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Epigenetic regulation of HCN channels: a window into neuroplasticity?

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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 action of a key neuronal transcription factor, 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 epileptoogenesis 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)