論 文 審 査 の 結 果 の 要 旨

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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. SIK1 C-terminal-truncated mutations were identified in patients with EIEE-30. To study the effect of these mutations on the etiology of EIEE-30, Badawi generated C-terminal- truncated SIK1-MT mice using CRISPR/Cas9-mediated genome editing as disease models. He studied these mice by focusing on the synaptic function and behaviors and found the following:

(1) The frequency of mEPSCs and the neuronal excitability were increased in pyramidal neurons in layer 5 of the mPFC of SIK1-MT mice.

(2) Repetitive behavior was increased and the social behavior was impaired in the SIK1-MT mice.

(3) Elevated excitatory synaptic transmission and neural excitability in the SIK1-MT mice were restored by risperidone treatment.

(4) Increased repetitive behavior, but not social behaviors, in SIK1-MT mice was ameliorated by risperidone treatment.

The committee chair and vice chairs evaluated that the thesis deserved a doctoral dissertation.