Hippocampal glutamate in temporal lobe epilepsy

J. W. Pan[1], K. Vives[2], R. Kuzniecky[3], D. D. Spencer[2], H. P. Hetherington[4]

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

Introduction: A frequently considered hypothesis in the pathophysiology of hippocampal epilepsy focuses on an excess of the major excitatory neurotransmitter, glutamate. This is supported by During and Spencer (1), who used hippocampal microdialysis to find that extracellular glutamate levels are higher in the epileptogenic hippocampus than the non-epileptogenic hippocampus. More recently, several reports using short echo in vivo MR spectroscopy have also found elevated total glutamate in MRI negative patients, although the locus of increase has been reported as either ipsilateral or contralateral hippocampus (2,3). We evaluate this question in unilateral MTLE patients using an optimized approach to glutamate spectroscopic imaging at 4T.

Methods: N=9 unilateral hippocampal epilepsy patients (age 32.9±11.5years) were studied in comparison to n=11 healthy controls using a 4T Varian Inova whole body MR system and ^{1}H volume TEM head coil. The ^{1}H spectroscopic imaging used a quad adiabatic refocused localized sequence, TE/TR 37/2000, 16x16 spatial encoding, a FOV of 192 x 192mm, over a 10mm slice (two scans, 32min). An IR delay was used to minimize macromolecule contributions. This sequence has been previously shown to intrinsically reduce J modulation losses (4). Shimming was performed using a Bo map with calculated 1st-3rd order shim corrections. The entire duration of the study was ~70min.

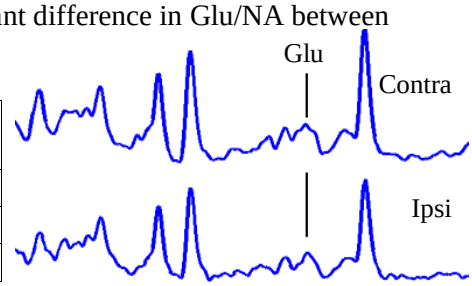
The ^{1}H data were analyzed using single voxel reconstructions, with the voxel positions referenced to the midbrain aqueduct. A LC model was used analyze the data, using spectra acquired from 6 compounds, NAA, creatine, aspartate, glutamate, glutamine and aspartate. Fits were rejected if the coefficient of variation for the fit was greater than 20%. Quantification of the ^{1}H spectra was performed relative to CSF in the ambient cistern measured in a high resolution proton density image, and corrected for tissue volume, coil loading and relaxation. Tissue volumes were determined from semi-automated image segmentation of T1 weighted images.

Results: Fig. 1 displays a scout, the selected loci and spectra from an epilepsy patient (right seizure focus). The Table summarizes the data from position #3 centered in the body of the hippocampus where adequate spectra were acquired from all patients and volunteers. Both the ipsilateral NAA and glutamate were significantly low ($p<0.001$, two tailed) in comparison to control hippocampi. As expected, the NAA/Cr was significantly low, while Glu/Cr was also significantly low ipsilaterally. With declines in both NAA and Glu, we did not detect a significant difference in Glu/NA between patient and control (data not shown).

Table

		NAA (mM)	Glu (mM)	Cr (mM)	NAA/Cr	Glu/Cr
Control		9.4±1.1	7.0±1.1	9.1±1.2	1.21±0.11	0.81±0.12
Epilepsy	Ipsi	8.3±1.1*,^	5.3±1.8*	9.2±1.4	1.05±0.10*	0.61±0.18*
	Contra	9.9±1.2^	6.8±1.8	10.0±1.9	1.15±0.14	0.71±0.13

*p<0.03, significantly different from control, ^p<0.03, significantly different between ipsi- and contra. All multiple comparisons corrected.



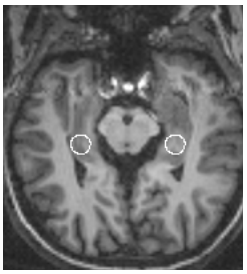


Fig. 1. Scout and spectra from an epilepsy patient. The positions of the spectra are indicated.

Conclusions: At high field, the quad adiabatic sequence measures concentrations that are consistent with literature values of NAA, glutamate and creatine. Also consistent with other data the creatine levels in these patients is not significantly perturbed, with the decline in NAA/Cr being largely due to NAA. Thus Glu/Cr is similar to NAA/Cr, reflecting a decline in Glu. It is most likely that the decline in total glutamate accompanies the decline in NAA, both characterizing mitochondrial insufficiency. Notably, a decline in total glutamate is not incompatible with an increase in extracellular glutamate given that the integrated content of extracellular glutamate (1-5uM in concentration) is negligible in comparison to the multi-millimolar levels of total glutamate.

References: (1) During and Spencer, Lancet 341(8861) 1993. (2) Woermann et al Ann Neurol 45:369 1999 (3) Simister et al Epilepsia 43:1021 2002. (4) Pan ISMRM 2003 #268