Granule Cell Layer Morphology and Wnt Signaling in Temporal Lobe Epilepsy

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Background and Hypothesis: Temporal lobe epilepsy (TLE) is the most common human seizure disorder and can develop after neurologic insults such as trauma or infection. No treatment exists to prevent the development of epilepsy during this critical period. Epileptogenesis is characterized by pathological neuronal network remodeling in the hippocampal dentate gyrus (DG). Previously, we found that Wnt pathway signaling is dysregulated in the kainate (KA) mouse model of TLE, such that Wnt antagonism exacerbated epileptogenic DG remodeling. We hypothesize that Wnt agonism will mitigate pathological DG remodeling of the granule cell layer (GCL) during epileptogenesis.

Project Methods: TLE was induced by unilateral intrahippocampal KA injection in POMC-eGFP transgenic mice, while controls received saline. Mice received injections of vehicle or Wnt agonist Chir99021 daily. eGFP+ immature dentate granule cells were characterized by confocal microscopy. GCL width and immature dentate granule neuronal migration in the ictal/ipsilateral and peri-ictal/contralateral DG were quantified. Quantitative analyses were performed to compare means of the 4 groups.

Results: We found that GCL width significantly increased in the ictal zone 2 weeks after seizure induction in both KA groups and was not mitigated by Chir treatment. Immature dentate granule cell migration also increased in the ictal zone in the KA groups and was not altered by Chir treatment. In the peri-ictal zone, GCL width and cell migration were unchanged across KA and saline control mice.

Conclusion and Potential Impact: The Wnt agonist Chir99201 did not appear to alter GCL morphology in control or KA mice. It is likely that Wnt signaling may impact neuronal functioning rather than morphology in DG remodeling, and this will be explored through future electrophysiological studies. The Wnt pathway remains a potential therapeutic target in the prevention of the development of epilepsy.