Reduced cerebral GABA in patients with amnestic Mild Cognitive Impairment (aMCI) may predict progression to Alzheimer's Disease (AD)

Napapon Sailasuta[1], Kent Harris[1], and Ralph Noeske[2]

[1]HMRI, Pasadena, CA, United States, [2]Research and Collaboration, GE Healthcare, Berlin, Germany

Introduction

Defining pre-clinical AD before onset of dementia has become a major challenge for Clinicians and Drug Discovery alike. Amnestic mild cognitive impairment (aMCI) is such a condition. We hypothesized that aMCI patients as well as established AD would show reduced cerebral concentrations of inhibitory neurotransmitter gamma amino butyric acid (GABA) and thereby serve as a useful, non-invasive MRS biomarker of aMCI and preclinical AD.

Methods

Seven HC, 4 MCI and 1 AD patients were enrolled. Diagnoses of MCI and AD were established with neuropsychological assessment. All human brain single voxel GABA spectra (2.5x2.5x3.0 $cm^{3)}$ were recorded in 10 min from posterior cingulate gyrus (PCG) on a GE 3T MRI scanner, using the MEGA-PRESS data acquisition approach (Sailasuta et al., 2001, Wang et al., 2006). A 12-channel head array coil was used for signal reception. GABA quantification was performed using GE SAGE off-line processing software and reported as ratio to unsuppressed water signal intensity. Statistics: R^2 correlation and student t-tests ($P<0.05$ for significance) were performed

Results

GABA level in PCG in combined MCI and AD group was significantly decreased: mean -13%, ($P=0.04$). R^2 vs NAA/Cr = 0.305: P=NS.

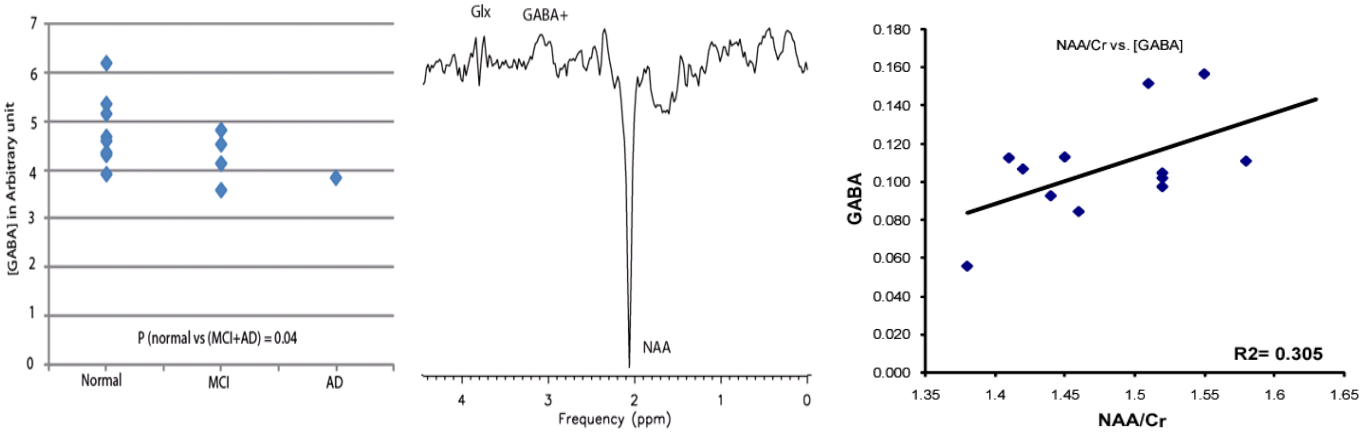

Figure: Left: Scatter plot GABA healthy elderly vs MCI/AD ($P<0.04$); center: typical GABA editied spectrum, Right: Regression GABA vs NAA/Cr $R^2 = 0.306$.

Discussion and Conclusion

Evidence from preclinical and clinical studies has associated changes in γ-aminobutyric acid (GABA) in numerous neurodegenerative disorders but to our knowledge this is the first in clinical aMCI, the best recognized precursor of Alzheimer's disease (AD). Apolipoprotein E4 (apoE4) is the major genetic risk factor; apoE4 gene accounts for 65-80% of all AD cases. Mice that had been genetically engineered to carry the apoE4 gene, loss of GABAergic neurons was observed (Li et al., 2009). Several postmortem studies of subjects with late stage AD, reduced GABA levels were observed in all brain regions including temporal cortex, occipital cortex, cerebellum, caudate and thalamus. (Hardy et al., 1987, Seidl et al., 2001) but none has carried out in living AD patients. In this preliminary study, we assess GABA levels in healthy elderly subjects (HC), mild cognitive impairment (MCI) and AD subjects. These preliminary results provide evidence for possible dysfunction of the GABAergic neurotransmission in aMCI, a recognized precursor of AD. MRS determination of [GABA] alone, or in combination with other MR biomarkers may predict progression, so that this simple measure may assist in therapeutic monitoring.

Acknowledgements : Work supported by NIH/NIDA K252001 (NS), L.K.Whittier Family Foundation (KH). The authors thank Dr. Michael Harrington, Ms. Sherri Lee and Dr. Sarah DeBoard Marion for their assistance in subjects classification.

References: Hardy J, Cowburn R, Barton A, Reynolds G, Dodd P, Wester P, O'Carroll AM, Lofdahl E, Winblad B (A disorder of cortical GABAergic innervation in Alzheimer's disease. Neurosci Lett 73:192-196.1987).

Li G, Bien-Ly N, Andrews-Zwilling Y, Xu Q, Bernardo A, Ring K, Halabisky B, Deng C, Mahley RW, Huang Y (GABAergic interneuron dysfunction impairs hippocampal neurogenesis in adult apolipoprotein E4 knockin mice. Cell Stem Cell 5:634-645.2009).

Sailasuta N, LeRoux P, Hurd R, Wang P, Sachs N, Ketter TA (Detection of cerebral Gamma-aminobutyric acid (GABA) in Bipolar Disorder Patients and Healthy Volunteers at 3T. Proc ISMRM 6:1011.2001).

Seidl R, Cairns N, Singewald N, Kaehler ST, Lubec G (Differences between GABA levels in Alzheimer's disease and Down syndrome with Alzheimer-like neuropathology. Naunyn Schmiedebergs Arch Pharmacol 363:139-145.2001).

Wang PW, Sailasuta N, Chandler RA, Ketter TA (Magnetic Resonance Spectroscopic Measurement of Cerebral Gamma-aminobutyric Acid Concnetrations in Patients with Bipolar Disorder. Acta Neuropsychiatrica 18:120-126.2006).