Dynamic Proton MRS Following the Infusion of [U-13C] Glucose to Measure Glutamate Metabolism in Temporal Lobe Epilepsy

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Purpose: Focal glucose hypometabolism in temporal lobe epilepsy (TLE) is associated with medical intractability, neurocognitive deficits and depression. Glutamate (Glu) is the primary excitatory neurotransmitter in the brain and has been implicated in seizure generation and propagation [(1)]. Increased levels of Glu in the epileptogenic hippocampus are thought to be the result of reduced Glu clearance via the glutamate-glutamine cycle and glutamine synthetase activity [(2, 3)]. However, reduced Glu concentrations have also been reported in the medial temporal lobe of TLE patients [(4)]. The aim of our study was to measure the Glu concentration and rate of Glu synthesis during the interictal state in the involved medial temporal lobe using ^{1}H MR spectroscopy (MRS) following an infusion of [U-^{13}C] glucose. We hypothesized that in the interictal state, the oxidation of glucose to glutamate would be reduced in the involved mesial temporal lobe of TLE subjects owing to a decrease in neuronal oxidative metabolism.

Methods: Seven adults with unilateral TLE confirmed by video EEG monitoring and 5 controls underwent structural MRI and ^{1}H MRS using a 3.0T Siemens Tim Trio MR scanner. Single voxel spectroscopy (PRESS TR/TE = 2000/30 ms, NA = 160; voxel size 1.7 x 3.7x 1.7 cm) was acquired in the bilateral mesial temporal lobes. After a baseline MRS study, a 20% w/v solution of 100% isotopically enriched [U-^{13}C] glucose was infused intravenously (3mg/kg/min) for 20 minutes. MR Spectra were then acquired every 7.5 minutes for up to 80 minutes following the infusion. All subjects fasted for >12 hours prior to the study and were free of clinical seizures for > 24 hours before the study. LCmodel was used to obtain semi-quantitative metabolite levels and ratios. Custom software using Matlab and SPM 9 was used to obtain tissue composition and metabolic information from the same anatomical position. Statistical differences were determined using an independent samples Kruskal-Wallis test where $p < 0.05$ was considered significant.

Results: Compared to controls, the mean Glu and combined glutamate-glutamine (Glx) levels measured in the involved mesial temporal lobe were significantly lower in the TLE group (p=0.010 and p= 0.011, respectively). As expected following ^{13}C glucose infusion, there was a reduction in the ^{1}H MRS detection of Glu in both control and TLE subjects (Fig.1) due to decreases in the ^{12}C bonded protons of Glu [(5)]. However, the slope of change in the Glu concentration in the epileptic mesial temporal lobe did not differ between TLE and controls (p=0.77).

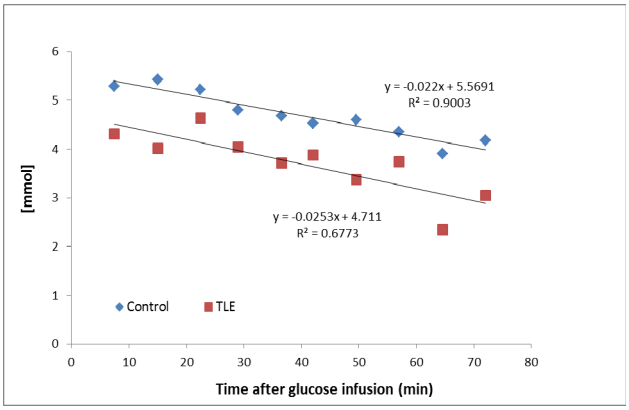

Fig. 1: The decrease in glutamate concentration following U-^{13}C glucose infusion in TLE and control subjects.

Discussion: These findings confirm that glutamate concentrations are decreased in the mesial temporal regions of persons with TLE during the interictal period. However the rate of metabolic turnover of Glu does not differ between subjects with epilepsy and normal controls, which suggest that the decreased Glu concentrations in the interictal state are not due to reduced oxidative metabolism, but to other factors.

References:

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