学位論文審査結果の要旨

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（学位論文審査結果の要旨）

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

著者らは論文において下記の内容を述べている。

Several members of the Bcl-2 gene family are dysregulated in human temporal lobe epilepsy and animal studies show that genetic deletion of some of 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 proapoptotic and a number of weaker proapoptotic BH3-only proteins that act as sensitizers by neutralization of antiapoptotic Bcl-2 family members. Noxa was originally characterized as a weaker proapoptotic, 'sensitizer' BH3-only protein, although recent evidence suggests it too may be potently proapoptotic. Expression of Noxa is under p53 control, a known seizure-activated pathway, although Noxa has been linked to energetic stress and autophagy. Here we characterized 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 proapoptotic 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.

以上のように本論文は、痙攣重積によって傷害された海馬領域においてNoxaの発現が上昇することを証明した。Noxaノックアウトマウスにカイニン酸を投与した実験では、痙攣誘発性神経細胞死の抑制を認めることはできなかったが、その際の脳波測定において電気生理学的に痙攣重症度が抑制されることが証明された論文であり、学術上極めて有益であり、学位論文として価値あるものと認めた。

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