significantly ($p<0.05$) higher ACC Cho and Cho/Cr, lower CSO NAAG, NAAG/Cr, tNAA and tNAA/Cr, lower DLPFC NAA, NAA/Cr and tNAA, higher DLPFC Gln/Cr and Cho/Cr, and lower thalamic NAA and tNAA in FEP subjects as compared to controls. Moreover, FEP subjects showed significantly lower CSO NAAG/NAA ratios as compared to controls ($p=0.021$) (Figure 3). In a multiple regression analysis, this effect remains significant when correcting for age, sex, diagnosis, smoking status and ethnicity.

Discussion

Together with lower CSO NAAG, lower CSO NAAG/NAA ratios in FEP subjects may indicate an important role for NAAG in the development of psychotic disorders, in particular schizophrenia. Previous studies indicate that glutamate carboxypeptidase II (GCP2), which converts NAAG to NAA and glutamate, regulates the synaptic concentration of NAAG and may be altered in schizophrenia [3]. These data are part of an ongoing study, so more data will be collected in order to confirm these interim findings.

References: 1. Marsman et al. 2013, Schizophr Bull; 2. Poels et al. 2014, Schizophr Res; 3. Begeron and Coyle 2012, Curr Med Chem; 4. Provencher 1993.
Funding: NIH grants R01MH096263, R01MH092443; in collaboration with Mitsubishi Tanabe Pharma Corporation