A 1H-MRS study of GABA in the auditory cortex in persons with autism spectrum disorder

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Introduction

Autism spectrum disorders (ASD), which includes Autistic Disorder, Asperger's Syndrome and Pervasive Developmental Disorder – Not Otherwise Specified, are clinically defined by impairments of social interaction, communication, and restricted/stereotyped behaviors. One emerging perspective on the pathophysiology of ASD is the excitation/inhibition imbalance (EI) theory (*1*), which proposes that relatively high ratios of excitatory to inhibitory neuronal processes could explain a reasonable portion of the ASD phenotype(*2*). Evidence for GABAergic inhibitory deficits converges from a variety of methods and has been of interest for some time (e.g., *3*), and is supported by a significant body of evidence. Significantly reduced $GABA_A$-receptor binding in high binding regions have been reported in the hippocampus (*4*) and several areas of cortex and cerebellum (*5*). Messenger RNA levels of glutamate decarboxylase (GAD), the enzyme that converts glutamate to GABA and is highly related to intraneuronal GABA, have been reported to be reduced by about 40% in cerebellar Purkinje cells in persons with autism (*6*) and up to 50% in parietal and/or cerebellar tissues (*7*). These and other evidence suggest that levels of GABA might be reduced in ASD subjects.

To date, there has only been a single study of GABA in ASD using MRS methods, likely due to the necessity and resulting challenges of using spectral editing techniques that are not needed to measure glutamate. In that study, GABA concentration was lower in the frontal lobe in ASD, and there was a corresponding decrease in the ratio of GABA to Glutamate, in line with the predictions based on reduced GAD expression (*8*).

Our current study is aimed at the auditory cortex, where we and others have previously reported electrophysiological abnormalities in gamma-band oscillations in ASD suggestive of changes in EI (e.g., *9*). Last year we reported elevated glutamate in the auditory cortex in ASD subjects compared to normal controls as measured by conventional MRS (*10*). We have now examined GABA levels in auditory cortex using J-difference MRS methods in ASD subjects and normal controls.

Methods

GABA levels were determined in the left temporal lobes for 9 ASD subjects and 11 age-match healthy controls (HC) using a MEGAPRESS sequence (*11*) optimized for GABA detection, with edit-on and edit-off frames interleaved, for a total of 512 acquisitions (256 edit-on and 256 edit-off frames) on a GE 3T HDx scanner with TR/TE= 2500ms/70ms. Edit-on and edit-off frames for each acquisition were separated, reconstructed, and fitted using SAGE (GE Healthcare). The processed edit-off spectra were subtracted from the edit-on spectra to produce the GABA spectra. The GABA peak area was divided by the area of the creatine peak in the edit-off spectra to produce the GABA/Cr ratio.

Results

The results are given in the table below. There was a significant difference in the GABA/Cr ratios in between HC and ASD.

Metabolite	HC Mean	ASD Mean	Result	p-value
GABA/Cr	0.345	0.245	ASD<Controls	0.016

Discussion

The significantly reduced levels of GABA in the ASD group, compared to healthy controls, provide support for the hypothesis of GABAergic inhibitory deficits in ASD. When combined with our previous results from last year showing increased levels of glutamate in ASD subjects, as measured by conventional MRS, these data also provide strong support for the excitation/inhibition imbalance (EI) theory. Future study should include both MEGAPRESS and short-echo PRESS measurement of glutamate from the same voxels in ASD participants.

References

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