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Loss of CLOCK Results in Dysfunction of Brain Circuits Underlying Focal Epilepsy

Highlights

- CLOCK transcription factor expression is low in human epileptogenic brain tissue
- Deletion of *Clock* in pyramidal cells causes seizures during sleep in mice
- Inhibition of CLOCK-deficient pyramidal cells in mouse and human is diminished

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In Brief

Li, Fu, et al. find that expression of the circadian transcription factor CLOCK is decreased in the "seizure focus" from patients with intractable epilepsy and that CLOCK loss of function in cortical excitatory neurons is sufficient for epileptogenesis in mouse.

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Loss of CLOCK Results in Dysfunction of Brain Circuits Underlying Focal Epilepsy

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SUMMARY

Because molecular mechanisms underlying refractory focal epilepsy are poorly defined, we performed transcriptome analysis on human epileptogenic tissue. Compared with controls, expression of *Circadian Locomotor Output Cycles Kaput* (*CLOCK*) is decreased in epileptogenic tissue. To define the function of CLOCK, we generated and tested the *Emx-Cre; Clock*$^{flox/flox}$ and *PV-Cre; Clock*$^{flox/flox}$ mouse lines with targeted deletions of the *Clock* gene in excitatory and parvalbumin (PV)-expressing inhibitory neurons, respectively. The *Emx-Cre; Clock*$^{flox/flox}$ mouse line alone has decreased seizure thresholds, but no laminar or dendritic defects in the cortex. However, excitatory neurons from the *Emx-Cre; Clock*$^{flox/flox}$ mouse have spontaneous epileptiform discharges. Both neurons from *Emx-Cre; Clock*$^{flox/flox}$ mouse and human epileptogenic tissue exhibit decreased spontaneous inhibitory postsynaptic currents. Finally, video-EEG of *Emx-Cre; Clock*$^{flox/flox}$ mice reveals epileptiform discharges during sleep and also seizures arising from sleep. Altogether, these data show that disruption of CLOCK alters cortical circuits and may lead to generation of focal epilepsy.

INTRODUCTION

Epilepsy, a disorder of recurrent unprovoked seizures, is a common disabling neurological condition affecting up to 1 in 26 individuals (England et al., 2012; Hauser et al., 1993; Hesdorffer et al., 2011). While single gene mutations in ion channels or neurotransmitter receptors are associated with generalized, inherited forms of epilepsy (Helbig et al., 2008; Lerche et al., 2013; Mantegazza et al., 2010), genetic causes do not account for the majority of patients with the disorder. Most patients have focal epilepsy, and their seizures arise from discrete pathological regions of abnormal brain tissue. Surgical resection of the "focus," where seizures originate, often ameliorates refractory, medication-resistant epilepsy (Englot and Chang, 2014). Despite its clinical importance, the molecular mechanisms defining epileptogenic tissue are poorly understood.

To determine molecular signatures of focal epilepsies, we have collected brain samples obtained from therapeutic resections of epileptogenic tissue associated with two common causes of focal epilepsy: focal cortical dysplasia (FCD) and tuberous sclerosis complex (TSC). FCD is the most common cause