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Rapamycin reveals an mTOR-independent repression of Kv1.1 expression during Epileptogenesis

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mTOR signaling is overactive and thought to be, at least in part, the underlying cause of several developmental and neurodegenerative diseases. mTOR is best characterized for its role in promoting translation of mRNAs. Therefore, it is often hypothesized that overactive mTOR in neurological disorders results in excessive protein synthesis. However, a number of studies suggest that there is a reduction or loss of protein expression with respect to voltage-gated ion channels. Previously, we demonstrated that mTOR activity represses the local translation of the voltage-gated potassium channel Kv1.1 in neuronal dendrites. Herein we demonstrate that in the hippocampus mTOR activity mediates the first phase of Kv1.1 repression in a rat model of temporal lobe epilepsy. This is followed by a second, mTOR-independent phase. Decreased Kv1.1 expression results in a reduced threshold for firing an action potential. Treatment with the mTOR inhibitor rapamycin decreases behavioral seizures and increases Kv1.1 expression, but only initially. Unexpectedly, we found that miR-129-5p levels, the microRNA that represses Kv1.1 mRNA translation, continue to rise even in the presence of rapamycin. The increase in miR-129-5p corresponded to an increase in seizure activity and a reduction in Kv1.1 expression during later stages of epileptogenesis. Our findings are the first to demonstrate a novel mTOR-independent phase in epileptogenesis and provide the molecular basis for the biphasic nature of Kv1.1 repression in temporal lobe epilepsy.

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Distinct pro-survival and cell death gene profiles within hippocampal subregions following multiple early life seizures

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In mature adults, harmful side-effects of recurrent seizures are known to be due to excessive release of glutamate, over-activation of glutamate receptors, and simultaneous alterations of the GABAergic system whereas non-lethal traumas render the brain more resistant to subsequent insults due to activation of certain genes and signaling cascades that raise the threshold for cell death. Multiple neonatal seizures produce spatial preconditioning at juvenile ages. For example, seizures cause robust injury to the CA1 and very little injury to the CA3 hippocampal subfield following a single injection of Kainic Acid (KA) (1×KA) induced on P20, but this damage is attenuated if the P20 rats have a history of two sustained neonatal seizures on P6 and P9 (3×KA). Further, the Dentate Gyrus (DG) is always resistant to injury regardless of age. Underlying mechanisms of age-dependent, spatially distinct neuroprotection and the responsible major signaling cascades remain unknown but are associated with high elevations of $[Ca^{2+}]_i$. Previously we profiled transcriptomes of the isolated CA1 sub-region after 1×KA and 3×KA. Herein we isolated transcriptomes of the CA3 and DG subregions under the same conditions. Autophagy genes were triggered by single or multiple seizures within the CA3, but many protective genes were also differentially upregulated, particularly after 3×KA in both age groups but with different expression profiles. The DG was absent in cell death genes. Instead, immunity, ion transport, and stabilizing genes were upregulated and proliferation and migration cues were down-regulated. Results indicate resistance to insult of the pyramidal fields after neonatal seizures is due to region specific attenuation of glutamate stimulated Ca^{2+} currents, reduced apoptosis, and induction of survival signaling pathways, whereas cell resistance of the DG is due to axonal vesicular, and energy dependent stabilizers and their vulnerability lies within disrupted proliferation and migratory domains.

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