論 文 の 内 容 の 要 旨

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論　文　題　目

An epilepsy-associated mutation of salt-inducible kinase 1 increases the susceptibility to epileptic seizures and interferes with adrenocorticotropic hormone therapy for infantile spasms in mice.
（Salt-induced kinase 1 遺伝子のてんかん関連変異はてんかん発作の感受性を高めるとともに、マウスの点頭てんかんに対する ACTH の効果を減弱させる。）

（論文の内容の要旨）

〔Background and Aims〕 Salt-inducible kinase 1 (SIK1) is an AMP-activated protein kinase (AMPK) with inducible expression in the adrenal cortex in response to the salt intake or adrenocorticotropic hormone (ACTH). Six mutations in the salt-inducible kinase 1 (SIK1)-coding gene have been identified in patients with early infantile epilepticencephalopathy (EIEE-30) accompanied by autistic symptoms. Two of the mutations are nonsense mutations that truncate the C-terminal region of SIK1. Although the relevance between the SIK1 mutation and autistic behaviors has been uncovered in SIK1-MT mice, the effect of the SIK1 mutation on epilepsy remains unknown.

〔Materials & Methods〕 To study the effects of these mutations on the disorder, we injected NMDA or PTZ into SIK1-MT males to induce epileptic seizures in mice. Activated brain regions were identified by immunohistochemistry against c-fos, Iba1, and GFAP. ACTH was administrated intraperitoneally to examine the rescue effect in SIK1-MT and wild-type control mice. We also analyzed electrophysiological properties of the cortical neurons in SS using patch clamp recordings.

〔Results〕 SIK1-MT mice grow normally without showing early lethality. In the SIK1-MT mice, we found NMDA-induced spasms are more severe .Using patch clamp electrophysiology, we found input resistance and the number of action potentials was increased in SIK1-MT mice and an increase in the density of c-fos positive cells in 12 out of 126 brain regions by immunohistochemistry against c-fos, and pretreatment of ACTH did not alleviate the severity of NMDA-induced spasms in SIK1-MT mice. We also found that SIK1 is involved in temporal lobe epilepsy by PTZ-induced seizure, and the neural circuits activated by PTZ and NMDA injection may be different base on the laminar distribution of c-fos positive cells in the somatosensory cortex.

〔Conclusion〕 Altogether, epilepsy-associated SIK1 mutant mice were subjected to NMDA- and PTZ-induced seizures, rodent models for infantile spasms, and temporal lobe epilepsy. As suggested in human clinical research, our data support the hypothesis that the SIK1 gene is closely associated with epileptic seizures and raise the notion that SIK1 may be involved in the molecular pathway underlying the ACTH therapy for infantile spasms.