学位論文の要旨

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主論文の題名

Deletion of the BH3-only protein Noxa alters electrographic seizures but does not protect against hippocampal damage after status epilepticus in mice

主論文の要旨

Several members of the Bcl-2 gene family are dysregulated in human temporal lobe epilepsy and animal studies show genetic deletion of some these proteins influence electrographic seizure responses to chemoconvulsants and associated brain damage. The BH3-only proteins form a subgroup comprising direct activators of Bax-Bak that are potently pro-apoptotic, and a number of weaker pro-apoptotic BH3-only proteins that act as sensitizers by neutralization of anti-apoptotic Bcl-2 family members. Noxa was originally characterised as a weaker pro-apoptotic, 'sensitizer' BH3-only protein, although recent evidence suggests it too may be potently pro-apoptotic. Expression of Noxa is under p53 control, a known seizure-activated pathway, although Noxa has been linked to energetic stress and autophagy. Here we characterised the response of Noxa to prolonged seizures and the phenotype of mice lacking Noxa. Status epilepticus induced by intra-amygdala kainic acid caused a rapid increase in expression of *noxa* in the damaged CA3 subfield of the hippocampus but not undamaged CA1 region. *In vivo* upregulation of *noxa* was reduced by pifithrin-α, suggesting transcription may be partly p53-dependent. Mice lacking *noxa* developed less severe electrographic seizures during status epilepticus in the model but, surprisingly, displayed equivalent hippocampal damage to wild-type animals. The present findings indicate Noxa does not serve as a pro-apoptotic BH3-only protein during seizure-induced neuronal death *in vivo*. This study extends the comprehensive phenotyping of seizure and damage responses in mice lacking specific Bcl-2 gene family members and provides further evidence that these proteins may serve roles beyond control of cell death in the brain

（注）２，０００字以内にまとめて記入すること。