

Stony Brook University The Graduate School

Doctoral Defense Announcement

Abstract

Imaging neuronal activation during seizures: A role for tissue plasminogen activator, microglia,
and zinc

By

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Epilepsy is a term defining different types of seizure disorders. Temporal Lobe Epilepsy (TLE) is the most common form of the disease in adults. It is characterized by partial complex seizures originating from the hippocampus, a specific area of the brain involved in learning and memory and while antiepileptic medications are effective, it remains untreatable in approximately 20% of patients. This brain region is susceptible to neuronal damage, such as head injury or trauma like a stroke, that can be accountable for an initial seizure episode, and subsequently undergoes pathological changes that result in chronic spontaneous recurrent seizures. The process is called epileptogenesis, or development of epilepsy.

Tissue plasminogen activator (tPA) is a modulator of seizure activity and neuronal degeneration. tPA, a serine protease responsible for the conversion of plasminogen to plasmin, is drastically upregulated under pathological conditions in the central nervous system (CNS). tPA activity contributes to CNS extracellular matrix breakdown, and the activation of the resident immune cells of the brain, the microglia. The literature supports a causal role for tPA and microglia during epileptogenesis which is explored further in this thesis.

Additional pathological changes during epileptogenesis include the accumulation of free zinc in brain regions involved by seizures. This accumulation is thought to contribute to recurrent neuronal overactivation and seizures. Previous research has demonstrated an interaction between tPA and zinc; in this Thesis I further explored this interaction during seizures.

I have employed a mouse model of TLE to address questions related to the involvement of tPA, microglia, and zinc during the development of epilepsy. Outcome measures for seizure severity include behavior, histology, and small animal positron emission tomography (PET) using the radiotracer 2-deoxy-2-[¹⁸F]fluoro-D-glucose (¹⁸FDG) whose uptake by neurons is indicative of neuronal activity. An increase in ¹⁸FDG uptake specifically in the hippocampus correlated with seizure severity. Wild type and tPA-deficient mice (tPA^{-/-}) were compared and statistical parametric mapping was innovatively employed to analyze the data. Microglial priming and ablation revealed an important role for these cells in mitigating acute seizure induction. Furthermore, tPA mediated zinc import into neurons was demonstrated using fluorescence assays, two-photon microscopy, and x-ray fluorescence microscopy, which suggests a paradoxically protective role for tPA in regulating excessive zinc clearance from the synaptic cleft during seizures.

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