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Authors
Baram, TZ
Brennan, G
McClelland, S
et al.

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Epigenetic regulation of HCN channels: a window into neuroplasticity?

T. Z. Baram, G. Brennan, S. McClelland, E. Magnetta, C. Dube

University of California-Irvine, Anatomy/Neurobiology; Pediatrics, Irvine, USA

The mechanisms generating epileptic neuronal networks following insults such as severe seizures are unknown. We have previously shown a down-regulation of hyperpolarizing cAMP-dependent cation-nonselective (HCN) channel type 1 (HCN1) during the process of seizure-induced epilepsy (Brewster *et al*., 2002), a finding confirmed almost universally by numerous groups around the world. We therefore sought the mechanisms regulating HCN1 repression as a potential unifying or common principle in the neuroplasticity that converts a normal neuron into an epileptic one. HCN1 repression required the actionf of a key neuronal transcription facotr, NRSF/REST. Further, interfering with the function of the neuron-restrictive silencer factor (NRSF/REST), an important transcription factor that influences neuronal phenotype, attenuated development of epilepsy after a provoking insult (McClelland *et al*., 2011). Epilepsy-provoking seizures increase the low NRSF levels in mature hippocampus several fold yet surprisingly, provoked repression of only a subset (~10%) of potential NRSF target genes. Accordingly, the repressed gene-set was rescued when NRSF binding to chromatin was blocked. Unexpectedly, genes selectively repressed by NRSF had midrange binding frequencies to the repressor, a property that rendered them sensitive to moderate fluctuations of NRSF levels. Genes selectively regulated by NRSF during epile-ptogenesis coded for ion channels, receptors and other crucial contributors to neuronal function (McClelland *et al*., eLife 2014). Thus, dynamic, selective regulation of NRSF target genes may play a role in influencing neuronal properties in pathological and physiological contexts, a lesson learned from the regulation of HCN channels (Noam *et al*., 2011)