News Release

A variant of a phosphorylation enzyme causes exaggerated long-term potentiation and learning disabilities

Key Points

- A knock-in model mouse for intellectual disability, reflecting a variant of phosphorylation enzyme CaMKIIα, was successfully developed.
- Abnormal synaptic plasticity and phosphorylation activity were identified in the brains of the model mice.
- Excessive activation of the phosphorylation enzyme was found to cause learning and memory impairments.

Summary

Intellectual disability (ID) is a neurodevelopmental disorder (NDD) characterized by impaired intellectual and adaptive functioning. In recent years, variants in the gene encoding calcium/calmodulin-dependent protein kinase II alpha (CaMKIIα), a key phosphorylation enzyme involved in synaptic plasticity, learning and memory, have been reported to be associated with ID. However, the mechanisms by which these variants contribute to the ID/NDD remain largely unclear. The research group, led by Professor Sayaka Takemoto-Kimura and Graduate Student Miao Pan (at the time) from the Department of Neuroscience, Research Institute of Environmental Medicine, Nagoya University, in collaboration with Department of Neuropsychopharmacology and Hospital Pharmacy, Department of Pathophysiology of Mental Disorders, Brain and Mind Research Center, Department of Pediatrics, Nagoya University Graduate School of Medicine, The Jikei University School of Medicine, and Gunma University Graduate School of Medicine, Graduate School of Medicine The University of Tokyo has successfully developed a disease model mouse harboring the variant reported in patients with intellectual disability. The research group discovered brain changes in the model mouse, including an enhancement of long-term potentiation in the hippocampus. The developed model mice exhibited behavioral characteristics resembling the clinical phenotype of ID and NDD, including deficits in social behavior, motor coordination, and spatial learning. Additionally, the mice showed enhanced CaMKIIα phosphorylation and stimulation-induced hippocampal long-term potentiation (LTP). These findings provide new insights into how enhanced activation of CaMKIIα variants, which play a critical role in memory regulation, may contribute to the pathogenesis of

ID/NDD. Moving forward, the model mice established in this study are expected to significantly advance our understanding of the mechanisms underlying ID/NDD and the future development of treatments.

Research Background

Neurodevelopmental disorders (NDDs) are a group of disorders that include autism spectrum disorder (ASD), intellectual disability (ID), and developmental coordination disorder (DCD). Recent studies have shown that a certain number of ID are associated with *de novo* variants. In particular, recent studies have suggested that *de novo* variants in CaMKII, which is involved in synaptic plasticity and learning and memory, may play a role in the cause of ID. However, the causal relationship between these variants and learning disabilities and the mechanism by which CaMKII variants cause ID have not yet been fully elucidated.

Research Results

In this study, the research group developed CaMKIIα-p.P212L heterozygous knock-in mice as a model mouse for ID that introduced the CaMKIIα *de novo* variant found in patients with ID. The previous study had shown that this variant promoted CaMKIIα activation, so we examined CaMKIIα activation in the brains of the model mice and confirmed that CaMKIIα phosphorylation was enhanced in synapses. Since CaMKIIα is an essential regulator of spine structure and function in dendrites, we next analyzed the shape of the spines. We sparsely labeled neurons in the CA1 region of the hippocampus with fluorescent protein, visualized the shape of dendritic spines, and found that the size of mushroom-shaped spines was enlarged in the hippocampus of the model mice.

Since the enlargement of dendritic spines suggests a change in synaptic plasticity, we next investigated LTP, a form of synaptic plasticity in the hippocampus. When 10 Hz stimulation was applied for 90 seconds to the hippocampus of wile-type mice, it did not induce LTP, which is consistent with previous studies. However, in the hippocampus of the model mice, LTP induction was observed, indicating that synaptic plasticity is enhanced and occurred even under low-frequency stimulation in these mice.

The model mice were found to exhibit behavioral characteristics resembling the clinical phenotype of ID/NDD in behavioral tests, such as alteration of social behavior and motor coordination disability. To further evaluate the cognitive behavior of the developed model mice, we conducted the Barnes maze test. This

test capitalizes on the natural tendency of mice to seek dark, enclosed spaces and features 12 holes on a circular platform, one of which leads to a dark escape box. After training, wild-type mice could move efficiently toward the escape box, but learning delays were observed in the model mice. Additionally, learning delays were also observed in the model mice during a visual discrimination test, a task based on visual cues.

These results suggest that variants that promote the activity of CaMKII, a vital memory regulator, enhance CaMKII phosphorylation signaling in spines and disrupt neural circuit function, which may lead to the complex cognitive and behavioral characteristics associated with ID/NDD.

Research Summary and Future Perspective

In this study, we developed a novel knock-in model mouse for ID/NDD. Analysis of this model revealed that the p.P212L variant of CaMKIIα enhances phosphorylation signaling, enlarges dendritic spines, and induces various behavioral changes, including learning and memory impairments. CaMKIIα is a phosphorylation enzyme responsible for neuronal calcium-dependent signaling that regulates learning and memory. Additionally, it also plays a key role in mediating the functions of other proteins associated with ID/NDD. Considering the above, this model mouse is pivotal for a deeper understanding of ID/NDD and is expected to contribute to future therapeutic development of ID/NDD.

Publication

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