Histological Correlations of Decreased NAA Levels in Human Temporal Lobe Epilepsy

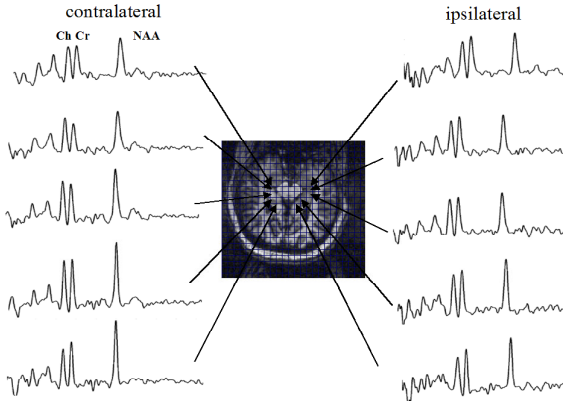
H. P. Hetherington[1], A. Cohen-Gadol[2], J. Kim[3], D. D. Spencer[2], J. W. Pan[4]

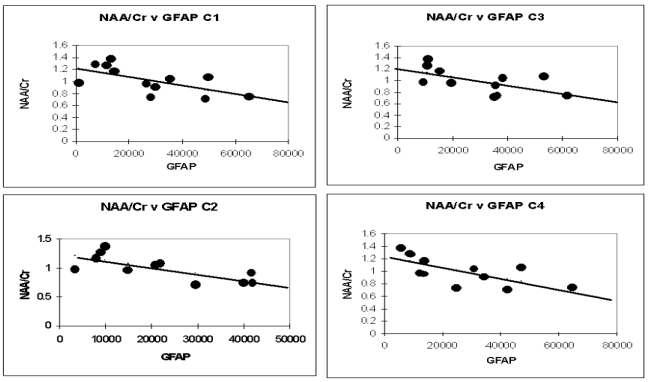
[1]Radiology, Physiology and Biophysics, Albert Einstein College of Medicine, Bronx, NY, United States, [2]Neurosurgery, Yale University, New Haven, CT, United States, [3]Pathology, Yale University, New Haven, CT, United States, [4]Neurology, Albert Einstein College of Medicine, Bronx, NY, United States

Introduction: Although *in vivo* ^{1}H spectroscopy is widely used to localize epleptogenic regions in a variety of human epilepsies, the underlying cellular and metabolic changes leading to these spectral alterations are not well established. Specifically, the reversibility of contralateral decreases in NAA with successful surgery has demonstrated that decreases in NAA are not solely due to neuronal loss. To better understand the cellular changes underlying decreased NAA in temporal epilepsy, we correlated *in vivo* presurgical hippocampal NAA/Cr ratios with histological measures of neuronal cell loss and astrocytic reaction from each of the CA1-4 sectors of the hippocampus.

Methods MR: Spectroscopy data were acquired on a 4T whole body Varian INOVA system in 13 patients with temporal lobe epilepsy and 15 controls. The data was acquired using a modified 3D LASER sequence (10x80x100mm^3 voxel) and two dimensions of phase encoding (24x24 resolution, FOV=192x192mm^2, 19 minute acquisition). Voxels spanning both hippocampi in the posterior to anterior directions were then fit in the spectral domain and the ratio of NAA/Cr was determined by dividing the resonance areas. **Pathology:** Following resection, the surgical specimens were placed in 10% buffered formalin and paraffin embedded. Paraffin sections, 6mm thick, were stained with hematoxylin and eosin, Luxol fast blue, or Nissl stain. Neuronal counts, adjusted using Abercrombie's formula, were compared to reference counts taken from an autopsy control population (n=26). We also evaluated the amount of GFAP staining in the CA sectors. GFAP antibody staining detects the intermediate filament expressed in activated astrocytes, providing a measure of astrocytic reaction to neuronal pathology.

Results: Displayed in figure 1 are representative spectral data from a patient with temporal lobe epilepsy. Comparison of the hippocampal NAA/Cr ratio with neuronal cell counts (CA1,CA3 and CA4) showed no statistically significant relationship, whereas a significant correlation was seen in the CA2 sector of the hippocampus (R=-0.64, p<0.03). In contrast the NAA/Cr ratio was highly correlated with GFAP staining in all CA sectors of the hippocampus with values ranging from R=-0.70 to -0.90 and p <0.02 to 0.01, Figure 2. The correlation was strongest in the CA2 sector of the hippocampus (R=-0.90,p<0.01). Finally correlation of GFAP staining with neuronal loss on a sector by sector basis revealed a statistically significant correlation also only in the CA2 sector (R=0.81,p< 0.002).





Discussion: The strong correlation between NAA/CR and GFAP staining in all four CA sectors suggests that decreases in NAA/Cr reflect recent or ongoing neuronal injury/impairment. The correlation of NAA/Cr and GFAP with neuronal loss only in the CA2 is consistent with the close identification of NAA/Cr and GFAP. Since it is believed that the CA2 is relatively spared by the initial insult, the CA2 may be the most sensitive to subsequent or ongoing seizure activity. Additionally, recent data suggests that the CA2 may have a role in generation of CA3 hippocampal oscillatory activity. These data indicate that NAA/CR measurements in temporal lobe epilepsy provide a highly sensitive non-invasive measure of the current status of neuronal impairment and recent or ongoing injury. Thus, NAA/Cr measurements could provide a sensitive measure for assessing longitudinal changes in patients with temporal lobe epilepsy.

Acknowledgement: This work was supported by the NIH through grants: NIH P01-NS39092, M01-RR12248