The Small Molecule Wnt Antagonist XAV939 Modulates Neuronal Network Remodeling in a Translational Mouse Model of Temporal Lobe Epilepsy

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Introduction

Epilepsy occurs frequently after cortical injury (e.g. TBI). While anti-epileptic medications can prevent early seizures, there are currently no treatments for delayed-onset epilepsy. Therapies targeting neuronal-network remodeling may prevent delayed epilepsy in high-risk patients. Mouse epilepsy models recapitulate aspects of human epilepsy, specifically spontaneous recurrent seizures and neuronal-network remodeling. We demonstrate that the Wnt pathway is dysregulated in the ictal and peri-ictal zones in a mouse model of temporal lobe epilepsy, and that a novel Wnt antagonist compound modulates neuronal-network remodeling in the hippocampus.

Learning Objectives

1.Epilepsy is characterized by rewiring of neuronal networks that causes neuronal hyper-excitability

2.Changes in neuronal connectivity differ in the ictal and peri-ictal zones. Molecular and structural processes that underlie these changes represent potential therapeutic targets in the development of epilepsy

3.The small molecule Wnt antagonist XAV939 modulates the neuronal network in peri-ictal regions by increasing neurogenesis and dendrite arborization in the

Methods

Seizures were induced by intrahippocampal kainate injection and compared with saline-injected controls in 3-4-month-old transgenic mice, in which adult-born dentate granule cells express GFP for 2-weeks after mitosis. Animals also received BRDU 48h-72h after seizure induction. Tissue was analyzed using immunohistochemistry and confocal microscopy, and transcriptome analysis was performed using RNA extracted from anatomically microdissected dentate gyrus.

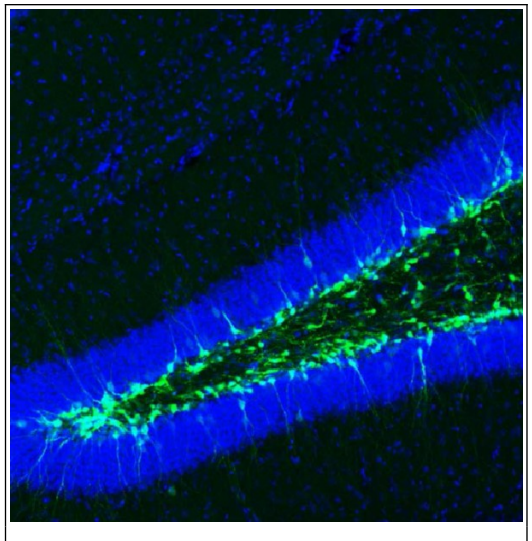
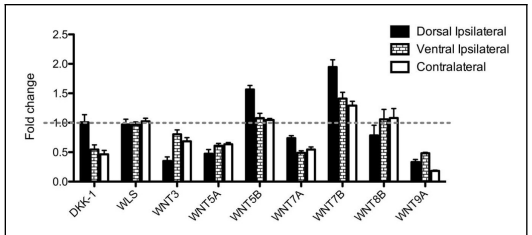


Image demonstrates coronal section hippocampal dentate gyrus with GFP+ dentate granule neurons

Results

Data demonstrate that hippocampal neurogenesis and dendritic arborization are increased in the peri-ictal regions, and decreased in the ictal zone 2-weeks after seizure. qPCR data demonstrate canonical Wnt pathway dysregulation in the hippocampus rapidly after seizure induction. We are using systemic administration of XAV939, a canonical Wnt antagonist, to investigate the Wnt pathway's role in neurogenesis and neuronal network formation. Our data demonstrate increased neurogenesis and dendritic length in the peri-ictal regions of mice treated with this Wnt antagonist.



qPCR data demonstrate Wnt pathway dysregulation in the hippocampus 3 days after seizure-induction

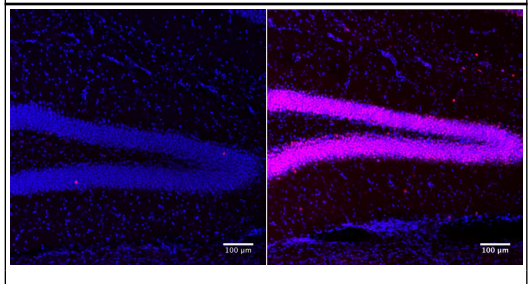
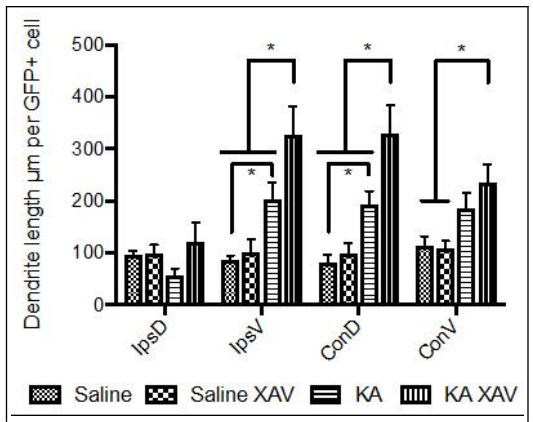


Image demonstrates marked difference in cfos expression 3h after saline (left) and generalized seizure (right)



Dendrite arbor length was markedly increased in the peri-ictal zones (ipsV, conD and conV), compared to the ictal zone (ipsD). This was further increased after Wnt antagonist treatment

Conclusions

Ictal and peri-ictal zone remodeling is critical in the development and maintenance of epilepsy. Our studies aim to understand the differences in neuronal network remodeling and the transcriptional changes responsible between these regions. We hypothesize the Wnt pathway is critical to changes induced by ictal activity and are utilizing small molecule modulation of Wnt activity to investigate this pathway as a putative target to prevent the development of epileptic circuits in peri-ictal regions.