IGF-I Promotes the Development of Epilepsy through Activation of Akt-mTOR Cascade

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Significance

- According to the Center for Disease Control and Prevention, epilepsy affects 65 million people worldwide.
- 5% of all cases of epilepsy are caused by traumatic brain injury (TBI)
- Epileptogenesis occurs during the latent period between the time of injury and the onset of seizures
- Insulin-like Growth Factor-I (IGF-I) is found in the cerebrospinal fluid of healthy individuals.
  - Following head injury, IGF-I levels are elevated in the brain tissue
  - Objective: To determine the role of IGF-I in epileptogenesis and find potential targets for antiepileptic drugs

Results

- Tissues lysed in buffer containing protease and phosphatase inhibitors. BCA analysis used to determine total concentration of protein in solution. Western blotting carried out and exposed films analyzed using Fiji (NIH) software.
- Ratio of Phosphorylated Protein = Phosphorylated Protein / Total Protein

Organotypic Hippocampal Culture Model of Epilepsy

Figure 1: Representative time course of epileptogenesis in an organotypic hippocampal culture. Colors correspond to the frequency of paroxysmal event occurrence in 10 s bins, with examples shown on the right. Deep blue, multiunit activity (top trace); light blue or yellow (middle trace); red, electrographic seizures (total events, bottom trace).

Methods

- In vivo: Acquired nine mice brain samples with three different treatments
- Control Brains: Normal brain dissection
- Sham Brains: Drilled opening into the skull
- CCI Brains: Drilled opening into the skull and delivered controlled impact to intact dura
- Brain samples dissected from four locations: Ipsilateral Cortex (IC), Contralateral Cortex (CC), Ipsilateral Hippocampus (IH) Contralateral Hippocampus (CH)
- In vitro: Organotypic hippocampal cultures maintained in the presence of IGF-I or vehicle, and harvested at various time points for analysis

Conclusion

- IGF-I is involved in post-traumatic signaling within the brain
- IGF-I is neuroprotective immediately after injury, but pro-epileptogenic longterm
- Both models suggest the pro-epileptogenic effects of IGF-I are mediated by Akt-mTOR signaling
- Modulation of the IGF-I-Akt-mTOR signaling may form a basis for new antiepileptic treatments

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