News Release

Selective ROCK2 inhibition May Offer a New Therapeutic Strategy for Schizophrenia
— Toward the Development of a New Treatment with Fewer Side Effects —

Key Points

- A selective Rho kinase 2 (ROCK2) inhibitor, KD025, was shown to improve cognitive impairments in mouse models of schizophrenia.
- KD025 was less likely to cause hypotension, a known side effect of conventional Rho kinase inhibitors, as well as motor, hormonal, and metabolic adverse effects commonly associated with existing antipsychotic drugs.
- Selective inhibition of ROCK2 represents a promising novel therapeutic target for schizophrenia, with the potential to reduce treatment-related side effects.

Summary

A research team led by Rinako Tanaka, Ph.D., Project Assistant Professor at Nagoya University, (currently Postdoctoral Fellow at the University of Alabama at Birmingham); Kiyofumi Yamada, Ph.D., Emeritus Professor (currently Visiting Professor at Fujita Health University); Hiroyuki Mizoguchi, Ph.D., Associate Professor; Norio Ozaki, M.D., Ph.D., Project Professor; and Taku Nagai, Ph.D., Professor at Fujita Health University, has demonstrated that selective inhibition of Rho kinase 2 (ROCK2) improves schizophrenia-related cognitive impairments and behavioral abnormalities in mice while showing a low risk of adverse effects.

Research Background

Current antipsychotic medications are effective in alleviating positive symptoms of schizophrenia, such as hallucinations and delusions. However, they often fail to adequately improve cognitive impairments, including deficits in thinking, memory, and other cognitive functions. In addition, many existing treatments cause adverse effects such as motor dysfunction, hormonal abnormalities, and metabolic disturbances, highlighting the need for safer and

more effective therapies.

The research group previously identified a schizophrenia-associated ARHGAP10 gene variant through genome analyses of Japanese patients. This gene is closely related to the activity of a molecule known as Rho-kinase (ROCK), which plays an important role in brain cell function.

In earlier studies using mice, the researchers found that inhibiting ROCK activity improved behavioral abnormalities, suggesting that abnormal ROCK signaling may contribute to the development of schizophrenia. Although ROCK inhibition has shown therapeutic potential, conventional ROCK inhibitors can induce hypotension, limiting their clinical applicability.

Research Results

In the present study, the researchers focused on ROCK2, a kinase subtype highly expressed in the brain, and examined whether selective inhibition could retain efficacy while minimizing side effects. They administered KD025, a ROCK2-selective inhibitor, to multiple mouse models that reproduce behavioral and cognitive features relevant to schizophrenia.

The results demonstrated significant improvements in cognitive impairments, including deficits in thinking, visual discrimination, and memory, as well as improvements in certain behavioral abnormalities.

In addition, in mice carrying genetic characteristics similar to those identified in patients, KD025 treatment restored dendritic spine density in the prefrontal cortex, a brain region critical for higher cognitive functions. These findings suggest that KD025 may exert beneficial effects not only on brain function but also on abnormalities in neuronal connectivity.

Importantly, oral administration of KD025 at behaviorally effective doses did not cause hypotension and adverse effects commonly associated with antipsychotic drugs, including extrapyramidal symptoms, hyperprolactinemia, and hyperglycemia.

These results suggest that selective ROCK2 inhibition may improve both neural connectivity and brain function while maintaining a favorable safety profile.

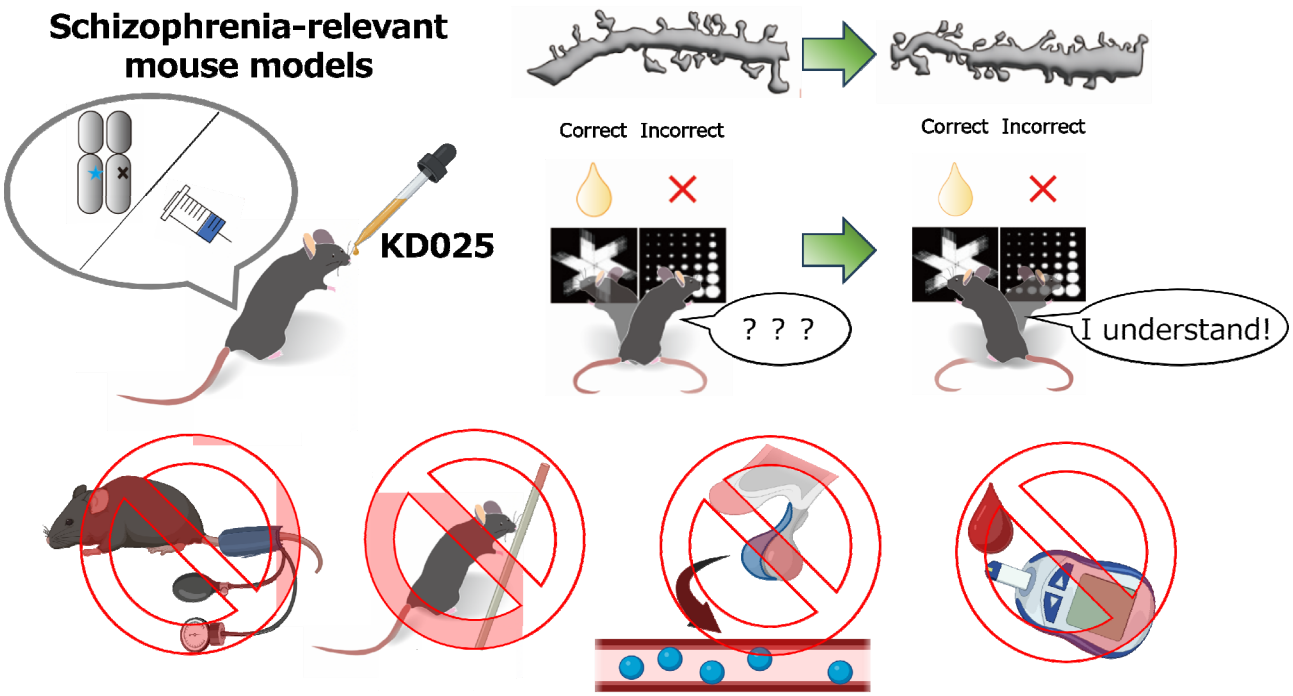

Figure Summary of this study

Research Summary and Future Perspective

This study demonstrates that ROCK2-targeted therapy has the potential to address cognitive dysfunction in schizophrenia, an area of unmet clinical need, while reducing the risk of side effects seen with current treatments. These findings suggest that ROCK2 is a promising novel therapeutic target for next-generation schizophrenia medications.

Future studies will focus on elucidating the precise molecular mechanisms by which KD025 improves neural function and synaptic connectivity, as well as further evaluating its safety and efficacy to support eventual clinical translation.

Publication

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