The role of Toll-like Receptor 3 in Epilepsy

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Backround:
Epilepsy is one of the most prevalent neurological disorders affecting around 60 million people worldwide. Despite the development of antiepileptic drugs, 35% of patients cannot be controlled with current pharmacologic therapeutic options. Toll-like receptors (TLRs) are a family of innate immune receptors that mediate neuroinflammatory processes in the brain. Inflammation plays a prominent role in the etiology of symptomatic epilepsies that result from traumatic brain injuries, stroke, encephalitis, and status epilepticus (SE). Here we investigated the involvement of TLR3 in the onset, development (epileptogenesis), and severity of epilepsy using mice deficient in TLR3 in the pilocarpine model of epilepsy.

Methods:
We utilized mice deficient in TLR3 ($TLR3^{-/-}$) and their respective wild-type ($TLR3^{+/+}$) littermates. In both groups, status epilepticus was induced using pilocarpine. Subsequently, mice were implanted for EEG monitoring with wireless bipolar EEG-electrodes and seizure frequency was analyzed using a telemetric EEG/video monitoring system (DSI, USA). In addition, all animals were sacrificed for stereological assessment of neuroinflammation in the hippocampus.

Results:
Analysis of Video-EEG recordings of both groups, ($TLR3^{-/-}$) and wild-type ($TLR3^{+/+}$) mice developed spontaneous epileptic seizures. Interictal epilepstic events recorded by EEG were significantly reduced in mice lacking TLR3 receptors compared to the wild-type (5.7±1.4 and 19.4±2 events per day respectively; p=0.0004). More important, total clinical seizures were drastically reduced to 0.45±0.2 seizures per day in the KO-mice compared to 5.6±1.3 in the control mice (p=0.0076) resulting in a ~80% reduction in seizure frequency by non-expression of the TLR-3 receptor.

Conclusion:
These results indicate a central involvement of seizure induction (epileptogenesis) by TLR3 and provide evidence for future research and possibly drug development to finally change the treatment paradigm of epilepsy from symptomatic seizure control to curable prevention of seizure development.