MR spectroscopic studies of early post status epilepticus in rats

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Target audience: MR researchers and animal imaging specialists

Introduction: The development of spontaneous recurrent seizures (epilepsy) is a complex process that commonly ensues after an initial cerebral insult. While it is well known that metabolic dysfunction is common during this process, whether it has a role in epileptogenesis remains unknown. We used MR spectroscopy and T2 relaxometry in a rodent model to understand how moderate variability in status epilepticus influences such metabolic injury in early epileptogenesis. This may enable identification of a MR based biomarker to predict the development of epilepsy.

Methods: ***Animal model:*** We modified the Hellier Dudek model of temporal lobe epilepsy to generate a range of status epilepticus duration. Male Sprague Dawley rats were injected hourly with 5mg/kg kainic acid until a stage 3/4/5 seizure was elicited. After this first seizure, a variable dose of additional kainate was given according to protocol until the rats reached a status duration of 1.5, 2 or 3hrs. Control rats were treated with saline. ***MR:*** Three days after status, animals underwent *in vivo* MRS and MRI study at 7-Tesla (Bruker Avance III). Single voxel (8mm^3) localized hippocampal PRESS acquisitions at TE 10ms and 40ms were separately performed over the left and right hippocampus using a body volume transmit and quadrature receive coil. Shimming was performed using a Bolero acquisition (*B0 l*oop *e*ncoded *r*ead*o*ut) achieving a typical σ(B0) of ~7Hz over the bilateral hippocampal region. Water suppression was performed using optimized VAPOR. LCM analysis was performed for determination of the metabolite profiles. Metabolites with Cramer Rao values of <10% were included in the analysis. T2 relaxometry (8 time points, TR 5sec) was acquired with 140um in-plane resolution using multi-slice multi-spin echo sequence with monoexponential least squares fit.

Results: Fig.1 shows data and an example of the fitting. Fig.1G summarizes the group results for the status groups (n=8 each group) and controls (n=10). There are significant changes in NAA/tCr, Glu/tCr, mI/tCr, Gln/tCr and GSH/tCr in the status groups relative to control. As expected, declines in NAA/tCr and Glu/tCr were found with increases in mI/tCr, Gln/tCr and GSH/tCr, consistent with significant declines in neuronal counts per Neu-N staining. The variability of the metabolite measures is substantial across the combined status groups. Linear regression analysis shows NAA/tCr and Glu/tCr are significantly correlated and offset from control data. mI/tCr relates significantly and positively to both lengthened hippocampal T2 and Gln/tCr, consistent with cellular edema and activation of glutamine synthetase in glia. The significant correlation between Gln/tCr and GSH/tCr is negative, consistent with increased glutathione consumption under conditions of glial activation. None of these regressions were seen in controls.

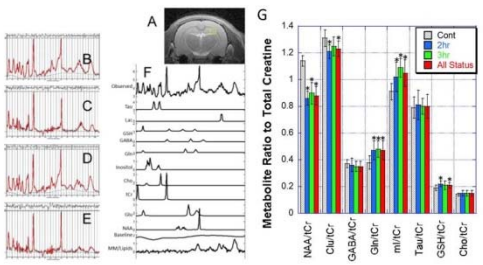

Fig. 1 A: Scout,. B,C: TE10ms, 40ms spectra from a kainate 3hr rat; D,E from a control rat. F shows the LCM analysis of the TE10ms spectrum B. G. Summary plot of all metabolites. Abbreviations: NAA N-acetyl aspartate with N-acetylaspartate glutamate; Glu glutamate; tCr total creatine (phosphocreatine and creatine), Cho choline and glycerophosphocholine; Inositol myo-inositol; Gln glutamine; GABA; GSH glutathione; Lac lactate, Tau taurine.

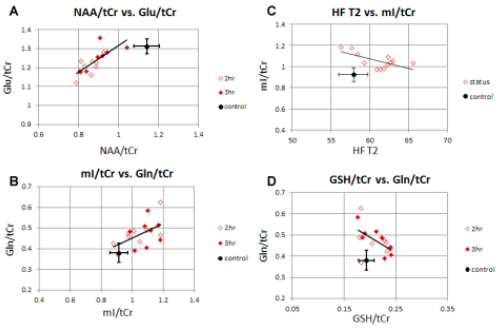

Fig2. The scatterplots from the status groups are shown with control values (mean, standard deviation). Shown are the regression lines for the combined status groups (thick black).

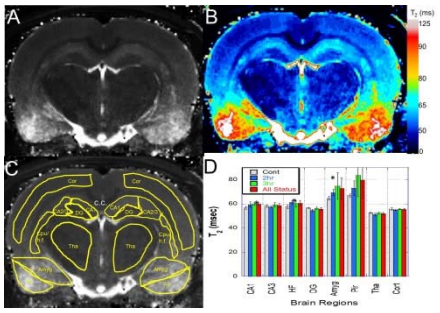

Fig3A,B. T_2 map of a 3-hr seizure brain in gray scale and color. C: ROI of different brain regions. D: summary plots of T_2 in different regions for control, 2 hr,3-hr, and all status seizure brains. Abbreviation: HF-hippocampal fissure, DG-dentate gyrus, Amy-amygdala, Pir-piriform cortex, ThaL thalamus; Cort-cortex

CONCLUSION The metabolic injury seen in the incremented kainate model displays variability that is linked with correlated changes in several metabolites. The nature of the injury can be considered to be classified as neuronal, glial or joint pathophysiological processes. The MR spectroscopic and imaging data can be informative towards individual identification of injury severity.