in vivo Measures of Hippocampal Bioenergetics are Correlated with Impaired Granule Cell Electrophysiology in Human Temporal Lobe Epilepsy

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Introduction: Although declines in cerebral PCr/ATP have been reported in the hippocampi of patients with temporal lobe epilepsy, the mechanisms and possible extent to which these bioenergetic declines manifest in altered function at a cellular level is not known. To investigate this issue we correlated *in vivo* presurgical measurements of hippocampal PCr/ATP from patients with temporal lobe epilepsy with cellular measures of dentate hyperexcitability, synaptic depression and Na+/K+ ATPase function from the resected tissue.

Methods MR: 14 surgical TLE patients were studied. Prior to hippocampal surgery, ^{31}P spectroscopic imaging data were acquired using a 4T Varian INOVA whole body system with a double-tuned TEM. The data were acquired using a non-selective excitation pulse (37.5°), three dimensions of phase encoding and a spherical sampling scheme (13x13x13 FOV=24x24x24 cm^3) resulting in a 48 minutes acquisition time. To minimize uncertainties in the anatomical sampling, the ^{31}P voxels were reconstructed using a 3D image guided single voxel reconstruction algorithm. **Electrophysiology**: Immediately after resection, tissue was placed on ice with artificial CSF. Hippocampal slices (400 µm) were prepared and maintained at 35°C in an interface slice chamber. Intracellular recordings of the dentate granule cells (2-4 cells/patient) were performed using4 M K-Acetate filled microelectrodes. Synaptic stimulation was delivered in the outer molecular layer using a twisted bipolar electrode. The excitability of the tissue was examined using low rates of stimulation (0.1 to 0.2 Hz). To metabolically challenge the tissue and provide measures of synaptic depression and rate of repolarization (evaluating Na-K ATPase function), we also examined the responses to trains of stimuli (10 Hz, 10 sec) which were delivered at an intensity twice that needed to evoke a single action potential from a membrane potential of –75 mV.

Results: Although we found no statistically significant correlation between the excitability of the tissue and synaptic depression with the bioenergetics, the rate of recovery of the membrane potential showed a highly significant correlation ($p<0.007$, $R = 0.85$) with PCr/ATP (Figure 1). These data show that the more normal levels of pre-operative PCr/ATP (Fig. 2a) were associated with more rapid rates of recovery (Fig. 2b) following the train and that those patients with very poor energetics (Fig 2c) had rates of recovery as low as 0.5 mV/s (Fig 2d), requiring up to five times longer to repolarize their membrane potentials. These data suggest that the primary effect of depressed bioenergetics is to slow the restoration of the ionic gradients needed for neural function as opposed to directly affecting the more rapid events involved in synaptic transmission.

Figure 1

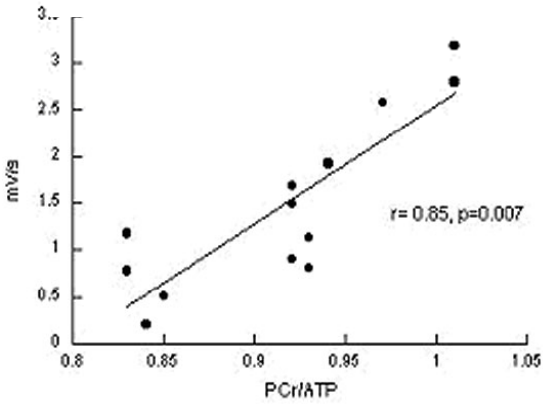
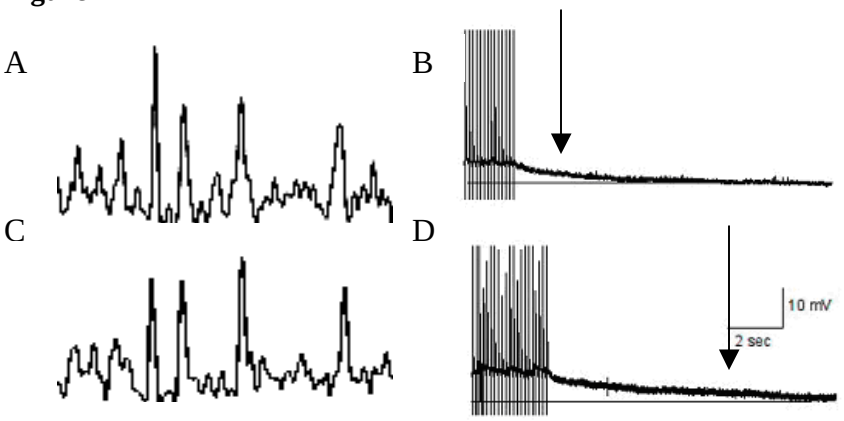


Figure 2



Discussion: These data provide some of the first evidence of a direct link between a measure of bioenergetics and alterations in electrophysiology in epileptic human tissue. The data suggest that adequate levels of PCr are critical in allowing the neurons to maintain the appropriate ionic gradients, as typically achieved via the Na+/K+ ATPase. The inability of the dentate to maintain ionic homeostasis may be a critical factor in allowing seizures to spread into the CA3, and dentate, consistent with the known pathology of hippocampal epilepsy.

Acknowledgement: This work was supported by the NIH: P01-NS39092, M01-RR12248 and the Dana Foundation