Mapping Hippocampal Activity during Epileptogenesis by Manganese Enhanced Magnetic resonance imaging(MEMRI)

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Introduction:

The neurobiological processes resulting in epilepsy, known as epileptogenesis, are incompletely understood. Currently there is no available therapy that effectively halts or retards the development or progression of the condition. The hippocampus plays a critical role in the development of epilepsy. Manganese enhanced Magnetic Resonance Imaging is a novel MRI technique, which demonstrates fine structural detail of the brain, particularly the hippocampus[1]. Also, MEMRI can be performed in vivo at several time points on the same animal to show the dynamic progression of structural brain changes [2]. This longitudinal study aims to characterise the progressive pathological changes in the hippocampus of the post-kainic acid status epilepticus (SE) rat model of temporal lobe epilepsy using MEMRI in vivo.

Material and Methods:

Male Wistar rats (7 weeks, 200-250 g) underwent stereotaxic surgery for the implantation of an intra-cerebroventricular (ICV) cannula and epidural EEG electrodes made from MRI-compatible materials. Fourteen rats were injected by low-dose kainic acid (KA,2.5-5 mg/kg, ip) to cause 4 h of sub-convulsive *status epilepticus* (SE). Ten control rats were injected with saline. Over a latent period of 3-6 weeks the animals developed spontaneous recurrent seizures. Serial MEMRI scans were performed at 1 week before, two days and six weeks after administration of KA on a BRUKER BIOSPIN 4.7T animal MRI scanner. A volume coil was used as excitation coil and a surface coil as the receive coil. T1 high resolution images was acquired by SNAP 3D T1 weighted sequence (TR 15ms, TE 5ms, Flip angle 25^o. spatial resolution:117x117x234um^3). 24 h video-EEG recordings were performed on a weekly basis up to 6 weeks after SE induction. Regions of interest were drawn based on a standard rat atlas [3] around the whole brain, left hippocampus and several subregions of the hippocampus (CA1, CA3 and dentate gyrus) (Fig. 1). The intensity in left dorsal hippocampus and subregions was normalised against the intensity of the left hemisphere. The statistics was performed by ANOVA.

Results and discussion:

Fig. 1 shows the good hippocampus structural detail seen in the MRI image after Mn^{2+} administration. A progressive increase in signal intensity was found in the hippocampus in the epileptic group compared to the control group (ANOVA $p<0.05$ Fig. 2), which indicated more neuronal activities in hippocampus in the epilepsy KA model. There were significant inverse correlations between the seizure frequency and the signal intensity in the hippocampus, the, DG and CA1 regions at the 6 week time point (Fig. 3B). This decrease in Mn2+ uptake/neuronal activity in animals with more recurrent seizures might reflect a protective mechanism of the brain against neuronal hyperexcitability. Importantly, early changes in the left dentate gyrus also significantly correlated with seizure outcome at a later stage (Fig. 3A), which may have implications for predicting seizure phenotype. Histological techniques will be performed to investigate the mechanism of changes in MRI imaging.

Conclusion:

This study demonstrated MEMRI is a powerful tool to show progressive changes in brain structures (i.e. hippocampus) during the course of epileptogenesis. MEMRI shows promise as a valuable tool to investigate the mechanisms underlying the development of the epilepsy and evaluate therapies using animal models.

Reference:

1. Nairismagi J, et al., Neuroimage; 2006 30(1):130-5
2. Van der Linden , et al, NMR Biomed. 2004 17(8):602-12
3. Paxinos and Watson, 1998.Academic Press, Inc.

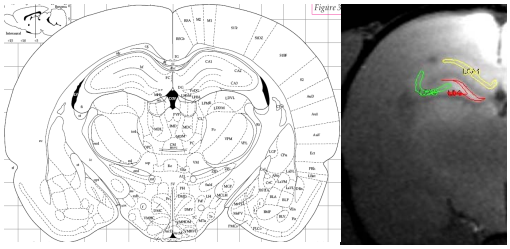

Fig 1.Regions of Interest (DG, CA3, and CA1) were delineated based on the rat atlas [3]

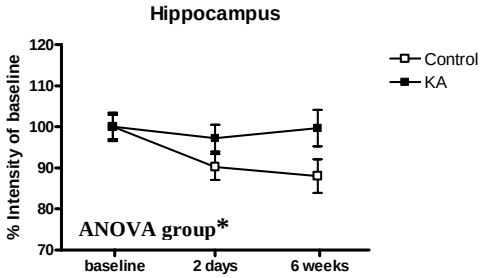

Fig.2 Intensity changes in several brain regions over 6 weeks. Data are expressed as % of baseline intensity. Significance is set at $p<0.05$. * indicates significant differences between the two groups tested at 2 days and 6 weeks (ANOVA).

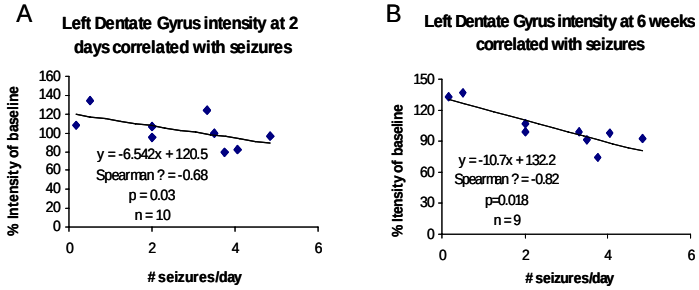

Fig. 3: Changes in MEMRI intensity of left dentate gyrus at 2 days (A) and 6 weeks (B) after SE induction significantly correlated with seizure outcome at 4-6 weeks.