News Release

Title

Inhibition of Rho-kinase ameliorates decreased spine density in the medial prefrontal cortex and methamphetamine-induced cognitive dysfunction in mice carrying schizophrenia-associated mutations of the *Arhgap10* gene

Key Points

- **Rho-kinase inhibitor, fasudil restored the decreased spine density of pyramidal neurons in the medial prefrontal cortex in *Arhgap10* S490P/NHEJ mice.**
- **Fasudil ameliorated the methamphetamine-induced cognitive dysfunction in *Arhgap10* S490P/NHEJ mice.**
- **Targeting RhoA/Rho-kinase signaling may provide new therapeutic approaches for the treatment of schizophrenia patients, including those with *Arhgap10* gene mutations.**

Summary

The pathoetiology of schizophrenia has not been fully understood because of its complexity and heterogeneity. However, copy-number variations in the *ARHGAP10* gene, which encodes Rho GTPase activating protein 10, are associated with schizophrenia. We explored the pathomechanism underlying *Arhgap10* mutations using model mice (*Arhgap10* S490P/NHEJ mice) that carry "double-hit" mutations in the *Arhgap10* gene and mimic the case of schizophrenia in a Japanese patient, both histologically and behaviorally.

Research Background

Model mice (*Arhgap10* S490P/NHEJ mice) that carry "double-hit" mutations in the *Arhgap10* gene mimic the schizophrenia in a Japanese patient, exhibiting altered spine density, methamphetamine-induced cognitive dysfunction, and activation of RhoA/Rho-kinase signaling. However, it remains unclear whether the activation of RhoA/Rho-kinase signaling due to schizophrenia-associated *Arhgap10* mutations causes the phenotypes of these model mice.

Research Results

We demonstrated the activation of Rho-kinase, which functions downstream of ARHGAP10 in the medial prefrontal cortex and striatum, in *Arhgap10* S490P/NHEJ mice. Furthermore, the brain permeable Rho-kinase inhibitor fasudil restored the decreased spine density of pyramidal neurons in the medial prefrontal cortex and the methamphetamine-induced cognitive dysfunction in *Arhgap10* S490P/NHEJ mice. Thus, our findings clarify how Rho-kinase contributes to the neuropathological changes in spine morphology and the cognitive vulnerability to methamphetamine caused by schizophrenia-associated mutations in the

Arhgap10 gene.

Research Summary and Future Perspective

Targeting RhoA/Rho-kinase signaling may provide new therapeutic approaches for the treatment of schizophrenia patients, including those with *Arhgap10* gene mutations.

Publication

Titile: Inhibition of Rho-kinase ameliorates decreased spine density in the medial prefrontal cortex and methamphetamine-induced cognitive dysfunction in mice carrying schizophrenia-associated mutations of the *Arhgap10* gene

Authors: Rinako Tanaka[1], Jingzhu Liao[1], Kazuhiro Hada[1], Daisuke Mori[2], Taku Nagai[1,3], Tetsuo Matsuzaki[1], Toshitaka Nabeshima[4,5], Kozo Kaibuchi[6,7], Norio Ozaki[2], Hiroyuki Mizoguchi[1], Kiyofumi Yamada[1,5]

Affiliations:

[1]Department of Neuropsychopharmacology and Hospital Pharmacy, Nagoya University Graduate School of Medicine, Nagoya, Aichi, 466-8560, Japan.

[2]Department of Psychiatry, Nagoya University Graduate School of Medicine, Nagoya, Aichi, 466-8560, Japan.

[3]Division of Behavioral Neuropharmacology, International Center for Brain Science (ICBS), Fujita Health University, Toyoake, Aichi, 470-1192, Japan.

[4]Laboratory of Health and Medical Science Innovation, Fujita Health University Graduate School of Health Sciences, Toyoake, Aichi, 470-1192, Japan.

[5]Japanese Drug Organization of Appropriate Use and Research, Nagoya, Aichi, 468-0069, Japan.

[6]Department of Cell Pharmacology, Nagoya University Graduate School of Medicine, Nagoya, Aichi, 466-8560, Japan.

[7]International Center for Brain Science, Fujita Health University, Toyoake, Aichi 470- 1129, Japan

Journal: Pharmacological Research

DOI: https://doi.org/10.1016/j.phrs.2022.106589

Japanese ver.

https://www.med.nagoya-u.ac.jp/medical_J/research/pdf/Pha_230105.pdf