論 文 の 内 容 の 要 旨

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論 文 題 目

Risperidone Mitigates Enhanced Excitatory Neuronal Function and Repetitive Behavior Caused by an ASD-Associated Mutation of SIK1（SIK1 の ASD 関連変異によって引き起こされた興奮性神経機能と反復行動はリスペリドンによって軽減される。）

（論文の内容の要旨）

〔Background and Aims〕 Salt inducible kinase 1 (SIK1) is a member of AMP-activated protein kinase (AMPK) proteins that modulates the function of transcriptional regulatory factors by phosphorylation both in cytosol and nucleus. Six mutations in the SIK1 coding gene have been identified in the early infantile epileptic encephalopathy (EIEE-30) patients accompanied by autistic symptoms, such as repetitive behavior and social behavioral deficits. Among these mutations, two are nonsense mutations that truncate the c-terminal nuclear localization domain (NLD). It has been shown that the C-terminal-truncated form of SIK1 protein affects the subcellular distribution of SIK1 protein, tempting to speculate the relevance to the pathophysiology of the symptoms.

〔Materials & Methods〕 To study the effects of these mutations on the disorder, Badawi generated SIK1 mutant (SIK1-MT) mice recapitulating the c-terminal truncated mutations using CRISPR/Cas9 technology. He studied the behaviors relevant to neurodevelopmental disorders and electrophysiological properties in pyramidal neurons in layer 5 of the medial prefrontal cortex in SIK1-MT and wild-type control mice using whole cell patch clamp technology on the acute brain slices. Risperidone was administrated intraperitoneally to examine the rescue effect.

〔Results〕 SIK1-MT mice grow normally without showing any abnormal morphological changes, early lethality or epileptic seizures. On the subcellular level, SIK1-MT protein was distributed in the nucleus and cytoplasm, whereas the distribution of wild-type SIK1 was restricted to the nucleus. Using patch clamp electrophysiology, we found the disruption of excitatory and inhibitory (E/I) synaptic balance due to an increase in excitatory synaptic transmission and an enhancement of neural excitability in the pyramidal neurons in layer 5 of medial prefrontal cortex (mPFC) in SIK1-MT mice. We also found the increased repetitive behavior and social behavioral deficits in SIK1-MT mice compared to the SIK1-WT mice. The Risperidone acute intraperitoneal administration attenuated the neural excitability and excitatory synaptic transmission, however; the disrupted E/I synaptic balance was unchanged because the inhibitory synaptic transmission was also reduced. Risperidone also restored the repetitive behavior, but not the social behavioral deficits.

〔Conclusion〕 Altogether, these findings suggest that the increased excitatory neural activity is responsible for the observed augmentation in repetitive behavior whereas the disrupted E/I synaptic balance accounts for the social behavioral deficits in SIK1-MT mice.