Long term 7 Tesla MRI and behavioral study on status-epilepticus induced neurodegeneration in rat and possible neuroprotective treatment

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Target audience: Neuroscientists who research pathomechanisms of chronical epilepsy, and clinicians who take care of patients suffering from epilepsy.

Purpose: Status epilepticus (SE) may lead to development of temporal lobe epilepsy (TLE) characterized by hippocampal neurodegeneration, associated with psychological and cognitive dysfunctions. Neuroprotective treatment during or shortly after SE could reduce psychological co-morbidities and improve treatment of possibly followed chronic epilepsy. This study aims to estimate SE-induced neurodegeneration and treatment-mediated reduction of neurodegeneration and behavioral dysfunction by long term MRI follow-up combined with a behavioral test battery.

Methods: A fractionated rat pilocarpine model that mimics clinical and neuropathological features of TLE was used. SE was interrupted either with a combination of diazepam (DZP) and phenobarbital (group PB, n=7) or with DZP alone (group DZP, n=7). Six additional rats were taken as controls. MR scans were performed before, and 24 h, 48 h, 1 week, 6 weeks, 3 months, 6 months and 8 months after SE onset to include acute, latent and chronic phases of epileptogenesis. All MR examinations were conducted on a 7 Tesla animal scanner (Pharmascan 70/16, Bruker, Ettlingen). The time-dependent volume changes of hippocampus, CSF space and whole brain volume were manually segmented from 3D-T1-weighted images. Six months after SE, all animals performed a behavioral testing battery consisting of tests for learning and memory, explorative and anxiety-associated behavior, and hyper-excitability.

Results: Spontaneous seizures were observed in all animals exhibiting SE. Increasing cellular edema occurred immediately after SE at cortex, basal ganglia, but most severely in hippocampus, with a maximum at 24 h to 48 h post SE (Fig.1, first row). Correspondingly, longest T2 relaxation times were measured in hippocampus (~ 72 ms) and thalamus (~ 65 ms) 48 h post SE . At 1 week post SE edema disappeared while continued degeneration of the tissue became obvious (Fig.1, second raw), resulting in loss of hippocampal volumes, which was mild in PB group and much more severe in DZP group: -0.34 % in PB group vs. -5.0% in DZP group at 1 week post SE; 3.6% in BP group vs. -20.5% in DZP group at 6 weeks post SE; and 15.1% in BP group vs. -11.3% in DZP group at 6 months, measured in ratio to initial volumes before SE. In the behavioral test battery PB-treated rats showed significantly better performance in learning and memory, i.e. in the Morris Water Maze - test PB-group showed shorter latency to find the platform than that of DZP group ($p < 0.05$), but exhibited no major differences in explorative and anxiety-associated behavior or hyper-excitability.

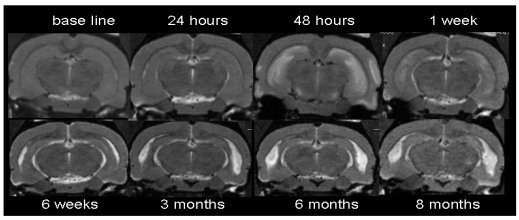

Figure 1. Brain changes induced by SE with severe volume loss and signal changes in the hippocampus.

Discussion: SE-induced neurodegeneration results in severe damages of hippocampal tissue as revealed in MR images (1), associated with spontaneous recurrent seizures and behavioral changes. Treatment with PB in addition to DZP when interrupting SE does not prevent chronic epilepsy but can reduce associated behavioral alterations such as improvement of performance in learning and memory.

Conclusion: SE-induced neurodegeneration is a long lasting process associated with behavioral changes that can be monitored by MRI and reduced by add-on treatment with PB.

References:

1. Briellmann RS, Kalnins RM, Berkovic SF, Jackson GD. Hippocampal pathology in refractory temporal lobe epilepsy: T2-weighted signal change reflects dentate gliosis. Neurology 2002;58(2):265-271.