Microdialysis in human hippocampal TLE: correlates with metabolic imaging

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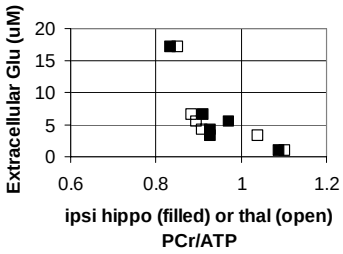
Introduction: A large body of imaging literature (PET and MR) and more recent ex vivo studies have increasingly argued for a pathophysiological role of energy metabolism and mitochondrial function in temporal lobe epilepsy, TLE. However, by virtue of the non-invasive nature imaging it is difficult to directly demonstrate a link between dysfunctional energetics with *in vivo* hyperexcitability. The use of microdialysis catheters in human TLE patients provides a unique opportunity to evaluate the extracellular milieu in the seizure focus (1), and with imaging, to determine how extracellular (ECF) measures of glutamate and GABA may relate to metabolic imaging measures.

Methods: N=7 unilateral hippocampal epilepsy patients (age, 33±12years) were studied. These patients were studied pre-operatively using ^{1}H and ^{31}P spectroscopic imaging using a 4T Varian Inova whole body MR system, ^{1}H and ^{31}P volume TEM head coils. ^{1}H hippocampal data was collected using a modified LASER sequence (10mm thick, 80x100mm in-plane FOV selection) with two dimensions of phase encoding (24x24, FOV=192x192mm, 19.2 min) angulating the plane along the temporal pole (2). Shimming was performed using Bo mapping with calculated 1^{st}-3^{rd} order corrections. ^{31}P spectroscopic imaging was performed using a pulse acquire acquisition utilizing a three-dimensional spherical sampling scheme (13x13x13, FOV = 24x24x24cm). The entire durations of the ^{1}H and ^{31}P studies were ~65 and 75min respectively. Microdialysis: Probes (0.3mm diameter) were attached to depth electrodes (the tip end of the electrode), which were implanted stereotaxically in regions of interest (MRI verified). To minimize any post surgical effects, the dialysis catheters were not used until 2-5days after implantation. The inter-ictal zero-flow study, which estimates true basal substrate levels, for details, see (3), was performed at least 6 hrs from any intracranially recorded seizure activity, and at least 2 hrs following any food intake. The duration of a typical dialysis study was 6hrs. 20ul dialysate samples were collected at progressively decreasing flow rates and the samples were stored at –80°C for later analysis using HPLC. Basal levels were determined using regression analysis with a 2nd polynomial order to a flow of zero. The microdialysis studies were typically performed within 3months of MR imaging.

Results: Because of the non-normal distribution of microdialysis data, rank correlations were used. Significant correlations were found for both extracellular glutamate and GABA. Notably with these early data, no correlation was found between GABA and high energy phosphates, nor ECF glutamate and NAA/Cr. An example of the data is shown in Figure 1.

Spearman rank correlations (R) and significance	Ipsi mean hippocampal NAA/Cr	Ipsi hippocampal PCr/ATP	Ipsi thalamic PCr/ATP
ECF glutamate	NS	–0.83, p<0.06	–1.00, p<0.003
ECF GABA	–0.86, p<0.007	NS	NS

Figure. Relationship between extracellular glutamate and ipsilateral hippocampal or thalamic PCr/ATP



Conclusions: In this preliminary study, we detected correlations between metabolic imaging and extracellular neurotransmitter levels. The relationship to the thalamus is very consistent with our previous data arguing for a metabolic network that closely related hippocampal pathology with thalamic PCr/ATP (to a greater extent than hippocampal PCr/ATP , 4). That extracellular ipsilateral glutamate may relate to hippocampal PCr/ATP suggests that control of ECF glutamate reflects immediate available tissue energetics, with either low energetics leading to higher steady state release or a decline in steady state clearance. Indeed, both lower energetics (4) and high basal extracellular glutamate levels have been detected in the epileptogenic hippocampus (5). The negative relationship of NAA/Cr with GABA may be consistent with a view that extracellular GABA is sensitive to mitochondrial capacity, wherein the elevation in GABA represents a response to deteriorating mitochondrial function.

Reference: (1) During and Spencer, Lancet 341(8861) 1993, (2) Chu et al, ISMRM 2004; p105. (3) Hutchinson PJ et al. Acta Neurochir Suppl. 81:359-362 2002 (4) Pan et al Am Epilepsy Soc 2003, #B.06 (5) Cavus et al. 2004 Ann Neurology, in press.