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

Authors

Peijun Li, Xiaoqin Fu, Nathan A. Smith, ..., William D. Gaillard, Gregorio Valdez, Judy S. Liu

Correspondence

peijun.li@va.gov (P.L.), judy_liu@brown.edu (J.S.L.)

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

Peijun Li,1,15,* Xiaojin Fu,1,2,15 Nathan A. Smith,1 Julie Ziebro,1 Julian Curiel,1 Milagros J. Tenga,3 Brandon Martin,1 Samuel Freedman,4 Christian A. Cea-Del Rio,4 Livio Obotii,1 Tammy N. Tsuchida,5 Chima Oluigbo,5,6 Amanda Yaun,5,6 Suresh N. Magge,5,6 Brent O’Neill,7 Amy Kao,6 Tesfaye G. Zelleke,8 Dewi T. Depositario-Cabacar,5 Svetlana Ghimbovschi,8 Susan Knoblauch,8 Chen-Ying Ho,8,9,13 Joshua G. Corbin,1 Howard P. Goodkin,10 Stefano Vicini,11 Molly M. Huntsman,4 William D. Gaillard,1,5 Gregorio Valdez,3,12 and Judy S. Liu1,14,16,*

1Center for Neuroscience Research, Children’s Research Institute, Children’s National Medical Center, Washington, DC 20010, USA
2The Second Affiliated Hospital and Yuying Children’s Hospital of Wenzhou Medical University, Wenzhou, Zhejiang 325027, China
3Virginia Tech Carilion Research Institute; Roanoke, VA 24014, USA
4Department of Pharmaceutical Sciences, Skaggs School of Pharmacy and Pharmaceutical Sciences, Department of Pediatrics, School of Medicine, University of Colorado Anschutz Medical Campus, Aurora, CO 80045, USA
5Comprehensive Pediatric Epilepsy Program, Division of Neurophysiology and Epilepsy, Children’s National Health Medical Center; Washington, DC 20010 USA
6Division of Neurosurgery, Children’s National Medical Center, Washington, DC 20010, USA
7Division of Pediatric Neurosurgery, School of Medicine, University of Colorado, Anschutz Medical Campus, Aurora, CO 80045, USA
8Center for Genetic Medicine, Children’s Research Institute, Children’s National Medical Center, Washington, DC 20010, USA
9Division of Pathology, Children’s National Medical Center; Washington, DC 20010, USA
10Departments of Neurology and Pediatrics, University of Virginia Health System, Charlottesville, VA 22908, USA
11Department of Pharmacology and Physiology, Georgetown University, Washington, DC 20057, USA
12Department of Biological Sciences, Virginia Tech; Blacksburg, VA 24061, USA
13Present address: Department of Pathology, University of Maryland School of Medicine, Baltimore, MD 21201, USA
14Present address: Department of Neurology, Department of Molecular Biology, Cell Biology, and Biochemistry, Brown University, Providence, RI 02903, USA
15These authors contributed equally
16Lead Contact

*Correspondence: peijun.li@va.gov (P.L.), judy_liu@brown.edu (J.S.L.)
https://doi.org/10.1016/j.neuron.2017.09.044

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*<sup>fl<sub>ox</sub>/fl<sub>ox</sub></sup> and *PV-Cre; Clock*<sup>fl<sub>ox</sub>/fl<sub>ox</sub></sup> mouse lines with targeted deletions of the Clock gene in excitatory and parvalbumin (PV)-expressing inhibitory neurons, respectively. The *Emx-Cre; Clock*<sup>fl<sub>ox</sub>/fl<sub>ox</sub></sup> mouse line alone has decreased seizure thresholds, but no laminar or dendritic defects in the cortex. However, excitatory neurons from the *Emx-Cre; Clock*<sup>fl<sub>ox</sub>/fl<sub>ox</sub></sup> mouse have spontaneous epileptiform discharges. Both neurons from *Emx-Cre; Clock*<sup>fl<sub>ox</sub>/fl<sub>ox</sub></sup> mouse and human epileptogenic tissue exhibit decreased spontaneous inhibitory postsynaptic currents. Finally, video-EEG of *Emx-Cre; Clock*<sup>fl<sub>ox</sub>/fl<sub>ox</sub></sup> 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...
دریافت فوری متن کامل مقاله

امکان دانلود نسخه تمام متن مقالات انگلیسی
امکان دانلود نسخه ترجمه شده مقالات
پذیرش سفارش ترجمه تخصصی
امکان جستجو در آرشیو جامعی از صدها موضوع و هزاران مقاله
امکان دانلود رایگان ۲ صفحه اول هر مقاله
امکان پرداخت اینترنتی با کلیه کارت های عضو شتاب
دانلود فوری مقاله پس از پرداخت آنلاین
پشتیبانی کامل خرید با بهره مندی از سیستم هوشمند رهگیری سفارشات