NAA/Cr tightly correlates with extracellular GABA in surgically treated hippocampal epilepsy

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Introduction: A long existing question in human epilepsy has been what role extracellular (EC) GABA has in the seizure focus, whether it increases inhibition, or if its insufficiency may be pro-convulsant. Animal and human studies of EC GABA in epilepsy have shown abnormalities in both GABA transport and release (1,2). It is also known that relatively mild mitochondrial injury results in increased GABA release (3). In this study we performed pre-operative spectroscopic imaging studies in patients with epilepsy and correlated them with microdialysis studies of extracellular GABA to determine whether such a mechanism may be operative in vivo.

Methods: N=14 patients were recruited from the Yale University Epilepsy Surgery Program. These patients (who underwent intracranial EEG monitoring) were comprised of n=8 surgically treated hippocampal epilepsy and n=6 neocortical (non-hippocampal) epilepsy. Patients were imaged within 1 month prior to the microdialysis/EEG procedures. The 1H data were acquired using a whole body 4T Varian Inova imaging spectrometer with a volume 1H TEM coil. Scout images were acquired with an inversion recovery gradient echo. The triply obliqued hippocampal slice was defined along the planum temporale prescribed from an off-sagittal slice. After scout imaging, 3D localized shimming was performed over the bilateral hippocampi using first, second and third order shims. The spectroscopic image was optimized to collect data on N-acetyl aspartate, creatine and choline using a 3D localized adiabatic LASER sequence with two dimensions of phase encoding, with TR/TE 2s/72ms. The spectroscopic image had a nominal voxel size of 0.64cc (24x24 encodes, FOV 192x192mm, acquisition time 19min). To provide reproducible volume selection along the hippocampal plane between subjects, a semi-automated single voxel selection and reconstruction routine was used (4). The spatial reconstruction utilized a cosine filter to confine the point-spread function with an effective sampling volume of 1cc. The 1H data were fit in the spectral domain with the resonance areas determined as ratios.

Probes were implanted stereotaxically with electrodes (Spencer probe, Ad-Tech Instrument Co.) into selected regions suspected of being involved in the seizures. The microdialysis study was performed on post-op day 3 while still on anti-epileptic medications in order to avoid post-operative effects but otherwise match the condition of the MR study. To avoid effects from ictal activity, behavioral stimuli or food intake, microdialysis was conducted in the evening at least 6 hrs from any seizure activity, and at least 2 hrs following any food intake.

Results: As expected the NAA/Cr values in the n=8 hippocampal epilepsy group were significantly lower than the neocortical group (0.90± 0.11 vs. 1.27±0.27; $p<0.025$). The EC GABA levels were not significantly different. While there was no significant correlation seen with patients with neocortical epilepsy (Figure 1, open squares), there was a very strong negative correlation between EC GABA and hippocampal NAA/Cr (filled diamonds, $R=-0.96$, $p<0.001$). Because of the observations that brain GABA may differ between men and women (5), the data were additionally evaluated by gender (Figure 1); but this did not result in any evident difference.

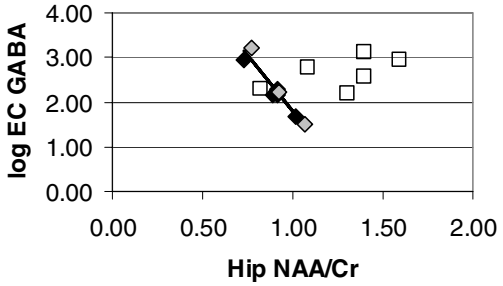

Figure 1. Regressions between log extracellular GABA with hippocampal NAA/Cr. Data from neocortical epilepsy patients (open squares) were not significant. Data from surgically treated hippocampal epilepsy patients show a very strong regression, $R=-0.96$, $p<1xe-4$. There were three women in this patient group (gray diamonds).

Discussion: In the dysfunctional hippocampus of temporal lobe epilepsy, elevations in EC GABA are highly correlated with depressed NAA/Cr. This is consistent with a view that loss in mitochondrial function is closely correlated with increased GABA release. A direct explanation is suggested by the data of Nguyen and Picklo, who found potent inhibition of the enzyme succinic semialdehyde dehydrogenase (SSAD) by lipid peroxidation products, known to accumulate in epilepsy. SSAD functions to replenish the mitochondrial TCA cycle intermediates through carbon skeletons provided from GABA (via the GABA shunt), and its inhibition may increase EC GABA concentrations. This process suggests that in this patient group mitochondrial injury results in increased EC GABA and inhibition to provide neuroprotection.

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