学 位 論 文 の 要 旨

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主論文の題名

MicroRNA-34a upregulation during seizure-induced neuronal death

主論文の要旨

MicroRNAs (miRNAs) are short, noncoding RNAs that function as posttranscriptional regulators of gene expression by controlling translation of mRNAs. A subset of miRNAs may be critical for the control of cell death, including the p53-regulated miRNA, miR-34a. Because seizures activate p53, and p53-deficient mice are reportedly resistant to damage caused by prolonged seizures, we investigated the role of miR-34a in seizure-induced neuronal death in vivo.

Status epilepticus was induced by intraamygdala microinjection of kainic acid in mice. This led to an early (2 h) upregulation of miR-34a in the CA3 and CA1 hippocampal subfields and lower protein levels of mitogen-activated kinase kinase kinase 9, a validated miR-34a target. Immunoprecipitation of the RNA-induced silencing complex component, Argonaute-2, eluted significantly higher levels of miR-34a after seizures. Injection of mice with pifithrin-a, a putative p53 inhibitor, prevented miR-34a upregulation after seizures. Intracerebroventricular injection of antagomirs targeting miR-34a reduced hippocampal miR-34a levels and had small modulatory effects on apoptosis-associated signaling, but did not prevent hippocampal neuronal death in models of either severe or moderate severity status epilepticus.

Prolonged seizures cause subfield-specific, temporally restricted upregulation of miR-34a, which may be p53 dependent, but miR-34a is probably not important for seizure-induced neuronal death in this model.