Session/Poster# Presenter

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NBCe1 Dependent Rapid Volume Pulsations of the Extracellular Space Perpetuate Seizure Activity in Post Traumatic Epilepsy

Post traumatic epilepsy (PTE) is a debilitating sequela of traumatic brain injury (TBI) resistant to standard anti-seizure medications. PTE develops after TBI-induced changes in neural circuits increase excitability and lower seizure threshold. Volumetric control of the extracellular space (ECS) is a poorly understood regulator of excitability. Shrinkage of ECS volume increases concentrations of contained neuroactive agents and enhances ephaptic interactions of active neurons. In acute, chemo-convulsant models of epilepsy, the sodium-bicarbonate cotransporter NBCe1 facilitates rapid volume pulsation (RVP) of the ECS, enhancing seizure activity. If this mechanism exists in a chronic model for PTE, it could be a novel therapeutic target.

This study utilized probe transients quantification to measure fast relative changes of ECS volume to investigate if RVPs occur after controlled cortical impact (CCI)â€"a chronic in-vivo model of PTE. In CCI injured rat neocortex, RVPs and epileptiform activity occurred concurrently, both spontaneously and with a low concentration chemoconvulsant (5-10 Î¼M 4-AP). At â‰¥3 weeks after CCI, shrinkages of the ECS averaged 7% (SD - 5%, 20 slices, 12 rats). Sham injured rats showed no spontaneous epileptiform activity, and a low concentration of chemoconvulsant induced activity only in 18% of slices (2/11, 5 rats). In slices from CCI injured rats, application of the NBCe1 blocker DIDS (4,4â€²-Diisothiocyano-2,2â€²-stilbenedisulfonic acid, 300 Î¼M) stopped RVPs and epileptiform discharges within 20 minutes (5 slices, 4 rats). In conclusion, this is the first study to show RVPs in a chronic model for PTE. These results reveal RVPs as a mechanism that increases hyperexcitability and hypersynchrony within neurocircuits through ECS volume shrinkage. Disabling the generation of RVPs by blocking NBCe1 may limit hyperexcitability and reduce volume transmission of neuroactive agents that promote neuronal synchrony, allowing seizure activity to resolve.